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Enantioselective construction of bicyclo[3.1.0]hexane derivatives through asymmetric deprotonation of *meso*-cyclic ketones

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Abstract—An efficient asymmetric synthesis of bicyclo[3.1.0]hexane derivatives was achieved. The three-step conversion of 6-hydroxytricyclo[3.2.1.0^{2,7}]octan-3-one **2**, (derived from 3-oxatricyclo[3.3.1.0^{2,4}]nonan-7-one **1** through an asymmetric deprotonation reaction) led to **6** in optically active form. Alternatively, the asymmetric deprotonation reaction of *meso*-cyclic ketones **9a** and **9b** with several chiral lithium amide bases was examined to give silyl enol ether **12** and triflate **21** with high enantioselectivity. The absolute configuration of the triflate **21** was determined by investigation of the chemical relationship between **21** and **6**.

1. Introduction

The enantioselective deprotonation reaction of *meso*-type carbonyl compounds is a useful technique for the desymmetrization of symmetric molecules. Lithium amide bases derived from chiral secondary amines are often employed for this purpose.[1] Non-racemic enolate formation, by the use of the chiral lithium amide base, has been applied to the asymmetric syntheses of various natural products.[2]

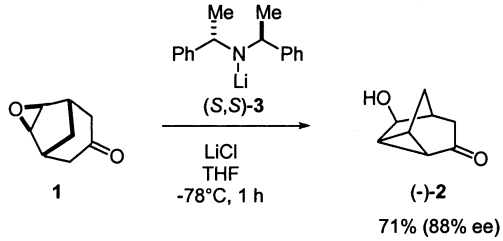
The bicyclo[3.1.0]hexane system is known to be an efficient intermediate for the synthesis of natural products or biologically active compounds.[3] The enantioselective formation of the bicyclo[3.1.0] skeleton has been developed particularly in the field of carbenoid chemistry.[4] Enzymatic manipulation for the asymmetric synthesis of the bicyclo[3.1.0] system has also been demonstrated.[5]

Enantioselective deprotonation was expected to be an efficient method for the preparation of the bicyclo[3.1.0]hexane system in asymmetric form. In this article, we demonstrate that the desymmetrization of *meso*-cyclic ketones, by use of chiral lithium amides, is effective for constructing optically active bicyclo[3.1.0] compounds.

2. Results and discussion

2.1. Conversion of 6-hydroxytricyclo[3.2.1.0^{2,7}]octan-3-one (2) into the bicyclo[3.1.0]hexane system

Recently, we demonstrated an efficient asymmetric transformation of *meso*-epoxy ketone **1** into tricyclic keto alcohol **2**.[6] In the presence of LiCl, a chiral lithium amide (*S*,*S*)-**3**[7] was an effective reagent for this transformation involving an enantioselective deprotonation-transannular C–C bond formation process, to give **2** with high enantioselectivity (Scheme 1). We expected that further transformation of the tricyclic hydroxy ketone **2** would allow easy construction of the bicyclo[3.1.0]system by cleavage of the C(3)–C(4) bond.



Scheme 1. Enantioselective deprotonation of **1**.

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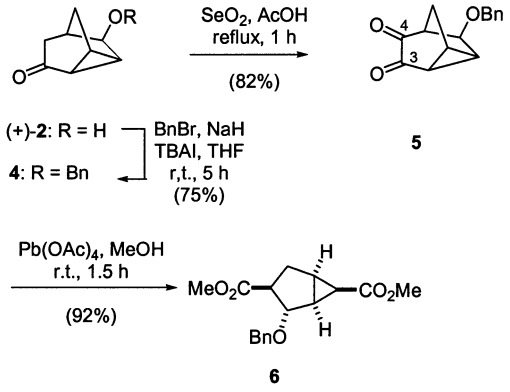
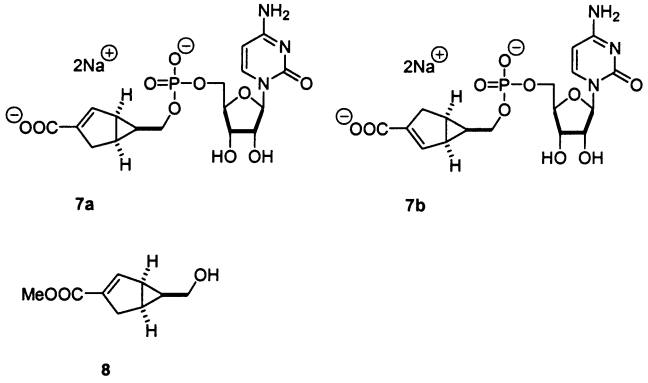
As shown in Scheme 2, after protection of the hydroxy group with benzyl bromide, oxidation with selenium dioxide was carried out to give α-diketone **5**. Cleavage of the C–C bond of **5** with lead tetraacetate successfully afforded diester **6**, which furnishes the bicyclo[3.1.0] core in asymmetric form.



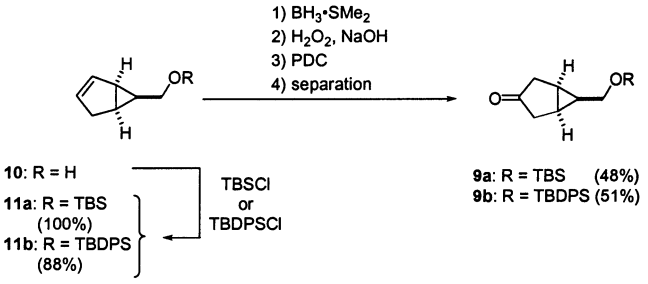
Scheme 2. Transformation of (+)-**2** into **6**.

