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Model Synthetic Study of Tutin, a Picrotoxane-Type Sesquiterpene: Stereoselective Construction of a *cis*-Fused 5,6-Ring Skeleton

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Picrotoxinin, coriamyrtin, and tutin are representative natural products classified as picrotoxane-type sesquiterpenes and they function as strong neurotoxins. Because they possess a *cis*-fused 5,6-ring skeleton with a highly congested functionalization, organic chemistry researchers have pursued the development of a stereoselective synthesis method for such skeleton. This study aims to stereoselectively synthesize the *cis*-fused 5,6-ring skeleton with two tetrasubstituted carbons at both angular positions using a model compound. The results revealed that the desymmetrization of the 2-methyl-1,3-cyclopentanedione moiety *via* the DL-proline-mediated intramolecular aldol reaction of a pentanal derivative bearing an isopropenyl group and the five-membered ring at the 3- and 5-position, respectively, provided the desired *cis*-fused skeleton. This reaction can construct four contiguous stereogenic centers of the bicyclic skeleton with the two angular positions in good yield with high stereoselectivity. Further, this reaction was applied to the kinetic resolution of the racemate using L-proline, providing the enantiomeric pure aldol product with the desired skeleton. This method can be utilized for total synthesis of picrotoxane-type sesquiterpenes.

Key words picrotoxane-type sesquiterpene; desymmetrization; intramolecular aldol reaction; proline

Introduction

Picrotoxane-type sesquiterpenes have been found in various plants since the 1900s,[1] and the novel natural products belonging to this family have been isolated in the recent years.[2–5] Among these, picrotoxinin (**1**), coriamyrtin (**2**), and tutin (**3**) are well-known natural products because they function as strong neurotoxins,[6] and are hence used in biological chemistry (Fig. 1a). From an organic chemistry viewpoint, **1**–**3** have attractive structures with a highly functionalized *cis*-fused 5,6-ring skeleton with two tetrasubstituted angular carbons. This structure has inspired organic chemistry researchers to develop efficient synthesis methods for these natural products. In fact, the total synthesis of **1** was reported by Shenvi,[7] Trost,[8] Yoshikoshi,[9] Yamada,[10] and Corey groups.[11] By contrast, there are only two reports on the synthesis of coriamyrtin (**2**) in the 1980s.[10,12] Moreover, as tutin (**3**) bears the *cis*-fused skeleton with all carbons functionalized, its total synthesis has only been achieved by the Yamada group,[13] albeit it has the disadvantage of requiring a total of 41 steps from an α-tetralone derivative.[14] Recently, there are reports on synthetic studies of picrotoxane-type skeleton (**4**), which lacks the hydroxy group in an angular position.[15–17] However, the applications of these methods toward the synthesis of **2** and **3** has not been explored. These backgrounds encouraged us to examine the total synthesis of **3**, a method of which can also be developed for the synthesis of **1** and **2**. Herein, we describe the stereoselective synthesis of the *cis*-fused 5,6-ring skeleton with the two tetrasubstituted angular carbons.

Results and Discussion

A major concern in the total synthesis of tutin (**3**) is the stereoselective formation of the two stereocenters in the two angular positions of the picrotoxane-type skeleton (**4**). The introduction of a one-carbon unit at the C-9 position of **4** could be achieved using a carbonyl compound. Thus, we chose enone **5** as the synthetic precursor of **3** (Fig. 1b). This study aimed to synthesize its model compound **6**, wherein the two oxy-functionalized groups at the 2- and 3-positions were removed. Because **6** possesses a β-hydroxy carbonyl moiety, we used

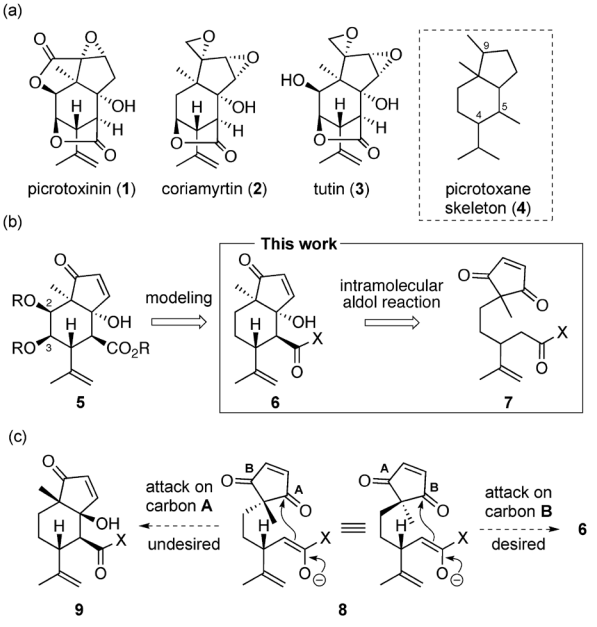

Fig. 1. (a) Structures of Representative Picrotoxane-Type Sesquiterpenes; (b) Synthetic Plan of Model Compound **6** for the Synthetic Precursor **5** of Tutin (**3**); (c) Two Reaction Pathways for the Intramolecular Aldol Reaction of **8**

This paper is dedicated to the memory of Prof. Dr. Toshiyuki Kan who sadly passed away on July 23, 2021.

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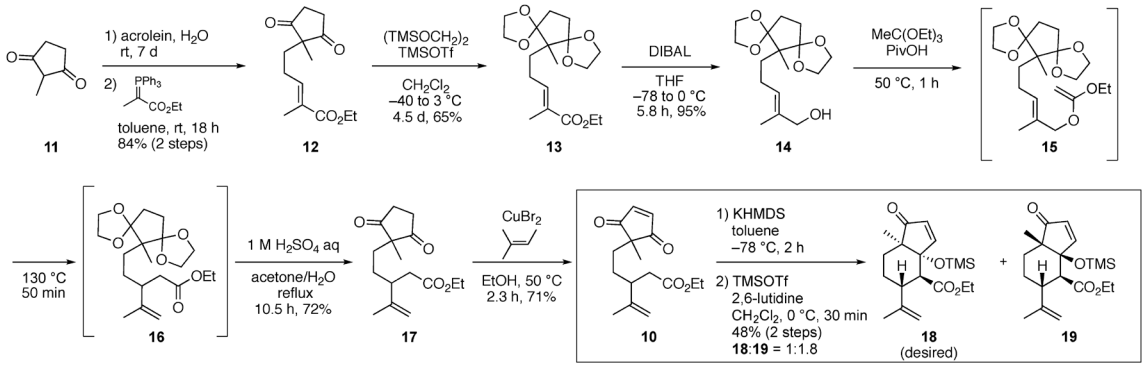


Ph = phenyl, Et = ethyl, Me = methyl.

