Tetrahedron Vol. 46, No. 24, pp. 8075-8082, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

SYNTHESIS OF (-)-PERIPLANONE-B, A SEX PHEROMONE COMPONENT OF THE AMERICAN COCKROACH (*PERIPLANETA AMERICANA*)†

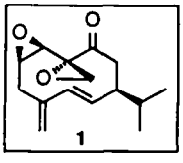
Shigefumi Kuwahara†† and Kenji Mori*
Department of Agricultural Chemistry, The University of Tokyo,
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

(*Received in Japan* 4 *July* 1990)

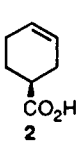
Abstract: The naturally occurring (-)-enantiomer of periplanone-B was synthesized stereoselectively starting from (*S*)-3-cyclohexene-1-carboxylic acid. The crystalline pheromone was obtained in 12% overall yield through 18 steps.

Periplanone-B **1** was isolated as a sex pheromone component of the American cockroach, *Periplaneta americana*, by Persoons *et al.* in 1974.[1] Its structure, including the absolute configuration, was established by Still's synthesis of (±)-**1**[2] coupled with chiroptical studies[3] of a resolved synthetic intermediate. Since then several research groups reported several different syntheses of (±)-**1**.[4] An enantioselective synthesis of (-)-**1** was also achieved in our laboratory.[5] However, it required as many as 28 steps from (+)-dihydrolimonene, resulting in 0.5% overall yield. We recently reported a more efficient synthesis of (-)-**1** starting from readily available (*S*)-(-)-3-cyclohexene-1-carboxylic acid **2**.[6] This paper describes the full details of the new stereoselective synthesis of (-)-periplanone-B.

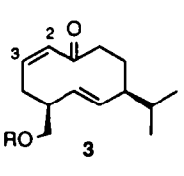
Survey of the previous syntheses made us adopt a ten-membered ring enone **3** as our synthetic intermediate. Because this enone **3** (R=TBDPS) was shown, in Takahashi's synthesis of (±)-**1**,[4c] to give the desired 2,3-β-epoxide exclusively by treatment of *t*-BuOOK. Other syntheses of periplanone-B employed **4**[2,4b] or **5**[4a,4c,4d] as the substrates for the 2,3-epoxidation. In each case, however, the stereoselectivity could not exceed 80%. For the construction of the ten-membered ring system, two approaches had been employed: (1) anionic oxy-Cope rearrangements,[2,4a, 4b] and (2) intramolecular alkylations.[4c,5] The latter method, used in the previous synthesis of (-)-**1**[5] and also in Takahashi's synthesis of (±)-**1**,[4c] made the synthetic processes lengthy. We therefore adopted the oxy-Cope route for the construction of the enone **3**. Thus we made a synthetic plan shown in Fig. 1. In order to obtain **3** *via* the oxy-Cope pathway, it is essential for the precursor **6** to have a (*Z*)-double bond on the side chain as depicted in Fig. 1. The alcohol **6** will be obtained readily from **7**. The preparation of the (*Z*)-β,γ-unsaturated ketone **7**, the optically active and (*Z*)-isomer of Still's intermediate,[2] was



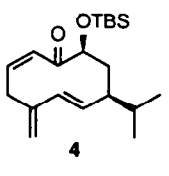
1



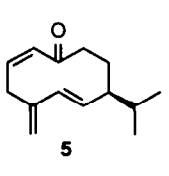
2



3



4



5

† Pheromone Synthesis, Part 123. Part 122, K. Mori, H. Watanabe, M. Fujiwhara and S. Kuwahara, *Liebigs Ann. Chem.* in press.

†† Present address: Laboratory of Agricultural Chemicals, Faculty of Agriculture, Ibaraki University, Ami-machi, Inashiki-gun, Ibaraki 300-03, Japan.

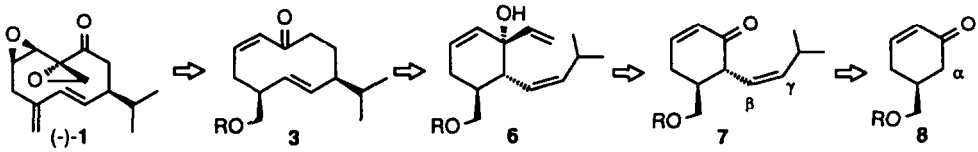
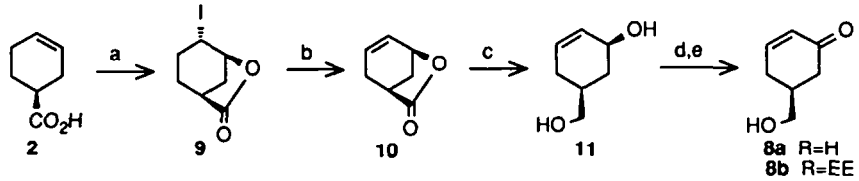


Fig. 1. Synthetic plan for (-)-periplanone-B.

the most crucial point in the present synthesis. As described later, we could achieve the conversion of **8** into **7** in two steps by using organoselenium chemistry.[7]

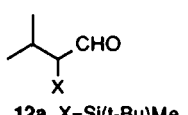
For the preparation of **8** with (*S*)-configuration, our synthesis began with the iodolactonization of **2**, $[\alpha]_D^{23}$ -99° ($CHCl_3$), which was readily obtainable through Helmchen's asymmetric Diels-Alder reaction[8a] or a classical optical resolution[8b] (Fig. 2). ^1H NMR analysis of the resulting iodolactone **9** in the presence of Pirkle's chiral solvating agent[9] showed **9** to be optically pure. Treatment of **9** with DBU followed by LAH reduction gave **11** *via* **10**. Selective oxidation of the diol **11** with MnO_2 gave **8a**, of which hydroxyl group was protected as an ethoxyethyl ether **8b**. Each of these steps proceeded almost quantitatively, and **8b** was obtained in 85% overall yield from **2**.



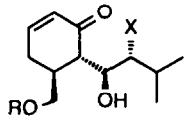
Reagents: a) KI_3, $NaHCO_3$ aq, CH_2Cl_2; b) DBU, benzene; c) LAH, THF; d) MnO_2, $CHCl_3$; e) ethyl vinyl ether, PPTS, CH_2Cl_2 (85% overall yield).