2.2. Enantioselective deprotonation of *meso*-bicyclo-[3.1.0]hexan-3-one derivatives

Horenstein et al. reported that a CMP-NeuAc (cytidine monophosphate *N*-acetylneuraminic acid) analog **7**, which was considered as a transition-state mimic of a sialyl donor, exhibited strong activity for sialyltransferase inhibition.[8] In their study, however, a bicyclic alcohol **8** was synthesized in racemic form as a key intermediate for the preparation of **7**. Therefore, the phosphates **7a** and **7b** were generated as an inseparable mixture in a 1:1 ratio; the inhibitory effect was investigated using the mixture of the diastereomers.[8] Consequently, the relationship between stereochemical structure and biological activity remains unclear. We thought it was necessary to clarify the effect of the stereochemistry of **7** to the sialyltransferase inhibition. For this purpose, enantioselective preparation of **8** was essential for the synthesis of both enantiomerically pure **7a** and **7b**. In order to perform the enantioselective synthesis of the bicyclo[3.1.0] system, the asymmetric deprotonation process of *meso*-bicyclo[3.1.0]hexan-3-one derivatives was investigated.



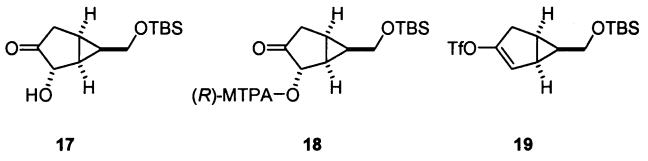
The *meso*-ketones substrates, **9a** and **9b**, were prepared by the reported method (Scheme 3).[8] A starting carbinol **10** was easily obtained from norbornadiene through the Meinwald rearrangement.[9] After protection by the TBS (*tert*-butyldimethylsilyl) or TBDPS (*tert*-butyldiphenylsilyl) group, **11a** and **11b** were converted to the *meso*-ketones **9a** and **9b**, respectively, by the following sequence: hydration by the hydroboration–oxidation process, oxidation with PDC (pyridinium dichromate), and separation of the two regioisomers by chromatography.



Scheme 3. Preparation of *meso*-ketones **9a** and **9b**.

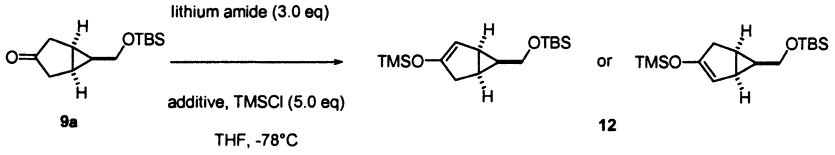
The deprotonation reaction of **9a** was first examined using several chiral amide bases, (*S*,*S*)-**3**,[7] (*R*)-**13**,[10] (*S*)-**14**,[11] (*S*)-**15**,[11] and (1*R*,2*S*)-**16**,[12] in the presence of HMPA (hexamethylphosphoramide) or lithium chloride at −78°C. The results are summarized in Table 1. In order to trap the resulting enolate, an internal quenching method was employed (runs 1–5).[13] The best result was observed when (*S*,*S*)-**3** was used as the amide base in the presence of lithium chloride (run 1). Although higher enantioselectivity was observed in the case of (*R*)-**13**, the yield of the product was relatively low (run 2). (1*S*,2*R*)-**16** was afforded a poor yield and low enantioselectivity (run 5). Under the other conditions, none of the desired silyl enol ether was obtained (runs 3, 4 and 6).

The ee (enantiomeric excess) of the silyl enol ether **12** was determined based on ^{1}H NMR analysis of the (*R*)-MTPA (α-methoxy-α-(trifluoromethyl)phenylacetyl) ester **18**, which was derived from **12** by a two-step conversion. Treatment of **12** with *m*-CPBA (*meta*-chloroperbenzoic acid) afforded α-hydroxy ketone **17** as the sole product. The next esterification with (*R*)-MTPA was also successful when a DCC (dicyclohexylcarbodiimide)–DMAP (*N*,*N*-dimethylaminopyridine) system was used. The two diastereomers of **18** were resolved in the ^{1}H NMR spectrum; thus the ee of **12** could be determined.



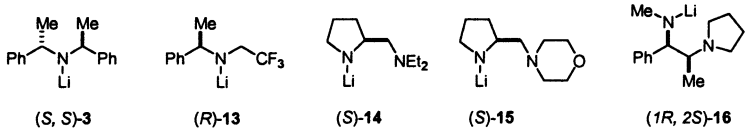
In order to be able to prepare **8**, the synthesis of the triflate **19** was required. Unfortunately, all attempts to convert **12** into **19** failed.

Table 1. Asymmetric deprotonation of **9a**



Run	Lithium amide	Additive	Time	Product[a]	Yield (%)	Ee (%)[b]
1	(*S*,*S*)-**3**	LiCl	20 min	(+)-**12**	52	86
2	(*R*)-**13**	LiCl	1 h	(−)-**12**	21	87
3	(*S*)-**14**	HMPA	2 h	–[c]	–	–
4	(*S*)-**15**	HMPA	2 h	–[c]	–	–
5	(1*R*,2*S*)-**16**	HMPA	2 h	(+)-**12**	15	12
6[d]	(1*R*,2*S*)-**16**	LiCl	2 h	–[c]	–	–

[a] Absolute configuration was not determined.
[b] Ee was determined by the ^{1}H NMR integration of the corresponding (*R*)-MTPA ester **18**: See text.
[c] Not detected.
[d] External quenching method was used.



As an alternative, we employed triflating agent **20** to trap the generated chiral enolate.[14] Table 2 lists the selected experiments of the enantioselective deprotonation–triflation reaction using the TBDPS-protected *meso*-ketone **9b** as a substrate.

The chiral lithium amide (*S*,*S*)-**3** was an effective base for enantioselectivity (run 1). When (*R*)-**13** was employed as the chiral base, the optimum ee was observed although the yield was low (run 2).

The absolute configuration of (−)-**21** was elucidated by the investigation of the chemical relationship with **6** which was defined in stereochemistry.[6] The triflate (−)-**21** was transformed to the homologated ester **22** by a palladium-catalyzed carbonylation reaction. The treatment of **22** with DIBAL (diisobutylaluminum hydride) followed by silylation of the generated hydroxy group was successful. A sequence of hydroboration with 9-BBN (9-borabicyclo[3.3.1]nonane) and oxidation proceeded regio- and stereoselectively to give (+)-**25**, having a positive specific rotation (Scheme 4).