Chart 1. Scheme for the Synthesis of Ester **10** and Its Intramolecular Aldol Reaction

the intramolecular aldol reaction for the synthesis, thereby retro-synthesizing **6** to **7** with a symmetrical 2-methyl-1,3-cyclopentenedione structure. The desymmetric strategy is a powerful tool for synthesizing a complex molecule with multiple stereogenic centers in organic synthesis.[18,19] In fact, reactions for desymmetrization of the 1,3-cyclopentanedione moiety have been reported by various groups.[20–27] However, their application in the synthesis of picrotoxane-type sesquiterpenes has not been explored. In this reaction, there are two possible reaction pathways starting from enolate intermediate **8**: an intramolecular attack of the enolate anion on carbon **A** to produce **9** or its attack on carbon **B** to produce **6** (Fig. 1c). The latter reaction can deliver the desired stereochemistries at the two angular positions. Although the synthesis of **6** requires strict reaction conditions to allow the accurate recognition of the two carbonyl groups, this reaction could also cause synchronous construction of the *trans* configuration between the carbonyl group and the isopropenyl group in **6** because the intramolecular reaction must occur avoiding their mutual steric repulsion. Thus, this desymmetric strategy could allow the formation of the four contiguous stereogenic centers in a highly stereoselective manner.

Based on the synthetic plan of **6**, the intramolecular aldol reaction of ester **10**, which was prepared from 2-methyl-1,3-cyclopentanedione (**11**), was investigated (Chart 1). The Michael reaction of **11** to acrolein, followed by the Wittig reaction with ethyl 2-(triphenylphosphoranylidene)propionate gave trisubstituted (*E*)-unsaturated ester **12** as a single isomer in high yield. After the bis-acetalization of **12** under the Noyori condition,[28] diisobutylaluminum hydride (DIBAL) reduction of the resulting ester **13** provided an allylic alcohol **14**. The Jonson–Claisen rearrangement[29] of **14** was adopted to construct the isopropenyl group in **10**. The formation of keteneacetal **15** proceeded smoothly by treatment of **14** with triethyl orthoacetate and pivalic acid (PivOH) at 50 °C. The reaction mixture was then heated at 130 °C to supply γ,δ-unsaturated ester **16**. Subsequent acid hydrolysis to remove the bis-acetal moieties was conducted in one-pot, affording diketone **17** in 72% yield. Finally, copper(II) bromide-mediated oxidation of the 1,3-cyclopentanedione moiety[30] in the presence of 2-methyl-2-butene delivered the desired compound **10**.

An investigation of the intramolecular aldol reaction of **10** under various conditions revealed that the use of potassium hexamethyldisilazide (KHMDS) in toluene gave the best result (Chart 1). In this reaction, the counter cation was an important factor because the exchange of potassium to sodium and lithium, respectively, in the base did not provide the aldol products. Further, the use of other bases, such as lithium diisopropylamide, sodium hydride, potassium *tert*-butoxide, resulted in the decomposition of **10**. Although the crude product obtained by exposure of KHMDS in toluene contained the two diastereomeric mixtures, the isolation of each compound in its pure form was difficult owing to the presence of inseparable byproducts. Thus, without purification, trimethylsilyl (TMS)-protection of the hydroxy group of the two desired products in the mixture was conducted using trimethylsilyl triflate (TMSOTf) and 2,6-lutidine, which led to the isolation of two aldol products as a 1.8 : 1 diastereomeric ratio, with in an overall 48% yield for the two-step reaction process.

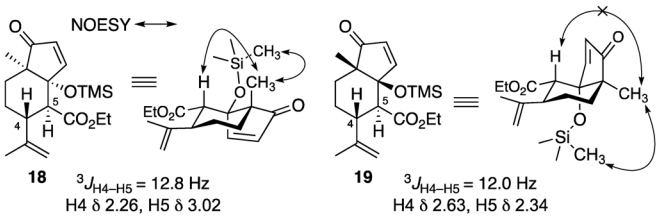
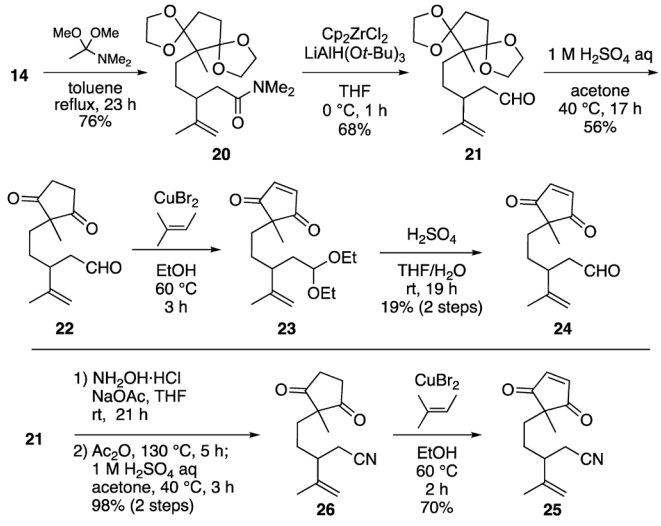


Fig. 2. Characteristic NMR Data of **18** and **19**

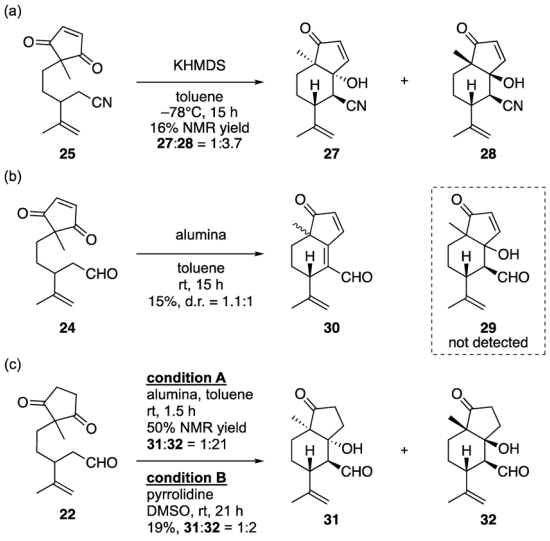
The NMR analysis of the two products **18** and **19** showed that the desired product, **18**, was a minor product (Fig. 2). The J_{H4-H5} values of **18** and **19** were 12.8 and 12.0 Hz, respectively, which confirmed the *trans* configurations between the ester and the isopropenyl group in both compounds. In addition, the nuclear Overhauser effect spectroscopy (NOESY) correlation between the proton of the Me group and TMS group at the angular positions was detected in **18** and **19** to ensure the presence of the *cis*-fused skeleton. By contrast, in the same spectrum, while the H-5 proton in **19** was not correlated to the angular methyl protons, that in **18** was correlated to the corresponding proton. These results showed that **18** bears the desired four contiguous stereogenic centers, and **19** is a diastereomer where the two angular stereogenic centers are opposite to those in **18**. Remarkably, the chemical shifts of H-4 and H-5 in **18** and **19** were dramatically different. While the chemical shift value of H-5 was lower than that of H-4 in **18**, H-5 was higher than H-4 in **19**. This fact would be helpful for the structure confirmation of the *cis*-fused 5,6-ring skeleton in the picrotoxane-type sesquiterpenes.

Because the intramolecular aldol reaction of **10** mainly gave



Cp = cyclopentadienyl, *t*-Bu = *tertiary*-butyl, Ac = acetyl.

