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# **Comprehensive studies of organic synthesis by utilizing chemical features of natural products**

(天然物の化学的特性を活かした有機合成反応の網羅的検討)



### **Doctoral dissertation**

(The Special Postgraduate Program in Biosphere Sustainability Science)

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And if whatever trees upon the earth were pens and the sea [was ink], replenished thereafter by seven [more] seas, the words of Allah would not be exhausted. Indeed, Allah is Exalted in Might and Wise (Al-Qur'an, 31: 27). The greatest things only own by God and all the knowledge or research that we found actually already His created.

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"You just need to study at school; therefore, you will not get discouraged in front of great people"—My Grandfather H. Muh. Sian

## Abbreviation

| <sup>1</sup> H-NMR     | Proton Nuclear Magnetic Resonance      |  |
|------------------------|--|--|
| <sup>13</sup> C-NMR    | Carbon Nuclear Magnetic Resonance      |  |
| 1D-NMR                 | One-Dimensional Nuclear Magnetic       |  |
|                        | Resonance                              |  |
| 2D-NMR                 | Two-Dimensional Nuclear Magnetic       |  |
|                        | Resonance                              |  |
| COSY                   | Correlated Spectroscopy                |  |
| HMOC                   | Heteronuclear Multiple-Quantum         |  |
|                        | Correlation Spectroscopy               |  |
| НМВС                   | Heteronuclear Multiple Bond            |  |
|                        | Correlation Spectroscopy               |  |
| HETCOR                 | Heteronuclear Correlation Spectroscopy |  |
| NOESY                  | Nuclear Overhauser Effect              |  |
|                        | Spectroscopy                           |  |
| TOCSY                  | Total Correlation Spectroscopy         |  |
| TFA-d                  | Deuterated trifluoroacetic acid        |  |
| TfOH                   | Triflic acid                           |  |
| TfOD                   | Deuterated triflic acid                |  |
| H/D                    | Hvdrogen/deuterium                     |  |
| TFA-                   | Trifluoroacetyl-                       |  |
| OSu                    | <i>N</i> -hydroxysuccinimide ester     |  |
| WSCD-HCl               | Water-Soluble Carbodiimide             |  |
|                        | Hydrochloride                          |  |
| NHS                    | <i>N</i> -hydroxysuccinimide           |  |
| Ar                     | Arene                                  |  |
| L-/D-Ile               | L-/D-Isoleucine                        |  |
| L-/D- <i>allo</i> -Ile | L-/D-allo-Isoleusine                   |  |
| Gly                    | Glycine                                |  |
| L-/D-Ala               | L-/D-Alanine                           |  |
| L-/D-Val               | L-/D-Valine                            |  |
| L-/D-Leu               | L-/D-Leucine                           |  |
| L-/D-Nva               | L-/D-Norvaline                         |  |
| L-/D-Nle               | L-/D-Norleucine                        |  |
| L-/D-Pro               | L-/D-Proline                           |  |
| L-/D-Phe               | L-/D-Phenylalanine                     |  |
| L-/D-Tyr               | L-/D-Tyrosine                          |  |
| Pyr                    | <i>N</i> -pyrrole                      |  |
| <i>N</i> -Me Pyr       | <i>N</i> -methyl pyrrole               |  |
| DCl                    | Deuterium chloride                     |  |

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#### 1.1 Introduction

Natural products hold a unique and enormous chemical diversity of which individual scaffolds have different reactivity and stability, chemical modification potentials, or specific functional groups at special position that involves in molecular interaction. The existence of chiral centers and stereochemistry are also important key in biomolecules that critically influence the properties of natural products. Organic synthesis gives opportunity for exploring a challenging molecular architecture that extent the discovery and invention of new synthetic strategies, methods, and analyses. Taking advantage from vast chemical features of natural products in organic synthesis, a wider range of applications and a comprehensive study for multipurpose in research and development are possibly achieved.

#### 1.1.1 Direct halogenations of carbohydrate's primary alcohols

Carbohydrate is the most abundant organic compounds in nature. In plant, carbohydrates act as chemical energy (glucose, starch, glycogen); are components of supportive structures in plants (cellulose), crustacean shells (chitin), and connective tissues in animals (glucosaminoglycans); and are essential components of nucleic acids (D-ribose and 2-deoxy-D-ribose). The chemistry of carbohydrates is essentially the chemistry of hydroxy groups and carbonyl groups and of the acetal bonds formed between these two functional groups.<sup>1</sup>

In midst of carbohydrates, sucrose (Figure 1) is produced worldwide in large quantities. This compound is highly functionalized molecules with complex stereochemistry, due to the presence of several hydroxylated stereogenic centers.<sup>2</sup> Sucrose is also accepted as a standard of sweet taste quality. Hence, the sweetness intensity and other taste properties of natural and synthetic sweeteners are frequently compared with sucrose. Interestingly, substitutions of halogen into certain carbohydrate skeleton gave different relative sweetness than sucrose (Table 1).<sup>3</sup> For example, 4,1',6'-trichloro-4,l',6'-trideoxygalactosucrose (Table 1)—known as sucralose—is daily used as one of the alternative sweetener that can enhance 2000-fold sweetness activity than sucrose. Moreover, selective halogenation on other primary center of sucrose offered the control of sweetness (Table 1). This will lead to the needs for selective synthesis of sucrose derivatives laborious with simple procedures.



Figure 1 Example of selected carbohydrates structure

| Compound   | Sweetness |
|--|-----------|
| 1'-chloro-1'-deoxysucrose                        | 20        |
| 6-chloro-6-deoxysucrose                          | Bitter    |
| 6'-chloro-6'-deoxysucrose                        | 20        |
| 1',6'-dichloro-1',6'-dideoxysucrose              | 500       |
| 6,6'-dichloro-6,6'-dideoxysucrose                | Not sweet |
| 1',4,6'-trichloro-1',4,6'-trideoxygalactosucrose | 2000      |
| Sucrose  | 1         |
| Galactosucrose                                   | Not sweet |

**Table 1** Relative sweetness of sucrose and galactosucrose derivatives<sup>3</sup>

The syntheses of halogenated sucrose at its primary positions, particularly those containing bromine and chlorine have been already studied well. Several approaches had been used for halo substituted from direct or protected hydroxy group of sucrose. Indirect methods such as the intermediate utilization of 6,6'-ditosyl intermediate;<sup>4</sup> selective cleavage of fully protected sucrose before further halogenation of the free primary alcohol counterpart;<sup>5–7</sup> or bulky functional groups protection and unprotection of one or two primary hydroxy groups<sup>8–10</sup> are reported. Then the direct replacement of primary hydroxy groups with halogen, e.g. direct chlorination of sucrose by well-known sulphuryl chloride (Table 2 : Method A)<sup>11</sup> that by the strict control of reaction condition at -78 °C, the halogenations position will give high

selectivity for monochlorinated at 6'-position. In contrast, at room temperature or higher temperature condition, sulphuryl chloride is not selective due to the direct 4'-chlorination<sup>12</sup> of sucrose observed.

 Table 2 Variance of methods for direct replacement only at sucrose primary hydroxy groups

 by a halogen substituent



| Method         | Reference                 | Reagents  | Product (% Yield)                 |
|----------------|---------------------------|---|-----------------------------------|
| A <sup>a</sup> | Ref. <sup>11</sup>        |   | 6,6'-dichloro-6,6'-dideoxysucrose |
|                |                           | SO <sub>2</sub> Cl <sub>2</sub> (21.2 equiv.),Py, | hexaacetate (29%);                |
|                |                           | CHCl <sub>3</sub>                                 | 6'-chloro-6'-deoxysucrose         |
|                |                           |   | heptaacetate (43%)                |
| р              | Ref. <sup>13</sup>        | $CH_3SO_2Br$ (17.2 equiv.),                       | 6,6'-dibromo-6,6'-dideoxysucrose  |
| В              |                           | DMF   | hexaacetate (24%)                 |
| С              | Ref. <sup>13</sup>        | NBrS (5 equiv.), PPh <sub>3</sub> (4.5            | 6,6'-dibromo-6,6'-dideoxysucrose  |
|                |                           | equiv.), DMF                                      | hexaacetate (21%)                 |
| D              | Ref. <sup>13</sup>        | $CH_3SO_2Cl$ (17.2 equiv.),                       | 6,6'-dichloro-6,6'-dideoxysucrose |
|                |                           | DMF   | hexaacetate (51%)                 |
| Е              | Ref. <sup>13</sup>        | NCS (6.2 equiv.), PPh <sub>3</sub> (6.2           | 6,6'-dichloro-6,6'-dideoxysucrose |
|                |                           | equiv.), DMF                                      | hexaacetate (69%)                 |
|                | Ref. <sup>14</sup>        | 1. $(Me_2N)_3P$ (27 equiv.),                      | 6,6'-dibromo-6,6'-dideoxysucrose  |
| F              |                           | CCl <sub>4</sub> (6.6 equiv.), DMF <sup>b</sup>   | hexaacetate (12%);                |
|                |                           | 2. KPF <sub>6</sub> (aq), Et <sub>4</sub> NBr     | 6-bromo-6-deoxysucrose            |
|                |                           | (3 equiv.), DMF                                   | heptaacetate (34%)                |
| G              | Ref. <sup>14</sup>        | 1. $(Me_2N)_3P$ (27 equiv.),                      | 6,6'-dichloro-6,6'-dideoxysucrose |
|                |                           | CCl <sub>4</sub> (6.6 equiv.), DMF <sup>b</sup>   | hexaacetate (15%);                |
|                |                           | 2. $KPF_6(aq)$ , $Me_4NCl$                        | 6-chloro-6-deoxysucrose           |
|                |                           | (6 equiv.), DMF                                   | heptaacetate (45.5%)              |
| н              | <b>Ref.</b> <sup>15</sup> | CCl <sub>4</sub> (3 equiv.),                      | 6,6'-dichloro-6,6'-dideoxysucrose |
| п              |                           | PPh <sub>3</sub> (6 equiv.), Pv                   | hexaacetate (92%)                 |

<sup>a</sup> Reaction mixture was maintained at -78 °C, poured into ice-cold sulphuric acid before purification, and conventional acetylation was conducted after column chromatography. Reactions at room temperature and 50 °C were resulted in 4,6,1',6'-tetrachloro sucrose and 4,6,1',4',6'-pentachloro sucrose, respectively, in their 2,3-sulphate form. <sup>b</sup> Conversion of RCH<sub>2</sub>OP<sup>+</sup>(NMe<sub>2</sub>)<sub>3</sub>Cl<sup>-</sup> before activation by KPF<sub>6</sub>(aq). The resulted RCH<sub>2</sub>OP<sup>+</sup>(NMe<sub>2</sub>)<sub>3</sub>PF<sub>3</sub><sup>-</sup> then treated with the anion (Cl<sup>-</sup> or Br<sup>-</sup>).

Direct halogenation without any protection on hydroxy group of sucrose is a challenging method for further study. Not only sulphuryl chloride, several other reagents<sup>13,14</sup> are available for the direct and selective replacement at primary hydroxy groups of sucrose by a halogen

substituent (Table 2: Method B–G). Unfortunately, these reagents might give a low yield in many experiments suggesting that acetal migration can occur and reagent purification steps may involve further chemical modification.<sup>15</sup> The high selectivity method within a mild reaction condition is needed for efficient method of carbohydrate-based products. However, the use of triphenylphosphine and carbon tetrachloride has been shown to be an efficient chlorinating reagent for sucrose (Table 2: Method H). The high selectivity for primary hydroxy group has been associated with a bulky halogenating complex formed from triphenylphosphine dihalide (Ph<sub>3</sub>PCX<sub>2</sub>) and pyridine.<sup>16</sup> This method is known as Appel reaction which is expected as an efficient method for establishment of halogenated sucrose at the primary positions will be useful to expend the novelty and diversity of carbohydrate-based products.

Selective halogenation by limiting amount of Appel reagents is particularly complicated, but separation of monoproduct from the mixture became another issue. Although many studies have successfully halogenated sucrose at the primary positions<sup>4,5,7,9,10,14,17-19</sup> during past decades, the properties of all former halodeoxysucrose derivatives were limited, especially for the NMR analyses. NMR analyses are important to describe the substitution site, but many reports are mainly focused the halogenation selectivity by consideration on identical comparison of optical rotation with the previous literature data which made the regioselectivity for sucrose as obscure due to unclear structural identifications of each monohalogenated sucrose (especially its halomethylene portions). Therefore, the needs to comprehensive analysis of all monohalogenated sucrose are essential. The objective focused in this study is to re-subject sucrose into Appel reaction, by following previous condition<sup>9</sup> to afford the mono- and di-substituted products at 6- and/or 6'-positions. The 1'monohalogenated sucrose was exclusively synthesized via chemoenzymatic reaction. Thus, allowing the comprehensive study of structure elucidation by extensive NMR analyses of halogenated sucroses at the primary positions, the regioselectivity of Appel reaction on sucrose primary alcohols was investigated.

Since the disaccharide, such as sucrose, already shown its potencies for direct halogenations from unprotected sucrose, many of researchers also challenged the interesting properties of longer chain of carbohydrate. Hough and co-worker<sup>20</sup> reported the subjection of raffinose (Figure 1) into sulphuryl chloride. Unlike previous utilization of Appel reagent in sucrose that selective only for primary alcohols, chlorinated proportion at the primary positions followed by chlorination at the 4-position of the galactopyranosyl moiety secondary alcohols was found in this typical reaction. Application of Appel reaction to melezitose for

direct chlorination only at primary alcohols is reported.<sup>21</sup> This result indicated that Appel reaction is superior for selective halogenations of carbohydrate primary alcohols.

Short chain fructooligosaccharide (FOS) of inulin type (Figure 1) is categorized as nondigestible prebiotic oligosaccharide.<sup>22,23</sup> In midst of FOS, 1-kestose is reported to have more sweetening power<sup>24</sup> and this great property can be explore further if its primary alcohol is modified with halogen. The 1'-kestose that elaborated with additional fructose moiety at 1'position from sucrose is then tried for halogenations through Appel reaction. Here in this study, the subjection of 1-kestose to Appel reagent is expected to introduce direct halogenations into its primary hydroxy groups which the full structural elucidation by utilizing 1D- and 2D-NMR can determine the precise halogenated position and can contribute to the synthesis of novel halogenated 1-kestose derivatives.

## 1.1.2 $\alpha$ -Amino acids chiral center and stereochemistry: unique consideration for direct acylation to synthesize $\alpha$ -amino aryl ketone via Friedel–Crafts acylation

The  $\alpha$ -amino acids are the most significant amino acids in the biological world, because they are the monomers from which proteins are constructed. Except for glycine, all proteinderived amino acids have at least one chiral center and the vast majority of  $\alpha$ -amino acids in ecosystem are of the L-series.<sup>1</sup> Enantiomerically pure *N*-protected  $\alpha$ -aminoaryl ketones are important building blocks to construct various biologically active compounds.<sup>25,26</sup> The most popular method for its synthesis, Weinreb amide,<sup>27</sup> is considerably less efficient due to the limitations of Grignard or organolithium reagents that apparently are non-commercially available and under a strong base condition that might hamper synthesis of the base sensitive *N*-protecting group of  $\alpha$ -amino-aryl ketones. The Friedel–Crafts reaction<sup>25,28–32</sup> becomes a favorable method for synthesis of *N*-protected  $\alpha$ -amino-aryl ketones<sup>33,34</sup> since direct acylation can be undergone with convenient optically pure  $\alpha$ -amino acid derivatives as skeletons into various substrates with a satisfactory yield of product (Figure 2).



**Figure 2** *N*-protected  $\alpha$ -amino-aryl ketone synthesis via Friedel–Crafts acylation by utilization of optical active *N*-protected  $\alpha$ -amino acids. "PG" stands for protecting group; "L" stands for as leaving group.

In the field of natural products chemical modification, ascertaining which intermediate has formed is a crucial step in preventing the formation of a racemic adduct during the reaction. In conventional Friedel–Crafts acylation, aromatic derivatives are reacted with acyl donor that is activated by Brønsted or Lewis acid as catalyst.<sup>29,35</sup> If  $\alpha$ -amino acids are modified and utilized as acyl donor for this typical reaction, the reaction pathway can produce several molecular species and several considerations should to be occured. Selection of suitable conditions for these reactions is necessary, especially the reactions for optically active amino acids. Several plausible routes using various active species<sup>36–38</sup> for aromatic acylation exist (Figure 3). First, if the  $\alpha$ -proton is deprotonated, and then ketene proportion may be formed, leading to the loss of chiral retention (Figure 3 (a)). Next, if no proton is eliminated during the process, the dissociated acylium cation seems more reliably to be formed (Figure 3 (b)). Thus, ascertaining what intermediate has been formed is a crucial step in preventing the formation of a racemic adduct during acylation.



**Figure 3** Plausible acylation routes of aromatic derivatives with modified α-amino acids with leaving group via (a) ketene or (b) acylium cation formation. "L" stands for as leaving group.<sup>34</sup>

The identification of chirality for  $\alpha$ -amino acids is normally conducted with their optical rotations and chiral high-performance liquid chromatography (HPLC). But the optical rotations are sometimes influenced by the measurement condition. It is also very difficult to set up condition of chiral HPLC for unreported compounds. Therefore, the demonstration of optically active isoleucine, which has two chiral centers in the molecules, and its diastereomer *allo*-isoleucine to identify chilarity of the Friedel–Crafts acylation product by <sup>1</sup>H-NMR, might offer more efficient method. The application of  $\alpha$ -amino acid modified with potential leaving group for synthesis of  $\alpha$ -amino aryl-ketone is assumed to be retarded its chirality which might act as useful acyl donor for Friedel–Crafts acylation.



Figure 4 Structures of isoleucine and its diastereomer, allo-isoleucine

In nature, L-isoleucine is usually found in living organism, meanwhile its diastereomer, D-*allo*-isoleucine, is commonly found in certain antibiotic and microbial peptide.<sup>39</sup> L-Isoleucine is known to be able to undergo racemization at  $\alpha$ -position to produce D-*allo*-isoleucine. In geochronology, the rate of racemization reaction of L-isoleucine into D-*allo*-isoleucine is relatively slow, which suitable for the analysis.<sup>40</sup> As for chiral *N*-protected  $\alpha$ -amino aryl-ketone synthesis, especially the reaction that involving direct acylation of  $\alpha$ -amino acids, the chirality of product is commonly determined by complexation with chiral shift reagent<sup>25</sup> which racemic  $\alpha$ -amino aryl-ketone can be detected by appearance of two separated proton signals by nuclear magnetic resonance (NMR).

Up to now, there is no reported study that has been checked the chirality of the  $\alpha$ -amino aryl-ketone based on isoleucine and its diastereomer *allo*-isoleucine. Since the asymmetric carbon at  $\alpha$ -position within these stereoisomers can be observed by <sup>1</sup>H-NMR,<sup>41</sup> utilization within isoleucine and its diastereomer *allo*-isoleucine (four types of stereoisomers, Figure 4) might be useful for describe a change in configuration of their chiral center during the chemical modification. Consideration of chiral center in  $\alpha$ -amino acids and stereochemistry for direct acylation to synthesis amino aryl ketone by utilizing isoleucine and its diastereomer *allo*-isoleucine can reveal the exploration of activated C-terminal of *N*-protected amino acid as acyl donor in Friedel–Crafts acylation using conventional catalyst of AlCl<sub>3</sub> (Figure 2). These chemical features of isoleucine and its diastereomer *allo*-isoleucine lead to the the new approach for synthesis of  $\alpha$ -amino aryl ketone. Utilization of  $\alpha$ -amino *N*-hydroxysuccinimide ester as a representative acyl donor in Friedel–Crafts acylation is introduced which will be described later in this thesis.

## 1.1.3 Hydrogen/deuterium exchange: Introducing deuterium isotope into aromatic moiety by acid catalyst

H/D exchange is known as one of the method for investigations of reaction mechanisms to clear ketene formation (or acylium cation formation, Figure 3). It also can be used for selective protonation/deuteration, which can greatly simplify the spectra of even the largest protein moieties.<sup>42</sup> Hydrogen/deuterium (H/D) exchange methods can generally be divided into three categories: 1) utilization of  $D_2O$  as the deuterium source; 2) the involvement of the addition of an acid or base; 3) the use of metal-promoted H/D exchange. Commonly, heterogeneous catalytic systems are frequently used for H/D exchange which conducts under harsh conditions and followed by dehalogenation, hydrogenation, hydrolysis, as well as epimerization and racemization.<sup>43,44</sup> A homogenous system is prefered in H/D exchange, especially in the case of optically active amino acids, the organic solvent must be considered for not causing any amino acid racemization during the reaction.

In midst of acid utilization for H/D exchange in aromatic moiety of natural products, a study that used a  $D_2O/D_2SO_4$  system found that conditions will lead to either partial or complete racemization of phenylalanine H/D exchange, which is indicated by the exchange of  $\alpha$ -protons.<sup>45</sup> Deuterated trifluoroacetic acid (TFA-*d*) is appropriate for slow H/D exchange,<sup>46</sup> but its application to aromatic amides and amines<sup>47</sup> is less effective for more electron-poor substrates such as acetophenone and its derivatives.<sup>48</sup> Triflic acid (TfOH) is known as a catalyst for direct *C*-acylation and almost all solvent for  $\alpha$ -amino acids. The utilization of its deuterated counterpart, deuterated triflic acid (TfOD), as a source of deuterium in H/D exchange is known for conducting mild reaction condition for aromatic substrates which advance to be used for several  $\alpha$ -amino acids without loss of chirality.<sup>34</sup>





An example of TfOD as catalysis, solvent, and also deuterium souce of the direct *C*-acylation of toluene and glutamic acid derivatives is shown in Scheme 1.<sup>49</sup> Based on this reaction, activation by TfOD can result in typical acylium cation that can prevent any loss of chirality of optically active starting material (Figure 3 (b)). A fine yield of the acylated product (94%) from the electrophilic aromatic substitution represents in this reaction which the rapid H/D exchange and high deuterium incorporation of aromatic moiety can be detected (68%–75% deuterium incorporation). In Scheme 2, a comparison also can be made between L-phenylalanine and L-tyrosine treated with TFA- $d^{48}$  and TfOD.<sup>49,50</sup> It shows that the aromatic proton deuterium incorporation is generally larger than treatment with TFA-*d* when TfOD is used. Thus, the absence of  $\alpha$ -proton exchange with TfOD indicates no loss of optical purity of amino acids and found to be superior for mild H/D exchange of aromatic compounds.



Scheme 2 H/D exchange in L-phenylalanine and L-tyrosine. Numbers in brackets give the percentage of deuterium in the side chain sites.<sup>48–50</sup>

These advantages are considered potential for broaden the application and structure elucidation of natural products, such as cycloDOPA (5,6-dihydroxyindoline-2-carboxylic acid, cDOPA, leukodopachrome). cDOPA is one of metabolites derived from tyrosine, one of intermediate in melanin formation (mammalian), and betanidin main skeleton (betalain pigment in plant). The exploration of H/D exchange of cDOPA by utilization of acid

deuterium source is expected to offer convenient method with high deuterium incorporation and high selectivity in the aromatic moiety.

#### **1.2** Outline of the study

This study investigates synthesis of natural products and modification based on its unique and enormous properties. Here in, direct halogenation of sucrose and 1-kestose,  $\alpha$ -amino acids extensive acylation, and hydrogen/deuterium exchange of cDOPA derivatives are offering organic synthesis that utilizing chemical features of natural products become feasible. The outline for this study was listed as below.

#### 1.2.1 Direct halogenation at primary alcohols of carbohydrate

A. Direct halogenation at primary alcohols of sucrose



<u>Tachrim, Z. P., et al., ChemistrySelect</u>, **2016**, *1*, 58–63.

Regioselective halogenations of sucrose primary alcohols can simplify the synthesis of carbohydrate-based products. The Appel reaction, using carbon tetrahalide (CBr<sub>4</sub> or CCl<sub>4</sub>) and triphenylphosphine, offers efficient conversion of primary hydroxy groups to halide. Previous halogenation of sucrose with limited amounts of Appel reagent gave obscure result—regarding the halogenation selectivity of sucrose primary alcohols at 6- and 6'-position. Within careful purification of its per-*O*-acetylated form, resubjection of sucrose into Appel reaction resulted in two mono- and one dihalogenated products only at 6- and/or 6'-position. Extensive NMR analyses support the revision of assignment of previous literatures. Comprehensive analysis of each monohalogenated sucrose at the primary positions, including the first reported 1'-monohalogenated sucrose primary alcohols by the Appel reaction followed the order of 6 > 6' >> 1'.



<u>Tachrim, Z. P.</u> et al, Arkivoc 2018, 341–348.

1-Kestose  $(O-\beta$ -D-fructofuranosyl- $(2\rightarrow 1)-\beta$ -D-fructofuranosyl- $(2\rightarrow 1)-\alpha$ -D-glucopyranoside) is a potential short chain fructooligosaccharide with an inulin-type skeleton. Halogenation of 1-kestose was conducted via the Appel reaction with the use of carbon tetrahalide (CBr<sub>4</sub> or CCl<sub>4</sub>) and triphenylphosphine, which was then followed by conventional acetylation. The per-*O*-acetylated form of 6,6',6''-trihalogenated derivatives of 1-kestose was conveniently isolated. Subsequent deprotection of the per-*O*-acetylated form resulted in yielding 6-, 6'-, and 6''-trihalogenated derivatives. The structure elucidation by 1D- and 2D-NMR established that halogenations are specific at the primary alcohols in the 6-, 6'-, and 6''-positions of the 1-kestose.

#### 1.2.2 α-Amino acids extensive acylation

A. Friedel–Crafts Acylation of TFA-aliphatic α-amino-N-hydroxysuccinimide ester derivatives



Tachrim, Z. P., et al., Molecules, 2017, 22, 1748-1762.

Chiral *N*-protected  $\alpha$ -amino aryl-ketones are one of the useful precursors used in the synthesis of various biologically active compounds and can be constructed via Friedel–Crafts acylation using *N*-protected  $\alpha$ -amino acids. One of the drawbacks of this reaction is the utilization of toxic, corrosive and moisture-sensitive acylating reagents. In peptide construction via amide bond formation, *N*-hydroxysuccinimide ester (OSu), which has high storage stability, can react rapidly with amino components and produces fewer side reactions than the acid chloride, including racemization. This study reports the first synthesis and utilization of *N*-trifluoroacetyl (TFA)-protected  $\alpha$ -amino acid-OSu as a potential acyl donor for Friedel–Crafts acylation into various arenes. The TFA-protected isoleucine derivative and its diastereomer TFA-protected *allo*-isoleucine derivative were investigated to check the retention of  $\alpha$ -proton chirality in the Friedel–Crafts reaction. Further utilization of OSu in other branched-chain and unbranched-chain amino acids results in an adequate yield of TFA-protected  $\alpha$ -amino acids results in an adequate yield of TFA-protected  $\alpha$ -amino aryl-ketone without loss of optical purity.

B. Friedel–Crafts Acylation of TFA-cyclic and aromatic  $\alpha$ -amino-N-hydroxysuccinimide ester derivatives



Tachrim, Z. P., et al., Heterocycles, 2018, in press.

The utilization of *N*-trifluoroacetyl (TFA)- $\alpha$ -amino acid *N*-hydroxysuccinimide ester (OSu) derivatives, a promising acylating agent with high storage stability, is reported for Friedel–Crafts acylation into arenes and *N*-heterocycles. The reaction between TFA-Phe-OSu derivatives and arenes introduces inter- and intra-molecular formation of *C*-acylation. TFA-Tyr-OSu derivatives, which possess hydroxy substituent in the aromatic moiety of phenylalanine, show specific inter-molecular acylation into benzene ring. The heterocyclic TFA-Pro-OSu also shows relatively high reactivity toward acylation.

#### 1.2.3 Hydrogen/deuterium exchange of cycloDOPA derivatives



Tachrim, Z. P. et al., Heterocycles, 2018, in press.

CycloDOPA (5,6-dihydroxy-indoline-2-carboxylic acid, leukodopachrome) is one of metabolites derived from L-tyrosine, one of intermediate in melanin formation (mammalian) and betanidin main skeleton (betalain pigment in plant). Synthesis of deuterated cDOPA via hydrogen/deuterium exchange by utilization of deuterium chloride (DCl) and deuterated triflic acid (TfOD) is reported. The novel fully deuterated aromatic cDOPA derivative can be formed depending on temperature and time of H/D exchange condition. The complete study of H/D exchange resulted in the selective deuterium between 4- and/or 7-position of aromatic hydrogen of cDOPA.

#### 2.1 Introduction

Carbohydrates are bio-renewable resources fundamental to life, such as energy storage, biological signaling, all recognition, and structural support in the plant kingdom. Common sugars are available in large amounts from natural products and renewable source of starting materials in organic synthesis. Among these carbohydrates, sucrose (Figure 1) is produced worldwide in large quantities. This compound is highly functionalized molecules with complex stereochemistry, due to the presence of several hydroxylated stereogenic centers.<sup>9</sup> Sucrose is also accepted as a standard of sweet taste quality. Hence, the sweetness intensity and other taste properties of natural and synthetic sweeteners are frequently compared with sucrose.

The major problem faced for direct modification of cabohydrides is all of its hydroxy groups having similar reactivity. Only by reaction within bulky reagents (e.g. halogenations), it can be differentiated between the primary and secondary hydroxy groups. Sucrose, one of the most widely used natural sweetener commercially available in large quantities, also faced the same situation. Due to novelty, its chemical modification and transformation become high potential for many purposes. In general, among primary alcohols of sucrose, the reactivity is by the order of 6-OH and/or 6'-OH, and then least reactive neopentyl-like 1'-OH.<sup>51</sup> The halogenated sucrose analogues at the primary positions are known to be the most versatile synthesis intermediates<sup>4,13,52,53</sup> or for reversible contraceptive action in male rat.<sup>54</sup> The different sweetness activity is observed, if certain primary position of sucrose is halogenated. For example, a commercial available artificial sweetener sucralose is introduced chlorination on sucrose at the 4-, 1'- and 6'-positions on on the molecule enhanced 2000-fold sweetness activity than sucrose (Table 1).<sup>3</sup> Since these backgrounds, the selective halogenations, particularly chlorination and bromination, only on primary hydroxy groups in sucrose have been intensively studied in the last decades.

Various methods are available for halogenation on sucrose primary centers. Indirect methods are included: the intermediate utilization;<sup>4,17–19</sup> selective cleavage of fully protected sucrose before further halogenation of the free primary alcohol counterpart;<sup>5–7</sup> or bulky functional groups protection and unprotection of one or two primary hydroxy groups.<sup>8–10</sup> Procedures are also available, in which are allowed the direct replacement of primary hydroxy groups with halogen, e.g. direct chlorination of sucrose by well-known sulphuryl chloride<sup>11</sup> that gave high selectivity for monochlorination at 6'-position or the usage of other

reagents.<sup>13,14</sup> However, the regioselectivity depends on the nature of the electrophilic reagent, catalyst, or solvent used for the reaction. The controls of these variables are served more efficiency rather than extensive protecting and deprotecting procedure which needed more steps.<sup>7,8,55</sup> Hence, the construction of the simple procedure will lead to great challenge for beneficial desired product of direct modification on sucrose primary positions. Appel reaction<sup>56</sup> is one of convenient method for halogenations of primary alcohols by the use of carbon tetrahalide (bromide or chloride) and triphenylphosphine (Figure 5 (a)). Appel reaction also previously had been introduced into sucrose, to afford more efficient<sup>16</sup> method for halogenation of sucrose at its primary alcohols.



**Figure 5** (a) Typical alcohol halogenation by Appel reaction; (b) Proposed mechanism of Appel reaction on primary alcohol.

In 1978, an excess amount of Appel reagent was introduced and resulted in dihalogenated sucrose at 6- and 6'-positions.<sup>15</sup> Further modification of this reaction was reported and observed that the mixture not only contained the diproducts but also two 6- and 6'-monohalo products, of which further purification and the separation of each isomer was difficult.<sup>57</sup> Many previous efforts<sup>15,55,58-60</sup> by Appel reaction utilized different proportion and condition for prior art of halogenations on sucrose primary alcohols at 6- and 6'-positions. By commonly maintaining the ratio 2:1 of triphenylphosphine and carbon tetrahalide, equivalency of these reagents to sucrose can be neglected if 6,6'-dihalogenated sucrose is the desired product. Meanwhile, regioselectivity for 6- and 6'-monohalogenated sucrose attainable by limiting the proportions of Appel reagents (e.g. carbon tetrahalide < 1.5 equiv. from sucrose) is not completely identified. Previously, it has been shown<sup>61</sup> that Appel reaction is regioselective for the 6-position prior to 6'-position. In contrast, by limiting the proportions

of Appel reagents, 6'-monohalogented sucrose can be obtained in relatively high yield.<sup>9</sup> Despite this success, re-subjection by similar reaction condition is remaining in the preponderant product of 6-analogue as a mixture with 6'-halo,<sup>10</sup> and no detailed consideration has been performed for this observation.

Selective halogenation by limiting amount of Appel conditions is particularly complicated, and separation of monoproduct from the mixture became another issue. For decades, many studies have successfully halogenated sucrose at the primary positions,<sup>4–11,13–</sup> <sup>15,17–19,55,58–61</sup> but the reports describing properties of all former halodeoxysucrose derivatives were limited, especially for the NMR analyses. NMR analyses are important to describe the substitution site, but many reports are mainly focused the halogenation selectivity by consideration on identical comparison of optical rotation with the previous literature data which made the regioselectivity for sucrose as obscure due to unclear structural identifications of each monohalogenated sucrose (especially its halomethylene portions). Therefore, the needs to comprehensive analysis of all monohalogenated sucrose are essential. The focused objective in this study is to re-subject sucrose into Appel reaction, by following previous condition<sup>9</sup> to afford the mono- and di-substituted products at 6- and/or 6'-position. The 1'monohalogenated sucrose was exclusively synthesized via chemoenzymatic reaction. Thus, allowing the comprehensive study of structure elucidation by extensive NMR analyses of halogenated sucroses at the primary positions, it was attempted to reveal the regioselectivity of Appel reaction on sucrose primary alcohols. Moreover, 1'-kestose that elaborated with additional fructose moiety at 1'-position was then used for checking the regioselectivity to support the identification of the most hindered and less reactive position for halogenations through Appel reaction. Full structural elucidation of halogenated sucrose and 1'-kestose structure on its primary positions are performed.

#### 2.2 Results and Discussion

Appel reaction, first reviewed by Rolf Appel,<sup>56</sup> is a method to convert an alcohol to the corresponding alkyl halide under mild conditions. By using triphenylphosphine and carbontetrahalide (bromide or chloride) on the system, product can be observed in relatively high yields. This reaction is somewhat similar to the Mitsunobu reaction, where the combination of a phosphine, a diazo compound as a coupling reagent, and a nucleophile are used to invert the stereochemistry of an alcohol or displace it. The reaction proceeds by activation of the triphenylphosphine with the tetrahalomethane, followed by the attack of the alcohol oxygen at phosphorus to generate an alkoxytriphenylphosphorane intermediate. The

oxygen is then transformed into a leaving group, and an  $S_N 2$  displacement by halide takes place, proceeding with inversion of configuration if the carbon is asymmetric (Figure 5 (b)).<sup>62</sup> In this chapter, direct halogenations at primary alcohols (sucrose and 1-kestose) then trial to subject to Appel reaction are described below.

#### 2.2.1 Direct halogenations at primary alcohols of sucrose

#### A. Halogenation of sucrose via Appel reaction

Direct substitution of sucrose (1) with 1.2 equiv. carbon tetrabromide and 2.4 equiv. triphenylphosphine at 60°C for 1.5 h,<sup>9</sup> afforded complex mixture of several unprotected halogenated sucrose derivatives. The separation of the mixture was complicated and identification for each isomer by <sup>1</sup>H NMR analysis was difficult due to observation of overlapped signals, especially the modified primary centers. Even though number of substituted carbon was readily distinguished by the upfiled location of their signals by <sup>13</sup>C NMR, it is not easy to interpret the substitution site in this form. Most of the previous studies on Appel reaction directly quenched these modified unprotected sucrose derivatives. In fact, the dihalogenated product from sucrose was easily obtained, but our attempts to isolate the monohalogenated products always remained as a mixture of a few isomers or contaminated with the by-product;<sup>57</sup> and no detail study was previously reported for this condition.



Scheme 3 Regioselective bromination of sucrose at the 6- and/or 6'-positions by Appel reactions (2–4)

The effort to isolate and identify all brominated products was conducted by conventional acetylation (Scheme 3) and found that the mixture consists of not only one<sup>9</sup> major product in the TLC. When ethyl acetate or dichloromethane system was used, it did not completely resolve the purification. Diethyl ether as the mobile phase was superior for the isolation, not only to obtain the dibrominated product (7% yield), but also two monobrominated products (7%–12% yield). Thus, pure compounds can be obtained for clear NMR assignments. Separation between the two per-O-acetylated monohalogenated

regioisomers on silica gel column is a formidable endeavor. This term causes the NMR assignment misinterpreted in previous study<sup>9</sup> and indeed the overlapping signals that associated with protons of several monoproducts<sup>10</sup> can hamper the identification of substitution site. In presents, four compounds were isolated from the mixture after column chromatography: two compounds of per-*O*-acetylated monobrominated counterparts (2 and 3), one compound of per-*O*-acetylated dibrominated counterpart (4), and unreacted proportion of sucrose octaacetate 5.

Each counterpart of per-*O*-acetylated halodeoxysucrose derivatives was subjected to 1D NMR (<sup>1</sup>H and <sup>13</sup>C) by the aid of 2D NMR (COSY, HETCOR, HMQC, HMBC, and NOESY), along with optical rotation. The composition was confirmed by HRMS analysis. The detail elucidation will be described in the next section. From the observation, the low isolated yield for each counterpart is due to: (i) seting up an optimized condition for the highest yields of each monohalogenated compound (or by increasing the molar ratio to promote more major dicompound) and (ii) complete isolation of each component to measure with reliable NMR analyses. However, Appel reaction can offer more efficient for direct modification on unprotected sucrose rather than blocking one or two of the primary position with bulky functional groups<sup>10</sup> that needed more steps for the synthesis.

Limitation of NMR analysis for several decades leads to incomplete proton and carbon signal assignments. Many studies mainly indentified the halogenated sucrose counterparts at the primary position by only depending on comparison with optical rotation or transforming it into the per-*O*-acetylated to facilitate the assignment by NMR analysis. Merely, their identification still remained majorly as a multiplet for halogenated methylene. In the middle of our approach to identify the monobrominated products, two main regions of the spectrum are characterized in the <sup>1</sup>H NMR. The proton resonances of aliphatic sugar groups were observed in the downfield, and it can be distinguished from the halogenated methylene groups that located in the upfield. As for NMR solvent, all the spin systems are more visible to be conducted in CDCl<sub>3</sub>, <sup>59</sup> rather than those in DMSO- $d_6$ .<sup>10</sup>



**Figure 6** Selected <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) signals of brominated sucrose derivatives at 6and 6'-positions (**2–4**).

Compound **2** (Figure 6) showed a clear doublet at  $\delta_H$  3.62 ppm (J = 6.6 Hz) corresponding to two protons of brominated methylene shown in the <sup>1</sup>H NMR spectrum. These spin systems are correlated with H-5' on COSY assignment (Figure 7 (a)), and ascertained the bromination position at C-6'. Multiplet assignment for H-5' can be differentiated by the COSY cross-peak between H-5' and H-4' and outer-space NOESY correlation of H-5' to H-3'. The halogenated terminal of C-6' at  $\delta_C$  31.3 ppm is most proved by HMBC technique with the observation of cross-peak with this carbon to H-4'. HETCOR and HMQC coupling between the protons and carbon at 6'-position support this assignment for recognition of the substitution site, which is supported by correlation of H-6' with H-4' and H-5'. The differentiation between signals of protons and carbons on the glucose and fructose rings with other positions, especially at the C-3, C-5, C-3', C-4', and C-5', were confirmed by HETCOR, HMQC and NOESY spectra. These assignments allowed the structure (gross) of **2** as per-*O*-acetylated 6'-bromo-6'-deoxysucrose heptaacetate.



Figure 7 (a) Selected COSY (500 MHz, CDCl<sub>3</sub>) correlation of 6'-bromo-6'-deoxysucrose heptaacetate (2); (b) selected COSY (500 MHz, CDCl<sub>3</sub>) correlation of 6-bromo-6-deoxysucrose heptaacetate (3).

For 6-bromo-6-deoxysucrose heptaacetate (3), a typical pair of double-doublet at  $\delta_{\rm H}$ 3.42 and 3.60 ppm (J = 4.6, 11.5 Hz and J = 3.0, 11.5 Hz) are shown in <sup>1</sup>H NMR (Figure 6). The observation of the large geminal coupling for these spin systems can be distinguished in COSY analyses by their correlation across the H-5 (Figure 7 (b)). Moreover, HMBC correlation among these spin systems with C-4 supports the identification of bromination of hydroxy groups at 6-position of sucrose. HETCOR and HMQC correlations of protons at 6position with C-6 ( $\delta_c$  31.1 ppm) also support this assignment, which confirmed by NOESY, to elucidate compound 3 as the complete structure of 6-bromo-6-deoxysucrose heptaacetate. Accordingly, spin systems on <sup>1</sup>H NMR of 6- and 6'-monobrominated sucroses can be differentiated. Based on alteration of these comprehensive assignments between 6- and 6'monobrominated sucroses, the previous study<sup>9</sup> reported the misinterpreted NMR analysis of 6'-bromo-6'-deoxysucrose heptaacetate (2). In their report, 6'-bromo-6'-deoxysucrose heptaacetate (2) was afforded a pair of double-doublet with the observation of geminal coupling in <sup>1</sup>H NMR. Hence, in this study, the assignment was revised from their previous compound of 6'-bromo-6'-deoxysucrose heptaacetate (2) to 6-bromo-6-deoxysucrose heptaacetate (3) and also refined new full description between these two monobrominated products (2 and 3) to support our comprehensive structure recognition.

As for 6,6'-dibromo-6,6'-dideoxysucrose hexaacetate (4), splitting pattern in the upfield region of <sup>1</sup>H NMR is consisting of combination to those of the 6- and 6'-monobrominated regioisomers (Figure 6). Appearance of a doublet at  $\delta_{\rm H}$  3.65 ppm (J = 6.6 Hz) corresponding to protons at 6'-position and double doublets at  $\delta_H$  3.52 and 3.40 ppm (J = 3.0, 11.5 Hz and J= 5.6, 11.5 Hz) corresponding to each proton at 6-position that contributed geminal coupling confirmed this dibromo analogue. Two primary carbons (C-6 and C-6') were distinguished by the upfield location of their signals. Two singlets at  $\delta_C$  31.5 ppm for C-6' and  $\delta_C$  31.1 ppm for C-6 are observed in <sup>13</sup>C NMR. Long range HMBC strictly distinguished carbon of this position by the correlation between H-4 and C-6 for 6-position and H-4' and C-6' for 6'position. Our comparison of 6,6'-dibromo-6,6'-dideoxysucrose hexaacetate (4) in DMSO- $d_6$  in which specific region of the dibromomethyl was shown as a multiplet for protons at 6- and 6'position,<sup>10</sup> made it difficult to identify each substituted position by <sup>1</sup>H NMR spectroscopy. In CDCl<sub>3</sub>, the splitting patterns of 6,6'-dibromo-6,6'-dideoxysucrose hexaacetate (4) for its brominated methylene identification were visible, in line with the previous report.<sup>59</sup> Moreover, the aid of COSY, HETCOR, HMQC, and NOESY constructed the complete structure of 6,6'-dibromo-6,6'-dideoxysucrose hexaacetate (4).

The relative configurations of **2–4** were assigned in the basis of through-space NOESY correlation. The anomeric carbon on all per-*O*-acetylated halodeoxysurose derivatives showed  $\alpha$ -1,2-glycosidic bond by the observation of NOESY correlation between H-1 and H-1'. As for halogenation on 6-position, only one of the diastereotopic proton lies on the same face with proton at 5-position by NOESY. Meanwhile, enantiotropic protons at 6'-position lies on the same face which supported by NOESY correlations, C-6' probably freely rotates but more constrain in C-6. In line with these NOESY analyses, limitary intra-molecular hydrogen bonding was only demonstrated on halogenated derivatives on 6'-position, thus shown by large distance between H-6' and its neighbor oxygen which observed by 3D modeling (Figure 8). Regulation of less steric orientation on brominated carbon that correlated to sucrose conformation alteration builds up the unmerged geminal coupling constant, and specific splitting pattern of protons on 6'-position then can be proposed.



**Figure 8** Possible configuration of 6'-bromo-6'-deoxysucrose heptaacetate (2) viewed along the fructofuranose ring. Dash line shows distance between O---H and arrow shows selected NOESY correlation.

Similarly with previous bromination reaction, direct substitution of sucrose (1) with 1.2 equiv. carbon tetrachloride and 2.4 equiv. triphenylphosphine at 60°C for 1.5 h<sup>9</sup> (Scheme 4) was conducted. The direct quenching of modified unprotected sucrose derivatives that contains a few isomers makes isolation of each compound difficult. Even though the dihalogenated product from sucrose was easily obtained, each monochlorinated product which was previously reported always as remained as a mixture<sup>10</sup> needs endeavor purification method. As mentioned in previously bromination of sucrose all of which halogenated product can be isolate after conventional acetylation (Scheme 3), thus the attempt to isolate chlorinated products was conducted by conventional acetylation (Scheme 4). When diethyl ether as the mobile phase was used for the isolation by column chromatography, two compounds of per-*O*-acetylated monohalogenated counterparts (**6** and **7**, 8%–13% yield), one compound of per-*O*-acetylated dihalogenated counterpart (**8**, 5% yield), and unreacted proportion of sucrose octaacetate **5** were found.



Scheme 4 Regioselective chlorination of sucrose at the 6- and/or 6'-positions by Appel reactions (6–8)



**Figure 9** Selected <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>) signals of chlorinated sucrose derivatives at 6and 6'-positions (**6–8**).

With the same tendency, per-*O*-acetylated mono- and di-chlorinated products (**6–8**) also showed a typical <sup>1</sup>H NMR profile from those in the per-*O*-acetylated mono- and dibrominated sucrose derivatives (Figure 9). Not only simplify the purification of monochlorinated products from the mixture, but also per-*O*-acetylated monochlorinated sucrose position of compounds **6** and **7** can be easily distinguished by <sup>1</sup>H NMR. Chlorinated position of compound **6** was identified by upfield spin system for protons at 6'-position appearing as a doublet (J = 6.6 Hz) at  $\delta_{\rm H} 3.77$  ppm (Figure 10 (a)). Different splitting pattern happened for 6-chloro-6-deoxysucrose heptaacetate (**7**) which contributed to geminal coupling for each spin system at 6-position was shown as a set of double-doublets (J = 4.6, 12.2 Hz and J = 3.0, 12.2 Hz) at  $\delta_{\rm H} 3.58$  and 3.73 ppm (Figure 10 (b)). Then, compound **8** was categorized as 6,6'-dichloro hexaacetate which appeared as a doublet (J = 6.3 Hz) at  $\delta_{\rm H} 3.79$ ppm toward protons at 6'-position and the observation of geminal coupling for each diastereotopic proton at 6-position which assigned as a set of double doublets (J = 4.9, 12.2 Hz and J = 3.0, 12.2 Hz) at  $\delta_{\rm H} 3.56$  and 3.67 ppm.



Figure 10 (a) Selected COSY (500 MHz,  $CDCl_3$ ) correlation of 6'-chloro-6'-deoxysucrose heptaacetate (6); (b) selected COSY (500 MHz,  $CDCl_3$ ) correlation of 6-chloro-6-deoxysucrose heptaacetate (7)

In line with brominated products, chlorinated position of compounds **6–8** was also shown by <sup>13</sup>C NMR spectroscopy which allowed the C-6 and C-6' primary carbon on upfield region for chlorinated alkyl signals to be distinguished. Monochlorinated sucrose can be easily identified by appearance of singlet at  $\delta_C$  43.9 ppm belongs to C-6' for 6'-chloro-6'deoxysucrose heptaacetate (**6**) and  $\delta_C$  43.0 ppm belongs to C-6 for 6-chloro-6-deoxysucrose heptaacetate (**7**) in <sup>13</sup>C NMR. Compound **8** showed two singlets at  $\delta_C$  44.0 ppm assigned for 6-position and  $\delta_C$  43.2 ppm assigned for 6'-position. The gross structure of two monochlorinated derivatives **6** and **7** and also dichlorinated derivative **8** were helped by the aid of COSY, HETCOR and HMQC. Furthermore, HMBC and NOESY correlations most proved the chlorinated site of these compounds.

To meet our purpose, acetylation was preferred to protect the halodeoxysucrose derivatives rather than other protection groups due to its more offered convenience for the separation and structural elucidation. It is also common opinion in many literatures that acetylation of the sugar derivatives facilitates and simplifies the NMR analysis.<sup>63</sup> However, up to date, detail of structure characterization for per-O-acetylated halodeoxysucrose derivatives at 6- or 6'-position (2–4 and 6–8) is not completely identified. Indeed, the <sup>1</sup>H NMR

assignment of proton at 6- and 6'-position has been reported as multiplets<sup>10</sup> and hampered the substitution site recognition for substitution. Comparison with the literature data for all compounds also described for supporting our comprehensive structural elucidation (see Table 3–8 for detail previous literature data comparison). Furthermore, our achievement for isolation of per-*O*-acetylated monohalogenated sucrose derivatives (**2**, **3**, **6** and **7**), by using silica gel column with diethyl ether system, completely resolved the <sup>1</sup>H NMR assignment. The multiplicity of overlapping protons of halomethylene moiety at 6- or 6'-position on previous report<sup>10</sup> can be identified by the observation of distinguishable signals with specific splitting pattern in the upfield region of <sup>1</sup>H NMR.

In Appel reaction, monohalosubstituted sucroses at the 6-position (**3** and **7**) emerged as the major products with yields of 12% and 13%, respectively. Based on these results, the regioselectivity for monohalogenation (bromination and chlorination) of unprotected sucrose by using limited proportions of Appel reaction followed the order 6>6'>>1'. The mechanism of Appel reaction involved formation of alkoxytriphenylphosphorane intermediates.<sup>56</sup> The regioselectivity was observed in this reaction presumably because of nucleophilic displacement of triphenylphosphine oxide by halide anion, which preferred 6-position rather than 6'-position. In the basis of the solution conformations of sucrose in aprotic solvents such as pyridine,<sup>64</sup> the 1'-position is the type of neopentyl-like, more hindered position, and considerably less reactive due to a bulky nucleophile under mild conditions of Appel reaction.<sup>63,64</sup> In the case of chlorination, selective displacement required a large excess of CCl<sub>4</sub> due to its volatility.<sup>10</sup> Moreover, the second substitution might occur in slow manner, therefore moderate yields of the diproducts **4** and **8** could be observed.

#### B. Chemoenzymatic synthesis of 1'-monohalogenated sucrose

Our comprehensive NMR analysis revealed that the use of limited proportion of Appel reagents resulted in unsubstituted hydroxy groups either at secondary position or the most hindered 1'-position. Based on NMR analysis (Figures 6, 7, 9, and 10), monohalogenated sucrose derivates at 6- or 6'-position can be distinguished. Multiplicity for protons at 6'-position of 6'-monohalo **2** and **6** are observed without geminal coupling at <sup>1</sup>H NMR. Theoretically, this term belongs to protons at 1'-position of 1'-monohalogenated sucrose counterpart (**10** or **11**). To ensure these results, the structure analysis was continued to exclusive synthesis of 1'-monohalgenated sucrose. The attempt to halogenate 1'-position was studied via chemoenzymatic reaction (Scheme 5).<sup>6,65–67</sup> From the selective enzymatic hydrolysis of **5** previously reported, several enzymes are available in cleavage at the 1'-acetyl group. Alcalase seems suitable for this purpose due to its shorter reaction time and higher

yield of sucrose heptaacetate (9) as the major product.<sup>65</sup> By the partly acetylated sucrose, 2,3,4,6,3',4'-hexa-*O*-acetyl-sucrose,<sup>6,68</sup> the free hydroxy group at 1'-position was not reactive with Appel reagents. Accordingly, compound 9 was then triflouromethanesulfonylated and halogenated by using lithium halides (bromide and chloride) to give 1'-bromo-1'-deoxysucrose heptaacetate (10) for bromination and 1'-chloro-1'-deoxysucrose heptaacetate (11) for chlorination. However, brominated chemoenzymatic product of 10 and its deacetylated counterpart (20) is firstly reported in this study (see Tables 9 and 10 for previous literature data comparison).



Scheme 5 Chemoenzymatic synthesis of 1'-monohalogenated sucrose derivatives (10 and 11)<sup>6,65-67</sup>

The assignment of the regioisomeric halogenated sucrose 1'-bromo-1'-deoxysucrose heptaacetate (**10**) can be verified by a distinct pair of doublets with a large geminal coupling constant (J = 12.0 Hz) at  $\delta_{\rm H}$  3.61 and 3.49 ppm assigned for protons at 1'-position in the <sup>1</sup>H NMR (Figure 11). NOESY correlation of these spin systems with proton at 1-position showed that bromination was conducted near the anomeric carbon. By the assignments of protons that showing a long range coupling at 1'-position to C-2' on HMBC, along with the HMQC correlation to unsure these protons associated on the same carbon, this particular spin-system of monobrominated at 1'-position can be differentiated from 6- and 6'-bromo sucroses (Figure 12). Next, the assignment of 1'-chloro-1'-deoxysucrose heptaacetate (**10**) in which a pair of germinal coupled methylene protons at  $\delta_{\rm H}$  3.74 and 3.57 ppm (J = 12.0 Hz) is clearly defined for each of proton signals in this counterpart.



Figure 11 Selected <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) signals of 1'-bromo-1'-deoxysucrose heptaacetate (10)



Figure 12 Selected COSY, HMQC, and HMBC (500 MHz, CDCl<sub>3</sub>) correlation of 1'-bromo-1'-deoxysucrose heptaacetate (10).

On <sup>13</sup>C NMR, the upfield signal at  $\delta_C$  33.5 ppm was assigned for 1'-bromo-1'deoxysucrose heptaacetate (10) and  $\delta_C$  45.3 ppm was assigned for 1'-chloro-1'-deoxysucrose heptaacetate (11). Long-ranged correlation on HMBC between H-3' with C-1' was a strong evidences for supporting this assignment (Figure 12). The gross structure of per-*O*-acetylated halodeoxysucrose on 1'-position was elucidated by COSY, HETCOR, HMQC, and HMBC. Through-space NOESY correlation indicated relative configuration of per-*O*-acetylated 1'halodeoxysucrose derivatives 10 and 11 where this halogenated methylene near the anomeric position  $\alpha$ -1,2-glycosidic bond can be distinguished. NOESY correlation of H-1'a and H-1'b to H-1 indicated <sup>1</sup>H NMR splitting pattern in conjunction with a large geminal coupling (J = 12.0 Hz) exemplify different spin system of each proton on halogenated 1'-position. In contrast to previous explanation of monohalogenated at 6- or 6'-position of **2**, **3**, **6**, and **7**, geminal coupling observed might be caused by intra-molecular hydrogen-bonding between the electron lone pair of the neighbor oxygen with the proton on this position. As an example, representation of small distance between protons at 1'-position and oxygen on fructopyranoside unit (2.3 Å) of 1'-bromo-1'-deoxysucrose heptaacetate (**10**) was observed by 3D models.

## C. Comprehensive comparison of halogenated sucrose with per-O-acetylated commercial available sucralose

Sucralose (12) is a commercially available artificial sweetener produced from sucrose which promoted chlorination on 4-, 1'- and 6'-positions of the sugar molecule. For complete assignment of comprehensive study on halogenated sucrose at the primary position, sucralose (12) was then protected by conventional acetylation and additionally assigned to NMR analysis. By the form of per-*O*-acetylated sucralose (13, Scheme 6), known as TOSPA (trichlorogalactosucrose pentaacetate), chlorinated tertiary carbon at the 4-position was located in the middle field of <sup>1</sup>H NMR spectrum (Figure 13). Thus, it made the chlorinated carbon at its halogenated primary center at 1'-, and 6'-positions easily identify by <sup>1</sup>H NMR. Specific coupling and splitting pattern of the chloromethyl proton at this position can be observed in the upfield region. A fair doublet (J = 5.7 Hz) at  $\delta_{\rm H} 3.77$  ppm corresponding to protons at 6'-position is differentiated from a pair of doublets (J = 12.0 Hz) at  $\delta_{\rm H} 3.60$  and 3.71 ppm corresponding to each proton at 1'-position. Furthermore, tertiary carbon at the 4-position was located in slightly middle field of <sup>13</sup>C NMR spectrum and allowing the two specific signals on upfield region at  $\delta_{\rm C} 44.4$  and 43.8 ppm to be briefly differentiate the 1'- and 6'-positions.



Scheme 6 Structure of sucralose (12) and sucralose pentaacetate (13)

Cross-peak between H-6' to H-5' on COSY distinguished the fine doublet at the upfield region as chloromethylene at 6'-position. NOESY correlation H-6' and H-4' and also H-5' strictly differentiated this assignment. Furthermore, the two primary chlorinated carbons are utmost elucidated by HMBC with the correlation from H-3' to C-1' and from H-4' to C-6' which all these spin systems are supported by HETCOR and HMQC. All of these assignments for the upfiled spin system on <sup>1</sup>H and <sup>13</sup>C NMR which also supported by 2D NMR, allowing brief structural analysis thus compared **6** with **11**, which showed the same tendency, in line with the sucralose pentaacetate (**13**).