Fig. 2. Preparation of **8b** from **5**.

Our attention was then turned to the introduction of the (*Z*)-side chain to the α-position of the ketone **8** to afford **7**. At first, aldol reactions of **8** (R=MOM, TBS or EE) with an α-silylaldehyde **12a**[10] were attempted in order to obtain **13a**. The β,γ-relative stereochemistry of **13a** was expected to become *anti* on the basis of Cram's rule.[10] Therefore, KH-promoted *syn*-elimination of the silyl alcohol **13a** seemed to give **7**. However, the reaction of lithium enolates of **8** with **12a** in the presence or absence of $ZnCl_2$[11] resulted in the recovery of **8** probably due to the rapid proton transfer from **12a** to the enolates. Attempts using tin enolates[12] were also unsuccessful.

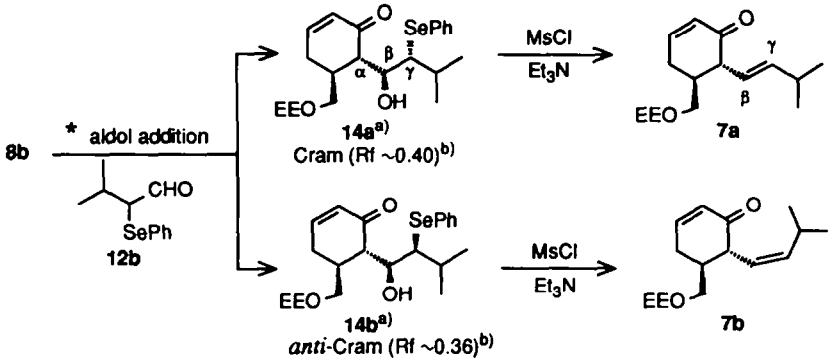


12a X=Si(t-Bu)Me_2
12b X=SePh



13a X=Si(t-Bu)Me_2
13b X=SePh

We then examined the aldol reaction of **8**[13] with α-phenylselenoisovaleraldehyde **12b**[14] instead of **12a**. In this case, too, the β,γ-relative stereochemistry of the resulting aldol **13b** was predicted to be *anti* according to Cram's rule.[15] It is well established that the elimination of PhSeOH from β-hydroxyselenides by treatment with MsCl and Et_3N proceeds *via anti*-stereochemistry.[16] As expected from these considerations, the undesired (*E*)-isomer **7a** was obtained predominantly *via* **14a** when the lithium enolate of **8b** was prepared



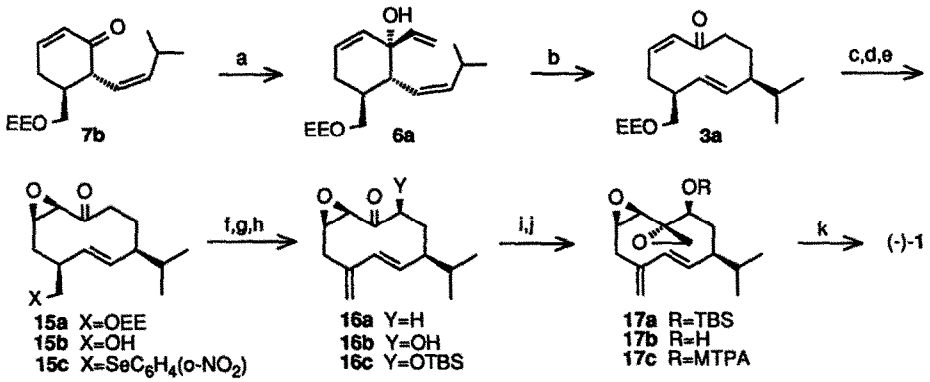
* condition	yield (%)[c] 7a	7b
A i) LDA, TMSCl; ii) MeLi, $ZnCl_2$, **12b**, ether, -78°C	64	11
B LDA, **12b**, THF, -78°C, 20min	30 (40)	55 (60)
C LDA, **12b**, THF, -78°C, 20min then -15°C, 3min	<5 (7)	51 (93)

a) The relative stereochemistry between C-α and C-β was not determined.
b) Merck Kieselgel 60, Art. 5715; *n*-hexane-ether (2:5).
c) GLC ratios are shown in parentheses.

Fig. 3. Two-step conversion of **8b** into **7b**.

from the corresponding TMS enol ether in ether and reacted with **12b** in the presence of $ZnCl_2$ (condition A in Fig. 3). Even in the absence of $ZnCl_2$, **7a** was obtained preferentially, although the selectivity was somewhat lower. The relative stereochemistry between C-β and C-γ of **14a** was deduced to be *anti* from the (*E*)-geometry of **7a** ($J_{\beta,\gamma}$=16Hz), while the α,β-relationship could not be assigned owing to the complexity of the ^{1}H NMR spectrum of **14a**. Quite surprisingly, the ratio of **7a** to **7b** reversed by changing the reaction condition from A into B. Furthermore, when the temperature of the reaction mixture in THF was raised rapidly from -78°C to -15°C over about 3 min (condition C), the aldol(s) **14a** leading to **7a** decomposed. Consequently, **7b** ($J_{\beta,\gamma}$=10Hz) was obtained in 93% selectivity. By the combination of condition C and careful chromatographic purification of **14b**, pure **7b** could be obtained in 51% overall yield from **8b**. The aldol reaction of the lithium enolate prepared directly from **8b** by treatment with LDA in ether[11] was also carried out. Judging from the TLC analysis, this condition gave **14a** as the major product in contrast to condition B. These results seem to mean that a primary factor in determining the β,γ-relative stereochemistry is the solvent employed in each condition.

