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Total Synthesis and Absolute Configuration of Liverwort Diterpenes, (−)-13(15)*E*,16*E*-3*β*,4*β*-Epoxy-18-hydroxysphenoloba-13(15),16-diene and (−)-13(15)*Z*,16*E*-3*β*,4*β*-Epoxy-18-hydroxysphenoloba-13(15),16-diene, by Use of the Ring Closing Metathesis Reaction Applied to Seven-Membered Carbocycles with a Trisubstituted Double Bond

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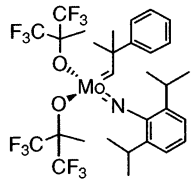
Seven-membered cyclic compounds possessing trisubstituted double bonds have been effectively constructed employing the Grubbs catalyst to effect olefin metathesis. The keto ester does not undergo cyclization; however, alcohols protected by the silyl groups smoothly cyclized into seven-membered compounds. The product was successfully converted to (−)-13(15)*E*,16*E*-3*β*,4*β*-epoxy-18-hydroxysphenoloba-13(15),16-diene and (−)-13(15)*Z*,16*E*-3*β*,4*β*-epoxy-18-hydroxysphenoloba-13(15),16-diene, liverwort diterpenes isolated from *Anastrophyllum auritum* to establish the absolute configuration.

Introduction

Although cyclic disubstituted olefins may be prepared by ring-closing metathesis reactions (RCM) by use of Schrock's (**1**),[1] Grubbs' (**2**),[2] or a new type of catalyst (**3**),[3] carbocycles having trisubstituted double bonds limited to five- or six-membered compounds[4] and only in particular cases seven-membered carbocycles were successfully formed.[5,6]



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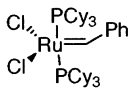

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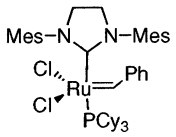

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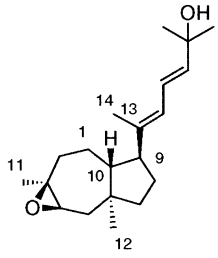
However, in the area of terpenoids, most of the double bonds exist in trisubstituted form owing to the isoprene rule.[7] We are interested in the construction of trisubstituted cyclic alkenes by RCM to synthesize various types of terpenoids, such as sphenolobane-type diterpenoids. Sphenolobane-type diterpenoids, such as **4** and **5**, have



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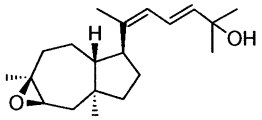

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been found in Hepaticae,[8] plants,[9] and marine sources[10] and have a seven-membered ring with a trisubstituted

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(8) (a) From *Anastrophyllum minutum*: Beyer, J.; Becker, H.; Toyota, M.; Asakawa, Y. *Phytochemistry* **1987**, *26*, 1085−089. (b) From *Anastrophyllum auritum*: Zapp, J.; Burkhardt, G.; Becker, H. *Phytochemistry* **1994**, *37*, 787−793. (c) From *Anastrophyllum donnianum*: Buchanan, M. S.; Connolly, J. D.; Rycroft, D. S. *Phytochemistry* **1996**, *43*, 1297−1301.

(9) From *Halimium viscosum*: Urones, J. G.; Marcos, I. S.; Garrido, N. M.; De Pascal Teresa, J.; Martín, A. S. F. *Phytochemistry* **1989**, *28*, 183−187.

(10) (a) From *Epipolasis reiswigi*: Kashman, Y.; Hirsch, S.; Koehn, F.; Cross, S. *Tetrahedron Lett.* **1987**, *28*, 5461−5464. (b) From *Epipolasis* sp.: Umeyama, A.; Nozaki, M.; Arihara, S. *J. Nat. Prod.* **1998**, *61*, 945−947.

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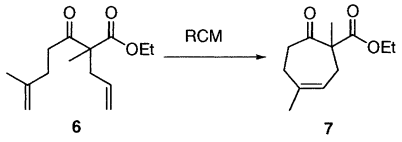
TABLE 1. RCM Reaction of 6[a]



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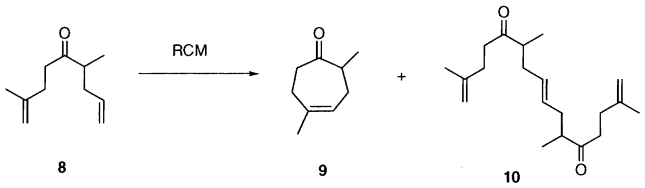
entry	catalysts	mol %	additive (equiv)	solvents	temp (°C)	time (days)	results (by GC)
1	**2**	5	none	CH_2Cl_2	rt	1	no reaction
2	**2**	10	none	PhH	60	2	no reaction
3	**2**	30	$Ti(O^iPr)_4$ (3)	CH_2Cl_2	40	3	**6**:**7** = 1.8:1
4	**2**	30	$Ti(O^iPr)_4$ (1)	CH_2Cl_2	40	13	**6**:**7** = 1:1
5	**2**	140	$Ti(O^iPr)_4$ (0.3)	CH_2Cl_2	40	4	**6**:**7** = 1:5.3
6	**2**	10	$Ti(O^iPr)_4$ (1)	PhH	60	1	**6**:**7** = 14.7:1
7	**1**	20	none	PhH	60	1	trace

[a] Reactions were carried out in 10 mM concentration except for entry 4 (5 mM).

