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Stereoselective hydrogenation of conjugate diene directed by hydroxy group and asymmetric synthesis of deoxypolypropionate units

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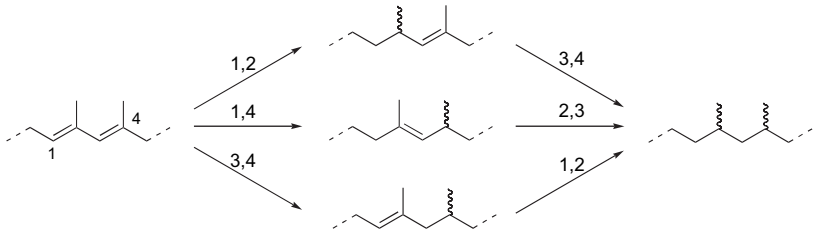
Abstract—Optically active cyclic compounds carrying a conjugate diene and two hydroxy groups were prepared through the intramolecular Büchner reaction with a chiral tether and succeeding stereoselective conversion. Hydrogenation of the diene in the first step was not regioselective but resulted in three regioisomeric monoenes. Nevertheless, the final saturated product carrying two stereogenic centers could be obtained in 98% stereochemical purity on further hydrogenation under optimized conditions. The high stereoselectivity throughout the multiple pathways is attributable to the effective direction by the hydroxy group. Ring cleavage of the produced stereochemically pure seven-membered ring compounds successfully resulted in synthetic intermediates for deoxypolypropionates.

1. Introduction

Polypropionates are ubiquitous natural products and often found in antibiotic macrolides. The carbon skeleton having skipped methyl groups is biologically synthesized by the propionyl-CoA or α-methylmalonyl-CoA cycle, which constructs chiral centers in a variety of patterns under strict stereocontrol.[1] For chemical synthesis of such compounds, many elegant stereocontrolled reactions have been developed, but the reactions controlling formation of multi-chiral centers are still limited.[2] Deoxypolypropionates have fewer chiral centers and can be directly produced by the hydrogenation of skipped methyl polyenes. However, this simple procedure has a major drawback in its stereocontrol due to the multiple reaction pathways.[3,4] For example, hydrogenation of a conjugate diene to give a saturated product consists of two steps and can proceed with three monoene intermediates. As shown in Scheme 1, one chiral center is generated in three different reactions, and thus, the logical consequence to obtain a single stereoisomer of the saturated compound is that both regiocontrol of the first step and stereocontrol of the selected pathway are necessary.

Alternatively, if all the six reactions under regio uncontrol are stereoselective, a single saturated product can be obtained. Here, the stereodirection must be the same in the generation steps for each stereochemical center. Hydroxy group may have such a stereodirecting ability since the hydrogenation of allyl or homoallyl alcohol results in saturated alcohols in moderate to high stereoselectivity.[5] If the hydroxy directing ability sufficiently and commonly functions for all the diene substrates and monoene intermediates, the



Scheme 1. Multiplicity in generation of chiral center in hydrogenation of a conjugate diene.

Keywords: Hydrogenation; Conjugate diene; Hydroxy direction; Deoxypolypropionate.
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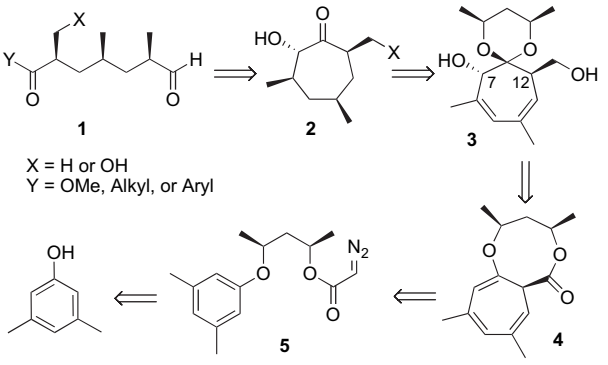
chiral centers are generated under the same direction irrespective of the regioselectivity.

Retrosynthesis of the present study is given in Scheme 2. Optically active 2,4-pentanediol (PD) is a popular chiral auxiliary, and exhibits strict stereocontrollability when it is used as a tether connecting two reactants.[6] The Büchner reaction is one of the successful examples and produces chiral cycloheptatriene derivatives in optically active forms from phenols.[7] In the present study, we planned to use such a compound **4**, prepared from 3,5-dimethylphenol via the PD-tethered Büchner reaction of **5**, to synthesize a chiral building block **1** (X=H or OH) that corresponds to a deoxytripropionate unit. A key step of this procedure is the hydrogenation of **3** at the conjugate diene to generate two chiral centers stereocontrolled by the substituents at C7 and/or C12, and thus, these chiral centers must also be stereoselectively generated. In this report, we would like to present the first example of the hydroxy-directed hydrogenation of a diene to give the saturated product stereoselectively in spite of total lack of regioselectivity. Ring cleavage to give **1** in keeping the stereochemical purity is also presented.[8]

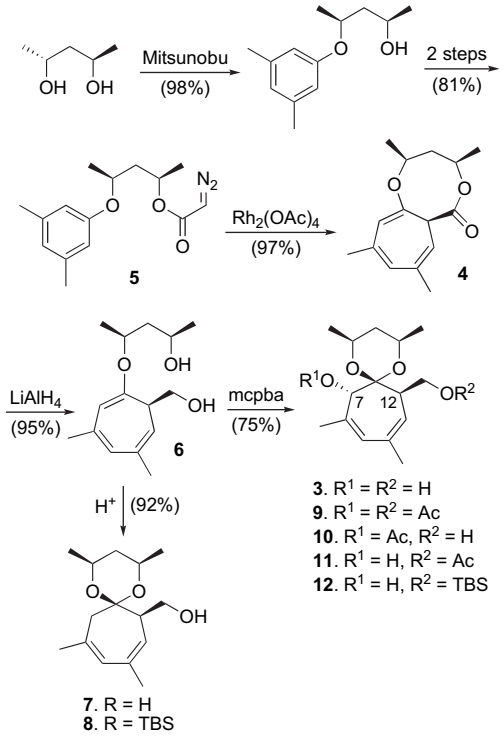


Scheme 2. Retrosynthesis of chiral polypropionate unit **1** via optically active cycloheptatriene **4**.

2. Synthesis of diene 3 via the chiral tethered Büchner reaction

Diene **7** was previously synthesized for study of the hydroboration, but was also employed for the present hydrogenation.[9] As shown in Scheme 3, substrate **5** for the chiral tethered Büchner reaction was prepared from optically pure (2*R*,4*R*)-2,4-pentanediol (>99.6% enantiomeric and diastereomeric purities) in three steps through the Mitsunobu reaction with 3,5-dimethylphenol (98% yield), esterification with diketene (91%), and diazo formation/deacetylation (89%). Treatment of **5** with $Rh_2(OAc)_4$ in dichloromethane at room temperature resulted in quantitative formation of **4** (97% after column chromatography), the stereochemical purity of which generated at the 11a-position was confirmed to be more than 99%. Reduction of **4** with lithium aluminum hydride gave stereochemically more stable compound **6** (95%). Acid treatment of **6** resulted in stereoselective acetal formation to give **7** (92%).

Oxidation of **6** to introduce an additional hydroxy group at C2 was achieved by the oxidation with *m*-CPBA in dichloromethane. The oxidation accompanied the acetal formation,

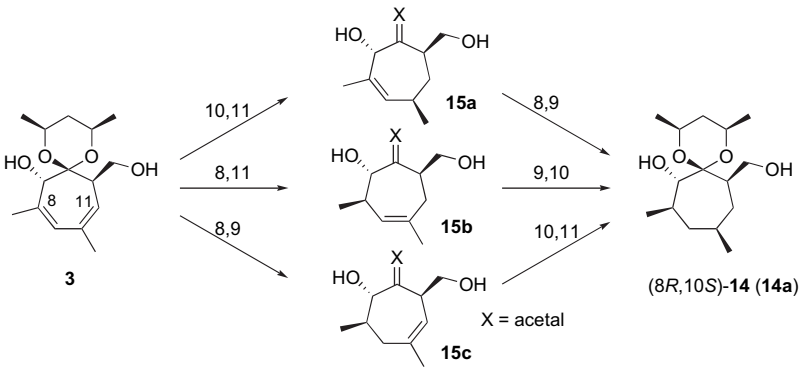


Scheme 3. Synthesis of **3** and its analogues.

and both the stereocenters generated at C1 and C7 in the product were fully controlled to give **3** as a single diastereomer (>98% pure). The oxidation must be stereodirected by the hydroxy group of the PD part as a chiral tether.[10] Instead of the strong stereoselectivity, isolated yield of **3** was low and irreproducible (27–40%), mainly due to the over oxidation. The yield became better when the reaction was quenched at −40 °C with KF to result in 57% in a gram scale experiment and up to 75% in a smaller scale. Stereochemistry of **3** at C7 was assigned to be trans to C12 based on the results with unsubstituted analogue.[10] This assignment was confirmed through the following synthesis. Protection of hydroxy groups of **3** was proceeded initially at the 12-hydroxymethyl to give **11** (AcCl/collidine, 41%) or **12** (TBSCl/imidazole, 49%), and finally gave **9** (Ac_2O/pyridine/DMAP, 68%). The 7-hydroxy protection was achieved with **12** by acetylation (Ac_2O/pyridine/DMAP) and treatment with TBAF to give **10** (19% for two steps). The yields for these derivations of **3** were not optimized.

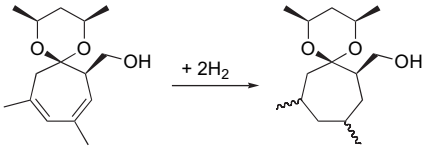
3. Stereoselectivity of hydrogenation of the dienes

The hydrogenation selectivity was preliminarily studied with the monohydroxy diene **7**. When the hydrogenation fully proceeded, the reaction mixture contained all four diastereomers of **13** (**13a**–**d**) (Scheme 4). The normalized isomeric ratios determined by the GLC analysis are given in order of retention times in Table 1. The major isomer is in the range of 44–62%, but the minor one is below 10%. By the Ni catalysis (entries 1–5), the other two isomers were obtained in similar amounts, and thus, the stereoface differentiating ratio to give each of the two new chiral centers is calculated to be 2–4. The poor selectivity suggests a weak stereo-directing effect of the hydroxy group of **7**. The



Scheme 4. Three possible pathways in the hydrogenation of diene **3** to **14a**.

