Pergamon

Tetrahedron, Vol. 53, No. 39, pp. 13307-13314, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00869-7

Enantioselective Construction of Alicyclic Bicyclo[3.1.0]hexane Framework by Double Stereodifferentiation and its Application for the Synthesis of Both Enantiomers of Vitamin D_3 CD Ring Synthons

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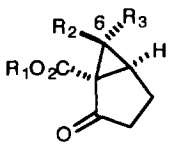
Abstract: Good diastereoselectivity (85:15) was observed in the intramolecular cyclopropanation of the chiral unsaturated α-diazo-β-keto ester **9f**, which possesses (*R*)-pantolactone as a chiral auxiliary. The reaction was catalyzed by a chiral bis-oxazoline copper (I) complex **17**. The absolute stereochemistry of each generated diastereomer (**10f** and **11f**) was elucidated. Both enantiomers of the vitamin D_3 CD ring synthons ((-)-**21** and (+)-**22**) were synthesized from (-)-**12** and (+)-**13**, respectively. © 1997 Elsevier Science Ltd.

There are many biologically interesting natural products possessing the cyclopentane ring,[1] and therefore a method for the synthesis of enantiomerically pure cyclopentane units would be of high utility. The bicyclo[3.1.0]hexanes (**1** to **5**)[2] (Fig. 1), which possess a variety of substitutions in the C_6-position, are a group of synthons useful in the synthesis of cyclopentanoid natural products, especially those which have both ring and side chain continuous chiral centers.[3] The first synthesis of C_6 exo methyl-substituted **4** in chiral form was achieved by our group using optical resolution.[2c] On the other hand, Taber reported the diastereoselective intramolecular cyclopropanation of an enantiomerically pure α-diazo-β-keto ester using naphthylborneol as the chiral auxiliary.[2d] Although moderate diastereoselectivity (80:20) was reported by using (dppp)$PdCl_2$ as a catalyst, the naphthylborneol chiral auxiliary as well as its enantiomer and the catalyst used were not readily available and the chemical yield in this reaction was low (38%). Surprisingly, to our knowledge, there are no other reported examples of high diastereoselectivity except for the naphtylborneol chiral auxiliary[4] in alicyclic bicyclo[3.1.0]hexane synthesis in intramolecular cyclopropanations.[5] Therefore, it would be necessary to find a convenient method for its practical use. In this paper, we wish to report another approach for synthesizing chiral bicyclo[3.1.0]hexane **4**. This approach uses a combination of a chiral auxiliary and chiral catalysts for the intramolecular cyclopropanation of the unsaturated α-diazo-β-keto esters, wherein both diastereoselectivity and chemical yield were improved in comparison with previous results.[2d] The determination of the absolute configuration of each diastereomeric cyclopropane and the mechanism of asymmetric induction are also discussed. Additionally, the potential of this asymmetric cyclopropanation was illustrated by the synthesis of both enantiomers of the vitamin D_3 CD ring synthon.

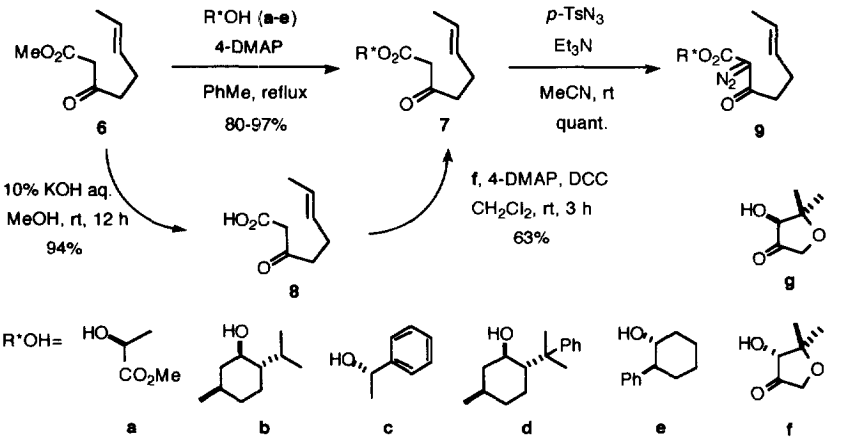


1 R_1=Me, R_2=$CH_2CH_2CH_2CH(CH_3)_2$, R_3=H
2 R_1=Et, R_2=H, R_3=CH=$CHCH_3$
3 R_1, R_2=Me, R_3=H
4 R_1=Me, R_2=H, R_3=Me
5 R_1=Me, R_2, R_3=H