Figure 13 Selected <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) of sucralose pentaacetate (13)

#### D. Deacetylation of per-O-acetylated halogenated sucrose

Complete structural elucidation of regioselective per-*O*-acetylated monohalogenated (2, 3, 6, 7, 10 and 11) and dihalogenated sucrose derivatives (4 and 8) was conducted by deprotection (Scheme 7) and also assigned for the precise NMR analyses. Due to complex mixtures were afforded by sodium methoxide, deacetylation was conducted using saturated ammonia in methanol. Structure elucidation of all regioisomeric halogenated sucrose derivatives, in particular for identification among the protons of the three possible substitution site at 6-, 1'- and 6'-position, was complicated because of several overlapping <sup>1</sup>H NMR signals. It is not easy to distinguish the sample that was contained small amounts of by-products on <sup>1</sup>H NMR for this deacetylated form. However, the per-*O*-acetylated form is advance for clear structure construction since its specific region and splitting pattern of the <sup>1</sup>H NMR spectra simply identify halogenated position rather than directly assigned the unprotected form.


Scheme 7 Deacetylation of per-*O*-acetylated halodeoxysucrose derivatives (2–4, 6–8, 10, and 11).

In the case of structure elucidation of sucralose (12, Scheme 6), most of chlorinated positions can be distinguished easily from other positions. The spin systems of protons at 4-, 1'- and 6'-positions in <sup>1</sup>H NMR are shown as a specific splitting pattern at  $\delta_{\rm H}$  4.49, 3.76 and 3.87 ppm, respectively. Meanwhile, all spin systems of regioisomeric halogenated sucrose derivatives are located in relatively middle field, of which protons on the sugar moiety (not only from halogenated methylene) appeared within same region and cause signal overlapping that is difficult to identify. Commonly, differentiation within the <sup>1</sup>H NMR specific region for modified unprotected sucrose is performed by comparison with sucrose. It has also been studied,<sup>12</sup> that the <sup>13</sup>C NMR assignment of the halogenated primary carbons (C-6, C-1', and C-6') can be tentatively predicted by the comparison with sucrose and galacto-sucrose based on epimerisation at C-4 chemical shift. However, although the halogenated counterparts are readily distinguished by the upfield location of their signals in <sup>1</sup>H and <sup>13</sup>C NMR, differentiation for the substitution site is still unsolved. In agreement, many previous studies elucidated the modified counterpart of halogenated unprotected sucrose by subjection into HMBC analysis.<sup>69</sup> In this study, the integration of several 2D NMR analyses (COSY, HETCOR, HMQC, HMBC, NOESY, and TOCSY) is needed for brief overlapping signal assignments to distinguish the substitution site and also to fully construct the gross structure of each unprotected halogenated sucrose derivative (14-21).



Figure 14 <sup>1</sup>H NMR signals (500 MHz,  $D_2O$ ) of (a) 6'-bromo-6'-deoxysucrose (14); (b) 6bromo-6-deoxysucrose (15); (c) 6,6'-dibromo-6,6'-deoxysucrose (16); (d) 1'-bromo-1'deoxysucrose (20).

Deacetylation on bromodeoxysucrose derivatives 2–4 and 10 gave bromodeoxysucrose derivatives 14–16 and 20. Firstly, in <sup>1</sup>H NMR of 6'-bromo-6'-deoxysucrose (14) (Figure 14 (a)), protons at 6'-position were shown as a multiplet at  $\delta_{\rm H}$  3.73–3.66 ppm, and thus by COSY correlation between H-6' and H-5' and close assignment by TOCSY correlation betweem H-6' and H-3' and H-6' and H-5', differentiation from protons at 6-position can be determined. The confirmation can also be seen by the cross-peak between H-4' and C-6' on HMBC. The overlapping <sup>1</sup>H NMR signals in the middle field are strictly differentiated by HMQC to identify protons at 6'-position. NOESY correlation between H-6' and H-4' also supported these assignments. Up to date, structural elucidation of compound 14 was hampered due to difficulties on its isolation—always remained as a mixture with the 6-halo derivatives.<sup>10,57</sup> Herein, detailed analyses of the first purified 6'-bromo-6'-deoxysucrose (14) was stated and even assigned 6-bromo-6-deoxysucrose (15) (including the monochlorinated products 17 and

18, as described leter) to clearly distinguished its structure. Next, monobrominated sucrose at 6-position of 6-bromo-6-deoxysucrose (15) can be clearly differentiated from 6'-bromo-6'deoxysucrose (14) by the observation of multiplet at  $\delta_H$  3.76–3.71 ppm of H-6 (Figure 14 (b)). These spin systems can be differentiated from other protons only by the cross peak between H-6 and H-5 on TOCSY and HMBC correlation from H-6 to C-4. Complete positional assignment for gross structure of 14 and 15 was supported by COSY, HETCOR, and HMQC.

It was difficult to assign the substituted position of 6,6'-dibromo-6,6'-dideoxysucrose (**16**) by <sup>1</sup>H NMR (Figure 14 (c)) where protons on 6- or 6'-brominated position are overlapped with other protons and appeared as a multiplet at  $\delta_H$  3.75–3.69 ppm for protons at 6'-position, at  $\delta_H$  3.63–3.60 and 3.69–3.65 ppm for protons at 6-position. Structure elucidation of 6,6'-dibromo-6,6'-dideoxysucrose (**16**) by TOCSY showed the correlation of H-6' with H-3', H-4', and H-5', allowing fructo-configuration of protons at 6'-position. Then, by through-space correlation NOESY, 6,6'-dibromo-6,6'-dideoxysucrose (**16**) showed that diastereotopic proton H-6b was in the same face with H-5 which spin system at 6-position to be assigned. The last, assignment for bromination on hindered 1'-bromo-1'-deoxysucrose (**20**) showed alteration between multiplet at  $\delta_H$  3.73–3.69 ppm for 1'a-H and broad singlet at 3.63 ppm for for H-1'b (Figure 14 (d)). Relative configuration of **20** by NOESY correlation showed 1'a-H was in the same face with H-1, signified this bromination splitting pattern on fructo-configuration. Large coupling constant on 1'-bromo-1'-deoxysucrose (**20**) can be observed by correlation of 1'a-H and H-1'b to C-2' and C-3'on HMBC.

The de-*O*-acetylated bromodeoxysucroses **14–16** and **20** are also assigned by <sup>13</sup>C NMR. In the case of monobrominated derivatives, <sup>13</sup>C NMR upfield region is shown as a singlet at  $\delta_C$  33.2 ppm that belongs to C-6' for compound **14** and  $\delta_C$  33.4 to C-6 for compound **15**. On long range HMBC, <sup>3</sup>*J*<sub>H-C</sub> correlation from H-4' to C-6' for compound **14** and <sup>3</sup>*J*<sub>H-C</sub> correlation from H-4 to C-6 for compound **15** also confirmed position of monobromination specific on 6'- or 6-position. Complicated assignment was found in <sup>13</sup>C NMR spectrum of compound **16**, as the coincide signals at the upfield region was difficult to elucidate. These signals can be critically elucidated only by HMBC in the appearance of the cross peak between H-4 and C-6 and also H-4' and C-6' in which  $\delta_C$  33.3 ppm is assigned as C-6, while  $\delta_C$  33.2 ppm is assigned as C-6'. Next, the <sup>13</sup>C NMR spectrum of 1'-bromo-1'-deoxysucrose (**20**) showed singlet  $\delta_C$  32.6 ppm to confirm the bromination at this anomeric position. Cross peak of H-3' with upfield singlet of C-1' in HMBC spectrum supported bromination on the anomeric position. In line with these assignments, COSY, HETCOR, HMQC, and NOESY also allowed full structure construction of all de-*O*-acetylated bromodeoxysucroses **14–16** and **20**.



Figure 15 <sup>1</sup>H NMR signals (500 MHz,  $D_2O$ ) of (a) 6'-chloro-6'-deoxysucrose (17); (b) 6bromo-6-deoxysucrose (18); (c) 6,6'-dibromo-6,6'-deoxysucrose (19); (d) 1'-bromo-1'deoxysucrose (21).

Deacetylations on per-*O*-acetylated chlorodeoxysucrose derivatives **6–8** and **11** resulted in yielding chlorodeoxysucrose derivatives **17–19** and **21**, respectively, which had the same tendencies with the previous formations of de-*O*-acetylated bromodeoxysucrose derivatives **14–16** and **20**. From the monochlorinated products, multiplet at  $\delta_H$  3.85–3.77 ppm in <sup>1</sup>H NMR (Figure 15 (a)) spectrum is assigned for compound **17** which was distinguished as chlorinated sucrose only at 6'-position center. Differentiation by cross peak of H-6' with H-5' on COSY and supported by TOCSY and NOESY cross peaks between H-6' and H-3', H-6' and H-4', and also H-6' and H-5' supported identification of this spin system. Meanwhile, compound **18** appeared as multiplet at  $\delta_H$  3.86–3.82 ppm for chlorination at 6-position (Figure 15 (b)). These multiplicities were supported by correlation between H-6 and H-5 on TOCSY that assigned chlorination only on the glucose moiety. Among the chlorinated sucrose derivatives, substituted site of 6,6'-dichloro-6,6'dideoxysucrose (**19**) is the most difficult to distinguished by <sup>1</sup>H NMR (Figure 15 (c)), which appeared as multiplet at  $\delta_{\rm H}$  3.84–3.78 ppm assigned for H-6' and at  $\delta_{\rm H}$  3.91–3.84 ppm assigned for H-6. Only by alteration within TOCSY correlation between H-6' and H-3' / H-4' / H-5' can differentiate chlorinated position on the fructose and glucose moiety. HMBC correlation from H-6' to C-4' and C-5' and from H-6 to C-3 and C-4 was fully consistent with this assignment. Then, as for 1'-chloro-1'-deoxysucrose (**21**), <sup>1</sup>H NMR (Figure 15 (d)) showed doublet at  $\delta_{\rm H}$  3.76 ppm (J = 4.0 Hz) which showed correlation on TOCSY within the cross peak between H-1' and H-4'. Outer-space correlation of NOESY also allowed this splitting pattern to assign proton on H-1' was close to H-1 indicating chlorination near the anomeric position. Strong evidence was presented by long ranged correlation HMBC that exhibited the cross peaks from H-1' to C-2' and C-3'.

As for <sup>13</sup>C NMR, the chlorination assignment of compound **17** at 6'-position can be performed by a distinguishable upfield singlet on <sup>13</sup>C NMR at  $\delta_{\rm C}$  45.1 ppm that was also supported by correlation with H-4' on HMBC. As for 6-chloro-6-deoxysucrose (**18**), cross peak of C-6 ( $\delta_{\rm C}$  44.2 ppm) on HMBC with H-4 gave a strong evidence for this assignment. Next, two singlets on upfiled region of 6,6'-dichloro-6,6'-dideoxysucrose (**19**) at  $\delta_{\rm C}$  45.2 and 44.3 ppm are assigned for C-6' and C-6, repectively. These signals are supported by the cross peak from C-6' to H-4' and to H-5' and C-6 to H-4 on HMBC, thus chlorination allowed on 6'- and 6-position was deduced. Last, singlet of C-1' at  $\delta_{\rm C}$  43.8 ppm on the upfield region of 1'-chloro-1'-deoxysucrose (**21**) <sup>13</sup>C NMR confirmed the substitution occurred only at 1'-position. HETCOR and HMQC supported all of these assignments for the gross structures of **17–19** and **21**.

Bhattacharjee and Mayer<sup>57</sup> reported the detail experimental study (retention time of the TLC separation, but without full description of NMR analysis) for unprotected halogenated sucrose that was synthesized by using an excess amount of Appel reagents. In this report, the attempt to isolate monohalogenated products (unprotected sucrose form) always remained as mixture—monochlorinated sucrose required more complex purification process—and they cannot solve these purification problems. Similar with this report, in 2011, Barros et al.<sup>10</sup> stated that mixtures of 6- and 6'-substituted sucrose were obtained for chlorination products, if limited proportion of Appel reagents were applied for sucrose. In this study, purification was conducted by the per-*O*-acetylated form, and after identification of each purified isomer, the de-*O*-acetylated was conducted. Therefore, pure de-*O*-acetylated modified sucrose at primary counterpart (**14–21**) can be identified. Complete structural elucidation of this study also compared with the previous literature data (see Table 13–19). However, structures and

substitution sites of all the unprotected halogenated sucrose derivatives (14–21) were consistent with those in per-O-acetylated forms (2–4, 6–8, 10, and 11).

## 2.2.2 Direct halogenations at primary alcohols of 1-kestose

## A. Halogenation of 1-kestose by Appel reaction

Inulin-type short-chain fructooligosaccharides (FOS) are fructose oligomers that consist of a terminal glucosyl unit and two to five fructosyl units. They are recognized as prebiotic indigestible organosaccharides<sup>70</sup> and due to this property, demand of FOS has been increasing in the food industry.<sup>23</sup> 1-Kestose (**22**, Figure 16) is one of FOS that has a  $\beta$ -D-fructofuranosyl group on O-1 of the D-fructosyl moiety of sucrose (**1**, Scheme 3). 1-Kestose **22** is naturally found in honey and some plants belonging to the *Amaryllidaceae* family.<sup>71–73</sup> The interest in 1-kestose **22**, as a low-calorie food ingredient, continues to increase due to its sweetening power. FOS syrup enriched by 1-kestose **22** can be used as an alternative sweetener for diabetics.<sup>24</sup> To produce 1-kestose **22**, the enzyme derived from the leaves of sugar beets have demonstrated transfructosylation activity in the present of sucrose **1**; thus, the products of transfer ring reaction were mainly 1-kestose **22** with smaller proportions of other oligosaccharides.<sup>74</sup> Commercial cellulolytic enzymes have also been studied for preparation of FOS with high 1-kestose concentrations (around 68.2%, calculated as short-chain FOS).<sup>23</sup>



Figure 16 Structure of 1-kestose (22) and undecaacetate of 1-kestose (23).

The simple direct halogenations of carbohydrate become one of the interest due to the previously reported study, revealing that specific substitution of sucrose primary hydroxy groups by chloride can enhance the sweetness activity,<sup>3</sup> and can potentially be used as an alternative sweetener. As previously mentioned, halogenations by utilization of Appel reaction are one of the convenient methods to convert the primary hydroxy group into a halo methylene group in the presence of triphenylphosphine and carbon tetrahalide.<sup>56</sup> Halogenation (particularly for chlorination and bromination) of primary alcohols of sucrose **1**<sup>51</sup>—the main precursor for enzyme-catalyst generation of 1-kestose **22**—has been studied since the 1970s,<sup>15</sup> but the reactivity of primary hydroxy groups attained by the Appel reaction has not been

completely identified due to limitation of structure analysis. As mentioned in previous explanation, sucrose **1** can be selectively brominated and chlorinated using the Appel reaction at only the 6- and 6'- positions with no halogenation at 1'-position supported by one- and two-dimensional (1D and 2D, respectively) NMR analyses (Schemes 3 and 4).<sup>75</sup>

As for trisaccharide modification, halogenation of the primary hydroxy groups of raffinose  $(O \cdot \alpha - D \cdot galactopyranosyl \cdot (1 \rightarrow 6) \cdot \alpha - D \cdot glucopyranosyl \cdot (1 \rightarrow 2) \cdot \beta - D \cdot fructofuranoside)$  has been reported previously.<sup>20</sup> Raffinose reacted with sulfuryl chloride and the authors have found that the chlorinated proportion at the primary positions was followed by chlorination on secondary alcohols at the 4-position of the galactopyranosyl moiety. To date, no study has been attempted to substitute primary alcohols of FOS using halogens. In midst of FOS, 1-kestose **22** has shown relatively high sweetness activity and is already commercially available. Therefore, modification of its primary alcohol would potentially increase the synthetic opportunity for alternative sweeteners. The aimed of this study is to synthesize halogenated 1-kestose **22** at the primary positions by using the Appel reaction to comprehensively study the structure elucidation supported by 1D and 2D NMR analyses.

Direct substitution of 1-kestose 22 with 4.7 equiv. carbon tetrahalide (bromide or chloride) and 9.1 equiv. triphenylphosphine at 70 °C for two hours (Scheme 8) produced a complex mixture with complicated <sup>1</sup>H-NMR spectrum due to observation of overlap signals, especially the modified primary centers. The mixture was separated after conventional acetylation. Further purification was conducted using an ether and hexane system as the representative mobile phase to isolate halogenated carbohydrate. The ethyl acetate or dichloromethane system cannot be used for the halogenated proportion.<sup>75</sup> The mixture mainly yielded halogenated 1-kestose derivatives in the pre-*O*-acetylated form (bromination **24** and chlorination **25**, Scheme 8).



**Scheme 8** Halogenation of 1-kestose (**22**) via Appel reaction with Ph<sub>3</sub>P and carbon tetrahalide to produce pre-*O*-acetylated form of halogenated 1-kestose derivatives (bromination **24** and chlorination **25**).

The <sup>1</sup>H NMR analyses for peracetylated **24** and **25** showed two regions that contribute to the proton resonance of aliphatic sugar groups in the downfield region and halogenated methylene groups located in the upfield region. Based on <sup>13</sup>C NMR, three halogenated methylene carbons in the upfield region were easily determined in the halogenated proportion in the 1-kestose derivatives, but the halogenated position remained unclear. Therefore, 2D NMR (COSY, HETCOR, HMQC, HMBC, NOESY, and TOCSY) analyses were used to determine the halogenated position. For this purpose, CDCl<sub>3</sub><sup>59,75</sup> was used as the solvent to increase the visibility of the spin system during the assignment. Undecaacetate 1-kestose<sup>71,76</sup> (**23**, Figure 16, see Table 20 in experiment section for 1D and 2D NMR and comparison of structure elucidation with the literature) was identified and used to understand the sugar skeleton of halogenated 1-kestose derivatives.

During investigation of brominated position on the 1-kestose derivative, <sup>1</sup>H-NMR of compound 24 showed eight proton signals in the upfield region. The excess of two protons corresponds to the H-1' glycosidic bond of  $O-\beta$ -D-fructofuranosyl- $(2\rightarrow 1)-\beta$ -D-fructofuranosyl, which showed a considerable geminal coupling with a typical pair of doublets at  $\delta_{\rm H}$  3.79 and 3.73 ppm (J = 10.3 Hz). The correlation between H-1'a and H-1'b with C-2' in HMBC, supported by HETCOR and HMQC, distinguished this spin system. The same tendency was also demonstrated by the undecaacetate of 1-kestose 23, which supported the glycosidic bond signals. The additional six proton signals in the upfield region highlighted the specific brominated proportion of compound 24. A clear pair of doublets at  $\delta_{\rm H}$  3.54 and 3.40 ppm (J = 2.3 and 11.5 Hz and J = 6.3 and 11.5 Hz, respectively) were observed by <sup>1</sup>H-NMR. The geminal coupling for these spin systems indicated the brominated methylene of the glucose ring at the 6-position, which was easily distinguished by its correlation with H-5 in COSY and with H-4 and H-5 in TOCSY (Figure 17 (a)). Moreover, the carbon brominated terminal at the 6-position ( $\delta_{\rm C}$  31.1 ppm) was also identified, as supported by HMBC analyses. The observation of the long range correlation between C-6 and H-4 clearly distinguished brominated position which supported by HMQC and HETCOR. The protons and carbons signals of the glucose ring were distinguished from signals of fructose rings, especially at the C-3, C-4, and C-5 positions, using TOCSY and NOESY, which were also supported by HETCOR, HMQC, and HMBC analyses.

Among fructose rings of 1-kestose, there are three possible primary alcohols at the 6'-, 1"-, and 6"-positions that are readily brominated. The upfield region of <sup>1</sup>H-NMR typically showed two types of doublets at  $\delta_{\rm H}$  3.66 ppm (J = 6.9 Hz) and 3.69 ppm (J = 7.4 Hz), indicating that bromination occurred only at the 6'- and 6"-positions of compound **24**, respectively. The correlation between H-6' and H-5' in COSY and between H-6' and H-4' / H-

5' in TOCSY differentiated the bromination at the 6'-position (Figure 17 (a)). Similarly, brominated 6"-position of compound **24** showed these particular correlations. The brominated terminals of C-6' at  $\delta_C$  32.0 ppm and C-6" at  $\delta_C$  32.7 ppm were determined mostly using HMBC with the observation of a cross peak of these carbons at H-4' and H-4", respectively. HETCOR and HMQC coupling between the protons and carbon at the 6'- and/or 6"-position supported the identification of the bromination position.

The aliphatic sugar groups between the two fructose rings of compound **24** were differentiated using TOCSY and NOESY, of which assignment was also supported by COSY, HETCOR, HMQC, and HMBC analyses. Based on <sup>1</sup>H- and <sup>13</sup>C-NMR and support of 2D NMR analysis, the 1"-position of compound **24** showed no bromination. The 1"-position of the fructose ring is known to be a neopentyl-like<sup>51,75</sup> terminal having the least reactive proportion. This phenomenon also occurred when sucrose was used.<sup>75</sup> According to these approaches, the bromination product of 1-kestose was determined to be 1",2,3,3',3",4,4',4"- octa-*O*-acetyl-6,6',6"-tribromo-6,6',6"-trideoxy-1-kestose (**24**).

For the chlorination product of 25, the spin system in <sup>1</sup>H-NMR showed eight proton signals in the upfield region. Unlike the previous bromination product 24 or undecaacetate 1kestose 23, the H-1' of compound 25 exhibited no geminal coupling and presented as a singlet at  $\delta_{\rm H}$  3.75 ppm supported by HMBC, HETCOR, and HMQC. The chlorinated proportion at the 6-position was shown as a pair of double doublets at  $\delta_{\rm H}$  3.68 and 3.57 ppm (J = 2.3, 12.0Hz and J = 5.7, 12.0 Hz, respectively). A clear correlation of this chlorinated methylene of the glucose ring with H-5 in COSY and H-4 and H-5 in TOCSY was observed (Figure 17 (b)). As for the <sup>1</sup>H-NMR spin system of 6'- and 6"-chloro of compound **25**, the overlapped signals at  $\delta_{\rm H}$  3.82–3.78 ppm demonstrated its correlation with H-5' and H-5" in COSY and with H-4', H-5', H-4", and H-5" in TOCSY. The brominated terminal of C-6' at  $\delta_C$  44.4 ppm and C-6" at  $\delta_{\rm C}$  44.6 ppm highlighted the correlated cross peaks of these carbons to H-4' and H-4'', respectively. HMBC strongly distinguished the chlorinated 6'- and 6"-positions of compound 25. These results support that the chlorinated product of 1-kestose is 1",2,3,3',3",4,4',4"-octa-O-acetyl-6,6',6"-trichloro-6,6',6"-trideoxy-1-kestose (25). As with brominated compound 24, chlorinated compound 25 showed no substitution at the 1"-position. The presence of Br and Cl isotopic peaks in ESI-MS of compounds 24 and 25 indicated tri-halogenated proportion of 1-kestose, respectively, which supported our analysis.



Figure 17 Selected COSY and TOCSY spectrum (500 MHz, CDCl<sub>3</sub>) of (a) 1'',2,3,3',3'',4,4',4''-octa-*O*-acetyl-6,6',6''-tribromo-6,6',6''-trideoxy-1'-kestose (24); (b) 1'',2,3,3',3'',4,4',4''-octa-*O*-acetyl-6,6',6''-trichloro-6,6',6''-trideoxy-1-kestose (25).

Based on our result, halogenations of 1-kestose 22 by 4.7 equiv. carbon tetrahalide (bromide or chloride) and 9.1 equiv. triphenylphosphine at 70 °C for two hours, the only primary alcohols of 1-kestose that can be contributed to halogenation was at 6-, 6'-, and/or 6"position. As mentioned in the previous paragraph, 1"-OH of 1'-kestose is considered as the most hindered position due to its location near the anomeric carbon (or so-called a neopentyllike<sup>51,75</sup> terminal). These results are in contradiction with chlorination of melezitose ( $\alpha$ -Dglucopyranosyl- $(1\rightarrow 3)$ - $\beta$ -D-fructofuranosyl- $(2\rightarrow 1)$ - $\alpha$ -D-glucopyranoside, 26) by Appel reaction (followed by acetylation after first column chromatography) in the previous study.<sup>21</sup> By the used of 4 equiv. carbon tetrachloride excess and 8 equiv. triphenylphosphine at 70 °C for two hours (Scheme 9), 6,1',6',6"-tetrachloro-6,1',6',6"-tetradeoxymelezitose heptaacetate (27) was isolated in less yield compared with preponderant 6,6',6"-trichloro-6,6',6"-trideoxymelezitose heptaacetate (28). The halogenated proportion at 1'-position of fructofuranosyl moiety might be formed due to the longer reaction time used in this report, thus unselectively halogenations occurred at 1'-position. However, no further details of reactivity in Appel reaction was described in this report (report written in Chinese).



Scheme 9 Previously reported chlorination of melezitose by Appel reactions (27 and 28).<sup>21</sup>

As for sucrose (1, main skeleton of 1-kestose), the only differentiation between the primary and secondary OH groups is relatively straightforward: the three primary ones (6-OH, 1'-OH and 6'-OH) are preferentially alkylated, acylated, oxidized or displaced by halogen—an over-generalization as this order of reactivity mainly covers comparatively bulky reagents which necessarily favor reaction at the 6-OH and 6'-OH groups.<sup>77</sup> Moreover, intra-molecular hydrogen bonds between 6'-OH and the pyranosidic oxygen atom of the glucose moiety, and between 1'-OH and O-2 that present in solid state, affected conformation of sucrose (Figure 18). In solution, only one of these bonds remains, involving O-2 and either 1'-OH or 3'-OH.<sup>2</sup> Therefore, it is already understood that on the bases of sucrose conformation, 1'-OH is the most hindered position. Accordingly, the highly selective displacement of the 6-OH and 6'-OH possibly preferred. However, this explanation is in line with our subjection of 1-kestose.

Direct substitution of 1-kestose 22 with 4.7 equiv. carbon tetrahalide (bromide or chloride) and 9.1 equiv. triphenylphosphine at 70  $^{\circ}$ C for two hours (Scheme 8) produces pre-*O*-acetylated form of halogenated 1-kestose derivatives only at 6,6',6"-position (bromination 24 and chlorination 25).



Figure 18 Sucrose (1) conformational equilibrium.<sup>2</sup>

## B. Deacetylation of per-O-acetylated trihalogenated 1-kestose

To synthesize and elucidate the novel 6,6',6''-trihalogenated 1-kestose derivatives, deacetylation was then conducted. Since suitable deacetylation conditions are generated using saturated ammonium in methanol for sucrose,<sup>75</sup> the undecaacetate of 1-kestose (**3**) was first tested for deacetylation and produced 1-kestose (**22**) within a satisfactory yield (Table 21 in experiment section). Deacetylation using other methods, such as sodium methoxide, cannot be used for 1-kestose halogenated derivatives. The per-*O*-acetylated trihalogenated derivatives of **24** and **25** were underwent deacetylation, which resulted in compound **29** and **30** (Scheme 10).



Scheme 10 Deacetylation of per-*O*-acetylated 1-kestose derivatives (23–25) to result in 1kestose (22) and deacetylated trihalogenated 1-kestose derivatives (29 and 30)

It was complicated to distinguish the halogenated proportion from the deacetylated compound **29** and/or **30**, since the halogenated methylene spin system at H-6, H-6', and H-6" overlapped with other signals such as H-3, H-1', and/or H-1" in the <sup>1</sup>H-NMR spectrum. Hence, the HMBC, HMQC, and HETCOR analyses, together with supports by COSY, TOCSY, and NOESY, are needed to elucidate the complete structure of deacetylated compounds **29** and **30** (Figure 19). However, structures and halogenation sites of all the deacetylated trihalogenated

1-kestose derivatives (29 and 30) were consistent with those in the corresponding per-O-acetylated forms (24 and 25).



**Figure 19** Selected <sup>1</sup>H-NMR (500 MHz, D<sub>2</sub>O) of 1-kestose (**22**), deacetylated tribrominated 1-kestose derivatives (**29**), deacetylated trichloronated 1-kestose derivatives (**30**)

## 2.3 Experimental section

All reagents used were of analytical grade. NMR spectra were obtained in  $CDCl_3$  or  $D_2O$  by JEOL EX270 (270 and 67.5 MHz) and JEOL ECA500 (500 and 125 MHz) spectrometer (JEOL, Tokyo, Japan). Optical rotations were measured at 23 °C on a JASCO DIP370 polarimeter (JASCO, Tokyo, Japan). HRMS spectra were obtained with a Waters UPLC ESI-TOF mass spectrometer (Waters, Milford, CT, USA).

## 2.3.1 Sucrose re-subjection into Appel reaction

*Bromination.* The bromination was performed in identical procedure.<sup>9</sup> A solution of sucrose (1; 2.00 g, 5.84 mmol) in pyridine (70 mL) was cooled in an ice bath and treated with triphenylphosphine (3.68 g, 2.4 equiv., 14.03 mmol). A solution of carbon tetrabromide (2.33 g, 1.2 equiv., 7.01 mmol) in pyridine (7 mL) was added dropwise. The reaction mixture was heated to  $60^{\circ}$ C and stirred for 1.5 h. After re-cooling the mixture, acetic anhydride (4.6 mL, 0.049 mol) was added, and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure; the residue was washed with methanol and

ethyl acetate and dissolved in a small amount of dichloromethane, then subjected to column chromatography on silica gel by elution with hexane/diethyl ether (1:1, 1:2 and 1:3) to yield:

*1',2,3,3',4,4'-hexa-O-acetyl-6,6'-dibromo-6,6'-dideoxysucrose*<sup>10,13,14,59,60</sup> (**4**; 0.28 g, 7%), eluted first, colorless oil.  $[\alpha]_D$  +37.6 (*c* = 1.0, CHCl<sub>3</sub>); ref.<sup>13</sup>  $[\alpha]_D$  +42.2 (*c* =1.0, CHCl<sub>3</sub>); ref.<sup>10</sup>  $[\alpha]_D$  +46.8 (*c* = 1.0, CHCl<sub>3</sub>); ref.<sup>14</sup>  $[\alpha]_D$  +52.5 (*c* = 0.4, CHCl<sub>3</sub>); ref.<sup>60</sup>  $[\alpha]_D$  +51 (CHCl<sub>3</sub>). <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.68 (1H, d, *J*<sub>1,2</sub> = 3.6 Hz, H-1), 5.50–5.37 (3H, m, H-3, H-3', H-4'), 5.07 (1H, t, *J*<sub>3,4</sub> = *J*<sub>4,5</sub> = 9.7 Hz, H-4), 4.88 (1H, dd, *J*<sub>1,2</sub> = 3.6 Hz, *J*<sub>2,3</sub> = 10.6 Hz, H-2), 4.37–4.28 (2H, m, H-5, H-5'), 4.24 (2H, s, H-1'), 3.65 (2H, d, *J*<sub>5',6'</sub> = 6.6 Hz, H-6'), 3.52 (1H, dd, *J*<sub>5,6a</sub> = 3.0 Hz, *J*<sub>6a,6b</sub> = 11.5 Hz, H-6a), 3.40 (1H, dd, *J*<sub>5,6b</sub> = 5.6 Hz, *J*<sub>6a,6b</sub> = 11.5 Hz, H-6b), 2.18 (3H, s, CH<sub>3</sub>), 2.16–2.09 (9H, m, 3 x CH<sub>3</sub>), 2.07 (3H, s, CH<sub>3</sub>), 2.02 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 170.0, 169.9, 169.9, 169.7, 169.4 (C=O), 104.3 (C-2'), 90.3 (C-1), 81.0 (C-5'), 77.0 (C-4'), 76.1 (C-3'), 70.5 (C-4), 70.1 (C-2), 69.2 (C-3), 69.1 (C-5), 62.3 (C-1'), 31.5 (C-6'), 31.1 (C-6), 20.6, 20.5, 20.5, 20.4, 20.4, 20.4 (CH<sub>3</sub>) ppm. HRMS (ESI): calcd. for C<sub>24</sub>H<sub>32</sub>O<sub>15</sub>NaBr<sub>2</sub> 741.0006, 742.9985, 744.9965 [M + Na]<sup>+</sup>; found 741.0015, 742.9984, 744.9982.

*1',2,3,3',4,4',6-hepta-O-acetyl-6'-bromo-6'-deoxysucrose*<sup>9</sup> (**2**; 0.29 g, 7%), eluted second, colorless oil. [*α*]<sub>D</sub>+39.2 (*c* = 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.65 (1H, d, *J*<sub>1,2</sub> = 3.6 Hz, H-1), 5.50–5.40 (2H, m, H-3, H-3'), 5.37 (1H, t, *J*<sub>3',4'</sub> = *J*<sub>4',5'</sub> = 5.1 Hz, H-4'), 5.06 (1H, t, *J*<sub>3,4</sub> = *J*<sub>4,5</sub> = 9.7 Hz, H-4), 4.88 (1H, dd, *J*<sub>1,2</sub> = 3.6 Hz, *J*<sub>2,3</sub> = 10.2 Hz, H-2), 4.35–4.24 (2H, m, H-5, H-5'), 4.24–4.17 (3H, m, H-6a, H-1'), 4.17–4.09 (1H, m, H-6b), 3.62 (2H, d, *J*<sub>5',6'</sub> = 6.6 Hz, H-6'), 2.18 (3H, s, CH<sub>3</sub>), 2.13–2.10 (12H, m, 4 x CH<sub>3</sub>), 2.05 (3H, s, CH<sub>3</sub>), 2.02 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 170.5, 170.0, 169.9, 169.8, 169.7, 169.4 (C=O), 104.3 (C-2'), 90.3 (C-1), 81.1 (C-5'), 77.1 (C-4'), 76.0 (C-3'), 70.1 (C-2), 69.3 (C-3), 68.5 (C-5), 68.1 (C-4), 62.2 (C-1'), 62.0 (C-6), 31.3 (C-6'), 20.6, 20.6, 20.5, 20.4, 20.4, 20.4, (CH<sub>3</sub>) ppm. HRMS (ESI): calcd. for C<sub>26</sub>H<sub>35</sub>O<sub>17</sub>NaBr 721.0955, 723.0935 [M + Na]<sup>+</sup>; found 721.0959, 723.0907.

*1',2,3,3',4,4',6'-hepta-O-acetyl-6-bromo-6-deoxysucrose*<sup>14</sup> (**3**; 0.48 g, 12%), eluted third, colorless oil. [α]<sub>D</sub>+56.4 (c = 1.0, CHCl<sub>3</sub>); ref.<sup>14</sup> [α]<sub>D</sub>+49.7 (c = 1.1, CHCl<sub>3</sub>). <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta = 5.74$  (1H, d,  $J_{1,2} = 3.6$  Hz, H-1), 5.49–5.40 (3H, m, H-3, H-3', H-4'), 5.11 (1H, t,  $J_{3,4} = J_{4,5} = 9.6$  Hz, H-4), 4.87 (1H, dd,  $J_{1,2} = 3.6$  Hz,  $J_{2,3} = 10.6$  Hz, H-2), 4.39–4.25 (H-5, m, 3H, H-6'), 4.25–4.21 (1H, m, H-5'), 4.20 (2H, s, H-1'), 3.60 (1H, dd,  $J_{5,6a}= 3.0$  Hz,  $J_{6a,6b}= 11.5$  Hz, H-6a), 3.42 (1H, dd,  $J_{5,6b}= 4.6$  Hz,  $J_{6a,6b}= 11.5$  Hz, H-6b), 2.17 (3H, s, CH<sub>3</sub>), 2.12–2.10 (12H, m, 4 x CH<sub>3</sub>), 2.07 (3H, s, CH<sub>3</sub>), 2.02 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>):  $\delta = 170.4$ , 170.0, 169.9, 169.8, 169.6, 169.2 (C=O), 103.9 (C-2'), 89.8 (C-1), 79.0 (C-5'), 75.7 (C-3'), 74.8 (C-4'), 70.6 (C-4), 70.1 (C-2), 69.4 (C-3), 68.8 (C-5), 63.3 (C-5))

6'), 63.0 (C-1'), 31.1 (C-6), 20.6, 20.6, 20.6, 20.5, 20.5 (CH<sub>3</sub>) ppm. HRMS (ESI): calcd. for  $C_{26}H_{35}O_{17}NaBr$  721.0955, 723.0935 [M + Na]<sup>+</sup>; found 721.0946, 723.0933.

*Chlorination.* Chlorination was similar to bromination as described above, except carbon tetrabromide in pyridine that was replaced with carbon tetrachloride (0.68 mL, 1.2 equiv., 7.01 mmol) to yield:

*1',2,3,3',4,4'-hexa-O-acetyl-6,6'-dichloro-6,6'-deoxysucrose*<sup>4</sup> (**8**; 0.18 g, 5%), eluted first, colorless oil.  $[α]_D$  +49.6 (c = 1.0, CHCl<sub>3</sub>); ref.<sup>4</sup>  $[α]_D$  +55 (c = 0.55, CHCl<sub>3</sub>); ref.<sup>13</sup>  $[α]_D$  +55.8 (c = 1.4, CHCl<sub>3</sub>); ref.<sup>11</sup>  $[α]_D$  +55.7 (c = 0.3, CHCl<sub>3</sub>); ref.<sup>18</sup>  $[α]_D$  +49.6 (c = 0.17, CHCl<sub>3</sub>). <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta = 5.68$  (1H, d,  $J_{1,2} = 3.6$  Hz, H-1), 5.50–5.35 (3H, m, H-3, H-3', H-4'), 5.10 (1H, t,  $J_{3,4} = J_{4,5} = 9.7$  Hz, H-4), 4.87 (1H, dd,  $J_{1,2} = 3.6$  Hz,  $J_{2,3} = 10.2$  Hz, H-2), 4.40–4.31 (1H, m, H-5), 4.29–4.24 (1H, m, H-5'), 4.23 (2H, s, H-1'), 3.79 (2H, d,  $J_{5,6b} = 4.9$  Hz,  $J_{6a,6b} = 12.2$  Hz, H-6b), 2.18 (3H, s, CH<sub>3</sub>), 2.16–2.08 (9H, m, 3 x CH<sub>3</sub>), 2.07 (3H, s, CH<sub>3</sub>), 2.02 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>):  $\delta = 170.0$ , 170.0, 169.7, 169.5, 169.3 (C=O), 104.4 (C-2'), 90.3 (C-1), 81.3 (C-5'), 76.4 (C-4'), 75.9 (C-3'), 70.1 (C-2), 69.6 (C-5), 69.5 (C-4), 69.4 (C-3), 62.4 (C-1'), 44.0 (C-6'), 43.2 (C-6), 20.7, 20.6, 20.5, 20.5, 20.4 (CH<sub>3</sub>) ppm. HRMS (ESI): calcd. for C<sub>24</sub>H<sub>32</sub>O<sub>15</sub>NaCl<sub>2</sub> 653.1016, 655.0986, 657.0957 [M + Na]<sup>+</sup>; 653.1030, 655.0972, 657.0950.

*1',2,3,3',4,4',6-hepta-O-acetyl-6'-chloro-6'-deoxysucrose*<sup>5,11</sup> (6; 0.33 g, 8%), eluted second, colorless oil. [α]<sub>D</sub>+45.2 (c = 1.0, CHCl<sub>3</sub>); ref.<sup>5</sup> [α]<sub>D</sub>+50 (c = 1.0, CHCl<sub>3</sub>); ref.<sup>11</sup> [α]<sub>D</sub>+54 (c = 0.4, CHCl<sub>3</sub>). <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta = 5.64$  (1H, d,  $J_{1,2} = 3.6$  Hz, H-1), 5.49–5.40 (H-3, m, 2H, H-3'), 5.37 (1H, t,  $J_{3',4'} = J_{4',5'} = 5.1$  Hz, H-4'), 5.06 (1H, t,  $J_{3,4} = J_{4,5} = 9.9$  Hz, H-4), 4.87 (1H, dd,  $J_{1,2} = 3.6$  Hz,  $J_{2,3} = 10.2$  Hz, H-2), 4.33–4.25 (1H, m, H-5), 4.25–4.17 (4H, m, H-6a, H-1', H-5'), 4.13 (1H, dd,  $J_{5,6b} = 2.0$  Hz,  $J_{6a,6b} = 12.2$  Hz, H-6b) 3.77 (2H, d,  $J_{5',6'} = 6.6$  Hz, H-6'), 2.18 (3H, s, CH<sub>3</sub>), 2.15–2.08 (12H, m, 4 x CH<sub>3</sub>), 2.05 (3H, s, CH<sub>3</sub>), 2.02 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>):  $\delta = 170.6$ , 170.0, 169.9, 169.8, 169.5 (C=O), 104.4 (C-2'), 90.3 (C-1), 81.3 (C-5'), 76.5 (C-4'), 76.0 (C-3'), 70.2 (C-2), 69.4 (C-3), 68.5 (C-5), 68.2 (C-4), 62.4 (C-1'), 62.0 (C-6), 43.9 (C-6'), 20.7, 20.6, 20.5, 20.4 (CH<sub>3</sub>) ppm. HRMS (ESI): calcd. for C<sub>26</sub>H<sub>35</sub>O<sub>17</sub>NaCl 677.1460, 679.1431 [M + Na]<sup>+</sup>; found 677.1463, 679.1426.

1',2,3,3',4,4',6'-hepta-O-acetyl-6-chloro-6-deoxysucrose<sup>5,14</sup> (7; 0.51 g, 13%), eluted third, colorless oil.  $[\alpha]_D$ +60.0 (c = 1.0, CHCl<sub>3</sub>); ref.<sup>5</sup>  $[\alpha]_D$ +69 (c = 1.0, CHCl<sub>3</sub>); ref.<sup>14</sup>  $[\alpha]_D$ +52.7 (c = 0.45, CHCl<sub>3</sub>). <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>):  $\delta = 5.74$  (1H, d,  $J_{1,2} = 3.6$  Hz, H-1), 5.49–5.39 (H-3, m, 3H, H-3', H-4'), 5.14 (1H, t,  $J_{3,4} = J_{4,5} = 9.7$  Hz, H-4), 4.87 (1H, dd,  $J_{1,2} = 3.6$  Hz,  $J_{2,3} = 10.6$  Hz, H-2), 4.41–4.26 (3H, m, H-5, H-6'), 4.25–4.21 (1H, m, H-5'), 4.20 (2H, s, H-1'),

3.73 (1H, dd,  $J_{5,6a} = 3.0$  Hz,  $J_{6a,6b} = 12.2$  Hz, H-6a), 3.58 (1H, dd,  $J_{5,6b} = 4.6$  Hz,  $J_{6a,6b} = 12.2$  Hz, H-6b), 2.17 (3H, s, CH<sub>3</sub>), 2.13–2.08 (12H, m, 4 x CH<sub>3</sub>), 2.06 (3H, s, CH<sub>3</sub>), 2.02 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>):  $\delta = 170.2$ , 169.8, 169.7, 169.6, 169.4, 169.1 (C=O), 103.7 (C-2'), 89.6 (C-1), 78.8 (C-5'), 75.5 (C-3'), 74.6 (C-4'), 70.0 (C-2), 69.4 (C-3), 69.2 (C-4), 69.2 (C-5), 63.1 (C-6'), 62.8 (C-1'), 43.0 (C-6), 20.4, 20.4, 20.4 (CH<sub>3</sub>) ppm. HRMS (ESI): calcd. for C<sub>26</sub>H<sub>35</sub>O<sub>17</sub>NaCl 677.1460, 679.1431 [M + Na]<sup>+</sup>; found 677.1464, 679.1449.

## 2.3.2 Chemoenzymatic Synthesis of 1'-Halodeoxysucrose Derivatives

2,3,3',4,4',6,6'-Hepta-O-acetyl-sucrose (9): The procedure was described in ref.<sup>65–67</sup> A solution of sucrose octaacetate (5; 1.00 g, 1.47 mmol) in 0.1 M sodium phosphate (pH 7.0)– DMF (3:1) was treated with *Alcalase 2.4 L* (2.50 g) and then incubated at 37°C for 24 h. The reaction was quenched by extracting the products with ethyl acetate. The extract was concentrated under reduced pressure and the residue was subjected to column chromatography on silica gel by elution with EtOAc/hexane (20:1 and 5:1) to yield **9** (0.25 g, 27%).

2,3,3',4,4',6,6'-hepta-O-acetyl-1'-bromo-1'-deoxysucrose (10): The procedure was described in ref.<sup>6</sup> A solution of pyridine (0.59 mL) and Tf<sub>2</sub>O (0.61 mL) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added dropwise to a solution of 9 (0.50 g, 0.78 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0°C. After 20 min, the mixture was poured into a saturated NaHCO<sub>3</sub> solution and partitioned with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with 1 M HCl and saturated NaHCO<sub>3</sub>, and then dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure. The residue was dissolved in DMF (10 mL) and LiBr (0.27 g, 4.0 equiv., 3.12 mmol) was added to the solution. After 2.5 h, the mixture was diluted with EtOAc (30 mL) and extracted with water (20 mL). The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and evaporated. The residue was subjected to column chromatography on silica gel by elution with hexane-EtOAc (2:1) to yield 10 (0.46 g, 85%) as colorless solid.  $[\alpha]_{D}$  +52.6 (c = 1.0, CH<sub>3</sub>Cl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 5.74-5.71$ (2H, m, H-1, H-3'), 5.47–5.40 (2H, m, H-3, H-4'), 5.08  $(1H, t, J_{4,5} = 9.5 \text{ Hz}, H-4)$ , 4.91 (1H, t,dd, J<sub>1,2</sub> = 4.6 Hz, J<sub>2,3</sub> = 10.3 Hz, H-2), 4.34–4.26 (4H, m, H-5, H-6a, H-6'), 4.24–4.20 (1H, m, H-5'), 4.16 (1H, d,  $J_{6a,6b} = 11.5$  Hz, H-6b), 3.61 (1H, d,  $J_{1'a,1'b} = 12.0$  Hz, H-1'a), 3.49 (1H, d,  $J_{1'a,1'b} = 12.0$  Hz, H-1'b), 2.17 (3H, s, CH<sub>3</sub>), 2.12 (3H, s, CH<sub>3</sub>), 2.11–2.09 (6H, m, 2 x CH<sub>3</sub>), 2.08 (3H, s, CH<sub>3</sub>), 2.04 (3H, s, CH<sub>3</sub>), 2.02 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta =$ 170.6, 170.4, 170.0, 169.9, 169.7, 169.6, 169.4 (C=O), 103.4 (C-2'), 89.7(C-1), 78.9 (C-5'), 76.1 (C-3'), 74.0 (C-4'), 69.9 (C-2), 69.6 (C-3), 68.4 (C-5), 68.0 (C-4), 63.1 (C-6'), 61.6 (C-6), 33.5 (C-1'), 20.7, 20.6, 20.6, 20.5, 20.5 (CH<sub>3</sub>) ppm. HRMS (ESI): calcd. for C<sub>26</sub>H<sub>35</sub>O<sub>17</sub>NaBr 721.0955, 723.0935 [M + Na]<sup>+</sup>; found 721.0959, 723.0931.

2,3,3',4,4',6,6'-hepta-O-acetyl-1'-chloro-1'-deoxysucrose<sup>8,68</sup> (11): The procedure was described in ref.<sup>6</sup> The procedure was similar to the synthesis of 10 as described above, except LiBr was replaced with LiCl (0.13 g, 4.0 equiv., 3.12 mmol) to yield 11 (0.37 g, 72%) as colorless solid.  $[\alpha]_D$  +46.4 (c = 1.0, CH<sub>3</sub>Cl<sub>3</sub>); ref.<sup>8</sup>  $[\alpha]_D$  +53.8 (c = 2.68, CH<sub>3</sub>Cl<sub>3</sub>); ref.<sup>68</sup>  $[\alpha]_D$  +55.0 (c = 1.2, CH<sub>3</sub>Cl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 5.72$  (1H, d,  $J_{1,2} = 4.0$  Hz, H-1), 5.69 (1H, d,  $J_{3',4'} = 6.3$  Hz, H-3'), 5.46–5.41 (2H, m, H-3, H-4'), 5.08 (1H, t,  $J_{4,5} = 9.7$  Hz, H-4), 4.91 (1H, dd,  $J_{1,2} = 4.0$  Hz,  $J_{2,3} = 10.3$  Hz, H-2), 4.36–4.27 (4H, m, H-5, H-6a, H-6'), 4.22 (1H, td,  $J_{4',5'} = 6.4$  Hz,  $J_{5',6'} = 3.6$  Hz, H-5'), 4.16 (1H, dd,  $J_{5,6b} = 2.9$  Hz,  $J_{6a,6b} = 13.2$  Hz, H-6b), 3.74 (1H, d,  $J_{1'a,1'b} = 12.0$  Hz, H-1'a), 3.57 (1H, d,  $J_{1'a,1'b} = 12.0$  Hz, H-1'b), 2.18 (3H, s, CH<sub>3</sub>), 2.13 (3H, s, CH<sub>3</sub>), 2.10 (6H, s, 2 x CH<sub>3</sub>), 2.07 (3H, s, CH<sub>3</sub>), 2.04 (3H, s, CH<sub>3</sub>), 2.02 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta = 170.6$ , 170.4, 170.0, 169.9, 169.8, 169.6, 169.4 (C=O), 103.9 (C-2'), 89.5 (C-1), 78.9 (C-5'), 75.4 (C-3'), 73.9 (C-4'), 69.9 (C-2), 69.6 (C-3), 68.4 (C-5), 68.0 (C-4), 63.0 (C-6'), 61.5 (C-6), 45.3 (C-1'), 20.6, 20.6, 20.6, 20.5 (CH<sub>3</sub>) ppm. HRMS (ESI): calcd. for C<sub>26</sub>H<sub>35</sub>O<sub>17</sub>NaCl 677.1460, 679.1431 [M + Na]<sup>+</sup>; found 677.1459, 679.1436.

#### 2.3.3 1-Kestose subjection into Appel Reaction

Bromination. Solution of 1-kestose (22, 0.10 g, 0.198 mmol) in pyridine (2 mL) was cooled in an ice bath and treated with triphenylphosphine (0.47 g, 1.8 mmol, 9.1 equiv), followed by dropwise addition of a solution of carbon tetrabromide (0.30 g, 0.93 mmol, 4.7 equiv) in pyridine (0.93 mL). The reaction mixture was stirred at 70 °C for 2 h. After cooling the mixture in an ice bath, acetic anhydride (3 mL, 32.0 mmol) and pyridine (2 mL) were added, and the mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and water. The organic layer was washed with 1 M HCl and brine, dried over MgSO<sub>4</sub>, reduced the solvent under high pressure and then purified by column chromatography on silica gel by elution with hexane/diethyl ether (1:6 and 1:10) to yield 1",2,3,3',3",4,4',4"-octa-O-acetyl-6,6',6"-tribromo-6,6',6"trideoxy 1-kestose (24; 0.0516 g, 25%) as colorless amorphous mass.  $[\alpha]_{\rm D}$  +22.4 (c = 1.0, CHCl<sub>3</sub>). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.70 (1H, d,  $J_{3',4'}$  = 8.0 Hz, H-3'), 5.67 (1H, d,  $J_{1,2}$  = 4.0 Hz, H-1), 5.50 (1H, d,  $J_{3'',4''} = 6.3$  Hz, H-3''), 5.48–5.42 (2H, m, H-3, H-4'), 5.32 (1H, t,  $J_{3''.4''} = 6.3$  Hz, H-4''), 5.03 (1H, t,  $J_{3,4} = 9.7$  Hz, H-4), 4.95 (1H, dd,  $J_{1,2} = 4.0$  Hz,  $J_{2,3} = 10.3$ Hz, H-2), 4.35–4.28 (2H, m, H-5, H-5'), 4.24 (2H, s, H-1"), 4.22–4.19 (1H, m, H-5"), 3.79  $(1H, d, J_{1'a,1'b} = 10.3 \text{ Hz}, H-1'a), 3.73 (1H, d, J_{1'a,1'b} = 10.3 \text{ Hz}, H-1'b), 3.69 (2H, d, J_{5'',6''} = 7.4$ Hz, H-6"), 3.66 (2H, d, J<sub>5',6'</sub> = 6.9 Hz, H-6'), 3.54 (1H, dd, J<sub>5,6a</sub> = 2.3 Hz, J<sub>6a,6b</sub> =11.5 Hz, H-6a), 3.40 (1H, dd, *J*<sub>5,6b</sub> = 6.3 Hz, *J*<sub>6a,6b</sub> =11.5 Hz, H-6b), 2.16–2.15 (6H, m, 2 x CH<sub>3</sub>), 2.14 (3H, s, CH<sub>3</sub>), 2.11 (3H, s, CH<sub>3</sub>), 2.09–2.07 (9H, m, 3 x CH<sub>3</sub>), 2.02 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 170.2, 170.0, 170.0, 169.8, 169.5 (C=O), 103.8 (C-2'), 103.1 (C-2"), 90.1 (C-1), 80.7 (C-5"), 79.8 (C-5'), 78.1 (C-4"), 77.2 (C-3"), 76.4 (C-4'), 75.8 (C-3'), 70.8 (C-4), 69.7 (C-2), 69.3 (C-3 & C-5), 62.0 (C-1"), 61.5 (C-1'), 32.7 (C-6"), 32.0 (C-6'), 31.1 (C-6), 20.8, 20.8, 20.7, 20.8, 20.6, 20.5, 20.5, 20.5 (CH<sub>3</sub>) ppm. HRMS (ESI): calcd. for C<sub>34</sub>H<sub>45</sub>O<sub>21</sub>Br<sub>3</sub>Na 1050.9881, 1052.9860 [M + Na]<sup>+</sup>; found 1050.9899, 1052.9880.

Chlorination. Chlorination was similar to bromination as described above, except carbon tetrabromide in pyridine was replaced with carbon tertrachloride (0.09 mL, 0.93 mmol, 4.7 equiv.) to yield 1",2,3,3',3'',4,4',4"-octa-O-acetyl-6,6',6"-trichloro-6,6',6"-trideoxy-1*kestose* (25; 0.0514 g, 28%) as colorless amorphous mass.  $[\alpha]_{\rm D}$  +26.6 (c = 1.0, CHCl<sub>3</sub>). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.70–5.66 (2H, m, H-1, H-3'), 5.50 (1H, d,  $J_{3'',4''} = 6.3$  Hz, H-3''), 5.48–5.41 (2H, m, H-3, H-4'), 5.33 (1H, t,  $J_{3'',4''}$  = 6.3 Hz, H-4''), 5.06 (1H, t,  $J_{3,4}$  = 9.7 Hz, H-4), 4.93 (1H, dd,  $J_{1,2} = 3.7$  Hz,  $J_{2,3} = 10.6$  Hz, H-2), 4.38–4.32 (1H, m, H-5), 4.28–4.22 (3H, m, H-1", H-5'), 4.17 (1H, q, *J*<sub>5",6"</sub> = 6.5 Hz, H-5"), 3.82–3.78 (4H, m, H-6', H-6"), 3.75 (2H, s, H-1'), 3.68 (1H, dd,  $J_{5,6a} = 2.3$  Hz,  $J_{6a,6b} = 12.0$  Hz, H-6a), 3.57 (1H, dd,  $J_{5,6b} = 5.7$  Hz,  $J_{6a,6b} = 12.0$  Hz, H-6a), 3.57 (1H, dd,  $J_{5,6b} = 5.7$  Hz,  $J_{6a,6b} = 12.0$  Hz, H-6a), 3.57 (1H, dd,  $J_{5,6b} = 5.7$  Hz,  $J_{6a,6b} = 12.0$  Hz, H-6a), 3.57 (1H, dd,  $J_{5,6b} = 5.7$  Hz,  $J_{6a,6b} = 12.0$  Hz, H-6a), 3.57 (1H, dd,  $J_{5,6b} = 5.7$  Hz,  $J_{6a,6b} = 12.0$  Hz, H-6a), 3.57 (1H, dd,  $J_{5,6b} = 5.7$  Hz,  $J_{6a,6b} = 12.0$  Hz, H-6a), 3.57 (1H, dd,  $J_{5,6b} = 5.7$  Hz,  $J_{6a,6b} = 12.0$  Hz,  $J_{6a,$ 12.0 Hz, H-6b), 2.16 (3H, s, CH<sub>3</sub>), 2.15–2.13 (6H, m, 2 x CH<sub>3</sub>), 2.11 (3H, s, CH<sub>3</sub>), 2.09 (3H, s CH<sub>3</sub>), 2.08 (3H, s, CH<sub>3</sub>), 2.07 (3H, s, CH<sub>3</sub>), 2.02 (3H, s, CH<sub>3</sub>). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ: 170.2, 170.1, 170.0, 170.0, 169.7, 169.5 (C=O), 103.8 (C-2'), 103.1 (C-2"), 90.0 (C-1), 80.6 (C-5"), 79.9 (C-5'), 77.2 (C-4"), 76.9 (C-3"), 75.7 C-4'), 75.5 (C-3'), 69.8 (C-5), 69.7 (C-2 & C-4), 69.4 (C-3), 62.2 (C-1'), 61.6(C-1'), 44.6 (C-6'), 44.4 (C-6'), 43.2 (C-6), 20.8, 20.7, 20.7, 20.6, 20.5, 20.5 (CH<sub>3</sub>) ppm. HRMS (ESI): calcd. for  $C_{34}H_{45}O_{21}Cl_3Na 919.1387 [M + Na]^+$ ; found 919.1395.

