Full paper

Running title :

Effective Synthesis of Photoreactive Homophenylalanine and Aroylalanine

Effective Synthesis of Optically Active Trifluoromethyldiazirinyl Homophenylalanine and Aroylalanine Derivatives with Friedel-Crafts Reactions in Triflic Acid.

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Abstract

Effective Friedel-Crafts reactions with 3-(3-methoxyphenyl)-3-(trifluoromethyl)-3*H*-diazirine and optically active *N*-TFA-Asp(Cl)-OMe in triflic acid afforded homophenylalanine derivatives effectively without loss of the optical purity.

Key words:

diazirine; photoaffinity labeling; Friedel-Crafts reaction; triflic acid;

Introduction

Photoaffinity labeling is a useful biochemical method in the investigations of structural and functional relationships between small biologically active compounds and biomolecules, such as enzymes, RNA, and DNA.[1] Various photophores, such as phenyldiazirine, arylazide and benzophenone, have been developed as the photophores. It would be ideal because we can furnish photolabeling groups with minimum structural alteration. It has been also established that (3-trifluoromethyl)phenyldiazirinyl function can be selectively activated without giving damages to peptides and proteins by irradiating at 350nm.[2] But it usually requires not only steps of manipulations to introduce photophores into the target molecules, but also independent construction of the (3-trifluoromethyl)phenyldiazirinyl groups. These encouraged us in establishing effective protocol to furnish the (3-trifluoromethyl)phenyldiazirinyl photophore.[3] It was expected that amino acid derivatives carrying photolabeling group would become powerful tool in the mechanistic investigations of biologically active peptides, and in studying their metabolic pathways.

We focused on developping the (3-trifluoromethyl)diazirinyl photophore into homophenylalanine (hPhe), since interesting biological behaviors have been discovered by replacing a phenylalanine in biological peptides with hPhe [4, 5] and also reported as a starting material for pharmaceutical products such as benazepril and enarapril, both of which inhibit angiotensin converting enzyme (ACE) [6, 7] Efficient synthesis of photoactivatable optically pure hPhe is important. Although several synthetic protocols for optically active hPhe have been reported with various methodologies including enzymatic resolution,[8] Suzuki-coupling,[9] diastereoselective Michael addition[10] and catalytic asymmetric hydrogenation[11], these required the

special reagents or precursors. It might not be sutable to apply those for preparation of diazirinylated hPhe because some conditions might decline the diazirine function. In this paper, we would like to report an effective method providing optically active diazirinyl hPhe with featuring Friedel-Crafts (F-C) reactions with 3-(3-methoxyphenyl)-3-(trifluoromethyl)-3*H*-diazirin **1**[12] and β-acid chloride of aspartic acid **2**[13] as key steps.

Results and Discussion

We chose β-acid chloride form of *N*-trifluoromethyl *(S)*-aspartic acid α-methyl ester **2** as the electrophilic precursor. When we first attempted the reaction between **1** and **2** at room temperature employing aluminium chloride as the activator, however, the desired reaction did not proceed and both **1** and **2** were recovered in CH_2Cl_2 or CH_3NO_2. (Fig.1, Run 1 and 2) The reflux conditions led decomposition of **2**. (Fig.1, Run 3 and 4) Although F-C reactions between *N*- aspartic anhydride derivatives and aromatics have been reported,[14-19] the aromatics had to be employed excess amounts as the solvents. It would be preferable if we could use stoichiometric amounts of aromatics in the process by taking account of not only operational feasibility as well as economic matters. The reaction did not proceed by employing titanium chloride, which had been effective for formylation[20] as the activator in CH_2Cl_2 or neat conditions. (Fig.1, Run 5 and 6) It was found that the desired reaction smoothly proceeded at 0 °C to give the adduct **3** and **4** in over 87% by employing stoichiometric amounts of **1**, when trifluoromethanesulfonic acid (TfOH) was employed as the solvent. The suspension at the initial stage became clear solution upon the onset of the reaction. The regioisomer **3** and **4** were readily separated by silica gel column chromatography. The NOESY spectrum of major product **3** gave the