Figure 1

We first synthesized various chiral α-diazo-β-keto esters (**9a** to **9f**), which were easily prepared by Taber's protocol[2d] as shown in Scheme 1, to investigate the efficiency of auxiliaries. Thus, as indicated in Scheme 1, unsaturated keto ester **6**[6] was treated with chiral alcohols (**a** to **f**) in the presence of a catalytic

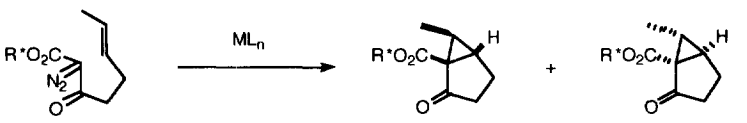
amount of 4-DMAP in toluene refluxing. This method gave **7** in good yields (80-97%) except for in the case of R*OH=(*R*)-pantolactone **f** (33%). In this case, **7f** was prepared by two steps that included the saponification of **6** followed by esterification of the resulting acid **8**. The α-diazo esters **9**, the precursors of bicyclo[3.1.0]hexanes, were then obtained by the treatment of **7** with *p*-toluenesulfonyl azide and triethylamine in nearly quantitative yields.



Scheme 1

The intramolecular cyclopropanation of α-diazo esters (**9a** to **9f**) was carried out under a variety of conditions, with the results shown in Table 1. The ratio of the resultant diastereomers was determined by GC

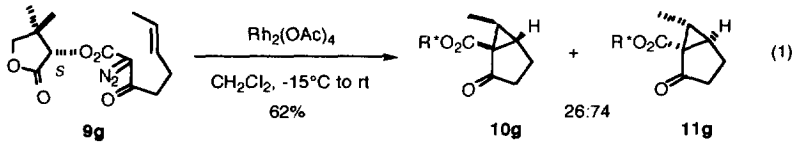
Table 1. Effect of Chiral Auxiliary and Catalyst in the Intramolecular Cyclopropanation of **9**



entry	substrate	catalyst[a]	conditions	yield[b]	10:11[c]
1	**9a**	$Rh_2(OAc)_4$	CH_2Cl_2, rt, 2 h	70	44:56
2	**9b**	$Rh_2(OAc)_4$	CH_2Cl_2, rt, 2 h	53	61:39
3	**9c**	$Rh_2(OAc)_4$	CH_2Cl_2, rt, 2 h	60	34:66
4	**9c**	$(MeO)_3P$·CuI	PhMe, reflux, 2 h	69	45:55
5	**9d**	$Rh_2(OAc)_4$	CH_2Cl_2, -15°C to rt, 10 h	80	32:68
6	**9e**	$Rh_2(OAc)_4$	CH_2Cl_2, -15°C to rt, 10 h	70	31:69
7	**9f**	$Rh_2(OAc)_4$	CH_2Cl_2, rt, 2 h	48	68:32
8	**9f**	$Rh_2(OAc)_4$	CH_2Cl_2, -15°C to rt, 10 h	56	73:27
9	**9f**	$Cu(TBS)_2$	PhMe, reflux, 5 h	81	56:44

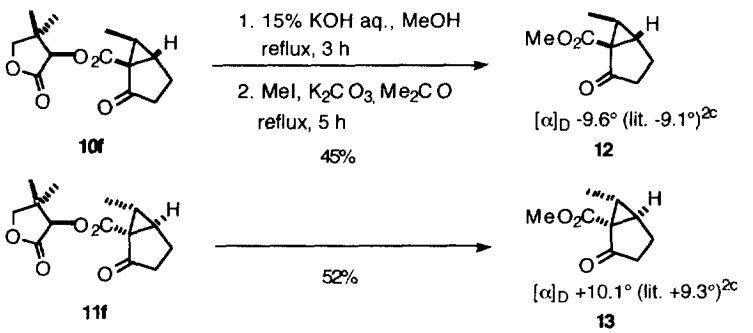
a) 10 mol% of catalyst was used. b) Isolated yield. c) Less polar: more polar in GC column.

