Tetrahedron: Asymmetry Vol. 4, No. 7, pp. 1537-1546, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Preparation of Chiral Cyclobutane Derivatives: Enantioselective Syntheses of the Key Intermediates for Cyclobutane Monoterpenes, Grandisol and Lineatin

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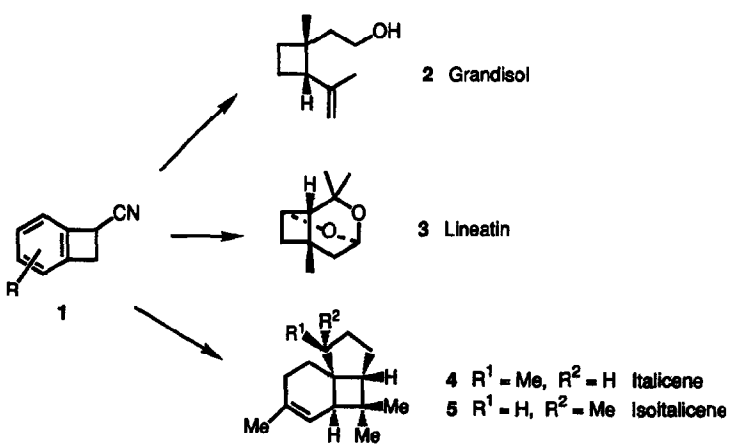
(*Received in Japan* 11 *March* 1993)

Abstract: Enantioselective synthesis of the key intermediates for cyclobutane monoterpenes, grandisol and lineatin was achieved by employing an enantioselective reduction of the prochiral cyclobutenone derivative as a key step.

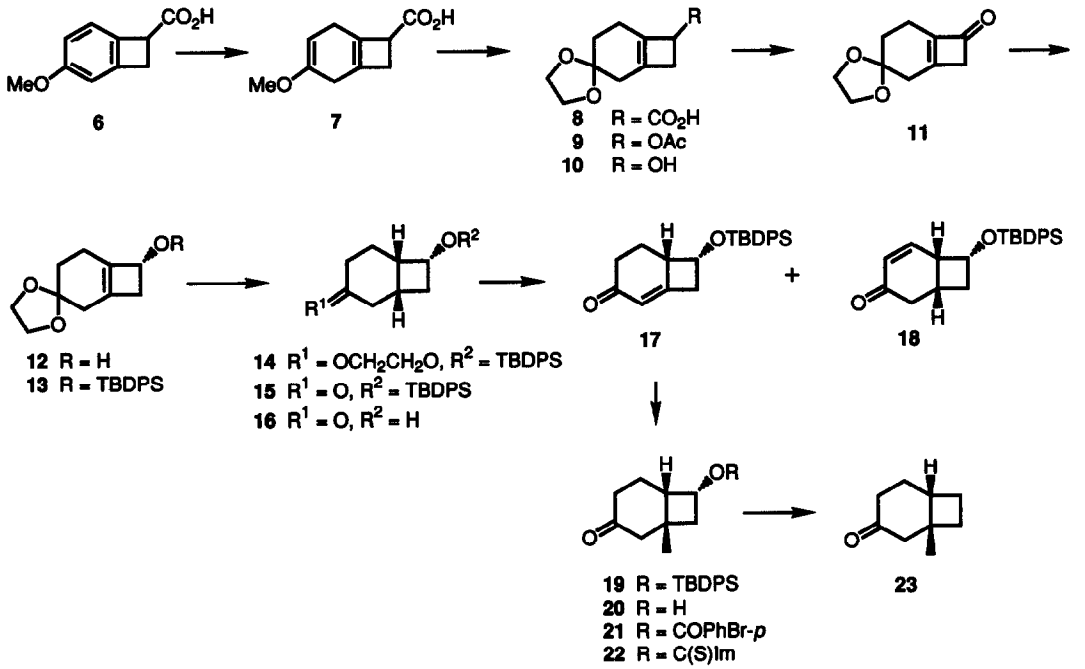
Recently we have established novel synthetic routes to cyclobutane monoterpenes, grandisol (**2**) and lineatin (**3**),[1] and also sesquiterpenes, italicene (**4**) and isoitalicene (**5**)[2] in racemic forms, starting from readily accessible benzocyclobutene derivatives (**1**).



As part of our ongoing effort directed at the exploitation of benzocyclobutene derivatives as starting materials for the synthesis of natural products bearing the cyclobutane ring system, we wished to develop their chiral synthesis. We planned to utilize an enantioselective reduction of a prochiral cyclobutenone derivative

for this purpose, since the applications of such asymmetric reduction to the cyclobutenone system have not been reported yet and here report an enantioselective synthesis of the key intermediates for grandisol and lineatin.