correlation signals between $C_{2'}$ OCH_3 and $C_{3'}$ H, which disclosed the substitution pattern. In the case of mainor product **4**, NOESY correlation was obtained $C_{4'}$ OCH_3 and both $C_{3'}$ and $C_{5'}$ H. (*R*)-**2** was also reacted with **1** in the same condition to afford (*R*)-**3** and **4** in good yield. (Fig.1, Run 7) Notably the higher temperature afforded complexed mixture because the decomposition of **1** and **2**. (Fig.1, Run 8) These results were consistent with the report that diazirinyl *N*-*N* double bond was easily decomposed in the presence of Lewis acid over 25 °C.[21] Unfortunately, 3-phenyl-3-(3-trifluoromethyl)-3*H*-diazirine, which has no activating methoxy substituent on benzene ring, did not react with (*S*)- or (*R*)- **2** in TfOH at 0°C. Higher temperature decomposed the diazirinyl ring at higher temperatures. We have already reported that the 3-phenyl-3-(3-trifluoromethyl)-3*H*-diazirine easily reacted with dichloromethyl methyl ether to give formylation product in TfOH.[22] These results indicated that the reactivity of both acyl donor and acyl acceptor also plays a critical role. Furthermore, trifluoromethyldiazirinyl moiety plays slightly as the electron withdrawing group for nucleophilic substitution of aromatic compounds.[23]

Figure.1

As the adduct 3 and 4 in hand, the newly introduced carbonyl group was then reduced to a hPhe derivative. It has already been reported that the diazirinyl *N*-*N* double bond was labiel under H_2-Pd/C conditions.[24] We found selective reduction of benzylic carbonyl to methylene could be performed with triethylsilane / TFA system to give **5** in good yield.[25] No decomposition of the diazirinyl ring was observed during the reduction. Finally deprotections of (*S*)- and (*R*)- **5** were performed using an alkaline condition to

afford diazirinyl hPhe **6** in good yield (90%). However, the conditions decomposed to result complex mixture when aroyl derivative **3** was employed. Deprotection of **3** could be achieved by treating with 6N HCl in acetic acid at 80 °C, affording **7** (Scheme 1).

Scheme 1

The enantiopurities of compounds **6** and **7** were determined with chiral HPLC (CHIROBIOTIC T, Astec)[26] which revealed these were >98% ee to prove no racemization during the synthesis. (Fig. 2)

Figure 2

Photolysise properties of diazirinyl compounds were examined with black light (15W). We have already demonstrated that the concentration of diazirinyl compound was to be set less than 1 mM to minimize the isomerization to the diazo compound.[27] Maximum absorptions at 360 nm for **6** and **7** were decreased upon irradiation times (Fig.3). The half-life of **6** and **7** was determined to be 8.5 and 3.2 min, respectively based on the intensity at 360 nm. We concluded the values are fast enough for photoaffinity labeling.

Figure 3

In these studies we have developed effective synthesis of photoreactive and enantiomerically pure hPhe and 2-methoxybenzoylalanine from 3-(3-methoxyphenyl)-3-(trifluoromethyl)-3*H*-diazirin and *(S)*- and *(R)*-aspartic acid derivative as the effective photolabeling probe without racemization. The key F-C reaction proceeded by employing

trifluoromethanesulfonic acid as the solvent. The following silane promoted reduction took place the transformation the benzylic carbonyl to methylene. The results will be contributed to the studies in structure-activity relationships for the side chain of aromatic α-amino acids.

Experimental

General methods. Optical rotation values were measured by a JASCO DIP-370 polarimeter. IR spectra were measured by a JASCO FTIR-4100. ^{1}H-, ^{13}C- and ^{19}F- NMR spectra were measured by a JEOL ECA 500 spectrometer. In the ^{1}H-NMR spectra, the chemical shifts are expressed in ppm downfield from the signal for tetramethylsilane used as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), and m (multiplet). In the ^{13}C-NMR spectra, the ^{13}C chemical shifts of the solvents were used as the internal standard ($^{13}CDCl_3$ 77.0ppm; or $^{13}CD_3OD$, 49.5ppm). In the 19F-NMR spectra, the chemical shifts are reported with default values without correction. MS spectra were obtained with a Hitachi NanoFrontier LD mass spectrometer. Chiral HPLCs were performed with CHIROBIOTIC T (Astec) 4.6 x 250 mm, eluted with 10% EtOH – H_2O; flow rate 1.0 ml/min; UV detection at 210 nm.