Chart 2. Scheme for the Synthesis of Aldol Precursors **22**, **24**, and **25**



DMSO = dimethyl sulfoxide.

Chart 3. Trial to the Intramolecular Aldol Reaction of **22**, **24**, and **25**

the undesired *cis*-fused skeleton **19**, we next examined the reaction using other substrates, the synthetic method of which is shown in Chart 2. The Eschenmoser–Claisen rearrangement[31] of allylic alcohol **14** in toluene at reflux afforded amide **20** in 76% yield. Reduction of the amide moiety by the Schwartz reagent, prepared from zirconocene dichloride and lithium tri-*tert*-butoxyaluminum hydride,[32] produced aldehyde **21**. The bis-acetal structure was removed under acidic hydrolysis conditions, releasing 1,3-cyclopentanedione **22**. To oxidize the five-membered ring, **22** was subjected to the same reaction conditions that were used for the conversion of **17** into **10**. However, the aldehyde moiety was simultaneously acetalized to produce **23**. Thus, the ethyl acetal was converted to the aldehyde in diluted sulfuric acid and tetrahydrofuran (THF) to obtain an aldol precursor **24** with 19% yield in 2 steps. Another precursor **25** was prepared from aldehyde **21** through an oxime formation, followed by acetic anhydride-mediated dehydration of the oxime and removal of the bis-acetal *via* a one-pot protocol, and then oxidation of the 1,3-cyclopentanedione moiety of the obtained nitrile **26**.

The results of the intramolecular aldol reaction using nitrile **25** and aldehyde **24** are shown in Charts 3a and 3b. The reaction of **25** with KHMDS in toluene resulted in the corresponding aldol products **27** and **28**, similar to ester **10**. However, the total yield and the production ratio of the desired compound **27** dramatically decreased. While the intramolecular aldol reaction of **24** occurred *via* the use of a weaker base, alumina, the dehydration of the aldol product **29** also proceeded to afford only **30** in 15% yield as a 1.1 : 1 diastereomeric mixture. Although we subjected **24** to various reaction conditions for producing **29** in good yield, it was unsuccessful due to the probable instability of **24** resulting from the cyclopentene-1,3-dione moiety.[33] Therefore, we changed the intramolecular aldol reaction reactant **24** to **22** bearing the 1,3-cyclopentanedione moiety (Chart 3c). The treatment of **22** with alumina provided aldol products **31** and **32** in 50% NMR yield, but the major product was **32** with undesired stereochemistries at the two angular positions (condition A). On the other hand, the use of pyrrolidine (condition B) increased the production ratio of the desired product **31**, albeit the yield and diastereoselectivity was unsatisfactory (19% isolated yield as a 1 : 2 mixture of **31** and **32**). The low yield was attributed to the competitive intermolecular aldol reaction of **22**, as compounds derived from the side reaction were detected.

The result obtained using pyrrolidine prompted DL-proline as the choice reagent for the intramolecular aldol reaction of **22**, as the intramolecular hydrogen network between one of the carbonyl groups and the enamine intermediate generated *in situ* will inhibit the intermolecular aldol reaction and increase the production ratio of **31**. The reaction proceeded smoothly to provide **31** with high diastereoselectivity, succeeding in its isolation in 73% yield[34] (Fig. 3a). The structure of **31** was confirmed by the NMR analysis of benzyl esters **33** and **34**. These were prepared from a 1.9 : 1 mixture of **31** and **32** through the Pinnick oxidation, the benzylation of the resulting carboxylic group, and their separation *via* silica gel chromatography (Fig. 3b). Similar to the NMR results for **18** and **19** in Fig. 2, both J_{H4-H5} values were more than 12.0 Hz and the chemical shift value of H-5 in **33** was lower than that in **34**. In addition, the NOESY spectrum of **33** showed the correlation of H-5 with the Me group and the hydroxy group in the angular positions. This indicates that **31** obtained by the DL-proline mediated intramolecular aldol reaction possessed the same four contiguous stereogenic centers in the *cis*-fused 5,6-ring skeleton of picrotoxane-type sesquiterpenes.

This intramolecular aldol reaction was applicable to the asymmetric synthesis of **31** *via* kinetic resolution (Fig. 3c). Thus, the change of DL-proline to L-proline induced the reaction of either enantiomer of *rac*-**22** preferentially, to provide optically active **31** and diastereomer **32** in 38 and 3% NMR yield, respectively, with the recovery of 20% NMR yield of **22**. Because the separation of these three mixtures was difficult, the optical purity of **31** was evaluated after the exposure to the two-step protocol similar to Fig. 3b and the isolation of **33**. The value of its enantiomeric excess (≥99% ee) demonstrated that the L-proline mediated intramolecular reaction proceeded *via* the strong intramolecular hydrogen network. We speculate that the preferred transition state (TS) of the reaction is **TS-A**, where the absolute configuration of the stereogenic center is *R* because **TS-B** derived from (*S*)-**22** results

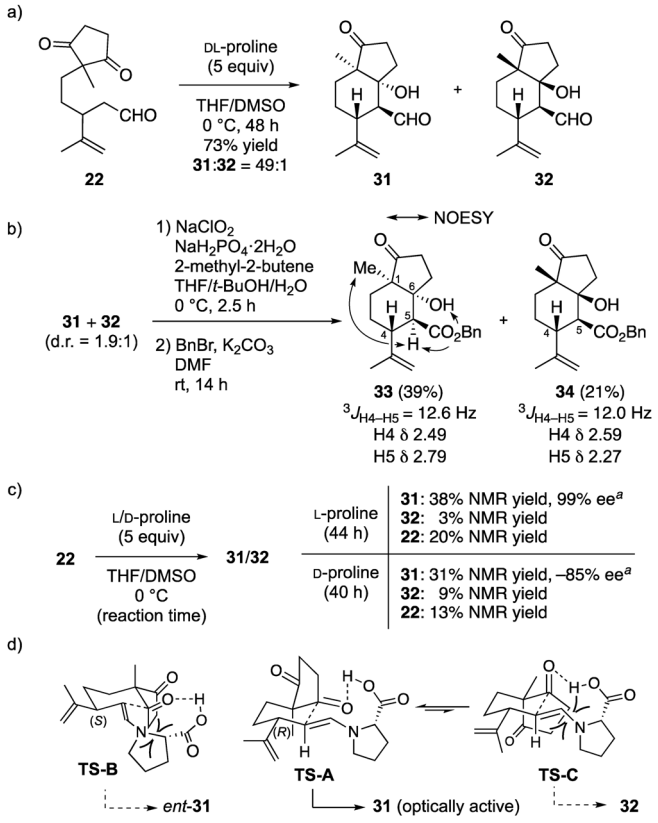


Fig. 3. (a) Intramolecular Aldol Reaction of **22** Using DL-Proline; (b) Conversion of **31** and **32** for Their Structure Determination; (c) Asymmetric Intramolecular Aldol Reaction for the Synthesis of **31** *via* Kinetic Resolution; (d) Considered Transition States in the Reaction of **22** with L-Proline

[a]The enantiomeric excess (ee) of **31** was evaluated after its transformation to **33**. Bn = benzyl. DMF = *N*,*N*-dimethylformamide.

in the steric hindrance between the 1,3-cyclopentanedione moiety and the pyrrolidine moiety (Fig. 3d). There is a similar steric repulsion in **TS-C** to produce **32**; thus, its generation was also disfavored. Thus, the absolute configuration of **33** synthesized *via* L-proline mediated intramolecular aldol reaction is estimated to be 1*R*, 4*R*, 5*S*, 6*R*. Although the use of D-proline induced the intramolecular aldol reaction with a conversion yield similar to L-proline, the production ratio of **32** increased (9% NMR yield) and the absolute ee value of *ent*-**33** derived from *ent*-**31** decreased (−85% ee), indicating that the enamine intermediate derived from D-proline may be unsuitable for this reaction.