#### 2.3.4 Acetylation of Sucralose

4,1',6'-Trichloro-4,1',6'-trideoxygalactosucrose<sup>78</sup> (12): <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta$  = 5.44 (1H, d,  $J_{1,2}$  = 4.0 Hz, H-1), 4.49 (1H, d,  $J_{3,4} = J_{4,5}$  = 4.0 Hz, H-4), 4.40–4.36 (2H, m, H-3', H-5), 4.15 (1H, dd,  $J_{2,3}$  = 10.3 Hz,  $J_{3,4}$  = 4.0 Hz, H-3), 4.09 (1H, t,  $J_{3',4'} = J_{4',5'}$  = 8.6 Hz, H-4'), 4.06–4.02 (1H, m, H-5'), 3.92 (1H, dd,  $J_{1,2}$  = 4.0 Hz,  $J_{2,3}$  = 10.3 Hz, H-2), 3.87 (2H, dd,  $J_{5',6'a}$  = 5.2 Hz,  $J_{5',6'b}$  = 2.9 Hz, H-6'), 3.76 (2H, brs, H-1'), 3.73 (2H, d,  $J_{5,6}$  = 6.3 Hz, H-6) ppm. <sup>13</sup>C-NMR (125 MHz, D<sub>2</sub>O):  $\delta$  = 103.3 (C-2'), 92.6 (C-1), 81.2 (C-5'), 75.9 (C-3'), 75.2 (C-4'), 70.7 (C-5), 68.0 (C-3), 67.5 (C-2), 62.9 (C-4), 61.3 (C-6), 44.7 (C-6'), 43.4 (C-1') ppm.

Compound **12** (0.21 g, 0.53 mmol) was dissolved in pyridine (8 mL) and treated with acetic anhydride (0.5 mL, 5.30 mmol). The mixture was then stirred overnight at room temperature. The solvent was removed under reduce pressure and subjected to column chromatography on

(13):

2,3,3',4',6-Penta-O-acetyl-4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose<sup>5,79</sup>

silica gel by elution with chloroform to yield **13** (0.25 g, 78%) as colorless liquid.  $[\alpha]_D$  +63.5 (c = 1.0, CHCl<sub>3</sub>); ref.<sup>79</sup>  $[\alpha]_D$  +66.8 (c = 0.9, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 5.70$  (1H, d,  $J_{3',4'} = 6.3$  Hz, H-3'), 5.68 (1H, d,  $J_{1,2} = 1.7$  Hz, H-1), 5.41 (1H, t,  $J_{3',4'} = J_{4',5'} = 6.3$  Hz, H-4'), 5.31–5.28 (2H, m, H-2, H-3), 4.60–4.54 (2H, m, H-4, H-5), 4.28–4.21 (3H, m, H-6, H-5'), 3.77 (2H, d,  $J_{5',6'} = 5.7$  Hz, H-6'), 3.71 (1H, d,  $J_{1'a,1'b} = 12.0$  Hz, H-1'a), 3.60 (1H, d,  $J_{1'a,1'b} = 12.0$  Hz, H-1'b), 2.15 (3H, s, CH<sub>3</sub>), 2.14 (3H, s, CH<sub>3</sub>), 2.12 (3H, s, CH<sub>3</sub>), 2.10 (3H, s, CH<sub>3</sub>), 2.10 (3H, s, CH<sub>3</sub>), 2.10 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta = 170.4$ , 170.0, 169.8, 169.6 (C=O), 104.3 (C-2'), 90.6 (C-1), 80.7 (C-5'), 76.0 (C-4'), 75.8 (C-3'), 67.9 (C-2), 67.7 (C-5), 66.8 (C-3), 63.5 (C-6), 58.9 (C-4), 44.4 (C-1'), 43.8 (C-6'), 20.8, 20.7, 20.7, 20.5 (CH<sub>3</sub>) ppm. HRMS (ESI): calcd. for C<sub>22</sub>H<sub>29</sub>O<sub>13</sub>NaCl<sub>3</sub> 629.0571, 631.0542 [M + Na]<sup>+</sup>; found 629.0574, 631.0544.

## 2.3.5 Acetylation of 1-kestose

1",2,3,3',3",4,4',4",6,6',6"-Undeca-O-acetvl-deoxy-1-kestose (23):<sup>76,80</sup> Solution of 1kestose (22, 0.03 g, 0.06 mmol) in pyridine (15 mL) was treated with acetic anhydride (1 mL, 10.7 mmol), and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and subjected to column chromatography on silica gel by elution with chloroform to yield 23 (0.055 g, 96%) as a colorless liquid.  $[\alpha]_D$  + 30.2 (c = 1.0, CHCl<sub>3</sub>); Ref.<sup>80</sup>  $[\alpha]_D$  +31.8 (*c* = 3.7, CHCl<sub>3</sub>). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.75 (1H, d,  $J_{1,2}$  = 3.4 Hz, H-1), 5.69 (1H, d,  $J_{3',4'} = 8.0$  Hz, H-3'), 5.48 (1H, d,  $J_{3'',4''} = 6.9$  Hz, H-3"), 5.46 (1H, t,  $J_{3',4'} = 8.0$  Hz, H-4'), 5.42 (1H, t,  $J_{3,4} = 9.7$  Hz, H-3), 5.34 (1H, t,  $J_{3'',4''} = 6.9$  Hz, H-4''), 5.08  $(1H, t, J_{3,4} = 9.7 \text{ Hz}, H-4), 4.91 (1H, dd, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{1,2} = 3.4 \text{ Hz}, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz}, H-2), 4.39-4.33 (3H, m, J_{2,3} = 10.3 \text{ Hz},$ H-5, H-6"), 4.33-4.24 (3H, m, H-6a, H-6'), 4.24-4.20 (3H, m, H-1", H-5'), 4.20-4.14 (2H, m, H-6b, H-5"), 3.69 (1H, d,  $J_{1'a,1'b} = 9.2$  Hz, H-1'a), 3.63 (1H, d,  $J_{1'a,1'b} = 9.2$  Hz, H-1'b), 2.19– 2.14 (3H, m, CH<sub>3</sub>), 2.13–2.12 (6H, m, 2 x CH<sub>3</sub>), 2.11–2.09 (15H, m, 5 x CH<sub>3</sub>), 2.06 (3H, s, CH<sub>3</sub>), 2.04 (3H, s, CH<sub>3</sub>), 2.01 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ: 170.7, 170.6, 170.5, 170.1, 169.9, 169.7, 169.6 (C=O), 103.4 (C-2'), 102.9 (C-2"), 89.2 (C-1), 78.4 (C-5"), 77.8 (C-5'), 76.5 (C-3"), 75.5 (C-4"), 74.9 (C-3'), 73.7 (C-4'), 70.0 (C-2), 69.8 (C-3), 68.2 (C-5), 68.2 (C-4), 63.7 (C-6"), 63.2 (C-6'), 62.7 (C-1"), 62.2 (C-1'), 61.7(C-6), 20.8, 20.7, 20.7, 20.6, 20.6, 20.5 (CH<sub>3</sub>) ppm. HRMS (ESI): calcd. for  $C_{40}H_{54}O_{27}Na 989.2750 [M + Na]^+$ ; found 989.2797.

## 2.3.6 Deacetylation of per-O-acetylated halogenated carbohydrates

#### A. Deacetylation of per-O-acetylated Halodeoxysucrose Derivatives

General procedure for deacetylation of per-O-acetylated halodeoxysucrose derivatives: Solutions of per-O-acetylated halodeoxysucrose derivatives 2–4, 6–8,

10 and 11 in dry methanol were treated with saturated ammonia in methanol and stirred overnight at room temperature. The solvent was removed under reduce pressure and subjected to column chromatography on silica gel (pre-washed by methanol) by elution with methanol/chloroform. The product then was washed by diethyl ether, ethyl acetate, acetonitrile, and water—chloroform (1:1). The method afforded the corresponding halodeoxysucrose derivatives 14–21.

**6'-Bromo-6'-deoxysucrose** (**14**; 48 mg, 98%): Colorless amorphous mass. [α]<sub>D</sub>+64.6 (c = 1.0, CH<sub>3</sub>OH). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta = 5.34$  (1H, d,  $J_{1,2} = 4.0$  Hz, H-1), 4.17 (1H, d,  $J_{3',4'} = 8.0$  Hz, H-3'), 4.04 (1H, t,  $J_{3',4'} = J_{4',5'} = 8.0$  Hz, H-4'), 4.02–3.98 (1H, m, H-5'), 3.84–3.78 (2H, m, H-5, H-6a), 3.73–3.66 (4H, m, H-3, H-6b, H-6'), 3.64 (2H, brs, H-1'), 3.50 (1H, dd,  $J_{1,2} = 4.0$  Hz,  $J_{2,3} = 9.7$  Hz, H-2), 3.36 (1H, t,  $J_{3,4} = J_{4,5} = 9.7$  Hz, H-4) ppm. <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O):  $\delta = 103.9$  (C-2'), 92.4 (C-1), 80.8 (C-5'), 77.0 (C-4'), 76.6 (C-3'), 72.7 (C-5), 72.6 (C-3), 71.1 (C-2), 69.5 (C-4), 61.0 (C-1'), 60.5 (C-6), 33.2 (C-6') ppm. HRMS (ESI): calcd. for C<sub>12</sub>H<sub>21</sub>O<sub>10</sub>NaBr 427.0216, 429.0195 [M + Na]<sup>+</sup>; found 427.0213, 429.0208.

**6-Bromo-6-deoxysucrose**<sup>14</sup> (**15**; 75 mg, 90%): Colorless amorphous mass. [α]<sub>D</sub>+43.6 (c = 1.0, CH<sub>3</sub>OH). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta = 5.38$  (1H, d,  $J_{1,2} = 4.0$  Hz, H-1), 4.18 (1H, d,  $J_{3',4'} = 8.6$  Hz, H-3'), 4.05 (1H, t,  $J_{3',4'} = J_{4',5'} = 8.6$  Hz, H-4'), 3.99 (1H, dt,  $J_{4,5} = 9.7$  Hz,  $J_{5,6} = 3.4$  Hz, H-5), 3.86 (1H, td,  $J_{4',5'} = 8.6$  Hz,  $J_{5',6'} = 3.4$  Hz, H-5'), 3.81–3.76 (2H, m, H-6'), 3.76–3.71 (3H, m, H-3, H-6), 3.63 (2H, brs, H-1'), 3.55 (1H, dd,  $J_{1,2} = 4.0$  Hz,  $J_{2,3} = 9.7$  Hz, H-2), 3.47 (1H, t,  $J_{3,4} = J_{4,5} = 9.7$  Hz, H-4) ppm. <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O):  $\delta = 103.7$  (C-2'), 92.1(C-1), 81.3 (C-5'), 76.2 (C-3'), 74.0 (C-4'), 72.1 (C-3), 71.2 (C-4), 71.0 (C-2), 70.7 (C-5), 62.5 (C-6'), 61.4 (C-1'), 33.4 (C-6) ppm. HRMS (ESI): calcd. for C<sub>12</sub>H<sub>21</sub>O<sub>10</sub>NaBr 427.0216, 429.0195 [M + Na]<sup>+</sup>; found 427.0231, 429.0208.

**6,6'-Dibromo-6,6'-dideoxysucrose**<sup>10</sup> (**16**; 94 mg, 80%): Colorless amorphous mass.  $[\alpha]_{\rm D}$  +37.4 (c = 1.0, CH<sub>3</sub>OH); ref.<sup>10</sup>  $[\alpha]_{\rm D}$  +27.4 (c = 1.0, CH<sub>3</sub>OH); ref.<sup>60</sup>  $[\alpha]_{\rm D}$  +37 (c = 1.0, CH<sub>3</sub>OH). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta = 5.35$  (1H, d,  $J_{1,2} = 4.0$  Hz, H-1), 4.17 (1H, d,  $J_{3',4'} = 8.6$  Hz, H-3'), 4.08 (1H, t,  $J_{3',4'} = J_{4',5'} = 8.6$  Hz, H-4'), 4.01–4.00 (2H, m, H-5, H-5'), 3.75–3.69 (3H, m, H-6', H-3), 3.69–3.65 (1H, m, H-6a), 3.64 (2H, brs, H-1'), 3.63–3.60 (1H, m, H-6b), 3.52 (1H, dd,  $J_{1,2} = 4.0$  Hz,  $J_{2,3} = 9.7$  Hz, H-2), 3.42 (1H, t,  $J_{3,4} = J_{4,5} = 9.5$  Hz, H-4) ppm. <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O):  $\delta = 103.8$  (C-2'), 92.3 (C-1), 80.5 (C-5'), 76.6 (C-4'), 76.4 (C-3'), 72.0 (C-3), 71.4 (C-4), 71.0 (C-5), 71.0 (C-2), 61.1 (C-1'), 33.3 (C-6), 33.2 (C-6') ppm. HRMS (ESI): calcd. for C<sub>12</sub>H<sub>20</sub>O<sub>9</sub>NaBr<sub>2</sub> 488.9372, 490.9351, 492.9331 [M + Na]<sup>+</sup>; found 488.9354, 490.9356, 492.9329.

**6'-Chloro-6'-deoxysucrose**<sup>81</sup> (**17**; 71 mg, 82%): Colorless amorphous mass. [α]<sub>D</sub>+59.0 (c = 1.0, CH<sub>3</sub>OH); ref.<sup>5</sup> [α]<sub>D</sub>+64 (c = 1.0, H<sub>2</sub>O). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta = 5.33$  (1H, d,  $J_{1,2} = 3.4$  Hz, H-1), 4.17 (1H, d,  $J_{3',4'} = 8.6$  Hz, H-3'), 4.06 (1H, t,  $J_{3',4'} = J_{4',5'} = 8.6$  Hz, H-4'), 3.97 (1H, dd,  $J_{4',5'} = 8.6$  Hz,  $J_{5',6'} = 5.7$  Hz, H-5'), 3.85–3.77 (4H, m, H-6a, H-6', H-5), 3.73–3.66 (2H, m, H-3, H-6b), 3.64 (2H, brs, H-1'), 3.49 (1H, dd,  $J_{1,2} = 3.4$  Hz,  $J_{2,3} = 9.7$  Hz, H-2), 3.36 (1H, t,  $J_{3,4} = J_{4,5} = 9.7$  Hz, H-4) ppm. <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O):  $\delta = 103.8$  (C-2'), 92.3 (C-1), 80.7 (C-5'), 76.3 (C-3'), 75.9 (C-4'), 72.6 (C-5), 72.5 (C-3), 71.0 (C-2), 69.4 (C-4), 60.9 (C-1'), 60.3 (C-6), 45.1 (C-6') ppm. HRMS (ESI): calcd. for C<sub>12</sub>H<sub>21</sub>O<sub>10</sub>NaCl 383.0721, 385.0691 [M + Na]<sup>+</sup>; found 383.0721, 385.0704.

**6**-*Chloro-6-deoxysucrose*<sup>4,5</sup> (**18**; 55 mg, 83%): Colorless amorphous mass. [α]<sub>D</sub> +39.2 (c = 1.0, CH<sub>3</sub>OH); ref.<sup>4</sup> [α]<sub>D</sub> +55 (c = 1, H<sub>2</sub>O); ref.<sup>5</sup> [α]<sub>D</sub> +46 (c = 1.0, H<sub>2</sub>O). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta = 5.36$  (1H, d,  $J_{1,2} = 3.4$  Hz, H-1), 4.16 (1H, d,  $J_{3',4'} = 8.6$  Hz, H-3'), 4.05 (1H, dt,  $J_{4,5} = 9.7$  Hz,  $J_{5,6} = 3.2$  Hz, H-5), 4.00 (1H, t,  $J_{3',4'} = J_{4',5'} = 8.6$  Hz, H-4'), 3.86–3.82 (3H, m, H-6, H-5'), 3.77 (2H, d,  $J_{5',6'} = 2.9$  Hz, H-6'), 3.72–3.69 (1H, m, H-3), 3.61 (2H, brs, H-1'), 3.52 (1H, dd,  $J_{1,2} = 3.4$  Hz,  $J_{2,3} = 9.7$  Hz, H-2), 3.47 (1H, t,  $J_{3,4} = J_{4,5} = 9.7$  Hz, 4H) ppm. <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O):  $\delta = 103.7$  (C-2'), 92.1 (C-1), 81.3 (C-5'), 76.1 (C-3'), 74.0 (C-4'), 72.1 (C-3), 71.3 (C-5), 71.0 (C-2), 69.9 (C-4), 62.5 (C-6'), 61.3 (C-1'), 44.2 (C-6) ppm. HRMS (ESI): calcd. for C<sub>12</sub>H<sub>21</sub>O<sub>10</sub>NaCl 383.0721, 385.0691 [M + Na]<sup>+</sup>; found 383.0721, 385.0695.

**6**,**6'**-*Dichloro-6*,**6'**-*dideoxysucrose*<sup>10,69</sup> (**19**; 59 mg, 94%): Colorless amorphous mass. [α]<sub>D</sub> +43.6 (c = 1.0, CH<sub>3</sub>OH); ref.<sup>4</sup> [α]<sub>D</sub> +60 (c = 0.5, H<sub>2</sub>O); ref.<sup>10</sup> [α]<sub>D</sub> +50.4 (c = 0.9, CH<sub>3</sub>OH); ref.<sup>58</sup> [α]<sub>D</sub> +58 (c = 0.5, H<sub>2</sub>O); ref.<sup>15</sup> [α]<sub>D</sub> +60 (c = 1, H<sub>2</sub>O). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta = 5.39$  (1H, d,  $J_{1,2} = 4.0$  Hz, H-1), 4.21 (1H, d,  $J_{3',4'} = 8.6$  Hz, H-3'), 4.14–4.08 (2H, m, H-5, H-4'), 4.00 (1H, td,  $J_{4',5'} = 8.0$  Hz,  $J_{5',6'} = 3.4$  Hz, H-5'), 3.91–3.84 (2H, m, H-6), 3.84–3.78 (2H, m, H-6'), 3.74 (1H, t,  $J_{2,3} = J_{3,4} = 9.7$  Hz, H-3), 3.67 (2H, brs, H-1'), 3.55 (1H, dd,  $J_{1,2} = 4.0$  Hz,  $J_{2,3} = 9.7$  Hz, H-2), 3.48 (1H, t,  $J_{3,4} = J_{4,5} = 9.7$  Hz, H-4) ppm. <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O):  $\delta = 103.9$  (C-2'), 92.3 (C-1), 80.7 (C-5'), 76.3 (C-3'), 75.6 (C-4'), 72.1 (C-3), 71.6 (C-5), 71.0 (C-2), 70.1 (C-4), 61.2 (C-1'), 45.2 (C-6'), 44.3 (C-6) ppm. HRMS (ESI): calcd. for C<sub>12</sub>H<sub>20</sub>O<sub>9</sub>NaCl<sub>2</sub> 401.0382, 403.0353, 405.0323 [M + Na]<sup>+</sup>; found 401.0400, 403.0364, 405.0331.

*1'-Bromo-1'-deoxysucrose* (**20**; 8.7 mg, 39%): Colorless amorphous mass.  $[\alpha]_D$  +36.4 ( $c = 1.0, CH_3OH$ ). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta = 5.40$  (1H, d,  $J_{1,2} = 4.0$  Hz, H-1), 4.42 (1H, d,  $J_{3',4'} = 8.6$  Hz, H-3'), 4.01 (1H, t,  $J_{3',4'} = J_{4',5'} = 8.6$  Hz, H-4'), 3.87 (1H, td,  $J_{4',5'} = 8.6$  Hz,  $J_{5',6'} = 2.9$  Hz, H-5'), 3.82–3.76 (5H, m, H-5, H-6, H-6'), 3.73–3.69 (2H, m, H-3, H-1'a), 3.63 (1H, brs, H-1'b), 3.52 (1H, dd,  $J_{1,2} = 4.0$  Hz,  $J_{2,3} = 9.7$  Hz, H-2), 3.44 (1H, t,  $J_{3,4} = J_{4,5} = 9.7$  Hz, H-4) ppm. <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O):  $\delta = 102.8$  (C-2'), 92.7 (C-1), 81.9 (C-5'), 77.0 (C-3'),

73.6 (C-4'), 72.7 (C-3 & C-5), 71.1 (C-2), 69.4 (C-4), 62.1(C-6'), 60.2 (C-6), 32.6 (C-1') ppm. HRMS (ESI): calcd. for  $C_{12}H_{21}O_{10}NaBr$  427.0216, 429.0195 [M + Na]<sup>+</sup>; found 427.0212, 429.0191.

*I'-Chloro-1'-deoxysucrose*<sup>8,82</sup> (**21**; 2.8 mg, 21%): Colorless amorphous mass.  $[\alpha]_D + 40.0 (c = 1.0, CH_3OH)$ ; ref.<sup>8</sup>  $[\alpha]_D + 60.4 (c = 1.0, H_2O)$ ; ref.<sup>68</sup>  $[\alpha]_D + 57.8 (c = 0.7, H_2O)$ . <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta = 5.40 (1H, d, J_{1,2} = 4.0 Hz, H-1)$ , 4.36 (1H, d,  $J_{3',4'} = 8.6 Hz, H-3'$ ), 4.01 (1H, t,  $J_{3',4'} = J_{4',5'} = 8.6 Hz, H-4'$ ), 3.88 (1H, td,  $J_{4',5'} = 8.6 Hz, J_{5',6'} = 3.4 Hz, H-5'$ ), 3.81 (1H, dd,  $J_{5,6a} = 2.9 Hz, J_{5,6b} = 5.7 Hz, H-5$ ), 3.80–3.77 (4H, m, H-6, H-6'), 3.77 (2H, brs, H-1'), 3.71 (1H, t,  $J_{3,4} = 9.7 Hz, H-3$ ), 3.52 (1H, dd,  $J_{1,2} = 4.0 Hz, J_{2,3} = 9.7 Hz, H-2$ ), 3.43 (1H, t,  $J_{3,4} = J_{4,5} = 9.7 Hz, H-4$ ) ppm. <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O):  $\delta = 103.1 (C-2')$ , 92.5 (C-1), 81.7 (C-5'), 76.2 (C-3'), 73.4 (C-4'), 72.5 (C-3 & C-5), 70.9 (C-2), 69.2 (C-4), 61.9 (C-6'), 60.0 (C-6), 43.8 (C-1') ppm. HRMS (ESI): calcd. for C<sub>12</sub>H<sub>21</sub>O<sub>10</sub>NaCl 383.0721, 385.0691 [M + Na]<sup>+</sup>; found 383.0723, 385.0695.

#### B. Deacetylation of per-O-acetylated halodeoxy-1-kestose derivative

Solutions of per-*O*-acetylated halodeoxy-1-kestose derivatives (**23–25**, 0.05 g) in 3 mL dry methanol were treated with 1.5 mL saturated ammonia in methanol and stirred overnight at room temperature. The solvent was removed under reduced pressure and subjected to column chromatography on silica gel (pre-washed by methanol) by elution with methanol/chloroform (3:1). The method produced the corresponding halodeoxysucrose derivatives **22**, **29**, and **30**.

*1-kestose*<sup>71</sup> (**22**, 0.034 g, 97%). <sup>1</sup>H-NMR (500 MHz, D<sub>2</sub>O)  $\delta$ : 5.37 (1H, d,  $J_{1,2} = 4.0$  Hz, H-1), 4.22 (1H, d,  $J_{3',4'} = 8.6$  Hz, H-3'), 4.13 (1H, d,  $J_{3'',4''} = 8.6$  Hz, H-3''), 4.02 (1H, t,  $J_{3'',4''} = 8.6$  Hz, H-4''), 3.98 (1H, t,  $J_{3',4'} = 8.6$  Hz, H-4'), 3.83–3.80 (2H, m, H-5', H-5''), 3.79–3.71 (8H, m, H-1'a, H-5, H-6, H-6', H-6''), 3.70–3.60 (4H, m, H-3, H-1'b, H-1''), 3.48 (1H, dd,  $J_{1,2} = 4.0$  Hz,  $J_{2,3} = 9.7$ , H-2), 3.41 (1H, t,  $J_{3,4} = 9.7$  Hz, H-4) ppm. <sup>13</sup>C-NMR (125 MHz, D<sub>2</sub>O)  $\delta$ : 104.2 (C-2''), 103.7 (C-2'), 92.9 (C-1), 81.6 (C-5'), 81.5 (C-5''), 77.0 (C-3' & C-3''), 74.9 (C-4''), 74.2 (C-4'), 73.0 (C-3), 72.8 (C-5), 71.6 (C-2), 69.6 (C-4), 62.7 (C-6''), 62.6 (C-6'), 61.3 (C-1'), 60.8 (C-1''), 60.5 (C-6) ppm.

6,6',6''-tribromo-6,6',6''-trideoxy-1-kestose (29, 0.030 g, 81%). [α]<sub>D</sub> = + 24.8 (c 1.0, MeOH). <sup>1</sup>H-NMR (500 MHz, D<sub>2</sub>O) δ: 5.36 (1H, d,  $J_{1,2}$  = 4.0 Hz, H-1), 4.27 (1H, d,  $J_{3',4'}$  = 8.6 Hz, H-3'), 4.16 (1H, d,  $J_{3'',4''}$  = 8.6 Hz, H-3''), 4.09–4.05 (2H, m, H-4', H-4''), 4.04–3.98 (3H, m, H-5, H-5', H-5''), 3.87 (1H, d,  $J_{1'a,1'b}$  = 10.3 Hz, H-1'a), 3.79–3.72 (3H, m, H-6a, H-6''), 3.72–3.65 (5H, m, H-1'b, H-1'', H-6b, H-3), 3.64–3.59 (2H, m, H-6'), 3.52 (1H, dd,  $J_{1,2}$  = 4.0 Hz,  $J_{2,3}$  = 10.0, Hz, H-2), 3.43 (1H, t,  $J_{3,4}$  = 10.0 Hz, H-4) ppm. <sup>13</sup>C-NMR (125 MHz, D<sub>2</sub>O) δ:

103.9 (C-2"), 103.3 (C-2'), 92.9 (C-1), 80.6 (C-5'), 80.4 (C-5"), 77.4 (C-4"), 76.9 (C-3"), 76.4 (C-3'), 76.3 (C-4'), 72.1 (C-3), 71.4 (C-4), 71.1 (C-5), 71.0 (C-2), 59.9 (C-1', C-1"), 34.2 (C-6), 33.5 (C-6'), 33.5 (C-6") ppm. HRMS (ESI): calcd. for  $C_{18}H_{29}Br_3O_{13}Na$  714.9035, 716.9015  $[M + Na]^+$ ; found 714.9053, 716.9034.

**6,6',6''-trichloro-6,6',6''-trideoxy-1-kestose** (**30**, 0.032 g, 85%).  $[\alpha]_D = +26.6$  (c 1.0, MeOH). <sup>1</sup>H-NMR (500 MHz, D<sub>2</sub>O)  $\delta$ : 5.36 (1H, d,  $J_{1,2} = 4.0$  Hz, H-1), 4.26 (1H, d,  $J_{3',4'} = 8.6$  Hz, H-3'), 4.16 (1H, d,  $J_{3'',4''} = 8.6$  Hz, H-3''), 4.11–4.05 (3H, m, H-4', H-4'', H-5), 4.01–3.94 (2H, m, H-5', H-5''), 3.89–3.73 (7H, m, H-6, H-6', H-6'', H-1'a), 3.71–3.60 (4H, m, H-1'b, H-1'', H-3), 3.52 (1H, dd,  $J_{1,2} = 4.0$  Hz,  $J_{2,3} = 9.7$  Hz, H-2), 3.47 (1H, t,  $J_{3,4} = 9.7$  Hz, H-4) ppm. <sup>13</sup>C-NMR (125 MHz, D<sub>2</sub>O)  $\delta$ : 103.9 (C-2''), 103.3 (C-2'), 92.8 (C-1), 80.6 (C-5'), 80.5 (C-5''), 76.6 (C-3''), 76.4 (C-3'), 76.2 (C-4''), 75.3 (C-4'), 72.2 (C-3), 71.6 (C-4), 71.0 (C-5), 70.1 (C-2), 60.2 (C-1'), 60.0 (C-1''), 45.4 (C-6''), 45.2 (C-6'), 44.3 (C-6) ppm. HRMS (ESI): calcd. for C<sub>18</sub>H<sub>29</sub>Cl<sub>3</sub>O<sub>13</sub>Na 581.0571, 583.0542 [M + Na]<sup>+</sup>; found 581.0587, 583.0568.

| Assign     | 2<br>CAS: 951768-18-6<br>(δ in ppm and J in Hz)  |  |   |   |  |  |  |  |  |
|------------|--|--|---|---|--|--|--|--|--|
| ment       | Ref <sup>9a</sup>                                |  | Observed  |   |  |  |  |  |  |
|            | $\delta^{1}$ H (400 MHz in CDCl <sub>3</sub> )   | $\frac{\delta^{13}C}{(100 \text{ MHz, CDCl}_3)}$ | $\frac{\delta^{1} \mathrm{H}}{(270 \mathrm{MHz}, \mathrm{CDCl}_{3})}$ | $\frac{\delta^{13}C}{(67.5 \text{ MHz, CDCl}_3)}$ |  |  |  |  |  |
| 1          | 5.75<br>(d, <i>J</i> = 3.6 Hz)                   | 89.8   | 5.65 (d)  | 90.3  |  |  |  |  |  |
| 2          | 4.87 (dd)  | 70.2   | 4.88 (dd)   | 70.1  |  |  |  |  |  |
| 3          | 5.45<br>(t, <i>J</i> = 9.9 Hz)                   | 69.5   | 5.50–5.40 (m)   | 69.3  |  |  |  |  |  |
| 4          | 5.11<br>(t, <i>J</i> = 9.7 Hz)                   | 70.6   | 5.06 (t)  | 68.1  |  |  |  |  |  |
| 5          | 4.30 (m)   | 68.8   | 4.35–4.24 (m)   | 68.5  |  |  |  |  |  |
| ба         | 4.36 (dd)  | 63 1   | 4.24–4.17 (m)   | 62.0  |  |  |  |  |  |
| 6b         | 4.30 (dd   | 03.4   | 4.17–4.09 (m)   | 02.0  |  |  |  |  |  |
| 1'a<br>1'b | 4.19 (m)   | 63.0   | 4.24–4.17 (m)   | 62.2  |  |  |  |  |  |
| 2'         | _  | 104.0  | _   | 104.3   |  |  |  |  |  |
| 3'         | 5.44 (d, <i>J</i> = 5.9 Hz)                      | 75.7   | 5.50–5.40 (m)   | 76.0  |  |  |  |  |  |
| 4'         | 5.42 (t, $J = 5.7$ Hz                            | 74.8   | 5.37 (t)  | 77.1  |  |  |  |  |  |
| 5'         | 4.21 (dd, <i>J</i> = 5.4 Hz, <i>J</i> = 10.6 Hz) | 79.1   | 4.35–4.24 (m)   | 81.1  |  |  |  |  |  |
| 6'a        | 3.60 (dd)  | 31.2   | 3 62 (d)  | 31.3  |  |  |  |  |  |
| 6′b        | 3.42 (dd)  | 51.2   | 5.02 (d)  | 51.5  |  |  |  |  |  |
| $J_{1,2}$  | 3.7  |  | 3.6   |   |  |  |  |  |  |
| $J_{2,3}$  | 10.4   | _  | 10.2  |   |  |  |  |  |  |
| $J_{3,4}$  | _  |  | 9.7   |   |  |  |  |  |  |

# 2.3.7<sup>1</sup>H and <sup>13</sup>C NMR Literature Comparison of Halodeoxysucrose Derivatives with Observation Data

**Table 3** <sup>1</sup>H and <sup>13</sup>C NMR comparison of 6'-bromo-6'-deoxysucrose heptaacetate (2) with literature data

|                       | 2 (con't)<br>CAS: 951768-18-6           |   |   |   |  |  |  |  |  |  |
|-----------------------|---|---|---|---|--|--|--|--|--|--|
| Assign                |   |   |   |   |  |  |  |  |  |  |
| ment                  | Ref <sup>9a</sup>                       |   | Observed                                | 1   |  |  |  |  |  |  |
|                       | $\delta$ $^{1}\mathrm{H}$               | $\delta^{13}$ C                             | $\delta^{1}$ H                          | $\delta^{13}$ C                             |  |  |  |  |  |  |
|                       | (400 MHz in CDCl <sub>3</sub> )         | (100 MHz, CDCl <sub>3</sub> )               | (270 MHz, CDCl <sub>3</sub> )           | (67.5 MHz, CDCl <sub>3</sub> )              |  |  |  |  |  |  |
| $J_{4,5}$             | -                                       |   | 9.7                                     |   |  |  |  |  |  |  |
| $J_{5,6a}$            | 4.4                                     |   |   |   |  |  |  |  |  |  |
| $J_{5,6b}$            | 5.6                                     |   | -                                       |   |  |  |  |  |  |  |
| $J_{6a,6b}$           | 12.1 or 11.9                            |   |   |   |  |  |  |  |  |  |
| $J_{3',4'}$           |   | -   | 5.1                                     | _   |  |  |  |  |  |  |
| $J_{4',5'}$           | -                                       |   | 5.1                                     |   |  |  |  |  |  |  |
| $J_{5',6'a}$          | 2.7                                     |   | 6.6                                     |   |  |  |  |  |  |  |
| $J_{5',6'\mathrm{b}}$ | 4.4                                     |   | 0.0                                     |   |  |  |  |  |  |  |
| $J_{,6'a,6'b}$        | 11.6 or 11.5                            |   | -                                       |   |  |  |  |  |  |  |
| СЦ                    | 2.17 (s), 2.13 (s), 2.12 (s), 2.11 (s), | 20.5.20.7.20.7.20.6.20.6                    | 2.18 (s). 2.13–2.10 (m), 2.05 (s), 2.02 | 20.6, 20.6, 20.5, 20.4, 20.4,               |  |  |  |  |  |  |
|                       | 2.10 (s), 2.07 (s), 2.02 (s)            | 20.3, 20.7, 20.7, 20.0, 20.0                | (s)                                     | 20.4  |  |  |  |  |  |  |
| C=O                   | _                                       | 170.5, 170.1, 170.0, 169.9,<br>169.6, 169.3 | _                                       | 170.5, 170.0, 169.9, 169.8,<br>169.7, 169.4 |  |  |  |  |  |  |

<sup>9</sup> Andrade, M. M., et al. *Eur. J. Org. Chem.* 2007, 7, 3655–3668. <sup>a</sup> 6'-bromo-6'-deoxysucrose heptaacetate (3) was misinterpreted in this report. In present study, it was then revised as 6-bromo-6-deoxysucrose heptaacetate (4)

| Assign          |                                     |                    | <b>3</b><br>CAS: 54429-71-9 (δ in ppm and J in Hz)    |   |  |  |  |  |  |
|-----------------|-------------------------------------|--------------------|---|---|--|--|--|--|--|
| ment            | <b>Ref</b> <sup>14</sup>            |                    | Obse  | rved  |  |  |  |  |  |
|                 | $\delta^{1}$ H (CDCl <sub>3</sub> ) | $\delta^{13}C^{a}$ | $\delta$ <sup>1</sup> H (270 MHz, CDCl <sub>3</sub> ) | $\delta^{13}$ C (67.5 MHz,CDCl <sub>3</sub> ) |  |  |  |  |  |
| 1               |                                     |                    | 5.74 (d)  | 89.8  |  |  |  |  |  |
| 2               |                                     |                    | 4.87 (dd)   | 70.1  |  |  |  |  |  |
| 3               | -                                   |                    | 5.49–5.40 (m)   | 69.4  |  |  |  |  |  |
| 4               |                                     |                    | 5.11 (t)  | 70.6  |  |  |  |  |  |
| 5               |                                     |                    | 4.39–4.25 (m)   | 68.8  |  |  |  |  |  |
| ба              | 3.54 (m)                            |                    | 3.60 (dd)   | 21.1  |  |  |  |  |  |
| 6b              | 5.54 (III)                          |                    | 3.42 (dd)   | 51.1  |  |  |  |  |  |
| 1′a             |                                     |                    | (4.20) (c)  | 63.0  |  |  |  |  |  |
| 1′b             |                                     |                    | 4.20 (8)  | 05:0  |  |  |  |  |  |
| 2'              |                                     | —                  | _   | 103.9   |  |  |  |  |  |
| 3'              |                                     |                    | 5.49–5.40 (m)   | 75.7  |  |  |  |  |  |
| 4'              |                                     |                    | 5.49–5.40 (m)   | 74.8  |  |  |  |  |  |
| 5'              |                                     |                    | 4.25–4.21 (m)   | 79.0  |  |  |  |  |  |
| 6'a<br>6'b      |                                     |                    | 4.39–4.25 (m)   | 63.3  |  |  |  |  |  |
| $J_{1,2}$       |                                     |                    | 3.6   |   |  |  |  |  |  |
| $J_{2,3}$       |                                     |                    | 10.6  |   |  |  |  |  |  |
| $J_{3,4}$       |                                     |                    | 9.6   |   |  |  |  |  |  |
| $J_{4,5}$       |                                     |                    | 9.6   | _   |  |  |  |  |  |
| $J_{5,6a}$      |                                     |                    | 3.0   |   |  |  |  |  |  |
| $J_{5,6b}$      |                                     |                    | 4.6   | ]   |  |  |  |  |  |
| $J_{6a,6b}$     |                                     |                    | 11.5  |   |  |  |  |  |  |
| CH <sub>3</sub> | 2.1 (m)                             |                    | 2.17 (s), 2.12–2.10 (m), 2.07 (s), 2.02 (s)           | 20.6, 20.6, 20.6, 20.5, 20.5                  |  |  |  |  |  |
| C=O             | _                                   |                    | _   | 170.4, 170.0, 169.9, 169.8, 169.6, 169.2      |  |  |  |  |  |

**Table 4** <sup>1</sup>H and <sup>13</sup>C NMR comparison of 6-bromo-6-deoxysucrose heptaacetate (**3**) with literature data

<sup>14</sup> Castro, B.; Chapleur, Y.; Gross, B. *Carbohydr. Res.* **1974**, *36*, 412–419. <sup>a</sup> No previous assignment

|        |                                     |                              |   |                              |  | (   | <b>4</b><br>CAS: 54484-76                            | 5-3  |   |                              |  |  |  |
|--------|-------------------------------------|------------------------------|---|------------------------------|--|---|--|--|---|------------------------------|--|--|--|
|        | D - C                               | 4                            | D.el3   | }                            |  | $(\delta)$                                | in ppm and $J$ in <b>D</b> of                        | n Hz)<br>59  | D-f   |                              |  |  |  |
| Assign | Ref                                 |                              | Ref   |                              | Ref  |   | Ker  |  | <b>Kef</b> <sup>*</sup>   | -                            | Obse   | rved   |  |
| ment   | $\delta^{1}$ H (CDCl <sub>3</sub> ) | $\delta^{13}$ C <sup>a</sup> | δ <sup>1</sup> H<br>(100<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta^{13}$ C <sup>a</sup> | $\begin{array}{c} \delta \ ^{\circ} H \\ (400) \\ MHz, \\ DMSO- \\ d_{6}) \end{array}$ | $\delta^{13}C$ (100 MHz,<br>DMSO- $d^6$ ) | δ <sup>1</sup> H<br>(500 MHz,<br>CDCl <sub>3</sub> ) | $\delta^{13}$ C<br>(125<br>MHz,<br>CDCl <sub>3</sub> )                                 | δ <sup>1</sup> H<br>(90 MHZ,<br>C <sub>6</sub> D <sub>6</sub> ) | $\delta^{13}$ C <sup>a</sup> | δ <sup>1</sup> H<br>(270 MHz,<br>CDCl <sub>3</sub> ) | δ <sup>13</sup> C<br>(67.5 MHz,<br>CDCl <sub>3</sub> ) |  |
| 1      |                                     |                              | 5.57 (d)  |                              | 5.63 (d,<br>J = 3.2<br>Hz)   | 90.0                                      | 5.65 (d, <i>J</i> = 3.6 Hz)                          | 170.09,<br>170.03,<br>169.48,  | 5.78 (d)  |                              | 5.68 (d)   | 90.3   |  |
| 2      |                                     |                              | 4.85 (q)  |                              | 4.82<br>(dd)   | 69.3                                      | 4.84 (dd, J<br>= 10.4, 3.7<br>Hz)                    | 169.35,<br>104.43,<br>90.36,   | 4.97 (dd)   |                              | 4.88 (dd)  | 70.1   |  |
| 3      |                                     |                              | 5.43 (q)  |                              | 5.31-<br>5.35<br>(m)   | 68.8                                      | 5.41 (dd, J<br>= 10.2, 9.5<br>Hz)                    | 81.09,<br>77.06,<br>76.14,   | 5.72 (t)  |                              | 5.50–5.37<br>(m)                                     | 69.2   |  |
| 4      | _                                   | _                            | 5.04 (t)  | _                            | 4.99 (t,<br>J = 9.7<br>Hz)   | 69.6 or 68.8                              | 5.03 (t, <i>J</i> = 9.7 Hz)                          | 70.61,<br>70.18,<br>69.28,   | 5.22 (t)  | _                            | 5.07 (t)   | 70.5   |  |
| 5      |                                     |                              | _   |                              | 4.16–<br>4.25<br>(m)   | _   | 4.29 (ddd, J<br>= 10.0, 5.3,<br>2.7 Hz)              | 69.19,<br>62.38,<br>31.61,<br>31.14,<br>20.75,<br>20.63,<br>20.59,<br>20.54,<br>20.52, | _   |                              | 4.37–4.28<br>(m)                                     | 69.1   |  |

**Table 5** <sup>1</sup>H and <sup>13</sup>C NMR comparison of 6,6'-dibromo-6,6'-dideoxysucrose hexaacetate (4) with literature data

|        | 4 (con't)<br>CAS: 54484-76-3        |                              |   |                              |   |   |  |  |   |                              |  |  |
|--------|-------------------------------------|------------------------------|---|------------------------------|---|---|--|--|---|------------------------------|--|--|
|        | D.C.                                | 4                            | D.C.  | 3                            | · ·   | $(\partial$                               | in ppm and $J$ in                                  | n Hz)<br>59  | D   | 0                            |  |  |
| Assign | Kel Kel                             |                              | Kei   |                              | Ker   |   | Rei  | -  | Obse  | rved                         |  |  |
| ment   | $\delta^{1}$ H (CDCl <sub>3</sub> ) | $\delta^{13}$ C <sup>a</sup> | δ <sup>1</sup> H<br>(100<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta^{13}$ C <sup>a</sup> | $ \begin{array}{c} \delta ^{1} \mathrm{H} \\ (400 \\ \mathrm{MHz}, \\ \mathrm{DMSO-} \\ d_{6} \end{array} $ | $\delta^{13}C$ (100 MHz,<br>DMSO- $d^6$ ) | $\delta^{1}$ H<br>(500 MHz,<br>CDCl <sub>3</sub> ) | δ <sup>13</sup> C<br>(125<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta^{1}$ H<br>(90 MHZ,<br>C <sub>6</sub> D <sub>6</sub> ) | $\delta^{13}$ C <sup>a</sup> | $\delta^{1}$ H<br>(270 MHz,<br>CDCl <sub>3</sub> ) | δ <sup>13</sup> C<br>(67.5 MHz,<br>CDCl <sub>3</sub> ) |
| 6а     | 3.54 (m)                            |                              |   |                              | 3.58-   |   | 3.49 (dd , J<br>= 11.5, 2.7<br>Hz)                 |  |   |                              | 3.52 (dd)  |  |
| 6b     |                                     |                              |   |                              | 3.78<br>(m)   | 32.6                                      | 3.37(dd, <i>J</i> =<br>11.6, 5.4<br>Hz)            |  | _   |                              | 3.40 (dd)  | 31.1   |
| 1'a    |                                     |                              |   |                              | 4.16–<br>4.25   | 62.3                                      | 4.22 (d, J = 12.5 Hz)<br>4.19 (d, J = 12.5 Hz)     |  | 4.44 (d)  | -                            | 4.24 (s)   | 62.3   |
| l'b    |                                     | _                            | _   | _                            | (m)   |   | 12.4 Hz)   | 20.48  | 4.23 (d)  | _                            |  |  |
| 2'     | -                                   |                              |   |                              | _   | 103.4                                     | -  |  | _   |                              |  | 104.3  |
| 3'     |                                     |                              |   |                              | 5.40 (d,<br>J = 6.4<br>Hz)  | 75.8                                      | 5.39 (d, <i>J</i> = 5.1 Hz)                        |  | 5.60 (d)  |                              | 5.50–5.37<br>(m)                                   | 76.1   |
| 4'     |                                     |                              |   |                              | 5.31-<br>5.35<br>(m)  | 76.0                                      | 5.37 (t, <i>J</i> = 5.0 Hz)                        |  | 5.46 (t)  |                              | 5.50–5.37<br>(m)                                   | 77.0   |
| 5'     |                                     |                              |   |                              | 4.29–<br>4.33<br>(m)  | 79.5                                      | 4.25 (td, <i>J</i> = 6.7, 4.8 Hz)                  |  | _   |                              | 4.37–4.28<br>(m)                                   | 81.0   |

|                              |  |                    |   |                          |   | (δ  | $\frac{4 \text{ (con't)}}{\text{CAS: 54484-70}}$<br>in ppm and J in<br>(con't) | 5-3<br>n Hz)   |   |                  |  |  |
|------------------------------|--|--------------------|---|--------------------------|---|---|--|--|---|------------------|--|--|
| Assign                       | <b>Ref</b> <sup>1</sup>                | 4                  | <b>Ref</b> <sup>13</sup>                              | 3                        | ]   | <b>Ref</b> <sup>10</sup>                  | Ref  | Ref <sup>59</sup>  |   | 0                | Observed   |  |
| ment                         | $\delta^{1}$ H<br>(CDCl <sub>3</sub> ) | $\delta^{13}C^{a}$ | $\delta^{1}$ H<br>(100<br>MHz,<br>CDCl <sub>3</sub> ) | $\int_{13}^{\delta} C^a$ | $ \begin{array}{c} \delta \ ^{1}\text{H} \\ (400 \\ \text{MHz,} \\ \text{DMSO-} \\ d_{6}) \end{array} $ | $\delta^{13}C$ (100 MHz,<br>DMSO- $d^6$ ) | $\delta^{1}$ H<br>(500 MHz,<br>CDCl <sub>3</sub> )                             | δ <sup>13</sup> C<br>(125<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta^{1}$ H<br>(90 MHZ,<br>C <sub>6</sub> D <sub>6</sub> ) | $\delta^{13}C^a$ | δ <sup>1</sup> H<br>(270 MHz,<br>CDCl <sub>3</sub> ) | δ <sup>13</sup> C<br>(67.5 MHz,<br>CDCl <sub>3</sub> ) |
| 6'a<br>6'b                   | 3.54 (m)                               |                    | -   |                          | 3.58–<br>3.78 (m)   | 33.0                                      | 3.62 (d, <i>J</i> = 6.6 Hz)  |  | -   |                  | 3.65 (d)   | 31.5   |
| $J_{1,2}$                    |  |                    | 3.5   |                          | 3.3   |   |  |  | 4.0   |                  | 3.6  |  |
| $J_{2,3}$                    | -                                      |                    | 10.0  |                          | 10.5  |   |  |  | 10.0  |                  | 10.6   |  |
| $J_{3,4}$                    | -                                      |                    | 10.0  | -                        |   |   |  |  | 10.0  |                  | 9.7  |  |
| $J_{4,5}$                    | -                                      |                    | 9.5   |                          |   |   |  |  | 10.0  |                  | 9.7  |  |
| $J_{5,6a}$                   | -                                      | —                  |   | —                        |   |   |  | —  |   |                  | 3.0  |  |
| $J_{5,6b}$                   | -                                      |                    |   |                          |   | -   | -  |  | -   |                  | 5.6  | _  |
| $J_{6a,6b}$                  | -                                      |                    |   |                          | -   |   |  |  |   |                  | 11.5   |  |
| $J_{1'a,1'b}$<br>$J_{3',4'}$ |  |                    | _   |                          |   |   |  |  | 12.5<br>5.0   |                  | -  |  |
| $J_{4',5'}$<br>$J_{5',6'}$   |  |                    |   |                          |   |   |  |  | - 3.0   |                  | 6.6  |  |

|                 |                                     | $\begin{array}{c} 4 \text{ (con't)} \\ \text{CAS: 54484-76-3} \\ (\delta \text{ in ppm and } J \text{ in Hz}) \\ (\text{con't}) \end{array}$ |  |                              |  |   |  |  |   |                              |  |  |  |
|-----------------|-------------------------------------|--|--|------------------------------|--|---|--|--|---|------------------------------|--|--|--|
| Assign<br>ment  | Ref                                 | 4  | Ref <sup>13</sup>                                  | ;<br>                        | $\delta^{1}$ H                                   | Ref <sup>10</sup>                         | Ref  | a 13   | Ref <sup>o</sup>  | 0                            | Obse   | rved   |  |
|                 | $\delta^{1}$ H (CDCl <sub>3</sub> ) | $\int_{13}^{\delta} C^a$   | $\delta^{1}$ H (100<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta^{13}$ C <sup>a</sup> | (400<br>MHz,<br>DMSO-<br><i>d</i> <sub>6</sub> ) | $\delta^{13}C$ (100 MHz,<br>DMSO- $d^6$ ) | δ <sup>1</sup> H<br>(500 MHz,<br>CDCl <sub>3</sub> )                     | $\delta^{13}C$ (125<br>MHz,<br>CDCl <sub>3</sub> ) | δ <sup>1</sup> H<br>(90 MHZ,<br>C <sub>6</sub> D <sub>6</sub> ) | $\delta^{13}$ C <sup>a</sup> | δ <sup>1</sup> H<br>(270 MHz,<br>CDCl <sub>3</sub> ) | δ <sup>13</sup> C<br>(67.5 MHz,<br>CDCl <sub>3</sub> ) |  |
| CH <sub>3</sub> | 2.1 (m)                             | _  | 7.84-7.99  |                              | 1.95–<br>2.06 (m)                                | 20.5, 20.4,<br>20.3, 20.2,<br>20.1        | 2.14(s),<br>2.08 (s),<br>2.08 (s),<br>2.07 (s),<br>2.03 (s),<br>1.99 (s) | _  | _   | _                            | 2.18 (s),<br>2.16–2.09<br>(m), 2.07<br>(s), 2.02 (s) | 20.6, 20.5,<br>20.5, 20.4,<br>20.4, 20.4               |  |
| C=O             | _                                   |  | _  |                              | _  | 169.6,<br>169.2, 169.1                    | _  |  |   |                              | _  | 170.0,<br>169.9,<br>169.9,<br>169.7,<br>169.4          |  |

<sup>10</sup> Barros, M. T.; Petrova, K. T.; Correia-da-Silva, P.; Potewar, T. M.; Correia-Da-Silva, P.; Potewar, T. M.; Correia-da-Silvaa, P.; Potewar, T. M. *Green Chem.* 2011, *13*, 1897–1906.
 <sup>13</sup> Khan, R.; Lal Bhardwaj, C.; Mufti, K. S.; Jenner, M. R. *Carbohydr. Res.* 1980, *78*, 185–189.
 <sup>14</sup> Castro, B.; Chapleur, Y.; Gross, B. *Carbohydr. Res.* 1974, *36*, 412–419.
 <sup>59</sup> Lees, W. J.; Whitesides, G. M. *J. Am. Chem. Soc.* 1993, *115*, 1860–1869.
 <sup>60</sup> Hough, L.; Sinchareonkul, L. V.; Richardson, A. C.; Akhtar, F.; Drew, M. G. B. *Carbohydr. Res.* 1988, *174*, 145–160.

|                 |                        |                          |                        |              | 6                            |                                   |  |
|-----------------|------------------------|--------------------------|------------------------|--------------|------------------------------|-----------------------------------|--|
|                 |                        |                          |                        | CAS: 5       | 0271-00-6                    |                                   |  |
|                 |                        |                          | $(\delta$              | in ppm       | and $J$ in Hz)               |                                   |  |
| Assistant       | Ref <sup>5</sup>       | <b>Ref</b> <sup>11</sup> |                        |              | Obser                        | ved                               |  |
| Assignment      | $\delta^{1}\mathrm{H}$ | S                        | $\delta^{1}\mathrm{H}$ | 8            |                              | $\delta^{13}C^{a}$                |  |
|                 | (100                   | $^{13}C^{a}$             | (100                   | $^{13}C^{a}$ | $\delta$ $^{1}\mathrm{H}$    | 0°C<br>(67.5                      |  |
|                 | MHz,                   |                          | MHz,                   |              | (270 MHz,CDCl <sub>3</sub> ) | (07.5)<br>MHz CDCl <sub>2</sub> ) |  |
|                 | CDCl <sub>3</sub> )    |                          | CDCl <sub>3</sub> )    |              |                              |                                   |  |
| 1               |                        |                          | 5.64 (d)               |              | 5.64 (d)                     | 90.3                              |  |
| 2               |                        |                          | 4.86 (dd)              |              | 4.87 (dd)                    | 70.2                              |  |
| 3               |                        |                          | _                      |              | 5.49–5.40 (m)                | 69.4                              |  |
| 4               |                        |                          | 5.05 (t)               |              | 5.06 (t)                     | 68.2                              |  |
| 5               | _                      |                          |                        |              | 4.33–4.25 (m)                | 68.5                              |  |
| <u>6a</u>       |                        |                          |                        |              | 4.25–4.17 (m)                | 62.0                              |  |
| <u>6</u> b      |                        |                          | _                      |              | 4.13 (dd)                    | 02:0                              |  |
| <u>1'a</u>      |                        |                          |                        |              | 4.25–4.17 (m)                | 62.4                              |  |
| l'b             |                        |                          |                        |              |                              | 104.4                             |  |
| 2'              |                        |                          | 5552                   |              | —                            | 104.4                             |  |
| 3'              | 5.45 (q)               |                          | 3.3 - 3.3              |              | 5.49–5.40 (m)                | 76.0                              |  |
|                 |                        |                          | (11)                   |              |                              |                                   |  |
| 4'              | 4.35 (t)               |                          | (m)                    |              | 5.37 (t)                     | 76.5                              |  |
| 5'              |                        |                          |                        |              | 4.25–4.17 (m)                | 81.3                              |  |
| 6'a             |                        | _                        | 3 76 (d)               |              | 2 77 (d)                     | 43.0                              |  |
| 6′Ъ             |                        |                          | 3.70 (u)               |              | 5.77 (u)                     | 43.9                              |  |
| $J_{1,2}$       |                        |                          | 3.5                    |              | 3.6                          |                                   |  |
| $J_{2,3}$       | _                      |                          | 10.0                   |              | 10.2                         |                                   |  |
| $J_{3,4}$       |                        |                          | 9.5                    |              | 9.9                          |                                   |  |
| $J_{4,5}$       |                        |                          | 9.5                    |              | 9.9                          |                                   |  |
| $J_{5,6b}$      |                        |                          |                        |              | 2.0                          | -                                 |  |
| $J_{6a,6b}$     |                        |                          |                        |              | 12.2                         |                                   |  |
| $J_{3',4'}$     | 5.0                    |                          |                        |              | 5.1                          |                                   |  |
| $J_{4',5'}$     | 5.0                    |                          |                        |              | 5.1                          |                                   |  |
| $J_{5',6'}$     |                        |                          |                        |              | 6.6                          |                                   |  |
|                 | _                      |                          | _                      |              | 2.18 (s), 2.15–2.08          | 20.7. 20.6. 20.6                  |  |
| CH <sub>3</sub> |                        |                          |                        |              | (m), 2.05 (s), 2.02          | 20.5, 20.4                        |  |
|                 |                        |                          |                        |              | (\$)                         | 2010, 2011                        |  |
|                 |                        |                          |                        |              |                              | 170.6, 170.0,                     |  |
| C=O             | —                      |                          |                        |              | —                            | 169.9, 169.8,                     |  |
|                 |                        | 1                        |                        | 1            |                              | 169.5                             |  |

**Table 6** <sup>1</sup>H and <sup>13</sup>C NMR comparison of 6'-chloro-6'-deoxysucrose heptaacetate (6) with literature data