analysis. It was found that the combination of (*R*)-pantolactone and rhodium (II) acetate was most effective in all the cases we examined. Lowering the reaction temperature produced a slight improvement in enantioselectivity (entry 7 vs. 8). The best selectivity in the case of R*OH=(*R*)-pantolactone[7] (**9f**) (73:27) was shown to be moderate; it was noted that each diastereomer was easily separated by simple silica-gel chromatography to give **10f** and **11f** with high optical purity. As enantiomeric (*S*)-pantolactone is commercially available and also readily obtainable from (*R*)-pantolactone by stereochemical inversion as reported by Corey,[8] the opposite diastereomer would also be preferentially synthesized. Indeed, the keto ester **9g** with (*S*)-pantolactone led to a 26/74 cyclization in favor of the opposite isomer **11g** (eq 1).



9g **10g** **11g**

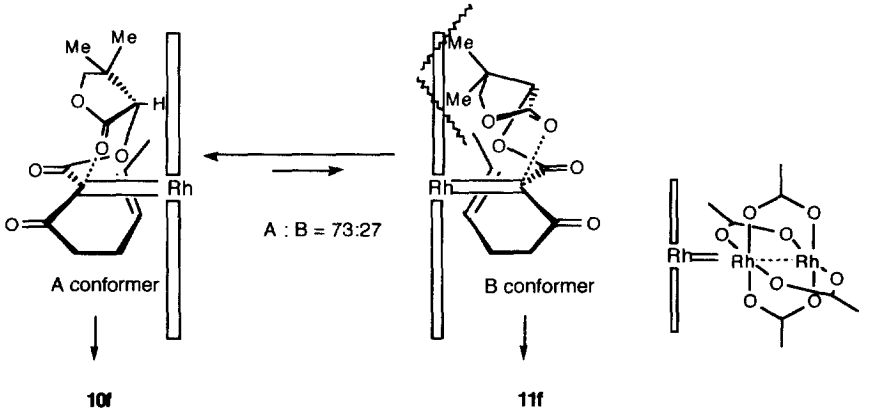
The absolute stereochemistry of each diastereomer was determined by converting **10f** and **11f** into the known methyl esters **12** and **13**[2c] using hydrolysis followed by esterification (Scheme 2).



10f **12** **11f** **13**

Scheme 2

The asymmetric induction of this cyclopropanation might be well explained by Davies' model[9] as shown in Fig. 2. According to his proposal, the carbonyl of the auxiliary interacts with the carbenoid in **9f**. Due to steric interactions between the chiral auxiliary and the wall of the catalyst, conformer **A** is favored over conformer **B** to give **10f** as the main product.

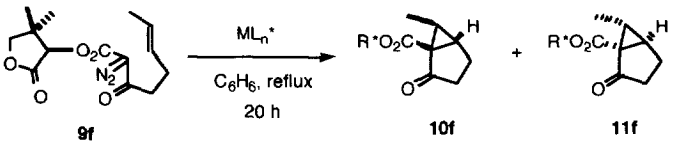


10f **11f**

Figure 2

It was assumed that the utilization of chiral catalysts would improve the selectivity if the catalyst and the auxiliary were used as a matched pair. Masamune reported that chiral bis-oxazoline Cu(I) (**14** to **17**) catalyzed the intermolecular cyclopropanation by double asymmetric synthesis through the use of a menthyl ester.[10] Indeed, the cyclopropanation of **9f** catalyzed by bis-oxazolines **15**, **16**, and **17** resulted in improved selectivity[11] as shown in Table 2. For instance, the best result (entry 4) led to the 85/15 cyclization in favor of isomer **10f**.