Conclusion

We established a stereoselective synthesis method for the four contiguous stereogenic centers of the *cis*-fused 5,6-ring skeleton with the two angular positions in picrotoxane-type sesquiterpenes. This method involves the DL-proline mediated intramolecular aldol reaction of *rac*-aldehyde **22** with an inner symmetrical 2-methyl-1,3-cyclopentanedione moiety, providing **31** in good yield with high stereoselectivity. We also succeeded in the kinetic resolution of the aldehyde *via* the use of L-proline, which afforded highly enantiomerically pure **31**. Although the intramolecular aldol reaction of ester **10** preferably provided the undesired diastereomer **19**, this synthetic methodology could also be developed for the synthesis of other natural products with the similar *cis*-fused skeleton. Further investigations toward the total synthesis of picrotoxane-type sesquiterpenes including tutin (**3**) are underway in our laboratory.

Experimental

General Method All commercially available reagents were used as received. All moisture and air sensitive reactions were carried out in glassware equipped with rubber septa (or a septum) under the positive pressure of argon or nitrogen. When necessary, the glassware was dried under reduced pressure by heating with a heat-gun and solvents were distilled prior to use. The substrates were azeotropically dried if needed by evaporation of their acetonitrile or toluene solution several times to remove trace water that may be contained to the substrates. The reaction mixture was magnetically stirred. Concentration was performed under reduced pressure.

The reactions were monitored by TLC and MS. Anhydrous $MgSO_4$ or Na_2SO_4 was used to dry organic layers after extraction, and it was removed by filtration through a cotton pad. The filtrate was concentrated and subjected to further purification protocols if necessary. This sequence was represented as "the general drying procedure" in the following experimental methods.

TLC was performed on Merck pre-coated silica gel 60 F-254 plates. Spots were visualized by exposure to UV light, or by immersion into a solution of 2% anisaldehyde, 5% H_2SO_4 in ethanol or a solution of 10% phosphomolybdic acid in ethanol, followed by heating at approx. 200 °C.

Column chromatography was performed on Kanto Chemical silica gel 60 N (Spherical, neutral, 40–50 or 63–210 μm). The other carrier materials were noted in each case.

The melting points were determined using an AS ONE ATM-02 apparatus and uncorrected. Optical rotations were determined using a JASCO P-2100 polarimeter with a 100 mm cell at 589 nm. IR spectra were recorded on JASCO FT/IR-4100 and Shimadzu IRAffinity-1S with an Attenuated Total Reflection (ATR) sampling unit, and the major absorbance bands are all reported in wavenumbers (cm^{-1}). High-Resolution MS (HRMS) were recorded on a JEOL JMS-T100LC spectrometer at School of Science and Technology, Kwansei Gakuin University and JEOL JMS-T100LP at Global Facility Center, Hokkaido University. The data are reported in units of mass to charge. NMR spectra were recorded on JEOL JNM-ECX-400 (400 MHz for ^{1}H and 101 MHz for ^{13}C) and JNM-ECX-500 (500 MHz for ^{1}H and 126 MHz for ^{13}C) with either TMS or residual proton of deuterated solvent ($CDCl_3$) as internal reference. The ^{1}H-NMR spectroscopic data are indicated by a chemical shift (δ), with the multiplicity, the coupling constants, the integration in parentheses in this order. The multiplicities are abbreviated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, and br: broad. The ^{13}C-NMR spectroscopic data are reported as the chemical shift (δ), with the hydrogen multiplicity obtained from the Distortionless Enhancement by Polarization Transfer (DEPT) spectra in parentheses. The multiplicities are abbreviated as s: C, d: CH, t: CH_2, and q: CH_3. When the number of the carbon was more than one, the number was added in the parentheses.

Synthesis of 12 To a solution of **11** (1.0 g, 8.9 mmol) in H_2O (17.8 mL) was added acrolein (750 mg, 13.4 mmol) at room temperature (r.t.). After stirring for 7 d at r.t., to the mix-

ture was added CH_2Cl_2. The aqueous mixture was extracted with CH_2Cl_2 and EtOAc. The general drying procedure gave a crude product including 3-(1-methyl-2,5-dioxocyclopentyl)-propanal, which was used to the next reaction without further purification.

To a solution of the crude product in toluene (86 mL) was added ethyl 2-(triphenylphosphoranylidene)propionate (3.75 g, 10.3 mmol) at r.t. After stirring for 18 h at r.t., the mixture was concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3/1) to give **12** (1.88 g, 7.45 mmol, 84% yield in 2 steps) as a colorless oil. Data for **12**: IR (ATR) ν 2980, 2929, 1716, 1705, 1651, 1454, 1273, 1113, 745 cm^{-1}. ^{1}H-NMR (400 MHz, 25 °C) δ: 6.56 (tq, J = 7.6, 1.4 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 2.87–2.65 (m, 4H), 2.07–2.01 (m, 2H), 1.78–1.74 (m, 2H), 1.76 (d, J = 1.4 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.14 (s, 3H). ^{13}C-NMR (101 MHz, 24 °C) δ: 216.2 (s, 2C), 168.0 (s), 139.7 (d), 129.3 (s), 60.7 (t), 56.5 (s), 35.2 (t, 2C), 33.5 (t), 23.9 (t), 20.0 (q), 14.4 (q), 12.5 (q). HRMS (electrospray ionization (ESI)) m/z $[M + Na]^+$ Calcd for $C_{14}H_{20}O_4Na$ 275.1259. Found 275.1257.

Synthesis of 13 To a mixture of **12** (1.70 g, 6.73 mmol) and 1,2-bis(trimethylsilyloxy)ethane (7.93 g, 38.4 mmol) in CH_2Cl_2 (67 mL) was added TMSOTf (300 mg, 1.35 mmol) at −40 °C. The mixture was stirred for 4.5 d at 3 °C. To the mixture was added saturated aqueous sodium hydrogen carbonate. The mixture was extracted with CH_2Cl_2. After the general drying procedure, the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 6/1 to 3/1) to give **13** (1.48 g, 4.35 mmol, 65% yield) as a colorless oil. Data for **13**: IR (ATR) ν 2978, 2881, 1703, 1649, 1456, 1368, 1113, 976, 748 cm^{-1}. ^{1}H-NMR (400 MHz, 25 °C) δ: 6.76 (tq, J = 7.6, 1.4 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.02–3.94 (m, 4H), 3.92–3.83 (m, 4H), 2.21–2.15 (m, 2H), 1.98–1.86 (m, 4H), 1.82 (d, J = 1.4 Hz, 3H), 1.60–1.53 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.14 (s, 3H). ^{13}C-NMR (101 MHz, 25 °C) δ: 168.6 (s), 143.6 (d), 127.3 (s), 117.6 (s, 2C), 64.8 (t, 2C), 64.3 (t, 2C), 60.5 (t), 50.2 (s), 32.4 (t, 2C), 28.3 (t), 23.6 (t), 17.1 (q), 14.4 (q), 12.3 (q). HRMS (ESI) m/z $[M + Na]^+$ Calcd for $C_{18}H_{28}O_6Na$ 363.1784. Found 363.1781.