The starting prochiral cyclobutenone (**11**) for an asymmetric reduction was prepared as follows. The Birch reduction of the acid (**6**)[3] with sodium metal in liquid ammonia in the presence of ethanol afforded the enol ether (**7**), which on treatment with ethylene glycol and *p*-toluenesulfonic acid gave the olefinic acid (**8**) in 90% yield. Oxidative acetoxylation of **8** with lead tetraacetate and copper(II) acetate[4] gave the corresponding acetate (**9**), in 70% yield, which was then hydrolyzed with methanolic potassium carbonate to provide the alcohol (**10**) in 74% yield. Swern oxidation[5] of the alcohol (**10**) gave the ketone (**11**) in 80% yield.



Scheme

With the requisite starting prochiral ketone available, a study was made of the best conditions for the enantioselective reduction to the chiral alcohol (**12**). We first attempted an enantioselective reduction of **11** with (*S*)-(-)-2-diphenylhydroxymethylpyrrolidine and borane, under the rection conditions developed by Corey[6] affording the chiral alcohol (**12**) in quantitative conversion yield. Optical purity of the alcohol (**12**) was estimated to be 58% e.e. on the basis of the NMR spectrum of its Mosher's ester. Although its absolute configuration could not be determined at this stage, it was assumed to have *R*-configuration based on the consideration of previously reported results.[6] Asymmetric reductions of the ketone (**11**) by employing other chiral reducing agents are summarized in the Table, in which the highest optical purity was obtained by using (-)-*B*-chlorodiisopinocamphenylborane as the reducing agent, furnishing the ent-alcohol (**12**) in 63% yield with 78% e.e.

Table. Enantioselective Reduction of the Cyclobutenone (11)

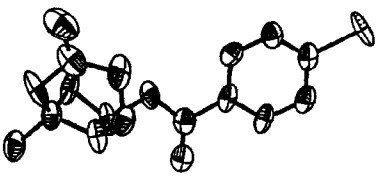
Reducing agent	Yield (%)	Enantiomeric excess (%)[a]	$[\alpha]_D$	Absolute configuration[b]	Reference
(*S*)-Oxazaborolidine, BH_3-THF	100	58	+6.25	*R*	6
(*R*)-(+)-1,1'-Bi-2-naphthol, $LiAlH_4$	88	36	+4.79	*R*	7
(-)-*B*-Chlorodiisopino-camphenylborane	63	78	-8.62	*S*	8
(*S*)-(+)-2-(Xylidinomethyl)-pyrrolidine, $LiAlH_4$	28	45	-5.30	*S*	9

a) Enantiomeric excess was determined by ^{1}H-NMR analysis of the corresponding MTPA ester.
b) Absolute configuration was determined on the basis of the X-ray analysis of the benzoate (**21**).

Having thus obtained the chiral cyclobutenol, its conversion to the important intermediates for the synthesis of grandisol and lineatin was then investigated. Silylation of the alcohol (**12**) with *tert*-butyldiphenylsilyl chloride gave the silyl ether (**13**), whose catalytic reduction over 5% palladium on carbon in tetrahydrofuran occurred from the less hindered side to furnish the acetal (**14**) as the sole product, stereoselectively, in 92% yield. Selective deprotection of the acetal group of **14** on treatment with *p*-toluenesulfonic acid gave the ketone (**15**), in 85% yield, which was recrystallized from methanol to afford the enantionerically pure ketone, mp, 75-76°C, $[\alpha]_D$ +30.8 (c=1.0, $CHCl_3$), based on the NMR analysis of the Mosher's ester of the alcohol (**16**) prepared from the silyl ether (**15**) by acid treatment. In order to introduce an angular methyl group, the ketone (**15**) was converted into the corresponding enones (**17**) in 47% yield accompanied by the regioisomer (**18**), in a ratio of 2:1, by utilizing the Saegusa's method[10] involving the palladium acetate mediated oxidation of the corresponding silyl enol ethers. The minor enone (**18**) could be recycled by conversion into the ketone (**15**) on catalytic reduction over 5% palladium on carbon in 98% yield. The conjugate addition of the methyl group to the enone (**17**) with dimethylcopper lithium in ether gave the ketone (**19**), in 95% yield, which on treatment with hydrochloric acid in methanol afforded the alcohol (**20**), in 77% yield, identical with the racemic authentic specimen except for its optical rotation. The absolute configuration of the alcohol (**20**) was unambiguously established at this stage as depicted in the Figure, supporting the presumed configuration, by means of the Bijvoet's anomalous-dispersion method in a X-ray analysis of the *p*-bromobenzoate (**21**).