<sup>5</sup> Khan, R.; Jenner, M. R.; Mufti, K. S. *Carbohydr. Res.* **1975**, *39*, 253–262. <sup>11</sup> Ballard, J. M.; Hough, L.; Richardson, A. C.; Fairclough, P. H. J. Chem. Soc., Chem. Commun. **1972**, 1524–1528. <sup>a</sup> No previous literature data

|                    |              |              |            |              | -                         |                                     |  |  |
|--------------------|--------------|--------------|------------|--------------|---------------------------|-------------------------------------|--|--|
|                    |              |              |            | C            | 1                         |                                     |  |  |
|                    |              |              |            |              | AS: 54429-73-1            |                                     |  |  |
|                    | Def          | 5            | Def        | (0 in<br>4   | Obsorved                  |                                     |  |  |
| Assignment         |              |              | Kei        |              |                           | Observed                            |  |  |
| -                  | 0 H          | δ            | s lu       | δ            | $\delta$ $^{1}\mathrm{H}$ | s 13 <b>c</b> a                     |  |  |
|                    | (100<br>MII- | $^{13}C^{a}$ | $0 \Pi$    | $^{13}C^{a}$ | (270                      | 0 C                                 |  |  |
|                    | MHZ,         | _            | $(CDCI_3)$ | _            | MHz,CDCl <sub>3</sub> )   | $(67.5 \text{ MHz}, \text{CDCl}_3)$ |  |  |
|                    | 5 74         |              |            |              |                           |                                     |  |  |
| 1                  | 5.74         |              |            |              | 5.74 (d)                  | 89.6                                |  |  |
|                    | (0)          | -            |            |              |                           |                                     |  |  |
| 2                  | 4.85         |              |            |              | 4.87 (dd)                 | 70.0                                |  |  |
|                    | (q)          | -            | _          |              |                           |                                     |  |  |
| 3                  | 5.45         |              |            |              | 5.49–5.39 (m)             | 69.4                                |  |  |
|                    | (q)          | _            |            |              | <b>7</b> 1 4 (1)          |                                     |  |  |
| 4                  | 5.13 (t)     |              |            |              | 5.14 (t)                  | 69.2                                |  |  |
| 5                  | -            |              |            |              | 4.41–4.26 (m)             | 69.2                                |  |  |
| <u>6a</u>          | -            |              | 3.58 (m)   |              | 3.73 (dd)                 | 43.0                                |  |  |
| <u>6b</u>          | _            |              |            |              | 3.58 (dd)                 |                                     |  |  |
| <u>1'a</u>         | _            |              |            |              | 4.20(s)                   | 62.8                                |  |  |
| 1′b                | _            |              |            |              |                           |                                     |  |  |
| 2'                 |              | _            |            |              |                           | 103.7                               |  |  |
| 3'                 | 5.43         |              |            |              | 5 49–5 39 (m)             | 75 5                                |  |  |
|                    | (d)          | _            |            |              | 5.19 5.59 (III)           |                                     |  |  |
| 4'                 | 5.21 (t)     |              |            |              | 5.49–5.39 (m)             | 74.6                                |  |  |
| 5'                 |              | —            |            | —            | 4.25–4.21 (m)             | 78.8                                |  |  |
| 6'a                |              |              |            |              | 4.41 - 4.26 (m)           | 63 1                                |  |  |
| 6'b                |              |              |            |              | 4.41 4.20 (III)           | 05.1                                |  |  |
| $J_{1,2}$          | 3.5          |              | _          |              | 3.6                       |                                     |  |  |
| $J_{2,3}$          | 10.0         |              |            |              | 10.6                      |                                     |  |  |
| $J_{3,4}$          | 9.5          |              |            |              | 9.7                       |                                     |  |  |
| $J_{4,5}$          | 9.5          |              |            |              | 9.7                       |                                     |  |  |
| $J_{5,6a}$         |              |              |            |              | 3.0                       | _                                   |  |  |
| $J_{5,6b}$         | -            |              |            |              | 4.6                       |                                     |  |  |
| $J_{6a,6b}$        |              |              |            |              | 12.2                      |                                     |  |  |
| J <sub>3',4'</sub> | 6.0          | 1            |            |              |                           |                                     |  |  |
| $J_{4',5'}$        | 6.0          | ]            |            |              |                           |                                     |  |  |
|                    |              | 1            |            | 1            | 2.17 (s), 2.13-           |                                     |  |  |
| CH <sub>3</sub>    | 2.2-2.0      |              | 2.1 (m)    |              | 2.08 (m), 2.06            | 20.4, 20.4, 20.4                    |  |  |
| -                  |              |              |            |              | (s), 2.02 (s)             |                                     |  |  |
| 0.0                |              | 1            |            | 1            |                           | 170.2, 169.8, 169.7,                |  |  |
|                    | _            |              | -          |              | _                         | 169.6, 169.4, 169.1                 |  |  |

**Table 7** <sup>1</sup>H and <sup>13</sup>C NMR comparison of 6-chloro-6-deoxysucrose heptaacetate (7) with literature data

<sup>5</sup> Khan, R.; Jenner, M. R.; Mufti, K. S. *Carbohydr. Res.* **1975**, *39*, 253–262. <sup>14</sup> Castro, B.; Chapleur, Y.; Gross, B. *Carbohydr. Res.* **1974**, *36*, 412–419. <sup>a</sup>No previous literature data

|                 |   |                              | 8  |  |  |  |  |  |
|-----------------|---|------------------------------|--|--|--|--|--|--|
|                 |   |                              | CAS: 40984-14-3                                | 3  |  |  |  |  |
|                 |   | 4                            | $(\delta \text{ in ppm and } J \text{ in } F$  | Hz)  |  |  |  |  |
|                 | Ref   | +                            | Observed                                       |  |  |  |  |  |
| Assignment      | $\delta^{1}H$ (100<br>MHz,<br>acetone-<br>$d_{6}$ ) | $\delta^{13}$ C <sup>a</sup> | $\delta^{1}$ H<br>(270 MHz,CDCl <sub>3</sub> ) | δ <sup>13</sup> C<br>(67.5 MHz,CDCl <sub>3</sub> ) |  |  |  |  |
| 1               | 5.7 (d)   |                              | 5.68 (d)                                       | 90.3   |  |  |  |  |
| 2               | 4.86 (q)  |                              | 4.87 (dd)                                      | 70.1   |  |  |  |  |
| 3               | 5.46 (t)  |                              | 5.50–5.35 (m)                                  | 69.4   |  |  |  |  |
| 4               | 5.1 (t)   |                              | 5.10 (t)                                       | 69.5   |  |  |  |  |
| 5               |   |                              | 4.40–4.31 (m)                                  | 69.6   |  |  |  |  |
| ба              |   |                              | 3.67 (dd)                                      | 12.2   |  |  |  |  |
| бb              |   |                              | 3.56 (dd)                                      | 43.2   |  |  |  |  |
| 1'a             |   |                              | 1 23 (s)                                       | 62 /   |  |  |  |  |
| 1′b             |   |                              | 4.23 (3)                                       | 02.4   |  |  |  |  |
| 2'              |   |                              | _  | 104.4  |  |  |  |  |
| 3'              | 5.5 (d)   |                              | 5.50–5.35 (m)                                  | 75.9   |  |  |  |  |
| 4'              | 5.42 (t)  |                              | 5.50–5.35 (m)                                  | 76.4   |  |  |  |  |
| 5'              |   |                              | 4.29–4.24 (m)                                  | 81.3   |  |  |  |  |
| 6'              | _   | _                            | 3.79 (d)                                       | 44.0   |  |  |  |  |
| $J_{1,2}$       | 3.5   |                              | 3.6  |  |  |  |  |  |
| $J_{2,3}$       | 10.0  |                              | 10.2   |  |  |  |  |  |
| $J_{3,4}$       | 10.0  |                              | 9.7  |  |  |  |  |  |
| $J_{4,5}$       | 10.0  |                              | 9.7  |  |  |  |  |  |
| $J_{5,6a}$      | -   |                              | 3.0  | _  |  |  |  |  |
| $J_{5,6b}$      | _   |                              | 4.9  | _  |  |  |  |  |
| $J_{ m 6a,6b}$  |   |                              | 12.2   |  |  |  |  |  |
| $J_{3',4'}$     | 5.5   |                              | _  |  |  |  |  |  |
| $J_{4',5'}$     | 5.5   |                              | _  |  |  |  |  |  |
| $J_{5',6'}$     |   |                              | 6.3  |  |  |  |  |  |
| CH <sub>3</sub> |   |                              | 2.18 (s), 2.16–2.08 (m),<br>2.07 (s), 2.02 (s) | 20.7, 20.6, 20.5, 20.5, 20.4                       |  |  |  |  |
| C=O             |   |                              | _  | 170.0, 170.0, 169.7, 169.5,<br>169.3               |  |  |  |  |

**Table 8**  $^{1}$ H and  $^{13}$ C NMR comparison of 6,6'-dichloro-6,6'-dideoxysucrose hexaacetate (8) with literature data

<sup>4</sup> Hough, L.; Mufti, K. S. *Carbohydr. Res.* **1972**, 25, 497–503. <sup>a</sup> No previous literature data

|                 |                         |                | 10   |                              |  |  |  |  |
|-----------------|-------------------------|----------------|--|------------------------------|--|--|--|--|
|                 |                         |                | CAS: –   |                              |  |  |  |  |
| Assignment      |                         |                | $(\delta \text{ in ppm and } J \text{ in Hz})$ |                              |  |  |  |  |
| Assignment      | Ref <sup>a</sup>        |                | Obse   | erved                        |  |  |  |  |
|                 | $\delta$ <sup>1</sup> H | $\delta^{13}C$ | $\delta$ <sup>1</sup> H                        | $\delta^{13}C$               |  |  |  |  |
|                 | _                       | -              | (500 MHz,CDCl <sub>3</sub> )                   | (125 MHz,CDCl <sub>3</sub> ) |  |  |  |  |
| 1               |                         |                | 5.74–5.71 (m)                                  | 89.7                         |  |  |  |  |
| 2               |                         |                | 4.91 (dd)                                      | 69.9                         |  |  |  |  |
| 3               |                         |                | 5.47–5.40 (m)                                  | 69.6                         |  |  |  |  |
| 4               |                         |                | 5.08 (t)                                       | 68.0                         |  |  |  |  |
| 5               |                         |                | 4.34–4.26 (m)                                  | 68.4                         |  |  |  |  |
| ба              |                         |                | 4.34–4.26 (m)                                  | (1.(                         |  |  |  |  |
| 6b              |                         |                | 4.16 (d)                                       | 01.0                         |  |  |  |  |
| 1'a             |                         |                | 3.61 (d)                                       | 22.5                         |  |  |  |  |
| 1′b             |                         |                | 3.49 (d)                                       | 55.5                         |  |  |  |  |
| 2'              |                         |                | _  | 103.4                        |  |  |  |  |
| 3'              |                         |                | 5.74–5.71 (m)                                  | 76.1                         |  |  |  |  |
| 4'              |                         |                | 5.47–5.40 (m)                                  | 74.0                         |  |  |  |  |
| 5'              | _                       | -              | 4.24–4.20 (m)                                  | 78.9                         |  |  |  |  |
| 6'a             |                         |                |  | (2.1                         |  |  |  |  |
| 6'b             |                         |                | 4.34–4.26 (m)                                  | 03.1                         |  |  |  |  |
| $J_{1,2}$       |                         |                | 4.6  |                              |  |  |  |  |
| $J_{2,3}$       |                         |                | 10.3   |                              |  |  |  |  |
| $J_{4,5}$       |                         |                | 9.5  | _                            |  |  |  |  |
| $J_{6a,6b}$     |                         |                | 11.5   |                              |  |  |  |  |
| $J_{1'a,1'b}$   |                         |                | 12.0   |                              |  |  |  |  |
| , .             | 1                       |                | 2.17 (s), 2.12 (s), 2.11–                      |                              |  |  |  |  |
| CH <sub>3</sub> |                         |                | 2.09 (m), 2.08 (s), 2.04 (s),                  | 20.7, 20.6, 20.6, 20.5, 20.5 |  |  |  |  |
| -               |                         |                | 2.02 (s)                                       |                              |  |  |  |  |
| C 0             | 1                       |                |  | 170.6, 170.4, 170.0, 169.9,  |  |  |  |  |
| C=U             |                         |                | _  | 169.7. 169.6. 169.4          |  |  |  |  |

 Table 9 <sup>1</sup>H and <sup>13</sup>C NMR comparison of 1'-bromo-1'-deoxysucrose heptaacetate (10) with

 literature data

<sup>a</sup>No previous literature data

|                             |                 |              |                          | 11           |  |                 |  |
|-----------------------------|-----------------|--------------|--------------------------|--------------|--|-----------------|--|
|                             |                 |              | CAS                      | : 64644      | 4-61-7                                       |                 |  |
|                             | 0               |              | $(\delta \text{ in pp})$ | m and        | J in Hz)                                     |                 |  |
| Assignment                  | Ref             |              | Ref <sup>oo</sup>        | r            | Observed                                     |                 |  |
| 1 issignitione              | $\delta^{1}$ H  | δ            | $\delta$ 'H              | δ            | $\delta^{1}$ H                               | $\delta^{13}$ C |  |
|                             | (60 MHz in      | $^{13}C^{a}$ | (100                     | $^{13}C^{a}$ | (500   | (125            |  |
|                             | $CDCl_3$        | _            | MHz in                   | _            | MHz.CDCl <sub>3</sub> )                      | $MHz.CDCl_3$    |  |
|                             | 02 013)         |              | CDCl <sub>3</sub> )      |              | 1.1112,02 013)                               |                 |  |
| 1                           | _               |              | 5.71 (d)                 |              | 5.72 (d)                                     | 89.5            |  |
| 2                           | 4.89 (dd)       |              | 4.89 (q)                 |              | 4.91 (dd)                                    | 69.9            |  |
| 3                           | 5.45 (t)        |              | 5.44 (t)                 |              | 5.46–5.41 (m)                                | 69.6            |  |
| 4                           | 5.05 (t)        |              | 5.06 (t)                 |              | 5.08 (t)                                     | 68.0            |  |
| 5                           | 4.15-4.40 (m)   |              |                          |              | 4.36–4.27 (m)                                | 68.4            |  |
| 6a                          | 4.15.4.40 (m)   |              |                          |              | 4.36–4.27 (m)                                | 61 5            |  |
| 6b                          | 4.13-4.40 (111) |              | -                        |              | 4.16 (dd)                                    | 01.5            |  |
| 1′a                         | 3.48 (d)        |              |                          |              | 3.74 (d)                                     | 15 2            |  |
| 1′b                         | 3.75 (d)        |              |                          |              | 3.57 (d)                                     | 43.5            |  |
| 2'                          | _               |              | _                        |              | _  | 103.9           |  |
| 3'                          | 5.65 (d)        |              | 5.68 (d)                 |              | 5.69 (d)                                     | 75.4            |  |
| 4'                          | 5.40(t)         |              | 5.4 (t)                  |              | 5.46–5.41 (m)                                | 73.9            |  |
| 5'                          | 4.15-4.40 (m)   |              |                          |              | 4.22 (td)                                    | 78.9            |  |
| 6'a                         | 4.15-4.40 (m)   |              | -                        |              | 4.36–4.27 (m)                                | 63.0            |  |
| <u>6'b</u>                  |                 |              |                          |              |  |                 |  |
| $J_{1,2}$                   | 4.1             |              | 3.5                      |              | 4.0  |                 |  |
| $J_{2,3}$                   | 10              | —            | 10.0                     | _            | 10.3   |                 |  |
| $J_{3,4}$                   | 9 or 10         |              | 9.5                      |              |  |                 |  |
| $J_{4,5}$                   | 9               |              | 9.5                      |              | 9.7  |                 |  |
| $J_{5,6a}$                  |                 |              |                          |              | • •  |                 |  |
| J <sub>5,6b</sub>           | -               |              | _                        |              | 2.9  | -               |  |
| J <sub>6a,6b</sub>          | 10              |              |                          |              | 13.2   |                 |  |
| <i>J</i> <sub>1'a,1'b</sub> | 12              |              |                          |              | 12.0   |                 |  |
| $J_{3',4'}$                 | 6.5 or 7        |              | 6.5                      |              | 6.3  |                 |  |
| $J_{4',5'}$                 | 7               |              | 6.5                      |              | 6.4  |                 |  |
| $J_{5',6'}$                 |                 |              | -                        |              | 3.6  |                 |  |
|                             | 1.98 (s), 1.99  |              |                          |              | 218(s) 213(s)                                |                 |  |
| CH <sub>2</sub>             | (s), 2.00 (s),  |              | 7.84-8.01                |              | 2.10(s), 2.13(s), 2.13(s), 2.10(s), 2.07(s). | 20.6, 20.6,     |  |
| CITy                        | 2.01(s), 2.08   |              | /.0101                   |              | 2.04(s), 2.02(s)                             | 20.6, 20.5      |  |
|                             | (s)             |              |                          |              | (5),(5)                                      |                 |  |
|                             |                 |              |                          |              |  | 170.6, 170.4,   |  |
| C=O                         | _               |              | _                        |              | _  | 170.0, 169.9,   |  |
|                             |                 |              |                          |              |  | 169.8, 169.6,   |  |
|                             |                 |              |                          |              |  | 169.4           |  |

 Table 10
 <sup>13</sup>C NMR comparison of 1'-chloro-1'-deoxysucrose heptaacetate (11) with

 literature data

<sup>8</sup> Gus, R. D. G.; Guthrie, R. D.; Jenkins, I. D.; Watters, J. J. *Autr. J. Chem.* **1980**, *33*, 2487–2497. <sup>68</sup> Khan, R.; Jenner, M. R.; Lindseth, H. *Carbohydr. Res.* **1980**, *78*, 173–183. <sup>a</sup> No previous literature data

|                 | <b>13</b><br>CAS: 55832-20-7<br>(δ in ppm and <i>L</i> in Hz) |                              |   |                              |  |  |
|-----------------|---|------------------------------|---|------------------------------|--|--|
| Assignment      | Ref <sup>5</sup>  |                              | <b>Ref</b> <sup>79</sup>  |                              | Observed   |  |
|                 | $\delta^{1}$ H<br>(100 MHz in<br>CDCl <sub>3</sub> )          | $\delta^{13}$ C <sup>a</sup> | $\delta^{1}$ H<br>(100<br>MHz in<br>C <sub>6</sub> D <sub>6</sub> ) | $\delta^{13}$ C <sup>a</sup> | $\delta^{1}$ H (500 MHz,CDCl <sub>3</sub> )          | $\delta^{13}C$ (125<br>MHz,CDCl <sub>3</sub> ) |
| 1               | 5.7 (d)   |                              | 5.79 (d)  |                              | 5.68 (d)   | 90.6   |
| 2               | 5.5–5.23 (m)  |                              | 5.56 (q)  |                              | 5.31–5.28 (m)  | 67.9   |
| 3               | 5.5–5.23 (m)  |                              | 5.68 (q)  |                              | 5.31–5.28 (m)  | 66.8   |
| 4               | 5.5–5.23 (m)  |                              |   |                              | 4.60–4.54 (m)  | 58.9   |
| 5               |   |                              |   |                              | 4.60–4.54 (m)  | 67.7   |
| 6a<br>6b        |   |                              | _   |                              | 4.28–4.21 (m)  | 63.5   |
| 1'a<br>1'h      | _   |                              |   |                              | 3.71 (d)<br>3.60 (d)                                 | 44.4   |
| 2'              |   |                              |   |                              | 5.00 (u)   | 104.3  |
| 3'              | 5 68 (d)  |                              | 5 78 (d)  |                              | 5 70 (d)   | 75.8   |
| 4'              | 5.00(a)   |                              | 5.38(t)   |                              | 5 41 (t)   | 76.0   |
| 5'              |   |                              |   |                              | 4.28–4.21 (m)  | 80.7   |
| 6'a             | _   |                              |   |                              |  |  |
| 6'b             |   |                              |   |                              | 3.77 (d)   | 43.8   |
| $J_{1,2}$       | 3.0   | -                            | 4.0   | _                            | 1.7  |  |
| $J_{2,3}$       |   |                              | 11.0  |                              |  |  |
| $J_{3,4}$       |   |                              | 3.5   |                              |  |  |
| $J_{4,5}$       |   |                              |   |                              | -  |  |
| $J_{5,6a}$      | _   |                              |   |                              |  |  |
| $J_{5,6b}$      |   |                              | _   |                              |  |  |
| $J_{1'a,1'b}$   |   |                              |   |                              | 12.0   |  |
| $J_{3',4'}$     | 6.0   |                              | 7.0   |                              | 6.3  |  |
| $J_{4',5'}$     | 6.0   |                              | 7.0   |                              | 6.3  |  |
| $J_{5',6'}$     | _   |                              | _   |                              | 5.7  |  |
| CH <sub>3</sub> | 7.84-7.95   |                              | 7.85–7.92   |                              | 2.15(s), 2.14(s),<br>2.12 (s), 2.10 (s),<br>2.10 (s) | 20.8, 20.7,<br>20.7, 20.5                      |
| C=O             | -   |                              | _   |                              | _  | 170.4, 170.0,<br>169.8, 169.6                  |

**Table 11** <sup>1</sup>H and <sup>13</sup>C NMR comparison of sucralose pentaacetate (**13**) with literature data

<sup>5</sup> Khan, R.; Jenner, M. R.; Mufti, K. S. *Carbohydr. Res.* **1975**, *39*, 253–262. <sup>79</sup> Fairclough, P. H.; Hough, L.; Richardson, A. C. *Carbohydr. Res.* **1975**, *40*, 285–298. <sup>a</sup> No previous literature data.
|                         |                                       |                | 14<br>CAS                               |                                   |  |  |  |  |  |
|-------------------------|---------------------------------------|----------------|---|-----------------------------------|--|--|--|--|--|
|                         | $(\delta \text{ in ppm and } Lin Hz)$ |                |   |                                   |  |  |  |  |  |
| Assignment              |                                       | . ca           | ( <i>o</i> in ppm and <i>J</i> in Hz,   | )                                 |  |  |  |  |  |
| U                       | K S I I I                             |                | Obse                                    | rvea                              |  |  |  |  |  |
|                         | ∂ 'H                                  | $\delta^{13}C$ | δ'H                                     | $\delta^{13}C$                    |  |  |  |  |  |
|                         |                                       | —              | $(500 \text{ MHz}, \text{D}_2\text{O})$ | $(125 \text{ MHz}, D_2 \text{O})$ |  |  |  |  |  |
| 1                       |                                       |                | 5.34 (d)                                | 92.4                              |  |  |  |  |  |
| 2                       |                                       |                | 3.50 (dd)                               | 71.1                              |  |  |  |  |  |
| 3                       |                                       |                | 3.73–3.66 (m)                           | 72.6                              |  |  |  |  |  |
| 4                       |                                       |                | 3.36 (t)                                | 69.5                              |  |  |  |  |  |
| 5                       |                                       |                | 3.84–3.78 (m)                           | 72.7                              |  |  |  |  |  |
| 6a                      |                                       |                | 3.84–3.78 (m)                           | 60.5                              |  |  |  |  |  |
| 6b                      |                                       |                | 3.73–3.66 (m)                           | 00.5                              |  |  |  |  |  |
| 1'                      |                                       |                | 3.64 (brs)                              | 61.0                              |  |  |  |  |  |
| 2'                      |                                       |                | _                                       | 103.9                             |  |  |  |  |  |
| 3'                      | _                                     | —              | 4.17 (d)                                | 76.6                              |  |  |  |  |  |
| 4'                      |                                       |                | 4.04 (t)                                | 77.0                              |  |  |  |  |  |
| 5'                      |                                       |                | 4.02–3.98 (m)                           | 80.8                              |  |  |  |  |  |
| 6'                      |                                       |                | 3.73–3.66 (m)                           | 33.2                              |  |  |  |  |  |
| $J_{1,2}$               |                                       |                | 4.0                                     |                                   |  |  |  |  |  |
| $J_{2,3}$               |                                       |                | 9.7                                     |                                   |  |  |  |  |  |
| $J_{3,4}$               |                                       |                | 9.7                                     |                                   |  |  |  |  |  |
| $J_{4,5}$               |                                       |                | 9.7                                     | -                                 |  |  |  |  |  |
| J <sub>3',4'</sub>      |                                       |                | 8.0                                     |                                   |  |  |  |  |  |
| $J_{4^\prime,5^\prime}$ |                                       |                | 8.0                                     |                                   |  |  |  |  |  |

**Table 12** <sup>1</sup>H and <sup>13</sup>C NMR comparison of 6'-bromo-6'-deoxysucrose (14) with literature data

<sup>a</sup> No previous literature data

|                 | 15<br>CAS: 99789-72-7 |                                       |                                     |                             |  |  |  |  |
|-----------------|-----------------------|---------------------------------------|-------------------------------------|-----------------------------|--|--|--|--|
|                 |                       | $(\delta \text{ in } r)$              | $J = \frac{1}{2} J = \frac{1}{2} J$ |                             |  |  |  |  |
| Assignment      |                       | <b>Ref</b> <sup>14</sup>              | Obse                                | erved                       |  |  |  |  |
|                 | $\delta^{1}H^{a}$     | $\delta^{13} \mathrm{C}^{\mathrm{b}}$ | $\delta^{1}\mathrm{H}$              | $\delta^{13}$ C             |  |  |  |  |
|                 | (CDCl <sub>3</sub> )  | -                                     | (500 MHz, D <sub>2</sub> O)         | (125 MHz, D <sub>2</sub> O) |  |  |  |  |
| 1               |                       |                                       | 5.38 (d)                            | 92.1                        |  |  |  |  |
| 2               |                       |                                       | 3.55 (dd)                           | 71.0                        |  |  |  |  |
| 3               | _                     |                                       | 3.76–3.71 (m)                       | 72.1                        |  |  |  |  |
| 4               |                       |                                       | 3.47 (t)                            | 71.2                        |  |  |  |  |
| 5               |                       |                                       | 3.99 (dt)                           | 70.7                        |  |  |  |  |
| <u>6a</u>       | 3.54 (m)              |                                       | 3.76–3.71 (m)                       | 33.4                        |  |  |  |  |
| 6b              | . ,                   |                                       |                                     | <i>c</i> 1 4                |  |  |  |  |
| <u> </u>        |                       |                                       | 3.63 (brs)                          | 61.4                        |  |  |  |  |
| 2'              |                       |                                       | _                                   | 103.7                       |  |  |  |  |
| 3'              |                       |                                       | 4.18 (d)                            | 76.2                        |  |  |  |  |
| 4'              |                       | _                                     | 4.05 (t)                            | 74.0                        |  |  |  |  |
| 5'              |                       |                                       | 3.86 (td)                           | 81.3                        |  |  |  |  |
| 6'              |                       |                                       | 3.81–3.76 (m)                       | 62.5                        |  |  |  |  |
| $J_{1,2}$       |                       |                                       | 4.0                                 |                             |  |  |  |  |
| $J_{2,3}$       | _                     |                                       | 9.7                                 |                             |  |  |  |  |
| $J_{3,4}$       |                       |                                       | 9.7                                 |                             |  |  |  |  |
| $J_{4,5}$       |                       |                                       | 9.7                                 |                             |  |  |  |  |
| $J_{5,6}$       |                       |                                       | 3.4                                 | -                           |  |  |  |  |
| $J_{3',4'}$     |                       |                                       | 8.6                                 |                             |  |  |  |  |
| $J_{4',5'}$     |                       |                                       | 8.6                                 |                             |  |  |  |  |
| $J_{5',6'}$     |                       |                                       | 3.4                                 |                             |  |  |  |  |
| CH <sub>3</sub> | 2.1 (m)               |                                       | _                                   |                             |  |  |  |  |

**Table 13** <sup>1</sup>H and <sup>13</sup>C NMR comparison of 6-bromo-6-deoxysucrose (15) with literature data

<sup>14</sup> Castro, B.; Chapleur, Y.; Gross, B. *Carbohydr. Res.* **1974**, *36*, 412–419. <sup>a</sup> Assigned as 6bromo-6-deoxysucrose heptaacetate (**3**). <sup>b</sup>No previous literature data

|             | <b>16</b><br>CAS: 33585-15-8<br>(δ in ppm and <i>L</i> in Hz) |  |   |  |  |  |  |  |  |
|-------------|---|--|---|--|--|--|--|--|--|
| Assignment  | Re  | (0 in ppin a                                 | Observed                                    |  |  |  |  |  |  |
|             | $\delta^{1}$ H<br>(400 MHz in<br>D <sub>2</sub> O)            | $\delta^{13}$ C (100 MHz, D <sub>2</sub> O ) | $\delta^{1}$ H (500 MHz, D <sub>2</sub> O ) | $\delta^{13}$ C (125 MHz, D <sub>2</sub> O ) |  |  |  |  |  |
| 1           | 5.39 (d, <i>J</i> = 3.9<br>Hz)                                | 92.4   | 5.35 (d)                                    | 92.3   |  |  |  |  |  |
| 2           | 3.56 (dd)   | 71.0   | 3.52 (dd)                                   | 71.0   |  |  |  |  |  |
| 3           | 3.64–3.69 (m)   | 72.1   | 3.75–3.69 (m)                               | 72.0   |  |  |  |  |  |
| 4           | 3.42 (t, <i>J</i> = 9.4<br>Hz)                                | 71.5   | 3.42 (t)                                    | 71.4   |  |  |  |  |  |
| 5           | 4.01–4.06 (m)   | 71.2   | 4.01–4.00 (m)                               | 71.0   |  |  |  |  |  |
| 6a<br>6b    | 3.70–3.79 (m)   | 33.4   | 3.69–3.65 (m)<br>3.63–3.60 (m)              | 33.3   |  |  |  |  |  |
| 1'a<br>1'b  | 3.64–3.69 (m)   | 61.2   | 3.64 (brs)                                  | 61.1   |  |  |  |  |  |
| 2'          | _   | 103.9  | _   | 103.8  |  |  |  |  |  |
| 3'          | 4.20 (d, <i>J</i> = 8.5<br>Hz)                                | 76.6   | 4.17 (d)                                    | 76.4   |  |  |  |  |  |
| 4'          | 4.11 (t, <i>J</i> = 8.0<br>Hz)                                | 76.7   | 4.08 (t)                                    | 76.6   |  |  |  |  |  |
| 5'          | 4.01–4.06 (m)   | 80.5   | 4.01–4.00 (m)                               | 80.5   |  |  |  |  |  |
| 6'          | 3.70–3.79 (m)   | 33.4   | 3.75–3.69 (m)                               | 33.2   |  |  |  |  |  |
| $J_{1,2}$   | 3.9   |  | 4.0   |  |  |  |  |  |  |
| $J_{2,3}$   | 9.9   |  | 9.7   |  |  |  |  |  |  |
| $J_{3,4}$   |   | _  | 9.5   | _  |  |  |  |  |  |
| $J_{4,5}$   | _   |  | 9.5   |  |  |  |  |  |  |
| $J_{3',4'}$ |   |  | 8.6   |  |  |  |  |  |  |
| $J_{4',5'}$ |   |  | 8.6   |  |  |  |  |  |  |

 Table 14
 <sup>1</sup>H and <sup>13</sup>C NMR comparison of 6,6'-dibromo-6,6'-dideoxysucrose (16) with

 literature data

<sup>10</sup> Barros, M. T.; Petrova, K. T.; Correia-da-Silvaa, P.; Potewar, T. M.; Correia-Da-Silva, P.; Potewar, T. M.; Correia-da-Silvaa, P.; Potewar, T. M. *Green Chem.* **2011**, *13*, 1897–1906.

|              | <b>17</b><br>CAS: 50270-99-0      |  |  |   |  |  |  |  |
|--------------|-----------------------------------|--|--|---|--|--|--|--|
| Assignment   |                                   | $(\delta \text{ in ppm an})$             | d J in Hz)                                 |   |  |  |  |  |
|              | R                                 | ef <sup>81a</sup>                        | Observ                                     | ved   |  |  |  |  |
|              | $\delta^{1}$ H (D <sub>2</sub> O) | $\delta^{13}$ C (D <sub>2</sub> O)       | $\delta^{1}$ H (500 MHz, D <sub>2</sub> O) | $\delta^{13}$ C<br>(125 MHz,<br>D <sub>2</sub> O) |  |  |  |  |
| 1            | _                                 |  | 5.33 (d)                                   | 92.3  |  |  |  |  |
| 2            | 3.56 (d)                          |  | 3.49 (dd)                                  | 71.0  |  |  |  |  |
| 3            | 3.76 (t)                          |  | 3.73–3.66 (m)                              | 72.5  |  |  |  |  |
| 4            | 3.43 (t)                          |  | 3.36 (t)                                   | 69.4  |  |  |  |  |
| 5            |                                   |  | 3.85–3.77 (m)                              | 72.6  |  |  |  |  |
| 6a           | 302382(m)                         | $104 \in 91 = 77 1$                      | 3.85–3.77 (m)                              | 60.3  |  |  |  |  |
| 6b           | 5.92–5.82 (III)                   | $104.0, \delta 1.3, 77.1, 767, 732, 717$ | 3.73–3.66 (m)                              | 00.3  |  |  |  |  |
| 1'a<br>1'b   | 3.71 (s)                          | 70.2, 61.8,                              | 3.64 (brs)                                 | 60.9  |  |  |  |  |
| 2'           | _                                 | 61.1, 45.9                               | _  | 103.8   |  |  |  |  |
| 3'           | 4.24 (d)                          |  | 4.17 (d)                                   | 76.3  |  |  |  |  |
| 4'           | 4.13 (t)                          |  | 4.06 (t)                                   | 75.9  |  |  |  |  |
| 5'           | 4.04 (dt)                         |  | 3.97 (dd)                                  | 80.7  |  |  |  |  |
| 6'a<br>6'b   | 3.92–3.82 (m)                     |  | 3.85–3.77 (m)                              | 45.1  |  |  |  |  |
| $J_{1,2}$    |                                   |  | 3.4  |   |  |  |  |  |
| $J_{2,3}$    | 9.6                               |  | 9.7  |   |  |  |  |  |
| $J_{3,4}$    | 9.6                               |  | 9.7  |   |  |  |  |  |
| $J_{4,5}$    | 9.6                               | _  | 9.7  | -   |  |  |  |  |
| $J_{3',4'}$  | 8.3                               |  | 8.6  | 1   |  |  |  |  |
| $J_{4',5'}$  | 8.3                               |  | 8.6  |   |  |  |  |  |
| $J_{5',6'a}$ | 5.6                               |  | 5.7  |   |  |  |  |  |

**Table 15** <sup>1</sup>H and <sup>13</sup>C NMR comparison of 6'-chloro-6'-deoxysucrose (17) with literature data

<sup>81</sup> Kakinuma, H.; Yuasa, H.; Hashimoto, H. *Carbohydr. Res.* **1998**, *312*, 103–115. <sup>a</sup>[1-<sup>2</sup>H]-6'chloro-6'deoxysucrose.

|                 | 18   |         |                               |           |                           |                   |  |  |  |  |
|-----------------|--|---------|-------------------------------|-----------|---------------------------|-------------------|--|--|--|--|
|                 |  |         | CAS                           | 5: 40984- | 18-7                      |                   |  |  |  |  |
|                 | $(\delta \text{ in ppm and } J \text{ in Hz})$ |         |                               |           |                           |                   |  |  |  |  |
| Assignment      | $\mathbf{Ref}^4$                               |         | <b>Ref</b> <sup>5</sup>       |           | Observed                  |                   |  |  |  |  |
|                 | s <sup>1</sup> u <sup>a</sup>                  | s 13 Cb | $\delta \ ^{1}\mathrm{H^{c}}$ | s 13 Cb   | $\delta$ $^{1}\mathrm{H}$ | $\delta^{13}$ C   |  |  |  |  |
|                 | 0 11   | 0 C     | (100 MHz,                     | 0 C       | (500 MHz,                 | (125 MHz,         |  |  |  |  |
|                 | _  | _       | CDCl <sub>3</sub> )           | _         | $D_2O)$                   | D <sub>2</sub> O) |  |  |  |  |
| 1               |  |         | 5.74 (d)                      |           | 5.36 (d)                  | 92.1              |  |  |  |  |
| 2               |  |         | 4.85 (q)                      |           | 3.52 (dd)                 | 71.0              |  |  |  |  |
| 3               |  |         | 5.45 (q)                      |           | 3.72–3.69 (m)             | 72.1              |  |  |  |  |
| 4               |  |         | 5.13 (t)                      |           | 3.47 (t)                  | 69.9              |  |  |  |  |
| 5               |  |         |                               |           | 4.05 (dt)                 | 71.3              |  |  |  |  |
| ба              |  |         |                               |           | 2.96 + 2.92 (m)           | 44.2              |  |  |  |  |
| 6b              |  |         | _                             |           | 5.80–5.82 (III)           | 44.2              |  |  |  |  |
| 1'              |  |         |                               |           | 3.61 (brs)                | 61.3              |  |  |  |  |
| 2'              |  |         |                               |           | _                         | 103.7             |  |  |  |  |
| 3'              |  |         | 5.43 (d)                      |           | 4.16 (d)                  | 76.1              |  |  |  |  |
| 4'              |  |         | 5.21 (t)                      |           | 4.00 (t)                  | 74.0              |  |  |  |  |
| 5'              | _  | _       |                               | ] _       | 3.86–3.82 (m)             | 81.3              |  |  |  |  |
| 6'              |  |         | _                             |           | 3.77 (d)                  | 62.5              |  |  |  |  |
| $J_{1,2}$       |  |         | 3.5                           |           | 3.4                       |                   |  |  |  |  |
| $J_{2,3}$       |  |         | 10.0                          |           | 9.7                       |                   |  |  |  |  |
| $J_{3,4}$       |  |         | 9.5                           |           | 9.7                       |                   |  |  |  |  |
| $J_{4,5}$       |  |         | 9.5                           |           | 9.7                       |                   |  |  |  |  |
| $J_{5,6a}$      |  |         |                               |           | 3.2                       |                   |  |  |  |  |
| $J_{5,6b}$      |  |         | _                             |           |                           | —                 |  |  |  |  |
| $J_{3',4'}$     |  |         | 6.0                           |           | 8.6                       |                   |  |  |  |  |
| $J_{4',5'}$     |  |         | 6.0                           |           | 8.6                       |                   |  |  |  |  |
| $J_{5',6'}$     |  |         | _                             |           | 2.9                       |                   |  |  |  |  |
| CH <sub>3</sub> | 1  |         | 7.8-8.0                       |           | _                         |                   |  |  |  |  |

**Table 16** <sup>1</sup>H and <sup>13</sup>C NMR comparison of 6-chloro-6-deoxysucrose (18) with literature data

<sup>4</sup> Hough, L.; Mufti, K. S. *Carbohydr. Res.* **1972**, *25*, 497–503. <sup>5</sup> Khan, R.; Jenner, M. R.; Mufti, K. S. *Carbohydr. Res.* **1975**, *39*, 253–262. <sup>a</sup>Not assigned. <sup>b</sup>No previous literature data. <sup>c</sup> Assigned as 6-chloro-6-deoxysucrose heptaacetate (**6**).

|             |   |                                   |                        | 10  |  |                                     |  |
|-------------|---|-----------------------------------|------------------------|---|--|-------------------------------------|--|
|             |   |                                   | CAR                    | <b>19</b>   |  |                                     |  |
|             |   | (                                 | CAS                    | : 40984-16-5  | ,                                      |                                     |  |
| Assignment  | <b>D</b> <sub>c</sub>                     | (<br><b>1</b> 0                   | o m pl                 | $\frac{\text{Diff} a \text{III} \mathbf{J} \text{III} \mathbf{\Pi} \mathbf{Z}_{j}}{\mathbf{P}_{o} \mathbf{f}^{69}}$ | Observed                               |                                     |  |
| Assignment  | s <sup>1</sup> u                          | $\delta^{13}C$                    | s                      | Nei   | s <sup>1</sup> u                       | $\delta^{13}C$                      |  |
|             |   | 0 C                               | $1$ $\mathbf{\mu}^{a}$ | $\delta^{13}$ C   | 0 H<br>(500                            | 0 C                                 |  |
|             | (400<br>MH <sub>2</sub> D <sub>2</sub> O) | $(100 \text{ MHz}, D_{2} \Omega)$ | 11                     | (D <sub>2</sub> O)  | (300 MH <sub>2</sub> D <sub>2</sub> O) | $(125 \text{ MHZ}, D_{2} \text{O})$ |  |
|             | 5.31 (d I -                               | D <sub>2</sub> O)                 | _                      |   | $MIIZ, D_2O)$                          | D <sub>2</sub> O)                   |  |
| 1           | 3.51 (u, J = 3.6  Hz)                     | 92.7                              |                        | 93.0  | 5.39 (d)                               | 92.3                                |  |
| 2           | 3.47 (dd)                                 | 71.4                              |                        | 73.2  | 3.55 (dd)                              | 71.0                                |  |
| 3           | 3.67 (t)                                  | 72.0                              |                        | 72.6  | 3.74 (t)                               | 72.1                                |  |
| 4           | 3.40 (t)                                  | 70.5                              |                        | 71.4  | 3.48 (t)                               | 70.1                                |  |
| 5           | 4.04 (m)                                  | 72.5                              |                        | 72.0  | 4.14-4.08                              | 71.6                                |  |
|             |   |                                   | -                      |   | (m)                                    |                                     |  |
| <u>6a</u>   | 3.78 (m)                                  | 44.7                              |                        | 45.4  | 3.91–3.84                              | 44.3                                |  |
| 60          |   |                                   | -                      |   | (m)                                    |                                     |  |
| <u>l'a</u>  | 3.59 (d, J =                              | 61.5                              |                        | 62.4  | 3.67 (brs)                             | 61.2                                |  |
| l'b         | 1.7 Hz)                                   | 1010                              | -                      | 1010  | X /                                    | 102.0                               |  |
| 2'          | -   | 104.3                             | -                      | 104.8   | -                                      | 103.9                               |  |
| 3'          | 4.13 (d)                                  | 76.7                              |                        | 77.7  | 4.21 (d)                               | 76.3                                |  |
| 4′          | 3.92 (m)                                  | 76.0                              |                        | 81.6  | 4.14–4.08<br>(m)                       | 75.6                                |  |
| 5'          | 4.04 (m)                                  | 81.0                              |                        | 76.9  | 4.00 (td)                              | 80.7                                |  |
| 6'          | 3.78 (m)                                  | 15 5                              |                        | 16.2  | 3.84-3.78                              | 45.2                                |  |
| 0           | 5.78 (III)                                | 45.5                              |                        | 40.2  | (m)                                    | 45.2                                |  |
| $J_{1,2}$   | 3.7                                       |                                   |                        |   | 4.0                                    |                                     |  |
| $J_{2,3}$   | 9.9                                       |                                   |                        |   | 9.7                                    |                                     |  |
| $J_{3,4}$   | 9.5 or 9.6                                |                                   |                        |   | 9.7                                    |                                     |  |
| $J_{4,5}$   | 9.5                                       | _                                 |                        | _   | 9.7                                    | _                                   |  |
| $J_{3',4'}$ | 8.6                                       |                                   |                        |   | 8.6                                    |                                     |  |
| $J_{4',5'}$ |   |                                   |                        |   | 8.0                                    |                                     |  |
| $J_{5',6'}$ |   |                                   |                        |   | 3.4                                    |                                     |  |

**Table 17** <sup>1</sup>H and <sup>13</sup>C NMR comparison of 6,6'-dichloro-6,6'-dideoxysucrose (**19**) with literature data

<sup>10</sup> Barros, M. T.; Petrova, K. T.; Correia-da-Silva, P.; Potewar, T. M.; Correia-Da-Silva, P.; Potewar, T. M.; Correia-da-Silvaa, P.; Potewar, T. M. *Green Chem.* **2011**, *13*, 1897–1906. <sup>69</sup> Hough, L.; Phadnis, S. P.; Tarelli, E. *Carbohydr. Res.* **1976**, *47*, 151–154. <sup>a</sup> Not assigned

|             |  |                  | 20                          |                             |  |  |  |  |  |
|-------------|--|------------------|-----------------------------|-----------------------------|--|--|--|--|--|
|             |  |                  | $CAS^{-}$                   |                             |  |  |  |  |  |
|             | $(\delta \text{ in ppm and } J \text{ in Hz})$ |                  |                             |                             |  |  |  |  |  |
| Assignment  | r  | ef. <sup>a</sup> | Obse                        | erved                       |  |  |  |  |  |
|             | $\delta^{1}\mathrm{H}$                         | $\delta^{13}C$   | $\delta^{1}\mathrm{H}$      | $\delta^{13}$ C             |  |  |  |  |  |
|             | _  | _                | (500 MHz, D <sub>2</sub> O) | (125 MHz, D <sub>2</sub> O) |  |  |  |  |  |
| 1           |  |                  | 5.40 (d)                    | 92.7                        |  |  |  |  |  |
| 2           |  |                  | 3.52 (dd)                   | 71.1                        |  |  |  |  |  |
| 3           |  |                  | 3.73–3.69 (m)               | 72.7                        |  |  |  |  |  |
| 4           |  |                  | 3.44 (t)                    | 69.4                        |  |  |  |  |  |
| 5           |  |                  | 3.82–3.76 (m)               | 72.7                        |  |  |  |  |  |
| 6           |  |                  | 3.82–3.76 (m)               | 60.2                        |  |  |  |  |  |
| 1'a         |  |                  | 3.73–3.69 (m)               | 32 6                        |  |  |  |  |  |
| 1′b         |  |                  | 3.63 (brs)                  | 32.0                        |  |  |  |  |  |
| 2'          |  |                  | _                           | 102.8                       |  |  |  |  |  |
| 3'          |  |                  | 4.42 (d)                    | 77.0                        |  |  |  |  |  |
| 4'          | _  | _                | 4.01 (t)                    | 73.6                        |  |  |  |  |  |
| 5'          |  |                  | 3.87 (td)                   | 81.9                        |  |  |  |  |  |
| 6'          |  |                  | 3.82–3.76 (m)               | 62.1                        |  |  |  |  |  |
| $J_{1,2}$   |  |                  | 4.0                         |                             |  |  |  |  |  |
| $J_{2,3}$   |  |                  | 9.7                         |                             |  |  |  |  |  |
| $J_{3,4}$   |  |                  | 9.7                         |                             |  |  |  |  |  |
| $J_{4,5}$   |  |                  | 9.7                         | -                           |  |  |  |  |  |
| $J_{3',4'}$ |  |                  | 8.6                         |                             |  |  |  |  |  |
| $J_{4',5'}$ |  |                  | 8.6                         |                             |  |  |  |  |  |
| $J_{5',6'}$ |  |                  | 2.9                         |                             |  |  |  |  |  |

**Table 18** <sup>1</sup>H and <sup>13</sup>C NMR comparison of 1'-bromo-1'-deoxysucrose (**20**) with literature data

<sup>a</sup> No previous literature data

| Assign | 21           CAS: 64644-62-8           (δ in ppm and J in Hz) |                                    |   |                    |   |  |  |  |  |  |  |  |
|--------|---|------------------------------------|---|--------------------|---|--|--|--|--|--|--|--|
| ment   | <b>Ref<sup>8</sup></b>  |                                    | Ref <sup>82</sup>                             | ,                  | Observed  |  |  |  |  |  |  |  |
|        | $\delta$ <sup>1</sup> H (60 MHz,D <sub>2</sub> O)             | $\delta^{13}$ C (D <sub>2</sub> O) | $\delta^{1}$ H (500 MHz in DMSO-<br>$d_{5}$ ) | $\delta^{13}C^{d}$ | $\delta$ <sup>1</sup> H (500 MHz, D <sub>2</sub> O) | $\delta^{13}$ C (125 MHz,D <sub>2</sub> O) |  |  |  |  |  |  |
| 1      | 5.44 (d)  | 93.3                               | 5.18  |                    | 5.40 (d)  | 92.5                                       |  |  |  |  |  |  |
| 2      |   | 71.8                               | 3.16  |                    | 3.52 (dd)   | 70.9                                       |  |  |  |  |  |  |
| 3      |   | 73.4                               | 3.41  |                    | 3.71 (t)  | 72.5                                       |  |  |  |  |  |  |
| 4      |   | 70.2                               | 3.11  |                    | 3.43 (t)  | 69.2                                       |  |  |  |  |  |  |
| 5      |   | 72.5                               | 3.63  |                    | 3.81 (dd)   | 72.5                                       |  |  |  |  |  |  |
| ба     |   | 61.0                               | $3.52 - 3.60^{a}$                             |                    | 2.90, 2.77 (m)                                      | 60.0                                       |  |  |  |  |  |  |
| 6b     |   | 01.0                               | $3.52 - 3.60^{a}$                             |                    | 5.00-5.77 (III)                                     | 00.0                                       |  |  |  |  |  |  |
| 1′a    | 3.45.4.20 (m. 20 H)   | 20H) 11 6                          | 3.67  |                    | 2.77 (brg)  | 13.8                                       |  |  |  |  |  |  |
| 1′b    | 5.45-4.20 (III, 2011)   | 44.0                               | 3.63  |                    | 5.77 (018)  | 43.0                                       |  |  |  |  |  |  |
| 2'     |   | 103.9                              | —   |                    | _   | 103.1                                      |  |  |  |  |  |  |
| 3'     |   | 77.2                               | 4.01  |                    | 4.36 (d)  | 76.2                                       |  |  |  |  |  |  |
| 4'     |   | 74.4                               | 3.76  | —                  | 4.01 (t)  | 73.4                                       |  |  |  |  |  |  |
| 5'     |   | 82.6                               | $3.52 - 3.60^{a}$                             |                    | 3.88 (td)   | 81.7                                       |  |  |  |  |  |  |
| 6′a    |   | 62.9                               | $3.52 - 3.60^{a}$                             |                    | 2.90, 2.77 (m)                                      | 61.0                                       |  |  |  |  |  |  |
| 6′b    |   | 02.8                               | 3.48  |                    | 5.80-5.77 (III)                                     | 01.9                                       |  |  |  |  |  |  |
| O2     |   |                                    | 4.77  |                    |   |  |  |  |  |  |  |  |
| 03     |   |                                    | 4.76  |                    |   |  |  |  |  |  |  |  |
| 04     |   |                                    | 4.77  |                    |   |  |  |  |  |  |  |  |
| 06     | _   | -                                  | 4.38  |                    | -   | -  |  |  |  |  |  |  |
| 03     |   | 4.94                               |   |                    |   |  |  |  |  |  |  |  |
| 04     |   |                                    | 5.30  |                    |   |  |  |  |  |  |  |  |
| 06     |   |                                    | 4.45  |                    |   |  |  |  |  |  |  |  |

| <b>Table 19</b> <sup>1</sup> H and <sup>13</sup> C NMR comparison of 1'-chloro-1'-deoxysucrose (21) with literature data |
|--|
|  |

|                        | <b>21</b> CAS: 64644-62-8 ( $\delta$ in ppm and J in Hz) (con't) |                                    |   |                    |   |  |  |  |  |
|------------------------|--|------------------------------------|---|--------------------|---|--|--|--|--|
| Assign                 | <b>Ref</b> <sup>8</sup>  |                                    | <b>Ref</b> <sup>82</sup>  |                    | Obse  | erved                                      |  |  |  |
| ment                   | $\delta^{1}$ H (60 MHz,D <sub>2</sub> O)                         | $\delta^{13}$ C (D <sub>2</sub> O) | $\delta$ <sup>1</sup> H (500 MHz in DMSO- <i>d</i> <sub>5</sub> ) | $\delta^{13}C^{d}$ | $\delta$ <sup>1</sup> H (500 MHz, D <sub>2</sub> O) | $\delta^{13}$ C (125 MHz,D <sub>2</sub> O) |  |  |  |
| $J_{1,2}$              | -  |                                    | 3.7   |                    | 4.0   |  |  |  |  |
| $J_{2,3}$              | 3  |                                    | 9.8   |                    | 9.7   |  |  |  |  |
| $J_{3,4}$              |  |                                    | 8.9   |                    | 9.7   |  |  |  |  |
| $J_{4,5}$              |  |                                    | 10.0  |                    | 9.7   |  |  |  |  |
| $J_{5,6a}$             |  |                                    | 2.2   |                    | 2.9   |  |  |  |  |
| $J_{5,6b}$             |  |                                    | 4.6   |                    | 5.7   | _  |  |  |  |
| $J_{6a,6b}$            |  |                                    | b   |                    |   | _  |  |  |  |
| $J_{1'a,1'b}$          |  |                                    | $12.2^{c}$  |                    |   |  |  |  |  |
| $J_{3',4'}$            |  |                                    | 8.6   |                    | 8.6   |  |  |  |  |
| $J_{4',5'}$            |  |                                    | 7.8   |                    | 8.6   |  |  |  |  |
| $J_{5',6'a}$           |  | _                                  | b   | _                  | 2.4   |  |  |  |  |
| $J_{5',6'\mathrm{b}}$  |  | _                                  | 4.8   | _                  | 5.4   | _  |  |  |  |
| $J_{6'a,6'b}$          | _  |                                    | $10.9^{c}$  |                    |   |  |  |  |  |
| $J_{2,\mathrm{OH2}}$   |  |                                    | 6.2   |                    |   |  |  |  |  |
| $J_{3, m OH3}$         |  |                                    | 5.0   |                    |   |  |  |  |  |
| $J_{4, m OH4}$         |  |                                    | 5.6   |                    |   |  |  |  |  |
| $J_{ m 6a,OH6}$        |  |                                    | 5.2   |                    |   |  |  |  |  |
| $J_{ m 6b,OH6}$        |  |                                    | 6.0   |                    | _   |  |  |  |  |
| $J_{3',\mathrm{OH3'}}$ |  |                                    | 8.0   |                    |   |  |  |  |  |
| $J_{4',{ m OH4'}}$     |  |                                    | 5.8   |                    |   |  |  |  |  |
| $J_{6'a,OH6'}$         |  |                                    | Ь   |                    |   |  |  |  |  |
| $J_{6'b,OH6'}$         |  |                                    | Ь   |                    |   |  |  |  |  |

<sup>8</sup> Gus, R. D. G.; Guthrie, R. D.; Jenkins, I. D.; Watters, J. J. *Autr. J. Chem.* **1980**, *33*, 28487–2497. <sup>82</sup> Christofides, J. C.; Davies, D. B.; Martin, J. A.; Rathbone, E. B. *J. Am. Chem. Soc.* **1986**, *108*, 5738–5743. <sup>a</sup> Due to overlap of signals, chemical shifts could not be determined accurately. <sup>b</sup> Due to overlap of signals, couplings could not be determined accurately. <sup>c</sup> Magnitudes but not signs were determined. <sup>d</sup> Not assigned

## 2.3.8<sup>1</sup>H and <sup>13</sup>C NMR Literature Comparison of Halodeoxy-1-kestose Derivatives with Observation Data