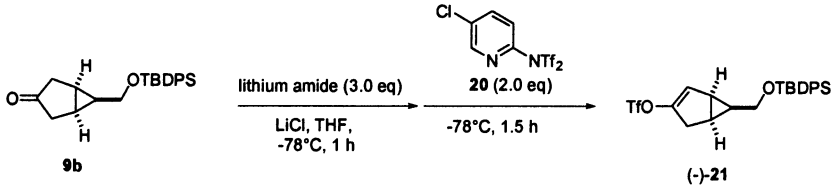
On the other hand, reduction of **6** with DIBAL gave diol **26** in good yield, which was successfully silylated to afford **27**. However, the hydrogenolysis of benzyl ether **27** did not give the debenzylated product **25** in satisfactory yield. In contrast to this result, the hydrogenolysis of **26**, followed by silylation of the two primary hydroxy groups, gave (−)-**25** in acceptable yield (Scheme 5). By comparison of the signs of the specific rotation, the stereochemistry of (−)-**25** implied the mirror image of (+)-**25**, which was described in Scheme 4. Therefore, the absolute configuration of (−)-**21** was unambiguously determined.

Further studies on the synthesis of enantiomerically pure **7a** and **7b** are now in progress.

3. Experimental

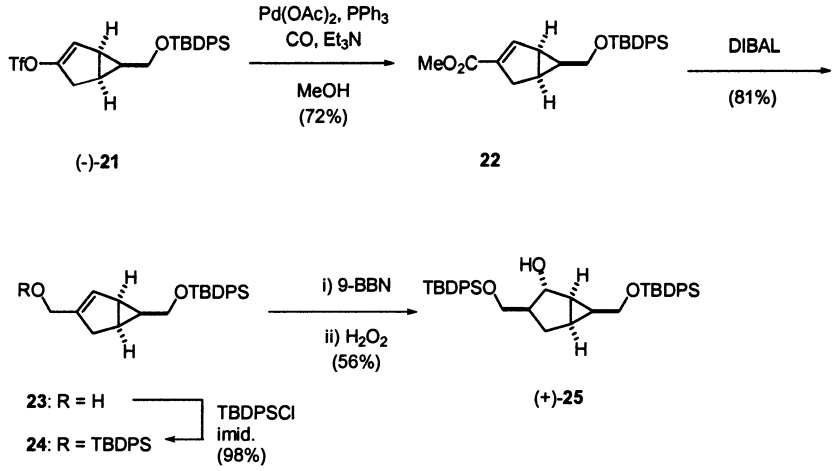
Melting points were measured using a Yanagimoto micro melting point hot-plate apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 or

Table 2. Asymmetric deprotonation of **9b**

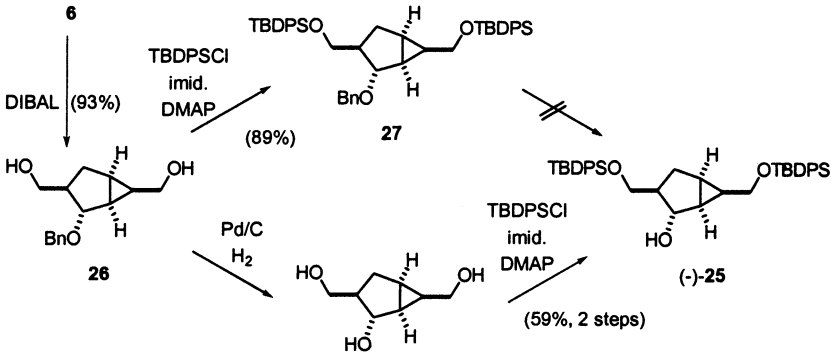


Run	Lithium amide	Product	Yield (%)	Ee (%)[a]
1	(*S*,*S*)-**3**	(+)-**21**	32	75
2	(*R*)-**13**	(−)-**21**	43	77

[a] Ee (%) was determined by HPLC analysis using a chiral column (Daicel CHIRALCEL OD).



Scheme 4. Transformation of (−)-**21** into (+)-**25**.



Scheme 5. Transformation of **6** into (−)-**25**.

FTIR-350 spectrophotometer. NMR spectra were obtained using a Varian VXR-500 or VXR-200 instrument. The chemical shifts are reported as δ ppm and couplings expressed in Hertz. FAB-MS were recorded with a VG-70SE instrument using *m*-nitrobenzyl alcohol as the matrix. Elemental analyses were carried out on a Yanaco MT-5 CHN analyzer. Optical rotations were obtained on a JASCO DIP-1000 polarimeter. Silica gel column chromatography was carried out with Wako-gel C-200. Merck Silica gel 60 F254 plates (No. 5744) were used for preparative TLC. THF (tetrahydrofuran) was used after distillation over sodium–benzophenone ketyl. Chiral amines were purchased or synthesized by reported methods.[7,10–12] All reactions were carried out under an argon atmosphere, unless stated otherwise.

3.1. (1*R*,2*R*,5*R*,6*R*,7*S*)-6-Benzyloxytricyclo[3.2.1.0^{2,7}]-octan-3-one, 4

NaH (60% in mineral oil, 241 mg, 6.03 mmol), TBAI (tetra-*n*-butylammonium iodide) (501 mg, 1.34 mmol), and benzyl bromide (850 μl, 7.15 mmol) were successively added to a solution of (+)-**2** (370 mg, 2.68 mmol) in THF (2 ml) at 0°C. The mixture was allowed to warm to room temperature, and stirred for 5 h. After cooling to 0°C, water was slowly added. The mixture was extracted with ether, and then the organic layer was washed with brine and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was subjected to silica gel column chromatography with ether–hexane (1:1) to afford **4** as a crystalline solid (461 mg, 75%). For an analytical sample, recrystallization from dichloromethane–ether was carried out to give colorless needles, mp 65–67°C. IR (KBr) cm^{-1}: 1690 (C=O), 1080 (C-O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.65 (1H, d, J=12.0), 1.86 (1H, t, J=8.0), 2.01 (1H, ddd, J=1.0, 2.0, 19.0), 2.08 (1H, dd, J=3.0, 19.0), 2.14–2.20 (2H, m), 2.30–2.35 (2H, m), 3.83 (1H, s) 4.59 (2H, d, J=2.0), 7.30–7.32 (1H, m), 7.34–7.36 (4H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.92, 26.60, 28.52, 32.36, 33.55, 41.96, 70.76, 81.81, 127.51, 127.65, 128.37, 138.07, 207.37. FAB-MS (positive ion mode) m/z: 229 $[M+1]^+$, 457 $[2M+1]^+$. $[\alpha]_D^{30}$ −3.2 (*c* 0.50, $CHCl_3$) [88% ee]. Anal. calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.93; H, 6.77%. The ee was determined by HPLC analysis with a chiral column (Daicel CHIRALCEL OD); eluent, isopropyl alcohol–hexane (1:1); flow rate, 0.2 ml/min; t_R=31.7 and 34.1 min.