Synthesis of 14 To a solution of **13** (1.48 g, 4.34 mmol) in THF (43 mL) was added DIBAL (1.03 M in *n*-hexane, 16.9 mL, 17.4 mmol) at −78 °C. The mixture was stirred for 50 min at −78 °C. After warming to 0 °C, the mixture was additionally stirred for 5 h. To the mixture was added 15% of aqueous Rochelle salt. The mixture was extracted with EtOAc. After the general drying procedure, the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/2) to give **14** (1.22 g, 4.09 mmol, 95% yield) as a colorless oil. Data for **14**: IR (ATR) ν 3763–3076, 2976, 2881, 1462, 1377, 1113, 1057, 974, 949, 727, 667 cm^{-1}. ^{1}H-NMR (400 MHz, 25 °C) δ: 5.41 (dt, J = 7.2, 1.2 Hz, 1H), 4.02–3.93 (m, 6H), 3.91–3.84 (m, 4H), 2.06–2.00 (m, 2H), 1.97–1.89 (m, 4H), 1.66 (d, J = 1.2 Hz, 3H), 1.52–1.47 (m, 2H), 1.30 (br t, J = 5.3 Hz, 1H), 1.13 (s, 3H). ^{13}C-NMR (101 MHz, 25 °C) δ: 134.2 (s), 127.8 (d), 117.7 (s, 2C), 69.3 (t), 64.8 (t, 2C), 64.3 (t, 2C), 50.3 (s), 32.5 (t, 2C), 29.3 (t), 22.4 (t), 17.1 (q), 13.7 (q). HRMS (ESI) m/z $[M + Na]^+$ Calcd for $C_{16}H_{26}O_5Na$ 321.1678. Found 321.1673.

Synthesis of 17 To a solution of **14** (1.22 g, 4.08 mmol) in $MeC(OEt)_3$ (20 mL) were added PivOH (41.7 mg, 409 μmol) at r.t. After warming to 50 °C, the mixture was stirred for 1 h. After warming to 130 °C, the mixture was additionally stirred for 50 min. After the mixture was cooled to r.t., acetone (20 mL), H_2O (20 mL), and 1 M sulfuric acid (5.1 mL) were added. The mixture was stirred for 10.5 h at reflux. After the mixture was cooled to 0 °C, saturated aqueous sodium hydrogen carbonate was added to the mixture. The aqueous mixture was extracted with Et_2O. After the general drying procedure, the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10/1 to 5/1) to give **17** (828 mg, 2.95 mmol, 72% yield) as a colorless oil. Data for **17**: IR (ATR) ν 3073, 2976, 2939, 1722, 1645, 1454, 1371, 1163, 1031, 897, 669 cm^{-1}. ^{1}H-NMR (400 MHz, 24 °C) δ: 4.73 (dq, J = 1.6, 1.4 Hz, 1H), 4.66 (d, J = 1.6 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 2.78–2.64 (m, 4H), 2.41 (m, 1H), 2.27 (dd, J = 14.5, 7.7 Hz, 1H), 2.21 (dd, J = 14.5, 7.2 Hz, 1H), 1.55 (d, J = 1.4 Hz, 3H), 1.53–1.41 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H), 1.24–1.11 (m, 2H), 1.04 (s, 3H). ^{13}C-NMR (101 MHz, 24 °C) δ: 216.50 (s), 216.45 (s), 172.3 (s), 145.1 (s), 113.2 (t), 60.4 (t), 56.6 (s), 43.9 (d), 39.1 (t), 35.3 (t, 2C), 33.0 (t), 27.2 (t), 19.0 (q), 18.4 (q), 14.3 (q). HRMS (ESI) m/z $[M + Na]^+$ Calcd for $C_{16}H_{24}O_4Na$ 303.1572. Found 303.1568.

Synthesis of 10 To a solution of **17** (150 mg, 535 μmol) in EtOH (2.0 mL) were added 2-methyl-2-butene (224 mg, 6.42 mmol) and $CuBr_2$ (717 mg, 3.21 mmol) at r.t. The mixture was stirred for 2 h at 50 °C. To the mixture was further added $CuBr_2$ (213 mg, 913 μmol) at 50 °C. After stirring at 50 °C for 20 min, to the mixture were added saturated aqueous sodium hydrogen carbonate and 10% of aqueous sodium thiosulfate. The aqueous mixture was extracted with EtOAc. The combined organic layers were washed with brine. After the general drying procedure, the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 9/1 to 8/1) to give **10** (105 mg, 377 μmol, 71% yield) as a yellow oil. Data for **10**: IR (ATR) ν 3075, 2978, 2931, 1732, 1701, 1645, 1454, 1371, 1172, 897, 771 cm^{-1}. ^{1}H-NMR (400 MHz, 24 °C) δ: 7.23 (s, 2H), 4.77 (dq, J = 1.8, 1.4 Hz, 1H), 4.70 (d, J = 1.8 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 2.44 (m, 1H), 2.31 (dd, J = 14.8, 8.1 Hz, 1H), 2.25 (dd, J = 14.8, 7.3 Hz, 1H), 1.62–1.49 (m, 2H), 1.57 (d, J = 1.4 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 1.17–1.04 (m, 2H), 1.12 (s, 3H). ^{13}C-NMR (101 MHz, 24 °C) δ: 207.88 (s), 207.85 (s), 172.3 (s), 148.3 (d, 2C), 145.0 (s), 113.1 (t), 60.4 (t), 50.3 (s), 43.9 (d), 39.1 (t), 32.1 (t), 27.5 (t), 19.1 (q), 18.3 (q), 14.3 (q). HRMS (ESI) m/z $[M + Na]^+$ Calcd for $C_{16}H_{22}O_4Na$ 301.1416. Found 301.1414.

Synthesis of 18 and 19 To a solution of **10** (11.2 mg, 40.2 μmol) in toluene (4.0 mL) were added dropwise KHMDS (0.5 M in toluene, 0.12 mL, 60 μmol) at −78 °C. After stirring for 2 h at −78 °C, to the mixture was added saturated aqueous ammonium chloride at −78 °C. After warming to r.t., the mixture was extracted with EtOAc. The general drying procedure gave a crude product including two diastereomeric aldol products, which was used next reaction without further purification.