Since the ketone (**20**) has already been transformed into lineatin (**3**) by us,[1] this synthesis constitutes its formal enantioselective synthesis. We next investigated the deoxygenation of the hydroxyl group of **20** to synthesize the key intermediate for grandisol. Thus, the alcohol (**20**) was converted into the corresponding thioimidazolide (**22**), in a usual manner, which on treatment with tri-*n*-butyltin hydride in the presence of

AIBN in refluxing benzene[11] afforded the ketone (**23**) in 35% yield. The spectroscopic data of **23** were identical with those of the authentic sample. Since the ketone (**23**) has also been converted into grandisol (**2**) by us,[1] this synthesis constitutes its formal enantioselective synthesis.



The ORTEP Drawing of the *p*-Bromobenzoate (**21**).

Thus we could achieve the chiral synthesis of the key intermediates for the cyclobutane monoterpenes, grandisol and lineatin by employing an enantioselective reduction of the prochiral cyclobutenone. This synthetic route should be applicable to the synthesis of other natural products possessing the cyclobutane ring system.

Experimental

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 Spectrophotometer. ^{1}H NMR spectra were obtained for solution in $CDCl_3$ on a JEOL PMX GSX 270 instrument, and chemical shifts are reported in ppm on the δ scale from internal tetramethylsilane. *J* values are given in Hz. Mass spectra were measured with a JEOL JMS D-300 spectrometer. TLC was carried out on precoated 0.25 mm silica gel 70 F_{254} (Wako) plates.

3,3-Ethylenedioxybicyclo[4.2.0]oct-1(6)-en-7-carboxylic Acid (8): To a stirred solution of the acid (**6**)(50 g, 281 mmol) in liq. ammonia (2 l), dry tetrahydrofuran (400 ml), and ethanol (100 ml) was added sodium metal (25.9 g, 1.12 mol) over the period of 2 h at -33°C. After addition of methanol (200 ml) to the solution, the mixture was concentrated to leave a residue, which was poured into water. The aqueous layer was washed with ethyl acetate and acidified with 10% hydrochloric acid. The acidic layer was extracted with ethyl acetate and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the enol ether (**7**), which, without further purification, was used in the next step. A solution of the enol ether (**7**), ethylene glycol (15.8 g, 282 mmol), and a catalytic amount of *p*-toluenesulfonic acid in dichloromethane (500 ml) was stirred for 30 min at ambient temperature and the mixture was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (6:4, v/v) afforded the acid (**8**)(53 g, 90%) as a colorless oil. IR ($CHCl_3$) 3300, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.82 (2H, t, *J*=7.3 Hz, 4-H_2), 2.05-3.10 (6H, m, CH_2×3),

3.63 (1H, br s, 7-H), 3.97-4.01 (4H, s, OCH_2CH_2O). MS *m/z* 210 (M^+)(Found 210.0883. Calcd for $C_{11}H_{14}O_4$: 210.0890).

7-Acetoxy-3,3-ethylenedioxybicyclo[4.2.0]oct-1(6)-ene (9): A solution of the acid (**8**)(1.8 g, 8.57 mmol), potassium acetate (5.0 g, 51.43 mmol), copper(II) acetate (31 mg, 0.17 mmol), and lead tetraacetate (4.86 g, 9.86 mmol) in toluene - acetic acid (40 ml, 1:1 v/v) was stirred for 2 h at 60°C. Ethylene glycol (0.5 ml) was then added to the solution and the mixture was further stirred for 30 min at room temperature. The insoluble materials were filtered off, and the filtrate was treated with water, and extracted with ethyl acetate. The organic layer was washed with saturated sodium hydrogen carbonate solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (8:2, v/v) afforded the acetate (**9**)(1.34 g, 70%) as a yellow oil. IR ($CHCl_3$). 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.80 (2H, t, *J*=6.1 Hz, 4-H_2), 2.05 (3H, s, Me), 2.10-3.95 (6H, m, CH_2×3), 3.98 (4H, s, OCH_2CH_2O), 5.35 (1H, br s, *CH*OAc). MS *m/z* 224 (M^+)(Found 224.1053. Calcd for $C_{12}H_{16}O_4$: 224.1048).

3,3-Ethylenedioxybicyclo[4.2.0]oct-1(6)-en-7-ol (10): A mixture of the acetate (**9**)(1.0 g, 4.46 mmol), potassium carbonate (740 mg, 5.36 mmol) and methanol (5 ml) was stirred for 2 h at 0°C. The insoluble material was filtered off, and the filtrate was treated with water and extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1:1, v/v) afforded the alcohol (**10**)(600 mg, 74%) as a colorless oil. IR ($CHCl_3$). 3450 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.70 (1H, br s, OH), 1.79 (2H, t, *J*=6.1 Hz, 4-H_2), 2.10-2.90 (6H, m, CH_2×3), 3.98 (4H, s, OCH_2CH_2O), 4.68 (1H, br s, 7-H). MS *m/z* 182 (M^+)(Found 182.0933. Calcd for $C_{10}H_{14}O_3$: 182.0941).