3.2. (1*R*,2*R*,5*S*,6*S*,7*S*)-6-Benzyloxytricyclo[3.2.1.0^{2,7}]-octane-3,4-dione, 5

A mixture of **4** (785 mg, 3.44 mmol), selenium dioxide (524 mg, 4.72 mmol), and acetic acid (50 ml) was heated under reflux for 1 h, and then poured into water. After extraction with ether, the organic layer was washed with saturated potassium carbonate aqueous

solution and brine and dried over magnesium sulfate. Evaporation of the solvent gave a yellow solid which was recrystallized from dichloromethane–ether to afford **5** as yellow needles (684 mg, 82%), mp 122.5–124°C. IR (KBr) cm^{-1}: 1740 (C=O), 1720 (C=O), 1080 (C-O). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.22 (1H, d, $J=13.5$), 2.31 (1H, t, $J=7.5$), 2.51–2.57 (2H, m), 2.64 (1H, ddd, $J=3.0$, 5.5, 13.5), 3.17 (1H, d, $J=5.0$), 4.22 (1H, s), 4.58 (1H, d, $J=12.0$), 4.63 (1H, d, $J=12.0$), 7.30–7.39 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.97, 27.80, 32.00, 32.19, 51.19, 71.52, 79.04, 127.71, 128.09, 128.58, 137.11, 190.00, 192.82. FAB-MS (positive ion mode) m/z: 243 $[M+1]^+$. $[\alpha]_D^{22}$ −80.4 (c 1.00, $CHCl_3$). Anal. calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.17; H, 5.72%.

3.3. Dimethyl (1*S*,2*S*,3*S*,5*R*,6*R*)-2-benzyloxybicyclo-[3.1.0]hexane-3,6-dicarboxylate, 6

Lead tetraacetate (90%, 1.37 g, 2.77 mmol) was added to a solution of **5** (607 mg, 2.51 mmol) in methanol (30 ml), and the mixture was stirred for 1.5 h at room temperature. After evaporation of the solvent, dichloromethane and saturated aqueous sodium bicarbonate solution were successively added to the residue. The resulting emulsion was passed through a Celite pad, and then extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated. The residue was subjected to silica gel column chromatography with ether–hexane (1:2) to give **6** as a colorless oil (700 mg, 92%). IR (neat) cm^{-1}: 1730 (C=O), 1200 (C-O), 1160 (C-O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.78 (1H, t, $J=8.5$), 1.98–2.05 (2H, m), 2.15 (1H, ddd, $J=1.5$, 7.0, 14.5), 2.49 (1H, ddd, $J=6.0$, 12.0, 14.5), 3.38 (1H, ddd, $J=4.5$, 7.0, 12.0), 3.64 (3H, s), 3.73 (3H, s), 4.62 (1H, d, $J=4.5$), 4.62 (1H, d, $J=12.0$), 4.66 (1H, d, $J=12.0$), 7.28–7.39 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.08, 26.22, 26.88, 32.10, 51.50, 51.80, 57.67, 72.10, 83.09, 127.54, 127.77, 128.30, 138.31, 171.29, 173.99. $[\alpha]_D^{26}$ −11.7 (c 1.04, $CHCl_3$) [95% ee]. HRMS (FAB) calcd for $C_{17}H_{21}O_5$ $[M+1]^+$: 305.1389. Found: 305.1404%. The ee was determined by HPLC analysis with a chiral column (Daicel CHIRALCEL OD); eluent, isopropyl alcohol–hexane (1:30); flow rate, 0.5 ml/min; $t_R=21.0$ and 24.5 min.

3.4. (±)-6α-(*tert*-Butyldimethylsilyloxymethyl)-1α,5α-bicyclo[3.1.0]hex-2-ene, 11a[8]

TBSCl (4.27 g, 28.3 mmol) was added to a solution of **10** (2.60 g, 23.6 mmol) and imidazole (4.02 g, 59.0 mmol) in DMF (5 ml) at 0°C. The reaction mixture was allowed to warm to room temperature, stirred for 30 min, and poured into water. After extraction with hexane, the organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give a residue. Silica gel column chromatography with ether–hexane (1:40) afforded **11a** as a colorless oil (5.30 g, 100%). IR (neat) cm^{-1}: 1093 (C-O). ^1H NMR (200 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.12–1.26 (1H, m), 1.62–1.73 (1H, m), 2.04–2.17 (2H, m), 2.42–2.56 (1H, m), 3.40 (1H, dd, $J=7.8$, 11.2), 3.49 (1H, dd, $J=6.4$, 11.2), 5.55–5.58 (1H, m), 5.64–5.69 (1H, m).

3.5. (±)-6α-(*tert*-Butyldiphenylsilyloxymethyl)-1α,5α-bicyclo[3.1.0]hex-2-ene, 11b[8]

TBDPSCl (4.16 ml, 16.0 mmol) was added to a solution of **10** (1.47 g, 13.3 mmol) and imidazole (2.27 g, 33.3 mmol) in DMF (3 ml) at 0°C. The reaction mixture was allowed to warm to room temperature, stirred for 30 min and poured into water. After extraction with hexane, the organic layer was washed with brine, dried over magnesium sulfate and evaporated to give a residue. Silica gel column chromatography with ether–hexane (1:30) afforded **11b** as a colorless oil (4.09 g, 88%). ^1H NMR (200 MHz, $CDCl_3$) δ: 1.03 (9H, s), 1.15–1.34 (1H, m), 1.56–1.69 (1H, m), 1.96–2.07 (2H, m), 2.34–2.48 (1H, m), 3.42–3.59 (2H, m), 5.39–5.41 (1H, m), 5.49–5.54 (1H, m), 7.31–7.44 (6H, m), 7.65–7.70 (4H, m).