Table 1. Diastereomeric ratio of **13a–d** obtained by the hydrogenation of **7**



Entry	Catalyst	Solvent	Time/h	Diastereomeric ratio[a]
1	RNi	EtOAc	5	4:59:19:18
2	RNi	THF	10	3:47:30:30
3	RNi	Benzene	10	6:48:21:25
4	RNi	Hexane	5	5:59:12:14
5	RNi[b]	Hexane	10	2:48:23:27
6	Pt/Al_2O_3	EtOH	10	—[c]
7	Pt/Al_2O_3	Hexane	5	4:62:21:13
8	Pd/C	EtOH	5	5:61:25:9
9	Pd/C	Hexane	5	9:44:38:9

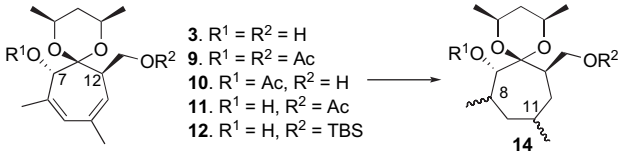
[a] The isomeric ratio was determined by GLC. The stereochemistries were not assigned.
[b] Prepared from the NDH type alloy and treated with glycolic acid.
[c] The hydrogenation was not completed.

distribution pattern of the isomers is somewhat different in the Pd catalyzed reaction indicating lower selectivity in the formation of one of the chiral centers (entries 8 and 9). During the course of any catalytic reaction, ^{1}H NMR of the reaction mixture showed formation of at least four regio- and stereoisomeric monoene intermediates. This finding suggests that the first step of the hydrogenation is not regioselective, and the observed stereoselectivity is a consequence of stereoselectivities in multiple reaction pathways.

The unpleasant results with **7** suggest its unfavorable conformation of the hydroxy group; it is not close enough to the diene site for the stereodirection. In support of this assumption, the Ni-catalyzed hydrogenation of **8**, where the hydroxy group of **7** was protected by a bulky TBS, was as quick to give an isomeric mixture as that with **1** in the first hydrogenation step. However, the steric effect of the TBS group on the hydrogenation rate became obvious in the second step to result in very slow and sluggish reaction for the full saturation. The difference between the first and second hydrogenation steps suggests a conformational change of the C12 substituent that is away from the diene, but becomes close to the olefinic bond of the monoenes. Hence, the hydroxy group of **7** was concluded to be unsuitable for the stereodirection of the hydrogenation of the diene.

Substrate **3** has an additional hydroxy group at C7, and the two hydroxy groups placed at both ends and different faces of the diene moiety. The hydrogenation of **3** was studied with the Ni, Pd, or Pt catalyst in methanol, ethyl acetate or hexane. The reactions were complete within 5 h at room temperature to afford a stereoisomeric mixture of **14** in a quantitative yield (Table 2, entries 1–3). The stereoselectivities as the fraction of major isomer **14a** were high in the mixture with minor **14b**, and two of the possible stereoisomers were not detected (<0.3%). The stereocontrollability of the catalysis is in the order; Ni≥Pt>Pd, in agreement with the hydrophilicity of the catalyst surface to allow the hydroxy-directed stereocontrol.[5] The solvent effect on the selectivity is not simple presumably because of change in contribution from the three pathways. The hydrogenation with the Ni catalyst at 0 °C (entry 4) and with an acid-treated Ni (entry 5) also resulted in high purity of over 90%, but again, the solvent effect on the selectivity is not comprehensible. So far, **3** was found to be a good substrate to give **14** in up to 98% stereochemical purity. The stereochemical analysis of the major isomer **14a** by ^{1}H NMR was not succeeded due to the conformational multiplicity, but was assigned to

Table 2. Stereochemical purity[a] of **14** obtained by the hydrogenation of **3** and its analogues **9**–**12** in different solvents at room temperature



Run	Substrate	Catalyst	Time	MeOH	EtOAc	Hexane
1	**3**	RNi	5 h	93	98	96
2		Pt/Al_2O_3	5 h	97	88	91
3		Pd/C	5 h	83	83	86
4		RNi[b]	12 h	95	97	92
5		RNi[c]	24 h	98	97	96
6	**9**	RNi	1 week	69	76	76
7		Pt/Al_2O_3	24 h	68	86	88
8		Pd/C	16 h	75	78	80
9	**10**	RNi	24 h	77	84	87
10	**11**	RNi	24 h	90	94	98
11	**12**	RNi	1 week	91	—[d]	—[d]

[a] Determined by GLC analysis after conversion to diacetate of **14**.
[b] The hydrogenation was performed at 0 °C.
[c] Prepared from the high-nickel alloy (NDH type) and treated with glycolic acid.
[d] The hydrogenation was very slow and sluggish.

be (8*R*,10*S*)-**14** based on the structures of its derivatives, which are given in following sections.

Protected substrates **9**–**12** were examined next to disclose the function of the hydroxy groups in the stereocontrol. When both the hydroxy groups were protected as the diacetate analogue **9**, the stereoselectivity became low though the other two stereoisomers were again undetectable (Table 2, entries 6–8). The hydrogenation rate over the Ni catalyst decreased, and the selectivity dropped down to less than 80%. Both the selectivity and the reaction rate also decreased with the Pd catalyst, but the decrease was smaller than that with the other catalysts. The differences between **7** and **3**, and between **3** and **9** suggest that only the 7-hydroxy group is indispensable to induce the high stereoselectivity by the Ni catalysis. Further details can be clarified by using monoacetate analogues **10** and **11**. The 7-acetoxy substrate **10** afforded low selectivity in the Ni hydrogenation, though the selectivity and reactivity are still better than those of **9** (entry 9). In contrast, the 12-acetoxymethyl substrate **11** resulted in high selectivity up to 98% (entry 10). As was observed with **8**, a TBS analogue **12** resulted in very slow second step of the hydrogenation presumably due to the steric fence by the bulky TBS group (entry 11).

The hydrogenation process with **3** was monitored by ^{1}H NMR under the most stereocontrolled conditions (RNi in EtOAc) at a larger substrate/catalyst ratio (100 mg/0.4 g). During the course of the reaction, three monoene intermediates were detected. Since all the monoenes are converted to the single stereoisomeric product (8*R*,10*S*)-**14**, (**14a**), their structures can be assigned as three regioisomers, **15a**–**c** as shown in Scheme 4. Time-dependent compositions of the reaction mixture were plotted in Figure 1. The diene **3** is consumed at an early stage to give almost equal amounts of **14a**, **15b**, and **15c** in addition to a small amount of **15a**, which still remained in the mixture after consumption of **3**, but was gradually decreased. Interconversion of the regioisomeric monoenes **15a**–**c** was not observed, when the hydrogenation was interrupted by replacing the hydrogen atmosphere to that of nitrogen. The minor intermediate **15a** was isolated from a reaction mixture and assigned to be 10*R* by the NOE between H10 and H12, which is agreeable to one of the intermediates to give (8*R*,10*S*)-**14**. The other two intermediates **15b** and **15c** could not be separated from **14**, but the planner structure of the lesser reactive intermediate **15c** could be determined by COSY spectra of the mixture. Considering the reactivities of monoenes **15a**–**c** and **14** generated at an early stage seems to be produced directly from **3**.

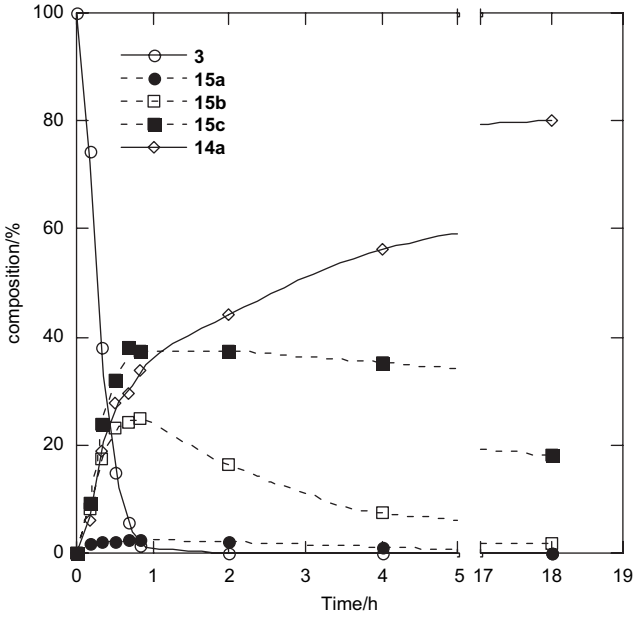


Figure 1. Product analysis during the hydrogenation of **3** over the Ni catalyst in ethyl acetate.

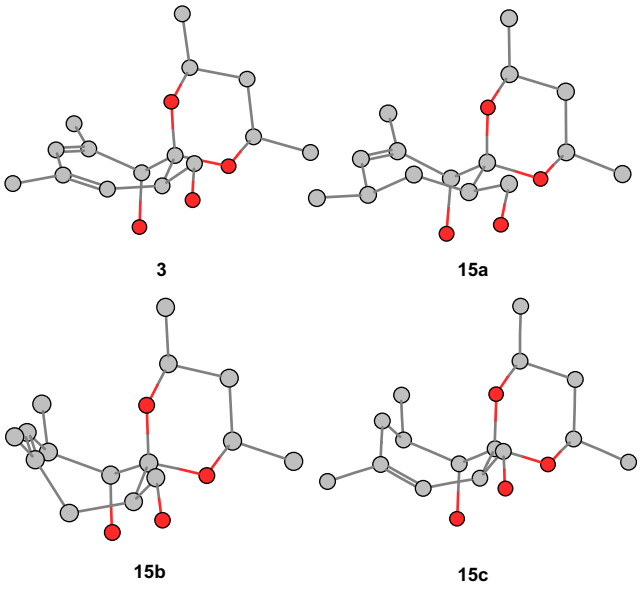


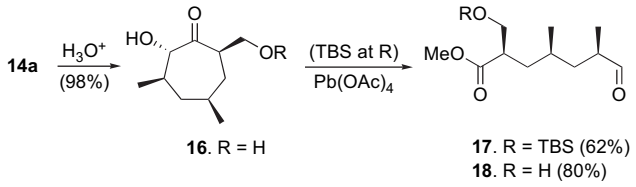
Figure 2. Optimized conformations of substrate **3** for the stereocontrolled hydrogenation and the intermediates **15a**–**c** estimated by MOPAC-02 at the PM5 level.

Overall, the hydrogenation of **3** was found to proceed through multiple pathways without regioselectivity, but the 7-hydroxy group effectively controls the reaction in the same stereodirection in any reaction involved. The conformations of substrate **3** and intermediates **15a**–**c** estimated by MOPAC-02 at the PM5 level are shown in Figure 2. Common feature of these compounds is seen at C7 and C12, which have essentially the same conformations among the compounds. The 7-hydroxy group fixed at the axial position must play a major role to direct the olefinic functions against the catalyst surface during the hydrogenation, while the 12-hydroxymethyl group at the equatorial position may cause steric control. The conformational difference between C7 and C12 positions is attributable to the difference in the steric hindrance caused by the acetal ring.