(*S*)-Methyl 4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl) phenyl)-4-oxo-2-(2,2,2-trifluoroacetamido)butanoate ((*S*)-**3**) and (*S*)-methyl 4-(4-methoxy-2-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-4-oxo-2-(2,2,2-trifluoroacetamido)butanoate ((*S*)-**4**)

Compound **1**[12] (24.7 mg, 0.11 mmol) and (*S*)- **2**[13] (29.0 mg, 0.11 mmol) were dissolved in TfOH (0.25 ml, 2.9 mmol) at 0 ℃. The yellow reaction mixture was stirred for two hours at the same temperature, then poured into cold water and AcOEt (30 : 30 ml). The organic layer was washed with

aqueous 1M HCl, saturated $NaHCO_3$, 1N HCl and saturated NaCl, then dried over $MgSO_4$, and filtered. The filtrate was concentrated, the residue was subjected to silica chromatography (AcOEt : n-hexane = 1 : 5) to afford pure (*S*)-**3** (34.4 mg, 71%) and (*S*)-**4** (13.6 mg, 28%) as a pale yellow oil.

(*S*)- **3**: $[\alpha]_D$ +77° (c 1.0, $CHCl_3$); IR (film) cm^{-1} : 3330, 1720, 1675, 1610; ^{1}H-NMR ($CDCl_3$) δ: 7.79 (1H, d, *J* = 8.0 Hz), 7.54 (1H, brd, *J* = 8.0 Hz), 6.80 (1H, d, *J* = 8.0 Hz), 6.66 (1H, s), 4.89-4.86 (1H, m), 3.91 (3H, s), 3.78 (1H, dd, *J* = 19.2, 4.3 Hz), 3.73 (3H, s), 3.57 (1H, dd, *J* = 18.9, 4.0 Hz); ^{13}C-NMR ($CDCl_3$) δ: 197.34, 170.12, 159.47, 156.91 (q, $^2J_{CF}$ = 37.6 Hz), 136.06, 131.46 , 126.42, 121.77 (q, $^1J_{CF}$ = 274.7 Hz), 118.80, 115.63 (q, $^1J_{CF}$ = 287.9 Hz), 109.63, 55.85, 53.15, 48.92, 45.29, 28.45 (q, $^2J_{CF}$ = 40.4 Hz); ^{19}F-NMR ($CDCl_3$) δ: -63.18, -74.34; ESI-MS *m/z*: 442 $(M+H)^+$, ESI-HRMS: calcd. for $C_{16}H_{14}F_6N_4O_5$ $(M+H)^+$, 442.0832; found, *m/z* 442.0826.

(*S*)- **4**: $[\alpha]_D$ +57° (c 1.0, $CHCl_3$); IR (film) cm^{-1} : 3330, 1725, 1690, 1610; ^{1}H-NMR ($CDCl_3$) δ: 7.82 (1H, d, *J* = 8.6 Hz), 7.63 (1H, brd, *J* = 7.4 Hz), 7.19 (1H, s), 7.02 (1H, d, *J* = 8.6 Hz), 4.97-4.94 (1H, m), 3.91 (3H, s), 3.86-3.82 (4H, m), 3.56 (1H, dd, *J* = 18.3, 3.4 Hz); ^{13}C-NMR ($CDCl_3$) δ: 196.22, 169.70, 163.71, 157.05 (q, $^2J_{CF}$ = 38.0 Hz), 132.51, 130.09, 129.53, 121.62 (q, $^1J_{CF}$ = 275.1 Hz), 117.60, 115.56 (q, $^1J_{CF}$ = 287.5 Hz), 115.20, 55.87, 53.25, 48.71, 40.81, 29.22 (q, $^2J_{CF}$ = 40.0 Hz); ^{19}F-NMR ($CDCl_3$) δ: -66.75, -72.86; ESI-MS *m/z*: 442 $(M+H)^+$, ESI-HRMS: calcd. for $C_{16}H_{14}F_6N_4O_5$ $(M+H)^+$, 442.0832; found, *m/z* 442.0828.