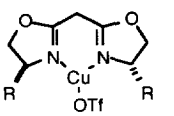
Table 2. Diastereoselective Cyclopropanations by Double Asymmetric Induction



9f **10f** **11f**

entry	catalyst[a]	yield[b]	10:11
1	**14**	86	64:36
2	**15**	55	78:22
3	**16**	58	82:18
4	**17**	53	85:15

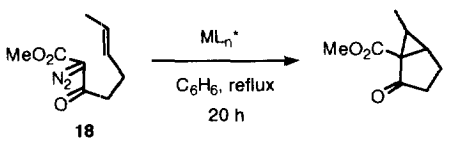
a) 10 mol% of catalyst was used. b) Isolated yield.



14 R=*t*-Bu
15 R=*i*-Pr
16 R=Ph
17 R=Bn

But, treatment of the achiral β-keto ester **18** with these oxazolines gave only 16-20% ee of the cyclopropane in favor of the enantiomer **12** (Table 3).

Table 3. Enantioselective Cyclopropanations of Achiral Diazo Keto Ester

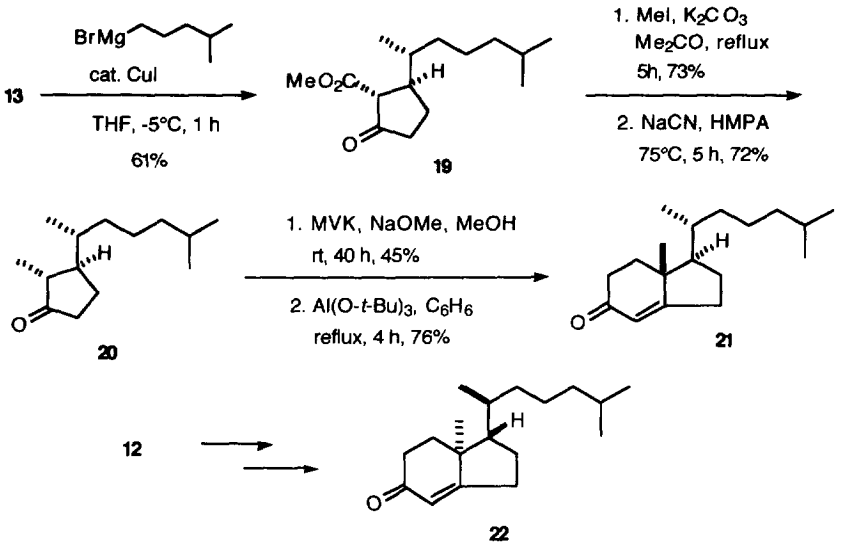


18

entry	catalyst	yield[a]	%ee[b]
1	**14**	64	8
2	**15**	52	16
3	**16**	60	8
4	**17**	56	20

a) Isolated yield. b) Determination by ^{1}H-NMR using Eu(tfc)$_3$.

Finally, both enantiomers of the vitamin D_3 CD ring synthons ((-)-**21** and (+)-**22**) were synthesized starting from cyclopropane (-)-**12** and (+)-**13** (Scheme 3). The addition of a Grignard reagent[12] to **13** for introducing the side chain gave **19**, which was converted into ketone **20** by methylation followed by demethoxycarbonylation.[13] The addition of methylvinylketone[14] to **20** then provided the diketone, which was subjected to an intramolecular aldol reaction[15] to give the CD ring synthon **21** ($[\alpha]_D^{22}$=+31.3° (*c* 0.4, $CHCl_3$) (lit. +32,[16] +38.2[17]). Using the same reaction sequence, (-)-**12** was converted into the *ent*-vitamin D_3 CD ring synthon **22** ($[\alpha]_D^{21}$=-49.6° (*c* 0.5, $CHCl_3$)). To our knowledge, the synthesis of antipode **22** of natural isomer **21** is the first such example and the compound would serve as new building block for the synthesis of vitamin D_3 analogs.



Scheme 3

In summary, the present diastereoselective cyclopropanation protocol catalyzed by a bis-oxazoline copper (I) complex and rhodium (II) acetate through the use of commercially available pantolactone as a chiral auxiliary is simple and flexible. This method would serve as a useful means for the synthesis of aliphatic bicyclo[3.1.0]hexane derivatives in enantiomerically pure form, and should prove useful for the synthesis of many other cyclopentanoid natural products and analogs.