4. Ring cleavage of (8*R*,10*S*)-14 (14a)

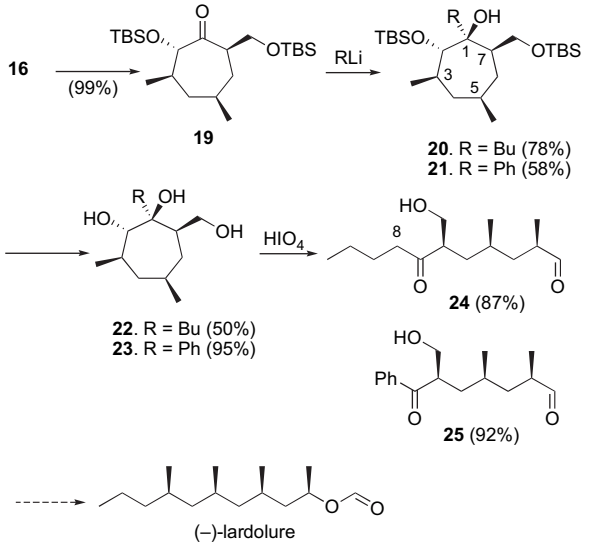
The stereochemically pure (8*R*,10*S*)-**14** (**14a**) was easily obtained by a single recrystallization of the hydrogenation mixture. Hydrolysis of **14a** with *p*-TsOH in 10% aqueous THF at room temperature yielded **16** (=**2**: X=OH) in 98% yield without any detectable isomerization, but elongation of the reaction time caused decomposition of **16** (Scheme 5).

Ring cleavage of **16** at the acyloin position was first carried out after the TBS protection of the primary OH, followed by reaction with lead tetraacetate in a mixture of methanol and benzene[11] to give **17** in 62% yield for two steps. This process was finally not adopted, because direct oxidation of **16** under the same conditions was found to give **18** in a better 80% yield.



Scheme 5.

The obtained **18** is considered to be a seven-carbon unit of a synthetic intermediate for deoxypolypropionates, and in a future study, elongation of the carbon chain either or both at the aldehyde and ester sides will be followed. Use of the hydroxymethyl instead of the ester leads inverted stereochemistry at C2. In this report, diversity of **14a** as a chiral intermediate was demonstrated by development of an alternative process, a carbon chain addition prior to the ring cleavage (Scheme 6). When **16** was protected with TBS at both of the hydroxy groups to give **19** (99%) and reacted with butyllithium or phenyllithium in ether at −78 °C, a single isomeric adduct **20** or **21** was obtained (78% or 58%, respectively). The lower yield with phenyllithium is attributable to steric reason, because the reaction of **19** with 2-pentyllithium or 2-pentylmagnesium bromide did not give any alkyl adduct, but only gave a reduced product, which consists of a single isomer and is identical with the reduction product of **19** with sodium borohydride (identified by ^{1}H NMR). Among all the products from **19**, **21** was only a compound showing fully separated peaks on ^{1}H NMR to allow the stereochemical analysis. By the NOESY spectrum of **21**, *ortho*-phenyl proton was proved to be close to H3 and H7, and H5 is close to H7 and a methyl of the TBS group, which is also close to H3. The NOE signals unambiguously

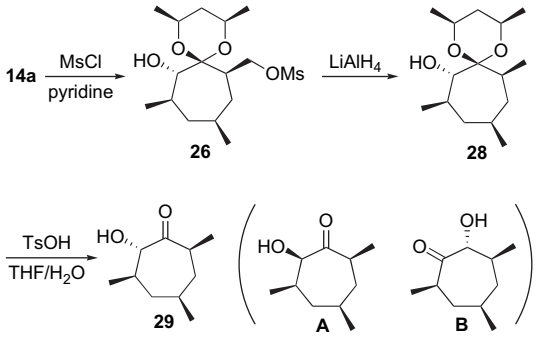


Scheme 6.

indicate the stereodirection of the phenyl addition to **19** in addition to the stereochemistry at the remaining four carbons that were carried over from the hydrogenation product **14a**. The stereochemistry of the nucleophilic addition was not further studied because asymmetric center generated at C1 is disappeared by the following ring cleavage step.

After deprotection of **21** with TBAF (95%), the trans-vicinal diol in **23** was cleaved to give **25** either by the lead tetraacetate oxidation (91%) or with sodium periodate in a mixture of acetic acid, acetone, and water (92%). Again, stereoisomerization was not observed during the conversion. Similarly, **20** was converted to **24** by the deprotection (50%, not optimized) and the periodate oxidation (87%). The obtained **24** could be an intermediate for (−)-lardolure, aggregation pheromone of an acarid mite,[12] formally via an introduction of a methyl at C8, removable of two oxygen atoms at C7 and C6 methylene, and the Baeyer–Villiger oxidation at C1.

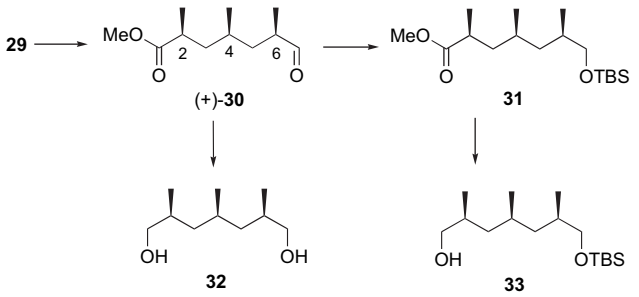
Hydroxy group in **24** can be utilized in the following reactions as a stereodirecting group and/or as an elimination group. However, it is not necessary for most of the polypropionates, and thus, we developed an additional conversion process where the deoxygenation was performed prior to the ring cleavage. Stereochemically pure **14a** was converted to **26** by mono-methanesulfonylation (73%), and the following reduction with lithium aluminum hydride in ether at 0 °C resulted in **28** in 91% yield (Scheme 7). The hydrolysis of **28** by the TsOH catalysis in THF/H_2O at room temperature resulted in **29** (=**2**: X=H) in 79% yield, where the ^{1}H NMR did not show existence of any diastereomer. It should be noted that acyloin might cause epimerization through an enol tautomer. Epimer **A** is a diastereomer of **29**, but epimer **B** generated via the same enol intermediate is an enantiomer of **29** and can be overlooked during the formation and reaction of **29**.



Scheme 7.

Oxidative cleavage of **29** with lead tetraacetate in benzene/methanol proceeded smoothly to give (+)-**30** as the sole product in 74% yield (Scheme 8). Aldehyde at C7 is a convenient end-group to expand it to preferred larger compounds by Wittig or aldol condensation, but in this study, selective reduction was demonstrated. When **30** was treated with sodium borohydride in methanol, **31** was obtained in 94% yield after TBS protection, while reduction of **30** with lithium aluminum hydride in ether resulted in diol **32** in 65% yield. The symmetric structure of **32** showing only six peaks in the ^{13}C NMR spectrum verifys the stereochemistry

of the hydrogenation of **3**. Ester **31** was reduced to **33**, which was identical to that obtained by the mono-TBS protection of **32**. GLC analysis of **33** derived from **32** with a chiral capillary column showed two separated peaks in a 1:1 ratio, while **33** derived from **31** showed a single peak, which indicates enantiomeric purity of **33** as well as that of **29**–**31** to be >99%. This clearly indicates the absence of epimerization during the formation and reaction of **29**. Overall, the optically active (+)-**30**, a common synthon for deoxypolypropionates, was synthesized in 11 steps from 3,5-dimethylphenol in 22% yield.[13]



Scheme 8.

5. Conclusion

In the present study, we have demonstrated that the optically active cycloheptatriene prepared from 3,5-dimethylphenol can be converted into several deoxypolypropionate units under sufficient stereocontrol. The hydrogenation of the diene substrate **3** was not regioselective in the first step, but gave a 98% pure stereoisomer after the full saturation. The results indicate that the hydroxy direction can overcome the multiple reaction pathways in the hydrogenation of diene, when the hydroxy group is properly incorporated in the diene though the tuning of the catalysis conditions is still necessary. The hydroxy group must work to direct the substrate in the absorption process to result in the stereoselectivities, but the stereocontrolled absorption does not cause the regioselectivity in the hydrogenation.

6. Experimental

6.1. General

All new compounds were characterized by NMR spectrometry using a JEOL EXcaliber-400 spectrometer at 400 MHz for the proton spectra and 100 MHz for the carbon spectra, and by IR with a JASCO FT/IR-410 spectrophotometer. The NMR spectra were also obtained by a JEOL ECA-600 spectrometer at 600 MHz for the proton spectra and 150 MHz for the carbon spectra. Optical rotations were measured with a Perkin–Elmer 241 or 243B polarimeter. High resolution mass spectrum was obtained by a JEOL JMS-AX505HF for electron impact ionization (EI) or a JEOL JMS-T100LC for electrospray ionization (ESI). Analytical GLC was performed on a Shimadzu GC17A with a proper capillary column under the digital flow control. All solvents were purified by distillation with proper drying agents. Raney nickel (RNi) was freshly prepared as W-2 type from an alloy ND type (Ni/Al=42:58) obtained by courtesy of Kawaken Fine Chemical Co. Ltd, Japan. RNi was also prepared from the NDH type (Ni/Al=50:50), and was treated in an aqueous solution of glycolic acid (1%, 100 °C, 1 h) before use. Palladium on carbon (5%) and platinum on alumina (5%) were used as received (Aldrich). Theoretical calculations were carried out by MOPAC-02 at the PM5 level using Fujitsu CAChe WorkSystem V5.

6.1.1. Synthesis of 5. To a mixture of 3,5-dimethylphenol (20.03 g), (*R*,*R*)-2,4-pentanediol (22.3 g, >99.5% ee, 1.3 equiv), and triphenylphosphane (47.6 g, 1.1 equiv) in anhydrous THF (400 mL) was added a solution of diisopropyl azodicarboxylate (35.4 mL, 1.1 equiv) in anhydrous THF (300 mL) in 5 h at room temperature under successive stirring. After stirring for 21 h, the mixture was concentrated, and treated with hexane. The generated crystal of triphenylphosphane oxide was removed by filtration through a Celite pad, and then filtrate was concentrated. Silica-gel column chromatography (elution with 20% ethyl acetate in hexane) of the residue afforded 33.51 g of a colorless oil (98% yield of mono-dimethylphenyl ether). $[\alpha]_D^{20}$ +14.6 (*c* 1.20, MeOH); IR (KCl, neat) 3400, 2980, 1620, 1480, 1380, 1320, 1230, 1160, 1080, 1060, 1010, 960, 920, 840, 740, 700, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.60 (s, 1H), 6.52 (s, 2H), 4.59 (m, 1H), 4.05 (m, 1H), 3.24 (br s, 1H), 2.31 (s, 6H), 2.02 (ddd, *J*=14.2, 6.3, 5.9 Hz, 1H), 1.66 (ddd, *J*=14.2, 8.3, 4.9 Hz, 1H), 1.32 (d, *J*=5.9 Hz, 3H), 1.26 (d, *J*=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.00, 138.78, 122.55, 113.69, 72.85, 66.14, 45.37, 23.46, 21.17, 19.74, 17.84; HRMS (EI) *m*/*z* (M^+) calcd for $C_{13}H_{12}O_2$ 208.1463, found 208.1502.