(*R*)-Methyl 4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl) phenyl)-4-oxo-2-(2,2,2-trifluoroacetamido)butanoate ((*R*)-**3**) and (*R*)-methyl 4-(4-methoxy-2-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-4-oxo-2-(2,2,2-trifluoroacetamido)butanoate ((*R*)-**4**)

The same treatment of **1** (24.7 mg, 0.11 mmol) and (*R*)- **2** (29.0 mg, 0.11

mmol) as described in above gave (*R*)-**3** (33.0 mg, 68%) and (*R*)-**4** (9.2 mg, 19%) as yellow oil. The ^{1}H-, ^{13}C- NMR and IR of these samples were identical to these record for (*S*)-**3** and **4**.

(*R*)-**3** $[\alpha]_D$ -76° (c 1.0, $CHCl_3$); (*R*)-**4**: $[\alpha]_D$ -58° (c 1.0, $CHCl_3$)

(*S*)-Methyl 4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl) phenyl)-2-(2,2,2-trifluoroacetamido)butanoate ((*S*)-**5**)

To a solution of (*S*)-**3** (169 mg, 0.38 mmol) in TFA (1.5 ml, 20 mmol), Et_3SiH (0.30 ml, 1.9 mmol) was added dropwise. The reaction mixture was stirred for two hours, and partitioned with AcOEt (80 ml). The organic layer was washed with saturated $NaHCO_3$, 1N HCl and saturated NaCl, then dried over $MgSO_4$ and filtered. After the filtrate was concentrated, the residue was subjected to silica chromatography (AcOEt : n-hexane = 1 : 10) to afford a colorless amorphous mass (115 mg, 76%).

$[\alpha]_D$ +65° (c 1.0, $CHCl_3$); IR (film) cm^{-1} : 3320, 1720, 1610; ^{1}H-NMR ($CDCl_3$) δ: 7.11 (1H, d, J = 7.4 Hz), 7.04 (1H, d, J = 7.4 Hz), 6.74 (1H, brd, J = 6.9 Hz), 6.57 (1H, s), 4.64-4.62 (1H, m), 3.81 (1H, s), 3.68 (1H, s), 2.64 (2H, t, J = 7.7 Hz), 2.25-2.22 (1H, m), 2.10-2.03 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 171.00, 157.40, 156.74 (q, $^{2}J_{CF}$ = 37.2 Hz), 130.41, 130.21, 128.69, 122.07 (q, $^{1}J_{CF}$ = 274.3 Hz), 118.90 , 115.63 (q, $^{1}J_{CF}$ = 287.5 Hz), 108.12 , 55.24, 52.65, 52.18, 31.03, 28.37 (q, $^{2}J_{CF}$ = 40.0 Hz), 25.32; ^{19}F-NMR ($CDCl_3$) δ: -66.54, -75.28. ESI-MS *m/z*: 400 $(M\text{-}N_2+H)^+$, ESI-HRMS: calcd. for $C_{16}H_{16}F_6NO_4$ $(M\text{-}N_2+H)^+$, 400.0978; found, *m/z* 400.0989.

(*R*)- Methyl 4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl) phenyl)-2-(2,2,2-trifluoroacetamido)butanoate ((*R*)-**5**)

The same treatment of (*R*)-**3** (168 mg, 0.38 mmol) as described in above gave (*R*)-**5** (121 mg, 80%) as yellow oil. The ^{1}H-, ^{13}C- NMR and IR of these

samples were identical to these record for (*S*)-**5**.

$[\alpha]_D$ -65° (c 1.0, $CHCl_3$).

(S)-2-amino-4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl) phenyl)butanoic acid (*(S)*-**6**)

To a solution of *(S)*-**4** (26.4 mg, 60 μmol) in MeOH (6.0 ml), 1N NaOH (0.50 ml) was added at room temperature. After stirring for 1 hour, silica gel (2 g) was added. The resulting mixture was then evaporated. The residue was subjected to silica chromatography (CH_2Cl_2 : MeOH : H_2O : acetic acid = 10 : 2 : 0.25 : 0.05) to afford a colorless solid (17.3 mg, 91%).