Experimental

Infrared (IR) spectra were measured with a Perkin-Elmer FT-IR 1760X spectrometer. NMR spectra were obtained with a JEOL JNM-GX 270 NMR spectrometer in $CDCl_3$, using tetramethylsilane as the internal standard. EI HRMS spectra were taken by a JEOL JMS-AX 500 mass spectrometer and SIMS HRMS were taken by a Hitachi M-2500 mass spectrometer. Optical rotations were measured with a HORIBA SEPA-300 polarimeter. GC analysis was performed on a Hitachi G-3000 capillary gas chromatograph using a GL Sciences Inc. 0.25x30 m TC-1 column. Amino alcohol-derived chiral catalysts **14-17** were prepared from corresponding bis-oxazoline ligands[10] according to literature procedure.[11]

(1R, 2S, 5R)-(-)-Menthyl 3-oxo-6-octenoate (7b). Ester **6** (90 mg, 0.53 mmol), 4-(dimethylamino)pyridine (13 mg, 0.1 mmol), *(1R, 2S, 5R)*-(-)-menthol (33 mg, 0.21 mmol), and toluene (5 ml) were stirred at 110 °C for 30 h. After cooling, the mixture was poured into saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residure by silica gel chromatography (10:1 hexane-EtOAc) gave **7b** (58 mg, 93%) as an oil. *Rf*=0.63 (silica, 9:1 hexane-EtOAc); $[\alpha]_D^{23}$ -50.4° (*c* 1.6, $CHCl_3$); IR (thin film) ν_{max} 2957, 1740, 1718, 1644, 1236, 967 cm^{-1}; ^{1}H-NMR δ 0.77 (3H, d, *J*=7.0Hz), 0.89 (3H, d, *J*=7.0Hz), 0.91 (3H, d, *J*=6.4Hz), 0.95-1.74 (7H, m), 1.72 (3H, d, *J*=4.6Hz), 1.80-2.39 (4H, m), 2.59 (2H, t, *J*=7.3Hz), 3.42 (2H, s), 4.73 (1H, dt, *J*=4.6, 11.0Hz), 5.26-5.58 (2H, m).

In a similar manner, **7a**, **7c**, **7d**, and **7e** were prepared.

(3R)-3-(4,4-Dimethyl-2-oxotetrahydrofuranyl) 3-oxo-6-octenoate (7f). A mixture of the ester **6** (1.64 g, 9.6 mmol), 10% KOH (200 ml), and MeOH (200 ml) was stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc and acidified with 10% HCl. The organic portion was separated, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by silica gel chromatography (3:1 hexane-EtOAc) afforded 1.42 g (94%) of the free acid **8** as an oil: *Rf*= 0.18 (silica, 3:1 hexane-EtOAc).

To a solution of acid **8** (1.42 g, 9.1 mmol) and (*R*)-pantolactone (1.2 g, 9.2 mmol) in CH_2Cl_2 (30 ml) at room temperature was added DMAP (210 mg, 1.7 mmol) and DCC (2.2 g, 10.7 mmol), and the resulting solution was stirred at room temperature for 3 h. The resulting urea was filtered off, and the solvent was removed in vacuo. Purification of the residue by silica gel chromatography (3:1 hexane-EtOAc) gave 1.54 g (63%) of the ester **7f** as an oil: *Rf*=0.45(silica, 3:1 hexane-EtOAc); $[\alpha]_D^{22}$ -11.0° (*c* 2.5, $CHCl_3$); IR (thin film) ν_{max} 2968, 1790, 1733, 1181 cm^{-1}; ^1H NMR δ 1.12 (3H, s), 1.27 (3H, s), 1.62 (3H, d, *J*=1Hz), 2.25-2.36 (2H, m), 2.64 (2H, t, *J*=7.3Hz), 3.54-3.70 (2H, m), 4.06 (2H, s), 5.39-5.49 (3H, m); ^{13}C NMR δ 18.7, 20.6, 23.6, 27.2, 41.3, 43.7, 49.7, 77.9, 78.4, 127.3, 129.5, 166.9, 172.9, 202.5; SIMS HRMS (NBA) *m/e* 269.1389, MH^+ calcd for $C_{14}H_{21}O_5$ 269.1388.