3,3-Ethylenedioxybicyclo[4.2.0]oct-1(6)-en-7-one (11): To a stirred solution of oxalyl chloride (0.527 ml, 6.04 mmol) in dry dichloromethane (12 ml) was added dropwise a solution of dimethyl sulfoxide (0.857 ml, 12.08 mmol) in dry dichloromethane (3 ml) at -50°C and the mixture was stirred for 2 min. A solution of the alcohol (**10**)(1.0 g, 5.49 mmol) in dry dichloromethane (5 ml) was added to this solution and further stirred for 15 min at the same temperature. After addition of triethylamine (3.83 ml, 27.45 mmol), the resulting mixture was allowed to warm to ambient temperature and treated with water, and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (8:2, v/v) afforded the ketone (**11**)(786 mg, 80%) as colorless solid. IR ($CHCl_3$). 1750 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.81 (2H, t, *J*=6.1 Hz, 4-H_2), 2.20-3.50 (2H, m, 5-H_2), 2.72 (2H, s, 2-H_2), 3.22 (2H, t, *J*=3.7 Hz, 8-H_2), 4.03 (4H, s, OCH_2CH_2O). MS *m/z* 180 (M^+)(Found 180.0782. Calcd for $C_{10}H_{12}O_3$ 180.0785). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.43; H, 6.81.

Asymmetric Reduction of the Ketone (11): (*a*) Using (*S*)-oxazaborolidine --- To a stirred solution of the ketone (**11**)(500 mg, 2.78 mmol) and (*S*)-oxazaborolidine (1.1 ml, 1M solution in THF) in dry tetrahydrofuran (5 ml) was added dropwise BH_3 THF (1.67 ml, 1M solution in THF) over the period of 30 min at 35°C under argon and the resulting mixture was further stirred for 10 min. Methanol was added to the solution and the mixture was concentrated to leave a residue, which was subjected to column chromatography

on silica gel. Elution with hexane-ethyl acetate (1:1, v/v) afforded the (*R*)-alcohol (**12**)(505 mg, 100%) as colorless oil. $[\alpha]_D$ +6.25 (c=1.0, $CHCl_3$). IR ($CHCl_3$). 3450 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.70 (1H, br s, OH), 1.79 (2H, t, *J*=6.1 Hz, 4-H_2), 2.10-2.90 (6H, m, CH_2×3), 3.98 (4H, s, OCH_2CH_2O), 4.68 (1H, br s, 7-H). MS *m/z* 182 (M^+)(Found 182.0933. Calcd for $C_{10}H_{14}O_3$ 182.0941).

A solution of the alcohol (**12**)(10.5 mg, 0.058 mmol), (*S*)-(-)-MTPACl (15.0 mg, 0.059 mmol), triethylamine (0.02 ml) and a catalytic amount of *N,N*-dimethylaminopyridine in dichloromethane (1 ml) was stirred for 12 h at room temperature under argon. The mixture was poured into water and extracted with dichloromethane. The extract was washed with 10% hydrochloric acid and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (95:5, v/v) afforded the MTPA ester (22.0 mg, 96%) as a colorless oil. The enantiomeric excess was determined based on its ^1H NMR spectrum.

(*b*) Using (*R*)-(+)-1,1'-bi-2-naphthol --- To a stirred solution of lithium aluminum hydride (0.83 ml, 1M solution in THF) was added dropwise ethanol 0.83 ml (1M solution in THF) at 0°C under argon. A solution of (*R*)-(+)-1,1'-bi-2-naphthol (239 mg, 0.83 mmol) in dry tetrahydrofuran (1.4 ml) was then added to the solution and the resulting mixture was further stirred for 1 h at ambient temperature. The above solution was added dropwise to a solution of the ketone (**11**)(50 mg, 0.278 mmol) in dry tetrahydrofuran (0.5 ml) at -78°C under argon. After being stirred for 12 h at the same temperature, the mixture was treated with water and extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1:1, v/v) afforded the (*R*)-alcohol (**12**)(44.5 mg, 88%) as a colorless oil. $[\alpha]_D$ +4.79 (c=0.27, $CHCl_3$).