3.6. α-(*tert*-Butyldimethylsilyloxymethyl)-1α,5α-bicyclo[3.1.0]hexan-3-one, 9a[8]

$BH_3{\cdot}SMe_2$ (2.27 ml, 23.9 mmol) was added to a solution of **11a** (9.76 g, 43.5 mmol) in THF (80 ml) at 0°C. The mixture was allowed to warm to room temperature, and allowed to stand for 45 min. Methanol (6 ml) and 3N sodium hydroxide aqueous solution (8.70 ml) were added to the mixture portionwise and 31% hydrogen peroxide aqueous solution was slowly added. The reaction mixture was heated under reflux for 1 h, poured into water, and extracted with ether. The organic layer was combined, washed with brine and dried over magnesium sulfate. Evaporation of the solvent gave a residue which was subjected to silica gel column chromatography with ethyl acetate–hexane (1:4). The resulting colorless oil (8.29 g) was dissolved in dichloromethane (30 ml). The solution was added dropwise to a suspension of PDC (25.7 g, 68.4 mmol) and HYFLO SUPER CEL® (25 g) in dichloromethane (150 ml) at 0°C, and the mixture was allowed to warm to room temperature. After stirring for 15 h, ether was added to the mixture and the reaction mixture was filtered. The filtrate was poured into water and extracted with ether. The organic layer was dried over magnesium sulfate and evaporated to give a residue, which was subjected to silica gel column chromatography with ether–hexane (1:8). Symmetric ketone **9a** was obtained as a colorless oil (5.02 g, 48%). IR (neat) cm^{-1}: 1743 (C=O), 1079 (C-O). ^1H NMR (200 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.87 (9H, s), 1.30 (1H, dddd, $J=7.8$, 7.8, 8.0, 8.0), 1.64–1.72 (2H, m), 2.22 (2H, dd, $J=1.8$, 18.8), 2.58 (2H, ddd, $J=1.8$, 4.6, 18.8), 3.51 (2H, d, $J=7.8$). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.34, 15.79, 18.23, 22.39, 25.85, 37.51, 58.19, 219.31.

3.7. α-(*tert*-Butyldiphenylsilyloxymethyl)-1α,5α-bicyclo-[3.1.0]hexan-3-one, 9b[8]

In a way similar to the above procedure, the ketone **9b** (2.13 g, 51%) was obtained as a colorless oil from **11b** (3.96 g, 11.4 mmol). IR (neat) cm^{-1}: 1742 (C=O), 1111

(C-O). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.04 (9H, s), 1.30 (1H, dddd, J=7.8, 7.8, 8.0, 8.0), 1.56–1.72 (2H, m), 2.15 (2H, d, J=21.0), 2.53 (2H, dd, J=4.4, 21.0), 3.56 (2H, d, J=7.8), 7.35–7.43 (6H, m), 7.63–7.68 (4H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.95, 19.13, 22.38, 26.75, 37.44, 59.06, 127.64, 129.63, 133.60, 135.45, 219.23.

3.8. (1*R**,5*S**,6*S**)-6-(*tert*-Butyldimethylsilyloxymethyl)-3-(trimethylsilyloxy)bicyclo[3.1.0]hex-2-ene, (+)-12

In a typical procedure (run 1, Table 1), *n*-butyllithium (1.56 M in hexane, 801 μl, 1.25 mmol) was added to a stirred solution of (*S*,*S*)-bis(α-methylbenzyl)amine hydrochloride (163 mg, 0.624 mmol) in THF (3 ml) at −78°C. The mixture was stirred for 30 min at 0°C and then cooled to −78°C. TMSCl (132 μl, 1.04 mmol) was added to the lithium amide solution at the same temperature. After 5 min, a solution of **9a** (50.0 mg, 0.208 mmol) in THF (3 ml) was added dropwise via syringe. The reaction mixture was stirred for 20 min at −78°C, and saturated sodium bicarbonate aqueous solution was added to the mixture. After extractive workup with hexane, the extract was dried over sodium sulfate and evaporated to give a residue which was subjected to silica gel column chromatography with ether–hexane (1:40). Silyl enol ether (+)-**12** (33.7 mg, 52%) was obtained as a colorless oil. IR (neat) cm^{-1}: 1629 (C=C), 1224 (C-O), 1091 (C-O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.05 (6H, s), 0.20 (9H, s), 0.90 (9H, s), 1.07 (1H, dddd, J=6.5, 7.0, 7.5, 8.0), 1.43 (1H, qd, J=8.0, 1.0), 1.84–1.87 (1H, m), 2.09 (1H, ddd, J=0.5, 1.5, 17.5), 2.50 (1H, ddd, J=1.0, 8.0, 17.5), 3.56 (1H, dd, J=6.5, 11.0), 3.60 (1H, dd, J=7.5, 11.0), 4.62 (1H, ddd, J=1.0, 1.0, 1.5). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.10, −5.02, −0.07, 14.71, 18.43, 23.66, 23.77, 26.03, 33.24, 57.89, 100.44, 155.69. $[\alpha]_D^{26}$ +59.6 (*c* 1.16, $CHCl_3$) [86% ee]. Anal. calcd for $C_{16}H_{32}O_2Si_2$: C, 61.48; H, 10.32. Found: C, 61.93; H, 9.92%.