To a solution of the above compound (20.0 g) and triethylamine (4 mL, 0.3 equiv) in dry dichloromethane (240 mL) was added diketene (8.9 mL, 1.2 equiv) under cooling with a water bath. After 8 h, the mixture was washed with water (×3). Re-extraction with dichloromethane and the washing process was repeated in three times and the combined organic layers were dried over sodium sulfate. Concentration and purification by column chromatography on silica-gel (elution with 20% ethyl acetate in hexane) gave 25.69 g of a colorless oil (91% yield of the acetoacetate ester). $[\alpha]_D^{20}$ +22.9 (*c* 1.05, MeOH); IR (KCl, neat) 2950, 2920, 1750, 1720, 1640, 1620, 1600, 1460, 1420, 1380, 1360, 1329, 1300, 1270, 1260, 1180, 1160, 1100, 1060, 1040, 960, 880, 840, 700, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.55 (s, 1H), 6.52 (s, 2H), 5.17 (m, 1H), 4.47 (m, 1H), 3.39 (s, 3H), 2.26 (s, 3H), 2.19 (s, 3H), 2.13 (ddd, *J*=14.2, 7.3, 6.4 Hz, 1H), 1.70 (ddd, *J*=14.2, 11.7, 5.9 Hz, 1H), 1.31 (d, *J*=5.9 Hz, 3H), 1.28 (d, *J*=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.77, 166.05, 157.17, 138.55, 122.07, 113.12, 69.73, 69.18, 49.83, 42.04, 29.61, 21.06, 19.86, 19.47; HRMS (EI) *m*/*z* (M^+) calcd for $C_{17}H_{24}O_4$ 292.1675, found 292.1699.

To a solution of the acetoacetate ester (6.60 g) and tosyl azide (5.79 g, 1.3 equiv) in dry acetonitrile (230 mL), triethylamine (8.2 mL, 2.6 equiv) was added in 10 min at 0 °C. After 3 h, aqueous sodium hydroxide (1 mol dm^{-3}, 120 mL) was added, and the mixture was allowed to stand for 10 h at room temperature. The mixture was extracted with ether (×3), and the combined extracts were washed

with aqueous sodium hydroxide (1 mol dm^{-3}) and brine, and then dried over sodium sulfate. Concentration and purification by column chromatography on silica-gel (elution with 20% ethyl acetate in hexane) gave 5.57 g of **5** as a colorless oil (89% yield). $[\alpha]_D^{20}$ +8.70 (*c* 1.4, MeOH); IR (KCl, neat) 3100, 3000, 2920, 2100, 1700, 1620, 1600, 1480, 1380, 1320, 1300, 1250, 1200, 1180, 1160, 1120, 1100, 1060, 1040, 1010, 980, 840, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.59 (s, 1H), 6.53 (s, 2H), 5.22 (m, 1H), 4.74 (br s, 1H), 4.49–4.41 (m, 3H), 2.30 (s, 6H), 2.17 (ddd, *J*=14.2, 7.8, 6.4 Hz, 1H), 1.71 (ddd, *J*=14.2, 6.4, 5.4 Hz, 1H), 1.34 (d, *J*=6.4 Hz, 3H), 1.31 (d, *J*=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.28, 19.83, 138.83, 122.22, 113.22, 70.04, 68.96, 46.15, 42.50, 21.42, 20.58; HRMS (EI) *m/z* (M^+) calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1441.

6.1.2. Synthesis of 4. A solution of **5** (3.08 g) in dry dichloromethane (160 mL) was added dropwise to rhodium-(II) acetate (ca. 10 mg) in dichloromethane (40 mL) in 5 h at room temperature, and the mixture was additionally stirred for 1 h. Concentration and purification by column chromatography on silica-gel (elution with 30% ethyl acetate in hexane) gave 2.66 g of **4** as colorless solid (97% yield). Mp 67.5–69.0 °C; $[\alpha]_D^{20}$ +82.3 (*c* 0.96, MeOH); IR (KCl, neat) 3200, 2980, 2920, 2880, 1720, 1710, 1620, 1610, 1490, 1440, 1400, 1380, 1360, 1320, 1240, 1180, 1160, 1140, 1130, 1080, 1050, 1020, 1000, 940, 880, 840, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.25 (s, 1H), 5.70 (d, *J*=5.4 Hz, 1H), 5.68 (s, 1H), 4.82 (m, 1H), 4.27 (m, 1H), 3.05 (d, *J*=5.4 Hz, 1H), 2.02 (s, 3H), 1.97 (ddd, *J*=15.6, 6.3, 3.9 Hz, 1H), 1.85 (s, 3H), 1.81 (dd, *J*=15.6, 3.9 Hz, 1H), 1.33 (d, *J*=6.3 Hz, 3H), 1.32 (d, *J*=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.98, 150.08, 135.09, 133.42, 129.49, 115.45, 113.60, 84.32, 72.98, 46.75, 45.34, 24.35, 22.49, 22.09, 21.25; HRMS (EI) *m/z* (M^+) calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1453.

6.1.3. Synthesis of 6. A solution of **4** (7.43 g) in anhydrous ether (300 mL) was cooled to 0 °C, and lithium aluminum hydride (1.38 g, 4.8 equiv) was added to this solution. After 2 h, a small amount of water was carefully added to the mixture. The mixture was extracted with ether (×3), washed with water and then brine, dried over sodium sulfate, and concentrated to give 7.12 g of **6** as a colorless oil (87%), which was enough pure for the next reaction. $[\alpha]_D^{20}$ −25.0 (*c* 1.14, MeOH); IR (KCl, neat) 3400, 2980, 2920, 2900, 2880, 1720, 1610, 1540, 1450, 1400, 1380, 1340, 1320, 1260, 1220, 1160, 1120, 1040, 950, 920, 840, 800, 760, 660 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.03 (s, 1H), 5.19 (s, 1H), 4.68 (d, *J*=6.3 Hz, 1H), 4.41 (m, 1H), 3.98 (m, 1H), 3.92 (dd, *J*=10.7, 9.8 Hz, 1H), 3.73 (dd, *J*=10.7, 4.9 Hz, 1H), 2.58 (br s, 2H, OH), 2.27 (ddd, *J*=9.8, 5.4, 4.9 Hz, 1H), 2.02 (s, 3H), 1.87 (m, PD–CH_2), 1.82 (s, 3H), 1.62 (ddd, *J*=12.2, 3.9, 2.4 Hz, 1H, PD–CH_2), 1.21 (d, *J*=6.3 Hz, 3H), 1.16 (d, *J*=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.42, 138.35, 128.79, 125.60, 118.28, 65.69, 61.44, 49.77, 40.37, 37.36, 25.01, 22.18, 22.13, 22.02; HRMS (EI) *m/z* (M^+) calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1697.

6.1.4. Synthesis of 7. A mixture of **6** (10.08 g) and pyridinium *p*-toluenesulfonate (900 mg) in dry THF was stirred for 5 h at room temperature. The mixture was washed with saturated sodium carbonate and purified by silica-gel column chromatography (elution with 30% ethyl acetate in hexane) to give **7** as a colorless oil (8.65 g, 84.0%). The reactions in a smaller scale (1–3 g) resulted in better yields (up to 91.3%). $[\alpha]_D^{20}$ +373 (*c* 1.0, methanol); IR (KCl, neat) 3550, 2980, 2920, 2880, 1450, 1390, 1350, 1120, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.72 (dd, $J_{8,7}$=4.4 Hz, $J_{8,9Me}$=1.5 Hz, 1H, H-8), 5.69 (s, 1H, H-5), 4.05 (m, 1H), 3.92 (ddd, $J_{7CH,7CH'}$=11.2 Hz, $J_{7CH,OH}$= 3.4 Hz, $J_{7CH,7}$=2.9 Hz, 1H, CH-7), 3.87 (m, 1H), 3.54 (ddd, $J_{7CH',7CH}$=11.2 Hz, $J_{7CH',OH}$=8.3 Hz, $J_{7CH',7}$=5.9 Hz, 1H, CH′-7), 3.11 (dd, $J_{OH,7CH'}$=8.3 Hz, $J_{OH,7CH}$=3.4 Hz, 1H, OH), 2.84 (d, $J_{12,12'}$=12.7 Hz, 1H, H-12), 2.10 (m, 1H, H-2), 1.96 (d, $J_{12',12}$=12.7 Hz, 1H, H-12′), 1.79 (d, $J_{9Me,8}$=1.5 Hz, 3H, CH_3-9), 1.67 (s, 3H, CH_3-11), 1.47 (dt, *J*=13.2, 2.4 Hz, 1H), 1.10 (d, *J*=5.9 Hz, 3H), 1.08 (m, 1H), 1.07 (d, *J*=5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.1, 138.0, 128.52, 128.47, 125.6, 117.9, 65.5, 61.3, 49.8, 40.3, 37.3, 24.9, 22.1, 22.0, 21.9; HRMS (EI) *m/z* (M^+) calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1696.

6.1.5. Synthesis of 3. To a solution of **6** (2.20 g) in dry dichloromethane (160 mL) was added *m*-CPBA (87% pure, 1.65 g, 1.2 equiv) at −78 °C. The mixture was warmed up to −40 °C in 10 min, and stirred for 1 h at the same temperature. Immediately after the addition of potassium fluoride (1.5 g), the mixture was filtered through a Celite pad. The filtrate was washed with water and then brine. The water layer was extracted with dichloromethane (×3) and the extracts were washed with water and then brine. The combined dichloromethane solutions were dried over sodium sulfate, concentrated, and purified by silica-gel column chromatography (elution with 30% ethyl acetate in hexane) to give 1.22 g of **3** as a colorless oil (57% yield). $[\alpha]_D^{20}$ +126.8 (*c* 1.00, MeOH); IR (KCl, neat) 3550, 2980, 2920, 2880, 1450, 1440, 1390, 1350, 1320, 1240, 1230, 1180, 1160, 1120, 1080, 1040, 1030, 1020, 1000, 980, 920, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.72 (s, 1H), 5.58 (d, *J*=4.4 Hz, 1H), 4.55 (d, *J*=5.9 Hz, 1H), 4.53 (m, 1H), 4.34 (m, 1H), 3.98 (ddd, *J*=10.7, 3.9, 2.4 Hz, 1H), 3.54 (ddd, *J*=10.7, 7.8, 5.9 Hz, 1H), 3.11 (dd, *J*=7.8, 3.9 Hz, 1H), 2.38 (m, 1H), 2.24 (d, *J*=5.9 Hz, OH), 1.95 (s, 3H), 1.75 (s, 3H), 1.56 (td, *J*=13.2, 2.4 Hz, 1H), 1.16 (d, *J*=5.9 Hz, 3H), 1.12 (d, *J*=5.9 Hz, 3H), 1.15 (m, 1H, PD–CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.26, 134.51, 127.25, 125.67, 110.54, 77.12, 67.66, 67.20, 62.69, 48.38, 39.93, 23.73, 22.69, 22.56, 21.72; HRMS (EI) *m/z* (M^+) calcd for $C_{15}H_{24}O_4$ 268.1675, found 268.1679.