To a solution of the crude product in CH_2Cl_2 (1.0 mL) were added TMSOTf (35.6 mg, 161 μmol) and 2,6-lutidine (41.8 mg, 322 μmol) at 0 °C. After stirring for 30 min at 0 °C, to the mixture was added saturated aqueous ammonium chloride. The mixture was extracted with Et_2O. After the general drying procedure, the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 20/1) to give a 1 : 1.8 mixture of **18** and **19** (6.8 mg, 19 μmol, 48% yield in 2 steps) as a colorless oil. The diastereomeric mixture was further purified by

preparative TLC (*n*-hexane/EtOAc = 4/1) to give **18** (2.1 mg) as a colorless oil and **19** (4.3 mg) as a colorless oil. Data for **18**: IR (ATR) *ν* 3076, 2937, 1716, 1647, 1456, 1373, 1082, 897, 839, 754 cm^{-1}. ^{1}H-NMR (500 MHz, 22 °C) *δ*: 8.08 (d, *J* = 6.3 Hz, 1H), 6.26 (d, *J* = 6.3 Hz, 1H), 4.70 (d, *J* = 1.5 Hz, 1H), 4.67 (dq, *J* = 1.5, 1.2 Hz, 1H), 4.20 (dq, *J* = 10.5, 7.1 Hz, 1H), 4.07 (dq, *J* = 10.5, 7.1 Hz, 1H), 3.02 (d, *J* = 12.8 Hz, 1H), 2.26 (ddd, *J* = 12.8, 7.3, 7.3 Hz, 1H), 1.70 (d, *J* = 1.2 Hz, 3H), 1.65–1.60 (m, 2H), 1.48 (m, 1H), 1.38 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.10 (s, 3H), 0.00 (s, 9H). ^{13}C-NMR (126 MHz, 24 °C) *δ*: 212.3 (s), 173.3 (s), 161.6 (d), 146.2 (s), 133.6 (d), 112.1 (t), 84.4 (s), 60.5 (t), 53.6 (d), 52.7 (s), 43.4 (d), 33.9 (t), 25.1 (t), 18.9 (q), 17.3 (q), 14.4 (q), 2.36 (q, 3C). HRMS (ESI) *m/z* $[M + Na]^+$ Calcd for $C_{19}H_{30}O_4SiNa$ 373.1811. Found 373.1820. Data for **19**: IR (ATR) *ν* 2980, 2920, 1734, 1647, 1456, 1373, 1174, 899, 852 cm^{-1}. ^{1}H-NMR (500 MHz, 24 °C) *δ*: 7.75 (d, *J* = 6.3 Hz, 1H), 6.17 (d, *J* = 6.3 Hz, 1H), 4.64 (dq, *J* = 1.7, 1.2 Hz, 1H), 4.54 (d, *J* = 1.7 Hz, 1H), 4.15 (dq, *J* = 10.9, 6.9 Hz, 1H), 4.12 (dq, *J* = 10.9, 6.9 Hz, 1H), 2.63 (ddd, *J* = 12.0, 8.0, 6.3 Hz, 1H), 2.34 (d, *J* = 12.0 Hz, 1H), 1.89–1.77 (m, 2H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.49 (m, 1H), 1.23 (t, *J* = 6.9 Hz, 3H), 1.14 (m, 1H), 1.05 (s, 3H), 0.09 (s, 9H). ^{13}C-NMR (126 MHz, 23 °C) *δ*: 209.7 (s), 171.5 (s), 164.3 (d), 148.9 (s), 130.4 (d), 109.2 (t), 83.9 (s), 60.6 (t), 58.6 (d), 54.2 (s), 39.4 (d), 29.2 (t), 26.9 (t), 23.8 (q), 21.9 (q), 14.2 (q), 2.51 (q, 3C). HRMS (ESI) *m/z* $[M + Na]^+$ Calcd for $C_{19}H_{30}O_4SiNa$ 373.1811. Found 373.1815.

Synthesis of 20 To a solution of **14** (147 mg, 493 *μ*mol) in toluene (2.5 mL) was added *N*,*N*-dimethylacetamide dimethyl acetal (stabilized with 5–10% MeOH, 228 mg, 205–217 mg as *N*,*N*-dimethylacetamide dimethyl acetal, 1.81–1.92 mmol) at r.t. The mixture was stirred at reflux for 23 h. After concentration of the mixture, the resulting residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1 to 1/3) to give **20** (137 mg, 372 *μ*mol, 76% yield) as a yellow oil. Data for **20**: IR (ATR) *ν* 2978, 2945, 2881, 1640, 1395, 1065, 749 cm^{-1}. ^{1}H-NMR (500 MHz, 20 °C) *δ*: 4.73 (s, 1H), 4.70 (s, 1H), 4.00–3.91 (m, 4H), 3.87–3.82 (m, 4H), 2.99 (s, 3H), 2.91 (s, 3H), 2.51 (br m, 1H), 2.42–2.30 (m, 2H), 1.94–1.82 (m, 4H), 1.67 (s, 3H), 1.43–1.34 (m, 4H), 1.07 (s, 3H). ^{13}C-NMR (126 MHz, 21 °C) *δ*: 172.3 (s), 147.4 (s), 117.74 (s), 117.71 (s), 111.3 (t), 64.9 (t), 64.7 (t), 64.3 (t), 64.2 (t), 50.2 (s), 44.5 (d), 38.3 (t), 37.6 (q), 35.5 (q), 32.6 (t), 32.4 (t), 27.2 (t), 27.0 (t), 19.4 (q), 17.2 (q). HRMS (ESI) *m/z* $[M + Na]^+$ Calcd for $C_{20}H_{33}O_5NNa$ 390.2251. Found 390.2245.

Synthesis of 21 To a solution of **20** (447 mg, 1.22 mmol) in THF (4.0 mL) were added Cp_2ZrCl_2 (427 mg, 1.46 mmol) and $LiAlH(Ot\text{-}Bu)_3$ (1.0 M in THF, 1.3 mL, 1.3 mmol) at 0 °C. After stirring for 1 h at 0 °C, to the mixture were added saturated aqueous Rochelle salt and Et_2O. The mixture was extracted with Et_2O. After the general drying procedure, the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 7/1 to 3/1) to give **21** (271 mg, 836 *μ*mol, 68% yield) as a pale yellow oil. Data for **21**: IR (ATR) *ν* 2977, 2948, 2881, 1722, 1069, 772 cm^{-1}. ^{1}H-NMR (500 MHz, 20 °C) *δ*: 9.65 (br t, *J* = 1.7 Hz, 1H), 4.77 (s, 1H), 4.74 (s, 1H), 3.99–3.93 (m, 4H), 3.89–3.81 (m, 4H), 2.56 (br m, 1H), 2.42 (dt, *J* = 7.5, 1.7 Hz, 2H), 1.94–1.82 (m, 4H), 1.64 (s, 3H), 1.42–1.36 (m, 4H), 1.07 (s, 3H). ^{13}C-NMR (126 MHz, 21 °C) *δ*: 202.9 (d), 146.2 (s), 117.6 (s, 2C), 112.4 (t), 64.8 (t), 64.7 (t), 64.2 (t, 2C), 50.1 (s), 47.6 (t), 42.7 (d), 32.5 (t), 32.4 (t), 27.3 (t), 27.0 (t), 18.9 (q), 17.1 (q). HRMS (ESI) *m/z* $[M + Na]^+$ Calcd for $C_{18}H_{28}O_5Na$ 347.1829. Found 347.1822.