**Table 20** <sup>1</sup>H and <sup>13</sup>C NMR literature comparison with observation data of 1-kestose undecaacetate (23) and per-*O*-acetylated trihalogenated 1-kestose derivatives (24 and 25)

|        |                                     |  | 2.   | 3                            |  | 24  |  | 25   | 25  |   |
|--------|-------------------------------------|--|--|------------------------------|--|---|--|--|---|---|
|        |                                     |  | CAS: 251   | 101-98-8                     |  | CAS: -  | CAS  | : -  |   |   |
|        |                                     |  | $(\delta \text{ in ppm and})$                            | nd $J$ in Hz                 | z)   |   | $(\delta \text{ in ppm and })$                       | J in Hz)   | $(\delta \text{ in ppm and})$                         | l J in Hz)                                      |
| Assign | Ref                                 | 76<br>•  | Ref. <sup>8</sup>  | 0                            | Obse   | rved  | Observe  | ed   | Observ  | ved   |
| ment   | $\delta^{1}$ H (CDCl <sub>3</sub> ) | $\delta^{13}C$ (100.6<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta^{1}H$ (100 or 220<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta^{13}$ C <sup>a</sup> | δ <sup>1</sup> H<br>(500 MHz,<br>CDCl <sub>3</sub> ) | $\delta^{13}C$ (125 MHz,<br>CDCl <sub>3</sub> ) | δ <sup>1</sup> H<br>(500 MHz,<br>CDCl <sub>3</sub> ) | $\begin{array}{c} \delta^{13}C\\ (125 \text{ MHz},\\ \text{CDCl}_3) \end{array}$ | $\delta^{1}\text{H}$ (500 MHz,<br>CDCl <sub>3</sub> ) | $\delta^{13}C$ (125 MHz,<br>CDCl <sub>3</sub> ) |
| 1      | 5.71 (d)                            | 90.3 (d)   | 5.71   |                              | 5.75 (d)   | 89.2  | 5.67 (d)   | 90.1   | 5.70–5.66 (m)   | 90.0  |
| 2      | 4.88 (dd)                           | 70.3 (d)   | 4.88   | -                            | 4.91 (dd)  | 70.0  | 4.95 (dd)  | 69.7   | 4.93 (dd)   | 69.7  |
| 3      | 5.42 (t)                            | 70.1 (d)   | 5.42   |                              | 5.42 (t)   | 69.8  | 5.48–5.42 (m)  | 69.3   | 5.48–5.41 (m)   | 69.4  |
| 4      | 5.22 (t)                            | 68.0 (d)   | 5.04   |                              | 5.08 (t)   | 68.2  | 5.03 (t)   | 70.8   | 5.06 (t)  | 69.7  |
| 5      | 4.40-4.20                           | 69.0 (d)   | 4.42–4.07<br>(11H<br>signals)                            |                              | 4.39–4.33<br>(m)                                     | 68.2  | 4.35–4.28 (m)  | 69.3   | 4.38-4.32 (m)   | 69.8  |
| ба     | (m,<br>overlap<br>13H               | 50.7 (4)   | 4.42–4.07<br>(11H<br>signals)                            |                              | 4.33–4.24<br>(m)                                     | (17   | 3.54 (dd)  | 21.1   | 3.68 (dd)   | 42.2  |
| бb     | signals)                            | 39.7 (t)   | 4.42–4.07<br>(11H<br>signals)                            |                              | 4.20–4.14<br>(m)                                     | 01./  | 3.40 (dd)  | 51.1   | 3.57dd)   | 43.2  |

|        |  |  | <b>23</b> (con CAS: 2510   | l't)<br>1-98-8   |   |  | <b>24</b> (con't)<br>CAS: -                                 |   | 25 (con't)<br>CAS: -  |   |  |
|--------|--|--|--|------------------|---|--|---|---|---|---|--|
|        |  | ( $\delta$ in ppm and J in Hz)                       |  |                  |   |  |   | and $J$ in Hz)  | ( $\delta$ in ppm and J in Hz)                              |   |  |
| Assign | Ref                                    | 76<br>•  | Ref. <sup>8</sup>  | 30               | Obse  | erved  | Obse  | erved   | Ob  | Observed  |  |
| ment   | $\delta^{1}$ H<br>(CDCl <sub>3</sub> ) | $\delta^{13}C$ (100.6<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta$ <sup>1</sup> H<br>(100 or<br>220<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta^{13}C^a$ | $\delta^{1}H$ (500<br>MHz,<br>CDCl <sub>3</sub> ) | δ <sup>13</sup> C<br>(125<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta$ <sup>1</sup> H<br>(500 MHz,<br>CDCl <sub>3</sub> ) | δ <sup>13</sup> C<br>(125 MHz,<br>CDCl <sub>3</sub> ) | $\delta$ <sup>1</sup> H<br>(500 MHz,<br>CDCl <sub>3</sub> ) | $\delta^{13}$ C<br>(125 MHz,<br>CDCl <sub>3</sub> ) |  |
| 1′a    |  | 627(4)   | 3.71   |                  | 3.69 (d)  | 62.2   | 3.79 (d)  | 61 5  | 2.75 (a)  | 61.6  |  |
| 1′b    |  | 05.7 (l)   | 3.62   |                  | 3.63 (d)  | 02.2   | 3.73 (d)  | 01.3  | 5.75 (8)  | 01.0  |  |
| 2'     |  | 104.3 (s)  |  |                  |   | 103.4  |   | 103.8   |   | 103.8   |  |
| 3'     | 5.37 (d)                               | 76.2 (d)   | 5.46   |                  | 5.69 (d)  | 74.9   | 5.70 (d)  | 75.8  | 5.70–5.66<br>(m)  | 75.5  |  |
| 4'     | а                                      | 75.3 (d)   | 5.32   |                  | 5.46 (t)  | 73.7   | 5.48–5.42 (m)   | 76.4  | 5.48–5.41 (m)   | 75.7  |  |
| 5'     | 4 40 4 20                              | 78.1 (d)   | 4.42–<br>4.07<br>(11H<br>signals)  |                  | 4.24–<br>4.20 (m)                                 | 77.8   | 4.35–4.28 (m)   | 79.8  | 4.28–4.22 (m)   | 79.9  |  |
| 6'     | 4.40–4.20<br>(m,<br>overlap<br>13H     | 62.5 (t)   | 4.42–<br>4.07<br>(11H<br>signals)  |                  | 4.33–<br>4.24 (m)                                 | 63.2   | 3.66 (d)  | 32.0  | 3.82–3.78 (m)   | 44.4  |  |
| 1"     | signais)                               | 64.4 (t)   | 4.42–<br>4.07<br>(11H<br>signals)  |                  | 4.24–<br>4.20 (m)                                 | 62.7   | 4.24 (s)  | 62.0  | 4.28–4.22 (m)   | 62.2  |  |

|                     |  |  | <b>23</b> (con   | ı't)             |   |  | 24 (0   | con't)  | 25   | (con't)   |
|---------------------|--|--|--|------------------|---|--|---|---|--|---|
|                     |  |  | CAS: 2510  | 1-98-8           |   |  | CAS: -  |   | CAS: -   |   |
|                     |  | (δ   | in ppm and   | J in Hz          | 2)  |  | $(\delta \text{ in ppm and } J \text{ in Hz})$              |   | ( $\delta$ in ppm and J in Hz)                     |   |
| Assign              | <b>Ref.</b> <sup>76</sup>              |  | Ref. <sup>80</sup> Obs                                       |                  | Obse  | erved Obse   |   | erved   | Observed   |   |
| ment                | $\delta^{1}$ H<br>(CDCl <sub>3</sub> ) | $\delta^{13}C$ (100.6<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta^{-1}H$ (100 or<br>220<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta^{13}C^a$ | $\delta^{1}H$ (500<br>MHz,<br>CDCl <sub>3</sub> ) | δ <sup>13</sup> C<br>(125<br>MHz,<br>CDCl <sub>3</sub> ) | $\delta$ <sup>1</sup> H<br>(500 MHz,<br>CDCl <sub>3</sub> ) | δ <sup>13</sup> C<br>(125 MHz,<br>CDCl <sub>3</sub> ) | $\delta^{1}$ H<br>(500 MHz,<br>CDCl <sub>3</sub> ) | $\delta^{13}$ C<br>(125 MHz,<br>CDCl <sub>3</sub> ) |
| 2''                 |  | 103.1 (s)  |  |                  |   | 102.9  |   | 103.1   |  | 103.1   |
| 3‴                  | 5.46 (d)                               | 76.6 (d)   | 5.68   |                  | 5.48 (d)  | 76.5   | 5.50 (d)  | 77.2  | 5.50 (d)   | 76.9  |
| 4''                 | а                                      | 76.0 (d)   | 5.22   |                  | 5.34 (t)  | 75.5   | 5.32 (t)  | 78.1  | 5.33 (t)   | 77.2  |
| 5″                  | 4.40–4.20<br>(m,                       | 79.1 (d)   | 4.42–<br>4.07<br>(11H<br>signals)                            |                  | 4.20–<br>4.14 (m)                                 | 78.4   | 4.22–4.19 (m)   | 80.7  | 4.17 (q)   | 80.6  |
| 6″                  | 13H<br>signals)                        | 62.9 (t)   | 4.42–<br>4.07<br>(11H<br>signals)                            |                  | 4.39–<br>4.33 (m)                                 | 63.7   | 3.69 (d)  | 32.7  | 3.82–3.78 (m)                                      | 44.6  |
| $J_{1,2}$           | 3.4                                    |  | 3.9  |                  | 3.4   |  | 4.0   |   | 3.7  |   |
| $J_{2,3}$           | 10.2                                   |  | 9.0  |                  | 10.3  |  | 10.3  |   | 10.6   |   |
| $J_{3,4}$           | 10.2                                   |  | 9.4  |                  | 9.7   |  | 9.7   |   | 9.7  |   |
| $J_{4,5}$           |  |  | 10.0   |                  |   |  | 2.3   |   | 2.3  |   |
| $J_{5,6a}$          |  | —  |  |                  |   | —  |   |   |  | —   |
| $J_{5,6\mathrm{b}}$ | —                                      | -  |  |                  |   |  | 6.3   |   | 5.7  |   |
| $J_{6a,6b}$         |  |  |  |                  |   |  | 11.5  |   | 12.0   |   |
| $J_{1'a,1'b}$       |  |  |  |                  | 9.2   |  | 10.3  |   |  |   |
| $J_{3',4'}$         | 8.6                                    |  | 7.0  |                  | 8.0   |  | 8.0   |   |  |   |

|                    |  |   | <b>23</b> (con'                                       | t)                 |   |   | 24 (c   | on't)   | <b>25</b> (cor  | n't)  |
|--------------------|--|---|---|--------------------|---|---|---|---|---|---|
|                    | CAS: 25101-98-8 ( $\partial$ in ppm and J in Hz)   |   |   |                    |   |   | CAS: - ( $\delta$ in ppm and J in Hz)                                     |   | CAS: - ( $\delta$ in ppm and J in Hz)   |   |
| Assign             | <b>Ref.</b> <sup>76</sup>  |   | <b>Ref.</b> <sup>80</sup>                             |                    | Observed  |   | Observed  |   | Observed  |   |
| ment               | $\delta^{1}$ H (CDCl <sub>3</sub> )  | $\delta^{13}C$ (100.6 MHz,<br>CDCl <sub>3</sub> ) | $\delta^{1}H$ (100 or 220<br>MHz, CDCl <sub>3</sub> ) | $\delta^{13}C^{a}$ | $\delta^{1}H$ (500 MHz,<br>CDCl <sub>3</sub> )  | $ \begin{array}{c} \delta^{13}C\\(125 \text{ MHz,}\\CDCl_3) \end{array} $ | $\delta^{1}$ H<br>(500 MHz,<br>CDCl <sub>3</sub> )                        | $\delta^{13}C$ (125 MHz,<br>CDCl <sub>3</sub> )         | $\delta^{1}$ H<br>(500 MHz,<br>CDCl <sub>3</sub> )  | $ \begin{array}{c} \delta^{13}C \\ (125 \text{ MHz,} \\ CDCl_3) \end{array} $ |
| $J_{4',5'}$        |  |   | 6.0   |                    |   |   |   |   |   |   |
| $J_{5',6'}$        |  |   |   |                    |   |   | 6.9   |   |   |   |
| J <sub>3",4"</sub> | 8.6  |   | 8.0   |                    | 6.9   | ]   | 6.3   |   | 6.3   | ] _   |
| $J_{4'',5''}$      |  |   | 8.0   |                    |   |   |   |   |   |   |
| $J_{5'',6''}$      |  |   |   |                    |   |   | 7.4   |   | 6.5   |   |
| CH <sub>3</sub>    | 2.09 (s),<br>2.12 (s),<br>2.11 (s),<br>2.09 (s),<br>2.08 (s),<br>2.07 (s),<br>2.05 (s),<br>2.02 (s),<br>2.00 (s) | 21.5–20.8   | 2.12<br>2.09<br>2.08<br>2.07<br>1.99<br>1.97          |                    | 2.19–2.14<br>(m),<br>2.13–2.12<br>(m),<br>2.11–2.09<br>(m),<br>2.06 (s),<br>2.04 (s),<br>2.01 (s) | 20.8,<br>20.7,<br>20.7,<br>20.6,<br>20.6,<br>20.5                         | 2.16–2.15<br>(m),<br>2.14 (s),<br>2.11 (s),<br>2.09-2.07 (m),<br>2.02 (s) | 20.8, 20.8,<br>20.7, 20.8,<br>20.6, 20.5,<br>20.5, 20.5 | 2.16 (s),<br>2.15–2.13 (m),<br>2.11 (s),<br>2.09 (s),<br>2.08 (s),<br>2.07 (s),<br>2.02 (s) | 20.8,<br>20.7,<br>20.7,<br>20.6,<br>20.5,<br>20.5                             |
| C=O                |  | 170.4–169.7                                       |   |                    |   | 170.7,<br>170.6,<br>170.5,<br>170.1,<br>169.9,<br>169.7,<br>169.6         |   | 170.2,<br>170.0,<br>170.0,<br>169.8,<br>169.5           |   | 170.2,<br>170.1,<br>170.0,<br>170.0,<br>169.7,<br>169.5                       |

<sup>76</sup> Pejin, B.; Iodice, C.; Tommonaro, G.; Sabovljevic, M.; Bianco, A.; Tesevic, V.; Vajs, V.; De Rosa, S. *Nat. Prod. Res.* **2012**, *26*, 209–215.

<sup>80</sup> Binkley, W. W.; Horton, D.; Bhacca, N. S. *Carbohydr. Res.* **1969**, *155*, 245–258. <sup>a</sup> Not assign.

|            |  | CAS 5  | 22<br>62-68-5   | <b>29</b><br>CAS:   | -<br>/: II-)  | <b>30</b><br>CAS: -                                     |   |                                |
|------------|--|--|---|---|---|---|---|--------------------------------|
| Assign-    | Ref  | ( <i>0</i> in ppm ;<br>f <sup>71</sup>                     | and J in HZ)<br>Observ                                  | ed  | ( <i>o</i> in ppm and<br>Observe                        | J IN HZ)<br>ed  | (0 in ppm and J in HZ)                                  |                                |
| ment       | <sup>1</sup> H in ppm<br>(200.13 MHz,<br>D <sub>2</sub> O) | <sup>13</sup> C in ppm<br>(50.32 MHz,<br>D <sub>2</sub> O) | <sup>1</sup> H in ppm<br>(500 MHz,<br>D <sub>2</sub> O) | $ \begin{array}{c} 1^{13}C \text{ in ppm} \\ (125 \text{ MHz}, \\ D_2O) \end{array} $ | <sup>1</sup> H in ppm<br>(500 MHz,<br>D <sub>2</sub> O) | $ \begin{array}{ c c c c c c c c c c c c c c c c c c c$ | <sup>1</sup> H in ppm<br>(500 MHz,<br>D <sub>2</sub> O) | $[13C in ppm] (125 MHz, D_2O)$ |
| 1          | 5.26   | 93.73  | 5.37 (d)  | 92.9  | 5.36 (d)  | 92.9  | 5.36 (d)  | 92.8                           |
| 2          | 3.38   | 72.39  | 3.48 (dd)   | 71.6  | 3.52 (dd)   | 71.0  | 3.52 (dd)   | 70.1                           |
| 3          | 3.59   | 73.85  | 3.70–3.60 (m)   | 73.0  | 3.72–3.65 (m)   | 72.1  | 3.71–3.60 (m)   | 72.2                           |
| 4          | 3.30   | 70.48  | 3.41 (t)  | 69.6  | 3.43 (t)  | 71.4  | 3.47 (t)  | 71.6                           |
| 5          | 3.64<br>3.68   | 73.67  | 3.79–3.71 (m)   | 72.8  | 4.04–3.98 (m)   | 71.1  | 4.11–4.05 (m)   | 71.0                           |
| ба         | 2.62   | 61.40  | 3.79–3.71 (m)   | 60.5  | 3.79–3.72 (m)   | 24.2  | 3.89–3.73 (m)   | 44.3                           |
| 6b         | 5.05   |  |   |   | 3.72–3.65 (m)   | 54.2  |   |                                |
| 1′a        | 3.54   | 62.17  | 3.79–3.71 (m)   | 61.2  | 3.87 (d)  | 50.0  | 3.89–3.73 (m)   | 60.2                           |
| 1′b        | 3.66   | 02.17  | 3.70–3.60 (m)   | 01.5  | 3.72–3.65 (m)   |   | 3.71–3.60 (m)   | 00.2                           |
| 2'         | _  | 104.50   | _   | 103.7   | _   | 103.3   | —   | 103.3                          |
| 3'         | 4.12   | 77.92  | 4.22 (d)  | 77.0  | 4.27 (d)  | 76.4  | 4.26 (d)  | 76.4                           |
| 4'         | 3.88   | 75.12  | 3.98 (t)  | 74.2  | 4.09–4.05 (m)   | 76.3  | 4.11–4.05 (m)   | 75.3                           |
| 5'         | 3.67<br>3.70   | 82.46  | 3.83–3.80 (m)   | 81.6  | 4.04–3.98 (m)   | 80.6  | 4.01–3.94 (m)   | 80.6                           |
| 6'a<br>6'b | 3.63   | 63.44  | 3.79–3.71 (m)   | 62.6  | 3.64–3.59 (m)   | 33.5  | 3.89–3.73 (m)   | 45.2                           |

**Table 21** <sup>1</sup>H and <sup>13</sup>C NMR literature comparison with observation data of 1-kestose (22) and trihalogenated 1-kestose derivatives (29 and 30)

|                    |                       | 22 (                      | con't)                | <b>29</b> (con <sup>2</sup>    | `t)                   | <b>30</b> (con't)<br>CAS: -                    |                       |                        |      |
|--------------------|-----------------------|---------------------------|-----------------------|--------------------------------|-----------------------|--|-----------------------|------------------------|------|
|                    |                       | CAS 5                     | 62-68-5               | CAS:                           | -                     |  |                       |                        |      |
| A                  |                       | $(\delta \text{ in ppm})$ | and J in Hz)          | $(\delta \text{ in ppm and })$ | J in Hz)              | $(\delta \text{ in ppm and } J \text{ in Hz})$ |                       |                        |      |
| Assign-            | Ref                   | . 71                      | Observ                | ed                             | Observe               | ed   | Observed              |                        |      |
| ment               | <sup>1</sup> H in ppm | <sup>13</sup> C in ppm    | <sup>1</sup> H in ppm | <sup>13</sup> C in ppm         | <sup>1</sup> H in ppm | <sup>13</sup> C in ppm                         | <sup>1</sup> H in ppm | <sup>13</sup> C in ppm |      |
|                    | (200.13 MHz,          | (50.32 MHz,               | (500 MHz,             | (125 MHz,                      | (500 MHz,             | (125 MHz,                                      | (500 MHz,             | (125 MHz,              |      |
|                    | D <sub>2</sub> O)     | D <sub>2</sub> O)         | $D_2O)$               | D <sub>2</sub> O)              | $D_2O)$               | D <sub>2</sub> O)                              | $D_2O)$               | D <sub>2</sub> O)      |      |
| 1″a                | 3.50                  | 61 70                     | 2.70, 2.60 (m)        | 60.8                           | 2.72, 2.65 (m)        | 50.0   | 2.71, 2.60 (m)        | 60.0                   |      |
| 1‴b                | 3.59                  | 01.70                     | 5.70–5.00 (III)       | 00.8                           | 5.72–5.05 (III)       | 39.9   | 5.71-5.00 (III)       | 00.0                   |      |
| 2''                | _                     | 104.96                    | _                     | 104.2                          | _                     | 103.9  | _                     | 103.9                  |      |
| 3''                | 4.02                  | 77.94                     | 4.13 (d)              | 77.0                           | 4.16 (d)              | 76.9   | 4.16 (d)              | 76.6                   |      |
| 4″                 | 3.91                  | 75.74                     | 4.02 (t)              | 74.9                           | 4.09–4.05 (m)         | 77.4   | 4.11–4.05 (m)         | 76.2                   |      |
| 5''                | 3.69                  | 82.36                     | 3.83-3.80 (m)         | 81.5                           | 4.04-3.98 (m)         | 80.4   | 4.01–3.94 (m)         | 80.5                   |      |
| 6″a                | 3.70                  | (2.50                     | 62 50                 | 2.70, 2.71 (m)                 | 62.7                  | 2.70, 2.72 (m)                                 | 22.5                  | 2.90, 2.72 (m)         | 15 A |
| 6‴b                | 3.64                  | 03.39                     | 5.79–5.71 (III)       | 02.7                           | 5.79-5.72 (III)       | 55.5   | 5.89–5.75 (III)       | 43.4                   |      |
| $J_{1,2}$          |                       |                           | 4.0                   |                                | 4.0,                  |  | 4.0                   |                        |      |
| $J_{2,3}$          |                       |                           | 9.7                   |                                | 10.0                  |  | 9.7                   |                        |      |
| $J_{3,4}$          |                       |                           | 9.7                   |                                | 10.0                  |  | 9.7                   | _                      |      |
| $J_{1'a,1'b}$      | ] —                   | _                         | _                     | ]                              | 10.3                  |  |                       |                        |      |
| $J_{3',4'}$        |                       |                           | 8.6                   |                                | 8.6                   |  | 8.6                   |                        |      |
| J <sub>3".4"</sub> |                       |                           | 8.6                   |                                | 8.6                   |  | 8.6                   |                        |      |

<sup>71</sup> Calub, T. M.; Waterhouse, A. L.; Chatterton, N. J. *Carbohydr. Res.* **1990**, *199*, 11–17.

### 2.4 Conclusion

Since halodeoxysucrose compounds at the primary counterpart are not completely established brief NMR assignments (See Table 3-19 in the experimental sections), this made the difficulties to distinguish between 6- and 6'-monohalo sucrose isomers based on <sup>1</sup>H-NMR, due to overlapped signals of protons at 6- and 6'-positions with some other positions. These tendencies also promoted ambiguous result for Appel reaction reactivity. In this study, comprehensive NMR analyses for each monohalogenated sucrose moiety at the primary position is described and even constructed the reactivity of the Appel reaction based on its isolated per-O-acetylated compounds. The NMR characterization was then revisited for 6'-bromo-6'-deoxysucrose heptaacetate (2) to show that structural assignment of this molecule in the previous report was misinterpreted and needed to revise their assignment as the 6-bromo-6-deoxysucrose heptaacetate (3). Due to this favor, the de-O-acetylated 6'-bromo-6'-deoxysucrose (14) can be purely assigned in this study. However, the regioselective Appel reaction of sucrose followed the halogenation order of 6>6'>>1'. Additionally, chemoenzymatic installation of monohalogenated sucrose derivatives at the 1'-position led to the first reported synthesis of compounds 1'-bromo-1'-deoxysucrose heptaacetate (10) and 1'-bromo-1'-deoxysucrose (20). The establishment of three monohalogenated sucrose isomers modified at the primary position will be useful to extend the novelty and diversity of carbohydrate-based products. Moreover, further modification at these primary positions with representative probe, such as benzophenone or [3-(trifluoromethyl)phenyl] diazirine, can be useful for photoaffinity labeling analysis of human sweet taste receptor.

1-Kestose, one of FOS with additional fructose moiety at 1'-position of sucrose, treatments with Appel reaction resulted in trihalogenated 1-kestose at the 6-, 6'-, and 6"-positions (See Table 20–21 in the experimental sections for detail NMR analysis). Isolation and structure elucidation were easily completed using the per-*O*-acetylated form which the 1D and 2D NMR supported the halogenated positions. The synthesis and structure elucidation of novel compounds 1",2,3,3',3",4,4',4"-octa-*O*-acetyl-6,6',6"-tribromo-6,6',6"-trideoxy-1-kestose (**24**) and 1",2,3,3',3",4,4',4"-octa-*O*-acetyl-6,6',6"-trichloro-6,6',6"-trideoxy-1-kestose (**25**) contribute to the introduction of halogenations of primary hydroxy groups of FOS, which can potentially be used as low-calorie and non-digestible sweeteners as artificial sugar for diabetics.

### 3.1 Introduction

The widely used *C*-acylation, Friedel–Crafts acylation<sup>28,29</sup> of aromatic compounds are efficient methods that result in satisfactory product yields.<sup>34</sup> Conventionally, the Friedel–Crafts acylation of aromatic derivatives with acyl donor requires at least 1 equiv. of AlCl<sub>3</sub> as catalyst.<sup>29,35</sup> The improvement on this reaction for various substrates, including  $\alpha$ -amino acid, is continuing at the time of writing this dissertation. Thus, to extend the acylation of  $\alpha$ -amino acid, this part is refined into two parts. The high storage stability of *N*-hydroxysuccinimide ester that impressively used for direct acylation and very reactive proportion of conventional acid chloride that still interesting to explore its ability, which both used as representative acyl donor in this chapter.



**Figure 20** *N*-protected  $\alpha$ -amino aryl-ketone synthesis methods<sup>33</sup>

Chiral *N*-protected  $\alpha$ -amino aryl-ketones are usually used as a precursor in the synthesis of various biologically active compounds.<sup>26,32</sup> There are several approaches for their syntheses, which generally can be devided as ones that use  $\alpha$ -amino acid derivatives or non-amino acid derivatives as reactants (Figure 20).<sup>33</sup> When non-amino acid is used as reagents, the multistep reactions, the use of special catalyst, and the requirement for time-consuming chiral resolution are the problems for this method. Meanwhile, utilization of  $\alpha$ -amino acid derivatives as reagents might offer convenient method since optically active  $\alpha$ -amino acid can be used as starting material. Among this method, Friedel–Crafts acylation<sup>28,29</sup> of arenes was taken part in

the most favorable strategy to synthesize  $\alpha$ -amino aryl-ketone (Figure 20), which results in satisfactory product yields.<sup>34</sup>



**Figure 21** Friedel–Crafts acylation with utilization of various acyl donors to synthesize *N*-protected α-amino aryl-ketone. Protecting group is abbreviated as "PG"

The  $\alpha$ -amino acid chloride<sup>25,26,31,32</sup> is widely used as an acyl donor to undergo Friedel– Crafts acylation due to its high reactivity (Figure 21). However, this acyl halide is unstable, sensitive to moisture and difficult to handle.<sup>83</sup> Therefore, it should be used instantly and cannot be stored. In some cases, utilization of  $\alpha$ -amino acid chloride also cannot prevent the racemization.<sup>26,83</sup> Moreover,  $\alpha$ -amino acid anhydride (Figure 21) can be employed as an acylating agent and can be used to obtain the  $\alpha$ -amino aryl-ketone without the *N*-protecting group. Unfortunately,  $\alpha$ -amino acid anhydride only shows reactivity for electron-rich arene acyl acceptor<sup>84</sup> and needed to be prepared by using a toxic gas, such as phosgene or triphosgene<sup>85</sup> Since  $\alpha$ -amino acid anhydride consists of two possible  $\alpha$ -amino acids, one of the non-acylated molecules will be wasted during the reaction. Recently, *N*-protected *N*-( $\alpha$ aminoacyl)benzotriazole (Figure 21) has been reported to acylate benzene by using Lewis acid.<sup>30</sup> Despite this *N*-acylbenzotriazole being more convenient to handle compared to  $\alpha$ amino acid chloride, only a moderate yield of  $\alpha$ -aminoacyl phenyl-ketone can be synthesized. However, the preparation of *N*-protected *N*-( $\alpha$ -aminoacyl)benzotriazole<sup>30,86,87</sup> was conducted under in situ conditions, which indicated that its isolation takes more effort.

N-Hydroxysuccinimide ester (OSu) derivatives of  $\alpha$ -amino acids have high storage stability<sup>88</sup> and have enough reactivity with amino components under moderate condition. Several hundreds of OSu modified in α-amino acid derivatives are commercially available which widely used as convenient reagents in peptide synthesis. The OSu modified in  $\alpha$ -amino acid is also known to be facilitated peptide synthesis as good alkoxy leaving group.<sup>89</sup> This utility indicated that the OSu derivatives may act as acyl donor for Friedel-Crafts reaction. In peptide construction *via* amide bond formation, it is known to produce fewer side reactions, including racemization. Moreover, it reacts cleanly, thus suitable for purification with partition.<sup>89</sup> The Friedel–Crafts acylation of electron-rich arene (ferrocene and pyrene) with Nhydroxysuccinimidyl benzoic or p-methoxybenzoic acid has been previously reported, of which reagents were activated by superacidic trifluoromethanesulfonic acid.<sup>90</sup> Up to date, no study has been reported the α-amino acid-OSu as representative skeleton for direct Friedel-Crafts acylation. In this work, the synthesis and properties of potential acyl donor for Friedel-Crafts acylation, N-trifluoroacetyl (TFA)-protected α-amino acid-OSu, are described. TFA protection of  $\alpha$ -amino acid is preferred due to its stability to Lewis Acid to undergo acylation with conventional Friedel–Crafts catalyst, AlCl<sub>3</sub>.

Until now, no study has been reported as the use of  $\alpha$ -amino acid-OSu for a representative skeleton in direct Friedel–Crafts acylation. In this study, the synthesis and properties of a potential acyl donor for Friedel–Crafts acylation, namely *N*-trifluoroacetyl (TFA)-protected  $\alpha$ -amino acid-OSu, are described. The demonstrated utility of optically active isoleucine, which has two chiral centers in the molecules, and its diastereomer *allo*-isoleucine to identify chilarity at the  $\alpha$ -proton of the Friedel–Crafts acylation products by nuclear magnetic resonance (NMR) is studied. The use of  $\alpha$ -amino acid-OSu derivatives is expected to extend the synthesis of various TFA-protected  $\alpha$ -amino aryl-ketone which assumed to retard its chirality which might act as a potential acyl donor for the Friedel–Crafts acylation.

#### 3.2 Result and discussion

# 3.2.1 Friedel–Crafts Acylation of aliphatic $\alpha$ -amino acid derivatives: Isoleucine derivatives synthesis and modification

Preparations of  $\alpha$ -amino aryl-ketone via Friedel–Crafts acylation is catalyzed by Lewis or Brønsted acid, which majorly utilized toxic, corrosive and moisture-sensitive acylating reagents such as acyl halides and anhydrides. *N*-Hydroxysuccinimide ester (Figure 22) or socalled "active ester" is readily accessible and stable compound, in which benzoic acid *N*hydroxysuccinimide esters had been reported efficiently acylated ferrocene and pyrene under a strong acidic condition.<sup>90</sup> *N*-hydroxysuccinimide ester might give merit as an acyl donor for Friedel–Crafts acylation due to its exhibiting high reactivity towards the amino group and widely used for synthesis of biomolecules by C-N bond formation (Amide bond formation, Figure 22).<sup>89</sup> *N*-Hydroxysuccinimide ester is having high reactivity and easy to purify. It reacts cleanly and rapidly, moreover, the co-product is water-soluble (Figure 22). It also can produce less side reactions during the coupling reaction, including racemization for amide bond formation.<sup>89</sup> Therefore, *N*-hydroxysuccinimide ester might act as promising acyl donor for synthesis of aryl-keto  $\alpha$ -amino acids.



Figure 22 *N*-Hydroxysuccinimide ester (OSu) as representative reagent for amide bond formation

L-Isoleucine is known to have the ability to undergo epimerization at the  $\alpha$ -position to produce D-*allo*-isoleucine. As for chiral *N*-protected  $\alpha$ -amino aryl-ketone synthesis, especially the reaction involving direct acylation of  $\alpha$ -amino acids, the chirality of product is commonly determined by complex formation with a chiral shift reagent.<sup>25</sup> This racemic  $\alpha$ -amino aryl-ketone can be detected by the appearance of two separated proton signals in <sup>1</sup>H-NMR spectrum. Up to now, there is no reported study that has checked the chirality of the TFA-protected  $\alpha$ -amino aryl-ketone based on isoleucine and its diastereomer *allo*-isoleucine. Since the asymmetric carbon at  $\alpha$ -position within these stereoisomers can be detected by NMR,<sup>41</sup> utilization within isoleucine and its diastereomer *allo*-isoleucine (four types of stereoisomers; Figure 4) might be useful in describing a change in configuration of their chiral center during the chemical modification.

Traditionally, the coupling of amino acids in amide bond formation is utilizing *N*-protecting group, such as urethane-based protecting group such as *t*-butyl (BOC), benzyl (Cbz) or fluorenylmethyloxycarbonyl (Fmoc) that predominantly causing recemization.<sup>91</sup> In spite of this problem that cause by other *N*-protecting group, TFA-protected amino acid might proceed chirality retention in Friedel–Crafts reaction.<sup>25,32</sup> Therefore, initially in this study, the corresponding amino acid of optical active L-isoleucine (L-Ile, L-**31**) underwent TFA protection by using ethyl trifluoroacetate in the presence of triethylamine in methanol<sup>92,93</sup> to

generate TFA-L-Ile (L-32, Scheme 11). Next, the L-32 was transformed into TFA-L-Ile-OSu (L-33) within 3 h at room temperature by utilization of 1.1 equiv. NHS (*N*-hydroxysuccinimide) and 1.0 equiv. of WSCD-HCl in  $CH_2Cl_2$  (Scheme 11). TFA-L-Ile-OSu (L-33) is expected as potential acyl donor for Friedel–Crafts acylation which was described in this study.



Scheme 11 Synthesis TFA-L-isoleucine-N-hydroxysuccinimide ester (TFA-L-Ile-OSu, L-33)

The L-33 is stable for storage at -20 °C for more than six months and can be readily used as an acyl donor to undergo Friedel–Crafts acylation into benzene 34. The L-33 was found to be solved in excess amount of benzene 34 (300 equiv.) which sufficient for the purpose in this study. Preliminarily, an excess amount (6 equiv.) of conventional Friedel– Crafts catalyst of AlCl<sub>3</sub> was tested for the reaction at room temperature (Scheme 12 (a)). The room temperature reaction took longer reaction time and found not only moderate proportion of desired phenyl ketone of TFA-L-Ile-Ph (L-35) but also the starting material still remained after 24 h. Thus, the reaction was conducted at higher temperature (70 °C, Scheme 12 (b)), and within 2 h, the reaction is completed to result in L-35 with a fine yield.



Scheme 12 Friedel–Craft acylation of benzene (34) with TFA-L-Ile-OSu (L-33), in which utilizing conventional catalyst of AlCl<sub>3</sub> was utilized at (a) room temperature and (b) 70  $^{\circ}$ C. <sup>a</sup> Calculated from consumption of TFA-L-Ile-OSu (L-33).

 Table 22 Friedel–Craft acylation of benzene 34 with TFA-L-Ile-OSu (L-33) using various

 Lewis acids as catalyst.

| ΓF | $FA \xrightarrow{N}_{H} \xrightarrow{C}_{O} \xrightarrow{N}_{O} \xrightarrow{I}_{O} \xrightarrow{300 \text{ equiv.}}_{\text{Lewis acid}} 34$ $TFA \xrightarrow{N}_{H} \xrightarrow{C}_{U} \xrightarrow{N}_{O} \xrightarrow{T}_{O} $ |                   |        |           |  |  |  |  |  |  |
|----|---|-------------------|--------|-----------|--|--|--|--|--|--|
|    | Entry   | Lewis acid        | Equiv. | Time      | L- <b>35</b><br>(% Yield) <sup>a</sup> |  |  |  |  |  |
|    | 1   | AlCl <sub>3</sub> | 1.5    | 3 d       | N.R. <sup>b</sup>                      |  |  |  |  |  |
|    | 2   | AlCl <sub>3</sub> | 3      | 9 h       | N.R. <sup>c</sup>                      |  |  |  |  |  |
|    | 3   | AlCl <sub>3</sub> | 6      | 2 h       | 86                                     |  |  |  |  |  |
|    | 4   | SnCl <sub>2</sub> | 6      | $7 d \le$ | N.R. <sup>e</sup>                      |  |  |  |  |  |
|    | 5   | ZnCl <sub>2</sub> | 6      | 7 d ≤     | N.R. <sup>e</sup>                      |  |  |  |  |  |
|    | 6   | FeCl <sub>3</sub> | 6      | 2 d       | N.R. <sup>e</sup>                      |  |  |  |  |  |
|    | 7   | TiCl <sub>4</sub> | 6      | 1 d       | N.R. <sup>e</sup>                      |  |  |  |  |  |
|    | 8   | GaCl <sub>3</sub> | 6      | 2 h       | 4 <sup>c,f</sup>                       |  |  |  |  |  |
|    | 9   | InCl <sub>3</sub> | 6      | 2 h       | N.R. <sup>b</sup>                      |  |  |  |  |  |

<sup>a</sup> N.R. stands for no reaction. <sup>b</sup> Starting material of TFA-L-Ile-OSu (L-**33**) remained. <sup>c</sup> A complex mixture was recovered. <sup>e</sup> Hydrolysis is preferred rather than acylation. TFA-L-Ile (L-**32**) was recovered. <sup>f</sup> Calculated from <sup>1</sup>H-NMR.

The success of previous utilization of Friedel–Crafts acylation at 70 °C for 2 h can establish desired product of L-**35** with a fine yield, then by the same temperature, lower amounts of AlCl<sub>3</sub> are also tested. When 1.5 equiv. of AlCl<sub>3</sub> was used (Table 22 Entry 1), the small proportion of AlCl<sub>3</sub> was not enough to conduct the reaction and starting material L-**33** still remained. The effort to increase the AlCl<sub>3</sub> proportion up to 3 equiv. (Table 22 Entry 2) resulted in complicated mixture. Therefore, utilization of 6 equiv. of AlCl<sub>3</sub> is believed to effective for this reaction (Table 22 Entry 3).

The screening of Lewis acid utilization for acylation of L-**33** to benzene has been examined. When the conventional catalyst AlCl<sub>3</sub> (Table 22, Entry 3) was replaced with other common Lewis acids (Table 22, Entries 4–7) under the same reaction conditions (6 equiv. Lewis acid, at 70 °C), instead of desired product formation, hydrolysis occurred and L-**35** was detected after quenching the reaction mixture. Another metal halide, GaCl<sub>3</sub>, contributed to the

acylation, which resulted in low yield of L-**35** (Table 22, Entry 8). Compared with GaCl<sub>3</sub>, InCl<sub>3</sub> showed the lowest reactivity due to remaining the starting material of L-**33** recovered after the reaction mixture was quenched (Table 22, Entry 9). However, the L-**35** was produced from acylation utilized by GaCl<sub>3</sub> and showed retention of  $\alpha$ -proton chirality, the chemical yield of the desired  $\alpha$ -amino phenyl-ketone is far less than that produced with the reaction utilizing AlCl<sub>3</sub>. If an excess AlCl<sub>3</sub> was used, the Lewis acid apparently will coordinate to the most basic site<sup>94</sup> (the carbonyl oxygen atoms of OSu and *N*-acyl groups) and Friedel–Crafts acylation can take place, resulting in a high yield of the desired product. Therefore, AlCl<sub>3</sub> is preferred to undergo the reaction due to its high reactivity and also the fact that it has a considerably lower cost that brings economic benefits.

L-Isoleucine (L-Ile, L-31) achived for modification into active ester of OSu and its application for synthesis of  $\alpha$ -amino phenyl ketone via Friedel–Crafts acylation led this study to extent the other isoleucine derivatives utilization. First, D-isoleucine (D-Ile, D-31) followed the similar modification with L-31. The optical active D-31 underwent TFA protection to generate TFA-D-Ile (D-32, Scheme 13 (a)). The resulted D-32 then modified at its C-terminal with OSu to form TFA-D-Ile-OSu (D-33) and utilized it for acylation into benzene 34 which produced phenyl ketone of TFA-L-Ile-Ph (L-35) with a fine yield.

The use of racemization reaction of L-isoleucine into D-*allo*-isoleucine is beneficial in geochronology.<sup>40</sup> The racemization rate for these derivatives is relatively slow which suitable for utilization in aging prediction methods. This chemical feature of diastereomer of isoleucine derivative, the optical active L-/D-*allo*-isoleucine (L-/D-*allo*-Ile, L-/D-**36**) can also be employed for checking the chirality retention of  $\alpha$ -amino acids during its modification. Hence, L-/D-*allo*-Ile (L-/D-**36**) is undergone the similar *N*-terminal protection methods of other isoleucine derivatives to result in TFA-L-/D-*allo*-Ile (L-/D-**37**, Scheme 13 (b) and (c)). By the same manner, TFA-L-/D-*allo*-Ile (L-/D-**37**) was modified into TFA-L-/D-*allo*-Ile-OSu (L-/D-**38**) which was then utilized as representative acyl donor to result in TFA-L-/D-*allo*-Ile-Ph (L-/D-**39**, Scheme 13 (b) and (c)).



**Scheme 13** Synthesis and application of (a) TFA-D-isoleucine-*N*-hydroxysuccinimide ester (TFA-D-Ile-OSu, D-**33**); (b) TFA-L-*allo*-isoleucine-*N*-hydroxysuccinimide ester (TFA-L-*allo*-Ile-OSu, D-**38**); (c) TFA-D-*allo*-isoleucine-*N*-hydroxysuccinimide ester (TFA-D-*allo*-Ile-OSu, D-**38**).



**Figure 23** Selected <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>) of (a) TFA-L-/D-Ile (L-/D-32) and TFA-L-/D-*allo*-Ile (L-/D-37); (b) TFA-L-/D-Ile-OSu (L-/D-33) and TFA-L-/D-*allo*-Ile-OSu (L-/D-38); (c) TFA-L-/D-Ile-Ph (L-/D-35) and TFA-L-/D-*allo*-Ile-ph (L-/D-39)

In Figure 23, the asymmetric carbon at  $\alpha$ -position within stereoisomers of isoleucine and its diastereomer *allo*-isoleucine can be detected as distinguishable methine proton signal by <sup>1</sup>H-NMR. The optically active L-/D-**32** and L-/D-**37** show nonequivalence signals arising from epidemically related  $\alpha$ -proton (Figure 23 (a)). The comparison between L-/D-**32** ( $\delta_{\rm H}$  4.68 ppm) and its diastereomer L-/D-**37** ( $\delta_{\rm H}$  4.76 ppm) shows differences of the chemical shift at the  $\alpha$ -proton appearing in <sup>1</sup>H-NMR spectra, which suggested that isoleucine derivatives are sufficient tools for checking the epimerization during the reaction. The characterization of isoleucine derivatives activated at C-terminal by OSu (L-/D-**33** and L-/D-**38**) by <sup>1</sup>H-NMR can serve the purpose for checking the chirality preservation<sup>41</sup> during the modification or reaction process, in which only the  $\alpha$ -proton signal of L-/D-**33** in <sup>1</sup>H-NMR ( $\delta_{\rm H}$  4.97 ppm, Figure 23 (b)) can be observed for identification of isoleucine derivatives and no trace of L-/D-**38** ( $\delta_{\rm H}$ 5.10 ppm) was detected (Figure 23 (b)).

Based on <sup>1</sup>H-NMR (Figure 23 (c)), the chiral center at  $\alpha$ -position of TFA- $\alpha$ -aminophenyl ketone derivatives L-/D-**35** that were synthesized via Friedel–Crafts acylation of TFA- $\alpha$ -amino-OSu derivatives with benzene **34** clearly shows no appearance of any nonequivalence signals except for that at  $\delta_{\rm H}$  5.60 ppm. Meanwhile, proton signal at  $\alpha$ -methine of L-/D-**39** should be detected at  $\delta_{\rm H}$  5.74 ppm. This indicates that either L-/D-**1c** or its diastereomer, different in chiral center only at the  $\alpha$ -position of L-/D-**39**, shows no epimerization after the acylation. Compared with the acylation of aryl *N*-hydroxysuccinimide ester derivatives and electron-rich arenes, such as ferrocene and pyrene,<sup>90</sup> L-/D-**33** and L-/D-**38** are reactive in relatively electron-poor acyl acceptors when conventional AlCl<sub>3</sub> is used. Thus, the activation is not necessary under harsh conditions, such as utilization of super acidic trifluoromethanesulfonic acid.<sup>33,34</sup> Moreover, L-/D-**33** and L-/D-**38** can dissolve well in benzene and thus, no solvent is needed for the reaction system. In comparison, the reported *N*protected *N*-( $\alpha$ -aminoacyl)benzotriazole, which was previously used as an acyl donor for the Friedel–Crafts reaction, showed low solubility for the selected acyl acceptor and utilized CH<sub>2</sub>Cl<sub>2</sub> as the solvent.<sup>30</sup>

However, when isoleucine derivative and its diastereomer *allo*-isoleucine derivative are utilized for checking the chiral center by <sup>1</sup>H-NMR (Figure 24), it can offer a simple analysis that is able to comprehensively examine all the processes of TFA-protected  $\alpha$ -amino acid-OSu synthesis as the acyl donor of Friedel–Crafts acylation. To support our understanding, the optical rotation of all corresponding L-/D- $\alpha$ -amino acid derivatives was also conducted for checking the retention given as  $\alpha$ -proton chirality during the process. Moreover, based on our finding of  $\alpha$ -protons in <sup>1</sup>H-NMR (Figure 23), it appears that the formation of acylium cation

(Figure 3 (b)), given as the common Friedel–Crafts intermediate, can successfully retard the  $\alpha$ -proton chirality.



**Figure 24** Correlation of isoleucine derivative and its diastereomer *allo*-isoleucine derivative for checking the chiral center by <sup>1</sup>H-NMR

For further applications of  $\alpha$ -amino acid-OSu as a potential acyl donor that can be easily activated by the conventional Friedel–Craft catalyst of AlCl<sub>3</sub>, L-**33** was then used in acylation reactions to convert it with various arenes (Table 23). The L-**33** reacted with 300 equiv. of arenes (**40–44**) by using the same condition with the previously optimized condition for acylation of benzene (**34**) which is utilized of 6 equiv. of AlCl<sub>3</sub> and reacted for 3 h. TFA-L-Ile-Ar (L-**45**, L-**47**, L-**49**–L-**51**) was the main isolate with a fine yield. The acylation into electron-donating arenes, such as toluene **40** and anisole **41** mainly occurs at a less hindered position (*p*-position is prior to *o*-position with ratio L-**45**:L-**46** is 5:1 and L-**47**:L-**48** is 18:1, respectively). From <sup>1</sup>H-NMR, only the  $\alpha$ -proton signal of desired L-**45**, L-**47**, and L-**49**–L-**51** can be observed which implies that there is no other diastereomers showing the  $\alpha$ -proton chirality retention of TFA-protected  $\alpha$ -amino aryl-ketone.

# $\label{eq:table23} \begin{array}{l} \mbox{Table 23 Friedel-Crafts reaction of TFA-L-Ile-OSu (L-33) into various arenes (40-44) that} \\ \mbox{were catalyzed by AlCl}_3 \mbox{ to yield TFA-L-Ile-Ar (L-45-L-51)} \end{array}$

|       |                     | $ \begin{array}{c} 0 \\ 0 \\ 0 \\ 0 \\ \end{array} \\ 0 \\ \end{array} \\ \begin{array}{c} 300 \text{ equiv. Arene,} \\ 6.0 \text{ equiv. AlCl}_3 \\ \hline 70 \text{ °C, 3 h} \\ \end{array} \\ \begin{array}{c} 0 \\ (S) \\ HN \\ \end{array} \\ \begin{array}{c} 0 \\ (S) \\ (S) \\ HN \\ \end{array} \\ \begin{array}{c} 0 \\ (S) \\ (S) \\ HN \\ \end{array} \\ \begin{array}{c} 0 \\ (S) \\ (S) \\ HN \\ \end{array} \\ \begin{array}{c} 0 \\ (S) \\ (S) \\ HN \\ \end{array} \\ \end{array} $ \\ \begin{array}{c} 0 \\ (S) \\ (S) \\ (S) \\ HN \\ \end{array} \\ \begin{array}{c} 0 \\ (S) \\ (S) \\ (S) \\ HN \\ \end{array} \\ \end{array} \\ \begin{array}{c} 0 \\ (S) \\ (S) \\ (S) \\ HN \\ \end{array} \\ \end{array} \\ \begin{array}{c} 0 \\ (S) \\ (S) \\ (S) \\ \end{array} \\ \end{array}  |        |
|-------|---------------------|--|--------|
|       | TFA-L-Ile-C         | A IFA<br>Su (L-33) TFA-L-Ile-Ar (L-40–L-46)  |        |
| Entry | Arene               | TFA-L-Ile-Ar   | %Yield |
| 1     | 40                  | $\begin{array}{c} \overbrace{(S)}^{I} \overbrace{(S)}^{O} \overbrace{(I-45)}^{I} + \overbrace{(S)}^{O} \overbrace{(I-45)}^{I} + \overbrace{(S)}^{O} \overbrace{(S)}^{I} \overbrace{(I-46)}^{I} \\ TFA-L-Ile-Ph(4-Me) (L-45) \\ TFA-L-Ile-Ph(2-Me) (L-46) \\ (5:1) \end{array}$   | 71     |
| 2     | OCH <sub>3</sub> 41 | $\begin{array}{c} \overbrace{(3)}^{\bullet} \overbrace{(3)}^{\bullet} \overbrace{(4-2)}^{\bullet} + \overbrace{(18:1)}^{\bullet} \overbrace{(18:1)}^{\circ} $ | 72     |
| 3     | 42                  | тFA-L-Ile-Ph(3,4-Me) (L- <b>49</b> )   | 78     |
| 4     | 43                  | TFA-L-Ile-Ph(2,4-Me) (L- <b>50</b> )   | 78     |
| 5     | 44                  | TFA-L-Ile-Ph(2,5-Me) (L-51)  | 79     |



Scheme 14 Typical reaction of acylation by Weinreb amides system

Unlike TFA-protected  $\alpha$ -amino acid-OSu that can utilize various commercially available acyl acceptors, Weinreb amides (N-methoxy-N-methylamides,<sup>27</sup> popular methods for the synthesis of  $\alpha$ -amino aryl-ketones,<sup>95</sup> Scheme 14) are considerably less efficient for direct acylation due to limitation of Grignard or organolithium reagents, which sometimes need to be synthesized before use. In this study, the urge for choosing TFA-protecting group is due to its stability in the presence of Lewis acid, which is an essential reagent for conventional Friedel-Crafts acylation. Moreover, because of extremely basic condition of the Weinreb amides system, only carbamate-based protecting group such as t-butyl (BOC), benzyl (Cbz) or fluorenylmethyloxycarbonyl (Fmoc), that stable under alkaline condition, is utilized. The limited study of previous TFA-protected  $\alpha$ -amino aryl-ketone synthesis during the last decade is due to this reason. Therefore, the introduction of TFA- $\alpha$ -amino-OSu played an important role as representative acyl donor for synthesis of new compound. For example, TFA-D-Ile-OSu (D-33) and TFA-L-/D-allo-Ile-OSu (L-/D-38) are considered as novel acyl donor for Friedel-Crafts acylation. The resulted amino phenyl-ketone of TFA-L-/D-Ile-Ph (D-35) and TFA-L-/D-allo-Ile-Ph (L-/D-39) are also novel compounds that contribute in the study of TFA-protected  $\alpha$ -amino aryl-ketone synthesis.

# 3.2.2 Friedel–Crafts Acylation of aliphatic $\alpha$ -amino acid derivatives: Synthesis and modification of various aliphatic $\alpha$ -amino acid derivatives

Friedel–Crafts acylation for synthesis of aryl-keto  $\alpha$ -amino acids is commonly utilized  $\alpha$ -amino acid chloride<sup>25,32</sup> which is known for its high reactivity for this reaction. Katritzky et al.<sup>30,86</sup> also reported the used of  $\alpha$ -aminoacyl benzotriazole as an amide-type acyl donor for comprehensive aryl-keto  $\alpha$ -amino acid synthesis without any optical loss. However, ester type of acyl donor utilized in  $\alpha$ -amino acids is still far to explore.

In 2000, Olah and co-workers<sup>96</sup> introduced the benzoic acid methyl ester as a novel acyl donor to undergo Friedel–Crafts acylation. Even by using the highly deactivated nitrobenzene and benzotrifluoride as acyl acceptor, acylation with benzoic acid methyl ester catalyzed by strong acid still showed good reactivity. Followed by this ester utilization, the benzoic acid *N*-

hydroxysuccinimide ester, benzoic acid tetrafluorophenyl ester, and benzoic acid phenyl ester are reported to be effective for acylation of ferrocene and pyrene under strong acid conditions. However, the contribution of ester as an acyl donor is broadening selection of active skeleton for more comprehensive acylation. In this part, potential acyl donor of TFA- $\alpha$ -amino acid-OSu is also tried for other aliphatic  $\alpha$ -amino acids as described below.

### Synthesis and application of TFA-glycine-N-hydroxysuccinimide ester



Scheme 15 Synthesis of TFA-Gly (52)

Glycine (Gly, **51**) is the simplest natural  $\alpha$ -amino acid that does not contain chiral center. It is an important  $\alpha$ -amino acid the formation of porphyrins (skeleton of metal-containing oxygen-transport protein in red blood cell (eukaryotes)) which can undergo the condensation with succinyl-coenzyme A (CoA) from citric acid cycle to yield  $\alpha$ -amino-aryl ketone.<sup>97</sup> Since glycine ketone is substantial in eukaryotes, glycine was also tried for Friedel–Crafts acylation. First, glycine (**51**) was underwent TFA protection to obtain TFA-Gly (**52**) in a satisfied yield (Scheme 15).



Scheme 16 Synthesis of TFA-Gly-OSu (53). <sup>a</sup> WSCD-HCl is directly added into reaction. Solvent was removed under reduced pressure. Then, residue was dissolved in ethyl acetate and washed by 1M HCl.

Next, TFA-Gly (**52**) was directly transformed to *N*-hydroxysuccinimide ester by of 1.0 equiv. of WSCD-HCl and 1.1 equiv. of NHS to yield TFA-Gly-OSu (**53**, Scheme 16). Utilization of dichloromethane (Scheme 16 (a)) was less effective as a solvent for this reaction, and then the solvent was changed to dimethylformamide that resulted in TFA-Gly-OSu (**53**) with an excellent yield (Scheme 16 (b)). The resultant **53** was then directly tested for Friedel–Crafts acylation by reaction with benzene at 70 °C to produce TFA-Gly-Ph (**54**, Scheme 17). In line with previous utilization of isoleucine derivatives, acylation of TFA-Gly-OSu (**53**) at 70 °C was sufficient to giving TFA-Gly-Ph (**54**) with a fine yield.



Scheme 17 Application of TFA-Gly-OSu (53) to result in TFA-Gly-Ph (54)

#### Synthesis and application of TFA-L-/D-alanine-N-hydroxysuccinimide esters



Scheme 18 Synthesis of TFA-L-/D-Ala (L-/D-56)

As natural  $\alpha$ -amino acid that contains a methyl group side chain in comparison to glycine **51**, optically pure L-/D-alanine (L-/D-Ala, L-/D-**55**) is the most primary amino acid released by muscle that is converted to glucose by liver for maintaining sugar level in blood of fasted man.<sup>98</sup> In this study, the important  $\alpha$ -amino acid of L-/D-Ala (L-/D-**55**) was directly *N*-terminal protected by TFA protection to result in TFA-L-/D-Ala (L-/D-**56**, Scheme 18). Ester formation for carbonyl activation of TFA-L-/D-Ala (L-/D-**56**) was conducted by utilization of WSCD-HCl and NHS to result in TFA-L-/D-Ala-OSu (L-/D-**57**, Table 24).

| $\begin{array}{c} & & \\$ |              |                         |                           |                                 |                 |  |  |  |
|--|--------------|-------------------------|---------------------------|---------------------------------|-----------------|--|--|--|
| Entry  | Material     | WSCD-HCl                | NHS                       | Solvent                         | 57              |  |  |  |
| Lintiy   | 56           | (equiv.)                | (equiv.)                  | Solvent                         | (% Yield)       |  |  |  |
| 1  | L-           | 1.3 <sup>a</sup>        | 1.3                       | DMF                             | 60 <sup>b</sup> |  |  |  |
| 2  | D-           | 1.3 <sup>a</sup>        | 1.3                       | DMF                             | 53 <sup>b</sup> |  |  |  |
| 3  | L-           | 1.3 <sup>a</sup>        | 1.1                       | Acetone                         | 53 <sup>b</sup> |  |  |  |
| 4  | D-           | 1.3 <sup>a</sup>        | 1.1                       | Acetone                         | 52 <sup>b</sup> |  |  |  |
| 5  | L-           | 1.3 <sup>a</sup>        | 1.1                       | $CH_2Cl_2$                      | 51 <sup>b</sup> |  |  |  |
| 6  | D-           | 1.3 <sup>a</sup>        | 1.1                       | CH <sub>2</sub> Cl <sub>2</sub> | 56 <sup>b</sup> |  |  |  |
| 7  | L-           | 1.0                     | 1.1                       | $CH_2Cl_2$                      | 52              |  |  |  |
| 8  | D-           | 1.0                     | 1.1                       | CH <sub>2</sub> Cl <sub>2</sub> | 42              |  |  |  |
| 9  | L-           | <b>1.0</b> <sup>a</sup> | 1.1                       | $\overline{CH_2Cl_2}$           | 75 <sup>c</sup> |  |  |  |
| 10   | D-           | <b>1.0</b> <sup>a</sup> | 1.1                       | $CH_2Cl_2$                      | 71 <sup>c</sup> |  |  |  |
| <sup>a</sup> WSCD-   | HCl is direc | tly added to react      | ion mixture. <sup>1</sup> | Solvent was                     | s removed under |  |  |  |

reduced pressure. Then, residue was dissolve in ethyl acetate and washed by  $H_2O$ , 1M HCl, sat. NaHCO<sub>3</sub>, and sat. NaCl. <sup>c</sup> Reaction mixture is directly washed by sat. NaCl.

Since TFA-Gly-OSu (53, Scheme 16) can be successfully synthesized by utilization of dimethylformamide, the reaction of L-/D-56 with 1.3 equiv. WSCD-HCl and 1.3 equiv. NHS was conducted in dimethylformamide used as the solvent. However, only moderate yield of L-/D-57 was produced (Table 24, Entries 1–2). The attempt to increase the yield of L-/D-57 was continued by replacing the solvent with acetone and dichloromethane (Table 24, Entries 2–6), but no improvement was found. The harsh condition might take place in the first place; thus the reagent proportion was lowered (Table 24, Entries 2–6). Since the yield of L-/D-57 was not improved after the tested condition, the consideration for the purification method by washing directly with sat. NaCl was performed, which can increase the fine yield of L-/D-57 (Table 24, Entries 2–6). Thus, the representative L-/D-57 can be readily used as acyl donor for Friedel–Crafts acylations.



Scheme 19 Application of TFA-L-/D-Ala-OSu (L-/D-57) to result in TFA-L-/D-Ala-Ph (L-/D-58) at (a) 70 °C and (b) room temperature

Conventional Friedel–Craft by utilization of AlCl<sub>3</sub> is applied for acylation of L-/D-**57** with benzene to produce TFA-L-/D-Ala-Ph (L-/D-**58**) at 70 °C for 2 h (Scheme 19 (a)). In the previous study, TFA *N*-( $\alpha$ -aminoacetyl)benzotriazole is reported to acylate benzene by the use of AlCl<sub>3</sub> at 20 °C for 3 h and resulted in  $\alpha$ -aminoacetyl phenyl-ketone in the moderate yield (63% yield).<sup>30</sup> For comparison, L-/D-**57** also tested at room temperature for 36 h which resulted in fine yield of L-/D-**58** (78–84% yield, Scheme 19 (b)). This result ensured L-/D-**58** reactivity as potential acyl donor for this reaction and its high solubility under excess of benzene is sufficient for resulting high yield of ketone product. In similar with isoleucine derivatives utilization, acylation by the used L-/D-**57** is efficient and resulted in L-/D-**58** without loss of chirality.

#### Synthesis and application of TFA-L-/D-valine-N-hydroxysuccinimide esters

After the success of simple  $\alpha$ -amino acids, such as glycine (**51**) and L-/D-alanine (L-/D-**55**), for synthesis of  $\alpha$ -amino phenyl ketones via *N*-hydroxysuccinimide ester formation, a branched-chain of natural  $\alpha$ -amino acid, such as L-/D-valine (L-/D-**59**), was also tested whether it is accepted as a potential acyl donor after conversion to the TFA- $\alpha$ -amino acid-OSu. First, optically pure L-/D-valine were protected by TFA protection and resulted in TFA-L-/D-valine (TFA-L-/D-Val, L-/D-**60**) (Scheme 20). Next, L-/D-**60** were transformed to TFA-L-/D-Val-OSu (L-/D-**61**) within fine yield (Scheme 20). The TFA-L-/D-Val-Ph (L-/D-**62**) were produced under conventional Friedel–Crafts condition after the reaction of L-/D-**61** with benzene for 4 h (Scheme 20). Organic synthesis and modification that based on L-/D-valine (L-/D-**59**) chemical feature in this study allowing the synthesis of novel compounds, TFA-D-Val-OSu (D-**60**) and TFA-D-Val-Ph (D-**61**), which contribute into vast exploration for peptide synthesis in the future.