TABLE 2. RCM Reaction of 8[a]



8 9 10

entry	catalysts	mol %	additive (equiv)	solvents	temp (°C)	time (days)	results (by GC)
1	**2**	5	none	CH_2Cl_2	rt	1	no reaction
2	**2**	30	$Ti(O^iPr)_4$ (3)	CH_2Cl_2	40	3	**8**:**9**:**10** = 1:1.4:1.4
3	**2**	10	none	PhH	60	2	**8**:**9**:**10** = 1:1.5:1
4	**1**	10	none	CH_2Cl_2	rt	1	no reaction
5	**1**	10	none	PhH	rt	1	no reaction

[a] Reactions were carried out in 10 mM concentration.

double bond (sometimes oxidized as an epoxide) fused to a five-membered ring. The absolute configuration of tormesol,[9] which was isolated from *Halimium viscosum*, has been elucidated and 9-epitormesol has been synthesized.[11,12] However, the absolute configuration of terpenoids such as **4** and **5**, found in the liverwort, has not been determined yet.[8] Therefore, we initiated a synthetic study of seven-membered carbocycles with trisubstituted double bonds using RCM and have successfully applied this methodology to the total synthesis of natural products **4** and **5** in optically active forms.

The strategy includes olefin metathesis reaction yielding a seven-membered carbocycle and the chiral compound may be made by the chiral imine Michael addition reaction.[13] This paper deals with the successful and effective construction of seven-membered carbocycles having a trisubstituted double bond by using RCM and the total synthesis of the particular diterpenes **4** and **5** to establish the absolute configuration as depicted.

Results and Discussion

Keto ester **6** was treated with catalyst **2** in either CH_2Cl_2 or PhH as illustrated in Table 1. As in entries 1 and 2, **6** did not react at all in CH_2Cl_2 or PhH. However, in the presence of $Ti(O^iPr)_4$,[14] the desired carbocycle **7** was obtained in the ratio of **6**:**7** = 14.7:1 to 1:1 depending on the conditions used (entries 3−6). It should be noted that catalyst **1** did not work to produce compound **7** (entry 7). Consequently, if the keto ester moiety was blocked by $Ti(O^iPr)_4$, only a small amount of the product was obtained.

We next used ketone **8** for the metathesis reaction, the results of which are listed in Table 2. Although the reaction of **8** with catalyst **2** gave no product in CH_2Cl_2 (entry 1), the desired product **9** was obtained as a mixture of **8**, **9**, and the dimer **10** in almost 1:1:1 ratio at elevated temperature in PhH or in the presence of $Ti(O^iPr)_4$ [14] (entries 2 and 3). It is also noteworthy that no product was obtained with catalyst **1** (entries 4 and 5). Thus, the ketone may provide a preventive effect for the metathesis reaction, since addition of $Ti(O^iPr)_4$ to block the carbonyl group brought a favorable effect for the reaction.

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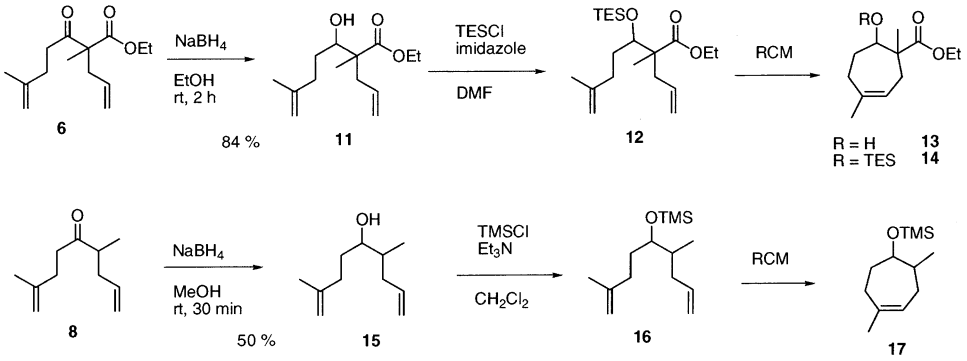
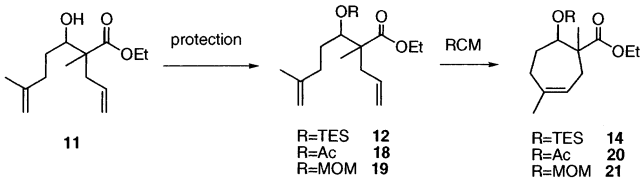
TABLE 3. RCM Reaction of 11, 12, 15, and 16[a]



entry	substrates	mol %	solvent	concn (mM)	time (h)	results (by GC)
1	**11**	10	CH_2Cl_2	5	24	**11**:**13** = 1.2:1
2	**12**	5	CH_2Cl_2	10	9.5	**12**:**14** = 1.3:1
3	**12**	10	CH_2Cl_2	10	24	**14** (quant.)
4	**15**	10	CH_2Cl_2	5	15.5	no reaction
5	**16**	10	CH_2Cl_2	5	24	**17** (quant.)

[a] Reactions were carried out at 40 °C with **2** as catalyst.

TABLE 4. RCM Reaction of 12, 18, and 19[a]



entry	substrates	catalysts	mol %	solvents	temp (°C)	results (yield %)
1	**12**	**2**	10	CH_2Cl_2	40	**14** (94)
2	**18**	**2**	10	CH_2Cl_2	40	**20** (61)
3	**19**	**2**	10	CH_2Cl_2	40	**21** (37)
4	**12**	**1**	20	PhH	60	**14** (quant.)
5	**18**	**1**	20	PhH	60	**20** (84)
6	**19**	**1**	20	PhH	60	**21** (79)

[a] Reactions were carried out in 10 mM concentration for 24 h.