The disubstituted cyclohexenone **7b** thus obtained was reacted with vinyllithium in ether[2] to give **6a**, which produced **3a** on treatment with KH in DME[17] (Fig. 4). The ten-membered ring enone **3a** was converted to **15b** *via* **15a** by epoxidation[4c] and deprotection. The diastereomeric homogeneity of **15b** was ensured by its 400 MHz ^{1}H NMR analysis. Selenylation of **15b** to **15c** followed by oxidative elimination gave **16a**. α-Hydroxylation[18,5] of the ketone **16a** yielded **16b**. According to the previous synthesis,[5] **16b** was treated successively with TBSCl, dimethylsulfonium methylide and $(n\text{-Bu})_4$NF to give (-)-periplanol-B **17b** *via* **16c** and **17a**. The product **17b** was shown to be optically pure by HPLC analysis of the corresponding (*R*)- and



Reagents: a) vinyllithium, ether (86%); b) KH, 18-crown-6, DME (86%); c) KH, t-BuOOH, THF; d) PPTS, EtOH (74%); e) (o-NO_2)C_6H_4SeCN, (n-Bu)$_3$P, THF (99%); f) H_2O_2, THF (90%); g) LiN(TMS)$_2$, MoO_5·HMPA·Py, THF (86%); h) TBSCl, imidazole, DMF; i) Me_3SI, n-BuLi, THF; j) (n-Bu)$_4$NF, THF, (73%); k) PDC, DMF (92%).

Fig. 4. Synthesis of (-)-periplanone-B.

(*S*)-MTPA esters **17c**. Finally oxidaton of **17b** gave (-)-periplanone-B (-)-**1**, m.p. 55.5-57.5°C; $[\alpha]_D^{21}$ -552° (*n*-hexane) (lit.[5] m.p. 57.0-57.5°C; $[\alpha]_D^{26}$ -553°). Its IR and ^{1}H NMR spectra were identical with those of an authentic sample.[5]

In conclusion, the present 18-step-synthesis of (-)-periplanone-B was accomplished in 12% overall yield *via* the stereoselective construction of **7b** to give about 300 mg of (-)-**1**. This is the highest yield that ever has been reported.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as KBr discs for solids on a Jasco IRA-102 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal standard at 60MHz in CCl_4 on a Hitachi R-24A spectrometer or at 100MHz in $CDCl_3$ on a JEOL JNM FX-100 spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP 140 polarimeter. Mass spectra were recorded at 70eV on a JEOL DX-303 spectrometer. Merck Kieselgel 60 Art. 7734 was used for SiO_2 column chromatography.

(1S,4S,5S)-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one **9**. To a stirred mixture of **2** [24.22 g, $[\alpha]_D^{23}$ -99° (c=1.01, $CHCl_3$)] in 0.5M $NaHCO_3$ aq (1150 ml) and CH_2Cl_2 (240 ml) was added a soln of KI (197 g) and I_2 (98 g) in water (590 ml). After stirring for 16h in the dark, the reaction mixture was quenched by the addition of $Na_2S_2O_3$ and ice, and extracted with CH_2Cl_2. The extract was washed with 10% $Na_2S_2O_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to gve 49.6 g of crude **9**. A small portion of crude **9** was recrystallized from *n*-hexane-acetone to give pure **9** as prisms, m.p. 127-133°C (dec); $[\alpha]_D^{22}$ -39.8° (c=2.99, $CHCl_3$); ν_{max} 1780 (vs), 1170 (s), 1140 (s), 1015 (s), 965 (s), 910 (s) cm^{-1}; δ (60MHz, $CDCl_3$) 1.50-2.10 (2H, m), 2.10-2.80 (4H, m), 2.78 (1H, d, J=12.0Hz), 4.49 (1H, t, J=4.5Hz), 4.80 (1H, t, J=5.0Hz). (Found: C, 33.43; H, 3.61. Calc for $C_7H_9O_2I$: C, 33.36; H, 3.60%).

^{1}H NMR (400MHz) analyses of (±)-**9** *and* (-)-**9** *in the presence of Pirkle's chiral solvating agent.* (*R*)-(-)-2,2,2-Trifluoro-1-(9-anthryl)ethanol (46 mg) was mixed with (±)-**9** (14 mg) or (-)-**9** (14 mg) in $CDCl_3$ (0.3 ml). Signals due to -CHI- of (±)-**9** were observed as completely separated two triplets at δ 4.34 and 4.40. In the case of (-)-**9**, only one triplet was observed at δ 4.39. This indicated the high optical purity of (-)-**9**.

(1S,5S)-6-Oxabicyclo[3.2.1]oct-3-en-7-one **10**. A mixture of crude **9** (49.0 g) and DBU (35 g) in benzene (580 ml) was stirred for 8h under reflux. After cooling to room temp, the mixture was filtered. The filtrate was washed with 0.5N HCl aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 27.3 g of crude **10**. A small portion of crude **10** was recrystallized from *n*-hexane-ether to give pure **10** as needles, m.p. 32-33°C; $[\alpha]_D^{21}$ -196° (c=2.32, $CHCl_3$); ν_{max} 1775 (s), 1135 (m), 950 (m), 900 (m) cm^{-1}; δ (100MHz, C_6D_6) 1.23 (1H, d, J=11.0Hz), 1.50-1.85 (2H, m), 1.85-2.18 (1H, m, J_1=18.0Hz), 2.20-2.40 (1H, m), 4.03 (1H, br.t, J=5.5), 5.10-5.35 (1H, m), 5.60-5.82 (1H, m). (Found: C, 67.57; H, 6.53. Calc for $C_7H_8O_2$: C, 67.73; H, 6.50%).

(1S,5S)-5-Hydroxymethyl-2-cyclohexen-1-ol **11**. To a stirred and ice-cooled suspension of LAH (6 g) in dry THF (400 ml) was added dropwise a

soln of crude **10** (26.8 g) in dry THF (80 ml). After stirring for 1h at room temp, the usual alkaline work-up gave 26.3 g of crude **11**. A portion was recrystallized from *n*-hexane-acetone to give pure **11** as prisms, m.p. 82-84°C; $[\alpha]_D^{21}$ -20.5° (c=2.19, 99.5% EtOH); ν_{max} 3260 (s), 3040 (m), 2980 (m), 2930 (m), 2900 (m), 2870 (m), 1645 (w), 1425 (m), 1040 (s), 1010 (s), 915 (m), 740 (m) cm^{-1}; δ (100MHz) 1.12-1.48 (1H, m), 1.78 (2H, s, OH), 1.75-2.27 (4H, m), 3.58 (2H, d, J=5.5Hz), 4.20-4.45 (1H, m), 5.60-5.90 (2H, m). (Found: C, 65.51; H, 9.44. Calc for $C_7H_{12}O_2$: C, 65.59; H, 9.44%).