Scheme 20 Synthesis and application of TFA-L-/D-Val-OSu (L-/D-61)

### Synthesis and application of TFA-L-/D-leucine-N-hydroxysuccinimide esters

The other typical branched-chain of natural  $\alpha$ -amino acid besides L-/D-valine (L-/D-**59**) is L-/D-leucine (L-/D-**63**) which also underwent modification to become potential acyl donor of  $\alpha$ -amino acid-OSu. The optically pure L-/D-**63** were protected by TFA protection and resulted in TFA-L-/D-Leu (L-/D-**64**, Scheme 20), respectively. Next, by the same condition when utilization of isoleucine derivatives, TFA-L-/D-Leu (L-/D-**64**) were transformed to TFA-L-/D-Leu-OSu (L-/D-**65**, Scheme 20) within fine yield.

The TFA-L-/D-Leu-Ph (L-/D-**66**) can be produced under a conventional Friedel–Crafts condition after the reaction of L-/D-**65** with benzene at 70 °C for 2 h (Scheme 21). The TFA-D-Leu-OSu (D-**65**) is considered as a novel compound which was synthesized in this study. Moreover, due to stability of TFA-L-/D-Leu-OSu (L-/D-**65**) for Friedel–Crafts acylation, the novel compound of TFA-L-/D-Leu-Ph (L-/D-**66**) can be synthesized successfully. Based on the comparison between optical acitive alanine, valine, or leucine, utilization of *N*-hydroxysuccinimide ester is independent with branched-chain of  $\alpha$ -amino acids in which

reaction of TFA- $\alpha$ -amino-OSu can result in fine yield of  $\alpha$ -amino phenyl ketone without loss of chirality.



Scheme 21 Synthesis and application of TFA-L-/D-Leu-OSu (L-/D-65). <sup>a</sup> Calculated from <sup>1</sup>H-NMR.

### Synthesis and application of TFA-L-/D-norvaline-N-hydroxysuccinimide esters

Comprehensively, the none-branched-chain of unnatural aliphatic  $\alpha$ -amino acid of optically pure L-/D-norvaline (L-/D-Nva, L-/D-67) is utilized in this study. After completion the TFA protection, the resultant TFA-L-/D-Nva (L-/D-68, Scheme 22) were directly transformed to TFA-L-/D-Nva-OSu (L-/D-69) using WSCD-HCl and NHS (Scheme 23). Within the same equiv. of NHS (1.1 equiv.) for this typical reaction, slightly higher proportion of WSCD-HCl from 1.0 equiv. (Scheme 23 (a)) into 1.1 equiv. (Scheme 23 (b)) was utilized, and TFA-L-/D-Nva-OSu (L-/D-69) formation can be improved. The reaction was conducted at 0 °C due to exothermic reaction when L-/D-67 were used.



Scheme 22 Synthesis of TFA-L-/D-Nva (L-/D-68)



Scheme 23 Synthesis of TFA-L-/D-Nva-OSu (L-/D-69) by utilizing (a) 1.0 equiv. of WSCD-HCl and (b) 1.1 equiv. of WSCD-HCl.

The representative acyl donors of L-/D-69 also showed high reactivity toward benzene **34** at 70 °C; that resulted in TFA-L-/D-Nva-Ph (L-/D-70) with a fine yield by 3 h (Scheme 24 (a)). Similar with natural  $\alpha$ -amino acids that were previously tested for the synthesis of  $\alpha$ -amino phenyl ketone derivatives, L-/D-69 showed high reactivity toward benzene and L-/D-70 can be formed at room temperature (Scheme 24 (b)). Although *N*-protected  $\alpha$ -amino-OSu derivatives is known for its stability and reactivity in peptide synthesis,<sup>89</sup> its application for unnatural  $\alpha$ -amino acids has still not been yet fully explored. Thus, the synthesized novel compound L-/D-69 which can be utilized for the synthesis of L-/D-70 can contribute to synthesis of new compounds and broaden exploitation for modification of the  $\alpha$ -amino acid structures.



**Scheme 24** Application of TFA-L-/D-Nva-OSu (L-/D-69) to result in TFA-L-/D-Nva-Ph (L-/D-**70**) at (a) 70 °C and (b) room temperature. <sup>a</sup>Calculated from <sup>1</sup>H-NMR.
#### Synthesis and application of TFA-L-/D-norleucine-N-hydroxysuccinimide esters

To expand the application of unnatural alphatic  $\alpha$ -amino acid exploration, the longer none-branched-side chain of L-/D-norleucine (L-/D-Nle, L-/D-71) was tested in this study. *N*-Terminal of L-/D-71 was protected with TFA to give TFA-L-/D-Nle (L-/D-72, Scheme 25). When TFA-L-/D-Nle (L-/D-72) subjected with WSCD-HCl and NHS for synthesis of TFA-L-/D-Nle-OSu (L-/D-73), there is no improvement for the product yield after reaction with different WSCD-HCl proportion (Scheme 26). Utilization of 1.0 equiv. of WSCD-HCl (Scheme 26 (a)) was found to produce not only L-/D-73 due to observation of unidentified compound by <sup>1</sup>H-NMR, while utilization of 1.1 of equiv. WSCD-HCl (Scheme 26 (b)) was preferred to conduct this reaction. The moderate yield of L-/D-73 was sufficient for further application as acyl donor for Friedel–Crafts acylation.



Scheme 25 Synthesis of TFA-L-/D-Nle (L-/D-72)



Scheme 26 Synthesis of TFA-L-/D-Nle-OSu (L-/D-73) by utilizing (a) 1.0 equiv. of WSCD-HCl and (b) 1.1 equiv. of WSCD-HCl. <sup>a</sup> Contaminated with unidentified compound, observed as another  $\alpha$ -proton signal in <sup>1</sup>H-NMR spectrum (ratio 1.00:0.06).

The longer aliphatic side-chain of L-/D-71, compared with L-/D-67, is not hampered its reactivity for the reaction with benzene to result in TFA-L-/D-Nva-Ph (L-/D-74). The L-/D-73 showed high reactivity for both reactions at 70 °C (Scheme 27 (a)) and at room temperature (Scheme 27 (b)). These results indicate that yield of  $\alpha$ -amino phenyl ketone without loss of chirality between optical active natural  $\alpha$ -amino acids of alanine, valine, or leucine, and unnatural  $\alpha$ -amino acids of norvaline and norleucine utilized for *N*-hydroxysuccinimide ester is independent with branched-chain or none-branched-chain of  $\alpha$ -amino acids. Moreover, the resulted TFA-L-/D-Nle-OSu (L-/D-73) and TFA-L-/D-Nle-Ph (L-/D-74) are novel compound which can be use for further application in bimolecular modification.



**Scheme 27** Application of TFA-L-/D-Nle-OSu (L-/D-73) to result in TFA-L-/D-Nle-Ph (L-/D-74) at (a) 70 °C and (b) room temperature. <sup>a</sup> Calculated from <sup>1</sup>H-NMR.

In this study, the introduction of two pure enantiomers of L- and D- $\alpha$ -amino acids that were modified into TFA- $\alpha$ -amino acid-OSu and their utilization as potential acyl donor to result in  $\alpha$ -amino aryl-ketone synthesis showed identical optical rotation with opposite sign. Hence, either TFA- $\alpha$ -amino acid-OSu construction or its application for acylation under Friedel–Craft condition show the chirality retention, in which line the utilization of L-/Disoleucine and its diastereomer L-/D-*allo*-isoleucine for detection of  $\alpha$ -amino aryl-ketone maintained optical activity confirmable by the appearance of nonequivalence  $\alpha$ -proton in <sup>1</sup>H-NMR spectra.

# Synthesis and application of TFA-L-/D-proline-N-hydroxysuccinimide esters

The L-/D-proline (L-/D-**75**) are the only aliphatic  $\alpha$ -amino acids of which secondary amino group, or somethimes name as an imino acid, attachs to a five-member ring in a molecule. Thus, proline is potentially tested for  $\alpha$ -amino acid aryl-ketone synthesis. As the substrate, L-/D-**75** first was *N*-TFA-protected to give TFA-L-/D-Proline (L-/D-**76**, Scheme 28), before transforming into TFA-L-/D-Pro-OSu (L-/D-**77**) within 3 h at room temperature by utilization of 1.1 equiv. NHS and 1 equiv. of WSCD-HCl in CH<sub>2</sub>Cl<sub>2</sub> (Scheme 28). Direct acylation of TFA-L-/D-Pro-OSu (L-/D-**77**) with 300 equiv. of benzene which was activated by 6 equiv. AlCl<sub>3</sub> can generate TFA-L-/D- Pro-Ph (L-/D-**78**)<sup>25,32,99</sup> with an excellent yield (81–84%, Scheme 28).



Scheme 28 Synthesis and utilization of TFA-L-/D-Pro-OSu (L-/D-77)

The observation of another  $\alpha$ -proton signal of proline derivatives (L-/D-**76**–L-/D-**78**) by <sup>1</sup>H-NMR analysis suggested the existance of *cis*- and *trans*-isomers. Isomerization of *N*-protected proline is known and plays a key role in the rate-determining steps of protein folding.<sup>100</sup> To ensure these results, <sup>1</sup>H-NMR comparison between TFA-L-Pro (L-**76**) with commercially available *N*-acetylated-L-Pro (Ac-L-Pro, L-**79**) is described in Figure 25. The optically pure L-**79** also shown two proportions of  $\alpha$ -protons signals in <sup>1</sup>H-NMR. Hence, it also suggested that all *N*-TFA-proline derivatives (L-/D-**76**–L-/D-**78**) exhibit no loss of chirallity.



Figure 25 Comparison of TFA-L-Pro (L-76) with Ac-L-Pro (L-79) in <sup>1</sup>H-NMR spectra

# 3.2.3 Friedel–Crafts acylation of aromatic *a*-amino acid derivatives: Synthesis and modification of phenylalanine and tyrosine derivatives synthesis and modification

In recent, there is less attention to the study of *N*-TFA non-aliphatic  $\alpha$ -amino acid ketones. This might be due to difficulties in the reactive precursor synthesis. *N*-Protected phenylalanine acid chloride<sup>101</sup> previously synthesized was known to be prolonged to racemization in peptide synthesis.<sup>91</sup> The utilization of azlactones in phenylalanine is also known for rapid racemization under a strong acidic condition.<sup>101</sup> Anhydro-*N*-carboxy-phenylalanine<sup>84</sup> was previously reported to be prepared by using a toxic gas of phosgene<sup>85</sup> and is considerably less effective due to the existence of two possible acyl donors one of which will be wasted after the reaction. The current *N*-protected phenylalanine benzotriazole<sup>30</sup> is reported to be more convenient to handle compared to  $\alpha$ -amino acid chloride, but the preparation was conducted under in situ conditions that indicate the isolation takes more effort.

In the previous part of this chapter, *N*-hydroxysuccinimide ester (OSu) of various aliphatic  $\alpha$ -amino acids showed advantageous properties for direct acylation by conventional Friedel–Crafts acylation.<sup>102</sup> In this study, the first utilization and modification of aromatic  $\alpha$ -amino acid, such as phenylalanine and tyrosine, is then tried as a potential acyl donor for acylation. Direct acylation via an active intermediate of OSu is also expected to have a high reactivity for acylation and a high availability for storage.



Scheme 29 Synthesis of TFA-L-/D-Phe-OSu (L-/D-82)

Initially, the optically active L-/D-phenylalanine (L-/D-Phe, L-/D-**80**) underwent *N*-TFA protection by using ethyl trifluoroacetate in the presence of triethylamine in methanol to generate TFA-L-/D-Phe (L-/D-**81**, Scheme 29). The L-/D-**81** was then transformed into TFA-L-/D-Phe-OSu (L-/D-**82**) within 3 h at room temperature by utilization of 1.1 equiv. NHS and 1 equiv. of WSCD-HCl in CH<sub>2</sub>Cl<sub>2</sub> (Scheme 29). The resulting TFA-L-/D-Phe-OSu (L-/D-**82**) was ready to use for acylation and could be stored at -20 °C for more than 3 months.

The corresponding TFA-L-/D-Phe-OSu (L-/D-82) were tested for acylation to benzene 34 by activation with a conventional Friedel–Crafts catalyst of AlCl<sub>3</sub> (Table 25). At 70°C, increasing the proportion of AlCl<sub>3</sub> (Table 25, Entries 1-4 and 7-8) or increasing the proportion of benzene (Table 25, Entries 5-6) resulted in a yield of desired inter-molecular product TFA-L-/D-Phe-Ph (L-/D-83) without improvement. Similarly, with lowering the temperature from 70 °C to room temperature (Table 25, Entries 3-4 and 13-14), no improvement can be achieved. This phenomenone was caused by the formation of an intramolecular cyclization product of TFA-L-/D-cPhe (L-/D-84)<sup>30</sup> in moderate yield (Table 25). Comparison of TFA- L-Phe-Ph (L-83) and TFA-L-cPhe (L-84) in <sup>1</sup>H-NMR spectra are shown in Figure 26. From this <sup>1</sup>H-NMR spectra, it clearly indicates aromatic signals in down field  $(\delta_{\rm H} 6.8-8.2 \text{ ppm})$  of inter-molecular product containing around twice aromatic proton proportion than intra-molecular product ( $\delta_{\rm H}$  7.2–8.0 ppm). From the integration of <sup>1</sup>H-NMR spectra, it can be concluded that in inter-molecular product the addition of benzene after acylation rection can be indentified. Based on this <sup>1</sup>H-NMR observation, formation of TFA-LcPhe (L-84) can be clarified. The competing intra-molecular reaction specifically occurred on aromatic  $\alpha$ -amino acid,<sup>30,31</sup> which presumably suggests that the generation of benzyl carbonium ion<sup>101</sup> is faster to react with an aromatic side chain of phenylalanine rather than into benzene. As this phenomenon can be observed by subjection of L-/D-82 at room temperature and by increasing the proportion of benzene (Table 25, Entries 11-16) under a high amount of AlCl<sub>3</sub>, intra-molecular cyclization of L-/D-84 still cannot be suppressed.

 Table 25 Friedel–Crafts reaction of TFA-L-/D-Phe-OSu (L-/D-82) into benzene 34 catalyzed by AlCl<sub>3</sub><sup>a</sup>



| Entry <sup>a</sup>  | Material<br>82 | Tempt. | AlCl <sub>3</sub><br>(equiv.) | Benzene<br>(equiv.) | Time | Inter-molecular<br>product<br>TFA-L-/D-Phe-Ph<br>(L-/D- <b>83</b> , % Yield) | Intra-molecular<br>product<br>TFA-L-/D-cPhe<br>(L-/D- <b>84</b> , %Yield) |
|---|----------------|--------|-------------------------------|---------------------|------|--|---|
| 1   | L-             | 70 °C  | 3                             | 300                 | 45 m | 9  | 45  |
| 2   | D-             | 70 °C  | 3                             | 300                 | 45 m | 8  | 44  |
| 3   | L-             | 70 °C  | 6                             | 300                 | 45 m | 38   | 50  |
| 4   | D-             | 70 °C  | 6                             | 300                 | 45 m | 43   | 52  |
| 5   | L-             | 70 °C  | 6                             | 600                 | 45 m | 31   | 58  |
| 6   | D-             | 70 °C  | 6                             | 600                 | 45 m | 34   | 61  |
| 7   | L-             | 70 °C  | 12                            | 300                 | 45 m | 26   | 55  |
| 8   | D-             | 70 °C  | 12                            | 300                 | 45 m | 33   | 50  |
| 9   | L-             | 70 °C  | 6                             | _b                  | 45 m | _  | 64  |
| 10  | D-             | 70 °C  | 6                             | _b                  | 45 m | —  | 69  |
| 11  | L-             | rt     | 12                            | 150                 | 2 d  | 40   | 59  |
| 12  | D-             | rt     | 12                            | 150                 | 2 d  | 37   | 61  |
| 13  | L-             | rt     | 12                            | 300                 | 2 d  | 46   | 43  |
| 14  | D-             | rt     | 12                            | 300                 | 2 d  | 42   | 40  |
| 15  | L-             | rt     | 12                            | 600                 | 2 d  | 40   | 54  |
| 16  | D-             | rt     | 12                            | 600                 | 2 d  | 41   | 57  |
| 17  | L-             | rt     | 12                            | _b                  | 2 d  | _  | 69  |
| 18  | D-             | rt     | 12                            | _b                  | 2 d  | _  | 79  |
| <sup>a</sup> Proportion was determined by <sup>1</sup> H NMR in acetone- $d_6$ . <sup>b</sup> Utilization with 300 equiv. |                |        |                               |                     |      |  |   |

CH<sub>2</sub>Cl<sub>2</sub> under reflux condition



Figure 26 Selected <sup>1</sup>H-NMR comparison of TFA-L-/D-Phe-Ph (L-/D-83) with TFA-L-/D-cPhe (L-/D-84)

The typical phenylalanine as acyl donor reaction with  $CH_2Cl_2$  in the absence of benzene that results in intra-molecular acylation is known well<sup>30,85,101</sup> and investigation of TFA-L-/D-Phe-OSu (L-/D-**82**) under this condition at 70°C (Table 25, Entries 9–10) and at room temperature (Table 25, Entries 17–18) showed similar ration of intra-molecular cyclization formation. Both the inter- and intra-molecular product is known to preserve the chirality supported by identical optical rotation with the opposite sign. Based on Table 25, utilization of TFA-L-/D-Phe-OSu (L-/D-**82**) showed relatively high reactivity toward acylation into benzene under activation by AlCl<sub>3</sub> to result in *N*-TFA α-amino-aryl ketones. In the contrary, anhydro-*N*-carboxy-DL-phenylalanine,<sup>85</sup> as previously reported, did not result in any α-amino-aryl ketones.

Since utilization with more excess benzene showed TFA-L-/D-cPhe (L-/D-84) considerably favored formation, TFA-L-/D-Phe-OSu (L-/D-82) was also tested to various arenes. The treatment of TFA-L-/D-Phe-OSu (L-/D-82) with 300 equiv. of benzene and 6 equiv. of AlCl<sub>3</sub> (Table 25, Entries 3–4) showed relatively efficient acylation, thus this condition was utilized for acylation into various arenes. Introduction of the reaction between TFA-L-/D-Phe-OSu (L-/D-82) and toluene 40 (Table 26, Entries 1-2) shows inter-molecular reaction as preferred one, which resulted in TFA-L-/D-Phe-Ph(4-Me) (L-/D-85) in much moderate yield (52–58%), rather than reaction between TFA-L-/D-Phe-OSu (L-/D-82) and benzene (Table 25). The methyl substituent acts as an electron donating group in aromatic moiety of toluene which might suppress intra-molecular formation of the acylated product. The occurrence of TFA-L-/D-Phe-Ph(4-OMe) (L-/D-86) were relatively in high yield (66-68%, Table 26, Entries 3-4), supporting the effect of the electron donating group that activated aromatic moiety for a fast electrophilic aromatic substitution during a conventional Friedel-Crafts acylation. The methoxy group of anisole might play an important role for the suppression of intra-molecular cyclization since no TFA-L-/D-cPhe (L-/D-84) was detected by <sup>1</sup>H-NMR. The acylation mostly occurs at a less hindered position (p-position) of toluene and anisole (ratio between L-/D-85 and L-/D-87 is 17:1 and L-/D-86 and L-/D-88 is 13:1, respectively). Regarding xylenes (Table 26 Entries 5–10), each of the di-methyl group substituent might induce inter- and intramolecular reactions. The high reactivity was shown in o-xylene that resulted in approximately 70% yield of TFA-L-/D-Phe-Ph (3,4-Me) (L-/D-89) which suppressed intra-molecular cyclization up to 15% yield. All the TFA-L-/D-Phe-arenes synthesized from TFA-L-/D-Phe-OSu retained their chirality and the reaction was easier to handle compared to phenylalanine acid chloride.<sup>101</sup>

Table 26 Friedel–Crafts reaction of TFA-L-/D-Phe-OSu (L-/D-82) into various arenes (40-44) catalyzed by AlCl<sub>3</sub>



| Entry | Material<br>82 | Arene               | TFA-L-Ile-Ar  | Inter-molecular<br>product<br>TFA-L-/D-Phe-Ar<br>(%Yield) | Intra-molecular<br>product<br>TFA-L-/D-cPhe<br>(L-/D- <b>84</b> , %Yield) |
|-------|----------------|---------------------|---|---|---|
| 1     | L-             |                     |   | 52  | 21  |
| 2     | D-             | 40                  | TFA-L-/D-Ile-Ph(4-Me) (L-/D-85)<br>TFA-L-/D-Phe-Ph(2-Me) (L-/D-87)<br>(17:1)  | 58  | 26  |
| 3     | L-             | OCH <sub>3</sub> 41 | $ \begin{array}{c}                                     $  | 68  | _   |
| 4     | D-             |                     | $TFA \rightarrow OCH_{3} \rightarrow TFA$ $TFA-L-/D-Phe-Ph(4-OMe) (L-/D-86) \rightarrow TFA-L-/D-Phe-Ph(2-OMe) (L-/D-88) $ $(13:1)$ | 66  | _   |

| Entry<br>(cont') | Material<br>82 | Arene                                      | TFA-L-Ile-Ar   | Inter-molecular<br>product<br>TFA-L-/D-Phe-Ar<br>(% Yield) | Intra-molecular<br>product<br>TFA-L-/D-cPhe<br>(L-/D- <b>84</b> , %Yield) |
|------------------|----------------|--|--|--|---|
| 5                | L-             |  | TFA-L-/D-Phe-Ph(3,4-Me) (L-/D- <b>89</b> )                   | 70   | 15  |
| 6                | D-             | 42   |  | 69   | 10  |
| 7                | L-             |  | O<br>HN<br>TFA<br>TFA-L-/D-Phe-Ph(2,4-Me) (L-/D- <b>90</b> ) | 49   | 36  |
| 8                | D-             | 43   |  | 44   | 33  |
| 9                | L-             |  |  | 31   | 54  |
| 10               | D- 44          | TFA-L-/D-Phe-Ph(2,5-Me) (L-/D- <b>91</b> ) | 36   | 43   |   |

To broaden the application of *N*-hydroxysuccinimide ester, TFA-L-/D-Phe-OSu (L-/D-**82**) were utilized for *N*-heterocycles of *N*-pyrrole **92** and *N*-methylpyrrole **93** (Scheme 30). Previously, *N*-TFA-L-phenylalanine-benzotriazole was reported as the only *N*-pyrrole and *N*methylpyrrole acylation products, with no intra-molecular cyclization product.<sup>30</sup> Similarly, when the optical active TFA-L-/D-Phe-OSu (L-/D-**82**) were treated with *N*-pyrrole **92**, TFA-L-/D-Phe-(2-Pyr)<sup>30</sup> (L-/D-**94**, Scheme 30 (a)), resulting in a moderate yield in which acylation occurred specifically at the C-2 position. Regarding acylation into *N*-methylpyrrole **93**, two isomers of C-2 position-acylated product of TFA-L-/D-Phe-(2-(*N*-Me)Pyr) (L-/D-**95**)<sup>30</sup> as the major one and C-3 position-acylated product of TFA-L-/D-Phe(3-(*N*-Me)Pyr) (L-/D-**96**) were found that can be detected by TLC. *N*-Methyl protecting group of *N*-methylpyrrole **93** might trigger further acylation at C-3 position. However, unlike utilization of *N*-TFA-Lphenylalanine-benzotriazole<sup>30</sup> that needed CH<sub>2</sub>Cl<sub>2</sub> as solvent to undergo the reaction, TFA-L-/D-Phe-OSu (L-/D-**82**) showed high solubility towards excess *N*-pyrrole and *N*-methylpyrrole. This indicates the efficiency of TFA-L-/D-Phe-OSu (L-/D-**82**) as a representative acyl donor for acylation reaction.



# Scheme 30 Friedel–Crafts reaction of TFA-L-/D-Phe-OSu (L-/D-82) into *N*-pyrrole 92 and *N*-methylpyrrole 93 catalyzed by AlCl<sub>3</sub>

Based on <sup>1</sup>H-NMR, the occurrence of overlapping two protons at 3- and 5-positions of *N*-methylpyrrole<sup>30</sup> was observed for C-2 position at  $\delta_{\rm H}$  6.62 ppm (d, J = 2.0 Hz) of the acylated product L-/D-**95** (Figure 27). Meanwhile, the proton signal of the 2-position of *N*-methylpyrrole for L-/D-**96** was shown at  $\delta_{\rm H}$  6.93 ppm as a singlet and the proton signal of the 5-position of *N*-methylpyrrole for L-/D-**96** appeared at slightly upfield region ( $\delta_{\rm H}$  6.20, dd, J = 4.3, 2.3 Hz, Figure 27). The <sup>13</sup>C-NMR supports the assignment demonstrated by the observation of C=O at  $\delta_{\rm C}$  189.8 ppm signal for the C-2 position-acylated product L-/D-**95.**<sup>30</sup>

carbon signal at  $\delta_{\rm C}$  185.0 ppm. Both utilization of optical active TFA-L-/D-Phe-OSu (L-/D-82) to 92 and *N*-methylpyrrole 93 showed no detection of intra-molecular adduct, thus indicating that these acyl acceptors react relatively fast with the active intermediate to giving TFA- $\alpha$ -amino-heterocycles ketones.



**Figure 27** Selected <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>) of TFA-L-Phe-(2-(*N*-Me)Pyr) (L-**95**) and TFA-L-Phe(3-(*N*-Me)Pyr) (L-**96**)

# Synthesis and application of TFA-L-/D-tyrosine-N-hydroxysuccinimide esters

Utilization of the *N*-hydroxysuccinimide ester (OSu) as a potential acyl donor for arylketones synthesis was extended to tyrosine derivatives. Following the optical active L-/Dtyrosine (L-/D-Tyr, L-/D-97) underwent *N*-TFA protection to result in TFA-L-/D-Tyr (L-/D-98, Scheme 31), TFA-protection for L-/D-97 utilized a high amount of reagents compare with other  $\alpha$ -amino acids (3 equiv. of ethyl trifluoroacetate in the presence of 8 equiv. of triethylamine in methanol). This can be due to the presence of hydroxy groups in aromatic moiety of tyrosine which influenced the acidity of the reaction system and hampered TFA protection in its *N*-terminal.



Scheme 31 Synthesis of TFA-L-/D-Tyr (L-/D-98)

The resultant L-/D-**98** were then directly transformed to TFA-L-/D-Tyr-OSu (L-/D-**99**) by utilization of NHS and WSCD-HCl in acetone (Table 27). The attempt to increase the formation of L-/D-**99** was conducted as shown in Table 27. When the amount of NHS was increased and WSCD-HCl amount was kept the same amounts of 1.0 equiv., the desired L-/D-**99** was isolated after purification with 0.1 M NaHCO<sub>3</sub> (Table 27 Entries 1–4, 7–8, and 11–12). Unfortunately, the products were contaminated with unidentifed compounds which were detected by <sup>1</sup>H-NMR. Next, the trial for isolating the pure L-/D-**99** was done by increasing the proportion of NHS (Table 27 Entries 7–10) and found that the contaminant still yielded and it was difficult to remove. From these results, it was suggested that purification of the products by 0.1 M NaHCO<sub>3</sub> is too harsh condition for L-/D-**99** formation. Thus, the purification process with 0.01 M NaHCO<sub>3</sub> was conducted (Table 27 Entries 5–6), and it resulted in L-/D-**99** in a fine yield and readily to be use for Friedel–Crafts acylation.

 Table 27 Synthesis of N-TFA-L-/D-tyrosine succinimide ester derivatives (TFA-L-/D-Tyr-OSu, L-/D-99)



TFA-L-/D-Tyr (L-/D-**98**)

TFA-L-/D-Tyr-OSu (L-/D-99)

| Entry <sup>a</sup>    | Start Material<br>98 | NHS<br>(equiv.) | WSCD-HCl<br>(equiv.) | Condition | L-/D- <b>99</b><br>(% Yield) |
|-----------------------|----------------------|-----------------|----------------------|-----------|------------------------------|
| 1                     | L- <sup>c</sup>      | 1.1             | 1.0                  | 2h, rt    | 66% <sup>g</sup>             |
| 2                     | D- <sup>c</sup>      | 1.1             | 1.0                  | 2h, rt    | 70% <sup>g</sup>             |
| 3                     | L- <sup>d</sup>      | 1.3             | 1.0                  | 2h, rt    | 60% <sup>g</sup>             |
| 4                     | D- <sup>d</sup>      | 1.3             | 1.0                  | 2h, rt    | 66% <sup>g</sup>             |
| 5 <sup>b</sup>        | L- <sup>d</sup>      | 1.3             | 1.0                  | 3h, rt    | 75%                          |
| <b>6</b> <sup>b</sup> | D- <sup>d</sup>      | 1.3             | 1.0                  | 3h, rt    | 74%                          |
| 7                     | L- <sup>e</sup>      | 1.3             | $1.0^{\mathrm{f}}$   | 2h, rt    | 70% <sup>g</sup>             |
| 8                     | D- <sup>e</sup>      | 1.3             | $1.0^{\mathrm{f}}$   | 2h, rt    | 72% <sup>g</sup>             |
| 9                     | L- <sup>c</sup>      | 1.3             | 1.4                  | 2h, rt    | 68% <sup>g</sup>             |
| 10                    | D- <sup>c</sup>      | 1.3             | 1.4                  | 2h, rt    | 63% <sup>g</sup>             |
| 11                    | L- <sup>c</sup>      | 1.8             | 1.0                  | 2h, rt    | 58% <sup>g</sup>             |
| 12                    | D- <sup>c</sup>      | 1.8             | 1.0                  | 2h, rt    | 54% <sup>g</sup>             |

<sup>a</sup> Solvent was removed under reduced pressure. Then, residue was dissolve in ethyl acetate and washed by sat. NaCl and 0.1 M NaHCO<sub>3</sub> in H<sub>2</sub>O. <sup>b</sup> Solvent was removed under reduced pressure. Then, residue was dissolve in ethyl acetate and washed by sat. NaCl and 0.01 M NaHCO<sub>3</sub> in H<sub>2</sub>O. <sup>c</sup> Conc. 0.08 M in acetone. <sup>d</sup> Conc. 0.04 M in acetone. <sup>e</sup> Conc. 0.06 M in acetone. <sup>f</sup>WSCD-HCl was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.06 M) before addition at 0 <sup>o</sup>C. <sup>g</sup> Contaminated with unidentified compounds, observed by appearance of unidentical  $\alpha$ -proton signals in <sup>1</sup>H-NMR (ratio 1.00:0.01~0.18).

Table 28 shows the Friedel–Crafts reaction of TFA-L-/D-Tyr-OSu (L-/D-**99**) into benzene **34** catalyzed by AlCl<sub>3</sub>. The hydroxy group in an aromatic moiety of TFA-L-/D-Tyr-OSu (L-/D-**99**) was not hampered in its reactivity to undergo acylation into benzene. Unlike TFA-L-/D-Phe-OSu (L-/D-**82**) utilization to benzene (Table 25), the TFA-L-/D-Tyr-Ph (L-/D-**100**, Table 28) utilization showed no appearance of intra-molecular product. When 6 equiv. AlCl<sub>3</sub> was used, the lower yield of TFA-L-Tyr-Ph (L-**100**, Table 28, Entry 1) was obtained, due to formation of a decarbonylated compound **101**. Decarbonylated compound **101** can significantly be determined by <sup>13</sup>C-NMR in which no C=O signals at downfield region were apparent in comparison with TFA-L-Tyr-Ph (L-**100**, Figure 28).

A higher proportion of AlCl<sub>3</sub> (24 equiv., Table 28, Entry 3–4) suppressed **101** formation and the resultant TFA-L-/D-Tyr-Ph (L-/D-**100**) was in a satisfactory yield without loss of chirality. Decarbonylated compound **101** at low proportion AlCl<sub>3</sub> might be due to activation of carbonyl groups of L-/D-**99**, faster than cleavage of OSu groups. Moreover, although the mechanism is still unknown, but it can be confirmed that decarbonylated compound **101** has lost its optical acivity property. Nevertheless, under an acidic condition offered by the system, hydroxy substituent in an aromatic moiety of tyrosine skeleton might be unnecessary to be protected, and utilization of TFA-L-/D-Tyr-OSu (L-/D-**99**) would be considerably more effective for direct synthesis of TFA-L-/D-Tyr-Ph (L-/D-**100**).

# Table 28 Friedel–Crafts reaction of TFA-L-/D-Tyr-OSu (L-/D-99) into benzene catalyzed by



TFA-L-/D-Tyr-OSu (L-/D-**99**)

TFA-L-/D-Tyr-Ph (L-/D-100)

101

| Entry | Material<br><b>99</b> | AlCl <sub>3</sub><br>(equiv.) | 100 (% Yield) | Ratio of <b>100</b> : <b>101</b> <sup>a</sup> |
|-------|-----------------------|-------------------------------|---------------|---|
| 1     | L-                    | 6                             | 49%           | 1.00:0.45                                     |
| 2     | L-                    | 12                            | 56%           | 1.00:0.21                                     |
| 3     | L-                    | 24                            | 78%           | 1.00:0.13                                     |
| 4     | D-                    | 24                            | 79%           | 1.00:0.10                                     |

<sup>&</sup>lt;sup>a</sup>Observed by <sup>1</sup>H-NMR



Figure 28 Selected <sup>13</sup>C NMR (67.5 MHz, acetone- $d_6$ ) comparison of TFA-L-Tyr-Ph (L-100) with decarbonylated compound 101

## 3.3 Experimental section

All reagents used were of analytical grade. FT-IR (Fourier-transform infrared spectroscopy) spectra were recorded on a FT-IR 4100 spectrometer (JASCO, Tokyo, Japan). NMR spectra were measured by an EX 270 spectrometer (JEOL, Tokyo, Japan). Optical rotations were measured at 23 °C on a JASCO DIP370 polarimeter (JASCO, Tokyo, Japan). HRMS-ESI spectra were obtained with a Waters UPLC ESI-TOF mass spectrometer (Waters, Milford, CT, USA).

#### 3.3.1 General procedure for the preparation of TFA-α-amino acid

The TFA- $\alpha$ -amino acid was prepared by reported procedure<sup>92,93</sup> with slightly modification. Triethylamine (33 mmol, 1.5 equiv.) was added to a solution of  $\alpha$ -amino acid (22 mmol) in MeOH (22 mL). After 5 min, ethyl trifluoroacetate (29 mmol, 1.3 equiv.) was added and the reaction mixture was allowed to stir for 24 h. The solvent was removed by rotary evaporation and the residue remained was dissolved in H<sub>2</sub>O and acidified with concentrated HCl. The resulting mixture was extracted with ethyl acetate for several times and the organic layers combined were washed with brine, dried by MgSO<sub>4</sub>, filtered, and

concentrated by rotary evaporation. Further subjection to high vacuum for overnight, if needed to solidify the product.

(2S,3S)-3-Methyl-2-(2,2,2-trifluoroacetamido)pentanoic acid (TFA-L-Ile, L-32):<sup>91,103</sup> Colorless amorphous mass.  $[\alpha]_{D} = +55$  (c 1.0, CHCl<sub>3</sub>). IR (neat) v: 3294, 2968, 1740, 1694  $cm^{-1}$ . <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 10.58 (br s, 1H, COOH), 6.86 (d, J = 8.2 Hz, 1H, NH), 4.68 (dd, J = 8.4, 4.5 Hz, 1H, CHNH), 2.13–1.98 (m, 1H, CHCH<sub>3</sub>), 1.60–1.44 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.36–1.19 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.01–0.94 (m, 6H, 2 x CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 175.4, 157.2 (q, <sup>2</sup> $J_{CF}$  = 38.0 Hz), 115.6 (q, <sup>1</sup> $J_{CF}$  = 287.7 Hz), 56.8, 37.6, 24.9, 15.2, 11.4 ppm. HRMS-ESI (m/z)  $[M + H]^+$  calcd for C<sub>8</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>3</sub> 228.0848, found 228.0858. (2R,3R)-3-Methyl-2-(2,2,2-trifluoroacetamido)pentanoic acid (TFA-D-Ile, **D-32):** Colorless amorphous mass.  $[\alpha]_D = -55$  (c 1.0, CHCl<sub>3</sub>). IR (neat) v: 3293, 2973, 1740, 1699  $cm^{-1}$ . <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 9.47 (br s, 1H, COOH), 6.79 (d, J = 7.9 Hz, 1H, NH), 4.68 (dd, J = 8.4, 4.5 Hz, 1H, CHNH), 2.12–1.99 (m, 1H, CHCH<sub>3</sub>), 1.61–1.44 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.36–1.19 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.01–0.95 (m, 6H, 2 x CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 175.3, 157.3 (q, <sup>2</sup> $J_{CF}$  = 37.8 Hz), 115.6 (q, <sup>1</sup> $J_{CF}$  = 287.5 Hz), 56.8, 37.6, 24.9, 15.1, 11.3 ppm. HRMS-ESI (m/z)  $[M + H]^+$  calcd for C<sub>8</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>3</sub> 228.0848, found 228.0850. (2S,3R)-3-Methyl-2-(2,2,2-trifluoroacetamido)pentanoic acid (TFA-L-allo-Ile, L-37): Colorless amorphous mass.  $[\alpha]_{D} = +24$  (c 1.0, CHCl<sub>3</sub>). IR (neat) v: 3287, 2971, 1719 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.70 (br s, 1H, CHCOOH), 6.77 (d, J = 8.2 Hz, 1H, NH), 4.76 (dd, J = 8.6, 3.6 Hz, 1H, CHNH), 2.17–2.05 (m, 1H, CHCH<sub>3</sub>), 1.53–1.38 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>),

1.33–1.17 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.01–0.90 (m, 6H, 2 x CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 175.6, 157.4 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.8 Hz), 115.7 (q, <sup>*1*</sup>*J*<sub>CF</sub> = 287.5 Hz), 55.8, 37.6, 26.1, 14.3, 11.5 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>8</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>3</sub> 228.0848, found 228.0852.

(2*R*,3*S*)-3-Methyl-2-(2,2,2-trifluoroacetamido)pentanoic acid (TFA-D-*allo*-Ile, D-37): Colorless amorphous mass.  $[\alpha]_D = -24$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v* : 3302, 2971, 1708 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 9.12 (br s, 1H, CHCOO*H*), 6.93 (d, *J* = 8.6 Hz, 1H, N*H*), 4.76 (dd, *J* = 8.9, 3.6 Hz, 1H, C*H*NH), 2.18–2.04 (m, 1H, C*H*CH<sub>3</sub>), 1.53–1.37 (m, 1H, C*H*<sub>2</sub>CH<sub>3</sub>), 1.33–1.17 (m, 1H, C*H*<sub>2</sub>CH<sub>3</sub>), 1.01–0.94 (m, 6H, 2 x CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 175.7, 157.4 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.0 Hz), 115.7 (q, <sup>*I*</sup>*J*<sub>CF</sub> = 287.7 Hz), 55.8, 37.5, 26.1, 14.3, 11.5 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>8</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>3</sub> 228.0848, found 228.0851.

**2-(2,2,2-Trifluoroacetamido)acetic acid (TFA-Gly, 52):**<sup>103–105</sup> Colorless amorphous mass. IR (neat) v: 3299, 2992, 1682 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CD<sub>3</sub>OD)  $\delta$ : 4.01 (s, 2H, CH<sub>2</sub>NH) ppm. <sup>13</sup>C NMR (67.5 MHz, CD<sub>3</sub>OD)  $\delta$ : 171.5, 159.4 (q, <sup>2</sup> $J_{CF}$  = 37.4 Hz), 117.4 (q, <sup>1</sup> $J_{CF}$  = 286.2 Hz), 41.7 ppm. HRMS-ESI (m/z)  $[M + H]^+$  calcd for C<sub>4</sub>H<sub>5</sub>F<sub>3</sub>NO<sub>3</sub> 172.0222, found 172.0241.

(*S*)-2-(2,2,2-Trifluoroacetamido)propanoic acid (TFA-L-Ala, L-56):<sup>103,106,107</sup> Colorless amorphous mass.  $[\alpha]_D = +38$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) v: 3330, 2952, 1752 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 9.23 (br s, 1H, COO*H*), 7.00 (br s, 1H, N*H*), 4.72–4.62 (m, 1H, CHCH<sub>3</sub>), 1.58 (d, J = 7.3 Hz, 3H, CHCH<sub>3</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 176.3, 156.9 (q, <sup>2</sup> $J_{CF} = 38.2$  Hz), 115.5 (q, <sup>1</sup> $J_{CF} = 287.9$  Hz), 48.5, 17.6 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>5</sub>H<sub>7</sub>F<sub>3</sub>NO<sub>3</sub> 186.0378, found 186.0389.

(*R*)-2-(2,2,2-Trifluoroacetamido)propanoic acid (TFA-D-Ala, D-56):<sup>107</sup> Colorless amorphous mass.  $[\alpha]_D = -38$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat)  $\nu$ : 3295, 2949, 1756 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.96 (br s, 1H, COO*H*), 6.99 (br s, 1H, N*H*), 4.73–4.62 (m, 1H, CHCH<sub>3</sub>), 1.58 (d, J = 7.3 Hz, 3H, CHCH<sub>3</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 176.0, 157.1 (q, <sup>2</sup> $J_{CF} = 38.2$  Hz), 115.5 (q, <sup>1</sup> $J_{CF} = 287.2$  Hz), 48.5, 17.2 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>5</sub>H<sub>7</sub>F<sub>3</sub>NO<sub>3</sub> 186.0378, found 186.0365.

(*S*)-3-Methyl-2-(2,2,2-trifluoroacetamido)butanoic acid (TFA-L-Val, L-60): <sup>103,104,106</sup> Colorless amorphous mass.  $[\alpha]_D = +53$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v* : 3286, 2969, 1739 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CD<sub>3</sub>Cl<sub>3</sub>)  $\delta$ : 10.35 (br s, 1H, CHCOO*H*), 6.81 (d, *J* = 7.9 Hz, 1H, N*H*), 4.65 (dd, *J* = 8.6, 4.6 Hz, 1H, C*H*NH), 2.41–2.29 (m, 1H, C*H*CH<sub>3</sub>), 1.05–0.99 (m, 5H, 2 x CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 175.5, 157.3 (q, <sup>2</sup>*J*<sub>CF</sub> = 36.3 Hz), 115.7 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.2 Hz), 57.4, 31.1, 18.7, 17.4 ppm. HRMS-ESI (*m*/*z*) [M + Na]<sup>+</sup> calcd for C<sub>7</sub>H<sub>10</sub>F<sub>3</sub>NO<sub>3</sub>Na 236.0510, found 236.0520.

(*R*)-3-Methyl-2-(2,2,2-trifluoroacetamido)butanoic acid (TFA-D-Val, D-60):<sup>104</sup> Colorless amorphous mass.  $[\alpha]_D = -53$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat)  $\nu$ : 3295, 2970, 1753 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CD<sub>3</sub>Cl<sub>3</sub>)  $\delta$ : 10.99 (br s, 1H, CHCOO*H*), 6.89 (d, J = 8.6 Hz, 1H, N*H*), 4.64 (dd, J = 8.6, 4.6 Hz, 1H, C*H*NH), 2.41–2.26 (m, 1H, C*H*CH<sub>3</sub>), 1.05–0.99 (m, 6H, 2 x CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 175.5, 157.3 (q, <sup>2</sup> $J_{CF} = 37.4$  Hz), 115.6 (q, <sup>1</sup> $J_{CF} = 287.7$  Hz), 57.4, 31.1, 18.7, 17.4 ppm. HRMS-ESI (*m*/*z*) [M + Na]<sup>+</sup> calcd for C<sub>7</sub>H<sub>10</sub>F<sub>3</sub>NO<sub>3</sub>Na 236.0510, found 236.0518

(*S*)-4-methyl-2-(2,2,2-trifluoroacetamido)pentanoic acid (TFA-L-Leu, L-64):<sup>91,104,108</sup> Colorless amorphous mass. [ $\alpha$ ]<sub>D</sub> = +24 (*c* 1.0, CHCl<sub>3</sub>). IR (neat)  $\nu$  : 3294, 2963, 1731 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CD<sub>3</sub>Cl<sub>3</sub>)  $\delta$ : 8.90 (br s, 1H, CHCOO*H*), 6.78 (br s, 1H, N*H*), 4.74–4.65 (m, 1H, C*H*NH), 1.88–1.64 (m, 3H, C*H*<sub>2</sub>C*H*), 1.00 (s, 3H, C*H*<sub>3</sub>), 0.98 (s, 3H, C*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 176.4, 157.2 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.0 Hz), 115.6 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.2 Hz), 51.1,

120

40.8, 24.8, 22.6, 21.6 ppm. HRMS-ESI (m/z) [M + H]<sup>+</sup> calcd for C<sub>8</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>3</sub> 228.0848, found 228.0859.

(*R*)-4-Methyl-2-(2,2,2-trifluoroacetamido)pentanoic acid (TFA-D-Leu, D-64):<sup>104</sup> Colorless amorphous mass.  $[\alpha]_D = -24$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat)  $\nu$ : 3300, 2965, 1733 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CD<sub>3</sub>Cl<sub>3</sub>)  $\delta$ : 8.54 (br s, 1H, CHCOO*H*), 6.73 (d, *J* = 7.6 Hz, 1H, N*H*), 4.74–4.65 (m, 1H, C*H*NH), 1.88–1.61 (m, 3H, C*H*<sub>2</sub>C*H*), 1.00 (s, 3H, C*H*<sub>3</sub>), 0.98 (s, 3H, C*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 175.9, 157.8 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.0 Hz), 115.6 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.0 Hz), 51.2, 40.2, 24.7, 22.4, 21.2 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>8</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>3</sub> 228.0848, found 228.0865.

(*S*)-2-(2,2,2-Trifluoroacetamido)pentanoic acid (TFA-L-Nva, L-68):<sup>104</sup> Colorless amorphous mass.  $[\alpha]_D = +58$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat)  $v: 3292 \text{ cm}^{-1}$ , 2967, 1732, 1696 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta: 6.76$  (d, J = 6.9 Hz, 1H, NH), 4.69 (td, J = 7.3, 5.4 Hz, 1H, CHNH), 2.06–1.92 (m, 1H, CHCH<sub>2</sub>), 1.88–1.74 (m, 1H, CHCH<sub>2</sub>), 1.50–1.35 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 0.98 (t, J = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta: 176.0$ , 157.3 (q, <sup>2</sup> $_{JCF} = 37.8$  Hz), 115.6 (q, <sup>1</sup> $_{JCF} = 287.3$  Hz), 52.4, 33.5, 18.4, 13.3 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>7</sub>H<sub>11</sub>F<sub>3</sub>NO<sub>3</sub> 214.0691, found 214.0693.

(*R*)-2-(2,2,2-Trifluoroacetamido)pentanoic acid (TFA-D-Nva, D-68):<sup>104</sup> Colorless amorphous mass.  $[\alpha]_D = -58$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) v: 3319, 2969, 1745, 1695 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta: 6.75$  (d, J = 6.6 Hz, 1H, NH), 4.69 (td, J = 7.5, 5.2 Hz, 1H, CHNH), 2.06–1.92 (m, 1H, CHCH<sub>2</sub>), 1.88–1.74 (m, 1H, CHCH<sub>2</sub>), 1.57–1.32 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 0.98 (t, J = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta: 176.2, 157.2$  (q, <sup>2</sup> $J_{CF} = 38.0$  Hz), 115.6 (q, <sup>1</sup> $J_{CF} = 287.3$  Hz), 52.4, 33.6, 18.4, 13.4 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>7</sub>H<sub>11</sub>F<sub>3</sub>NO<sub>3</sub> 214.0691, found 214.0696.

(*S*)-2-(2,2,2-Trifluoroacetamido)hexanoic acid (TFA-L-Nle, L-72):<sup>104</sup> Colorless amorphous mass.  $[\alpha]_D = +67$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat)  $\nu$ : 3314, 2936, 1728 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.73 (br s, 1H, N*H*), 4.67 (td, J = 7.4, 5.4 Hz, 1H, C*H*NH), 2.08–1.94 (m, 1H, CHC*H*<sub>2</sub>), 1.89–1.75 (m, 1H, CHC*H*<sub>2</sub>), 1.42–1.26 (m, 4H, 2 x CH<sub>2</sub>), 0.92 (t, J = 6.9 Hz, 3H, CH<sub>2</sub>C*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 176.1, 157.2 (q, <sup>2</sup> $J_{CF} = 38.0$  Hz), 115.6 (q, <sup>1</sup> $J_{CF} = 287.5$  Hz), 52.6, 31.3, 27.0, 22.1, 13.6 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>8</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>3</sub> 228.0848, found 228.0850.

(*R*)-2-(2,2,2-Trifluoroacetamido)hexanoic acid (TFA-D-Nle, D-72):<sup>104</sup> Colorless amorphous mass.  $[\alpha]_D = -67$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat)  $\nu$ : 3302, 2936, 1740 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.74 (br s, 1H, N*H*), 4.69 (td, J = 7.4, 5.4 Hz, 1H, C*H*NH), 2.06–1.94 (m, 1H, CHCH<sub>2</sub>), 1.89–1.75 (m, 1H, CHCH<sub>2</sub>), 1.41–1.31 (m, 4H, 2 x CH<sub>2</sub>), 0.92 (t, J = 6.9 Hz,

3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 176.2, 157.1 (q, <sup>2</sup>*J*<sub>*CF*</sub> = 38.0 Hz), 115.6 (q, <sup>*1*</sup>*J*<sub>*CF*</sub> = 287.7 Hz), 52.5, 31.4, 27.0, 22.1, 13.6 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>8</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>3</sub> 228.0848, found 228.0843.

(*S*)-1-(2,2,2-Trifluoroacetyl)pyrrolidine-2-carboxylic acid (TFA-L-Pro, L-76): Colorless amorphous mass.  $[\alpha]_D = -86$  (*c* 1.0, CHCl<sub>3</sub>); Lit. <sup>99</sup>  $[\alpha]_D = -65.19$  (*c* 1.08, benzene). IR (neat)  $v: 1739, 1705 \text{ cm}^{-1}$ . <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta: 4.59$  (1H, dd, J = 8.4, 3.8 Hz, CH<sub>2</sub>CH), 3.90–3.69 (2H, m, CH<sub>2</sub>), 2.36–1.99 (4H, m, 2 x CH<sub>2</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta: [176.2 \& 176.0], 156.1$  (q, <sup>2</sup> $J_{CF} = 37.8 \text{ Hz}$ ), 116.0 (q, <sup>1</sup> $J_{CF} = 287.0 \text{ Hz}$ ), [60.0 & 59.1], 48.0 & 47.2], [31.5 & 28.3], [24.8 & 21.0] ppm (*cis*- and *trans*- mix). HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>7</sub>H<sub>9</sub>F<sub>3</sub>NO<sub>3</sub> 212.0535, found 212.0536.

(*R*)-1-(2,2,2-Trifluoroacetyl)pyrrolidine-2-carboxylic acid (TFA-D-Pro, D-76): Colorless amorphous mass.  $[\alpha]_D = +86$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) v : 1738, 1709 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 4.59 (1H, dd, J = 8.2, 3.6 Hz, CH<sub>2</sub>CH), 3.87–3.67 (2H, m, CH<sub>2</sub>), 2.37–1.96 (4H, m, 2 x CH<sub>2</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : [175.9 & 175.7], 156.1 (q, <sup>2</sup>J<sub>CF</sub> = 37.8 Hz), 116.0 (q, <sup>1</sup>J<sub>CF</sub> = 286.8 Hz), [60.0 & 59.1], [48.0 & 47.2], [31.5 & 28.3], [24.8 & 21.0] ppm (*cis*- and *trans*- mix). HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>7</sub>H<sub>9</sub>F<sub>3</sub>NO<sub>3</sub> 212.0535, found 212.0555.

(*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido)propanoic acid (TFA-L-Phe, L-81): Colorless amorphous mass.  $[\alpha]_D = +13$  (*c* 1.0, MeOH); Lit. <sup>103</sup>  $[\alpha]_D = +17.2$  (*c* 2, ethanol). IR (neat) *v* : 3319, 3099, 3033, 2929, 1739, 1706 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.38–7.30 (3H, m, Ar-H), 7.14 (2H, d, *J* = 7.6 Hz, Ar-H), 6.70 (1H, br d, *J* = 5.6 Hz, N*H*), 4.94 (1H, q, *J* = 5.6, 5.6, 5.6 Hz, C*H*NH), 3.31 (1H, dd, *J* = 14.2, 5.6 Hz, C*H*<sub>2</sub>CH), 3.22 (1H, dd, *J* = 14.2, 5.6 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.2, 156.7 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.2 Hz), 134.2, 129.2 (2 x CH), 129.0 (2 x CH), 127.8, 115.5 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.2 Hz), 53.2, 36.9 ppm. HRMS-ESI (*m/z*) [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>11</sub>F<sub>3</sub>NO<sub>3</sub> 262.0691, found 262.0699.

(*R*)-3-phenyl-2-(2,2,2-trifluoroacetamido)propanoic acid (TFA-D-Phe, D-81): Colorless amorphous mass.  $[\alpha]_D = -13$  (*c* 1.0, MeOH); Lit.<sup>104</sup>  $[\alpha]_D = -17.2$  (*c* 2, ethanol). IR (neat) *v* : 3320, 3093, 3033, 2934, 1740, 1702 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.34–7.30 (3H, m, Ar-H), 7.14 (2H, d, *J* = 7.3 Hz, Ar-H), 6.68 (1H, br d, *J* = 5.6 Hz, N*H*), 4.95 (1H, q, *J* = 5.6, 5.6, 5.6 Hz, C*H*NH), 3.32 (1H, dd, *J* = 14.2, 5.6 Hz, C*H*<sub>2</sub>CH), 3.22 (1H, dd, *J* = 14.2, 5.6 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 174.6, 156.8 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.4 Hz), 134.2, 129.2 (2 x CH), 129.0 (2 x CH), 127.8, 115.5 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.3 Hz), 53.3, 36.9 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>11</sub>F<sub>3</sub>NO<sub>3</sub> 262.0691, found 262.0694.

# 3.3.2 Procedure for the preparation of TFA-L-/D-tyrosine (L-/D-98)

Triethylamine (136 mmol, 8 equiv.) was added to a solution of  $\alpha$ -amino acid (17 mmol) in MeOH (40 mL). After 5 min, ethyl trifluoroacetate (51 mmol, 3 equiv.) was added and the reaction was allowed to stir for 7 d. The solvent was removed by rotary evaporation and the residue that remained was dissolved in H<sub>2</sub>O and acidified with concentrated HCl. The mixture was extracted with ethyl acetate for several times and the organic layers were combined and washed with brine, dried by MgSO<sub>4</sub>, filtered, and concentrated by rotary evaporation. Further subjection into high vacuum for overnight, if needed to solidify the product (TFA-L-/D-tyrosine, L-/D-**98**).

(*S*)-3-(4-hydroxyphenyl)-2-(2,2,2-trifluoroacetamido)propanoic acid (TFA-L-Tyr, L-98): Yellowish amorphous mass.  $[\alpha]_D = +26$  (*c* 1.0, MeOH). IR (neat) v: 3302, 3098, 2932, 1734 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 8.55 (1H, br s, OH), 7.19 (2H, d, J = 8.2 Hz, Ar-H), 6.83 (2H, d, J = 8.6 Hz, Ar-H), 4.78 (1H, td, J = 9.7, 4.6 Hz, CHNH), 3.31 (1H, dd, J = 14.2, 4.6 Hz, CH<sub>2</sub>CH), 3.08 (1H, dd, J = 14.2, 9.7 Hz, CH<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 171.6, 157.3 (q, <sup>2</sup> $J_{CF} = 36.9$  Hz), 157.1, 131.0 (2 x CH), 128.2, 116.8 (q, <sup>1</sup> $J_{CF} = 287.2$  Hz), 116.0 (2 x CH), 55.0, 36.4 ppm. HRMS-ESI (*m*/*z*) [M+Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>10</sub>F<sub>3</sub>NO<sub>4</sub>Na 300.0460, found 300.0444.

(*R*)-3-(4-hydroxyphenyl)-2-(2,2,2-trifluoroacetamido)propanoic acid (TFA-D-Tyr, D-98): Yellowish amorphous mass.  $[\alpha]_D = -26$  (*c* 1.0, MeOH). IR (neat) *v*: 3295, 3098, 2932, 1732 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 8.51 (1H, br s, OH), 7.15 (2H, d, *J* = 8.2 Hz, Ar-H), 6.80 (2H, d, *J* = 8.2 Hz, Ar-H), 4.78 (1H, td, *J* = 9.6, 4.9 Hz, CHNH), 3.29 (1H, dd, *J* = 14.2, 4.9 Hz, CH<sub>2</sub>CH), 3.05 (1H, dd, *J* = 14.2, 9.6 Hz, CH<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 171.9, 157.5 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.1 Hz), 157.0, 131.0 (2 x CH), 128.1, 116.8 (q, <sup>*I*</sup>*J*<sub>CF</sub> = 287.3 Hz), 116.1 0 (2 x CH), 55.0, 36.4 ppm. HRMS-ESI (*m*/*z*) [M+Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>10</sub>F<sub>3</sub>NO<sub>4</sub>Na 300.0460, found 300.0469.

# 3.3.3 General Procedure for the Preparation of TFA-α-Amino Acid N-Hydroxysuccinimide Ester

NHS (*N*-hydroxysuccinimide, 1.1 equiv.) was added to a solution of TFA- $\alpha$ -amino acid (1.0 mmol) in pre-cooled CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The suspension of WSCD-HCl (water soluble carbodiimide hydrochloride, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide monohydrochloride, 1.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added drop-wise at 0 °C and the reaction was stirred for 2–4 h. The solvent was removed by rotary evaporation. The residue that remained was dissolved in ethyl acetate; washed with water, sat. NaHCO<sub>3</sub>, sat. NaCl,

dried over MgSO<sub>4</sub>, and then evaporated. The product was solidified by washing with hexane to be used for further reaction. For TFA- $\alpha$ -Amino Acid *N*-Hydroxysuccinimide Ester **53** detail experiment are refer to Scheme 16; L-/D-**57** detail experiment are refer to Table 24; L-/D-**69** detail experiment are refer to Scheme 23; L-/D-**73** detail experiment are refer to Scheme 26; L-/D-**99** detail experiment are refer to Table 27.