In the next trials, ketone was reduced and alcohols **11** and **15** and also their protected versions **12** and **16** were investigated. As Table 3 indicates, alcohol **11** afforded almost half conversion into the seven-membered alcohol **13** (entry 1). However, alcohol **15** did not produce a cyclic alcohol (entry 4). Compound **12**, the protected version with TES, with 5 mol % of catalyst **2** in CH_2Cl_2 afforded the desired compound as a mixture with the starting material in an almost 1:1 ratio (entry 2). Therefore, 10 mol % of catalyst **2** was used in the next reaction for a prolonged period (24 h) to afford **14** in quantitative yield (entry 3). Similar conditions were employed for compound **16**, and the seven-membered carbocycle **17** was produced quantitatively (entry 5).

With these results in mind, other protecting groups were studied. Table 4 illustrates the results. Both catalysts **1** and **2** worked efficiently to produce TES-protected compound **12** (entries 1 and 4). However, protecting groups having more oxygen atom are less reactive toward metathesis reactions even in the case of catalyst **1** (entries 2, 3, 5, and 6). Therefore, the TES protecting group was the best choice in these cases and catalyst **1** worked more efficiently, but catalyst **2** can also give satisfactory results for our purposes due to the higher price of **1** and the easier handling of catalyst **2**.

We utilized the seven-membered ester **14** for further elaboration of the fused five-membered ring. Compound **14** was oxidized with Jones reagent and the conventional decarboxylation afforded cycloheptenone **9** in 47% yield. The phenylethylamine technology[13] was applied to this ketone to yield ester **22** in 47% yield (40% recovery of ketone **9**). The absolute configuration of **22** is presumed to be *S*, since the CD spectrum showed the (+)-Cotton effect as generally observed in these series of ketones.[13e,15] Chiral HPLC suggested that the ee was 97%. Keto ester **22** was reduced by $LiAlH_4$ to the diol, which was monotosylated with TsCl in pyridine. TES chloride was introduced into the reaction mixture before workup, providing the differently protected diol **23**. In the absence of TESCl the cyclic ether was always produced during workup for tosylation. The tosylate was substituted by cyanide ion and intramolecular aldol cyclization afforded unsaturated nitrile **25** after dehydration with $SOCl_2$ (Scheme 1).

Nitrile **25** was reduced with Mg in MeOH.[16] The product was a mixture of four compounds judged by GC-MS, and the mixture was further methylated (MeLi) to yield methyl ketones. The separation at this stage was not successful, therefore, the mixture was subjected to the equilibration conditions (K_2CO_3, MeOH) to show only two peaks in GC-MS, and **30** and **32**, thermodynamically more stable compounds, were isolated. The steric energy of the diastereoisomeric pair of compounds **30** and **31**, as well as **32** and **33**, was calculated with CONFLEX with use of MM2[17] parameters to determine the more stable isomers. Thus, **30** and **32** were found to be more stable

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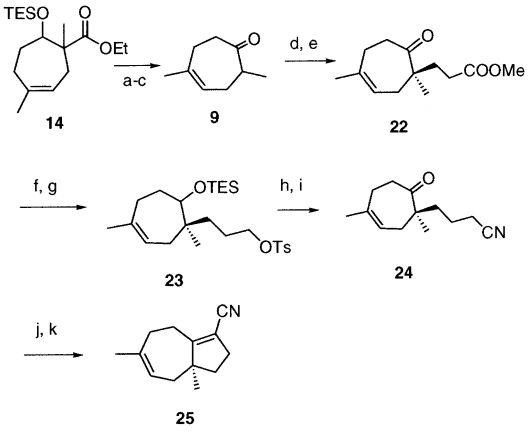
(16) Profitt, J. A.; Whatt, D. S.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 127−128.

(17) Materia Ver.3.2, CONFLEX module was used; cf.: (a) Goto, H.; Ôsawa, E. *Tetrahedron Lett.* **1992**, *33*, 1343−4346. (b) Goto, H.; Ôsawa, E. *J. Chem. Soc., Perkin Trans 2* **1993**, 187−198. (c) Tori, M.; Ikawa, M.; Sagawa, T.; Furuta, H.; Sono, M.; Asakawa, Y. *Tetrahedron* **1996**, *52*, 9999−10010.

SCHEME 1[a]



[a] Reagents and conditions: (a) Jones oxidation, 0 °C, 1.5 h; (b) 10% KOH-EtOH, rt; (c) 6 M HCl, rt ,47% (3 steps); (d) (*S*)-(−)-phenylethyl amine, TsOH, PhH, reflux, overnight; (e) methyl acrylate, rt, 4 days, 47% (2 steps, 40% recovery); (f) $LiAlH_4$, Et_2O, rt, 1 h; (g) TsCl, py, −30 °C, overnight; then TESCl, 0 °C, 1 h; (h) KCN, 18-crown-6 ether, DMF, 50 °C, overnight; (i) Jones acetone, 0 °C, 2 h, 71% (3 steps); (j) tBuOK, THF, 0 °C, 2 h; (k) $SOCl_2$, py, 0 °C, 3 h, 74% (2 steps).

isomers, in which **30** had the desired stereochemistry for our synthesis, which was later confirmed by NOE experiment for epoxide **28**. Alternatively, the reduction products of nitrile **25** were separated by HPLC to afford **26** and **27**. When **26** was methylated (MeLi), the mixture of **30** and **31** was produced. This mixture was equilibrated to isolate only **30**. Ketone **30** was converted (*m*CPBA) to epoxide **28**, the stereochemistry of which was revealed by NOESY experiment to be that shown in Scheme 2. Similarly, epoxide **29** was derived from nitrile **27** and the stereochemistry was also established at this stage. Thus, the equilibration was complete in these systems and epoxidation occurred only from the β-side of the molecule due to the steric hindrance of the methyl group at the juncture position.