(5S)-5-Hydroxymethyl-2-cyclohexen-1-one **8a**. A mixture of crude **11** (25.8 g) and MnO_2 (130 g) in $CHCl_3$ (950 ml) was stirred for 26h at room temp. The mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was chromatographed over SiO_2 (300 g, ether-THF) and distilled to give 19.9 g (86.4% from **2**) of **8a**, b.p. 104-109°C/0.4 Torr; n_D^{22} 1.5091; $[\alpha]_D^{22}$ +81.3° (c=1.02, $CHCl_3$); ν_{max} 3450 (s), 3050 (w), 2940 (m), 2900 (m), 1675 (vs), 1390 (s), 1250 (s), 1085 (s), 1030 (s), 740 (s) cm^{-1}; δ (60MHz, $CDCl_3$) 1.90-2.85 (5H, m), 3.02 (1H, t, J=5.0Hz, OH), 3.35-3.75 (2H, m), 5.98 (1H, d, J=10.0Hz), 6.80-7.20 (1H, m). (Found: C, 66.20; H, 8.00. Calc for $C_7H_{10}O_2$: C, 66.64; H, 7.99%).

(5S)-5-[(1-Ethoxyethoxy)methyl]-2-cyclohexen-1-one **8b**. To a stirred soln of **8a** (19.5 g) and ethyl vinyl ether (22 ml) in dry CH_2Cl_2 (130 ml) was added PPTS (0.7 g) under cooling with water bath. The soln was stirred overnight at room temp. It was poured into ice-sat $NaHCO_3$ aq and extracted with CH_2Cl_2. The extract was washed with brine, dried (K_2CO_3) and concentrated *in vacuo*. The residue was distilled to give 30.2 g (98.6%) of **8b**, b.p. 95-101°C/0.15 Torr; n_D^{21} 1.4636; $[\alpha]_D^{21}$ +47.7° (c=1.09, n-hexane); ν_{max} 3030 (w), 2980 (m), 2900 (m), 1675 (s), 1615 (w), 1380 (s), 1245 (m), 1170 (m), 1130 (s), 1090 (s), 1055 (s) cm^{-1}; δ (60MHz) 1.13 (3H, t, J=7.0Hz), 1.21 (3H, d, J=5.0Hz), 1.90-2.80 (5H, m), 3.00-3.80 (4H, m), 4.56 (1H, q, J=5.0Hz), 5.85 (1H, d, J=10.0Hz), 6.65-7.05 (1H, m). (Found: C, 66.24; H, 8.94. Calc for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%).

3-Methyl-2-phenylselenobutanal **12b**. To a stirred and ice-cooled soln of diphenyldiselenide (91 g) in dry CH_2Cl_2 (1500 ml) was added dropwise bromine (46.5 g). After stirring for 10min at room temp, morpholine (51 ml) was added to the mixture under ice-cooling. The stirring was continued for 15min at room temp. Isovaleroaldehyde (50 g) was then added to the mixture in a single portion under ice-cooling. The mixture was stirred for 5h at room temp. It was washed with water, 1N HCl aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (1250 g, *n*-hexane-benzene) and distilled to give 90.14 g (64%) of **12b**, b.p. 116.5-117°C/0.6 Torr; n_D^{22} 1.5680; ν_{max} 3075 (w), 2980 (s), 2950 (m), 2890 (m), 2825 (m), 2730 (w), 1710 (s), 1580 (m), 1480 (m), 1460 (m), 1385 (m), 1370 (m), 1165 (m), 1130 (m), 1070 (m), 1050 (m), 1010 (m), 1000 (m), 740 (s), 690 (s) cm^{-1}; δ (60MHz) 1.02 (3H, d, J=6.0Hz), 1.12 (3H, d, J=6.0Hz), 1.70-2.35 (1H, m), 3.23 (1H, dd, J=5.0, 8.5Hz), 7.00-7.50 (5H, m), 9.27 (1H, d, J=5.0Hz). (Found: C, 54.67; H, 5.80. Calc for $C_{11}H_{14}OSe$: C, 54.78; H, 5.85%).

(5S,6S,1'R,2'R*)-5-[(1-Ethoxyethoxy)methyl]-6-(1'-hydroxy-3'-methyl-2'-phenylselenobutyl)-2-cyclohexen-1-one* **14b**. A soln of LDA was prepared by the addition of *n*-BuLi (1.57N in *n*-hexane, 31 ml) to a stirred soln of $(i\text{-}Pr)_2NH$ (7.0 ml) in dry THF (50 ml) below 0°C under Ar. To this soln was added dropwise a soln of **8b** (8.00 g) in dry THF (80 ml) over a period of 20min at -10~-5°C. After stirring for 20 min, the reaction mixture was cooled to -78°C by using Dry Ice-acetone bath. To the soln was added dropwise a soln of **12b** (11.0 g) in dry THF (50 ml) over a period of 10 min. After stirring for 20 min at -78°C, the reaction temp was raised to -15°C by replacing the Dry Ice-acetone bath with ice-NaCl bath and stirring vigorously for 3min. The mixture was poured into sat NH_4Cl aq immediately and extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60 Art. 9385, 400 g; *n*-hexane-ether) to give 9.88 g (56%) of **14b**, Rf (Merck Kieselgel 60 Art. 5715; *n*-hexane-ether=2:5) 0.36; ν_{max} 3500 (m), 3070 (w), 2980 (s), 2940 (s), 2900 (s), 1670 (s), 1580 (m), 1385 (s), 1135 (s), 1085 (s), 1060 (s), 740 (s) cm^{-1}; δ (100MHz) 0.85-1.35 (12H, m), 1.95-2.60 (4H, m), 2.60-2.90 (2H, m), 3.30-3.80 (5H, m), 3.85-4.10 (1H, m), 4.50 (0.5H, q, J=5.0Hz), 4.70 (0.5H, q, J=5.0Hz), 6.00 (1H, dt, J=10.0, 2.0Hz), 6.86 (1H, dt, J=10.0, 4.0Hz), 7.10-7.35 (3H,m), 7.50-7.70 (2H, m). (Found: m/z 440.1503. Calc for $C_{22}H_{32}O_4Se$: 440.1466). When the reaction mixture was quenched at -78°C without raising the reaction temp, **14a** (Rf 0.40) was also isolated in 32% yield along with **14b** (60% yield).