$[\alpha]_D$ -15° (c 2.0, MeOH); IR (film) cm^{-1} : 2950, 1680; ^{1}H-NMR (CD_3OD) δ: 7.22 (1H, d, *J* = 7.4 Hz), 6.79 (1H, d, *J* = 7.4 Hz), 6.68 (1H, s), 4.33 (1H, q, *J* = 4.8 Hz), 3.82 (3H, s), 2.73 (2H, t, *J* = 7.4 Hz), 2.27-2.18 (1H, m), 2.07-2.01 (1H, m); ^{13}C-NMR (CD_3OD) δ: 173.82, 159.24, 132.56, 131.76, 129.42, 123.65 (q, $^1J_{CF}$ = 273.5 Hz), 119.90, 109.14, 55.92, 53.69, 31.64, 29.57 (q, $^2J_{CF}$ = 40.4 Hz), 27.44; ^{19}F -NMR (CD_3OD) δ: -66.38; ESI-MS *m/z*: 318 $(M+H)^+$, ESI-HRMS: calcd. for $C_{13}H_{15}F_3N_3O_3$ $(M+H)^+$, 318.1060; found, *m/z* 318.1067; chiral HPLC t_R = 13.2 min

(R)- 2-Amino-4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl) phenyl)butanoic acid (*(R)*- **6**)

The same treatment of (*R*)-**4** (26.0 mg, 60 μmol) as described in above gave (*R*)-**6** (16.8 mg, 90%) as yellow oil. The ^{1}H-, ^{13}C- NMR and IR of these samples were identical to these record for (*S*)-**6**

$[\alpha]_D$ +15° (c 2.0, MeOH); chiral HPLC t_R = 17.0 min

(*S*)-2-Amino-4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl) phenyl)-4-oxobutanoic acid ((*S*)-**7**)

To a stirred solution of (*S*)-**3** (31.6 mg, 72 μmol) in acetic acid (12 ml), concentrated HCl (12 ml) was added. The reaction mixture was stirred for 12 hours at 50℃, then concentrated. The residue was subjected to silica chromatography (CH_2Cl_2 : MeOH : H_2O : acetic acid = 10 : 2 : 0.25 : 0.05) to afford a colorless solid (22.3 mg, 94%).

$[\alpha]_D$ -14° (c 2.0, MeOH);IR (film) cm^{-1} : 2940, 1670, 1610; ^{1}H-NMR (CD_3OD) δ: 7.87 (1H, d, J = 8.0 Hz), 6.95 (1H, d, J = 8.6 Hz), 6.81 (1H, s), 3.99-3.97 (4H, m), 3.72 (1H, d, J = 19.5 Hz), 3.55 (1H, d, J = 19.5 Hz) ; ^{13}C-NMR (CD_3OD) δ: 199.11, 179.04, 160.88, 136.24, 132.52, 128.79, 123.34 (q, $^1J_{CF}$ = 273.9 Hz), 119.74, 111.08, 56.54, 51.84, 29.54 (q, $^2J_{CF}$ = 40.4 Hz), 23.2; ^{19}F -NMR (CD_3OD) δ: -66.83; ESI-MS *m/z*: 332 $(M+H)^+$, ESI-HRMS: calcd. for $C_{13}H_{13}F_3N_3O_4$ $(M+H)^+$, 332.0853; found, *m/z* 332.0866; chiral HPLC t_R = 10.2 min.

(*R*)-2-Amino-4-(2-methoxy-4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl) phenyl)-4-oxobutanoic acid ((*R*)-**7**)

The same treatment of (*R*)-**4** (31.8 mg, 72 μmol) as described in above gave (*R*)-**7** (21.0 mg, 88%) as yellow oil. The ^{1}H-, ^{13}C- NMR and IR of these samples were identical to these record for (*S*)-**6**

$[\alpha]_D$ +14° (c 2.0, MeOH); chiral HPLC t_R = 15.0 min

Photolysis of the diazirinyl compounds in methanol

Methanolic solution of (*S*)- **6** or **7** (0.5 mM) was placed in a quartz cuvette. After replacing the inner atmosphere with nitrogen, photolysis was carried out with 15 W black-light (UVP Inc., San Gabriel, California, USA) at a distance 2 cm from the surface of light source.