Vinylmagnesium bromide was used for chain elongation of **28** and PCC oxidation of vinyl alcohol **34** produced a mixture of enals **35** and **36** (2.6:1). The direct formation of the side chain with use of Horner−Emmons reagent failed presumably due to the steric hindrance of the carbonyl group of **28**. Trimethyl phosphonoacetate was used for further elongation followed by methylation (MeLi) to afford a mixture of **4** and **5**, which was separated by HPLC (Scheme 3). The ^1H and ^{13}C NMR data of synthetic **4** and **5** were identical with those of the natural products. The specific rotations of the synthetic samples for **4** and **5** were −37.4 (*c* 0.66, $CHCl_3$) and −42.0 (*c* 0.84, $CHCl_3$), while those of the natural samples were −14.0 (*c* 2.7, $CHCl_3$) and −25.2 (*c* 0.26, $CHCl_3$), establishing the absolute configuration of these diterpenes as depicted in the formula.

In conclusion, we have successfully utilized the Grubbs[1] reagent for construction of trisubstituted seven-membered carbocycles in excellent yield and the total synthesis of liverwort diterpenes **4** and **5** was achieved to establish the absolute configurations as depicted in the formulas for the first time. Noteworthy is that the absolute configurations of sphenolobanes found in Hepaticae are opposite those found in higher plants, such as tormesol.[9]

Experimental Section[18]

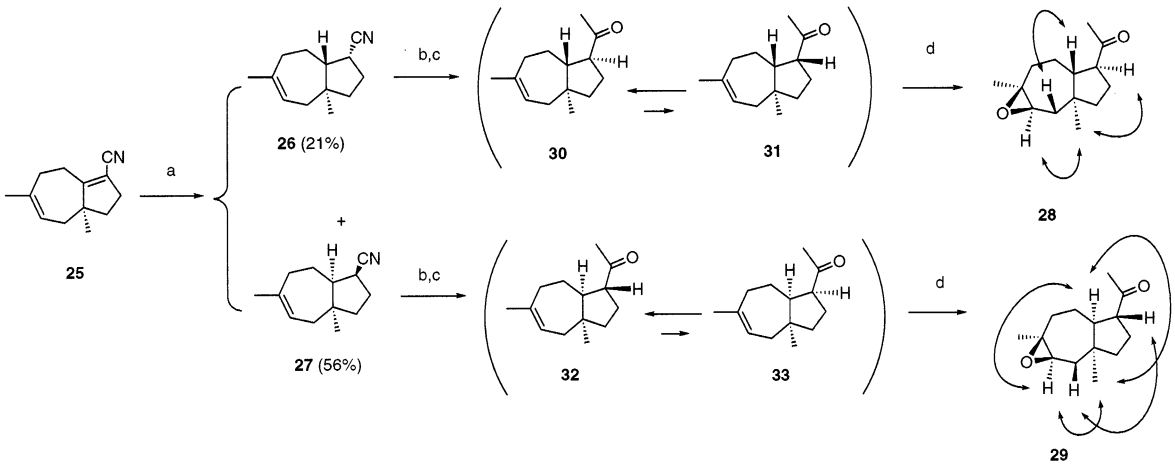
2,5-Dimethylcyclohept-4-en-1-one (9). Jones reagent was added to a solution of TES ether **14** (4.08 g, 13 mmol) in acetone (300 mL) at 0 °C until the mixture turned from green to orange and the mixture was stirred for 1.5 h. 2-Propanol was added until the mixture turned green. Water was added, and the solvent was evaporated to give a residue, which was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a keto ester. A solution of keto ester in EtOH (30 mL) was treated with 10% KOH solution (20 mL) at room temperature. The mixture was stirred for 2.5 h and the solvent was evaporated to give a residue, which was washed with ether. HCl (6 M, 40 mL) and EtOH (10 mL) were added to the aqueous layer. The mixture was stirred overnight at room temperature and the solvent was evaporated to give a residue, which was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford ketone **9** (0.843 g, 47%): oil; FTIR 1700 cm^{-1}; ^1H NMR (200 MHz,) δ 0.88 (1H, t, J = 6.8 Hz), 1.07 (3H, d, J = 6.8 Hz), 1.74 (3H, s), 2.06−2.45 (3H, m), 2.58 (1H, dq, J = 14.2, 3.6 Hz), 2.66−2.90 (2H, m), 5.51 (1H, br t, J = 5.6 Hz); ^{13}C NMR (50 MHz) δ 16.3 (CH_3), 25.8 (CH_3), 29.5 (CH_2), 32.2 (CH_2), 40.8 (CH_2), 45.9 (CH), 122.8 (CH), 137.4 (C), 215.4 (C); MS (EI) *m*/*z* 138 (M^+), 123, 96, 81 (base), 67; HRMS (EI) found *m*/*z* 138.1051 (M^+), $C_9H_{14}O$ requires 138.1044.