(*c*) Using (-)-DIP-Cl --- To a stirred solution of (-)-*B*-chlorodiisopinocamphenylborane (78.5 mg, 0.24 mmol) in dry tetrahydrofuran (0.8 ml) was added dropwise a solution of the ketone (**11**)(40 mg, 0.22 mmol) in dry tetrahydrofuran (0.8 ml) at -25°C under argon. After being stirred for 5 h, the mixture was allowed to warm to room temperature, and the solvent was removed in vacuo. The residue was dissolved into ether and diethanolamine (51.4 mg, 0.49 mmol) was added to this solution and the resulting mixture was further stirred for 2 h. The separated solid was filtered off and the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1:1, v/v) afforded the (*S*)-alcohol (ent-**12**)(25.5 mg, 63%) as a colorless oil. $[\alpha]_D$ -8.62 (c=0.26, $CHCl_3$).

(*d*) Using (*S*)-(+)-(xylidinomethyl)pyrrolidine --- To a stirred suspension of lithium aluminum hydride (0.28 ml, 1M solution in THF) in ether (0.5 ml) was added a solution of (*S*)-(+)-(xylidinomethyl)pyrrolidine (68.0 mg, 0.33 mmol) in ether (0.3 ml) over the period of 10 min at room temperature under argon. After being stirred for 1 h at the same temperature, a solution of the ketone (**11**)(20 mg, 0.11 mmol) in ether (0.5 ml) was added dropwise to the solution at -78°C and the resulting mixture was further stirred for 3 h. The mixture was treated with 5% hydrochloric acid and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1:1, v/v) afforded the (*S*)-alcohol (ent-**12**)(5.67 mg, 28%) as a colorless oil. $[\alpha]_D$ -5.30 (c=0.11, $CHCl_3$).

(+)-7*R*-*tert*-Butyldiphenylsiloxy-3,3-ethylenedioxybicylo[4.2.0]oct-1(6)-ene (13): A solution of the alcohol (**12**)(500 mg, 2.75 mmol) obtained by the above method (*a*), tert-butyldiphenylsilyl chloride (831 mg, 3.03 mmol), triethylamine (0.57 ml, 4.12 mmol) and a catalytic amount of *N,N*-dimethylaminopyridine in dichloromethane (10 ml) was stirred for 12 h at 0°C under argon. The mixture was poured into water and extracted with dichloromethane. The organic layer was washed with brine and dried over Na_2SO_4.

Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (95:5, v/v) afforded the (*R*)-silyl ether (**13**)(1.16 g, 100%) as a colorless oil. $[\alpha]_D$ +12.80 (c=1.0, $CHCl_3$). IR ($CHCl_3$). 1120 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.06 (9H, s, ^tBu), 1.66 (2H, t, *J*=6.1 Hz, 4-H_2), 1.80-2.88 (6H, m, CH_2×3), 3.75-3.98 (4H, m, OCH_2CH_2O), 4.74 (1H, br s, 7-H), 7.20-7.45 (6H, m, ArH), 7.55-7.78 (4H, m, ArH). MS *m/z* 420 (M^+)(Found 420.2112. Calcd for $C_{26}H_{32}O_3Si$ 420.2119).

(+)-(1*R*, 6*S*, 7*R*)-7-endo-*tert*-Butyldiphenylsiloxy-3,3-ethylenedioxybicyclo[4.2.0]octane (14): A mixture of the olefin (140 mg, 0.33 mmol), 5% palladium on carbon (20 mg), and dry tetrahydrofuran (2 ml) was stirred at ambient temperature under an atmospheric pressure of hydrogen for 4 h. The insoluble material was filtered off and the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (95:5, v/v) afforded the ether (**14**)(130 mg, 92%) as a colorless oil. $[\alpha]_D$ +11.90 (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.03 (9H, s, ^tBu), 1.20-2.45 (10H, m), 3.80-4.03 (4H, m, OCH_2CH_2O), 4.12 (1H, dd, *J*=6.7 and 14.7 Hz, 7-H), 7.30-7.45 (6H, m, ArH), 7.60-7.70 (4H, m, ArH). MS *m/z* 422 (M^+)(Found 422.2279. Calcd for $C_{26}H_{34}O_3Si$ 422.2277).