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Figure legends

Figure 1

Friedel-Crafts reactions with diazirinyl compound **1** and optically pure aspartic acid derivative **2**.

Scheme 1

Synthesis of optically pure diazirinyl homophenylalanine derivatives. Reagents and conditions: (a) Triethylsilane, trifluoroacetic acid, (*S*)- 76%, (*R*)- 80%; (b) NaOH, MeOH, (*S*)- 91%, (*R*)- 90%; (c) 6N HCl, acetic acid, 80 °C, (*S*)- 94%, (*R*)- 88%.

Figure 2

Chiral HPLC chromatogram of synthetic diazirinyl (*S*)- or (*R*)- **6** and (*S*)- or (*R*)- **7** with chiral HPLC.

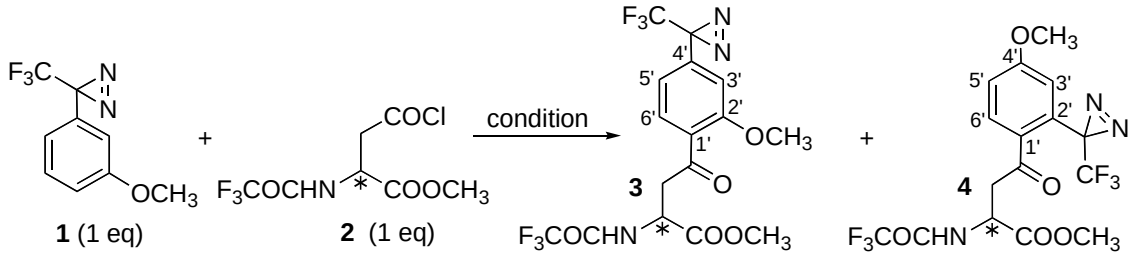
Condition; CHIROBIOTIC T (Astec) 4.6 x 250 mm, eluted with 10% EtOH – H_2O; flow rate 1.0 ml/min; UV detection at 210 nm.

Figure 3

Photolysis of the 0.5 mM of (*S*)-**6** (a) and (*S*)-**7** (b) in methanol with 15 W black light.

The photolysis reaction mixture, at the times (in min), was indicated with numbers.

1 Figure 1



2

entry	catalyst	solvent	temperature	time (h)	yield
1	$AlCl_3$	CH_2Cl_2	rt	12h	0[a]
2	$AlCl_3$	CH_3NO_2	rt	12h	0[a]
3	$AlCl_3$	CH_2Cl_2	reflux	12h	0[b]
4	$AlCl_3$	CH_3NO_2	reflux	12h	0[b]
5	$TiCl_4$	CH_2Cl_2	50° C	3h	0[b]
6	$TiCl_4$		0° C	2h	0[a]
7	TfOH		0° C	2h	(*S*)– 71 (**3**), 28 (**4**) (*R*)– 68 (**3**), 19 (**4**)
8	TfOH		50° C	2h	0[b]

3 [a] no reaction occurred, [b] the starting material **1** was decomposed.