3.9. (1*R**,2*R**,5*R**,6*S**)-6-(*tert*-Butyldimethylsilyloxymethyl)-2-hydroxybicyclo[3.1.0]hexan-3-one, 17

A solution of (+)-**12** (40.0 mg, 0.128 mmol) in dichloromethane (2 ml) was added to a mixture of *m*-CPBA (80%, 27.6 mg, 0.128 mmol), sodium bicarbonate (53.8 mg, 0.640 mmol) and dichloromethane (3 ml) at 0°C. After stirring for 20 min, ether (5 ml) and 10% sodium hydroxide aqueous solution (3 ml) were added, and the mixture was allowed to warm to room temperature and vigorously stirred for 3 h. The resulting mixture was extracted with ether, dried over magnesium sulfate and evaporated to give a residue. Silica gel column chromatography with ether–hexane (1:1) afford **17** as a colorless oil (18.1 mg, 55%). IR (neat) cm^{-1}: 3396 (-OH), 1751 (C=O), 1083 (C-O). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.87 (9H, s), 1.46 (1H, dddd, J=7.0, 7.2, 8.0, 9.2), 1.70 (1H, dd, J=7.2, 9.2), 1.81 (1H, ddd, J=6.4, 7.2, 7.2), 2.28 (1H, d, J=20.0), 2.49 (1H, bs), 2.74 (1H, dd, J=6.4, 20.0), 3.48 (1H, dd, J=8.0, 11.6), 3.60 (1H, dd, J=7.0, 11.6), 3.82 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.38, 15.74, 18.25, 22.71, 22.72, 25.85, 35.06, 58.47, 71.23, 218.92. $[\alpha]_D^{26}$ −19.6 (*c* 1.09, $CHCl_3$) [86% ee]. Anal. calcd for $C_{13}H_{24}O_3Si$: C, 60.89; H, 9.43. Found: C, 61.05; H, 9.26.

3.10. (*R*)-MTPA ester of (1*R**,2*R**,5*R**,6*S**)-6-(*tert*-butyldimethylsilyloxymethyl)-2-hydroxybicyclo[3.1.0]-hexan-3-one, 18

(*R*)-MTPA (6.2 mg, 26.4 μmol) and DMAP (0.4 mg, 3.27 μmol) were added to a solution of **17** (4.5 mg, 17.6 μmol) in dichloromethane (2 ml) at room temperature. DCC (7.3 mg, 35.4 μmol) was added to the mixture at 0°C and the resulting mixture was allowed to warm to room temperature and stirred for 2 h. After evaporation, silica gel column chromatography with ethyl acetate–hexane (1:15) gave a mixture of two diastereomers of **18** as an oil (8.2 mg, 99%). The diastereomeric ratio was judged based on ^{1}H NMR integration. Selected signals of ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.91 (s, major diastereomer) and 5.07 (s, minor diastereomer).

3.11. *N*-(5-Chloro-2-pyridyl)triflimide, 20[14]

This compound was prepared by a literature procedure.

3.12. (1*R*,5*S*,6*S*)-6-(*tert*-Butyldiphenylsilyloxymethyl)-bicyclo[3.1.0]hex-2-ene-3-yl triflate, (−)-21

In a typical procedure (run 2, Table 2), *n*-butyllithium (1.59 M in hexane, 723 μl, 1.15 mmol) was added to a stirred solution of (*R*)-*N*-(2,2,2)-trifluoroethyl)-1-phenylethylamine hydrochloride (138 mg, 0.576 mmol) in THF (3 ml) at −78°C. The mixture was stirred for 30 min at 0°C, and then cooled to −78°C. A solution of **9b** (70.0 mg, 0.192 mmol) in THF (3 ml) was added dropwise to the lithium amide solution at the same temperature, and the resulting mixture was stirred for 1 h. A solution of **20** (151 mg, 0.384 mmol) in THF (1.5 ml) was added via syringe and the mixture was stirred for 1.5 h. After water was added, the mixture was allowed to warm to room temperature and extracted with ether. The extract was washed with 10% aqueous sodium hydroxide solution, dried over potassium carbonate and evaporated to give a residue, which was subjected to silica gel column chromatography with ether–hexane (1:100). Triflate (−)-**21** was obtained as a colorless oil (40.7 mg, 43%). IR (neat) cm^{-1}: 1644 (C=C), 1425 (S=O), 1213 (C-F), 1141 (S=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.04 (9H, s), 1.35 (1H, dddd, J=7.0, 7.0, 7.5, 8.0), 1.61 (1H, ddd, J=7.0, 7.5, 8.0), 1.92–1.95 (1H, m), 2.33 (1H, dd, J=1.5, 17.5), 2.72 (1H, dd, J=8.5, 17.5), 3.61 (1H, dd, J=7.5, 11.5), 3.66 (1H, dd, J=7.0, 11.5), 5.45 (1H, m), 7.36–7.42 (6H, m), 7.65–7.68 (4H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.95, 19.19, 22.64, 23.45, 26.80, 31.02, 57.69, 117.58, 127.61, 127.64, 129.63, 133.84, 135.56, 147.99. $[\alpha]_D^{26}$ −57.8 (*c* 0.92, $CHCl_3$) [77% ee]. Anal. calcd for $C_{24}H_{27}F_3O_4SSi$: C, 58.04; H, 5.48. Found: C, 58.07; H, 5.75%. The ee was determined by HPLC analysis with a chiral column (Daicel CHIRALCEL OD); eluent, hexane; flow rate, 0.5 ml/min; t_R=15.7 and 16.6 min.

3.13. Methyl (1*S*,5*S*,6*S*)-6-(*tert*-butyldiphenylsilyloxymethyl)bicyclo[3.1.0]hex-2-ene-3-carboxylate, 22

A mixture of palladium(II) acetate (4.6 mg, 0.0203 mmol), triphenylphosphine (10.6 mg, 0.0404 mmol), (−)-**21** (335 mg, 0.675 mmol), triethylamine (188 μl, 1.35 mmol), methanol (1.09 ml, 27.0 mmol) and DMF (*N*, *N*-dimethylformamide) (5 ml) was stirred for 24 h at room temperature under a carbon monoxide atmosphere. After addition of water, the mixture was extracted with ether. The organic layer was washed with water, dried over magnesium sulfate and evaporated to give a residue. Silica gel column chromatography with ethyl acetate–hexane (1:15) gave **22** as a colorless oil (197 mg, 72%). IR (neat) cm^{-1}: 1718 (C=O), 1243 (C-O), 1104 (C-O). ^1H NMR (200 MHz, $CDCl_3$) δ: 1.03 (9H, s), 1.46 (1H, dddd, $J=6.4$, 7.8, 8.0, 8.2), 1.81 (1H, qd, $J=8.0$, 1.4), 2.08–2.18 (1H, m), 2.35 (1H, ddd, $J=1.4$, 2.0, 18.8), 2.67 (1H, ddd, $J=2.0$, 8.0, 18.8), 3.40 (1H, dd, $J=8.2$, 11.2), 3.56 (1H, dd, $J=6.4$, 11.2), 3.68 (3H, s), 6.62 (1H, q, $J=2.0$), 7.32–7.42 (6H, m), 7.60–7.68 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.15, 21.40, 24.26, 26.79, 29.18, 31.04, 51.21, 57.83, 127.55, 129.48, 133.84, 133.88, 135.20, 135.54, 142.31, 164.82, 165.26. $[\alpha]_D^{22}$ −110.8 (*c* 1.27, $CHCl_3$) [77% ee]. The ee was determined by HPLC analysis with a chiral column (Daicel CHIRALCEL OD); eluent, isopropyl alcohol–hexane (1:300); flow rate, 0.5 ml/min; $t_R=16.2$ and 18.8 min.