(+)-(1*R*, 6*S*, 7*R*)-7-endo-*tert*-Butyldiphenylsiloxybicyclo[4.2.0]octan-3-one (15): A solution of the ether (**14**)(3.40 g, 8.10 mmol) and a catalytic amount of *p*-toluenesulfonic acid in acetone (100 ml) was stirred for 1 h at ambient temperature. After removal of the solvent, the residue was dissolved into ethyl acetate and the organic layer was washed with saturated sodium hydrogen carbonate solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (95:5, v/v) afforded the ketone (**14**)(2.59 g, 85%) as a colorless solid. Recrystallization from methanol at 0°C gave the enantiomerically pure ketone as colorless needles (42.5%), mp 75-76°C. $[\alpha]_D$ +30.80 (c=1.0, $CHCl_3$). IR ($CHCl_3$). 1710 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.04 (9H, s, ^tBu), 1.75-2.03 (2H, m), 2.23-2.55 (6H, m), 2.59-2.80 (2H, m), 4.37 (1H, dd, *J*=7.9 and 15.8 Hz, 7-H), 7.30-7.50 (6H, m, ArH), 7.55-7.65 (4H, m, ArH). MS *m/z* 321 (M^+-57). Anal. Calcd for $C_{24}H_{30}O_2Si$: C, 76.15; H, 7.98. Found: C, 76.12; H, 8.11. The enantiomeric excess was again determined by ^1H NMR analysis of the its Mosher' s ester.

(+)-(1*R*, 6*S*, 7*R*)-7-endo-Hydroxybicyclo[4.2.0]octan-3-one (16): A solution of the silyl ether (**15**)(500 mg, 1.32 mmol) and 10% hydrochloric acid (1 ml) in methanol (9 ml) was stirred at ambient temperature for 24 h. After removal of the solvent, the residue was dissolved into ethyl acetate, and the organic layer was washed with saturated sodium hydrogen carbonate solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1:1, v/v) afforded the alcohol (**15**)(180 mg, 81%) as a colorless oil. $[\alpha]_D$ +10.0 (c=0.18, $CHCl_3$). IR ($CHCl_3$). 1710 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.67-2.8 (10H, m), 4.44 (1H, dd, *J*=7.3 and 15.3 Hz, 7-H). MS *m/z* 140 (M^+)(Found 140.0829. Calcd for $C_8H_{12}O_2$ 140.0836).

(+)-(6*S*, 7*R*)-7-endo-*tert*-Butyldiphenylsiloxybicyclo[4.2.0]oct-1-en-3-one (17) and (+)-(1*R*, 6*S*, 7*R*)-7-endo-*tert*-Butyldiphenylsiloxybicyclo[4.2.0]oct-4-en-3-one (18): To a stirred solution of the ketone (**15**)(786 mg, 2.08 mmol) in dry tetrahydrofuran (5 ml) in the presence of lithium diisopropylamide (1.7 ml, 2.50 mmol, 1.5M solution in hexane) was added trimethylsilyl chloride (0.34 ml, 2.70 mmol) at -78°C under

argon and the resulting mixture was further stirred for 1 h at the same temperature. The solution was allowed to warm to room temperature over the period of 1 h and treated with water. The mixture was extracted with ethyl acetate and the extract was washed with saturated sodium hydrogen carbonate solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was dissolved into acetonitrile (10 ml). This solution was added to a solution of palladium acetate (1.0 g, 4.45 mmol) in acetonitrile (40 ml) at ambient temperature and the resulting mixture was further stirred for 10 h at the same temperature. Removal of the solvent gave a black residue, which was taken up to dichloromethane. Insoluble material was then filtered off through a Celite pad and the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (95:5, v/v) afforded the enone (**18**)(200 mg, 26%) as a colorless solid, mp 68-71°C, as the second eluant. $[\alpha]_D$ +236.8 (c=1.0, $CHCl_3$). IR ($CHCl_3$). 1670 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.03 (9H, s, ^tBu), 1.90-2.12 (1H, m, 8-H), 2.14-2.50 (4H, m, 1-H, 2-H_2, and 8-H), 3.03-3.19 (1H, m, 6-H), 4.43 (1H, dd, *J*= 8.0 and 15.0 Hz, 7-H), 6.31 (1H, dd, *J*=1.8 and 10.4 Hz, 4-H), 6.96 (1H, ddd, *J*=1.2, 3,7, and 10.4 Hz, 5-H), 7.30-7.50 (6H, m, ArH), 7.57-7.70 (4H, m, ArH). MS *m/z* 319 (M^+-57). Anal. Calcd for $C_{24}H_{28}O_2Si$: C, 76.55; H, 7.49. Found: C, 76.65; H, 7.54.

Further elution with the same solvent system afforded the enone (**17**)(371 mg, 47%) as a colorless solid, mp 65-68°C, as the first eluant. $[\alpha]_D$ -39.0 (c=1.0, $CHCl_3$). IR ($CHCl_3$). 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.07 (9H, s, ^tBu), 1.67-1.83 (1H, m, 5-*H*H), 2.20-2.65 (3H, m), 3.07 (1H, ddd, *J*=2.4, 6.1, and 16.5 Hz, 8-*H*H), 3.12-3.20 (1H, m, 6-H), 4.72 (1H, dt, *J*=1.2 and 6.7 Hz, 7-H), 5.89 (1H, br s, 2-H), 7.26-7.48 (6H, m, ArH), 7.50-7.60 (4H, m, ArH). MS *m/z* 376 (M^+). Anal. Calcd for $C_{24}H_{28}O_2Si$: C, 76.55; H, 7.49. Found: C, 76.61; H, 7.50.