(5S,6R,1'Z)-5-[(1-Ethoxyethoxy)methyl]-6-(3'-methyl-1'-butenyl)-2-cyclohexen-1-one **7b**. To a stirred soln of **14b** (12.00 g) and Et_3N (23 ml) in dry CH_2Cl_2 (200 ml) was added dropwise a soln of MsCl (12.5 g) in dry CH_2Cl_2 (100 ml) over a period of 45min under ice-cooling. After stirring for 15min, the reaction mixture was quenched with 29% NH_3 aq. The organic layer was separated and washed with 0.5N AcOH aq and sat $NaHCO_3$ aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (150 g, *n*-hexane-ether) to give 6.59g (91%) of **7b**, n_D^{20} 1.4791; $[\alpha]_D^{20}$ +90.7° (c=3.00, *n*-hexane); ν_{max} 3040 (w), 2960 (m), 2930 (m), 2880 (m), 1675 (s), 1380 (m), 1130 (m), 1100 (s), 1055 (s), 740 (m) cm^{-1}; δ (100MHz) 0.98 (3H, d, J=6.5Hz), 1.02 (3H, d, J=6.5Hz), 1.22 (3H, t, J=7.5Hz), 1.31 (3H, d, J=5.0Hz), 2.00-2.40 (1H, m), 2.40-2.80 (3H, m), 3.10-3.80 (5H, m), 4.64 (0.5H, q, J=5.0Hz), 4.69 (0.5H, q, J=5.0Hz), 5.12 (1H, t, J=10.0Hz), 5.57 (1H, t, J=10.0Hz), 5.93-6.16 (1H, m, J_1=10.0Hz), 6.82-7.09 (1H, m, J_1=10.0Hz); GLC (Column, 5% FFAP, 2m X 4mm at 100°C + 7.5°C/min; Carrier gas, N_2, 0.9Kg/cm^2): Rt 15.0min (single peak). (Found: m/z 266.1909. Calc for $C_{16}H_{26}O_3$: 266.1882). In the same manner as described above, **14a** gave **7a** in 95% yield, ν_{max} 3040 (w), 2970 (s), 2880 (s), 1675 (s), 1460 (m), 1380 (s), 1335 (m), 1250 (m), 1130 (s), 1095 (s), 1055 (s), 965 (s), 925 (m), 865 (m), 775 (m), 740 (m) cm^{-1}; δ (100MHz) 1.04 (6H, d, J=6.5Hz), 1.22 (3H, t, J=6.5Hz), 1.30 (3H, d, J=5.0Hz), 2.00-2.60 (4H, m), 2.98 (1H, ddd, J=10.0, 8.0, 2.0Hz), 3.20-3.80 (4H, m), 4.61 (0.5H, q, J=5.0Hz), 4.66 (0.5H, q, J=5.0Hz), 5.24 (1H, dd, J=16.0, 8.0Hz), 5.55 (1H, ddd, J=16.0, 6.0, 2.0Hz), 6.02 (1H, dt, J=10.0, 2.0Hz), 6.92 (1H, dt, J=10.0, 4.0Hz); GLC (the same conditions as described above): Rt 15.5min. The GLC ratios shown in Fig. 3 were determined by analyzing samples obtained by treatment of crude mixtures of **14a** and **14b** with MsCl and Et_3N in CH_2Cl_2.

(1S,5S,6R,1'Z)-5-[(1-Ethoxyethoxy)methyl]-6-(3'-methyl-1'-butenyl)-1-vinyl- 2-cyclohexen-1-ol **6a**. To a stirred soln of tetravinyltin (2.7 g) in dry ether (27 ml) was added dropwise PhLi (1.2N in ether, 34 ml) at room temp. After stirring for 30min, the mixture was cooled to -78°C. To the

resulting suspension was added dropwise a soln of **7b** (6.39 g) in dry ether (70 ml) and the stirring was continued for 10min. The reaction mixture was quenched with sat NH_4Cl aq and diluted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (200 g, *n*-hexane-ether) to give 6.05 g (86%) of **6a**, n_D^{20} 1.4793; $[\alpha]_D^{20}$ +137° (c=1.11, *n*-hexane); ν_{max} 3590 (w), 3500 (m), 3100 (w), 2990 (s), 2950 (s), 2890 (s), 1655 (m), 1630 (w), 1140 (s), 1100 (s), 1060 (s), 995 (s), 930 (s) cm^{-1}; δ (100MHz) 0.94 (3H, d, J=6.5Hz), 1.00 (3H, d, J=6.5Hz), 1.19 (3H, t, J=7.0Hz), 1.28 (3H, d, J=5.0Hz), 1.65-2.37 (3H, m), 1.91 (1H, s, OH), 2.37-2.90 (2H, m), 3.00-3.80 (4H, m), 4.60 (0.5H, q, J=5.0Hz), 4.63 (0.5H, q, J=5.0Hz), 5.00 (1H, t, J=11.0Hz), 5.14 (1H, dd, J=10.0, 2.0Hz), 5.18 (1H, dd, J=17.0, 2.0Hz), 5.48 (1H, t, J=11.0Hz), 5.50 (1H, dt, J=10.0, 2.0Hz), 5.82 (1H, dt, J=10.0, 2.5Hz), 5.92 (1H, dd, J=17.0, 10.0Hz). (Found: m/z 276.2132. Calc for $C_{18}H_{30}O_3$-H_2O: 276.2089).

(2Z,5S,6E,8S)-5-[(1-Ethoxyethoxy)methyl]-8-isopropyl-2,6-cyclodecadien-1-one **3a**. KH (29.29% in mineral oil, 9.0 g) was washed three times with *n*-pentane under Ar and suspended in dry DME (50 ml). To the stirred mixture was added dropwise a soln of **6a** (2.95 g) in dry DME (38 ml). After the addition, 18-crown-6 (13.5 g) was added in a single portion and the stirring was continued for 70min at room temp. The reaction mixture was cooled to -78°C and diluted with *n*-pentane (50 ml). MeOH (2 ml) was added dropwise to the vigorously stirred mixture. The mixture was diluted with sat NH_4Cl aq and extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (120 g, *n*-hexane-ether) to give 2.53 g (86%) of **3a**, n_D^{20} 1.4796; $[\alpha]_D^{20}$ +75.0° (c=1.06, *n*-hexane); ν_{max} 2970 (s), 2890 (s), 1690 (s), 1620 (m), 1130 (s), 1085 (s), 1055 (s), 980 (m) cm^{-1}; δ (100MHz) 0.89 (6H, t, J=6.0Hz), 1.22 (3H, t, J=7.5Hz), 1.32 (3H, d, J=5.0Hz), 1.35-2.05 (4H, m), 2.05-2.75 (5H, m), 3.18-3.83 (4H, m), 4.68 (1H, q, J=5.0Hz), 4.80-5.50 (2H, m), 5.74 (1H, ddd, J=11.0, 9.0, 7.0Hz), 6.28 (1H, d, J=11.0Hz). (Found: m/z 294.2228. Calc for $C_{18}H_{30}O_3$: 294.2195).