6.1.6. Preparation of 9. A mixture of **3** (177 mg), acetic anhydride (0.5 mL), pyridine (0.5 mL), and a small amount of 4-dimethylaminopyridine was stirred for 30 min. After addition of water, the mixture was extracted with ether (×3), washed with saturated ammonium chloride (×2), and dried over sodium sulfate. Concentration and purification by column chromatography on silica-gel resulted in 156 mg of **9** as a colorless oil (68% yield). $[\alpha]_D^{20}$ +179 (*c* 1.05, MeOH); IR (KCl, neat) 2973, 2935, 1741, 1442, 1374, 1229, 1198, 1175, 1119, 1090, 1024, 963, 920, 816 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.77 (s, 1H), 5.53 (s, 1H), 5.47 (d, *J*=4.4 Hz, 1H), 4.43 (dqd, *J*=12.2, 6.3, 2.4 Hz, 1H), 4.27 (dd, *J*=10.7, 3.9 Hz, 1H), 4.15 (dd, *J*=10.7, 9.3 Hz, 1H), 3.96 (dqd, *J*=12.2, 6.3, 2.4 Hz, 1H), 2.53 (m, 1H), 2.06

(s, 3H), 1.99 (s, 3H), 1.78 (s, 3H), 1.75 (s, 3H), 1.47 (ddd, *J*=13.2, 2.4, 2.4 Hz, 1H), 1.10 (d, *J*=6.3 Hz, 3H, PD–Me), 1.04 (d, *J*=6.3 Hz, 3H, PD–Me), 1.07 (ddd, *J*=13.2, 12.2, 12.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.06, 169.42, 136.18, 134.79, 128.96, 126.61, 108.75, 79.08, 67.52, 67.31, 64.96, 47.38, 39.74, 23.38, 22.61, 22.39, 21.32, 21.13, 20.93; HRMS (EI) *m/z* (M^+) calcd for $C_{19}H_{28}O_6$ 352.1886, found 352.1892.

6.1.7. Preparation of 12. To a solution of **3** (1.14 g) in dry dichloromethane (15 mL) was added a mixture of *tert*-butyldimethylsilyl chloride (749 mg, 1.3 equiv) and imidazole (730 mg, 2.6 equiv) in DMF (20 mL) and dichloromethane (100 mL) in 2.5 h. After stirring for 12 h, saturated sodium bicarbonate solution was added, and then the mixture was extracted with dichloromethane (×3), washed with saturated sodium bicarbonate (×2), and dried over sodium sulfate. Concentration and purification by column chromatography on silica-gel (10% ethyl acetate in hexane) gave **12** (800 mg) as a colorless oil (49% yield). $[\alpha]_D^{20}$ +65.4 (*c* 0.38, CH_2Cl_2); IR (KCl, neat) 3455, 2929, 2856, 1722, 1445, 1385, 1254, 1175, 1108, 1007, 948, 837, 777, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.72 (s, 1H), 5.64 (d, *J*=3.9 Hz, 1H), 4.56 (d, *J*=6.3 Hz, 1H), 4.31 (qdd, *J*=11.7, 5.9, 2.4 Hz, 1H), 4.07 (m, 1H), 4.01 (dd, *J*=9.8, 3.9 Hz, 1H), 3.60 (t, *J*=9.8 Hz, 1H), 2.51 (m, 1H), 1.97 (s, 3H), 1.91 (d, *J*=5.9 Hz, OH, 1H), 1.77 (d, *J*=1.5 Hz, 3H), 1.47 (td, *J*=12.7, 2.4 Hz, 1H), 1.16 (d, *J*=5.9 Hz, 3H), 1.05 (d, *J*=5.9 Hz, 3H), 1.03 (m, 1H), 0.87 (s, 9H), 0.04 (d, *J*=4.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.52, 137.83, 127.63, 127.31, 106.25, 75.10, 66.79, 66.45, 63.25, 48.91, 39.90, 26.02, 24.74, 22.92, 22.56, 22.25, 18.37, −5.12, −5.18; HRMS (EI) *m/z* (M^+) calcd for $C_{21}H_{38}O_4Si$ 382.2539, found 382.2575.

6.1.8. Synthesis of 10. A mixture of **12** (173.4 mg), acetic anhydride (2 mL), pyridine (3 mL), 4-dimethylaminopyridine (ca. 20 mg) was stirred for 1 h. After the addition of saturated ammonium chloride solution, the mixture was extracted with ether (×3), washed with saturated ammonium chloride solution (×2), and then dried over sodium sulfate. Concentration and purification by column chromatography on silica-gel (elution with 10% ethyl acetate in hexane) gave 112 mg of a colorless oil (58%). A solution of this compound (99.6 mg) in THF (3 mL) was treated with TBAF (ca. 150 mg) for 9 h. Extraction with ether (×3), washed with water (×2), dried over sodium sulfate, and purification by silica-gel column chromatography (elution with 20% ethyl acetate in hexane) afforded 26.5 mg of **10** as a colorless oil (37% yield). $[\alpha]_D^{20}$ +148.7 (*c* 1.2, CH_2Cl_2); IR (KCl, neat) 3545, 2971, 2933, 1745, 1443, 1373, 1235, 1184, 1131, 1075, 1050, 1023, 963, 918, 842 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.79 (s, 1H), 5.66 (s, 1H), 5.58 (d, *J*=4.1 Hz, 1H), 4.47 (dqd, *J*=6.2, 5.5, 2.8 Hz, 1H), 4.03 (dqd, *J*=6.2, 5.5, 2.8 Hz, 1H), 3.96 (ddd, *J*=11.0, 4.1, 2.1 Hz, 1H), 3.71 (ddd, *J*=11.0, 7.6, 6.2 Hz, 1H), 3.09 (dd, *J*=7.6, 4.1 Hz, 1H, OH), 2.46 (ddd, *J*=6.2, 4.1, 2.1 Hz, 1H), 2.09 (s, 3H), 1.83 (s, 3H), 1.80 (dd like, 3H), 1.58 (ddd, *J*=13.7, 2.8, 2.8 Hz, 1H), 1.15 (d, *J*=5.5 Hz, 3H, PD–Me), 1.13 (d, *J*=5.5 Hz, 3H, PD–Me), 1.14 (ddd, *J*=13.7, 6.2, 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 169.74, 48.83, 134.74, 134.42, 129.36, 125.75, 108.75, 77.05, 67.73, 67.05, 62.73, 39.65, 24.01, 22.52, 22.48, 21.73, 21.31; HRMS (ESI) *m/z* ($M+Na^+$) calcd for $C_{17}H_{26}O_5Na$ 333.1678, found 333.1625.

6.1.9. Preparation of 11. To a solution of **3** (245.5 mg) and collidine (0.19 mL, 2 equiv) in dry dichloromethane (8 mL) was added acetyl chloride (0.05 mL, 1 equiv) at once. After 5 h, collidine (0.19 mL) and acetyl chloride (0.05 mL) were added again. After 1 h, saturated sodium bicarbonate solution was added, and the mixture was extracted with dichloromethane (×3), washed with water (×2), dried over sodium sulfate, and then purified by column chromatography on silica-gel to result in 115 mg of **11** as white solid (41% yield). Mp 91.0–94.0 °C; $[\alpha]_D^{20}$ +279 (*c* 0.95, MeOH); IR (KCl, neat) 3487, 2971, 1739, 1444, 1386, 1251, 1193, 1156, 1038, 949, 837, 813, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74 (s, 1H), 5.47 (d, *J*=3.9 Hz, 1H), 4.55 (d, *J*=5.4 Hz, 1H), 4.46 (dqd, *J*=11.7, 5.9, 2.4 Hz, 1H), 4.33 (dd, *J*=10.7, 3.9 Hz, 1H), 4.27 (dqd, *J*=11.2, 6.3, 2.4 Hz, 1H), 4.19 (dd, *J*=10.7, 9.3 Hz, 1H), 2.58 (ddd, *J*=9.3, 3.9, 3.9 Hz, 1H), 2.02 (s, 3H), 1.97 (d, *J*=1.0 Hz, 3H), 1.86 (d, *J*=5.4 Hz, 1H, OH), 1.76 (dd like, 3H), 1.49 (ddd, *J*=13.2, 2.4, 2.4 Hz, 1H), 1.15 (d, *J*=5.9 Hz, 3H, PD–Me), 1.08 (d, *J*=6.3 Hz, 3H, PD–Me), 1.08 (ddd, *J*=13.2, 11.7, 11.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.5, 139.8, 134.5, 127.3, 126.4, 109.2, 77.8, 67.4, 67.2, 65.2, 46.3, 39.6, 23.5, 22.6, 22.3, 21.4, 21.2; HRMS (EI) *m/z* (M^+) calcd for $C_{17}H_{26}O_5$ 310.1780, found 310.1785.

6.1.10. Hydrogenation of 3 to give 14a. Analytical runs were performed with 5±0.5 mg of **3** in 3 mL of a solvent in the presence of a catalyst (500 mg of RNi, 10 mg of Pd/C or 10 mg of Pt/Al_2O_3) under hydrogen atmospheric pressure. The mixture was analyzed by GLC after converting to the diacetate analogues by the treatment with acetic anhydride/pyridine. The major isomer **14a** shows a peak at 38.1 min with a TC-1 column (30 m×0.25 mm, 135 °C, 30 cm s^{-1}), while the other minor isomer **14b** shows a peak at 41.3 min. Synthetic run was performed with 976 mg of **3** over 0.6 g of the Raney nickel in ethyl acetate (5 mL) to give a colorless solid (1.05 g, 98%). Stereochemically pure **14a** was obtained by the recrystallization of the hydrogenation mixture from hexane/ether (=8:2) in 78% yield. Mp 92.0–93.9 °C; $[\alpha]_D^{20}$ +55.8 (*c* 0.88, MeOH); IR (KCl, neat) 3441, 3349, 2950, 1454, 1422, 1388, 1371, 1310, 1270, 1253, 1224, 1180, 1146, 1105, 1083, 1062, 1031, 996, 953, 933, 898, 874, 849, 835, 752, 690, 618 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.13 (m, 1H), 4.08 (m, 1H), 3.88 (d, *J*=7.6 Hz, 1H), 3.79 (dd, *J*=11.0, 7.6 Hz, 1H), 3.38 (dd, *J*=11.0, 2.1 Hz, 1H), 2.97 (br s, OH), 2.25 (br s, OH), 2.16 (m, 1H), 1.65 (m, 1H), 1.59 (dt, *J*=13.7, 2.1 Hz, 2H), 1.47 (m, 1H), 1.37 (m, 1H), 1.25 (dt, *J*=13.7, 2.1 Hz, 1H), 1.20 (m, 1H), 1.15 (m, 1H), 1.22 (d, *J*=6.2 Hz, 3H), 1.17 (d, *J*=6.2 Hz, 3H), 1.09 (d, *J*=6.9 Hz, 3H), 0.85 (d, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 103.71, 71.71, 66.38, 66.20, 65.18, 43.38, 39.50, 38.83, 35.81, 35.18, 24.08, 23.15, 22.20, 21.95; HRMS (EI) *m/z* (M^+) calcd for $C_{15}H_{28}O_4$ 272.1988, found 272.1976; Anal. calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Obsd C, 65.81; H, 10.40.