Synthesis of 22 To a stirred solution of **21** (36.5 mg, 113 *μ*mol) in acetone (1.0 mL) was added 1 M sulfuric acid (100 *μ*L) at r.t. After stirring at 40 °C for 17 h, to the mixture was added saturated aqueous sodium hydrogen carbonate at r.t. The mixture was extracted with EtOAc. After the general drying procedure, the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5/1 to 3/1) to give **22** (15.0 mg, 63.5 *μ*mol, 56% yield) as a colorless oil.

Data for **22**: IR (ATR) *ν* 2967, 2936, 1716, 1452, 1056, 897 cm^{-1}. ^{1}H-NMR (500 MHz, 19 °C) *δ*: 9.62 (dd, *J* = 2.3, 1.7 Hz, 1H), 4.82 (s, 1H), 4.75 (s, 1H), 2.83–2.68 (m, 4H), 2.56 (m, 1H), 2.42 (ddd, *J* = 16.4, 8.5, 2.3 Hz, 1H), 2.34 (ddd, *J* = 16.4, 6.3, 1.7 Hz, 1H), 1.62–1.50 (m, 2H), 1.59 (s, 3H), 1.23–1.17 (m, 2H), 1.10 (s, 3H). ^{13}C-NMR (126 MHz, 20 °C) *δ*: 216.54 (s), 216.47 (s), 201.8 (d), 144.8 (s), 113.6 (t), 56.6 (s), 47.4 (t), 41.6 (d), 35.3 (t, 2C), 32.7 (t), 27.5 (t), 19.4 (q), 18.5 (q). HRMS atmospheric pressure chemical ionization *m/z* $[M - H]^-$ Calcd for $C_{14}H_{19}O_3$ 235.1340. Found 235.1337.

Synthesis of 31 *via* the Use of DL-Proline To a solution of **22** (18.8 mg, 79.6 *μ*mol) in THF (1.5 mL) and DMSO (150 *μ*L) was added DL-proline (45.8 mg, 398 *μ*mol) at 0 °C. After stirring for 48 h at 0 °C, to the mixture was added brine. The mixture was extracted with EtOAc. The combined organic layer was successively washed with brine. The general drying procedure afforded a crude product including a 49 : 1 mixture of **31** and **32**. The crude solid product was purified by trituration with toluene/*n*-hexane (1/1) to give **31** (13.7 mg, 58.0 *μ*mol, 73% yield) as a white solid. Data for **31**: mp 121–124 °C. IR (ATR) *ν* 3438, 2973, 2936, 1719, 1376, 1071, 952 cm^{-1}. ^{1}H-NMR (500 MHz, 20 °C) *δ*: 9.77 (s, 1H), 4.94 (br s, 1H), 4.86 (br s, 1H), 2.84 (br s, 1H), 2.57–2.52 (m, 2H), 2.51–2.39 (m, 2H), 2.30 (m, 1H), 1.95 (m, 1H), 1.79 (s, 3H), 1.73 (m, 1H), 1.55 (m, 1H), 1.45–1.40 (m, 2H), 1.11 (s, 3H). ^{13}C-NMR (126 MHz, 20 °C) *δ*: 219.1 (s), 207.1 (d), 145.3 (s), 113.6 (t), 80.8 (s), 55.3 (d), 53.4 (s), 44.3 (d), 32.9 (t), 31.5 (t), 28.5 (t), 26.6 (t), 20.2 (q), 12.9 (q). HRMS (ESI) *m/z* $[M - H]^-$ Calcd for $C_{14}H_{19}O_3$ 235.1340. Found 235.1337.

Synthesis of 32 *via* the Use of Alumina To a solution of **22** (27.3 mg, 116 *μ*mol) in toluene (1.0 mL) was added alumina (200 mg) at r.t. After stirring for 1.5 h at r.t., the mixture was filtered and concentrated to give a crude product including a 21 : 1 mixture of **32** and **31** (50% NMR yield). The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 8/1 to 4/1) to give **32** (8.4 mg, 36 *μ*mol, 31% yield) as a colorless oil and a mixture of **32** and side products. Data for **32**: ^{1}H-NMR (500 MHz, 16 °C) *δ*: 9.64 (d, *J* = 2.9 Hz, 1H), 4.79 (br s, 1H), 4.78 (br s, 1H), 2.86 (br s, 1H), 2.67 (ddd, *J* = 12.0, 12.0, 2.9 Hz, 1H), 2.57 (dd, *J* = 20.1, 10.3 Hz, 1H), 2.34–2.19 (m, 2H), 2.06–1.97 (m, 3H), 1.65 (s, 3H), 1.59 (m, 1H), 1.45 (m, 1H), 1.17 (m, 1H), 1.00 (s, 3H). ^{13}C-NMR (126 MHz, 17 °C) *δ*: 217.5 (s), 206.9 (d), 145.3 (s), 113.2 (t), 79.3 (s), 56.1 (d), 53.9 (s), 42.4 (d), 34.5 (t), 30.9 (t), 28.7 (t), 28.5 (t), 19.6 (q), 19.2 (q).

Synthesis of *rac*-33 and 34 To a solution a 1.9 : 1 mixture of **31** and **32** (5.5 mg, 23 *μ*mol) in THF (300 *μ*L), *t*-BuOH (300 *μ*L), H_2O (300 *μ*L), and 2-methyl-2-butene (100 *μ*L) were added $NaClO_2$ (6.8 mg, 75 *μ*mol) and $NaH_2PO_4 \cdot 2H_2O$ (12.0 mg, 76.9 *μ*mol) at 0 °C. After stirring for 2.5 h at 0 °C, to the mixture was added $NaSO_3 \cdot 7H_2O$ then 1 M hydrochloric acid. The mixture was extracted with EtOAc. The general drying

procedure afforded a crude product including two carboxylic acids, which was used to the next reaction without further purification.