3.14. (1*S*,5*S*,6*S*)-6-(*tert*-Butyldiphenylsilyloxymethyl)-3-(hydroxymethyl)bicyclo[3.1.0]hex-2-ene, 23

DIBAL (1.0 M in toluene, 788 μl, 0.788 mmol) was added dropwise to a solution of **22** (160 mg, 0.394 mmol) in toluene (5 ml) at −78°C, and the mixture was allowed to warm to room temperature. After stirring for 30 min, 10% sodium hydroxide aqueous solution was added at 0°C, and the resulting mixture was stirred for 5 min. The mixture was extracted with ether, washed with brine, dried over magnesium sulfate and evaporated. Purification by silica gel column chromatography with ethyl acetate–hexane (1:6) gave **23** as a colorless oil (120 mg, 81%). IR (neat) cm^{-1}: 3339 (-OH), 1112 (C-O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.04 (9H, s), 1.26–1.31 (1H, m), 1.65–1.70 (1H, m), 1.97 (1H, bd, $J=17.5$ Hz), 1.99–2.02 (1H, m), 2.43 (1H, dd, $J=8.0$, 17.5), 3.40 (1H, dd, $J=8.0$, 11.0), 3.58 (1H, dd, $J=6.5$, 11.0), 3.85 (2H, s), 5.35–5.36 (1H, m), 7.36–7.44 (6H, m), 7.66–7.68 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.17, 19.38, 23.35, 26.83, 27.89, 31.89, 58.35, 61.07, 123.99, 127.45, 127.52, 129.50, 134.11, 135.61, 135.65, 144.59. $[\alpha]_D^{18}$ −109.3 (*c* 1.50, $CHCl_3$) [77% ee]. The ee was determined by HPLC analysis with a chiral column (Daicel CHIRALCEL OD); eluent, isopropyl alcohol–hexane (1:20); flow rate, 0.5 ml/min; $t_R=12.9$ and 14.0 min.

3.15. (1*S*,5*S*,6*S*)-3,6-Bis(*tert*-butyldiphenylsilyloxymethyl)bicyclo[3.1.0]hex-2-ene, 24

TBDPSCl (80 μl, 0.308 mmol) was added to a solution of **23** (96.4 mg, 0.255 mmol) and imidazole (43.4 mg, 0.638 mmol) in DMF (3 ml) at 0°C. The mixture was stirred for 1 h at room temperature, poured into water, extracted with hexane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated to give a residue, which was subjected to silica gel column chromatography with ethyl acetate–hexane (1:40) to afford **24** (155 mg, 98%). For an analytical sample, recrystallization from hexane was carried out to afford colorless prisms, mp 74–75°C. IR (KBr) cm^{-1}: 1111 (C-O). ^1H NMR (200 MHz, $CDCl_3$) δ: 1.02 (18H, s), 1.12–1.33 (1H, m), 1.59–1.71 (1H, m), 1.92 (1H, d, $J=17.6$), 1.96–2.04 (1H, m), 2.48 (1H, dd, $J=8.0$, 17.6), 3.50 (2H, d, $J=7.4$), 3.95 (2H, s), 5.42 (1H, s), 7.28–7.42 (12H, m), 7.62–7.68 (8H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.23, 19.35, 23.61, 26.80, 26.89, 27.92, 31.99, 58.60, 62.26, 123.10, 127.47, 127.61, 129.39, 129.56, 133.76, 134.21, 134.26, 135.51, 135.59, 144.29. $[\alpha]_D^{18}$ −60.5 (*c* 1.20, $CHCl_3$) [82% ee]. Anal. calcd for $C_{40}H_{48}O_2Si_2$: C, 77.87; H, 7.84. Found: C, 78.04; H, 7.84%. The ee was determined by HPLC analysis with a chiral column (Daicel CHIRALCEL OD); eluent, hexane; flow rate, 0.5 ml/min; $t_R=19.3$ and 22.4 min.

3.16. (1*R*,2*R*,3*S*,5*R*,6*S*)-3,6-Bis(*tert*-butyldiphenylsilyloxymethyl)bicyclo[3.1.0]hexan-2-ol, (+)-25

A solution of **24** (54.2 mg, 87.8 μmol) in THF (3 ml) was added to a mixture of 9-BBN (0.5 M in THF, 526 μl, 0.263 mmol) and THF (2 ml). The mixture was heated under reflux for 30 min, and cooled to 0°C. Ethanol (0.3 ml), 3 M sodium hydroxide aqueous solution (0.2 ml) and 31% hydrogen peroxide aqueous solution (0.2 ml) were successively added to the reaction mixture. The mixture was heated under reflux for 1 h, poured into water, and extracted with ether. The organic layer was dried over magnesium sulfate and evaporated to give a residue. Silica gel column chromatography with ethyl acetate–hexane (1:8) gave (+)-**25** as a colorless oil (31.0 mg, 56%). IR (neat) cm^{-1}: 3391 (-OH), 1112 (C-O). ^1H NMR (500 MHz, $CDCl_3$) δ: 0.76 (1H, ddd, $J=2.5$, 11.0, 14.0), 1.02 (9H, s), 1.03 (9H, s), 1.20–1.27 (1H, m), 1.47 (1H, t, $J=8.5$), 1.55–1.61 (1H, m), 1.85 (1H, ddd, $J=7.5$, 10.5, 14.0), 2.17 (1H, bs), 2.53–2.57 (1H, m), 3.26 (1H, t, $J=9.5$), 3.44–3.48 (2H, m), 3.70–3.73 (2H, m), 7.27–7.42 (12H, m), 7.59–7.66 (8H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.04, 19.19, 21.81, 24.49, 24.58, 26.85, 29.76, 59.78, 60.33, 65.02, 75.95, 127.53, 127.56, 127.73, 129.55, 129.75, 133.19, 133.21, 133.91, 133.94, 135.49, 135.60. $[\alpha]_D^{22}$ +15.1 (*c* 1.44, $CHCl_3$) [84% ee]. Anal. calcd for $C_{40}H_{50}O_3Si_2$: C, 75.66; H, 7.94. Found: C, 75.65; H, 7.77%. The ee was determined by HPLC analysis with a chiral column (Daicel CHIRALCEL OD); eluent, isopropyl alcohol–hexane (1:200); flow rate, 0.5 ml/min; $t_R=30.6$ and 35.0 min.