6.1.11. Isolation of the hydrogenation intermediate 15a. The hydrogenation of **3** (28 mg) over Raney nickel (0.5 g) was interrupted for 2 min. Column chromatography of this

mixture allowed to isolate 3.2 mg of **15a** (12% yield), but other two intermediates **15b** and **15c** were not separated from **14a**. Both **15a** and the mixture of **15b** and **15c** were converted to **14a** by the same hydrogenation. $[\alpha]_D^{20}$ −114.9 (*c* 0.49, CH_2Cl_2); IR (KCl, neat) 3474, 3364, 2965, 1444, 1415, 1385, 1175, 1129, 1109, 1043, 1005, 987, 941, 910, 861, 842 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.51 (s, 1H), 4.68 (s, 1H), 4.18 (m, 1H), 3.95 (m, 1H), 3.77–3.71 (m, 2H), 3.09 (dd, *J*=11.0, 5.5 Hz, 1H), 2.70 (m, 1H), 2.43 (ddd, *J*=12.4, 5.5, 2.7 Hz, 1H), 1.83 (s, 3H), 1.65–1.57 (m, 3H), 1.27 (d, *J*=13.7 Hz, 1H), 1.23 (d, *J*=6.2 Hz, 3H), 1.15 (d, *J*=6.2 Hz, 3H), 0.97 (d, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.35, 132.42, 102.24, 69.94, 66.77, 65.87, 65.28, 46.05, 39.85, 36.02, 30.80, 25.75, 23.76, 22.29; HRMS (EI) *m/z* (M^+) calcd for $C_{15}H_{26}O_4$ 270.1831, found 270.1856.

6.1.12. Synthesis of 16 from 14a. A mixture of **14a** (50.5 mg), *p*-toluenesulfonic acid (ca. 20 mg), and water (0.1 mL) in THF (2 mL) was stirred for 13.5 h. After the extraction with dichloromethane (×3), the organic layer was dried over sodium sulfate and concentrated to give essentially pure **16** as a colorless oil (33.8 mg, 98% yield). $[\alpha]_D^{20}$ +94.3 (*c* 0.44, MeOH); IR (KCl, neat) 3290, 2960, 2898, 1703, 1456, 1376, 1072, 1047, 1015, 968, 852 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 4.00 (dd, $J_{1,2}$=10.3 Hz, $J_{1,OH}$=5.5 Hz, 1H, H-1), 3.78 (ddd, $J_{7,7'}$=15.1 Hz, $J_{7,OH}$=7.6 Hz, $J_{7,6}$=4.8 Hz, 1H, H-7), 3.69 (ddd, $J_{7,7'}$=15.1 Hz, $J_{7',OH}$=4.1 Hz, $J_{7',6}$= 6.2 Hz, 1H, H-7′), 3.55 (d, $J_{1,OH}$=5.5 Hz, 1H, OH-1), 2.66 (m, 1H, H-6), 2.05 (dd, $J_{7,OH}$=7.6 Hz, $J_{7',OH}$=4.1 Hz, 1H, OH-7), 1.82 (ddd, $J_{3,3'}$=14.4 Hz, *J*=7.6, 4.8 Hz, 1H, H-3), 1.64 (ddd, $J_{5,5'}$=12.4 Hz, *J*=4.1, 2.1 Hz, 1H, H-5), 1.61–1.52 (m, 3H, H-2, 4, 5′), 1.19 (m, 1H, H-3′), 1.11 (d, $J_{2,Me\text{-}2}$= 6.2 Hz, 1H, Me-2), 1.00 (d, $J_{4,Me\text{-}4}$=6.2 Hz, 1H, Me-4); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 216.34, 80.25, 65.18, 52.49, 46.34, 37.90, 35.20, 34.04, 24.46, 19.60; HRMS (EI) *m/z* (M^+) calcd for $C_{10}H_{18}O_3$ 186.1256, found 186.1247.

6.1.13. Synthesis of 18 by the $Pb(OAc)_4$ oxidation of 16. Lead tetraacetate (1.28 g, 6 equiv for **16**) was washed with anhydrous ether (5 mL×2) in a flask. A solution of **16** (92.3 mg) in dry benzene (10 mL) and then dry methanol (10 mL) were added to the flask. After 10 min, water was added. The mixture was extracted with ether (×4), washed with water (×2) and then brine, dried over sodium sulfate, and concentrated to give 150 mg of crude **18**. This was purified by column chromatography on silica-gel (elution with 60% ethyl acetate in hexane) to give 85.6 mg of **18** as a colorless solid (80% yield). $[\alpha]_D^{20}$ +7.0 (*c* 0.34, CH_2Cl_2); IR (KCl, neat) 3454, 2956, 1731, 1461, 1381, 1172, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 9.56 (d, $J_{1,2}$=2.1 Hz, 1H, H-1), 3.71 (m, 2H, H-7), 3.70 (s, 3H, H-8), 2.70 (m, 1H, H-6), 2.44 (m, *J*=2.1 Hz, 1H, H-2), 2.06 (br s, 1H, OH-7), 1.72–1.66 (m, 2H, H-3, 5), 1.50 (m, 1H, H-4), 1.19 (ddd, *J*=13.7, 8.9, 4.8 Hz, 1H, H-5′), 1.14 (m, 1H, H-3′), 1.06 (d, $J_{2,Me\text{-}2}$=6.9 Hz, 3H, Me-2), 0.92 (d, $J_{4,Me\text{-}4}$=6.9 Hz, 3H, Me-4); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 204.98, 175.66, 63.99, 51.85, 45.36, 43.90, 38.00, 35.46, 28.43, 19.78, 13.97; HRMS (EI) *m/z* (M^+) calcd for $C_{11}H_{20}O_4$ 216.1362, found 216.1361.

6.1.14. Synthesis of 17. Oxidation was performed similar to that of **16** to give **18** except for mono protection with a TBS group prior to the oxidation (62% in two steps). $[\alpha]_D^{20}$ −26.9 (*c* 0.65, CH_2Cl_2); IR (KCl, neat) 2955, 2857, 1738, 1462, 1385, 1256, 1171, 1103, 838, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 9.56 (d, *J*=2.1 Hz, 1H), 3.72 (m, 1H), 3.65 (d, *J*=4.8 Hz, 3H), 3.62 (m, 1H), 2.72–2.66 (m, 2H), 2.53 (m, 1H), 2.42 (m, 1H), 1.68–1.57 (m, 2H), 1.16 (m, 1H), 1.14 (d, *J*=6.9 Hz, 3H), 0.90 (dd, *J*=6.9, 1.4 Hz, 3H), 0.84 (d, *J*=2.1 Hz, 9H), 0.00 (dd, *J*=5.5, 2.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 205.09, 175.18, 64.72, 51.47, 46.46, 43.91, 41.06, 35.22, 28.64, 25.74, 19.74, 18.15, 17.31, −5.53, −5.56; HRMS (EI) *m/z* (M^+) calcd for $C_{17}H_{34}O_4Si$ 330.2226, found 330.2224.

6.1.15. Synthesis of 19. To a mixture of *tert*-butyldimethylsilyl chloride (333 mg, 5.1 equiv), imidazole (304 mg, 10.4 equiv) and 4-dimethylaminopyridine (25 mg) in dry dimethylformamide (5 mL) was added **16** (79.7 mg). The mixture was stirred for 14 h at room temperature. The reaction mixture was poured into ice-water, and extracted with ether (×3). The combined extracts were washed with water (×2), dried over potassium carbonate, and concentrated under vacuum to give a yellow oil (221.4 mg). The oil was purified by a short silica-gel column (elution with 10% ethyl acetate in hexane) to give TBS ether **19** (176 mg, 98.8% yield). $[\alpha]_D^{20}$ +11.48 (*c* 0.63, CH_2Cl_2); IR (KCl, neat) 2955, 2929, 2858, 1714, 1462, 1389, 1362, 1254, 1102, 1006, 940, 837, 778, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.74 (dd, *J*=9.6, 6.2 Hz, 1H), 3.58 (d, *J*=6.2 Hz, 1H), 3.57 (d, *J*=9.6, 6.2 Hz, 1H), 3.08 (m, 1H), 1.94 (d, *J*=13.7 Hz, 1H), 1.72 (m, 1H), 1.47 (dd, *J*=13.7, 2.1 Hz, 1H), 1.00 (d, *J*=6.2 Hz, 3H), 0.98–0.90 (m, 2H), 0.89 (d, *J*=6.2 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), −0.02 (s, 6H), −0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 213.08, 83.84, 64.06, 43.02, 39.49, 38.38, 34.00, 26.00, 25.78, 25.69, 24.00, 20.58, 18.44, 18.16, 18.12, −2.96, −4.58, −5.07, −5.37; HRMS (ESI) *m/z* (M+Na^+) calcd for $C_{22}H_{46}O_3Si_2Na$ 437.2883, found 437.2852.

6.1.16. Synthesis of 20. To a solution of **19** (9.6 mg) in ether (1 mL) was added a solution of butyllithium (2.4 mol dm^{-3} in hexane, 0.23 mL, 24 equiv) at room temperature. After 1.5 h, the reaction mixture was poured into water, and extracted with ether (×3). The combined extracts were washed with water and brine, dried over sodium sulfate, and concentrated under vacuum to give a colorless oil (12.9 mg). The oil was purified by silica-gel column chromatography (elution with 6% ethyl acetate in hexane) to give **20** (8.2 mg, 78% yield). The adduct **20** was added to a solution of tetrabutylammonium fluoride (230 mg, 4.9 equiv) in THF (5 mL) at room temperature. The mixture was stirred for 3 h at room temperature, poured into water, and extracted with ether (×3). The combined extracts were washed with water (×1) dried over sodium sulfate, and concentrated under vacuum to give a brown oil (55 mg). The oil was purified by silica-gel column chromatography (elution with 30% ethyl acetate in hexane) to give **22** as a dark brown oil (22.1 mg, 50.2% yield). $[\alpha]_D^{20}$ −28.0 (*c* 0.48, CH_2Cl_2); IR (KCl, neat) 3404, 2955, 2927, 2871, 1795, 1712, 1458, 1377, 1260, 1119, 1040, 885, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.80 (dd, *J*=11.0, 8.2 Hz, 1H), 3.69 (dd, *J*=11.0, 3.4 Hz, 1H), 3.49 (d, *J*=10.3 Hz, 1H), 2.06 (m, 1H), 1.71–1.64 (m, 4H), 1.56–1.50 (m, 2H), 1.45 (m, 1H), 1.37–1.22 (m, 4H), 1.14 (m, 1H), 1.01 (d, *J*=6.9 Hz, 1H), 0.97 (m, 1H), 0.90 (t,

J=6.9 Hz, 3H), 0.87 (d, J=6.9 Hz, 3H), 0.86–0.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 80.38, 79.75, 66.84, 44.79, 43.73, 35.38, 35.28, 32.96, 25.78, 25.15, 23.59, 20.05, 14.11; HRMS (ESI) m/z (M+Na$^+$) calcd for $C_{14}H_{28}O_3Na$ 267.1936, found 267.1891.