Methyl (1*S*)-3-(1,4-Dimethyl-7-oxocyclohept-3-enyl)-propanoate (22). To a solution of ketone **9** (1.98 g, 14 mmol) in PhH (40 mL) was added (*S*)-(−)-phenylethylamine (2.4 mL, 18 mmol) and TsOH (0.40 g). The mixture was heated under reflux overnight with a Dean−Stark water separator. The mixture was extracted with ether and the organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was treated with methyl acrylate (1.95 mL, 22 mmol) at room temperature for 4 days. A 90% AcOH solution was added, and the mixture was heated at 60 °C for 3 h and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated to afford a residue (2.74 g), which was purified by silica gel column chromatography (elution with hexanes−EtOAc gradient; 0−20%) to yield keto ester **22** (1.52 g, 47%) and ketone **9** (0.793 g, 40%). Keto ester **22** was analyzed with HPLC (Chiralcel OD-H, hexane:2-propanol = 9:1): Oil; $[\alpha]^{21}_D$ +56.4 (*c* 1.1, $CHCl_3$); FTIR 1740, 1700 cm^{-1}; ^1H NMR (200 MHz) δ 1.06 (3H, s), 1.67 (3H, s), 1.74−1.96 (2H, m), 2.11 (1H, ddd, J = 15.2, 7.4, 1.4 Hz), 2.22−2.49 (5H, m), 2.59 (1H, dt, J = 11.4, 6.2 Hz), 2.90 (1H, ddd, J = 15.2, 9.2, 6.2 Hz), 5.46 (1H, ddq, J = 13.6, 6.2, 1.4 Hz); ^{13}C NMR (50 MHz) δ 21.8 (CH_3), 25.1 (CH_3), 29.2 (CH_2), 31.8 (CH_2), 33.1 (CH_2), 35.0 (CH_2), 37.4 (CH_2), 51.5 (CH_3), 53.0 (C), 121.1 (CH), 137.2 (C), 174.0 (C), 215.9 (C); MS (EI) *m*/*z* 224 (M^+), 206, 192, 151, 137 (base), 107, 81; HRMS (EI) found *m*/*z* 224.1417 (M^+), $C_{13}H_{20}O_3$ requires 224.1413; CD $[\theta]_{296\ nm}$ +2650 (4.83×10^{-3} M, $CHCl_3$).

(1*S*)-4-(1,4-Dimethyl-7-oxocyclohept-3-enyl)butanecarbonitrile (24). A solution of keto ester **22** (3.0 g, 13 mmol) in ether (135 mL) was reduced with $LiAlH_4$ (763 mg, 20 mmol) at room temperature for 1 h. Water (0.76 mL), 15% NaOH solution (0.76 mL), and water (2.28 mL) were added successively. After filtration, the solvent was evaporated to give a diol (2.77 g), which was used in the next step without purification. To a solution of diol in pyridine (135 mL) was added TsCl (5.11 g, 27 mmol) at 0 °C, and the reaction mixture was stirred overnight at −30 °C. Then, the mixture was treated with TESCl (4.5 mL, 27 mmol) at 0 °C for 24 h. Water was added, and the mixture was extracted with ether. The organic layer was washed with 10% $CuSO_4$ solution, water, and brine, dried ($MgSO_4$), and evaporated to give tosylate **23** (7.66 g), which was used in the next step without purification. To a solution of tosylate **23** in DMF (135 mL) was added 18-

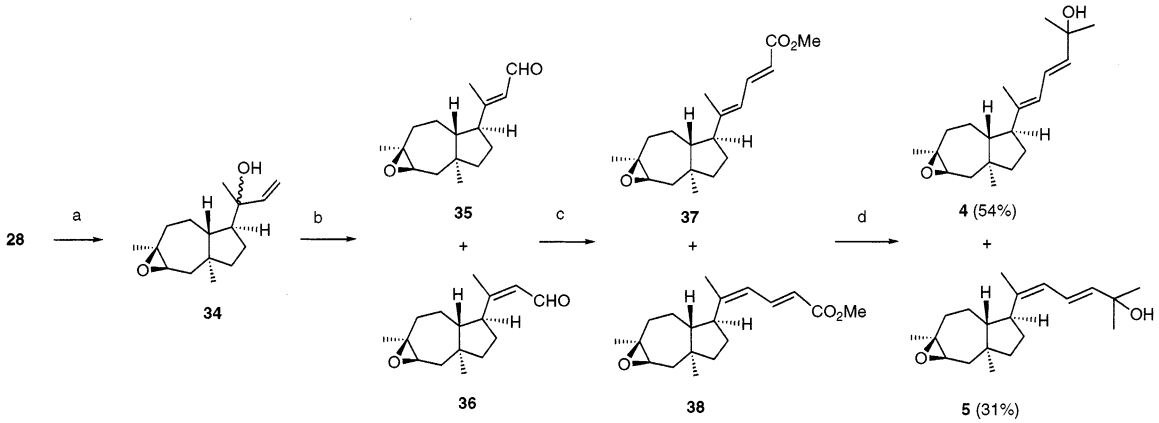
(18) General procedures are described in the Supporting Information.

SCHEME 2[a]



[a] Reactions and conditions: (a) Mg, MeOH then HPLC; (b) MeLi, Et_2O; (c) K_2CO_3, MeOH, reflux; (d) mCPBA, CH_2Cl_2.

SCHEME 3[a]



[a] Reagents and conditions: (a) CH_2=$CHMgBr$, THF; (b) PCC, CH_2Cl_2 (63%, 2 steps); (c) $(MeO)_2POCH_2CO_2Me$, NaH, THF (22%); (d) MeLi, Et_2O, then HPLC.

crown-6 ether (5.31 g, 20 mmol) and KCN (1.13 g, 17 mmol), and the mixture was heated at 50 °C overnight. Water was added, and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give a nitrile (5.62 g), which was used in the next step without purification. A solution of nitrile in acetone (135 mL) was treated with Jones reagent at 0 °C until the mixture turned from green to orange and the mixture was stirred for 2 h. 2-Propanol was added until the mixture turned green. Water was added, and the solvent was evaporated to give a residue, which was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue, which was purified by silica gel column chromatography (elution with hexane−EtOAc gradient; 0−30%) to yield keto nitrile **24** (1.96 g, 71%): oil; $[\alpha]^{19}_D$ +55.4 (*c* 1.2, $CHCl_3$); FTIR 2240, 1700 cm^{-1}; ^1H NMR (300 MHz) δ 1.08 (3H, s), 1.56−1.63 (4H, m), 1.68 (3H, s), 2.17 (1H, ddq, J = 15.6, 6.9, 0.9 Hz), 2.24−2.34 (5H, m), 2.37 (1H, dd, J = 15.6, 6.3 Hz), 2.67 (1H, ddd, J = 11.4, 6.9, 6.0 Hz), 2.82 (1H, ddd, J = 11.4, 8.1, 6.3 Hz), 5.46 (1H, tq, J = 6.9, 1.5 Hz); ^{13}C NMR (75 MHz) δ 17.6 (CH_2), 20.7 (CH_2), 22.4 (CH_3), 25.1 (CH_3), 31.8 (CH_2), 34.8 (CH_2), 37.3 (CH_2), 37.5 (CH_2), 53.2 (C), 119.4 (C), 120.9 (CH), 137.0 (C), 215.8 (C); MS (EI) *m*/*z* 205 (M^+, base), 190, 162, 151, 109, 97; HRMS (EI) found *m*/*z* 205.1471 (M^+), $C_{13}H_{19}NO_3$ requires 205.1467.