4

Scheme 1

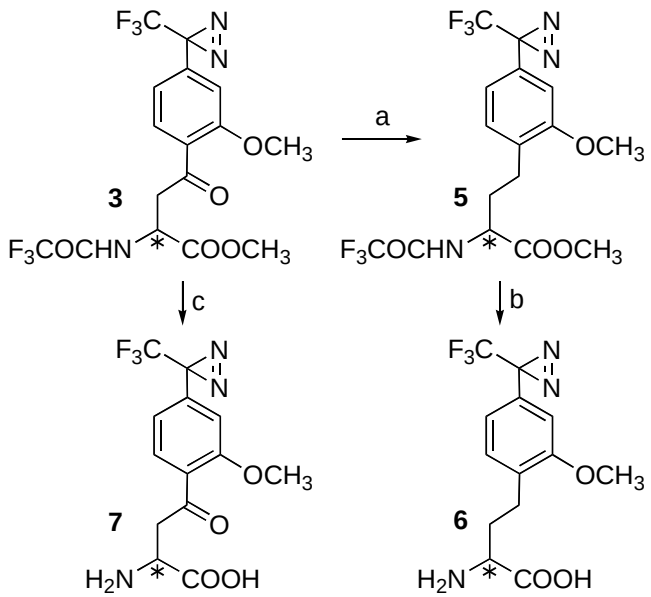
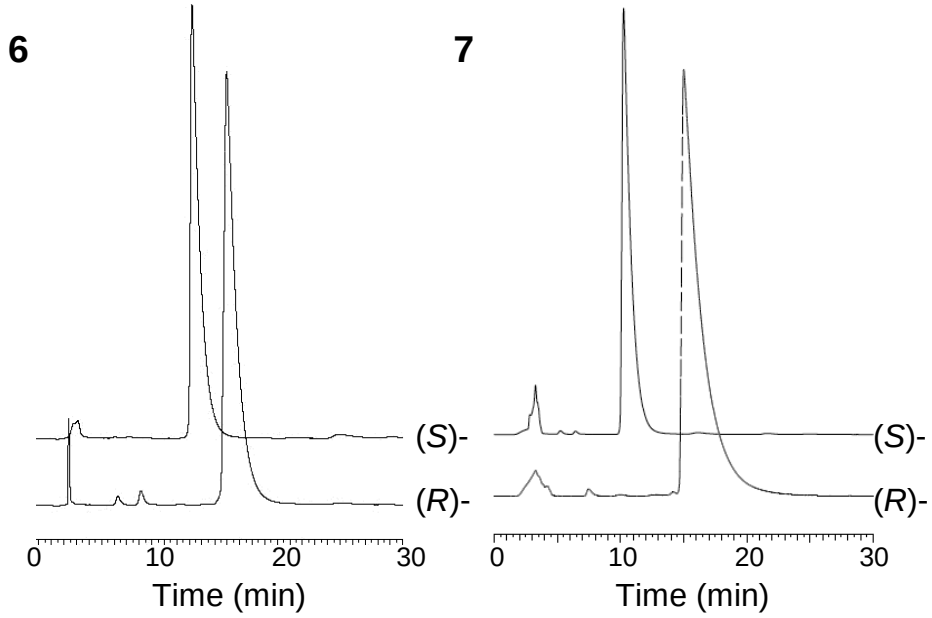
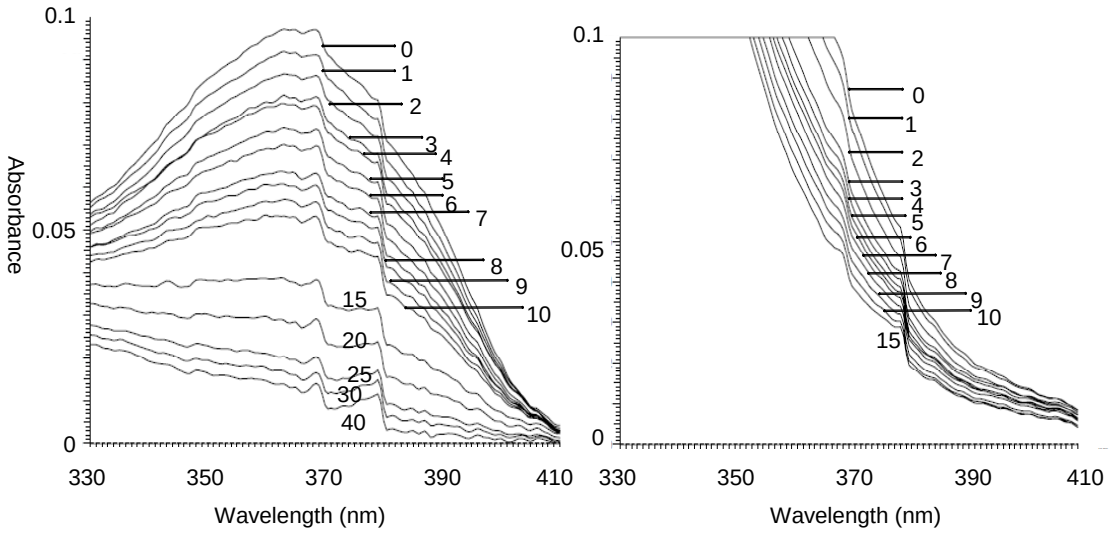


Figure 2



1 Figure 3

2 (a) (b)



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