To a solution of the crude product in DMF (500 μL) were added K_2CO_3 (6.0 mg, 47 μmol) and BnBr (6.0 mg, 35 μmol) at r.t. After stirring for 14 h at r.t., to the mixture was added saturated aqueous ammonium chloride. The mixture was extracted with EtOAc. The combined organic layer was successively washed with brine. After the general drying procedure, the residue was purified by preparative TLC (*n*-hexane/EtOAc = 4/1) to give **33** (3.1 mg, 9.1 μmol, 39% yield in 2 steps) as a white solid and **34** (1.7 mg, 5.0 μmol, 21% yield in 2 steps) as a white solid. Data for **33**: mp 97–100 °C. IR (ATR) ν 3473, 3028, 2967, 2934, 1741, 1701, 1164, 901 cm^{-1}. ^{1}H-NMR (500 MHz, 19 °C) δ: 7.39–7.33 (m, 5H), 5.15 (d, J = 12.0 Hz, 1H), 5.12 (d, J = 12.0 Hz, 1H), 4.75 (brs, 2H), 2.79 (d, J = 12.6 Hz, 1H), 2.51–2.33 (m, 4H), 2.13 (brs, 1H), 1.74–1.68 (m, 5H), 1.42–1.37 (m, 3H), 1.10 (s, 3H). ^{13}C-NMR (126 MHz, 18 °C) δ: 219.7 (s), 172.4 (s), 146.6 (s), 135.6 (s), 128.8 (d, 2C), 128.71 (d, 2C), 128.65 (d), 111.5 (t), 80.6 (s), 67.0 (t), 53.6 (s), 53.0 (d), 45.1 (d), 33.2 (t), 31.8 (t), 29.0 (t), 26.3 (t), 20.8 (q), 13.0 (q). HRMS (ESI) m/z $[M + Na]^+$ Calcd for $C_{21}H_{26}O_4Na$ 365.1723. Found 365.1721. HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL/min, 254 nm): t_R = 12.8, 16.3 min. Data for **34**: mp 120–124 °C. IR (ATR) ν 3501, 3032, 2940, 1732, 1165, 772 cm^{-1}. ^{1}H-NMR (500 MHz, 20 °C) δ: 7.39–7.30 (m, 5H), 5.14 (d, J = 12.0 Hz, 1H), 5.06 (d, J = 12.0 Hz, 1H), 4.68 (brs, 1H), 4.59 (brs, 1H), 4.57 (brs, 1H), 2.62–2.52 (m, 2H), 2.27 (d, J = 12.0 Hz, 1H), 2.26 (m, 1H), 2.13 (m, 1H), 2.00 (m, 1H), 1.78 (dd, J = 12.6, 9.7 Hz, 1H), 1.55 (s, 3H), 1.55–1.44 (m, 2H), 1.17 (m, 1H), 1.04 (s, 3H). ^{13}C-NMR (126 MHz, 20 °C) δ: 217.7 (s), 175.0 (s), 146.1 (s), 135.1 (s), 128.9 (d, 2C), 128.76 (d), 128.7 (d, 2C), 112.8 (t), 77.2 (s), 67.2 (t), 53.3 (s), 52.3 (d), 43.9 (d), 34.6 (t), 31.5 (t), 28.3 (t), 28.1 (t), 19.6 (q), 18.8 (q). HRMS (ESI) m/z $[M + Na]^+$ Calcd for $C_{21}H_{26}O_4Na$ 365.1723. Found 365.1719.

Synthesis of Optically Active 33 *via* the Use of L-Proline To a solution **22** (41.5 mg, 176 μmol) in THF (3.4 mL) and DMSO (340 μL) was added L-proline (101 mg, 878 μmol) at 0 °C. After stirring for 44 h at 0 °C, to the mixture was added brine. The mixture was extracted with EtOAc. The combined organic layer was successively washed with brine. The general drying procedure afforded a crude product including a 12 : 1 mixture of **31** and **32** (41% NMR yield) and **22** (20% NMR yield). The crude product was used to the next reaction without further purification.

To a solution the crude product in THF (800 μL), *t*-BuOH (800 μL), H_2O (800 μL), and 2-methyl-2-butene (400 μL) were added $NaClO_2$ (54.5 mg, 603 μmol) and $NaH_2PO_4 \cdot 2H_2O$ (90.1 mg, 578 μmol) at 0 °C. After stirring for 2 h at 0 °C, to the mixture was added $NaSO_3 \cdot 7H_2O$ then 1 M hydrochloric acid. The mixture was extracted with EtOAc. The general drying procedure afforded a crude product, which was used to the next reaction without further purification.

To a solution of the crude product in DMF (2.0 mL) were added K_2CO_3 (49.7 mg, 360 μmol) and BnBr (44.7 mg, 264 μmol) at r.t. After stirring for 30 min at r.t., to the mixture was added saturated aqueous ammonium chloride. The mixture was extracted with Et_2O. The combined organic layer was washed with brine. After the general drying procedure, the residue was purified by silica gel column chromatography (toluene/CH_2Cl_2 = 1/1 to 0/1, then CH_2Cl_2/EtOAc = 15/1 to 8/1) to give an impure product **33**. The product was further purified by trituration with *n*-hexane to give **33** (8.3 mg, 24 μmol, >99% ee, 14% yield in 3 steps) as a white solid. Additional data: $[\alpha]_D^{27}$ +14.7 (*c* 0.280, $CHCl_3$). HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL/min, 254 nm): t_{major} = 13.0 min.

Synthesis of *ent*-33 *via* the Use of D-Proline To a solution **22** (26.8 mg, 113 μmol) in THF (2.2 mL) and DMSO (220 μL) was added D-proline (67.5 mg, 586 μmol) at 0 °C. After stirring for 40 h at 0 °C, to the mixture was added brine. The mixture was extracted with EtOAc. The combined organic layer was successively washed with brine. The general drying procedure afforded a crude product including a 3.3 : 1 mixture of *ent*-**31** and *ent*-**32** (40% NMR yield) and **22** (13% NMR yield). The crude product was used to the next reaction without further purification.

To a solution the crude product in THF (500 μL), *t*-BuOH (500 μL), H_2O (500 μL), and 2-methyl-2-butene (200 μL) were added $NaClO_2$ (41.7 mg, 461 μmol) and $NaH_2PO_4 \cdot 2H_2O$ (60.3 mg, 387 μmol) at 0 °C. After stirring for 2.5 h at 0 °C, to the mixture was added $NaSO_3 \cdot 7H_2O$ then 1 M hydrochloric acid. The mixture was extracted with EtOAc. The general drying procedure afforded a crude product, which was used to the next reaction without further purification.

To a solution of the crude product in DMF (1.5 mL) were added K_2CO_3 (31.8 mg, 248 μmol) and BnBr (28.8 mg, 170 μmol) at r.t. After stirring for 1.5 h at r.t., to the mixture was added saturated aqueous ammonium chloride. The mixture was extracted with Et_2O. The combined organic layer was washed with brine. After the general drying procedure, the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 15/1 to 4/1) to give an impure product *ent*-**33**. The product was further purified by preparative TLC (CH_2Cl_2/EtOAc = 15/1) to give *ent*-**33** (6.3 mg, 18.4 μmol, −85% ee, 16% yield in 3 steps) as a white solid. Additional data: $[\alpha]_D^{26}$ −8.42 (*c* 0.260, $CHCl_3$). HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL/min, 254 nm): t_{major} = 16.5 min; t_{minor} = 12.9 min.

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Supplementary Materials This article contains supplementary materials.

References and Notes

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33) For examples, we exposed **24** to 5 equivalents of pyrrolidine in THF/DMSO, but the desired aldol product was not obtained owing to its Michael addition reaction. Although the use of DL-proline led to the detection of **29**, the reaction provided a lot of products including 14% NMR yield of a 1.5 : 1 diastereomeric mixture of **29**. The structure of the major product was not determined.
34) Considering the results in Fig. 3c, this reaction may generate *ent*-**32** preferably. However, we did not verify this hypothesis owing to the trace production of **32**.