(*1S*)-8-Cyano-1,4-dimethylbicyclo[5.3.0]deca-3,7-diene (25). To a solution of keto nitrile **24** (177 mg, 0.86 mmol) in THF (10 mL) was added a solution of ^{t}BuOK (1M, 1.3 mL, 1.3 mmol) in THF at 0 °C over 2 h. HCl (1 M) was added, and the mixture was evaporated to afford to a residue, which was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to an alcohol (460 mg), which was used in the next step without purification. A solution of alcohol in pyridine (9 mL) was treated with $SOCl_2$ (0.13 mL, 1.7 mmol) at 0 °C for 3 h. Water was added, and the mixture was extracted with ether. The organic layer was washed with 10% $CuSO_4$ solution and brine, dried ($MgSO_4$), and evaporated to give a residue, which was purified by silica gel column chromatography (elution with hexane−EtOAc gradient; 0−20%) to yield diene **25** (120 mg, 74%): oil; $[\alpha]^{17}_D$ −100.1 (*c* 1.07, $CHCl_3$); FTIR 2210, 1630 cm^{-1}; ^1H NMR (300 MHz) δ 1.00 (3H, s), 1.69−1.86 (2H, m), 1.78 (3H, s), 1.96−2.17 (5H, m), 2.39−2.59 (2H, m), 2.69−2.86 (1H, m), 5.48 (1H, td, J = 6.8, 1.5 Hz); ^{13}C NMR (75 MHz) δ 23.0 (CH_3), 25.5 (CH_3), 25.9 (CH_2), 30.4 (CH_2), 31.3 (CH_2), 38.9 (CH_2), 39.0 (CH_2), 49.7 (C), 105.9 (C), 117.2 (C), 122.2 (CH), 140.3 (C), 171.8 (C); MS (EI) *m*/*z* 187 (M^+, base), 172, 145, 119, 104, 91; HRMS (EI) found *m*/*z* 187.1355 (M^+), $C_{13}H_{17}N$ requires 187.1361.

(1*S*,7*R*,8*R*)-8-Cyano-1,4-dimethylbicyclo[5.3.0]dec-3-ene (26) and (1*S*,7*S*,8*S*)-8-Cyano-1,4-dimethylbicyclo-[5.3.0]dec-3-ene (27). To a solution of **25** (306 mg, 1.6 mmol) in MeOH (16 mL) was added Mg turnings (1.54 g, 11 mmol) with stirring overnight at room temperature. Saturated NH_4-Cl solution was added, and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give a residue (310 mg), which was

purified by HPLC (Develosil 60-10, 20ϕ × 250 mm, hexane:EtOAc = 9:1, 9.0 mL/min) to yield **26** (65.8 mg, 21%), **27** (174 mg, 56%), and a mixture of other isomers (41.2 mg, 13%). **26**: oil; $[\alpha]^{19}_D$ −94.2 (*c* 1.2, $CHCl_3$); FTIR 2230 cm^{-1}; ^1H NMR (600 MHz) δ 0.93 (3H, s), 1.39 (1H, qd, J = 10.8, 1.2 Hz), 1.57−1.73 (4H, m), 1.78 (3H, t, J = 1.4 Hz), 1.85 (1H, br d, J = 14.0 Hz), 2.04 (1H, dddd, J = 13.7, 11.0, 8.2, 5.2 Hz), 2.10 (1H, dd, J = 14.0, 5.5 Hz), 2.11 (1H, m), 2.14 (1H, dtd, J = 14.0, 10.2, 1.4 Hz), 3.04 (1H, td, J = 9.9, 4.9 Hz), 5.41 (1H, ddt, J = 8.9, 4.4, 1.4 Hz); ^{13}C NMR (150 MHz) δ 17.7 (CH_3), 23.8 (CH_2), 26.6 (CH_2), 27.0 (CH_3), 32.3 (CH), 33.3 (CH_2), 40.0 (CH_2), 41.1 (CH_2), 42.4 (C), 55.0 (CH), 122.1 (CH), 122.9 (C), 139.3 (C); MS (EI) *m*/*z* 189 (M^+), 174, 133, 121, 68 (base); HRMS (EI) found *m*/*z* 189.1525 (M^+), $C_{13}H_{19}N$ requires 189.1517. **27**: $[\alpha]^{23}_D$ +66.2 (*c* 1.0, $CHCl_3$); FTIR 2230 cm^{-1}; ^1H NMR (400 MHz) δ 1.05 (3H, s), 1.55 (1H, ddd, J = 13.2, 5.9, 3.7 Hz), 1.64 (3H, s), 1.67−2.00 (6H, m), 2.00−2.23 (2H, m), 2.29 (1H, dd, J = 15.8, 5.5 Hz), 2.57 (1H, d, J = 15.8 Hz), 3.02 (1H, m), 5.26 (1H, br d, J = 5.5 Hz); ^{13}C NMR (100 MHz) δ 25.5 (CH_3), 27.0 (CH_2), 29.4 (CH_2), 29.8 (CH_3), 34.7 (CH_2), 36.7 (CH), 37.0 (CH_2), 41.6 (CH_2), 45.9 (C), 51.1 (CH), 121.0 (CH), 121.4 (C), 136.7 (C); MS (EI) *m*/*z* 189 (M^+), 174, 133, 119, 81, 68 (base); HRMS (EI) found *m*/*z* 189.1516 (M^+), $C_{13}H_{19}N$ requires 189.1517.