(3R)-3-(4,4-Dimethyl-2-oxotetrahydrofuranyl) (1S, 5S, 6S)-2-oxo-6-methylbicyclo[3.1.0]hexane-1-carboxylate (10f) and (3R)-3-(4,4-dimethyl-2-oxotetrahydrofuranyl) (1R, 5R, 6R)-2-oxo-6-methylbicyclo[3.1.0]hexane-1-carboxylate (11f). A solution of **7f** (2.1 g, 7.8 mmol) in Et_3N (1.8 g, 17.4 mmol) and CH_3CN (20 ml) was treated with *p*-TsN_3 (1.17 g, 9.6 mmol). The reaction mixture was stirred at room temperature for 1 h and added to a separatory funnel containing ether and saturated NH_4Cl. The phases were separated, the aqueous layer was back-extracted with ether, and the combined organic solutions were washed with 10% NaOH, saturated $NaHCO_3$, and brine prior to drying ($MgSO_4$). Solvent evaporation furnished 2.1 g (91%) of **9f** which was used without further purification: *Rf*=0.48 (silica, 3:1 hexane-EtOAc).

To a solution of **9f** (2.1 g, 7.1 mmol) in benzene (20 ml) was added bis-oxazoline **17** (0.28 g, 0.71 mmol) and the reaction solution was heated at reflux for 20 h. After cooling, the catalyst was filtered off, and the solvent was removed in vacuo. Purification of the residue by silica gel chromatography (1:1 hexane-EtOAc) gave **10f** (0.85g, 45%) and **11f** (0.15mg, 8%) as an oil: **10f**: *Rf*=0.45 (silica, 1:1 hexane-EtOAc); $[\alpha]_D^{22}$ +32.3° (*c* 0.6, $CHCl_3$); IR (thin film) ν_{max} 2968, 1790, 1730, 1155, 1084 cm^{-1}; ^1H NMR δ 1.17 (3H, s), 1.19 (3H, s), 1.24 (3H, d, *J*=6.1Hz), 1.77-2.37 (6H, m), 4.02 (2H, s), 5.37 (1H, s); ^{13}C NMR δ 12.9, 19.8, 21.0, 22.7, 29.6, 33.3, 35.1, 40.1, 44.6, 75.5, 76.1, 165.7, 171.9, 206.0; SIMS HRMS (NBA) *m/e* 267.1238, MH^+ calcd for $C_{14}H_{19}O_5$ 267.1232; **11f**: *Rf*=0.31 (silica, 1:1 hexane-EtOAc); $[\alpha]_D^{22}$ -6.8° (*c* 0.6, $CHCl_3$); IR (thin film) ν_{max} 2968, 1790, 1733, 1154, 1083 cm^{-1}; ^1H NMR δ 1.16 (3H, s), 1.23 (3H, s), 1.39 (3H, d, *J*=6.4Hz), 1.80-2.53 (6H, m), 4.06 (2H, s), 5.42 (1H, s); ^{13}C NMR δ 12.8, 19.9, 21.2, 22.9, 30.4, 33.4, 36.6, 40.2, 43.3, 75.3, 76.2, 165.6, 172.0, 206.4.

In a similar manner, **10a-e** and **11a-e** were prepared and the diastereomeric ratio was determined by GC analysis (GL Sciences Inc. 0.25x30 m TC-1 column). **10a** and **11a**: 150°C, 10.4 (44%), 10.7 (56%) min; **10b** and **11b**: 150°C, 21.0 (61%), 22.0 (39%) min; **10c** and **11c**: 200°C, 6.0 (34%), 6.2 (66%) min; **10d** and **11d**: 220°C, 22.7 (32%), 25.1 (68%) min; **10e** and **11e**: 190°C, 23.5 (31%), 26.6 (69%) min.