A mixture of the enone (**18**)(123 mg, 0.327 mmol), a catalytic amount of 5% palladium on carbon, and dry tetrahydrofuran (5 ml) was stirred under an atmospheric pressure of hydrogen for 3 h. The mixture was fitered to remove the insoluble material and the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (95:5, v/v) afforded the ketone (**15**)(121 mg, 98%) as a colorless solid, identical with the authentic specimen.

(+)-(1*R*, 6*S*, 7*R*)-7-endo-*tert*-Butyldiphenylsiloxy-1-methylbicyclo[4.2.0]octan-3-one (19): To a stirred solution of the lithium dimethylcuprate [prepared from CuI (281 mg, 1.47 mmol) and a 1.16M ethereal solution of methyllithium (2.54 ml, 2.95 mmol)] in ether (20 ml) was added a solution of the enone (**17**)(370 mg, 0.98 mmol) in ether (5 ml) at -20°C under argon. The solution was further stirred for 1 h at the same temperature and allowed to warm to room temperature. After treatment with saturated ammonium chloride solution, the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (9:1, v/v) afforded the ketone (**19**)(353 mg, 95%) as a colorless oil. $[\alpha]_D$ +21.60 (c=1.0, $CHCl_3$). IR ($CHCl_3$). 1700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.02 (9H, s, ^tBu), 1.06 (3H, s, Me), 1.87 (1H, dd, *J*=6.7 and 12.2 Hz, 8-H), 1.85-2.00 (1H, m, 5-H), 2.12 (1H, ddd, *J*=3.1, 7.9, and 12.2 Hz, 8-H), 2.20-2.45 (3H, m, 4-H, 5-H, and 6-H), 2.22 (1H, d, *J*=16.5 Hz, 2-H), 2.37 (1H, d, *J*=16.5 Hz, 2-H), 2.79 (1H, ddd, *J*=4.3, 10.4, and 18.3 Hz, 4-H), 4.54 (1H, dd, *J*= 7.9 and 15.3 Hz, 7-H), 7.30-7.50 (6H, m, ArH), 7.58-7.64 (4H, m, ArH). MS *m/z* 335 (M^+-57). Anal. Calcd for $C_{25}H_{32}O_2Si$: C, 76.48; H, 8.41. Found: C, 76.58; H, 8.41.

(-)-(1*R*, 6*S*, 7*R*)-7-endo-Hydroxy-1-methylbicyclo[4.2.0]octan-3-one (20): A solution of the silyl ether (**19**)(420 mg, 1.07 mmol) in methanol (9 ml) in the presence of 10% hydrochloric acid (1 ml) was stirred at ambient temperature for 24 h. After removal of the solvent, the residue was dissolved into ethyl acetate, and the organic layer was washed with saturated sodium hydrogen carbonate solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1:1, v/v) afforded the alcohol (**20**)(127 mg, 77%) as a colorless oil. $[\alpha]_D$ -25.20 (c=0.35, $CHCl_3$). IR ($CHCl_3$). 1700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.19 (3H, s, Me), 1.81 (1H, dd, *J*=6.7 and 12.8 Hz, 8-H), 1.86-2.00 (2H, m, 5-H_2), 2.07-2.20 (1H, m, 8-H), 2.22-2.40 (2H, m, 4-H and 6-H), 2.24 (1H, d, *J*=16.5 Hz, 2-H), 2.43 (1H, d, *J*=16.5 Hz, 2-H), 2.60 (1H, ddd, *J*=4.9, 9.2, and 18.3 Hz, 4-H), 4.60 (1H, dd, *J*= 7.9 and 15.3 Hz, 7-H). MS *m/z* 154 (M^+)(Found 154.0988. Calcd for $C_9H_{14}O_2$ 154.0993).