3.17. (1*S*,2*S*,3*R*,5*S*,6*R*)-2-Benzyloxy-3,6-bis(hydroxymethyl)bicyclo[3.1.0]hexane, 26

DIBAL (1.0 M in toluene, 4.30 ml, 4.3 mmol) was added dropwise to a solution of **6** (257 mg, 0.845 mmol) in toluene (1 ml) at −78°C, and the mixture was allowed to warm to room temperature. After stirring for 1 h,

the mixture was poured into 10% aqueous HCl solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and evaporated. Purification by silica gel column chromatography with ethyl acetate–hexane (2:1) gave **26** (195 mg, 93%) which was recrystallized from dichloromethane–hexane to afford colorless needles, mp 109–110.5°C. IR (KBr) cm^{-1}: 3246 (-OH). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.17 (1H, ddd, $J=2.5$, 11.0, 14.0), 1.27 (1H, dddd, $J=7.5$, 8.0, 8.5, 8.5), 1.64–1.72 (2H, m), 1.83 (2H, bs), 2.10 (1H, ddd, $J=7.0$, 11.0, 14.0), 2.69–2.77 (1H, m), 3.60–3.66 (5H, m), 4.50 (1H, d, $J=11.5$), 4.66 (1H, d, $J=11.5$), 7.28–7.37 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.87, 24.36, 24.60, 27.50, 57.72, 57.94, 62.85, 72.35, 81.49, 127.67, 127.78, 128.38, 138.17. $[\alpha]_D^{22}$ +33.8 (*c* 1.24, $CHCl_3$) [96% ee]. Anal. calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.24; H, 8.11%. The ee was determined by HPLC analysis with a chiral column (Daicel CHIRALCEL OJ); eluent, isopropyl alcohol–hexane (1:5); flow rate, 0.8 ml/min; $t_R=12.9$ and 15.7 min.

3.18. (1*S*,2*S*,3*R*,5*S*,6*R*)-2-Benzyloxy-3,6-bis(*tert*-butyldiphenylsilyloxymethyl)bicyclo[3.1.0]hexane, 27

TBDPSCl (80 μl, 0.454 mmol) was added to a solution of **26** (20.8 mg, 83.8 μmol) and imidazole (30.9 mg, 0.638 mmol) in DMF (1 ml) at 0°C. The mixture was stirred for 1 h at room temperature, poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and evaporated to give a residue. The residue was subjected to silica gel column chromatography with ether–hexane (1:20) to give **27** as a colorless oil (54.1 mg, 89%). IR (KBr) cm^{-1}: 1110, 1070. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.00 (9H, s), 1.04 (9H, s), 1.11–1.28 (3H, m), 1.52–1.58 (1H, m), 2.04–2.10 (1H, m), 2.67–2.72 (1H, m), 3.40 (1H, dd, $J=6.0$, 11.0), 3.54 (1H, dd, $J=6.0$, 11.0), 3.57 (1H, d, $J=7.5$), 3.61 (1H, dd, $J=8.0$, 11.5), 3.76 (1H, dd, $J=8.0$, 11.5), 4.38 (1H, d, $J=7.5$), 4.52 (1H, d, $J=7.5$), 7.23–7.40 (17H, m), 7.60–7.67 (8H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ:19.18, 19.22, 21.95, 24.43, 25.43, 26.84, 26.88, 27.84, 58.02, 59.96, 63.91, 72.26, 81.12, 127.33, 127.55, 127.58, 127.59, 128.23, 129.53, 133.72, 133.75, 134.02, 134.04, 135.59, 135.62, 135.65, 138.67. $[\alpha]_D^{20}$ −8.8 (*c* 2.18, $CHCl_3$) [95% ee]. Anal. calcd for $C_{47}H_{56}O_3Si_2$: C, 77.85; H, 7.78. Found: C, 78.02; H, 8.06. The ee was determined by HPLC analysis with a chiral column (Daicel CHIRALCEL OD); eluent, isopropyl alcohol–hexane (1:30); flow rate, 0.1 ml/min; $t_R=33.4$ and 35.7 min.

3.19. Conversion of 26 into (−)-25

A mixture of **26** (80.4 mg, 0.324 mmol), 5% palladium on carbon (10.5 mg) and methanol (2 ml) was stirred for 95 h under a hydrogen atmosphere. After filtration, the filtrate was concentrated to give a residue, which was dissolved in DMF (1 ml). Imidazole (111 mg, 1.63 mmol) and DMAP (6.1 mg, 49.9 μmol) were added to the mixture. After addition of TBDPSCl (200 μl, 0.769 mmol) at 0°C, the mixture was stirred for 30 min, poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and evaporated to give a residue. Silica gel column chromatography with ethyl acetate–hexane (1:8) gave (−)-**25** (121 mg, 59%) as a colorless oil. $[\alpha]_D^{14}$ −17.2 (*c* 1.79, $CHCl_3$) [97% ee]. Other spectral data were identical with those of (+)-**25** described above. The ee was determined by HPLC analysis with a chiral column (Daicel CHIRALCEL OD); eluent, isopropyl alcohol–hexane (1:200); flow rate, 0.5 ml/min; $t_R=30.6$ and 35.0 min.

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