(1S, 5S, 6S)-Methyl 2-oxo-6-methylbicyclo[3.1.0]hexane-1-carboxylate (12) and (1R, 5R, 6R)-Methyl 2-oxo-6-methylbicyclo[3.1.0]hexane-1-carboxylate (13). A mixture of ester **10f** (1.97 g, 7.4 mmol), 15% KOH (20 ml), and MeOH (50 ml) was stirred at reflux for 3 h. The cooled reaction mixture was diluted with EtOAc and acidified with 10% HCl. The organic portion was separated, dried ($MgSO_4$), and concentrated in vacuo to give the carboxylic acid (730 mg) which was used without purification.

A mixture of the carboxylic acid (730mg), MeI (9.4 g, 66.2 mmol) and K_2CO_3 (1.4 g, 10.1 mmol) in acetone (35 ml) was heated at reflux for 5 h. After cooling, the reaction mixture was filtered and concentrated in vacuo. Purification of the residue by silica gel chromatography (5:1 hexane-EtOAc) gave **12** (560mg, 45%) as an oil: **12**: *Rf*=0.22 (silica, 5:1 hexane-EtOAc); $[\alpha]_D^{23}$ -9.6° (*c* 0.5, $CHCl_3$); IR (thin film) ν_{max} 2954, 1730, 1439, 1353, 1286, 1203 cm^{-1}; ^1H NMR δ 1.26 (3H, d, *J*=6.4Hz), 1.74-1.79 (1H, m), 2.01-2.44 (5H, m), 3.79 (3H, s); ^{13}C NMR δ 12.6, 21.0, 29.2, 33.7, 35.7, 44.2, 52.2, 167.1, 207.2; **13**: $[\alpha]_D^{22}$ +10.1° (*c* 0.7, $CHCl_3$).

(2R, 3R)-2-Methoxycarbonyl-3-[(1R)-1,5-dimethylhexyl]cyclopentanone (19). To a suspension of magnesium turnings (260 mg, 10.8 mmol) in dry THF (2ml) at room temperature were added 5 drops of 4-methylpentylbromide (part of 2.1 g, 12.8 mmol) and a small crystal of iodine. The solution was stirred at room temperature until the violet color had disappeared before THF (20 ml) was added. The remaining 4-methylpentylbromide was added dropwise to the reaction mixture, which was maintained at 25°C. The reaction mixture was stirred at 25°C for 20 min and then cooled to -20°C, and cuprous iodide (2.1 g, 10.8 mmol) was added. After 5 min, **13** (520 mg, 3.1 mmol) in dry THF (2 ml) was added dropwise. After 5 min, the reaction mixture was warmed to room temperature and poured into a mixture of saturated NH_4Cl and ether. The organic phase was separated, washed with saturated NH_4Cl and then with brine, and dried ($MgSO_4$). Removal of the solvent in vacuo and purification by silica gel chromatography (5:1 hexane-EtOAc) gave the keto ester **19** (480 mg, 61%) as an oil: *Rf*=0.44 (silica, 5:1 hexane-EtOAc); $[\alpha]_D^{22}$ +42.5° (*c* 0.6, $CHCl_3$); IR (thin film) ν_{max} 2955, 2869, 1759, 1731, 1465, 1259, 1121cm^{-1}; ^1H NMR δ 0.87 (6H, d, *J*=6.6), 0.89 (3H, d, *J*=6.1), 1.13-1.57 (10H, m), 2.17-2.55 (3H, m), 2.95 (1H, d, *J*=11.6), 3.75 (3H, s); ^{13}C NMR δ 17.0, 22.5, 22.7, 24.4, 25.3, 27.9, 34.0, 37.2, 38.7, 39.1, 46.8, 52.4, 59.6, 170.7, 211.3; EI HRMS *m/e* 223.1712, M-MeO$^+$ calcd for $C_{14}H_{23}O_2$ 223.1699.

(2R, 3R)-2-Methyl-3-[(1R)-1,5-dimethylhexyl]cyclopentanone (20). A mixture of keto ester **19** (480 mg, 1.9 mmol), MeI (4.3 g, 30.5 mmol) and K_2CO_3 (1.3 g, 9.4 mmol) in acetone (20 ml) was heated at reflux for 5 h. After cooling, the reaction mixture was filtered and concentrated in vacuo. Purification of the residue by silica gel chromatography (5:1 hexane-EtOAc) gave crude methylated product (370 mg).