(+)-(1*R*, 6*S*, 7*R*)-7-endo-(4-Bromobenzoyl)oxy-1-methylbicyclo[4.2.0]octan-3-one (21): A solution of the alcohol (**19**)(67 mg, 0.04 mmol), 4-bromobenzoyl chloride (11.5 mg, 0.05 mmol), triethylamine (0.012 ml), and a catalytic amount of *N,N*-dimethylaminopyridine in dichloromethane (2 ml) was stirred for 2 h at room temperature. The mixture was treated with water and extracted with dichloromethane. The extract was washed with 10% hydrochloric acid and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (95:5, v/v) afforded the benzoate (**21**)(15 mg, 100%) as colorless prisms, mp 79-80°C. $[\alpha]_D$ +44.9 (c=0.1, $CHCl_3$). IR ($CHCl_3$). 1710 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.31 (3H, s, Me), 1.94-2.06 (2H, m, 5-H_2), 2.10 (1H, dd, *J*=7.3 and 12.8 Hz, 8-H), 2.26-2.40 (1H, m, 4-H), 2.32 (1H, d, *J*=16.5 Hz, 2-H), 2.40-2.62 (2H, m, 4-H and 8-H), 2.48 (1H, d, *J*=15.9 Hz, 2-H), 2.63-2.74 (1H, m, 6-H), 5.52 (1H, dd, *J*= 7.9 and 15.9 Hz, 7-H), 7.60 (2H, d, *J*=8.5 Hz, ArH), 7.88 (2H, d, *J*=8.5 Hz, ArH). MS *m/z* 336 and 338 (M^+)(Found 336.0364 and 338.0330. Calcd for $C_{16}H_{17}O_3Br$ 336.0362 and 338..0340).

X-Ray Analysis of the Benzoate (21): All the measurements were performed on a Rigaku AFC-5 diffractometer using Cu Kα radiation. The unit cell dimensions were determined by least-squares calculation from 20 high-angle reflections. Intensity data were collected by using the $2\theta/\omega$ scan technique for $6° < 2\theta < 130°$ with an average scan rate of 1°/min. In total 1532 independent reflections were collected, and 1434 satisfying the condition $Fo < 3\sigma < (F)$ were used for calculation. Crystal data for **21**: $C_{16}H_{17}O_3Br$. *Mr*=337.21. Orthorhombic *a*=12.8066(43) Å, *b*=19.762(11)Å, *c*=5.9406(23)Å, V=1503(1)$Å^3$, *Dc*=1.49 gcm^{-3}. Z=4. Space group $P2_12_12_1$. The structure was solved by the heavy-atom method and refined by the block-diagonal least-squares method with anisotropic thermal parameters for all non-hydrogen atoms. The final R factor was finally reduced to 0.075.

(+)-(1*R*, 6*S*, 7*R*)-7-endo-Imidazolylthiocarbonyloxy-1-methylbicyclo[4.2.0]octan-3-one (22): A solution of the alcohol (20)(127 mg, 0.83 mmol) and thiocarbonyldiimidazole (327 mg, 1.65 mmol) in dry tetrahydrofuran (2 ml) was heated at reflux for 1 h under argon. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1:1, v/v) afforded the thioimidazolide (**22**)(218 mg, 100%) as colorless solid, mp 45-48°C. $[\alpha]_D$ +37.5 (c=2.2, $CHCl_3$). IR ($CHCl_3$). 1710 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.32 (3H, s, Me), 2.03 (1H, d, *J*=7.3 Hz, 5-H), 2.08 (1H, d, *J*=6.1 Hz, 5-H), 2.22 (1H, dd, *J*=7.3 and 12.8 Hz, 8-H), 2.27-2.50 (2H, m, 4-H_2), 2.35 (1H, d, *J*=15.9 Hz, 2-H), 2.50 (1H, d, *J*=16.5 Hz, 2-H), 2.57 (1H, ddd, *J*=3.7, 8.6, and 13.4 Hz, 8-H), 2.72-2.84 (1H, m, 6-H),

5.81 (1H, dd, *J*= 7.9 and 15.9 Hz, 7-H), 7.06 (1H, s, Im), 7.60 (1H, s, Im), 8.32 (1H, s, Im). MS *m/z* 264 (M^+)(Found 264.0925. Calcd for $C_{13}H_{16}N_2O_2S$ 264.0931).

(+)-(1*R*, 6*S*)-1-Methylbicyclo[4.2.0]octan-3-one (23): To a refluxing solution of the thioimidazolide (**22**)(220 mg, 0.83 mmol) in benzene (80 ml) was added a solution of tri-*n*-butyltin hydride (0.34 ml) and a catalytic amount of AIBN in benzene (10 ml) and the resulting mixture was further heated at reflux for 1 h. After evaporation of the solvent, a residue was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (95:5, v/v) afforded the ketone (**23**)(40 mg, 35%) as colorless oil. $[\alpha]_D$ +8.0 (c=0.1, $CHCl_3$). IR ($CHCl_3$). 1700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.18 (3H, s, Me), 2.21 (1H, d, *J*=15.3 Hz, 2-H), 2.40 (1H, d, *J*=15.9 Hz, 2-H). MS *m/z* 138 (M^+)(Found 138.1038. Calcd for $C_9H_{14}O$ 138.1043).

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