6.1.17. Synthesis of 21. To a solution of **19** (130 mg) in ether (10 mL) was added phenyllithium (1 M, 1.6 mL, 5 equiv) at −78 °C. After the mixture was warmed up to room temperature over 2 h, the reaction mixture was poured into water, and extracted with ether (×3). The combined extracts were washed with water (×1) and brine (×1), dried over sodium sulfate, and concentrated under vacuum to give a pale yellow oil (129.5 mg). The oil was purified by MPLC (elution with 2% ethyl acetate in hexane) to give **21** as a colorless oil (89.3 mg, 58.4% yield). $[\alpha]_D^{20}$ −17.9 (c 1.30, CH_2Cl_2); IR (KCl, neat) 3473, 2953, 2928, 2857, 1471, 1389, 1255, 1061, 1006, 935, 834, 776, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.45 (d, J=7.6 Hz, 2H), 7.22 (t, J=7.6 Hz, 2H), 7.13 (t, J=7.6 Hz, 1H), 4.25 (s, OH), 3.57 (d, J=4.8 Hz, 1H), 3.54 (dd, J=9.6, 2.1 Hz, 1H), 3.39 (dd, J=9.6, 2.1 Hz, 1H), 2.32 (dd, J=10.3, 2.1 Hz, 1H), 2.07 (m, 1H), 1.94 (ddd, J=13.7, 10.3, 2.7 Hz, 1H), 1.89 (m, 1H), 1.69 (dt, J=13.7, 2.1 Hz, 1H), 1.50 (dd, J=13.7, 2.1 Hz, 1H), 1.40 (ddd, J=13.7, 10.3, 2.1 Hz, 1H), 0.96 (d, J=6.2 Hz, 3H), 0.95 (d, J=6.2 Hz, 3H), 0.78 (s, 9H), 0.71 (s, 9H), −0.09 (s, 3H), −0.16 (s, 3H), −0.23 (s, 3H), −0.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 148.15, 127.14, 126.25, 125.71, 84.86, 83.46, 68.64, 46.30, 43.08, 38.83, 38.70, 32.83, 26.04, 25.77, 24.89, 21.61, 18.07, 18.04, 18.03, −4.17, −4.34, −6.03; HRMS (ESI) m/z (M+Na$^+$) calcd for $C_{28}H_{52}O_3Si_2Na$ 515.3353, found 515.3322.

6.1.18. Synthesis of 23. Phenyl adduct **21** (89 mg) was added to a solution of tetrabutylammonium fluoride (238 mg, 5.1 equiv) in THF (10 mL) at room temperature. The mixture was stirred for 5 h at room temperature. The reaction mixture was poured into water, and extracted with ether (×3). The combined extracts were washed with water (×1), dried over sodium sulfate, and concentrated under vacuum to give a colorless oil (64.1 mg). The oil was purified by silica-gel column chromatography (elution with 30% ethyl acetate in hexane) to give **23** (45.1 mg, 94.8% yield). $[\alpha]_D^{20}$ −15.7 (c 0.88, CH_2Cl_2); IR (KCl, neat) 3399, 2952, 2928, 1601, 1494, 1456, 1376, 1134, 1045, 949, 876, 844, 757, 708, 626 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.50 (d, J=7.6 Hz, 2H), 7.35 (t, J=7.6 Hz, 2H), 7.27 (t, J=7.6 Hz, 1H), 3.83 (br s, OH), 3.61 (t, J=8.9 Hz, 1H), 3.50 (dd, J=10.3, 2.7 Hz, 1H), 3.38 (d, J=10.3 Hz, 1H), 2.78 (br s, OH), 2.15–2.08 (m, 2H), 1.84 (dt, J=13.7, 2.1 Hz, 1H), 1.77 (m, 1H), 1.70 (m, 1H), 1.63 (d, J=13.7 Hz, 1H), 1.09 (m, 1H), 1.00 (d, J=6.2 Hz, 3H), 0.84 (d, J=6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 142.94, 128.35, 127.39, 126.55, 84.64, 84.51, 65.72, 48.41, 47.48, 36.68, 34.54, 34.12, 23.99, 18.85; HRMS (ESI) m/z (M+Na$^+$) calcd for $C_{16}H_{24}O_3Na$ 287.1623, found 287.1627.

6.1.19. Reaction of 19 with 2-PenMgBr or $NaBH_4$. 2-Pentylmagnesium bromide (0.2 mL of 1 mol dm^{-3} solution in ether) was added to a stirred solution of **19** (11.3 mg) in ether (1 mL) at room temperature under nitrogen. The mixture was stirred for 2 h, then quenched with water and extracted with ether. The combined organic layers were dried and evaporated to give a reduced product (9.6 mg, 84% yield). Separately, sodium borohydride was added to a stirred solution of **19** (3.2 mg) in MeOH (1 mL) at room temperature under nitrogen. The mixture was stirred for 1 h, then quenched with water and extracted with ether. The combined organic layers were dried and evaporated to give reduction product (87% yield). The products obtained by both the methods were identical by the ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.92 (d, J=2.7 Hz, 1H), 3.68 (dd, J=9.6, 4.1 Hz, 1H), 3.61 (dd, J=9.6, 3.4 Hz, 1H), 3.32 (dd, J=8.2, 2.7 Hz, 1H), 2.72 (br s, 1H), 1.92 (ddd, J=12.4, 2.1, 1.4 Hz, 1H), 1.67–1.55 (m, 3H), 1.41–1.36 (m, 2H), 1.21 (m, 1H), 0.95 (d, J=6.2 Hz, 3H), 0.88–0.83 (m, 2H), 0.89 (d, J=6.2 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (d, J=3.4 Hz, 6H).

6.1.20. Synthesis of 25 with $Pb(OAc)_4$. To a solution of **23** (4.1 mg) in benzene (1 mL) and MeOH (1 mL) was added lead tetraacetate (130 mg, 18 equiv), which was washed with ether (×3) just before use, at room temperature. After 15 min, the reaction mixture was poured into ethylene glycol (3 mL), and extracted with ether (×3) after the addition of water. The combined extracts were washed with aqueous sodium sulfite and then brine, dried over sodium sulfate, and concentrated under vacuum to give a colorless oil (6 mg). The oil was purified by silica-gel column chromatography (elution with 30% ethyl acetate in hexane) to give **25** (4.7 mg, 90.8% yield). $[\alpha]_D^{20}$ −1.93 (c 0.67, CH_2Cl_2); IR (KCl, neat) 3443, 2927, 1722, 1680, 1596, 1448, 1380, 1223, 1047, 792, 713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.54 (d, J=1.4 Hz, 1H), 7.54 (dd, J=7.6, 1.4 Hz, 2H), 7.57 (t, J=7.6 Hz, 1H), 7.47 (t, J=7.6 Hz, 2H), 3.88 (m, 1H), 3.81–3.76 (m, 2H), 2.44 (dt, J=6.9, 2.1 Hz, 1H), 2.15 (br s, OH), 1.81 (ddd, J=13.7, 6.9, 2.7 Hz, 1H), 1.75 (ddd, J=13.7, 6.9, 1.4 Hz, 1H), 1.47 (m, 1H), 1.34 (ddd, J=13.7, 6.9, 2.7 Hz, 1H), 1.09 (ddd, J=13.7, 6.9, 1.4 Hz, 1H), 1.03 (d, J=6.9 Hz, 3H), 0.89 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 204.92, 204.34, 137.12, 133.43, 128.81, 128.31, 64.17, 45.84, 43.93, 37.84, 36.07, 28.48, 20.35, 14.04; HRMS (ESI) m/z (M+Na$^+$) calcd for $C_{16}H_{22}O_3Na$ 285.1467, found 285.1452.

6.1.21. Synthesis of 25 with HIO_4. To a solution of **23** (5 mg, 0.024 mmol) in a mixture of acetone (1 mL) and water (1 mL) were added sodium periodate (41 mg, 8 equiv) and then acetic acid (excess) at room temperature. This solution was stirred for 40 min. The reaction mixture was poured into water, and extracted with ether (×3). The combined extracts were washed with water and then brine and dried over sodium sulfate, and concentrated under vacuum to give a pale yellow oil (8.8 mg). The oil was purified by silica-gel column chromatography (elution with 30% ethyl acetate in hexane) to give **25** (6 mg, 91.6% yield).

6.1.22. Synthesis of 24 with HIO_4. To a solution of **22** (20.3 mg) in acetone (2 mL) and water (2 mL) were added sodium periodate (114 mg, 6.4 equiv) and acetic acid (40 mg, 8 equiv) at room temperature. This solution was stirred for 20 min. The reaction mixture was poured into water, and extracted with ether (×3). The combined extracts were washed with water and brine, dried over sodium sulfate, and concentrated under vacuum to give a colorless oil

(25.1 mg). The oil was purified by silica-gel column chromatography (elution with 30% ethyl acetate in hexane) to give **24** as a yellow oil (17.4 mg, 86.5% yield). $[\alpha]_D^{20}$ +10.5 (*c* 0.6, CH_2Cl_2); IR (KCl, neat) 3454, 2930, 2714, 1713, 1463, 1380, 1258, 1126, 1050, 814, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 9.55 (d, J=2.1 Hz, 1H), 3.71–3.65 (m, 2H), 2.83 (dt, J=6.9, 2.1 Hz, 1H), 2.53–2.41 (m, 3H), 1.70 (dtd, J=13.7, 6.9, 2.1 Hz, 1H), 1.62 (dtd, J=13.7, 6.9, 2.7 Hz, 1H), 1.53 (dt, J=15.1, 7.6 Hz, 2H), 1.42 (m, 1H), 1.31–1.22 (m, 3H), 1.13 (m, 1H), 1.06 (d, J=6.9 Hz, 3H), 0.91 (d, J=6.9 Hz, 3H), 0.88 (d, J=6.9 Hz, 3H), 0.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 214.70, 204.89, 63.78, 51.28, 43.91, 43.11, 37.94, 35.24, 28.52, 25.39, 22.28, 20.11, 14.12, 13.85; HRMS (ESI) *m/z* (M+Na^+) calcd for $C_{14}H_{22}O_3Na$ 265.17796, found 265.1726.