(4S,5E,7S,9R,10R)-9,10-Epoxy-7-[(1-ethoxyethoxy)methyl]-4-isopropyl-5-cyclodecen-1-one **15a**. KH (35% in mineral oil, 3.9 g) was washed three times with *n*-pentane and suspended in dry THF (220 ml). *t*-BuOOH (4.17M in toluene, 17 ml) was added to the mixture below 0°C and the stirring was continued for 15min. The reaction mixture was cooled to -20°C and a soln of **3a** (2.08 g) in dry THF (37 ml) was added dropwise over a period of 10min. After stirring for 80min, the mixture was poured into ice-water and extracted with ether. The extract was washed with 10% Na_2SO_3 aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 2.57 g of crude **15a**, ν_{max} 2970 (s), 2880 (s), 1720 (s), 1380 (m), 1130 (s), 1085 (s), 1055 (s), 975 (s), 795 (m) cm^{-1}. This was employed for the next step without further purification.

(4S,5E,7S,9R,10R)-9,10-Epoxy-7-hydroxymethyl-4-isopropyl-5-cyclodecen-1-one **15b**. PPTS (0.17 g) was added to a stirred soln of crude **15a** (2.57 g) in abs EtOH (60 ml). After stirring for 20min at 50°C, the mixture was poured into a mixture of sat $NaHCO_3$ aq and brine, and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (100 g, benzene-THF) to give 1.24 g (74% from **3a**) of **15b** as crystals. Recrystallization of the product from $(i\text{-}Pr)_2O$ gave pure **15b** as needles, m.p. 124.5-125°C; $[\alpha]_D^{20}$ -57.4° (c=0.566, $CHCl_3$); ν_{max} 3430 (m), 2980 (m), 2950 (m), 2900 (m), 1715 (s), 1420 (m), 1080 (m), 1040 (m), 1010 (m), 980 (s), 805 (w), 795 (w) cm^{-1}; δ (400MHz, $CDCl_3$) 0.82 (3H, d, J=6.2Hz), 0.89 (3H, d, J=6.2Hz), 1.17 (1H, dt, J=10.5, 13.2Hz), 1.47-1.63 (3H, m), 1.79 (1H, dddd, J=13.2, 6.2, 3.9, 1.3Hz), 2.04 (1H, dddd, J=13.2, 11.5, 11.5, 1.3Hz), 2.28-2.40 (3H, m), 2.55 (1H, ddd, J=16.0, 11.5, 1.3Hz), 3.26 (1H, ddd, J=10.5, 4.7, 2.9Hz), 3.51 (1H, dd, J=10.5, 7.1Hz), 3.63 (1H, dd, J=10.5, 7.1Hz), 3.71 (1H, d, J=4.7Hz), 5.02 (1H, dd, J=16.0, 9.2Hz), 5.55 (1H, dd, J=16.0, 7.0Hz). (Found: C, 70.56; H, 9.29. Calc for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31%).

(4S,5E,7S,9R,10R)-9,10-Epoxy-4-isopropyl-7-[(o-nitrophenyl)selenomethyl]-5-cyclodecen-1-one **15c**. To a soln of **15b** (0.950 g) and o-$(NO_2)C_6H_4SeCN$ (1.15 g) in THF (22 ml) was added (*n*-Bu)$_3$P (1.25 ml). After stirring for 50min at room temp, the mixture was diluted with CH_2Cl_2. The soln was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (80 g, benzene-ether) to give 1.67 g (99%) of **15c** as crystals. A portion was recrystallized from *n*-hexane-acetone to give pure **15c** as yellow needles, m.p. 158-159°C; $[\alpha]_D^{22}$ -104° (c=1.14, $CHCl_3$); ν_{max} 2960 (w), 2940 (w), 2870 (w), 1715 (m), 1590 (m), 1565 (w), 1515 (s), 1420 (w), 1330 (s), 1305 (s), 1250 (w), 970 (m), 730 (m) cm^{-1}; δ (100MHz) 0.86 (3H, d, J=6.0Hz), 0.92 (3H, d, J=6.0Hz), 1.15-2.20 (5H, m), 2.20-2.75 (4H, m), 2.80-3.10 (2H, m), 3.24 (1H, ddd, J=10.2, 4.7, 2.9Hz), 3.72 (1H, d, J=4.7Hz), 5.14 (1H, dd, J=15.9, 8.7Hz), 5.65 (1H, dd, J=15.9, 7.5Hz), 7.32 (1H, ddd, J=8.3, 5.8, 2.9Hz), 7.42-7.65 (2H, m), 8.27 (1H, ddd, J=8.3, 1.5, 0.8Hz). (Found: C, 56.56; H, 5.97; N, 3.42. Calc for $C_{20}H_{25}O_4NSe$: C, 56.87; H, 5.97; N, 3.32%).