(2*S*,3*S*)-2,5-Dioxopyrrolidin-1-yl 3-methyl-2-(2,2,2-trifluoroacetamido)pentanoate (TFA-L-Ile-OSu, L-33):<sup>109</sup> Colorless amorphous mass.  $[\alpha]_D = -4.0$  (*c* 1.0, CHCl<sub>3</sub>); ref.<sup>109</sup>  $[\alpha]_D = -63.6$  (c 1, CH<sub>3</sub>OH). IR (neat) *v*: 3265, 2965, 1785, 1740 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.41 (d, *J* = 8.6 Hz, 1H, N*H*), 4.97 (dd, *J* = 8.6, 5.3 Hz, 1H, C*H*NH), 2.89 (s, 4H, 2 x CH<sub>2</sub>), 2.23–2.08 (m, 1H, C*H*CH<sub>3</sub>), 1.75–1.60 (1H, m, C*H*<sub>2</sub>CH<sub>3</sub>), 1.45–1.29 (1H, m, CH<sub>2</sub>CH<sub>3</sub>), 1.11 (d, *J* = 6.9 Hz, 3H, CHCH<sub>3</sub>), 1.02 (t, *J* = 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.5 (2 x CO), 166.3, 156.9 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.4 Hz), 115.5 (q, <sup>*I*</sup>*J*<sub>CF</sub> = 287.9 Hz), 55.3, 38.0, 25.5 (2 x CH<sub>2</sub>), 24.7, 14.8, 11.3 ppm. HRMS-ESI (*m*/*z*) [M + Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>Na 347.0831, found 347.0822.

(2*R*,3*R*)-2,5-Dioxopyrrolidin-1-yl 3-methyl-2-(2,2,2-trifluoroacetamido)pentanoate (TFA-D-Ile-OSu, D-33): Colorless amorphous mass. [ $\alpha$ ]<sub>D</sub> = +4.0 (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3285, 2968, 1789, 1731 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.97 (d, *J* = 8.2 Hz, 1H, N*H*), 4.97 (dd, *J* = 8.6, 4.9 Hz, 1H, C*H*NH), 2.86 (s, 4H, 2 x CH<sub>2</sub>) 2.20–2.05 (m, 1H, C*H*CH<sub>3</sub>), 1.71–1.56 (m, 1H, C*H*<sub>2</sub>CH<sub>3</sub>), 1.41–1.21 (m, 1H, C*H*<sub>2</sub>CH<sub>3</sub>), 1.07 (d, *J* = 6.9 Hz, 3H, CHC*H*<sub>3</sub>), 1.00 (t, *J* = 7.4 Hz, 3H, CH<sub>2</sub>C*H*<sub>3</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.7 (2 x CO), 166.2, 156.9 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.2 Hz), 115.5 (q, <sup>*I*</sup>*J*<sub>CF</sub> = 287.5 Hz), 55.3, 37.7, 25.4 (2 x CH<sub>2</sub>), 24.6, 14.7, 11.1 ppm. HRMS-ESI (*m*/*z*) [M + Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>Na 347.0831, found 347.0833.

(2*S*,3*R*)-2,5-Dioxopyrrolidin-1-yl 3-methyl-2-(2,2,2-trifluoroacetamido)pentanoate (TFA-L-*allo*-IIe-OSu, L-38): Colorless amorphous mass.  $[\alpha]_D = -4.0$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3316, 2929, 1788, 1752 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.06 (d, *J* = 9.2 Hz, 1H, N*H*), 5.10 (dd, *J* = 9.2, 4.0 Hz, 1H, C*H*NH), 2.86 (s, 4H, 2 x CH<sub>2</sub>), 2.31–2.15 (m, 1H, C*H*CH<sub>3</sub>), 1.54–1.41 (m, 1H, C*H*<sub>2</sub>CH<sub>3</sub>), 1.37–1.23 (m, 1H, C*H*<sub>2</sub>CH<sub>3</sub>), 1.05 (d, *J* = 6.9 Hz, 3H, CHC*H*<sub>3</sub>), 1.00 (t, *J* = 7.4 Hz, 3H, CH<sub>2</sub>C*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.4 (2 x CO), 166.8, 157.0 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.2 Hz), 115.5 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 54.1, 38.2, 25.9, 25.5 (2 x CH<sub>2</sub>), 14.1, 11.6 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>16</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 325.1011, found 325.1013.

# (2R,3S)-2,5-Dioxopyrrolidin-1-yl 3-methyl-2-(2,2,2-trifluoroacetamido)pentanoate (TFA-

**D**-*allo*-**Ile**-**OSu**, **D**-**38**): Colorless amorphous mass.  $[\alpha]_D = +4.0$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3327, 2971, 1752 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.07 (d, J = 9.2 Hz, 1H, NH), 5.10 (dd, J = 9.1, 4.1 Hz, 1H, CHNH), 2.86 (s, 4H, 2 x CH<sub>2</sub>), 2.28–2.17 (m, 1H, CHCH<sub>3</sub>), 1.57–1.39 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.37–1.22 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.05 (d, J = 6.9 Hz, 3H, CHCH<sub>3</sub>), 1.00 (t, J = 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.7 (2 x CO), 166.7, 157.1 (q, <sup>2</sup> $J_{CF} = 38.2$  Hz), 115.5 (q, <sup>1</sup> $J_{CF} = 287.3$  Hz), 54.1, 37.9, 25.8, 25.4 (2 x CH<sub>2</sub>), 14.0, 11.4 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>16</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 325.1011, found 325.1014.

**2,5-Dioxocyclopentyl 2-(2,2,2-trifluoroacetamido)acetate** (**TFA-Gly-OSu**, **53**) <sup>105</sup>: Colorless amorphous mass. IR (neat) *v*: 3313, 2998, 1690 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CD<sub>3</sub>OD)  $\delta$ : 4.44 (s, 2H, CH<sub>2</sub>NH), 2.84 (s, 4H, 2 x CH<sub>2</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 170.1 (2 x CO), 165.7 158.2 (q, <sup>2</sup>J<sub>CF</sub> = 37.4 Hz), 116.8 (q, <sup>1</sup>J<sub>CF</sub> = 287.0 Hz), 39.5, 26.2 (2 x CH<sub>2</sub>) ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>8</sub>H<sub>7</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>Na 291.0205, found 291.0208.

(*S*)-2,5-Dioxopyrrolidin-1-yl 2-(2,2,2-trifluoroacetamido)propanoate (TFA-L-Ala-OSu, L-57): Colorless amorphous mass.  $[\alpha]_D = -46$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3332, 2999, 1793, 1734 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.39 (d, *J* = 7.3 Hz, 1H, N*H*), 5.08–4.97 (m, 1H, CHCH<sub>3</sub>), 2.86 (s, 4H, 2 x CH<sub>2</sub>), 1.68 (d, *J* = 7.3 Hz, 3H, CHCH<sub>3</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.8 (2 x CO), 167.4, 156.8 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.4 Hz), 115.6 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.2 Hz), 46.7, 25.5 (2 x CH<sub>2</sub>), 17.6 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>10</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 283.0542, found 283.0555.

(*R*)-2,5-Dioxopyrrolidin-1-yl 2-(2,2,2-trifluoroacetamido)propanoate (TFA-D-Ala-OSu, D-57): Colorless amorphous mass.  $[\alpha]_D = +46$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3350, 2999, 1798, 1726 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.73 (d, *J* = 7.6 Hz, 1H, N*H*), 5.05–4.94 (m, 1H, CHCH<sub>3</sub>), 2.85 (s, 4H, 2 x CH<sub>2</sub>), 1.66 (d, *J* = 7.3 Hz, 3H, CHCH<sub>3</sub>) ppm.<sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 169.0 (2 x CO), 167.1, 156.8 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.2 Hz), 115.4 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.3 Hz), 46.7, 25.4 (2 x CH<sub>2</sub>), 17.1 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>10</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 283.0542, found 283.0553.

(*S*)-2,5-Dioxopyrrolidin-1-yl 3-methyl-2-(2,2,2-trifluoroacetamido)butanoate (TFA-L-Val-OSu, L-61):<sup>109</sup> Colorless amorphous mass.  $[\alpha]_D = -22$  (*c* 1.0, CHCl<sub>3</sub>); ref. <sup>109</sup>  $[\alpha]_D = -73.3$  (c 1, CH<sub>3</sub>OH). IR (neat) *v*: 3310, 2979, 1796, 1725 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CD<sub>3</sub>Cl<sub>3</sub>)  $\delta$ : 7.49 (d, *J* = 8.9 Hz, 1H, N*H*), 4.88 (dd, *J* = 8.7, 5.4 Hz, 1H, C*H*NH), 2.84 (s, 4H, 2 x CH<sub>2</sub>), 2.47–2.34 (m, 1H, C*H*CH<sub>3</sub>), 1.08 (d, *J* = 6.9 Hz, 6H, 2 x CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.9 (2 x CO), 166.1, 157.1 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.2 Hz), 115.5 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.5 H), 55.9, 31.2, 25.4 (2 x CH<sub>2</sub>), 18.3, 17.2 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>14</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 311.0855, found 311.0858.

(*R*)-2,5-Dioxopyrrolidin-1-yl 3-methyl-2-(2,2,2-trifluoroacetamido)butanoate (TFA-D-Val-OSu, D-61): Colorless amorphous mass.  $[\alpha]_D = +22$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3298, 2975, 1725 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CD<sub>3</sub>Cl<sub>3</sub>)  $\delta$ : 6.93 (d, *J* = 8.6 Hz, 1H, N*H*), 4.95 (dd, *J* = 8.9, 4.9 Hz, 1H, C*H*NH), 2.87 (s, 4H, 2 x CH<sub>2</sub>), 2.53–2.35 (m, 1H, C*H*CH<sub>3</sub>), 1.09 (d, *J* = 6.9 Hz, 6H, 2 x CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.4 (2 x CO), 166.4, 157.0 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.0 Hz), 115.5 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 55.9, 31.7, 25.5 (2 x CH<sub>2</sub>), 18.4, 17.2 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>14</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 311.0855, found 311.0857.

(*S*)-2,5-Dioxopyrrolidin-1-yl 4-methyl-2-(2,2,2-trifluoroacetamido)pentanoate (TFA-L-Leu-OSu, L-65) <sup>109</sup>: Colorless amorphous mass.  $[\alpha]_D = -42$  (*c* 1.0, CHCl<sub>3</sub>); ref. <sup>109</sup>  $[\alpha]_D = -50.8$  (c 1, CH<sub>3</sub>OH). IR (neat) *v*: 3295, 2967, 1734, 1712 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CD<sub>3</sub>Cl<sub>3</sub>)  $\delta$ : 6.86 (d, *J* = 8.6 Hz, 1H, N*H*), 5.04 (td, *J* = 8.9, 4.9 Hz, 1H, C*H*NH), 2.86 (s, 4H 2 x CH<sub>2</sub>), 2.00–1.72 (m, 3H, CH<sub>2</sub>CH), 1.02 (d, *J* = 2.3 Hz, 3H, CH<sub>3</sub>), 1.00 (d, *J* = 2.3 Hz, 3H, CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$  168.6 (2 x CO), 167.2, 156.9 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.2 Hz), 115.5 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 49.3, 41.0, 25.5 (2 x CH<sub>2</sub>), 24.7, 22.6, 21.5 ppm. HRMS-ESI (*m*/*z*) [M + Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>Na 347.0831, found 347.0832.

(*R*)-2,5-Dioxopyrrolidin-1-yl 4-methyl-2-(2,2,2-trifluoroacetamido)pentanoate (TFA-D-Leu-OSu, D-65): Colorless amorphous mass.  $[\alpha]_D = +42$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3305, 2965, 1733, 1719 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CD<sub>3</sub>Cl<sub>3</sub>)  $\delta$ : 6.97 (br s, 1H, N*H*), 5.05 (td, *J* = 8.7, 4.9 Hz, 1H), 2.86 (s, 4H, 2 x CH<sub>2</sub>), 2.00–1.74 (m, 3H, CH<sub>2</sub>CH), 1.03–0.98 (m, 6H, 2 x CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.6 (2 x CO), 167.2, 156.9 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.2 Hz), 115.5 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 49.3, 41.0, 25.5 (2 x CH<sub>2</sub>), 24.7, 22.6, 21.5 ppm. HRMS-ESI (*m/z*) [M + Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>Na 347.0831, found 347.0830.

(*S*)-2,5-Dioxopyrrolidin-1-yl 2-(2,2,2-trifluoroacetamido)pentanoate (TFA-L-Nva-OSu, L-69): Colorless amorphous mass.  $[\alpha]_D = -27$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3325, 2962, 1744, 1711 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.83 (d, *J* = 7.3 Hz, 1H, N*H*), 5.03 (td, *J* = 8.0, 5.5 Hz, 1H, C*H*NH), 2.87 (s, 4H, 2 x CH<sub>2</sub>), 2.17–2.02 (m, 1H, CHC*H*<sub>2</sub>), 1.99–1.85 (m, 1H, CHC*H*<sub>2</sub>), 1.59–1.40 (m, 2H, C*H*<sub>2</sub>CH<sub>3</sub>), 1.01 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>C*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.6 (2 x CO), 166.9, 156.9 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.0 Hz), 115.5 (q, <sup>*I*</sup>*J*<sub>CF</sub> = 287.7 Hz), 50.7, 34.0, 25.5 (2 x CH<sub>2</sub>), 18.2, 13.3 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>14</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 311.0855, found 311.0856.

(*R*)-2,5-Dioxopyrrolidin-1-yl 2-(2,2,2-trifluoroacetamido)pentanoate (TFA-D-Nva-OSu, D-69): Colorless amorphous mass.  $[\alpha]_D = +27$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3322, 2962, 1744, 1711 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.11 (d, *J* = 8.2 Hz, 1H, N*H*), 5.02 (td, *J* = 8.1, 5.4 Hz, 1H, C*H*NH), 2.86 (s, 4H, 2 x CH<sub>2</sub>), 2.15–2.01 (m, 1H, CHCH<sub>2</sub>), 1.98–1.84 (m, 1H, CHCH<sub>2</sub>), 1.60–1.43 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 1.00 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR

(67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.6 (2 x CO), 166.9, 156.9 (q,  ${}^{2}J_{CF}$  = 38.2 Hz), 115.5 (q,  ${}^{1}J_{CF}$  = 287.9 Hz), 50.7, 34.0, 25.5 (2 x CH<sub>2</sub>), 18.2, 13.3 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>14</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 311.0855, found 311.0861.

(*S*)-2,5-Dioxopyrrolidin-1-yl 2-(2,2,2-trifluoroacetamido)hexanoate (TFA-L-Nle-OSu, L-73): Colorless amorphous mass.  $[\alpha]_D = -18$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3332, 2958, 1721, 1703 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.34 (d, *J* = 8.2 Hz, 1H, N*H*), 4.98 (td, *J* = 8.2, 5.3 Hz, 1H, C*H*NH), 2.85 (s, 4H, 2 x CH<sub>2</sub>), 2.16–2.03 (m, 1H, CHC*H*<sub>2</sub>), 1.99–1.85 (m, 1H, CHC*H*<sub>2</sub>), 1.52–1.32 (m, 4H, 2 x CH<sub>2</sub>), 0.93 (t, *J* = 7.1 Hz, 3H, CH<sub>2</sub>C*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.8 (2 x CO), 166.8, 156.9 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.2 Hz), 115.5 (q, <sup>*I*</sup>*J*<sub>CF</sub> = 287.7 Hz), 50.8, 31.5, 26.9, 25.4 (2 x CH<sub>2</sub>), 21.9, 13.5 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>16</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 325.1011, found 325.1021.

(*R*)-2,5-Dioxopyrrolidin-1-yl 2-(2,2,2-trifluoroacetamido)hexanoate (TFA-D-Nle-OSu, D-73): Colorless amorphous mass.  $[\alpha]_D = +18$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3324, 2958, 1724, 1708 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.89 (br s, 1H, N*H*), 5.01 (td, *J* = 7.8, 5.5 Hz, 1H, C*H*NH), 2.87 (s, 4H, 2 x CH<sub>2</sub>), 2.18–2.04 (m, 1H, CHC*H*<sub>2</sub>), 2.00–1.86 (m, 1H, CHC*H*<sub>2</sub>), 1.52–1.36 (m, 4H, 2 x CH<sub>2</sub>), 0.94 (t, *J* = 7.1 Hz, 3H, CH<sub>2</sub>C*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.6 (2 x CO), 166.9, 156.9 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.4 Hz), 115.5 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.3 Hz), 50.8, 31.7, 26.8, 25.5 (2 x CH<sub>2</sub>), 21.9, 13.6 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>16</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 325.1011, found 325.1016.

(*S*)-2,5-dioxopyrrolidin-1-yl 1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (TFA-L-Pro-OSu, L-77): Colorless amorphous mass.  $[\alpha]_D = -85$  (*c* 1.0, CHCl<sub>3</sub>); Lit. <sup>109</sup>  $[\alpha]_D = -98$  (*c* 1.0, CH<sub>3</sub>OH). IR (neat) v: 3376, 2988, 1830, 1786, 1758 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 4.89 (1H, t, J = 6.3 Hz, CH<sub>2</sub>CH), 3.95–3.70 (2H, m, CH<sub>2</sub>), 2.84 (4H, s, 2 x CH<sub>2</sub>), 2.45–2.35 (2H, m, CH<sub>2</sub>), 2.30–2.04 (2H, m, CH<sub>2</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.6, 166.9, 166.4, 155.9 (q, <sup>2</sup> $J_{CF} = 38.2$  Hz), 115.9 (q, <sup>1</sup> $J_{CF} = 286.8$  Hz), [57.9 & 57.4], [48.0 & 47.1], [32.1 & 28.7], 25.5, [24.8 & 21.0] ppm (*cis*- and *trans*- mix). HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 309.0698, found 309.0708.

(*R*)-2,5-dioxopyrrolidin-1-yl 1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (TFA-D-Pro-OSu, D-77): Colorless amorphous mass. [ $\alpha$ ]<sub>D</sub> = +85 (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v* : 3376, 2987, 1827, 1785, 1758 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 4.88 (1H, t, *J* = 6.1 Hz, CH<sub>2</sub>C*H*), 3.92–3.68 (2H, m, *CH*<sub>2</sub>), 2.84 (4H, s, 2 x *CH*<sub>2</sub>), 2.47–2.35 (2H, m, *CH*<sub>2</sub>), 2.26–2.11 (2H, m, *CH*<sub>2</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.5, 166.8, 166.4, 155.9 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.2 Hz), 115.9 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.0 Hz), [58.0 & 57.4], [48.0 & 47.1], [32.1 & 28.7], 25.5, [24.8 & 21.0] ppm (*cis*- and *trans*- mix). HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 309.0698, found 309.0725. (*S*)-2,5-dioxopyrrolidin-1-yl 3-phenyl-2-(2,2,2-trifluoroacetamido)propanoate (TFA-L-Phe-OSu, L-82): Colorless amorphous mass.  $[\alpha]_D = -34$  (*c* 1.0, MeOH). IR (neat)  $\nu$  : 3310, 3109, 3033, 2947, 1826, 1818, 1785, 1762, 1737, 1723 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.34–7.27 (5H, m, Ar-H), 6.87 (1H, br d, J = 5.9 Hz, NH), 5.27 (1H, q, J = 5.9, 5.9, 5.9 Hz, CHNH), 3.42 (1H, dd, J = 14.3, 5.9 Hz, CH<sub>2</sub>CH), 3.28 (1H, dd, J = 14.3, 5.9 Hz, CH<sub>2</sub>CH), 2.85 (4H, s, 2 x CH<sub>2</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.5 (2 x CO), 166.1, 156.6 (q, <sup>2</sup> $J_{CF} = 38.0$  Hz), 133.4, 129.5 (2 x CH), 128.9 (2 x CH), 127.9, 115.3 (q, <sup>1</sup> $J_{CF} = 287.2$  Hz), 51.5, 37.2, 25.5 (2 x CH<sub>2</sub>) ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>14</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 359.0855, found 359.0857.

(*R*)-2,5-dioxopyrrolidin-1-yl 3-phenyl-2-(2,2,2-trifluoroacetamido)propanoate (TFA-D-Phe-OSu, D-82): Colorless amorphous mass. [ $\alpha$ ]<sub>D</sub> = +34 (*c* 1.0, MeOH). IR (neat) *v* : 3308, 3111, 3033, 2946, 1826, 1816, 1785, 1761, 1735, 1721 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.35–7.28 (5H, m, Ar-H), 6.79 (1H, br d, *J* = 5.9 N*H*), 5.28 (1H, q, *J* = 5.9, 5.9, 5.9 Hz, C*H*NH), 3.42 (1H, dd, *J* = 14.3, 5.9 Hz, C*H*<sub>2</sub>CH), 3.30 (1H, dd, *J* = 14.3, 5.9 Hz, C*H*<sub>2</sub>CH), 2.86 (4H, s, 2x CH<sub>2</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 168.5 (2 x CO), 166.1, 156.6 (q, <sup>2</sup>*J*<sub>CF</sub> = 38.4 Hz), 133.3, 129.5 (2 x CH), 128.9 (2 x CH), 127.9, 115.3 (q, <sup>1</sup>*J*<sub>CF</sub> = 288.1 Hz), 51.5, 37.2, 25.5 (2 x CH<sub>2</sub>) ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>14</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> 359.0855, found 359.0856.

# (S)-2,5-dioxopyrrolidin-1-yl

#### 3-(4-hydroxyphenyl)-2-(2,2,2-

trifluoroacetamido)propanoate (TFA-L-Tyr-OSu, L-99): Yellowish amorphous mass. [α]<sub>D</sub> = -29 (*c* 1.0, MeOH). IR (neat) v: 3324, 1820, 1792, 1755 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, ACETONE-D<sub>6</sub>) δ: 8.86 (1H, d, J = 8.6 Hz, NH), 8.15 (1H, br s, OH), 7.10 (2H, d, J = 8.2 Hz, Ar-H), 6.67 (2H, d, J = 8.2 Hz, Ar-H), 5.03 (1H, td, J = 10.2, 4.6 Hz, CHNH), 3.28 (1H, dd, J = 14.2, 4.6 Hz, CH<sub>2</sub>CH), 3.04 (1H, dd, J = 14.2, 10.2 Hz, CH<sub>2</sub>CH), 2.73 (4H, s, 2 x CH<sub>2</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, ACETONE-D<sub>6</sub>) δ: 170.2 (2 x CO), 167.2, 157.6 (q, <sup>2</sup> $J_{CF}$  = 38.0 Hz), 157.3, 131.2 (2 x CH), 126.9, 116.6 (q, <sup>1</sup> $J_{CF}$  = 287.2 Hz), 116.2 (2 x CH), 53.2, 36.3, 26.2 (2 x CH<sub>2</sub>) ppm. HRMS-ESI (*m*/*z*) [M+Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub>Na 397.0623, found 397.0625.

# (R)-2,5-dioxopyrrolidin-1-yl

#### 3-(4-hydroxyphenyl)-2-(2,2,2-

trifluoroacetamido)propanoate (TFA-D-Tyr-OSu, D-99): Yellowish amorphous mass.  $[\alpha]_D$ = +29 (*c* 1.0, MeOH). IR (neat) v: 3323, 1820, 1788, 1732 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 8.87 (1H, d, J = 8.6 Hz, NH), 8.15 (1H, br s, OH), 7.10 (2H, d, J = 8.6 Hz, Ar-H), 6.67 (2H, d, J = 8.6 Hz, Ar-H), 5.03 (1H, td, J = 9.9, 4.8 Hz, CHNH), 3.28 (1H, dd, J = 14.3, 4.8 Hz, CH<sub>2</sub>CH), 3.04 (1H, dd, J = 14.2, 9.9 Hz, CH<sub>2</sub>CH), 2.74 (4H, s, 2 x CH<sub>2</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 170.1 (2 x CO), 167.2, 157.6 (q, <sup>2</sup> $_{J_{CF}}$  = 37.4 Hz), 157.4, 131.2 (2 x CH), 127.0, 116.7 (q, J = 287.7 Hz), 116.2 (2 x CH), 53.3, 36.3, 26.2 (2 x CH<sub>2</sub>) ppm. HRMS-ESI (*m*/*z*) [M+Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub>Na 397.0623, found 397.0636.

#### 3.3.4 General procedure for the preparation of TFA-protected $\alpha$ -amino aryl-ketones

TFA- $\alpha$ -amino acid-OSu (0.1–0.5 mmol) was suspended in arenes or *N*-heterocycles (300 equiv.). Into the suspension, pulverized AlCl<sub>3</sub> was added and then stirred at a temperature of 70 °C. The reaction was monitored by the consumption of starting material on TLC. The solvent was reduced by rotary evaporation, then the mixture was poured into an ethyl acetate-H<sub>2</sub>O two-phase system. The organic layer was washed with H<sub>2</sub>O, sat. NaCl, dried over MgSO<sub>4</sub>, and then evaporated. The crude product was purified by silica column chromatography (ethyl acetate/hexane 1:3 or and diethyl ether/hexane 1:5).

**2,2,2-Trifluoro-***N*-((2*S*,3*S*)-3-methyl-1-oxo-1-phenylpentan-2-yl)acetamide (TFA-L-Ile-Ph, L-35): Colorless needles.  $[\alpha]_D = +70$  (*c* 2.0, CHCl<sub>3</sub>). IR (neat) *v*: 3317, 3073, 2972, 1722, 1694 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.97 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.66 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.4 Hz, 2H, Ar-H), 5.60 (dd, *J* = 8.6, 4.3 Hz, 1H, CHNH), 2.10–1.95 (m, 1H, CHCH<sub>3</sub>), 1.40–1.25 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.12–0.95 (m, 4H, overlap CH<sub>2</sub>CH<sub>3</sub> and CHCH<sub>3</sub>), 0.82 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.5, 157.1 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), 134.7, 134.3, 129.0 (2 x CH), 128.7 (2 x CH), 115.9 (q, <sup>1</sup>*J*<sub>CF</sub> = 288.1 Hz), 58.4, 38.7, 23.7, 16.2, 11.4 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>2</sub> 288.1211, found 288.1212.

**2,2,2-Trifluoro-***N*-((2*R*,3*R*)-3-methyl-1-oxo-1-phenylpentan-2-yl)acetamide (TFA-D-Ile-Ph, D-35): Colorless needles. [ $\alpha$ ]<sub>D</sub> = -70 (*c* 2.0, CHCl<sub>3</sub>). IR (neat) *v*: 3337, 3069, 2969, 1721, 1699 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.98 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.66 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.6 Hz, 2H, Ar-H), 5.60 (dd, *J* = 8.6, 4.0 Hz, 1H, CHNH), 2.10–1.95 (m, 1H, CHCH<sub>3</sub>), 1.40–1.23 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.12–0.95 (m, 4H, overlap CH<sub>2</sub>CH<sub>3</sub> and CHCH<sub>3</sub>), 0.82 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm.<sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.5, 157.1 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.2 Hz), 134.7, 134.3, 129.0 (2 x CH), 128.7 (2 x CH), 115.9 (q, <sup>1</sup>*J*<sub>CF</sub> = 288.3 Hz), 58.4, 38.7, 23.7, 16.2, 11.4 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>2</sub> 288.1211, found 288.1215.

**2,2,2-Trifluoro-***N***-((2***S***,3***S***)<b>-3-methyl-1-oxo-1-(p-tolyl)pentan-2-yl)acetamide** (**TFA-L-Ile-Ph(4-Me), L-45):** Colorless needles.  $[\alpha]_D = +83$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3302, 3023, 2925, 1700 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.87 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.32 (d, *J* = 8.6 Hz, 2H, Ar-H), 5.56 (dd, *J* = 8.6, 4.3 Hz, 1H, C*H*NH), 2.45 (s, 3H, C*H*<sub>3</sub>), 2.06–1.95 (m, 1H, C*H*CH<sub>3</sub>), 1.39–1.26 (m, 1H, C*H*<sub>2</sub>CH<sub>3</sub>), 1.11–0.94 (m, 4H, overlap C*H*<sub>2</sub>CH<sub>3</sub> and CHC*H*<sub>3</sub>), 0.82 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.0, 157.1 (q, <sup>2</sup>*J*<sub>CF</sub> =

37.2 Hz), 145.5, 132.1 (2 x CH), 129.7 (2 x CH), 128.8, 115.9 (q,  ${}^{I}J_{CF} = 287.9$  Hz), 58.3, 38.9, 23.7, 21.8, 16.2, 11.4 ppm. HRMS-ESI (m/z) [M + H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>19</sub>F<sub>3</sub>NO<sub>2</sub> 302.1368 found 302.1353.

# 2,2,2-Trifluoro-N-((2S,3S)-1-(4-methoxyphenyl)-3-methyl-1-oxopentan-2-yl)acetamide

(**TFA-L-Ile-Ph(4-OMe), L-47):** Colorless oil.  $[\alpha]_D = +66$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3320, 3079, 2934, 1726, 1675 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.96 (d, J = 8.9 Hz, 2H, Ar-H), 6.99 (d, J = 8.9 Hz, 2H, Ar-H), 5.53 (dd, J = 8.7, 4.5 Hz, 1H, CHNH), 3.90 (s, 3H, OCH<sub>3</sub>), 2.08-1.93 (m, 1H, CHCH<sub>3</sub>), 1.42-1.20 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.10-0.95 (m, 4H, overlap CH<sub>2</sub>CH<sub>3</sub> and CHCH<sub>3</sub>), 0.82 (t, J = 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 195.6, 164.5, 157.0 (q, <sup>2</sup> $J_{CF} = 37.2$  Hz), 131.1 (2 x CH), 127.5, 115.9 (q, <sup>1</sup> $J_{CF} = 288.6$  Hz), 114.2 (2 x CH), 58.0, 55.6, 39.0, 23.7, 16.2, 11.4 ppm. HRMS-ESI (*m*/*z*) [M + Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>18</sub>F<sub>3</sub>NO<sub>3</sub>Na 340.1136 found 340.1145.

*N*-((2*S*,3*S*)-1-(3,4-Dimethylphenyl)-3-methyl-1-oxopentan-2-yl)-2,2,2-trifluoroacetamide (TFA-L-IIe-Ph(3,4-Me), L-49): Colorless needles.  $[\alpha]_D = +82$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3343, 3075, 2979, 1742, 1691 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.71 (d, *J* = 11.2 Hz, 2H, Ar-H), 7.29 (s, 1H, Ar-H), 5.56 (dd, *J* = 8.7, 4.1 Hz, 1H, CHNH), 2.35 (s, 6H, 2 x CH<sub>3</sub>), 2.06– 1.95 (m, 1H, CHCH<sub>3</sub>), 1.40–1.26 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.08–0.93 (m, 4H, overlap CH<sub>2</sub>CH<sub>3</sub> and CHCH<sub>3</sub>), 0.81 (t, *J* = 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.2, 157.1 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.2 Hz), 144.3, 137.6, 132.5, 130.2, 129.7, 126.5, 115.9 (q, <sup>*I*</sup>*J*<sub>CF</sub> = 287.9 Hz), 58.3, 38.9, 23.7, 20.1, 19.8, 16.2, 11.4 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>2</sub> 316.1524, found 316.1506.

*N*-((2*S*,3*S*)-1-(2,4-Dimethylphenyl)-3-methyl-1-oxopentan-2-yl)-2,2,2-trifluoroacetamide (TFA-L-IIe-Ph(2,4-Me), L-50): Colorless needles.  $[\alpha]_D = +49$  (*c* 0.25, CHCl<sub>3</sub>). IR (neat) *v*: 3294, 3097, 2969, 1714, 1685 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.63 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.14-7.02 (m, 2H, Ar-H), 5.49 (dd, *J* = 8.4, 4.1 Hz, 1H, CHNH), 2.49 (s, 3H, CH<sub>3</sub>), 2.38 (s, 3H, CH<sub>3</sub>), 1.99–1.87 (m, 1H, CHCH<sub>3</sub>), 1.32–1.19 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.07–0.87 (m, 4H, overlap CH<sub>2</sub>CH<sub>3</sub> and CHCH<sub>3</sub>), 0.81 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 199.9, 157.1 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), 143.2, 139.5, 133.3, 132.2, 129.4, 126.6, 115.9 (q, <sup>*1*</sup>*J*<sub>CF</sub> = 288.3 Hz), 59.8, 38.5, 24.1, 21.2, 21.0, 15.9, 11.2 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>2</sub> 316.1524, found 316.1526.

*N*-((2*S*,3*S*)-1-(2,5-Dimethylphenyl)-3-methyl-1-oxopentan-2-yl)-2,2,2-trifluoroacetamide (TFA-L-Ile-Ph(2,5-Me), L-51): Colorless needles.  $[\alpha]_D = +68$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3302, 3024, 2934, 1714, 1686, 1567 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.5 (s, 1H, Ar-H), 7.3 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.2 (d, *J* = 7.6 Hz, 1H, Ar-H), 5.5 (dd, *J* = 8.6, 4.0 Hz, 1H, CHNH), 2.4 (s, 3H, CH<sub>3</sub>), 2.4 (s, 3H, CH<sub>3</sub>), 2.0–1.8 (m, 1H, CHCH<sub>3</sub>), 1.4–1.2 (m, 1H,

CH<sub>2</sub>CH<sub>3</sub>), 1.1–0.9 (m, 3H overlap CH<sub>2</sub>CH<sub>3</sub> and CHCH<sub>3</sub>), 0.8 (t, J = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 200.7, 157.1 (q, <sup>2</sup>J<sub>CF</sub> = 37.2 Hz), 135.9, 135.6, 135.0, 133.3, 132.3, 129.3, 115.9 (q, <sup>1</sup>J<sub>CF</sub> = 287.9 Hz), 60.1, 38.4, 24.1, 20.7, 20.3, 15.9, 11.3 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>2</sub> 316.1524, found 316.1530.

**2,2,2-Trifluoro-***N*-((2*S*,3*R*)-3-methyl-1-oxo-1-phenylpentan-2-yl)acetamide (TFA-L-*allo*-IIe-Ph, L-39): Colorless needles.  $[\alpha]_D = +79$  (*c* 2.0, CHCl<sub>3</sub>). IR (neat) *v*: 3335, 3068, 2971, 1741, 1693 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.98 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.65 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.6 Hz, 2H, Ar-H), 5.74 (dd, *J* = 8.9, 3.0 Hz, 1H, CHNH), 2.09–1.94 (m, 1H, CHCH<sub>3</sub>), 1.62–1.49 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.38–1.21 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.06 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 0.76 (d, *J* = 6.9 Hz, 3H, CHCH<sub>3</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.1, 157.3 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.1 Hz), 134.4, 134.0, 129.1 (2 x CH), 128.7 (2 x CH), 115.9 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 57.1, 38.7, 27.3, 13.4, 12.0 ppm. HRMS-ESI (*m*/*z*) [M + Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>2</sub>Na 310.1031, found 310.1039.

**2,2,2-Trifluoro-***N*-((2*R*,3*S*)-3-methyl-1-oxo-1-phenylpentan-2-yl)acetamide (TFA-D-*allo*-IIe-Ph, D-39): Colorless needles.  $[\alpha]_D = -79$  (*c* 2.0, CHCl<sub>3</sub>). IR (neat) *v*: 3331, 3067, 2969, 1738, 1692 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.98 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.66 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.4 Hz, 2H, Ar-H), 5.74 (dd, *J* = 8.7, 2.8 Hz, 1H, CHNH), 2.07–1.94 (m, 1H, CHCH<sub>3</sub>), 1.66–1.48 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.38–1.21 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 1.06 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 0.76 (d, *J* = 6.9 Hz, 3H, CHCH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.1, 157.3 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), 134.4, 134.1, 129.1 (2 x CH), 128.7 (2 x CH), 115.9 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.9 Hz), 57.1, 38.7, 27.3, 13.4, 12.0 ppm. HRMS-ESI (*m*/*z*) [M + Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>2</sub>Na 310.1031, found 310.1040.

**2,2,2-Trifluoro-***N***-(2-oxo-2-phenylethyl)acetamide (TFA-Gly-Ph, 54):** <sup>32</sup> Colorless oil. IR (neat) *v*: 3327, 3103, 2927, 1733, 1703 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.99 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.68 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.54 (t, *J* = 7.4 Hz, 2H, Ar-H), 4.83 (d, *J* = 4.3 Hz, 2H, CH<sub>2</sub>NH) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 192.1, 157.1 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.6 Hz), 134.6, 133.6, 129.1 (2 x CH), 127.9 (2 x CH), 115.7 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.3 Hz), 46.1 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>10</sub>H<sub>9</sub>F<sub>3</sub>NO<sub>2</sub> 232.0585, found 232.0595.

(S)-2,2,2-trifluoro-*N*-(1-oxo-1-phenylpropan-2-yl)acetamide (TFA-L-Ala-Ph, L-58) <sup>25,30,110</sup>: Colorless oil. = -7.0 (*c* 1.0, CHCl<sub>3</sub>). Lit.<sup>110</sup> [ $\alpha$ ]<sub>D</sub> = -8.6 (*c* 0.17, CHCl<sub>3</sub>). IR (neat) *v*: 3331, 3070, 2991, 1738, 1701 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.99 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.67 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.54 (t, *J* = 7.4 Hz, 2H, Ar-H), 5.60–5.50 (m, 1H, CHCH<sub>3</sub>), 1.53 (d, *J* = 7.3 Hz, 3H, CHCH<sub>3</sub>) ppm.<sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.0, 156.5 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.6 Hz), 134.5, 132.9, 129.1 (2 x CH), 128.8 (2 x CH), 115.7 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.3 Hz), 50.8, 19.2 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>11</sub>F<sub>3</sub>NO<sub>2</sub> 246.0742, found 246.0748. (*R*)-2,2,2-Trifluoro-*N*-(1-oxo-1-phenylpropan-2-yl)acetamide (TFA-D-Ala-Ph, D-58): Colorless oil.  $[\alpha]_D = +7.0$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3337, 3091, 2948, 1725, 1700 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.99 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.67 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.54 (t, *J* = 7.4 Hz, 2H, Ar-H), 5.60–5.49 (m, 1H, CHCH<sub>3</sub>), 1.53 (d, *J* = 6.9 Hz, 3H, CHCH<sub>3</sub>) ppm. <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.0, 156.5 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.6 Hz), 134.5, 132.9, 129.1 (2 x CH), 128.8 (2 x CH), 115.7 (q, <sup>*1*</sup>*J*<sub>CF</sub> = 287.7 Hz), 50.8, 19.2 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>11</sub>F<sub>3</sub>NO<sub>2</sub> 246.0742, found 246.0750.

(*S*)-2,2,2-Trifluoro-*N*-(3-methyl-1-oxo-1-phenylbutan-2-yl)acetamide (TFA-L-Val-Ph, L-62):<sup>25</sup> Colorless oil.  $[\alpha]_D = +83$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3347, 3071, 2972, 1728, 1679 cm<sup>-1</sup>. (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.99 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.66 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.7 Hz, 2H, Ar-H), 7.32 (br s, 1H, N*H*), 5.61 (dd, *J* = 8.6, 4.0 Hz, 1H, C*H*NH), 2.39–2.23 (m, 1H, C*H*CH<sub>3</sub>), 1.07 (d, *J* = 6.9 Hz, 3H, CHC*H*<sub>3</sub>), 0.80 (d, *J* = 6.9 Hz, 3H, CHC*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.2, 157.3 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.6 Hz), 134.4, 129.1 (2 x CH), 128.7 (2 x CH), 115.9 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 58.6, 32.2, 20.0, 16.4 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>15</sub>F<sub>3</sub>NO<sub>2</sub> 274.1055, found 274.1057.

(*R*)-2,2,2-Trifluoro-*N*-(3-methyl-1-oxo-1-phenylbutan-2-yl)acetamide (TFA-D-Val-Ph, D-62): Colorless oil.  $[\alpha]_D = -83$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3344, 3070, 2972, 1720, 1672 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.99 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.66 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.3 Hz, 2H, Ar-H), 7.30 (br s, 1H, N*H*), 5.61 (dd, *J* = 8.7, 3.8 Hz, 1H, C*H*NH), 2.39–2.22 (m, 1H, C*H*CH<sub>3</sub>), 1.07 (d, *J* = 6.9 Hz, 3H, CHC*H*<sub>3</sub>), 0.79 (d, *J* = 6.9 Hz, 3H, CHC*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.2, 157.3 (q, <sup>2</sup>*J*<sub>CF</sub> = 36.7 Hz), 134.4, 129.1 (2 x CH), 128.7 (2 x CH), 115.9 (q, <sup>*I*</sup>*J*<sub>CF</sub> = 287.7 Hz), 58.6, 32.1, 19.9, 16.3 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>15</sub>F<sub>3</sub>NO<sub>2</sub> 274.1055, found 274.1057.

(*S*)-2,2,2-Trifluoro-*N*-(4-methyl-1-oxo-1-phenylpentan-2-yl)acetamide (TFA-L-Leu-Ph, L-66): Colorless oil.  $[\alpha]_D = +26$  (*c* 2.0, CHCl<sub>3</sub>). IR (neat) *v*: 3334, 3092, 2963, 1726, 1683 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.98 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.66 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.54 (t, *J* = 7.6 Hz, 2H, Ar-H), 5.68 (td, *J* = 8.9, 2.6 Hz, 1H, CHNH), 1.79–1.49 (m, 3H, CH<sub>2</sub>CH), 1.10 (d, *J* = 5.9 Hz, 3H, CHCH<sub>3</sub>), 0.89 (d, *J* = 6.3 Hz, 3H, CHCH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.4, 156.9 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), 134.4, 133.6, 129.1 (2 x CH), 128.7 (2 x CH), 115.8 (q, <sup>*I*</sup>*J*<sub>CF</sub> = 287.7 Hz), 52.9, 42.7, 25.1, 23.3, 21.7 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>2</sub> 288.1211, found 288.1214.

(*R*)-2,2,2-Trifluoro-*N*-(4-methyl-1-oxo-1-phenylpentan-2-yl)acetamide (TFA-D-Leu-Ph, D-66): Colorless oil.  $[\alpha]_D = -26$  (*c* 2.0, CHCl<sub>3</sub>). IR (neat) *v*: 3335, 3094, 2931, 1731, 1685 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.98 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.66 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.54 (t, *J* = 7.3 Hz, 2H, Ar-H), 5.68 (td, *J* = 9.1, 2.5 Hz, 1H, CHNH), 1.79–1.53 (m,

3H, CH<sub>2</sub>CH), 1.10 (d, J = 5.9 Hz, 3H, CHCH<sub>3</sub>), 0.89 (d, J = 5.9 Hz, 3H, CHCH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.4, 156.9 (q, <sup>2</sup> $J_{CF} = 37.4$  Hz), 134.4, 133.6, 129.1 129.1 (2 x CH), 128.7 129.1 (2 x CH), 115.8 (q, <sup>1</sup> $J_{CF} = 287.7$  Hz), 52.9, 42.6, 25.1, 23.2, 21.7 ppm. HRMS-ESI (m/z) [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>2</sub> 288.1211, found 288.1220.

(*S*)-2,2,2-Trifluoro-*N*-(1-oxo-1-phenylpentan-2-yl)acetamide (TFA-L-Nva-Ph, L-70): Colorless oil.  $[\alpha]_D = +46$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3341, 3074, 2979, 1733 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.98 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.67 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.54 (t, *J* = 7.3 Hz, 2H, Ar-H), 7.44 (br s, 1H, N*H*), 5.62 (td, *J* = 7.4, 4.5 Hz, 1H, C*H*NH), 2.08–1.95 (m, 1H, CHC*H*<sub>2</sub>), 1.76–1.62 (m, 1H, CHC*H*<sub>2</sub>), 1.48–1.17 (m, 2H, C*H*<sub>2</sub>CH<sub>3</sub>) 0.90 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>C*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.0, 156.8 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.1 Hz), 134.5, 133.6, 129.1 (2 x CH), 128.7 (2 x CH), 115.8 (q, <sup>1</sup>*J*<sub>CF</sub> = 286.8 Hz), 54.4, 35.2, 18.0, 13.7 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>15</sub>F<sub>3</sub>NO<sub>2</sub> 274.1055, found 274.1064.

(*R*)-2,2,2-Trifluoro-*N*-(1-oxo-1-phenylpentan-2-yl)acetamide (TFA-D-Nva-Ph, D-70): Colorless oil.  $[\alpha]_D = -46$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3339, 3073, 2977, 1732 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.99 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.67 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.54 (t, *J* = 7.4 Hz, 2H, Ar-H), 7.45 (br s, 1H, N*H*), 5.62 (td, *J* = 7.3, 4.4 Hz, 1H, C*H*NH), 2.08–1.95 (m, 1H, CHC*H*<sub>2</sub>), 1.76–1.62 (m, 1H, CHC*H*<sub>2</sub>), 1.48–1.13 (m, 2H, C*H*<sub>2</sub>CH<sub>3</sub>), 0.90 (t, *J* = 7.3 Hz, 3H, CH<sub>2</sub>C*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.0, 156.8 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), 134.5, 133.6, 129.1 (2 x CH), 128.7 (2 x CH), 115.8 (q, <sup>1</sup>*J*<sub>CF</sub> = 288.3 Hz), 54.4, 35.2, 18.1, 13.7 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>15</sub>F<sub>3</sub>NO<sub>2</sub> 274.1055, found 274.1058.

(*S*)-2,2,2-Trifluoro-*N*-(1-oxo-1-phenylhexan-2-yl)acetamide (TFA-L-Nle-Ph, L-74): Colorless oil.  $[\alpha]_D = +60$  (*c* 0.5, CHCl<sub>3</sub>). IR (neat) *v*: 3326, 3068, 2960, 1728, 1687 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.98 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.66 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.4 Hz, 2H, Ar-H), 7.46 (br s, 1H, N*H*), 5.61 (td, *J* = 7.3, 4.6 Hz, 1H, C*H*NH), 2.12–1.98 (m, 1H, CHC*H*<sub>2</sub>), 1.77–1.63 (m, 1H, CHC*H*<sub>2</sub>), 1.41–1.15 (m, 4H, 2 x CH<sub>2</sub>), 0.83 (t, *J* = 6.9 Hz, 3H, CH<sub>2</sub>C*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.0, 156.8 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), 134.4, 133.6, 129.0 (2 x CH), 128.6 (2 x CH), 115.8 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 54.5, 32.7, 26.7, 22.2, 13.6 ppm. HRMS-ESI (*m*/*z*) [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>2</sub> 288.1211, found 288.1224.

(*R*)-2,2,2-Trifluoro-*N*-(1-oxo-1-phenylhexan-2-yl)acetamide (TFA-D-Nle-Ph, D-74): Colorless oil.  $[\alpha]_D = -60$  (*c* 0.5, CHCl<sub>3</sub>). IR (neat) *v*: 3327, 3069, 2961, 1732, 1691 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.99 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.67 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.54 (t, *J* = 7.3 Hz, 2H, Ar-H), 7.47 (br s, 1H, N*H*), 5.61 (td, *J* = 7.3, 4.6 Hz, 1H, C*H*NH), 2.12–1.98 (m, 1H, CHC*H*<sub>2</sub>), 1.78–1.63 (m, 1H, CHC*H*<sub>2</sub>), 1.39–1.14 (m, 4H, 2 x CH<sub>2</sub>), 0.83 (t, *J* = 6.9 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.0, 156.8 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), 134.4, 133.6, 129.1 (2 x CH), 128.6 (2 x CH), 115.8 (q,  ${}^{1}J_{CF} = 287.7$  Hz), 54.5, 32.7, 26.7, 22.2, 13.6 ppm. HRMS-ESI (m/z) [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>2</sub> 288.1211, found 288.1216.

(*S*)-1-(2-benzoylpyrrolidin-1-yl)-2,2,2-trifluoroethanone (TFA-L-Pro-Ph, L-78):<sup>25,32,99</sup> Colorless needles.  $[\alpha]_D = -81$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) *v*: 3361, 3136, 1776, 1711, 1695 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.99 (2H, d, *J* = 7.9 Hz, Ar-H), 7.62 (1H, t, *J* = 7.9 Hz, Ar-H), 7.50 (2H, t, *J* = 7.9 Hz, Ar-H), 5.57 (1H, dd, *J* = 9.2, 4.0 Hz, CH<sub>2</sub>CH), 3.99–3.77 (2H, m, CH<sub>2</sub>), 2.42–2.29 (2H, m, CH<sub>2</sub>), 2.18–1.98 (2H, m, CH<sub>2</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : [195.6 & 195.3], 155.5 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), [134.4 & 134.0], [133.7 & 133.3], 129.0, 128.8, 128.5, 128.4, 116.3 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.2 Hz), [62.6 & 62.1], [48.3 & 47.3], [31.3 & 28.5], [24.8 & 20.8] ppm (*cis*- and *trans*- mix). HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>2</sub> 272.0898, found 272.0898.

(*R*)-1-(2-benzoylpyrrolidin-1-yl)-2,2,2-trifluoroethanone (TFA-D-Pro-Ph, D-78): Colorless needles.  $[\alpha]_D = +81$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) v: 3362, 3135, 1773, 1711, 1696 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.99 (2H, d, J = 7.6 Hz, Ar-H), 7.62 (1H, t, J = 7.6 Hz, Ar-H), 7.50 (2H, t, J = 7.6 Hz, Ar-H), 5.58 (1H, dd, J = 9.1, 3.8 Hz, CH<sub>2</sub>CH), 4.00–3.77 (2H, m, CH<sub>2</sub>), 2.41–2.30 (1H, m, CH<sub>2</sub>), 2.15–1.97 (2H, m, CH<sub>2</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : [195.6 & 195.3], 155.5 (q, <sup>2</sup> $J_{CF} = 37.4$  Hz), [134.4 & 134.0], [133.7 & 133.3], 129.0, 128.8, 128.5, 128.4, 116.3 (q, <sup>1</sup> $J_{CF} = 287.2$  Hz), [62.6 & 62.1], [48.3 & 47.4], [31.2 & 28.5], [24.7 & 20.8] ppm (*cis*- and *trans*- mix). HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>2</sub> 272.0898, found 272.0916.

(*S*)-2,2,2-trifluoro-*N*-(1-oxo-1,3-diphenylpropan-2-yl)acetamide (TFA-L-Phe-Ph, L-83): Colorless needles;  $[\alpha]_D = +14.0$  (*c* 1.0, MeOH). IR (neat) *v* : 3326, 3065, 3032, 1728, 1686 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.96 (2H, d, *J* = 7.4 Hz, Ar-H), 7.66 (1H, t, *J* = 7.4 Hz, Ar-H), 7.52 (2H, t, *J* = 7.4 Hz, Ar-H), 7.31 (1H, br d, *J* = 6.3 Hz, N*H*), 7.23–7.20 (3H, m, Ar-H), 6.92 (2H, dd, *J* = 6.4, 2.8 Hz, Ar-H), 5.82 (1H, q, *J* = 6.3, 6.3, 6.3 Hz, C*H*NH), 3.37 (1H, dd, *J* = 14.2, 6.3 Hz, C*H*<sub>2</sub>CH), 3.12 (1H, dd, *J* = 14.2, 6.3 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 195.9, 156.5 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.6 Hz), 134.4, 134.2, 133.8, 129.4 (2 x CH), 129.1 (2 x CH), 128.8 (2 x CH), 128.5 (2 x CH), 127.4, 115.7 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 55.3, 38.2 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>15</sub>F<sub>3</sub>NO<sub>2</sub> 322.1055, found 322.1065.

(*R*)-2,2,2-trifluoro-*N*-(1-oxo-1,3-diphenylpropan-2-yl)acetamide (TFA-D-Phe-Ph, D-83): Colorless needles;  $[\alpha]_D = -14.0$  (*c* 1.0, MeOH). IR (neat)  $\nu$ : 3326, 3066, 3032, 1720, 1684 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.96 (2H, d, J = 7.3 Hz, Ar-H), 7.65 (1H, t, J = 7.3 Hz, Ar-H), 7.52 (2H, t, J = 7.3 Hz, Ar-H), 7.40 (1H, br d J = 5.9 Hz, NH), 7.23–7.20 (3H, m, ArH), 6.92 (2H, dd, J = 6.3, 3.0 Hz, Ar-H), 5.82 (1H, q, J = 5.9, 5.9, 5.9 Hz, CHNH), 3.37 (1H, dd, J = 14.2, 5.9 Hz, CH<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 195.9, 156.5 (q, <sup>2</sup> $J_{CF} = 37.4$  Hz), 134.4, 134.2, 133.8, 129.4 (2 x CH), 129.1 (2 x CH), 128.7 (2 x CH), 128.5 (2 x CH), 127.4, 115.6 (q, <sup>1</sup> $J_{CF} = 287.7$  Hz), 55.3, 38.2 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>15</sub>F<sub>3</sub>NO<sub>2</sub> 322.1055, found 322.1065.

(*S*)-2,2,2-trifluoro-*N*-(1-oxo-2,3-dihydro-1*H*-inden-2-yl)acetamide (TFA-L-cPhe, L-84):<sup>30</sup> Colorless amorphous mass;  $[\alpha]_D = -1.4$  (*c* 1.0, acetone); -3.1 (*c* 1.6, DMF); Lit. <sup>30</sup>  $[\alpha]_D = -3.2$  (*c* 1.6, DMF). IR (neat) *v* : 3301, 3108, 2954, 1733, 1700 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 8.97 (1H, br d, *J* = 5.4 Hz, N*H*), 7.75–7.68 (2H, m, Ar-H), 7.58 (1H, d, *J* = 7.4 Hz, Ar-H), 7.47 (1H, t, *J* = 7.4 Hz, Ar-H), 4.74 (1H, ddd, *J* = 8.6, 5.4, 5.4 Hz, C*H*NH), 3.68 (1H, dd, *J* = 16.8, 8.6 Hz, C*H*<sub>2</sub>CH), 3.20 (1H, dd, *J* = 16.8, 5.4 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 201.2, 157.7 (q, <sup>2</sup>*J*<sub>CF</sub> = 36.9 Hz), 152.1, 136.3, 135.9, 128.7, 127.6, 124.4, 117.0 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 56.0, 33.2 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>9</sub>F<sub>3</sub>NO<sub>2</sub> 244.0585, found 244.0586.

(*R*)-2,2,2-trifluoro-*N*-(1-oxo-2,3-dihydro-1*H*-inden-2-yl)acetamide (TFA-D-cPhe, D-84): Colorless amorphous mass;  $[\alpha]_D = +1.6$  (*c* 1.0, acetone); +3.1 (*c* 1.6, DMF). IR (neat)  $\nu$ : 3300, 3109, 2955, 1733, 1699 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 8.94 (1H, br d, J = 5.3 Hz, N*H*), 7.75–7.68 (2H, m, Ar-H), 7.58 (1H, d, J = 7.4 Hz, Ar-H), 7.47 (1H, t, J = 7.4 Hz, Ar-H), 4.74 (1H, ddd, J = 8.4, 5.3, 5.3 Hz, C*H*NH), 3.68 (1H, dd, J = 16.8, 8.4 Hz, C*H*<sub>2</sub>CH), 3.20 (1H, dd, J = 16.8, 5.3 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 201.2, 157.7 (q, <sup>2</sup> $_{CF} = 36.3$  Hz), 152.1, 136.3, 135.9, 128.7, 127.6, 124.4, 117.0 (q, <sup>1</sup> $_{CF} = 287.7$  Hz), 56.0, 33.2 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>9</sub>F<sub>3</sub>NO<sub>2</sub> 244.0585, found 244.0588.

(*S*)-2,2,2-trifluoro-*N*-(1-oxo-3-phenyl-1-(*p*-tolyl)propan-2-yl)acetamide (TFA-L-Phe-Ph(4-Me), L-85): Colorless needles;  $[\alpha]_D = +16$  (*c* 1.0, MeOH). IR (neat) *v* : 3304, 3091, 3034, 2932, 1708, 1680 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.87 (2H, d, *J* = 8.2 Hz, Ar-H), 7.33 (4H, d, *J* = 8.2 Hz, Ar-H), 7.23–7.20 (1H, m, Ar-H), 6.92–6.88 (2H, m, Ar-H), 5.77 (1H, ddd, *J* = 5.9, 5.9, 5.9 Hz, CHNH), 3.38 (1H, dd, *J* = 14.2, 5.9 Hz, CH<sub>2</sub>CH), 3.11 (1H, dd, *J* = 14.2, 5.9 Hz, CH<sub>2</sub>CH), 2.46 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 195.4, 156.4 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), 145.6, 134.4, 131.2, 129.7 (2 x CH), 129.4 (2 x CH), 128.8 (2 x CH), 128.4 (2 x CH), 127.3, 115.6 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 55.1, 38.2, 21.6 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>2</sub> 336.1211, found 336.1180.

(*R*)-2,2,2-trifluoro-*N*-(1-oxo-3-phenyl-1-(*p*-tolyl)propan-2-yl)acetamide (TFA-D-Phe-Ph(4-Me), D-85): Colorless needles;  $[\alpha]_D = -16$  (*c* 1.0, MeOH). IR (neat)  $\nu$ : 3301, 3090, 3034, 2931, 1708, 1680 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.87 (2H, d, J = 8.2 Hz, Ar-H), 7.33 (4H, d, J = 8.2 Hz, Ar-H), 7.23–7.20 (1H, m, Ar-H), 6.93–6.89 (2H, m, Ar-H), 5.78 (1H, ddd, J = 5.8, 5.8, 5.8 Hz, CHNH), 3.37 (1H, dd, J = 14.0, 5.8 Hz, CH<sub>2</sub>CH), 3.11 (1H, dd, J = 14.0, 5.8 Hz, CH<sub>2</sub>CH), 2.45 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 195.3, 156.5 (q, <sup>2</sup> $J_{CF} = 38.0$  Hz), 145.7, 134.3, 131.2, 129.8 (2 x CH), 129.4 (2 x CH), 128.9 (2 x CH), 128.5 (2 x CH), 127.4, 115.7 (q, <sup>1</sup> $J_{CF} = 287.7$  Hz), 55.1, 38.3, 21.7 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>2</sub> 336.1211, found 336.1186.