Sodium cyanide (370 mg, 7.6 mmol) was dissolved in dry HMPA (20 ml) at 75°C. Methylated product (370 mg) in HMPA (5 ml) was added dropwise to the reaction mixture, and it was stirred for 5 h. After cooling, it was poured into 5% HCl and extracted with ether. The organic layer was washed with water, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by silica gel chromatography (5:1 hexane-EtOAc) gave ketone **20** (210 mg, 72%) as an oil: *Rf*=0.59 (silica, 5:1 hexane-EtOAc); $[\alpha]_D^{20}$ +46.0° (*c* 2.2, $CHCl_3$); IR (thin film) ν_{max} 2957, 2930, 2872, 1742, 1460 cm^{-1}; ^1H NMR δ 0.88 (6H, d, *J*=6.7Hz), 0.98 (3H, d, *J*=6.7Hz), 1.09 (3H, d, *J*=7.0), 1.13-2.40 (14H, m); ^{13}C NMR δ 14.1, 17.8, 22.5, 22.7, 23.2, 25.2, 27.9, 32.6, 34.7, 37.3, 39.2, 46.9, 50.3, 222.0; EI HRMS *m/e* 210.1986, M$^+$ calcd for $C_{14}H_{26}O$ 210.1985.

(1R, 7aR)-1-[(1R)-1,5-Dimethylhexyl]-1,2,3,6,7,7a-hexahydro-7a-methyl-5H-inden-5-one (21). To a solution of the ketone **20** (120 mg, 0.57 mmol) in dry MeOH (7 ml) was added NaOMe (0.2 ml, 1 mmol, 28% solution in MeOH) at 0°C. After 10 min, freshly distilled methyl vinyl ketone (150 mg, 2.1 mmol) was added to the solution and the mixture was stirred for 3h at 0°C and then warmed to room temperature. After 20 h, additional methyl vinyl ketone (100 mg, 1.4 mmol) was added to the solution and stirring was continued for 20 h. The reaction was quenched by the addition of saturated NH_4Cl. The resulting solution was extracted with ether, and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by silica gel chromatography (5:1 hexane-EtOAc) to give the diketone (72 mg, 45%) as an oil: *Rf*=0.32 (silica, 5:1hexane-EtOAc).

A solution of diketone (34 mg, 0.12 mmol) in dry C_6H_6 (5 ml) containing Al(O-*t*-Bu)$_3$ (50 mg, 0.2 mmol) was heated at reflux for 4 h. The reaction mixture was cooled to 0°C and neutralized by the addition of 5% HCl. The mixture was extracted with ether and washed with water, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by silica gel chromatography (5:1 hexane-EtOAc) gave the enone **21** (24 mg, 76%) as an oil: *Rf*=0.43 (silica, 5:1hexane-EtOAc); $[\alpha]_D^{21}$ -49.6° (*c* 0.5, $CHCl_3$); IR (thin film) ν_{max} 2955, 2869, 1673, 1468 cm^{-1}; ^{1}H NMR δ 0.88 (6H, d, *J*=6.4Hz), 0.97 (3H, d, *J*=6.4Hz), 1.09 (3H, s), 1.13-2.62 (17H, m), 5.74 (1H, br s); ^{13}C NMR δ 16.1, 18.7, 22.5, 22.8, 23.7, 26.8, 28.0, 28.9, 33.5, 34.3, 35.8, 37.0, 39.4, 45.0, 55.8, 121.4, 180.2, 199.3; SIMS HRMS (NBA) *m/e* 263.2380, MH$^+$ calcd for $C_{18}H_{31}O$ 263.2374.

Acknowledgment We thank Dr. Naoto Senda of Hitachi Instrument Enginerring Co., Ltd. for the SIMS HRMS measurements and Dr. K. Nagasawa (RIKEN) for the helpful discussion about the Robinson annulation.

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(*Received in Japan* 14 *May* 1997; *accepted* 25 *July* 1997)