(4S,5E,9R,10R)-9,10-Epoxy-4-isopropyl-7-methylene-5-cyclodecen-1-one **16a**. A mixture of **15c** (1.60 g) and 35% H_2O_2 (4.2 ml) in THF was stirred for 13h at room temp. The reaction mixture was poured into sat $NaHCO_3$ aq and extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (50g, *n*-hexane-ether) to give 0.752 g (90%) of **16a** as crystals. A small portion of the product was recrystallized from *n*-hexane to give pure **16a** as needles, m.p. 49.5-50.5°C; $[\alpha]_D^{20}$ -435° (c=0.565, n-hexane); ν_{max} 3100 (w), 3040 (w), 2980 (s), 2950 (m), 2890 (m), 1715 (s), 1615 (w), 1410 (m), 1070 (m), 985 (s), 910 (m), 800 (m) cm^{-1}; δ (100MHz) 0.85 (3H, d, J=7.5Hz), 0.90 (3H, d, J=7.5Hz), 1.30-2.00 (3H, m), 2.00-2.70 (4H, m), 2.82 (1H, dd, J=12.6, 3.4Hz), 3.16 (1H, ddd, J=10.2, 4.8, 3.4Hz), 3.62 (1H, d, J=4.8Hz), 4.97 (1H, br.s), 4.99 (1H, dd, J=16.0, 10.0Hz), 5.11 (1H, br.s), 5.95 (1H, d, J=16.0Hz). (Found: m/z 220.1480. Calc for $C_{14}H_{20}O_2$: 220.1463).

(2S,4S,5E,9R,10R)-9,10-Epoxy-2-hydroxy-4-isopropyl-7-methylene-5-cyclodecen-1-one **16b**. A soln of $LiN(TMS)_2$ was prepared by the addition of *n*-BuLi (1.57N in *n*-hexane, 3.5 ml) to a soln of $HN(TMS)_2$ (1.2 ml) in dry THF (22 ml) at 0-5°C under Ar. To this soln was added dropwise a soln of **16a** (0.695 g) in dry THF (9 ml) at -78°C. After stirring for 1h, MoOPH (3.10 g) was added in a single portion at -20°C. The mixture was stirred for 25min and quenched with 10% Na_2SO_3 aq. The reaction mixture was poured into brine and extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (50 g, *n*-hexane-ether) to give 0.638 g (86%) of **16b** as crystals. A portion of the product was recrystallized from *n*-hexane-$(i\text{-}Pr)_2O$ to give pure **16b** as needles, m.p. 116-119°C; $[\alpha]_D^{20}$

-422° (c=0.915, ether); ν_{max} 3360 (m), 3090 (w), 3030 (w), 2970 (m), 2880 (m), 1715 (s), 1610 (w), 1445 (m), 1255 (m), 1040 (m), 1010 (m), 980 (s), 970 (s), 905 (m), 805 (m) cm^{-1}; δ (100MHz) 0.82 (3H, d, J=6.4Hz), 0.94 (3H, d, J=6.4Hz), 1.35-2.55 (6H, m), 2.86 (1H, dd, J=13.2, 3.3Hz), 3.21 (1H, ddd, J=10.2, 4.7, 3.3Hz), 3.84 (1H, d, J=4.7Hz), 4.09 (1H, br.d, J=9.9Hz), 4.98 (1H, s), 5.00 (1H, dd, J=16.3, 10.5Hz), 5.14 (1H, s), 5.97 (1H, d, J=16.3Hz). (Found: C, 71.03; H, 8.51. Calc for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%).

(2S,4S,5E,9R,10R)-2-t-Butyldimethylsilyloxy-9,10-epoxy-4-isopropyl-7-methylene-5-cyclohexen-1-one **16c**. To a soln of **16b** (0.615 g) and imidazole (0.390 g) in DMF (8 ml) was added *t*-Bu(Me)$_2$SiCl (0.52 g). After stirring for 17h at room temp, the reaction mixture was poured into sat $NaHCO_3$ aq and extracted with *n*-pentane. The extract was washed with sat $NaHCO_3$ aq and brine, dried (K_2CO_3) and concentrated *in vacuo* to give 0.948 g of crude **16c** as crystals, ν_{max} 3090 (w), 2970 (s), 2940 (s), 2870 (m), 1730 (m), 1250 (s), 1095 (s), 1070 (s), 980 (s), 860 (s), 835 (s), 775 (s) cm^{-1}. This was employed for the next step without further purification.

(1S,3S,4E,8R,9R,10R)-1-t-Butyldimethylsilyloxy-8,9-epoxy-10,10-epoxymethano-3-isopropyl-6-methylene-4-cyclodecene **17a**. To a stirred suspension of Me_3SI (2.60 g) in THF (30 ml) was added dropwise a soln of *n*-BuLi in *n*-hexane (1.57N, 7.8 ml) at -5~0°C. After the addition, the cooling bath was removed and the mixture was stirred for 10min. To the mixture was added dropwise a soln of **16c** (0.948 g) in dry THF (15 ml) at -15°C and the stirring was continued for 10min at -15°C and for 20min at 0°C. The mixture was diluted with brine and extracted with ether. The extract was dried ($MgSO_4$) and concentrated *in vacuo* to give 0.941 g of crude **17a**, ν_{max} 3090 (w), 2970 (s), 2940 (s), 2870 (m), 1250 (m), 1090 (s), 1070 (s), 980 (m), 930 (s), 835 (s), 810 (s), 770 (s) cm^{-1}. This was employed for the next step without further purification.

(1S,3S,4E,8R,9R,10S)-8,9-Epoxy-10,10-epoxymethano-3-isopropyl-6-methylene-4-cyclodecen-1-ol **17b**. To a soln of **17a** (0.941 g) in THF (5 ml) was added (*n*-Bu)$_4$NF (1M in THF, 4 ml). After stirring for 10min at room temp, the reaction mixture was poured into brine and extracted with ether. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (35 g, *n*-hexane-ether) to give 0.466 g (73% from **16b**) of **17b** as crystals. Recrystallization of the product from *n*-hexane-(*i*-Pr)$_2$O gave pure **17b** as needles, m.p. 115-116.5°C; $[\alpha]_D^{21}$ 468° (c=0.154, ether); ν_{max} 3530 (s), 3100 (w), 3050 (w), 2990 (s), 2950 (s), 2910 (s), 1800 (w), 1650 (w), 1610 (w), 1455 (m), 1415 (m), 1390 (m), 1370 (m), 1265 (m), 1160 (m), 1140 (m), 1095 (m), 1060 (s), 1040 (m), 1020 (m), 985 (s), 970 (s), 960 (s), 920 (s), 900 (s), 845 (m), 815 (s), 795 (s), 720 (m) cm^{-1}; δ (300MHz, C_6D_6) 0.67 (1H, d, J=5.8Hz, OH), 0.82 (3H, d, J=6.9Hz), 0.83 (3H, d, J=6.7Hz), 1.25 (1H, ddd, J=12.4, 5.8, 1.0Hz), 1.28-1.42 (1H, m), 1.43 (1H, dd, J=12.4, 10.5Hz), 1.57-1.69 (1H, m), 2.39 (1H, d, J=5.9Hz), 2.59 (1H, dd, J=12.0, 4.0Hz), 2.68 (1H, d, J=5.9Hz), 2.75 (1H, dt, J=10.1, 4.0Hz), 2.99 (1H, d, J=4.0Hz), 3.01 (1H, dd, J=12.0, 10.1Hz), 3.57 (1H, ddd, J=10.5, 5.8, 1.0Hz), 4.86 (2H, s), 5.84-5.98 (2H, m). (Found: C, 71.62; H, 8.85. Calc for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%).