(1*S*,7*R*,8*S*)-8-Acetyl-1,4-dimethylbicyclo[5.3.0]dec-3-ene (30). A solution of **26** (46.6 mg, 0.25 mmol) in ether (1.2 mL) was treated with MeLi (1.14 M, 1.1 mL, 1.3 mmol) in ether at 0 °C and stirred overnight at room temperature. Water was added, and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give a residue (39.7 mg). The residue was dissolved in MeOH (4 mL), and K_2CO_3 (266 mg, 1.9 mmol) was added. The mixture was heated at 45 °C for 24 h. Water was added, and the solvent was evaporated. The residue was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give ketone **30** (37.3 mg), which was used in the next step without purification: oil; $[\alpha]^{19}_D$ +35.5 (*c* 0.7, $CHCl_3$); FTIR 1710 cm^{-1}; ^1H NMR (300 MHz) δ 0.74 (3H, s), 1.10−1.27 (1H, m), 1.43 (1H, q, J = 3.0 Hz), 1.47 (1H, dd, J = 8.7, 5.7 Hz), 1.41−1.51 (1H, m), 1.57−1.71 (2H, m), 1.74 (3H, s), 1.78 (1H, td, J = 11.1, 3.0 Hz), 1.89−2.15 (4H, m), 2.15 (3H, s), 2.67 (1H, td, J = 11.1, 6.3 Hz), 5.38 (1H, m); ^{13}C NMR (75 MHz) δ 18.1 (CH_3), 24.7 (CH_2), 25.2 (CH_2), 27.1 (CH_3), 29.7 (CH_3), 33.8 (CH_2), 40.2 (CH_2), 40.5 (CH_2), 42.2 (C), 56.3 (CH), 56.7 (CH), 122.3 (CH), 139.4 (C), 212.2 (C); MS (EI) *m*/*z* 206 (M^+), 188, 163, 121, 107, 95 (base); HRMS (EI) found *m*/*z* 206.1684 (M^+), $C_{14}H_{22}O$ requires 206.1670.

(1*S*,3*R*,4*S*,7*R*,8*S*)-8-Acetyl-3,4-epoxy-1,4-dimethylbicyclo-[5.3.0]decane (28). A solution of ketone **30** (37.3 mg, 0.18 mmol) in CH_2Cl_2 (4 mL) was treated with *m*CPBA (70%, 78.9 mg, 0.32 mmol) at 0 °C for 1.5 h. $Na_2S_2O_3$ (2 M) solution was added, and the mixture was extracted with ether. The organic layer was washed with 2 M $Na_2S_2O_3$ solution and brine, dried ($MgSO_4$), and evaporated to give a residue, which was purified by silica gel column chromatography (elution with hexane−EtOAc gradient; 0−50%) to yield epoxide **28** (20.5 mg, 51%): oil; $[\alpha]^{19}_D$ +37.2 (*c* 1.0, $CHCl_3$); FTIR 1710 cm^{-1}; ^1H NMR (600 MHz) δ 0.92 (3H, s), 1.29 (1H, dq, J = 13.2, 1.1 Hz), 1.31 (1H, dd, J = 11.3, 6.9 Hz), 1.33 (3H, s), 1.43 (1H, d, J = 13.7 Hz), 1.47 (1H, dd, J = 8.8, 5.5 Hz), 1.53 (1H, ddq, J = 14.1, 6.6, 1.4 Hz), 1.60−1.66 (2H, m), 1.68 (1H, td, J = 11.3, 2.7 Hz), 2.00−2.08 (2H, m), 2.14 (3H, s), 2.28 (1H, q, J = 6.9 Hz), 2.69 (1H, td, J = 11.3, 6.9 Hz), 2.74 (1H, t, J = 7.2 Hz); ^{13}C NMR (150 MHz) δ 17.4 (CH_3), 23.3 (CH_3), 23.7 (CH_2), 25.3 (CH_2), 29.6 (CH_3), 35.8 (CH_2), 39.5 (CH_2), 40.6 (CH_2), 44.3 (C), 55.5 (CH), 56.4 (CH), 60.0 (C), 60.7 (CH), 211.4 (C); MS (EI) *m*/*z* 222 (M^+), 207, 179, 161, 137, 121, 107, 93 (base); HRMS (EI) found *m*/*z* 222.1606 (M^+), $C_{14}H_{22}O_2$ requires 222.1620.