6.1.23. Synthesis of 26. To a solution of **14a** (192 mg) and triethylamine (0.25 mL, 2.4 equiv) in dry dichloromethane (25 mL) was added methanesulfonyl chloride (66 μL, 1.2 equiv) at 0 °C. Saturated sodium bicarbonate solution was added after 25 min, and then the mixture was extracted with dichloromethane (×3), washed with water (×2), and dried over sodium sulfate. Concentration and purification by column chromatography on silica-gel (elution with 50% ethyl acetate in hexane) gave **26** (217 mg) as a colorless oil (73% yield). $[\alpha]_D^{20}$ +43.0 (*c* 0.56, CH_2Cl_2); IR (KCl, neat) 3550, 2952, 1457, 1354, 1175, 1119, 1016, 935, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 4.54 (dd, $J_{13,13'}$=9.6 Hz, $J_{13,12}$=4.1 Hz, 1H, H-13), 4.06 (m, 1H, H-4), 4.01 (dd, 1H, H-13′), 4.00 (m, 1H, H-2), 3.87 (d, $J_{7,8}$=6.2 Hz, 1H, H-7), 2.97 (s, 3H, Me), 2.34 (s, 1H, OH-7), 2.30 (m, 1H, H-12), 1.63 (m, 1H, H-11), 1.61 (m, 1H, H-8), 1.53 (m, 1H, H-10), 1.52 (m, 1H, H-11′), 1.50 (m, 1H, H-3), 1.42 (m, 1H, H-9), 1.17 (m, 1H, H-9′), 1.16 (d, J=6.2, 3H, PD–Me), 1.14 (d, J=6.2 Hz, 3H, PD–Me), 1.09 (m, 1H, H-3′), 1.08 (d, $J_{8,Me\text{-}8}$=6.9 Hz, 3H, Me-8), 0.88 (d, $J_{10,Me\text{-}10}$= 6.2 Hz, 3H, Me-10); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 100.80, 34.96, 71.59, 71.57, 66.23, 65.39, 40.36, 39.64, 39.27, 38.72, 37.08, 34.50, 24.02, 23.07, 21.94, 21.87; HRMS (ESI) *m/z* (M+Na^+) calcd for $C_{18}H_{30}O_6SNa$ 373.1661, found 373.1664.

6.1.24. Synthesis of 28. To a solution of **26** (271 mg) in anhydrous ether (20 mL) was added lithium aluminum hydride (65 mg) at 0 °C, and the mixture was stirred for 24 h at the same temperature. After addition of water, the mixture was extracted with ether (×4), washed with water (×2), and then brine. After drying over sodium sulfate, the mixture was concentrated and purified by a short silica-gel column (elution with 30% ethyl acetate in hexane) to give 185 mg of **26** as a colorless oil (91% yield). $[\alpha]_D^{20}$ +50.2 (*c* 0.62, MeOH); IR (KCl, neat) 3555, 2952, 1455, 1384, 1291, 1176, 1114, 1013 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 4.03 (qdd, J=17.9, 6.2, 2.8 Hz, 1H, H-4), 3.95 (qdd, J=17.9 Hz, $J_{2,Me\text{-}2}$=6.2 Hz, J=2.8 Hz, 1H, H-2), 3.84 (d, $J_{7,8}$=6.9 Hz, 1H, H-7), 2.51 (s, 1H, OH-7), 2.00 (qdd, $J_{12,Me\text{-}12}$=6.9 Hz, J=2.8 Hz, 1H, H-12), 1.63 (qddd, J=6.9, 2.1, 2.1, 2.1 Hz, 1H, H-8), 1.55 (m, 1H, H-10), 1.47 (m, 1H, H-12), 1.47 (m, 1H, H-3), 1.39 (m, 1H, H-11), 1.28 (m, 1H, H-11), 1.14 (d, $J_{4,Me\text{-}4}$=6.2 Hz, 1H, Me-4), 1.13 (d, $J_{2,Me\text{-}2}$=6.2 Hz, 1H, Me-2), 1.11 (m, 1H, H-11), 1.06 (m, 1H, H-3), 1.07 (d, $J_{8,Me\text{-}8}$=6.9 Hz, 1H, Me-8), 0.86 (d, $J_{12,Me\text{-}12}$=6.9 Hz, 1H, Me-12), 0.83 (d, $J_{10,Me\text{-}10}$=6.2 Hz, 1H, Me-10); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 101.31, 72.04, 65.70, 64.75, 41.37, 39.75, 39.46, 38.90, 35.57, 35.46, 24.18, 23.28, 22.08, 21.96, 17.25; HRMS (ESI) *m/z* (M+Na^+) calcd for $C_{15}H_{28}O_3Na$ 279.1936, found 279.1915.

6.1.25. Synthesis of 29. To a solution of **28** (33.2 mg) in THF/H_2O (=12:1, 6.5 mL) was added *p*-toluenesulfonic acid (5 mg) at room temperature, and the mixture was stirred for 20 h. The mixture was extracted with ether and the extract was washed with water and then brine, dried over sodium sulfate, concentrated, and purified by silica-gel column chromatography to give 17.4 mg of **29** as a colorless oil (79% yield). $[\alpha]_D^{20}$ +96.5 (*c* 1.2, CH_2Cl_2); IR (KCl, neat) 3461, 2956, 1696, 1456, 1375, 1256, 1074, 852 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 4.00 (dd, $J_{2,3}$=11.0 Hz, $J_{OH,2}$=6.9 Hz, 1H, H-2), 3.55 (d, $J_{OH,2}$=6.9 Hz, 1H, OH), 2.58 (m, H-7), 1.76 (ddd, J=14.4, 5.5, 2.1 Hz, 1H, H-4), 1.63 (ddd, J=13.7, 4.8, 2.1 Hz, 1H, H-6), 1.47 (m, 1H, H-3), 1.42 (m, 1H, H-5), 1.38 (m, 1H, H-6′), 1.14 (m, 1H, H-4′), 1.13 (d, $J_{Me\text{-}7,7}$=7.6 Hz, 3H, Me-7), 1.10 (d, $J_{Me\text{-}3,3}$= 6.9 Hz, 3H, Me-3), 0.95 (d, $J_{Me\text{-}5,5}$=6.9 Hz, 3H, Me-6); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 217.11, 78.29, 46.91, 45.20, 40.44, 38.78, 33.90, 24.64, 19.91, 9.65; HRMS (ESI) *m/z* (M+Na^+) calcd for $C_{10}H_{18}O_2Na$ 193.1204, found 193.1120.

6.1.26. Oxidative cleavage of 29 to give (+)-30. A solution of **29** (12.8 mg) in anhydrous methanol (2 mL) and dry benzene (2 mL) was added to lead tetraacetate (204 mg, 6 equiv) that was employed after washing with dry ether (×2). After 10 min, small amount of ethylene glycol was added followed by water. Extraction with ether (×4), washed with water (×2), dried over sodium sulfate, and then purification by silica-gel column chromatography (elution with 10% ethyl acetate in hexane) gave 11 mg of **30** as a colorless oil (74% yield). $[\alpha]_D^{20}$ +19.4 (*c* 1.05, CH_2Cl_2); IR (KCl, neat) 2969, 1736, 1461, 1380, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 9.56 (d, $J_{7,6}$=2.1 Hz, 1H, H-7), 3.64 (s, 3H), 2.55 (m, 1H, H-6), 2.43 (m, 1H, H-6), 1.70 (ddd, J=13.7, 9.6, 4.8 Hz, 1H, H-3), 1.65 (ddd, 1H, H-5), 1.45 (m, 1H, H-4), 1.13 (d, $J_{2,Me\text{-}2}$=6.9 Hz, 3H, Me-2), 1.16 (m, 1H, H-5′), 1.07 (m, 1H, H-3′), 1.05 (d, $J_{6,Me\text{-}6}$=6.9 Hz, 3H, Me-6), 0.89 (d, $J_{4,Me\text{-}4}$=6.9 Hz, 3H, Me-4); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 205.12, 177.17, 51.51, 43.89, 40.92, 38.06, 37.22, 28.49, 19.90, 18.17, 13.87; HRMS (ESI) *m/z* (M+Na^+) calcd for $C_{11}H_{20}O_4Na$ 239.1259, found 239.1260.

6.1.27. Reduction of 30 by $LiAlH_4$ to give 32. To a solution of **30** (4.1 mg) in anhydrous ether (0.5 mL) was added lithium aluminum hydride (ca. 15 mg, large excess) at 0 °C. After addition of water, the mixture was extracted with ether (×3) and then dichloromethane (×2). Combined organic layers were dried over sodium sulfate, concentrated, and purified by silica-gel column chromatography (elution with 50% ethyl acetate in hexane) to give 2.3 mg of **32** as a colorless oil (65%). $[\alpha]_D^{20}$ 0.00 (*c* 0.09, CH_2Cl_2); IR (KCl, neat) 3333, 2918, 1461, 1378, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.51 (dd, $J_{1,1'}$=10.3 Hz, $J_{1,2}$=4.8 Hz, 2H, H-1, 7), 3.37 (dd, $J_{1,1'}$=10.3 Hz, $J_{1,2}$=6.9 Hz, 2H, H-1′, 7′), 1.71 (m, 2H, H-2, 6), 1.58 (m, 1H, H-4), 1.31 (ddd, 2H, H-3, 5), 0.89 (m, 2H, H-3′, 5′), 0.91 (d, $J_{2,Me\text{-}2}$=6.9 Hz, 6H, Me-2, 6), 0.89 (d, $J_{4,Me\text{-}4}$=6.9 Hz, 3H, Me-4); ^{13}C NMR

($CDCl_3$, 150 MHz) δ 68.11, 41.15, 33.14, 27.80, 21.04, 17.62.

6.1.28. Stereospecific conversion of 30 to 33. To a solution of **30** (10.0 mg) in methanol was added sodium borohydride (ca. 15 mg, excess) at 0 °C. After stirring for 2 h, the mixture was extracted with ether (×3), dried over sodium sulfate, and concentrated to give 9.4 mg of a colorless oil (94% crude yield). This oil was added to a mixture of *tert*-butyldimethylsilyl chloride (11.4 mg, 1.5 equiv), imidazole (17.5 mg, 5 equiv), and DMF (1.0 mL). After stirring for 11 h, the mixture was treated with water, extracted with ether (×3), washed with water (×2) and then brine, dried over sodium sulfate, and concentrated to give 16.1 mg of **31** as a pale yellow oil. This mixture was dissolved in ether, and treated with lithium aluminum hydride (12 mg, excess). After extraction with ether (×3), the combined extracts were washed with water (×2) and brine, dried over sodium sulfate, and concentrated to give **33** as a colorless oil (8 mg). The obtained **33** by this procedure was identical with the racemic **33** produced as shown next.

6.1.29. Preparation of racemic 33 from 32 and its GLC analysis. Racemic mixture of **33** was prepared from **32** (0.6 mg) by the treatment with a mixture of *tert*-butyldimethylsilyl chloride (1.0 mg), imidazole (3.5 mg), and DMF (0.3 mL) for 5 min. The extracts contained mostly mono-TBS ether deduced from TLC analysis, and was subjected to a chiral GLC analysis (DEX-CB, 25 m, 0.25 mm id, 30 cm s^{-1}, 140 °C) to show two separated peaks at 34.6 and 35.1 min, while the same analysis of **33** prepared from **31** showed a single peak at 35.3 min.

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