Determination of the optical purity of **17b**. According to the previous method,[5b] (*R*)- and (*S*)-MTPA esters **17c** were prepared and analyzed by HPLC (Column: Nucleosil® 50-5, 25cm x 4.6mm; Solvent: *n*-hexane-THF=80:1; Flow rate, 1.6ml/min; detected at 254nm). Rt, (*R*)-MTPA ester: 16.75min (single peak); (*S*)-MTPA ester: 22.53min (single peak). Therefore the optical purity of **17b** was determined to be 100%.

(3S,4E,8R,9R,10R)-8,9-Epoxy-10,10-epoxymethano-3-isopropyl-6-methylene-4-cyclodecen-1-one **1**. PDC (4.7 g) was added to a soln of **17b** (0.315 g) in DMF (9 ml). After stirring for 2h at room temp, the mixture was poured into water and extracted with ether. The extract was washed with brine, filtered through a short SiO_2 column and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (10 g, *n*-hexane-ether) to give 0.319 g of **1** as crystals. Recrystallization of the product from *n*-hexane gave 0.284 g (92%) of pure **1** as needles, m.p. 55.5-57.5°C; $[\alpha]_D^{21}$ -552° (c=0.111, *n*-hexane); ν_{max} 3040 (w), 2970 (m), 2910 (w), 2890 (w), 1705 (vs), 1610 (w), 1460 (m), 1390 (w), 1370 (w), 1325 (w), 1310 (m), 1275 (w), 1020 (m), 980 (m), 910 (s), 905 (s), 890 (w), 845 (m), 825 (m), 815 (m), 795 (w) cm^{-1}; δ (400MHz, C_6D_6) 0.69 (3H, d, J=6.7Hz), 0.72 (3H, d, J=6.8Hz), 1.28 (1H, m), 1.94 (1H, dd, J=9.7, 5.8Hz), 2.00 (1H, d, J=5.6Hz), 2.01-2.09 (1H, m), 2.33 (1H, dd, J=11.0, 9.7Hz), 2.55 (1H, dd, J=12.1, 4.0Hz), 2.62 (1H, d, J=5.6Hz), 2.74 (1H, dt, J=10.0, 4.0Hz), 2.87 (1H, dd, J=12.1, 10.0Hz), 2.85 (1H, d, J=4.0Hz), 4.78 (1H, br.s), 4.80 (1H, br.s), 5.92 (1H, dd, J=16.0, 8.6Hz), 5.96 (1H, d, J=16.0Hz). (Found: C, 72.26; H, 8.11. Calc for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%). The IR and ^1H NMR spectra were identical with those of an authentic sample.[5b]

Acknowledgement---We are grateful to Dr. T. Takeuchi of Fuji Chemical Industries, Ltd. for his generous gifts of (+)- and (-)-pantolactone. Our thanks are due to the Fujisawa Foundation for financial support.

REFERENCES

1. Persoons, C. J.; Verwiel, P. E. J.; Talman, E.; Ritter, F. J. *J. Chem. Ecol.* **1979**, *5*, 219 and references cited therein.
2. Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493.
3. Adams, M. A.; Nakanishi, K.; Still, W. C.; Arnold, E. V.; Clardy,J.; Persoons, C. J. *J. Am. Chem. Soc.* **1979**, *101*, 2495.
4. a) Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038; b) Hauptmann, H.; MÜhlbauer, G.; Walker, M. P. C. *Tetrahedron Lett.* **1986**, *27*, 1315; c) Takahashi, T.; Kanda, Y.; Nemoto, H.; Kitamura, K.; Tsuji, J.; Fukazawa, Y. *J. Org. Chem.* **1986**, *51*, 3393; d) Cauwberghs, S. G.; De Clercq, P. J. *Tetrahedron Lett.* **1988**, *29*, 6501.
5. a) Kitahara, T.; Mori, M.; Koseki, K.; Mori, K. *Tetrahedron Lett.* **1986**, *27*, 1343; b) Kitahara, T.; Mori, M.; Mori, K. *Tetrahedron* **1987**, *43*, 2689.
6. Kuwahara, S.; Mori, K. *Heterocycles* **1989**, *28*, 167.
7. For a review see, Paulmier, C. *"Selenium Reagents and Intermediates in Organic Synthesis"*, Pergamon Press, Oxford (**1986**).
8. a) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095; b) Schwartz, H. M.; Wu, W-S; Marr, P. W.; Jones, J. B. *J. Am. Chem. Soc.* **1978**, *100*, 5199.
9. Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org Chem.* **1977**, *42*, 384.

10. Hudrlik, P. F.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 6251.
11. House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.
12. Mukaiyama, T.; Stevens, R. W.; Iwasawa, N. *Chem. Lett.* **1982**, 353.
13. a) Kowalski, C. J.; Dung, J-S *J. Am. Chem. Soc.* **1980**, *102*, 7950; b) Clive, D. L. J.; Russell, C. G.; Suri, S. C. *J. Org. Chem.* **1982**, *47*, 1632.
14. Lerouge, P.; Paulmier, C. *Tetrahedron Lett.* **1984**, *25*, 1983.
15. a) Léonard-Coppens, A. M.; Krief, A. *Tetrahedron Lett.* **1976**, 3227; b) Halazy, S.; Krief, A. *ibid.* **1981**, *22*, 1833; c) Sarkar, T. K.; Ghosh, S. K. *ibid.* **1987**, *28*, 2061.
16. Reich, H. J.; Chow, F.; Shah, S. K. *J. Am. Chem. Soc.* **1979**, *101*, 6638.
17. Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242.
18. Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.