(*S*)-2,2,2-trifluoro-*N*-(1-(4-methoxyphenyl)-1-oxo-3-phenylpropan-2-yl)acetamide (TFA-L-Phe-Ph(4-OMe), L-86): Colorless amorphous mass;  $[\alpha]_D = +27$  (*c* 1.0, MeOH). IR (neat) v: 3300, 3089, 3033, 2961, 2934, 1712, 1671 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.94 (2H, d, *J* = 8.9 Hz, Ar-H), 7.40 (1H, br d, *J* = 5.6 Hz, N*H*), 7.23–7.20 (3H, m, Ar-H), 6.98 (2H, d, *J* = 8.9 Hz, Ar-H), 6.95–6.91 (2H, m, Ar-H), 5.75 (1H, ddd, *J* = 5.6, 5.6, 5.6 Hz, C*H*NH), 3.90 (3H, s, OC*H*<sub>3</sub>), 3.35 (1H, dd, *J* = 14.0, 5.6 Hz, C*H*<sub>2</sub>CH), 3.11 (1H, dd, *J* = 14.0, 5.6 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 194.1, 164.6, 156.4 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), 134.4, 131.2 (2 x CH), 129.4 (2 x CH), 128.5 (2 x CH), 127.3, 126.6, 115.7 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 114.3 (2 x CH), 55.6, 54.9, 38.6 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>3</sub> 352.1161, found 352.1158.

(*R*)-2,2,2-trifluoro-*N*-(1-(4-methoxyphenyl)-1-oxo-3-phenylpropan-2-yl)acetamide (TFA-D-Phe-Ph(4-OMe), D-86): Colorless amorphous mass;  $[\alpha]_D = -27$  (*c* 1.0, MeOH). IR (neat) v: 3352, 3090, 3033, 2944, 2926, 1727, 1671 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.94 (2H, d, *J* = 8.9 Hz, Ar-H), 7.37 (1H, br d, *J* = 5.6 Hz, N*H*), 7.23–7.20 (3H, m, Ar-H), 6.98 (2H, d, *J* = 8.9 Hz, Ar-H), 6.94–6.90 (2H, m, Ar-H), 5.74 (1H, ddd, *J* = 5.6, 5.6, 5.6 Hz, C*H*NH), 3.91 (3H, s, OC*H*<sub>3</sub>), 3.35 (1H, dd, *J* = 14.0, 5.6 Hz, C*H*<sub>2</sub>CH), 3.11 (1H, dd, *J* = 14.0, 5.6 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 194.1, 164.5, 156.4 (q, <sup>2</sup>*J*<sub>CF</sub> =37.6 Hz), 134.5, 131.1 (2 x CH), 129.3 (2 x CH), 128.3 (2 x CH), 127.2, 126.5, 115.7 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.3 Hz), 114.2 (2 x CH), 55.4, 54.8, 38.4 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>3</sub> 352.1161, found 352.1169.

#### (S)-N-(1-(3,4-dimethylphenyl)-1-oxo-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide

(TFA-L-Phe-Ph(3,4-Me), L-89): Colorless needles;  $[\alpha]_D = +16$  (*c* 1.0, MeOH). IR (neat)  $\nu$ : 3326, 3031, 2945, 2935, 1732, 1685 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.71 (2H, d, J = 6.9 Hz, Ar-H), 7.46 (1H, br d, J = 5.9 Hz, NH), 7.28–7.19 (4H, m, Ar-H), 6.93 (2H, d, J = 7.8 Hz, Ar-H), 5.79 (1H, ddd, J = 4.9, 5.9, 5.9 Hz, CHNH), 3.35 (1H, dd, J = 13.8, 5.9 Hz, CH<sub>2</sub>CH), 3.10 (1H, dd, J = 13.8, 4.9 Hz, CH<sub>2</sub>CH), 2.33 (3H, s, CH<sub>3</sub>), 2.32 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 195.5, 156.4 (q, <sup>2</sup> $J_{CF} = 37.4$  Hz), 144.4, 137.6, 134.4, 131.5, 130.2, 129.8, 129.4 (2 x CH), 128.4 (2 x CH), 127.2, 126.5, 115.7 (q, <sup>1</sup> $J_{CF} = 287.7$  Hz), 55.1, 38.3, 20.0, 19.6 ppm. HRMS-ESI (m/z) [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>19</sub>F<sub>3</sub>NO<sub>2</sub> 350.1368, found 350.1356.

# (R)-N-(1-(3,4-dimethylphenyl)-1-oxo-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide

(TFA-D-Phe-Ph(3,4-Me), D-89): Colorless needles;  $[\alpha]_D = -16$  (*c* 1.0, MeOH). IR (neat) *v*: 3329, 3031, 2946, 2925, 1735, 1687 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.71 (2H, d, *J* = 6.9 Hz, Ar-H), 7.45 (1H, br d, *J* = 5.9 Hz, N*H*), 7.28–7.19 (4H, m, Ar-H), 6.93 (2H, d, *J* = 7.8 Hz, Ar-H), 5.79 (1H, ddd, *J* = 4.9, 5.9, 5.9 Hz, CHNH), 3.35 (1H, dd, *J* = 13.8, 5.9 Hz, CH<sub>2</sub>CH), 3.10 (1H, dd, *J* = 13.8, 4.9 Hz, CH<sub>2</sub>CH), 2.34 (3H, s, CH<sub>3</sub>), 2.32 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 195.5, 156.4 (q, <sup>2</sup>*J*<sub>CF</sub> =37.2 Hz), 144.4, 137.6, 134.4, 131.5, 130.2, 129.8, 129.4 (2 x CH), 128.4 (2 x CH), 127.3, 126.5, 115.7 (q, <sup>1</sup>*J*<sub>CF</sub> = 288.3 Hz), 55.1, 38.3, 20.0, 19.7 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>19</sub>F<sub>3</sub>NO<sub>2</sub> 350.1368, found 350.1362.

# (S)-N-(1-(2,4-dimethylphenyl)-1-oxo-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide

(TFA-L-Phe-Ph(2,4-Me), L-90): Colorless needles;  $[\alpha]_D = +11$  (*c* 1.0, MeOH). IR (neat) *v*: 3301, 3090, 3032, 2931, 1706, 1675 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.69 (1H, d, *J* = 8.6 Hz, Ar-H), 7.48 (1H, br d, *J* = 5.4 Hz, N*H*), 7.21–7.18 (3H, m, Ar-H), 7.15–7.11 (2H, m, Ar-H), 6.87–6.83 (2H, m, Ar-H), 5.74 (1H, ddd, *J* = 5.4, 5.4, 5.4 Hz, C*H*NH), 3.32 (1H, dd, *J* = 14.0, 5.4 Hz, C*H*<sub>2</sub>CH), 3.04 (1H, dd, *J* = 14.0, 5.4 Hz, C*H*<sub>2</sub>CH), 2.40 (6H, s, 2 x C*H*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.3, 156.5 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.8 Hz), 144.0, 140.9, 134.4, 133.7, 130.5, 129.6, 129.3 (2 x CH), 128.5 (2 x CH), 127.3, 126.8, 115.7 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 56.3, 37.8, 21.6, 21.5 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>19</sub>F<sub>3</sub>NO<sub>2</sub> 350.1368, found 350.1375.

#### (R)-N-(1-(2,4-dimethylphenyl)-1-oxo-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide

(TFA-D-Phe-Ph(2,4-Me), D-90): Colorless needles;  $[\alpha]_D = -11$  (*c* 1.0, MeOH). IR (neat)  $\nu$ : 3302, 3091, 3019, 2931, 1708, 1676 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.69 (1H, d, J = 8.9Hz, Ar-H), 7.45 (1H, br d, J = 5.4 Hz, NH), 7.21–7.19 (3H, m, Ar-H), 7.16–7.12 (2H, m, Ar-H), 6.86–6.83 (2H, m, Ar-H), 5.74 (1H, ddd, J = 5.4, 5.4, 5.4 Hz, CHNH), 3.32 (1H, dd, J =14.2, 5.4 Hz, CH<sub>2</sub>CH), 3.05 (1H, dd, J = 14.2, 5.4 Hz, CH<sub>2</sub>CH), 2.40 (6H, s, 2 x CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 197.3, 156.5 (q, <sup>2</sup> $J_{CF} = 37.6$  Hz), 144.0, 140.9, 134.4, 133.7, 130.5, 129.6, 129.3 (2 x CH), 128.5 (2 x CH), 127.3, 126.8, 115.7 (q, <sup>1</sup> $J_{CF} = 287.3$  Hz), 56.3, 37.8, 21.5, 21.5 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>19</sub>F<sub>3</sub>NO<sub>2</sub> 350.1368, found 350.1371.

# (S)-N-(1-(2,5-dimethylphenyl)-1-oxo-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide

(**TFA-L-Phe-Ph(2,5-Me), L-91):** Colorless needles;  $[\alpha]_D = +10$  (*c* 1.0, MeOH). IR (neat) *v*: 3303, 3033, 2927, 1708, 1679 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.45–7.38 (2H, m, Ar-H), 7.17–7.05 (4H, m, Ar-H), 6.80–6.74 (2H, m, Ar-H), 5.63 (1H, ddd, J = 5.6, 5.6, 5.6 Hz, CHNH), 3.16 (1H, dd, J = 14.2, 5.6 Hz, CH<sub>2</sub>CH), 2.93 (1H, dd, J = 14.2, 5.6 Hz, CH<sub>2</sub>CH),

2.25 (3H, s, *CH*<sub>3</sub>), 2.23 (3H, s, *CH*<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 198.2, 156.5 (q, <sup>2</sup>*J*<sub>*CF*</sub> = 37.6 Hz), 137.1, 135.7, 134.5, 133.6, 133.3, 132.5, 129.7, 129.2 (2 x CH), 128.4 (2 x CH), 127.2, 115.7 (q, <sup>1</sup>*J*<sub>*CF*</sub> = 287.0 Hz), 56.6, 37.6, 20.7, 20.7 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>19</sub>F<sub>3</sub>NO<sub>2</sub> 350.1368, found 350.1366.

#### (R)-N-(1-(2,5-dimethylphenyl)-1-oxo-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide

(**TFA-D-Phe-Ph(2,5-Me), D-91):** Colorless needles;  $[\alpha]_D = -10$  (*c* 1.0, MeOH). IR (neat) *v*: 3325, 3031, 2928, 1726, 1685 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.45–7.38 (2H, m, Ar-H), 7.16–7.05 (4H, m, Ar-H), 6.79–6.74 (2H, m, Ar-H), 5.63 (1H, ddd, *J* = 5.8, 5.8, 5.8 Hz, CHNH), 3.16 (1H, dd, *J* = 14.2, 5.8 Hz, CH<sub>2</sub>CH), 2.93 (1H, dd, *J* = 14.2, 5.8 Hz, CH<sub>2</sub>CH), 2.25 (3H, s, CH<sub>3</sub>), 2.23 (3H, s, CH<sub>3</sub>) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 198.2, 156.5 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.2 Hz), 137.1, 135.6, 134.5, 133.6, 133.3, 132.4, 129.6, 129.2 (2 x CH), 128.4 (2 x CH), 127.2, 115.7 (q, <sup>1</sup>*J*<sub>CF</sub> = 286.8 Hz), 56.6, 37.6, 20.7, 20.7 ppm. HRMS-ESI (*m*/*z*) [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>19</sub>F<sub>3</sub>NO<sub>2</sub> 350.1368, found 350.1373.

(*S*)-2,2,2-trifluoro-*N*-(1-oxo-3-phenyl-1-(1*H*-pyrrol-2-yl)propan-2-yl)acetamide (TFA-L-Phe-(2-Pyr), L-94):<sup>30</sup> Colorless amorphous mass;  $[\alpha]_D = +40$  (*c* 1.0, CHCl<sub>3</sub>). Lit.<sup>30</sup>  $[\alpha]_D = +44.3$  (*c* 1.6, CHCl<sub>3</sub>). IR (neat)  $\nu$ : 3308, 1701, 1654 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 9.49 (1H, br s, N*H*), 7.24–7.20 (3H, m, Ar-H), 7.13-7.11 (1H, m, Ar-H), 7.03–6.95 (3H, m, Ar-H & C*H*), 6.34 (1H, dd, *J* = 6.4, 2.5 Hz, C*H*), 5.48 (1H, dd, *J* = 13.8, 5.9 Hz, C*H*NH), 3.35 (1H, dd, *J* = 13.8, 5.9 Hz, C*H*<sub>2</sub>CH), 3.17 (1H, dd, *J* = 13.8, 5.9 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 184.8, 156.4 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), 134.7, 129.4 (2 x CH), 129.0, 128.5 (2 x CH), 127.4, 126.6, 118.3, 115.7 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 111.8, 55.3, 39.8 ppm. HRMS-ESI (*m*/*z*) [M+Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>Na 333.0821, found 333.0824.

(*R*)-2,2,2-trifluoro-*N*-(1-oxo-3-phenyl-1-(1*H*-pyrrol-2-yl)propan-2-yl)acetamide (TFA-D-Phe-(2-Pyr), D-94): Colorless amorphous mass;  $[\alpha]_D = -40$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat)  $\nu$ : 3309, 1701, 1655 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 9.50 (1H, br s, N*H*), 7.24–7.20 (3H, m, Ar-H), 7.13–7.10 (1H, m Ar-H), 7.02–6.98 (3H, m, Ar-H & C*H*), 6.34 (1H, dd, *J* = 6.4, 2.5 Hz, C*H*), 5.48 (1H, dd, *J* = 13.8, 5.9 Hz, C*H*NH), 3.35 (1H, dd, *J* = 13.8, 5.9 Hz, C*H*<sub>2</sub>CH), 3.17 (1H, dd, *J* = 13.8, 5.9 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 184.8, 156.4 (q,  ${}^{2}J_{CF} = 38.0$  Hz), 134.7, 129.4 (2 x CH), 129.0, 128.5 (2 x CH), 127.4, 126.6, 118.3, 115.7 (q,  ${}^{1}J_{CF} = 287.7$  Hz), 111.8, 55.2, 39.8 ppm. HRMS-ESI (*m*/*z*) [M+Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>13</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>Na 333.0821, found 333.0821.

(*S*)-2,2,2-trifluoro-*N*-(1-(1-methyl-1*H*-pyrrol-2-yl)-1-oxo-3-phenylpropan-2-yl)acetamide (TFA-L-Phe-(2-(*N*-Me)Pyr), L-95): Yellowish amorphous mass;  $[\alpha]_D = +53$  (*c* 1.0, CHCl<sub>3</sub>); Lit. <sup>30</sup>  $[\alpha]_D = +43.6$  (*c* 1.6, CHCl<sub>3</sub>). IR (neat) v: 3289, 3123, 3088, 1724 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.36 (1H, br s, N*H*), 7.26–7.20 (4H, m, Ar-H), 7.04–6.99 (2H, m, Ar-H & C*H*), 6.62 (2H, d, *J* = 2.0 Hz, C*H*), 5.32 (1H, dd, *J* = 13.8, 6.3 Hz, C*H*NH), 3.67 (3H, s, C*H*<sub>3</sub>), 3.31 (1H, dd, *J* = 13.8, 6.3 Hz, C*H*<sub>2</sub>CH), 3.15 (1H, dd, *J* = 13.8, 6.3 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 189.8, 156.4 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), 135.1, 129.5 (2 x CH), 128.3 (2 x CH), 128.0, 127.1, 124.1, 122.3, 115.7 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 109.8, 56.2, 39.2, 36.7 ppm. HRMS-ESI (*m*/*z*) [M+Na]<sup>+</sup> calcd for C<sub>16</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>Na 347.0978, found 347.0975.

(*R*)-2,2,2-trifluoro-*N*-(1-(1-methyl-1*H*-pyrrol-2-yl)-1-oxo-3-phenylpropan-2-yl)acetamide (TFA-D-Phe-(2-(*N*-Me)Pyr), D-95): Yellowish amorphous mass;  $[\alpha]_D = -53$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat)  $\nu$ : 3264, 3123, 3088, 1725 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.37 (1H, br s, N*H*), 7.26–7.20 (4H, m, Ar-H), 7.03–6.99 (2H, m, Ar-H & C*H*), 6.62 (2H, d, *J* = 2.0 Hz, C*H*), 5.33 (1H, dd, *J* = 13.8, 6.4 Hz, C*H*NH), 3.67 (3H, s, C*H*<sub>3</sub>), 3.31 (2H, dd, *J* = 13.8, 6.4 Hz, C*H*<sub>2</sub>CH), 3.15 (1H, dd, *J* = 13.8, 6.4 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 189.8, 156.4 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.6 Hz), 135.1, 129.5 (2 x CH), 128.3 (2 x CH), 128.0, 127.1, 124.1, 122.3, 115.7 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 109.8, 56.2, 39.2, 36.7 ppm. HRMS-ESI (*m*/*z*) [M+Na]<sup>+</sup> calcd for C<sub>16</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>Na 347.0978, found 347.0976.

(*S*)-2,2,2-trifluoro-*N*-(1-(1-methyl-1*H*-pyrrol-3-yl)-1-oxo-3-phenylpropan-2-yl)acetamide (TFA-L-Phe-(3-(*N*-Me)Pyr), L-96): Yellowish amorphous mass;  $[\alpha]_D = +48$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) v: 3307, 1704, 1654 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.25–7.21 (3H, m, Ar-H), 7.03 (1H, d, J = 4.3 Hz, Ar-H), 7.00–6.96 (2H, m, Ar-H & CH), 6.93 (1H, s, CH), 6.20 (1H, dd, J = 4.3, 2.3 Hz, CH), 5.48 (1H, dd, J = 13.8, 5.6 Hz, CHNH), 3.90 (3H, s, CH<sub>3</sub>), 3.34 (1H, dd, J = 13.8, 5.6 Hz, CH<sub>2</sub>CH), 3.13 (1H, dd, J = 13.8, 5.6 Hz, CH<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 185.0, 156.3 (q, <sup>2</sup> $J_{CF} = 37.1$  Hz), 135.0, 133.0, 129.4 (2 x CH), 128.4 (2 x CH), 127.8, 127.3, 120.9, 115.7 (q, <sup>1</sup> $J_{CF} = 287.7$  Hz), 109.2, 55.4, 40.0, 37.6 ppm. HRMS-ESI (*m*/*z*) [M+Na]<sup>+</sup> calcd for C<sub>16</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>Na 347.0978, found 347.0979.

(*R*)-2,2,2-trifluoro-*N*-(1-(1-methyl-1*H*-pyrrol-3-yl)-1-oxo-3-phenylpropan-2-yl)acetamide (TFA-D-Phe-(3-(*N*-Me)Pyr), D-96): Yellowish amorphous mass;  $[\alpha]_D = -48$  (*c* 1.0, CHCl<sub>3</sub>). IR (neat) v: 3302, 1703, 1649 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.25–7.22 (3H, m, Ar-H), 7.03 (1H, d, J = 4.0 Hz, Ar-H), 7.00–6.96 (2H, m, Ar-H & CH), 6.93 (1H, s, CH), 6.20 (1H, dd, J = 4.3, 2.3 Hz, CH), 5.48 (1H, dd, J = 13.8, 5.6 Hz, CHNH), 3.90 (3H, s, CH<sub>3</sub>), 3.34 (1H, dd, J = 13.8, 5.6 Hz, CH<sub>2</sub>CH), 3.13 (1H, dd, J = 13.8, 5.6 Hz, CH<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>)  $\delta$ : 185.0, 156.3 (q, <sup>2</sup> $J_{CF} = 37.4$  Hz), 135.0, 133.0, 129.4 (2 x CH), 128.4 (2 x CH), 127.8, 127.3, 120.9, 115.7 (q, <sup>1</sup> $J_{CF} = 287.7$  Hz), 109.2, 55.4, 40.0, 37.6 ppm. HRMS-ESI (*m*/*z*) [M+Na]<sup>+</sup> calcd for C<sub>16</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>Na 347.0978, found 347.0980.
# (*S*)-2,2,2-trifluoro-*N*-(3-(4-hydroxyphenyl)-1-oxo-1-phenylpropan-2-yl)acetamide (TFA-L-Tyr-Ph, L-100): Colorless amorphous mass. $[\alpha]_D = +45$ (*c* 1.0, MeOH). IR (neat) *v* : 3464, 3311, 1713, 1682 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, ACETONE-D<sub>6</sub>) $\delta$ : 8.65 (1H, br d, *J* = 7.3 Hz, N*H*), 8.25 (1H, s, O*H*), 8.07 (2H, d, *J* = 7.4 Hz, Ar-H), 7.67 (1H, t, *J* = 7.4 Hz, Ar-H), 7.56 (2H, t, *J* = 7.4 Hz, Ar-H), 7.11 (2H, d, *J* = 8.2 Hz, Ar-H), 6.76 (2H, d, *J* = 8.2 Hz, Ar-H), 5.77 (1H, ddd, *J* = 8.9, 7.3, 5.2 Hz, C*H*NH), 3.26 (1H, dd, *J* = 14.2, 5.2 Hz, C*H*<sub>2</sub>CH), 3.00 (1H, dd, *J* = 14.2, 8.9 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, ACETONE-D<sub>6</sub>) $\delta$ : 197.4, 157.2, 157.2 (q, <sup>2</sup>*J*<sub>CF</sub> = 36.9 Hz), 135.8, 134.6, 131.2 (2 x CH), 129.7 (2 x CH), 129.3 (2 x CH), 127.8, 116.9 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.7 Hz), 116.1 (2 x CH), 57.0, 36.9 ppm. HRMS-ESI (*m*/*z*) [M+Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>3</sub>Na 360.0818, found 360.0820.

(*R*)-2,2,2-trifluoro-*N*-(3-(4-hydroxyphenyl)-1-oxo-1-phenylpropan-2-yl)acetamide (TFA-D-Tyr-Ph, D-100): Colorless amorphous mass.  $[\alpha]_D = -45$  (*c* 1.0, MeOH). IR (neat)  $\nu$ : 3464, 3309, 1710, 1677 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 8.64 (1H, br d, J = 7.6 Hz, N*H*), 8.24 (1H, s, O*H*), 8.07 (2H, d, J = 7.4 Hz, Ar-H), 7.67 (1H, t, J = 7.4 Hz, Ar-H), 7.56 (2H, t, J = 7.4 Hz, Ar-H), 7.11 (2H, d, J = 8.6 Hz, Ar-H), 6.76 (2H, d, J = 8.6 Hz, Ar-H), 5.77 (1H, ddd, J = 8.6, 7.6, 5.1 Hz, C*H*NH), 3.26 (1H, dd, J = 14.3, 5.1 Hz, C*H*<sub>2</sub>CH), 3.00 (1H, dd, J = 14.3, 8.6 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 197.4, 157.2, 157.2 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.4 Hz), 135.8, 134.6, 131.2 (2 x CH), 129.7 (2 x CH), 129.4 (2 x CH), 127.8, 116.9 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.2 Hz), 116.1 (2 x CH), 57.0, 36.9 ppm. HRMS-ESI (*m*/*z*) [M+Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>3</sub>Na 360.0818, found 360.0814.

**2,2,2-trifluoro**-*N*-(**2**-(**4-hydroxyphenyl**)-**1-phenylethyl**)**acetamide** (101): Yellowish amorphous mass. IR (neat) v: 3329, 1693 cm<sup>-1</sup>. <sup>1</sup>H-NMR (270 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 8.82 (1H, br d, J = 8.6 Hz, N*H*), 8.18 (1H, s, O*H*), 7.44 (2H, d, J = 7.9 Hz, Ar-H), 7.38–7.24 (3H, m, Ar-H), 7.09 (2H, d, J = 8.6 Hz, Ar-H), 6.74 (2H, d, J = 8.6 Hz, Ar-H), 5.24 (1H, ddd, J = 8.6, 8.6, 6.9 Hz, C*H*NH), 3.15 (1H, d, J = 8.6 Hz, C*H*<sub>2</sub>CH), 3.12 (1H, d, J = 6.9 Hz, C*H*<sub>2</sub>CH) ppm. <sup>13</sup>C-NMR (67.5 MHz, ACETONE-D<sub>6</sub>)  $\delta$ : 156.9, 156.8 (q, <sup>2</sup> $_{CF}$  = 36.3 Hz), 142.3, 131.0 (2 x CH), 129.4 (2 x CH), 129.3 (2 x CH), 128.3, 127.7, 117.1 (q, <sup>1</sup> $_{CF}$  = 288.3 Hz), 115.9 (2 x CH), 56.8, 41.5 ppm.

### 3.4 Conclusion

To summarize, through the reaction of aliphatic TFA-protected  $\alpha$ -amino acid-OSu (L-/D-33, L-/D-38, 53, L-/D-57, L-/D-61, L-/D-65, L-/D-69, L-/D-73, and L-/D-77) with arenes under conventional Friedel-Crafts conditions, it is more convenient to synthesize chiral TFAprotected  $\alpha$ -amino aryl-ketones as its skeleton can be obtained from optically active material. The TFA-protected  $\alpha$ -amino acid-OSu showed high reactivity and is easier to handle during the reaction than acid chloride. Utilization of TFA-α-amino acid-OSu derivatives having a side chain of an aromatic moiety (L-/D-82 and L-/D-99) for acyl acceptor in Friedel-Crafts acylation reaction with AlCl<sub>3</sub> as a catalyst might introduce an inter-molecular reaction with arenes and heterocycles. Rapid intra-molecular cyclization is possible in the reaction for TFA-L-/D-Phe-OSu (L-/D-82). All TFA-protected  $\alpha$ -amino acid-OSu can contribute as an excellent acyl donor to Friedel–Crafts acylation without loss of chirality at the  $\alpha$ -carbon. This typical reaction can play an important role in further study to broaden application for the synthesis of new bioactive compounds. The novel compounds explored in this study also can contribute to new synthetic pathways and can be a part of the comprehensive future study to their exploitation in the organic synthesis, for example studying the complex bio-synthesis of acetyl-CoA in human from simple  $\alpha$ -amino aryl ketone starting material.

## Chapter 4 Hydrogen/deuterium exchange of aromatic compounds

### (cycloDOPA derivatives)

### 4.1 Introduction

CycloDOPA (5,6-dihydroxy-indoline-2-carboxylic acid, leukodopachrome, cDOPA, **102**, Scheme 32), known as metabolites of aromatic  $\alpha$ -amino acid of tyrosine,<sup>111</sup> is one of intermediate in eumelanin pathway (melanin formation in mammalian)<sup>112–114</sup> and main skeleton of betanidin (betalain pigment in plant).<sup>115,116</sup> In spite of its simple structure, which can be constructed from intra-molecular cyclization of L-DOPA **103**, a few studies have been reported for the synthesis and its commercial sources are also limited. First synthesis of cDOPA has been reported in 1968.<sup>117</sup> Based on this study, the skeleton of cDOPA was generated once at early stage and isolated as its peracetylated form, *O*,*O*,*N*-triacetyl cDOPA methyl ester (Ac<sub>3</sub>-cDOPA-OMe, **104**, Scheme 32).<sup>118</sup>



Scheme 32 Synthesis of cDOPA 102

Hydrogen/deuterium (H/D) exchange, the displacement of hydrogen bonded to carbon by deuterium, is one of the methods to broaden the variety of isotopically labeled material.<sup>119</sup> Based on the recent progress of the mass equipment, H/D exchange also provides analysis with stable isotopes to reveal the biosynthetic pathways.<sup>120</sup> Previously, the introduction of deuterated trifluoroacetic acid (TFA-*d*) for H/D exchange of hydrogen in the aromatic ring of cDOPA was reported.<sup>117</sup> The selective H/D exchange (within ~50% deuterium incorporation) of hydrogen in the aromatic moiety can be formed only at 7-position after the treatment at 83 °C, but no incorporation of deuterium was found when treated at 70 °C. Although the deuterium incorporation in cDOPA can be utilized for analysis of me metabolic pathway, to date, the synthesis of fully deuterated cDOPA had not been studied. An acid-catalyzed H/D exchange is known as an efficient method for incorporating deuterium into an aromatic moiety.<sup>43,119</sup> Recently, our detail analysis of chemical stability for cDOPA revealed that cDOPA was stable in acidic conditions and easily broken over pH 4 to be converted dihydroxyindole derivatives.<sup>118</sup> Moreover, deprotection of Ac<sub>3</sub>-cDOPA-OMe **104** under acidic condition enabled formation of cDOPA **102** also to demonstrate stability of cDOPA <sup>118</sup> that indicates its potential for H/D exchange in acidic condition. Since HCl system can be applied for deacetylation to result in cDOPA (Scheme 32), deuterium chloride (DCl) system is expected to introduce deuterium to cDOPA moiety.

Triflic acid (TfOH), or so-called superacid, is known for its ability as a catalyst that acts as solvent for utmost amino acids.<sup>34</sup> The recent report found that deuterated triflic acid (TfOD) can be used for H/D exchange of aromatic amino acids such as phenylalanine, tyrosine,<sup>49</sup> or L-DOPA<sup>50</sup> under mild conditions to give over 90% deuterium incorporation only in its aromatic moiety. Since cDOPA is stable at acidic condition, TfOD also can be introduced for synthesis of deuterium-labeled cDOPA derivatives. Here in this study, the comprehensive H/D exchange and analysis of deuterium incorporation for cDOPA is studied. The stable and readily synthesized cDOPA can be utilized for synthesis of the novel fully-deuterated aromatic moiety of cDOPA derivatives via H/D exchange. The introduction of DCl and TfOD system is expected to broaden the formation study of deuterium-labeled cDOPA derivatives.

### 4.2 **Results and Discussion**

The cDOPA **102** can be synthesized from oxidation of commercially available L-DOPA **103** and isolated as its peracetylated form of *O*,*O*,*N*-triacetyl cDOPA methyl ester (Ac<sub>3</sub>cDOPA-OMe, **104**, Scheme 32).<sup>117</sup> The further deacetylation of Ac<sub>3</sub>-cDOPA-OMe **104** under strongly acidic conditions at 80 °C represents the stability of cDOPA **102**<sup>118</sup> is feasible for H/D exchange. Since acid-induced H/D exchange,<sup>46</sup> such as utilization with deuterium chloride (DCl) or deuterated triflic acid (TfOD), is known as the convenient method for H/D exchange of aromatic moiety, two possible exchangeable protons in aromatic ring of cDOPA are enable to undergo H/D exchange at 4- and 7-positions. The skeleton of cDOPA **102** was priorly subjected to 2D NMR analysis for ascertaining its each counterpart. Based on <sup>1</sup>H-NMR, the aromatic proton at 4-position was shown as a singlet at  $\delta_{\rm H}$  6.84 ppm, while proton at 7-position was shown as a singlet at  $\delta_{\rm H}$  6.90 ppm, both of which were distinguished by HMBC analysis (Figure 29).



Figure 29 Selected HMBC (500 MHz, D<sub>2</sub>O) of cDOPA 102

Since the deacetylation of Ac<sub>3</sub>-cDOPA-OMe **104** by 6 M HCl was conducted at 80 °C allowing the formation of cDOPA **102** with a fine yield (Scheme 32), the H/D exchange for synthesis of deuterium-labeled cDOPA derivatives was attempted by using DCl system. Accordingly, Ac<sub>3</sub>-cDOPA-OMe **104** was first subjected to 20% DCl/D<sub>2</sub>O at 80 °C and the deuterium incorporated form of its unprotected cDOPA **102** was observed by <sup>1</sup>H-NMR. In Figure 30 (b), when 20% DCl/D<sub>2</sub>O was utilized, the aromatic hydrogen of cDOPA at the 7-position can be fully deuterated (99% D) meanwhile the 4-position was deuterated up to 60% by 4 h. In contrast, deuteration of the 4-position was hampered meanwhile 7-position almost fully deuterated within less than 1 h. These large differences in the deuterium incorporation between 4- and 7-positions cannot be maintained due to long H/D exchange time to increase deuterium incorporation at the 4-position (Figure 30 (b)).

Utilization of 5% and 10%  $DCl/D_2O$  as the lower DCl concentration showed the 7position was deuterated almost up to twice higher than the 4-position dependent to time (Figure 30 (c) and (d)). In contrast to 20% DCl/D<sub>2</sub>O utilization, lower DCl concentration needed longer reaction time for H/D exchange at the 7-position. At the 7-position of cDOPA derivative, deuterium exchange takes place approximately 80% and 95% after 6 h when 5% and 10% DCl/D<sub>2</sub>O were utilized, respectively. Thus, 5% or 10% DCl/D<sub>2</sub>O is considered to be less suitable for H/D exchange of cDOPA.



Figure 30 Deprotection and hydrogen/deuterium exchange of O, O, N-triacetyl cDOPA methyl ester (104) at 80 °C dependent on concentration of (a) 35% DCl/D<sub>2</sub>O, (b) 20% DCl/D<sub>2</sub>O, (c) 5% DCl/D<sub>2</sub>O, and (d) 10% DCl/D<sub>2</sub>O. The time-course of H/D exchange for cDOPA (102) was determined by <sup>1</sup>H NMR.

When 35% DCl/D<sub>2</sub>O was used at 80  $^{\circ}$ C (Figure 30 (a)), hydrogen of aromatic ring at the 4- and the 7-position were fully deuterated (99% deuterium incorporation) within 4 h. The high concentration of DCl is effective for rapid H/D exchange of both aromatic hydrogen

atoms of cDOPA at the 4- and 7-positions which are suitable for synthesizing the fullydeuterated aromatic ring of cDOPA derivative. Thus, 35% DCl/D<sub>2</sub>O was subjected to Ac<sub>3</sub>cDOPA-OMe **104** for synthesis of the fully deuterated cDOPA (**105**, Scheme 33). Compound **105** can be isolated by evaporation and removal of excess DCl with CH<sub>3</sub>CN washing. During the isolation process, no loss of deuterated counterpart was observed by <sup>1</sup>H-NMR. Compound **105** is stable and feasible to undergo <sup>13</sup>C-NMR measurement in D<sub>2</sub>O aqueous solution.



Scheme 33 Synthesis of deuterated cDOPA derivative (105) Deuterium incorporation (% D) for each position is shown in square brackets.

For further understanding of selective H/D exchange on cDOPA, unprotected cDOPA **102** was also directly subjected to H/D exchange at various temperatures. The H/D exchange of cDOPA **102** was started with utilization of 20% DCl/D<sub>2</sub>O. This DCl concentration is considered to be a suitable condition for the selective deuteration of cDOPA, since within less than 1 h of Ac<sub>3</sub>-cDOPA-OMe **104** subjection, the differences of H/D exchange at 4- and 7-positions can be observed (Figure 30 (a)). When cDOPA **102** was subjected to the reaction 20% DCl/D<sub>2</sub>O at 80 °C, hydrogen at the 7-position of aromatic cDOPA can be fully deuterated meanwhile the 4-position can be only deuterated approximately 40% after 4 h. The slower H/D exchange within the same DCl concentration and temperature for direct cDOPA **102** (Figure 31 (a)) rather than subjection of Ac<sub>3</sub>-cDOPA-OMe **104** (Figure 30 (a)) might be due to the presence of accumulated acetic acid as byproduct of deacetylation that increases the system of acidity during H/D exchange to enhance condition for the H/D exchange.

When the 7-position can be fully deuterated after 4 h, decrease of temperature to 70  $^{\circ}$ C resulted in deuteration of cDOPA aromatic moiety at the 4-position as only 30% or so (Figure 31 (b)). Similarly, the 4-position of cDOPA showed approxymately 20% deuterium incorporation while the 7-position showed nearly 90% deuterium incorporation after 6 h when H/D exchange was conducted at 60  $^{\circ}$ C (Figure 31 (c)). As for 50  $^{\circ}$ C (Figure 31 (d)), the same tendency also was shown within prolonged time, in which the 4-position of cDOPA showed only around 20% deuterium incorporation and the 7-position showed almost 90% deuterium incorporation after 12 h of the treatment. These results indicated that by lowering the temperature, the H/D exchange at the 4-position is slower than the 7-position, which is

depending on H/D exchange time. The further subjection of cDOPA **102** with 20% DCl at 60 °C for 6 h, followed by evaporation and removal of excess HCl, can result in deuterated cDOPA derivative at the 7-position (compound **106**, Scheme 34). The selective deuterium-labeled of compound **106** is stable and deuterated counterparts at 7-position (88% D) and 4-position (23% D) also showed no loss of deuterium incorporation during the isolation process.



Figure 31 Hydrogen/deuterium exchange of cDOPA (102) by 20% DCl/D<sub>2</sub>O dependent on temperature of (a) 80  $^{\circ}$ C, (b) 70  $^{\circ}$ C, (c) 60  $^{\circ}$ C, and (d) 50  $^{\circ}$ C.



Scheme 34 Synthesis of deuterated cDOPA derivative (106) <sup>a</sup> Recovery percentage. Deuterium incorporation (% D) for each position is shown in square brackets.

Triflic acid (TfOH) is categorized as a strong Brønsted acid and known for its ability to solve mostly amino acid skeleton.<sup>34,49,121</sup> The deuterated triflic acid (TfOD) can be used to promote H/D exchange<sup>34</sup> of aromatic amino acids, such as phenylalanine, tyrosine,<sup>49</sup> or L-DOPA<sup>50</sup> under a mild condition (rt or 0 °C) to give over 90% deuterium incorporation only in its aromatic moiety. To complete the synthesis of deuterated cDOPA derivatives, cDOPA **102** was then treated with TfOD. At room temperature (Figure 32 (a)), approximately 90% deuterium incorporation takes place at the 4- and 7-positions of cDOPA aromatic ring after 1 h. The degree of exchange did not change even with longer incubation time.



Figure 32 Hydrogen/deuterium exchange of cDOPA (102) with triflic acid (TfOD, 40 equiv.) at (a) rt and (b) 0  $^{\circ}$ C

In Figure 32 (b), H/D exchange of cDOPA at lower temperature (0 °C) showed faster H/D exchange at the 4-position than the 7-position. Within 40 min, proton at the 4-position deuterium can be achieved as 84% D and the 7-position was deuterated 36% D based on observation with <sup>1</sup>H-NMR. Elongation time for H/D exchange at 0 °C showed that the two sites can be deuterated approximately 90% after 6 h. TfOD is suitable for H/D exchange of cDOPA aromatic moiety at room temperature (nearly 90% deuterium incorporation after 1 h, Figure 32 (a)), compared with previous utilization of TFA-d that needed high temperature to conduct only 50% deuterium at the 7-position.<sup>117</sup> It is possible due to TfOD known to be relatively strong acid rather than TFA-d.<sup>34,122</sup> By utilizing TfOD at room temperature for 1 h, full deuterated aromatic moiety of cDOPA derivatives 107 can be formed (Scheme 35 (a)). Next, the selective deuterated cDOPA at the 4-position of compound 108 can be synthesized by utilizing TfOD at 0 °C for 40 m (Scheme 35 (b)). The treatments of pH adjustment with NaOD, freeze drying, and then gel filtration chromatography (Sephadex G-10 eluted with HCl (pH = 3)) were conducted for the isolation of deuterated cDOPA (107 and 108) derivatives from TfOD utilization (See Figure 33 for details). The attempt to remove of excess TfOD was difficult to conduct after all further treatments, although deuterium incorporation of deuterated cDOPA derivatives using TfOD showed no significant differences in the deuterium incorporation (% D) during the process.



Scheme 35 Synthesis of deuterated cDOPA derivatives (107 and 108) <sup>a</sup> % Yield measured from UV-Vis spectra (TfOD/D<sub>2</sub>O). Deuterium incorporation (% D) for each position is shown in square brackets.



Index:

C1: cDOPA 102 is treated with TfOD at 0 °C for 40 m and directly subjected into NMR.

P1: C2 after pH (2–3) adjustment by NaOD.

F1: P2 after overnight freeze drying.

G1: F1 after separation by gel filtration chromatography (Sephadex G-10 eluted by HCl (pH = 3), 27% recovery in Cl<sup>-</sup> salt measured from UV-Vis spectra).

C2: cDOPA 102 is treated with TfOD at rt for 1 h and directly subjected into NMR.

P2: C2 after pH (2–3) adjustment by NaOD.

F2: P2 after overnight freeze drying.

G2: F2 after separation by gel filtration chromatography (Sephadex G-10 eluted by HCl (pH = 3), 26% recovery in Cl<sup>-</sup> salt measured from UV-Vis spectra).

Figure 33 Excess TfOD removal trials for deuterated cDOPA derivatives (107 and 108)

The fully and partially deuterated cDOPA derivatives (105–108) via H/D exchange can be formed by the utilization of DCl or TfOD system. The deuterium counterpart of deuterated cDOPA derivatives of **105–108** can be determined by <sup>1</sup>H-NMR (Figure 34). Based on <sup>1</sup>H-NMR (Figure 34), there is no change of proton NMR signal integrations corresponding to the heterocyclic side chain of deuterated cDOPA derivatives. Thus, the H/D exchanges indicated occurred only specific in aromatic moiety of cDOPA. H/D exchange is basically complex process with complicated intermediate that can be affected by temperature, deuterium source, and pH. Thus, the site-selectivity between H/D exchanges of the 4- and 7-positions on the aromatic ring of cDOPA treated with DCl or TfOD possibly due to differences of acidity. H-4 is suggested to be more difficult to conduct H/D exchange than H-7 and since TfOH is categorized as superacid which has higher acidity than HCl, thus at lower temperature H-4 can be selectively deuterated. Moreover, H/D exchange in TfOD system might occur selectively due to intra-molecular exchange between two sites that have approximately equal proton affinity in their conjugate acid form (1,2-hydride shifts where the hydrate is transferred in the ring plane).<sup>123</sup> However, the controllable deuterated cDOPA derivatives can be used to infer biological macromolecules due to its beneficial detection with spectroscopic methods.



102,105, 106, or 108



Figure 34 Selected <sup>1</sup>H-NMR profile of cDOPA (102) and deuterated cDOPA derivatives (105–106, 108)

### 4.3 Experimental section

*General methods.* <sup>1</sup>H-NMR spectra were measured by a Jeol EX 270 spectrometer (JEOL, Tokyo, Japan) for determining the H/D exchange proportion. MS data were obtained with a Waters LCT Premier XE instrument. HRMS-ESI spectra were obtained with a Waters UPLC ESI-TOF mass spectrometer (Waters, Milford, CT, USA). All reagents used were of analytical grade. Optical rotations were measured at 23 °C on JASCO DIP370 polarimeter (JASCO, Tokyo, Japan). TfOD (98% D) was purchased from Sigma–Aldrich. DCl (35 wt% in D<sub>2</sub>O, 99% D) was purchased from Wako. The cDOPA derivatives (**102** and **104**) were synthesized by reported methods with slight modification.

**L-DOPA methyl ester hydrochloride.** The  $SOCl_2$  (5.0 mL, 70 mmol) was added slowly at -5 °C dry MeOH (20 ml). L-DOPA (**103**, 1.00 g, 50 mmol) was added to the reaction mixture. The reaction mixture was stirred at rt for 1 h and refluxed at 85 °C for 1 h. After the reaction, the reaction mixture was concentrated to afford colorless amorphous mass of L-DOPA methyl ester hydrochloride that was directly used for the next step without further purification.

**O,O,N-Triacetyl cDOPA methyl ester** (104). To a chilled solution of L-DOPA methyl ester hydrochloride (800 mg, 3.230 mmol) in 88 mM phosphate buffer (400 ml; pH 8, prepared by mixing 0.4 g of KH<sub>2</sub>PO<sub>4</sub> and 9.57 g of Na<sub>2</sub>HPO<sub>4</sub> in 800 ml water), a solution of K<sub>3</sub>[Fe(CN)<sub>6</sub>] (6.48 g, 19.68 mmol) in phosphate buffer (200 ml) was added at 4 °C. After 8 sec, a solution of Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (5.12 g, 29.41 mmol) in phosphate buffer (100 ml) at 4 °C was added and stirred for 30 sec. The reaction mixture was made pH 1 with concentrated HCl, concentrated and co-evaporated with toluene for several times. The residue was suspended in Ac<sub>2</sub>O (40 ml) and pyridine (40 ml) and the suspension was stirred at room temperature for 4 h, then filtered by Celite<sup>®</sup>. The insoluble material was washed with CH<sub>2</sub>Cl<sub>2</sub> and the filtrate was concentrated. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (80 ml) and 1 M HCl (80 ml). The organic layer was washed with sat. NaHCO<sub>3</sub>, water and brine, dried over MgSO<sub>4</sub>, filtrated, and concentrated. The residue was purified by silica gel column chromatography  $(CH_2Cl_2/$ MeOH = 80 / 1) to afford *O*,*O*,*N*-triacetyl cDOPA methyl ester (104): Colorless amorphous mass.  $[\alpha]_{D} = -73$  (c 1, CHCl<sub>3</sub>), <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ : 8.06 (1H, s), 6.99–6.95 (1H, m), 5.18 (0.3 H, d, J = 8.6 Hz), 4.94 (1H, d, J = 8.6 Hz), 3.78 (3H, s), 3.57 (1H, dd, J = 17.0, 10.7 Hz), 3.25 (1H, d, J = 16.5 Hz), 2.29–2.11 (9H, m) ppm. <sup>13</sup>C-NMR (67.5 MHz, CDCl<sub>3</sub>) δ: 171.0, 168.6, 168.0, 167.8, 140.7, 140.2, 137.7, 126.5, 118.5, 111.7, 61.2, 52.5, 32.4, 22.9 , 20.0, 20.0 ppm. HRMS (ESI): calcd for  $C_{16}H_{18}NO_7$  [M + H]<sup>+</sup> 336.1083, found 336.1086.

**cDOPA hydrochloride (102, cDOPA).** *O*,*O*,*N*-Triacetyl cDOPA methyl ester (**104**, 134.5 mg, 0.40 mmol) was dissolved in 20% HCl. The reaction mixture was stirred at 80°C for 4 h, and concentrated. The residue was washed with CH<sub>3</sub>CN to remove excess HCl to afford product as brown amorphous mass (88.0 mg, 0.38 mmol, 95%).  $[\alpha]_D = -85$  (c 1.0, H<sub>2</sub>O), ref.<sup>118</sup>  $[\alpha]_D = -91.4$  (c 0.5 H<sub>2</sub>O). <sup>1</sup>H-NMR (270 MHz, D<sub>2</sub>O)  $\delta$ : 6.90 (1H, s), 6.84 (1H, s), 4.85 (1H, dd, J = 9.7, 6.8 Hz), 3.50 (1H, dd, J = 16.2, 9.6 Hz), 3.27 (1H, dd, J = 16.2, 6.6 Hz) ppm. <sup>13</sup>C-NMR (67.5 MHz, D<sub>2</sub>O)  $\delta$ : 171.6, 146.6, 145.0, 126.5, 125.6, 112.6, 106.9, 61.1, 33.0 ppm. HRMS (ESI): calcd for C<sub>9</sub>H<sub>10</sub>NO<sub>4</sub> [M + H]<sup>+</sup> 196.0610, found 196.0612.

General procedures for H/D exchange with DCl. The O,O,N-triacetyl cDOPA methyl ester (**104**, 45 mg, 0.13 mmol) or cDOPA (**102**, 45 mg, 0.19 mmol) was dissolved in DCl (2.34 mL) and stirred at specific temperature (mentioned in Figure 30 and 31). The part of reaction mixture (250  $\mu$ L) was diluted with D<sub>2</sub>O (200  $\mu$ L) in ice bath and then subjected to <sup>1</sup>H-NMR, depending on time.

General procedures for H/D exchange with TfOD. The cDOPA (**102**, 45 mg, 0.19 mmol) was dissolved in TfOD (672  $\mu$ L, 7.6 mmol) and stirred at specific temperature (mentioned in Figure 32). The part of reaction mixture (67.2  $\mu$ L) was diluted with D<sub>2</sub>O (500  $\mu$ L) for subjection to <sup>1</sup>H-NMR, depending on time.

**cDOPA-4,7-***d*<sub>2</sub> (**105**) The *O,O,N*-triacetyl cDOPA methyl ester (**104**, 49.3 mg, 0.15 mmol) was dissolved in 35% DCl (2.56 mL, 28.7 mmol). The reaction mixture was stirred at 80 °C for 4 h, and concentrated under low pressure. The residue was washed with MeCN and diluted with a small amount of D<sub>2</sub>O, and then centrifuged. The supernatant liquid then concentrated to afford product as brown amorphous mass (32.1 mg, 0.14 mmol, 94%). [ $\alpha$ ]<sub>D</sub> – 73 (c 1.0, D<sub>2</sub>O). <sup>1</sup>H-NMR (270 MHz, D<sub>2</sub>O)  $\delta$ : 6.90 (0.01H, s), 6.82 (0.01H, s), 4.89 (1H, t, *J* = 9.7 Hz), 3.50 (1H, dd, *J* = 16.2, 9.6 Hz), 3.28 (1H, dd, *J* = 16.2, 6.6 Hz) ppm. <sup>13</sup>C-NMR (67.5 MHz, D<sub>2</sub>O)  $\delta$ : 172.4, 146.8, 145.1, 127.0, 126.0, 112.6 (*J* = 21.2 Hz), 106.9 (*J* = 23.2 Hz), 61.5, 33.3 ppm. HRMS (ESI): calcd for C<sub>9</sub>H<sub>8</sub>D<sub>2</sub>NO<sub>4</sub> [M + H]<sup>+</sup> 198.0735, found 198.0724.

**cDOPA-7-***d* (106) The cDOPA (102, 49.2 mg, 0.21 mmol) was dissolved in 20% DCl (2.56 mL, 16.6 mmol). The reaction mixture was stirred at 60 °C for 6 h, and concentrated under low pressure. The residue was washed with MeCN and diluted with a small amount of D<sub>2</sub>O, then centrifuged. The supernatant liquid was then concentrated to afford product as brown amorphous mass (48.2 mg, 0.21 mmol, 98%). [ $\alpha$ ]<sub>D</sub> –76 (c 1.0, D<sub>2</sub>O). <sup>1</sup>H-NMR (270 MHz, D<sub>2</sub>O)  $\delta$ : 6.90 (0.12H, s), 6.80 (0.77H, s), 4.91 (1H, t, *J* = 7.9 Hz), 3.50 (1H, dd, *J* = 16.2, 9.6 Hz), 3.27 (1H, dd, *J* = 16.2, 6.6 Hz) ppm. <sup>13</sup>C-NMR (67.5 MHz, D<sub>2</sub>O)  $\delta$ : 172.3, 146.8, 145.1, 126.8, 126.0, 112.8, 106.7 (*J* = 23.2 Hz), 61.5, 33.3 ppm. HRMS (ESI): calcd for C<sub>9</sub>H<sub>9</sub>DNO<sub>4</sub> [M + H]<sup>+</sup> 197.0673, found 197.0666.

**cDOPA-4-***d* (**108**) The cDOPA (**102**, 4.4 mg, 0.019 mmol) was dissolved in TfOD (67.2 μL, 0.76 mmol) and stirred at 0 °C for 40 min. The reaction mixture was diluted with D<sub>2</sub>O (500 μL), measured the deuterium incorporation by <sup>1</sup>H-NMR and then UV-Vis spectroscopy (UV (TfOD/D<sub>2</sub>O):  $\lambda_{\text{max}}$  (ε) = 285 (4328) nm, 99%). [α]<sub>D</sub> –78 (c 0.78, TfOD/D<sub>2</sub>O). <sup>1</sup>H-NMR (270 MHz, D<sub>2</sub>O) δ: 6.90 (0.64H, s), 6.84 (0.16H, s), 4.95 (1H, dd, *J* = 9.7, 6.8 Hz), 3.53 (1H, dd, *J* = 16.2, 9.6 Hz), 3.32 (1H, dd, *J* = 16.2, 6.8 Hz) ppm. <sup>13</sup>C-NMR (67.5 MHz, D<sub>2</sub>O) δ: 173.1, 146.8, 145.2, 127.2, 126.3, 112.8 (*J* = 21.2 Hz), 107.3, 62.0, 33.5 ppm. HRMS (ESI): calcd for C<sub>9</sub>H<sub>9</sub>DNO<sub>4</sub> [M + H]<sup>+</sup> 197.0673, found 197.0679.

### 4.4 Conclusion

In conclusion, H/D exchange of cDOPA derivatives under DCl and TfOD allowing the formation of fully or partially deuterated cDOPA derivatives (**105–108**). When DCl was utilized at 60 °C, H/D exchange of cDOPA shifted at the 7-position was faster than 4-position. In contrast, utilization of TfOD at 0 °C enabled the H/D exchange at the 4-position to be faster than the 7-position of aromatic cDOPA moiety. Isolation of the deuterated cDOPA derivatives formed by the H/D exchange reaction utilizing DCl was simpler than those obtained by TfOD subjection. H/D exchange in cDOPA might simplify the analysis of complex biomolecules with stable isotopes to reveal the biosynthetic pathways of cDOPA, for example in the biosynthesis of betanin in plants or melanine in mammals.

# Chapter 5 Conclusion and future prospect

Natural products offer a privileged starting point in the search for highly specific and potent modulators of biomolecular function. Optimization of organic synthesis has the power to utilize chemical features of natural products in the laboratory and applies their developed synthetic strategies and technologies to construct novel compounds. Comprehensive study for exploration of structurally diverse variance of carbohydrates and  $\alpha$ -amino acids in this study can impact the chemical biology and drug development.

Direct halogenation of unprotected carbohydrates, such as sucrose and 1-kestose, employed the selective reaction at their primary alcohols only. By modifying the reagents for this typical reaction, the reactivity can be controlled, which can lead to completion of the structure analysis, revision of the previously elucidated ambiguous structure, and also exploration for synthesis of new compounds. It is an endeavoring study to distinguish the positions of the halogenations for unprotected carbohydrate by mass spectrometry or NMR analyses. Especially, the first synthesis of selectve halogenation for sucrose has been reported three decades ago. The NMR analysis of the mono-halogenated products has not been fully assigned and none of the study can doubt the reported results until now. The careful purification and identification for protected carbohydrates are important; therefore utilization of another protecting group, such as methyl or benzyl ether, in the next study should also be taken for consideration. Since position of the specific halogenated sucrose and 1-kestose at their primary positions is potentially tested their sweetness activity and might be use as alternative sweetneer for diabetics.

Introduction of representative acyl donors for Friedel–Crafts acylation which conducts the *C*-terminal activation of *N*-protected  $\alpha$ -amino acids, with TFA- $\alpha$ -amino *N*hydroxysuccinimide ester, offered convinient methods for synthesis of TFA- $\alpha$ -amino-aryl ketone. The extensive acylation by this functional group administered the chance for expansion of new structural design that is suitable for formation of acylium cation, and its stability can be considered as more efficient method than the use of acid chlorides. Several similar active esters, such as pentafluorophenyl diphenylphosphinate (FDPP), are potentially to be used as acylation reagents due to its reactivity. Moreover, demonstration of isoleucine and its diastereomer for checking the chirality center during the modification held a convinient chemical feature in peptide synthesis in future study. The resulted TFA- $\alpha$ -aminoaryl ketone also can contribute to prelimiary study of drug design or biomolecular identification.

H/D exchange on aromatic moiety is far more advance in reaserch for so-called deuterated medicine synthesis. The success of selective deuteration on aromatic moiety of cDOPA derivatives can open the perception of H/D exchange condition. Acid-catalyst utilization using DCl or TfOD is advantageous for homogenous H/D exchange reaction. The new finding of another homogenous H/D exchange catalyst suggested that rare metal super acids, such as lanthanide triflates should be explored. Since TfOD separation from reaction mixture is complicated for cDOPA derivatives due to its stability in acidic solvent, heterogenous reaction system is highly recommeded in future study. The use of TfOH mediated SiO<sub>2</sub> had been explored and might be useful for heterogenous H/D exchange if deuterium can be introduced in the system. Moreover, deuterated aromatic moiety of cDOPA derivatives can be utilized for revealing the mechanism of natural product bio-synthetic pathways in plant or mamalian.

Since synthesis of  $\alpha$ -amino-aryl ketone via Friedel–Crafts acylation required activation by acid catalyst and synthesis of deuterium-labelled compounds usually conducted by the use of acid as deuterium source, preparation of selective deuterium incorporated at aromatic moiety of  $\alpha$ -amino-aryl ketone is suggested. Introduction for one-step acylation and H/D exchange reaction is recommended by utilizing deuterated super acid as catalyst and deuterium source. Moreover, introduction of deuterium in amino acid derivatives can be useful in proteomics for expression, identification, and quantification of protein in plants or animals. The deuterated analogues can also mimic certain enzyme substrate that might be used as potential approach for investigating enzyme-substrate binding process and revealing the bioactivity for certain bio-molecule in human.

Direct halogenation of carbohydrate, extensive acylation of  $\alpha$ -amino acids, and selective H/D exchange of aromatic compounds are taken into comprehensive studies of organic synthesis that was utilized chemical features of natural products. These establishements are beneficial in the field of molecular chemistry and allowing for modification of vast structure deversity for major biomolecules, including sugars an protein. Thus, the collaboration study for multipurpose laboratory researches and commercial needs can support the development of organic synthesis and modification of natural products based on its chemical features, and it should be considered for economic benefits.

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