13(15)*E*-3β,4β-Epoxy-17,18,19,20-tetranorsphenolob-13-(15)-en-16-al (35) and 13(15)*Z*-3β,4β-Epoxy-17,18,19,20-tetranorsphenolob-13(15)-en-16-al (36). A solution of epoxide **28** (20.5 mg, 0.092 mmol) in THF (1 mL) was treated with vinylmagnesium bromide (0.95 M, 0.6 mL, 0.57 mmol) in THF at 0 °C, and the mixture was stirred overnight at room temperature. Water was added, and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give a residue (29.4 mg), which was used in the next step without purification. The residue was dissolved in CH_2Cl_2 (5 mL), and was treated with PCC (135.8 mg, 0.630 mmol) at room temperature for 24 h. After filtration, the solvent was evaporated to give a residue (36.8 mg), which was purified by silica gel column chromatography (elution with hexane−EtOAc gradient; 0−50%) to yield a mixture of aldehydes **35** and **36** (14.4 mg, 63%): oil; FTIR 1670 cm^{-1}; ^1H NMR (300 MHz) δ 0.95 (t, J = 9.9 Hz), 1.33 (s), 1.20−1.74 (m), 2.11 (s), 1.88−2.19 (m), 2.32 (q, J = 6.6 Hz), 2.46 (td, J = 10.8, 6.3 Hz), 2.62−2.81 (m), 3.58 (td, J = 6.6, 6.3 Hz), 5.84 (d, J = 8.1 Hz), 5.95 (dd, J = 8.1, 0.9 Hz), 9.96 (d, J = 8.1 Hz), 9.99 (d, J = 8.1 Hz); ^{13}C NMR (75 MHz) δ 14.6, 17.5, 23.1, 23.3, 26.8, 35.9, 39.9, 40.0, 41.1, 44.4, 53.1, 57.8, 60.0, 60.7, 127.8, 165.6, 189.8, 191.3; MS (EI) *m*/*z* 248 (M^+), 230, 197, 159, 145, 119, 95 (base); HRMS (EI) found *m*/*z* 248.1799 (M^+), $C_{16}H_{24}O_2$ requires 248.1776.

Methyl 13(15)*E*,16*E*-3β,4β-Epoxy-19,20-dinorsphenoloba-13(15),16-diene-18-carboxylate (37) and Methyl 13(15)*Z*,-16*E*-3β,4β-Epoxy-19,20-dinorsphenoloba-13(15),16-diene-18-carboxylate (38). To a solution of trimethyl phosphonoacetate (58.1 mg, 0.32 mmol) in THF (2 mL) was added a solution of LHMDS (1 M, 0.24 mL, 0.24 mmol) in THF at room temperature over 1.5 h. A solution of aldehydes **35** and **36** (14.4 mg, 0.058 mmol) in THF (3 mL) was added, and the mixture was stirred for 3 h. Water was added at 0 °C, and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give a residue, which was purified by silica gel column chromatography (elution with hexane−EtOAc gradient; 0−30%) and HPLC (Nucleosil 50-5, 4.6ϕ × 250 mm, hexane:EtOAc = 3:1, 1.0 mL/min) to yield esters **37** and **38** (3.9 mg, 22%): oil; FTIR 1720, 1630 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 0.50 (s), 0.59 (s), 0.68 (s), 0.88−1.48 (m), 1.22 (s), 1.36 (d, J = 1.2 Hz), 1.48−1.71 (m), 1.85 (td, J = 13.8, 6.3 Hz), 2.01−2.20 (m), 2.53−2.65 (m), 3.04 (td, J = 10.8, 6.3 Hz), 3.49 (s), 3.54 (s), 5.85 (d, J = 12.3 Hz), 5.92 (d, J = 12.3 Hz), 6.03 (d, J = 15.0 Hz), 6.04 (d, J = 15.3 Hz), 7.90 (dd, J = 15.3, 11.7 Hz), 8.02 (dd, J = 15.0, 11.7 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 13.6, 17.8, 17.9, 20.0, 23.8, 24.0, 26.5, 26.8, 36.9, 37.0, 40.5, 40.7, 42.0, 42.1, 44.6, 44.7, 44.9, 51.5, 53.9, 58.2, 58.6, 59.7, 60.7, 119.9, 120.3, 125.1, 126.8, 140.6, 141.7, 151.3, 151.5, 168.1, 168.2; MS (EI) *m*/*z* 304 (M^+), 286, 178, 145, 125, 93 (base); HRMS (EI) found *m*/*z* 304.2050 (M^+), $C_{19}H_{28}O_3$ requires 304.2039.

(−)-13(15)*E*,16*E*-3β,4β-Epoxy-18-hydroxysphenoloba-13(15),16-diene (4) and (−)-13(15)*Z*,16*E*-3β,4β-Epoxy-18-hydroxysphenoloba-13(15),16-diene (5). A solution of the mixture of esters **37** and **38** (3.9 mg, 0.013 mmol) in ether (1.5 mL) was treated with MeLi (1.14 M, 0.045 mL, 0.051 mmol) in ether at 0 °C for 3 h. Water was added, and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give a residue, which was purified by HPLC (Nucleosil 50-5, 7.5ϕ × 250 mm, hexane:EtOAc = 75:15, 1.0 mL/min) to yield **4** (2.1 mg, 54%) and **5** (1.2 mg, 31%). **4**: oil; $[\alpha]^{22}_D$ −37.4 (*c* 0.66, $CHCl_3$); FTIR 3430 cm^{-1}; ^1H NMR (400 MHz) δ 0.92 (3H, s), 1.32 (3H, s), 1.35 (6H, s), 1.68 (3H, d, J = 1.1 Hz), 1.76−1.89 (1H, m), 2.03 (1H, dd, J = 13.5, 6.6 Hz), 2.25−2.37 (2H, m), 2.76 (1H, t, J = 7.3 Hz), 5.73 (1H, d, J = 15.4 Hz), 5.81 (1H, d, J = 10.6 Hz), 6.44 (1H, dd, J = 15.4, 10.6 Hz); ^{13}C NMR (75 MHz) δ 13.0 (CH_3), 17.5 (CH_3), 23.2 (CH_2), 23.4 (CH_3), 26.2 (CH_2), 29.9 (CH_3), 29.9 (CH_3), 36.1 (CH_2), 39.9 (CH_2), 41.3 (CH_2), 44.0 (CH_2), 52.7 (C), 57.5 (CH), 60.2 (C), 61.1 (C), 71.0 (C), 122.9 (CH), 125.2 (C), 139.2 (CH), 140.3 (C); MS (EI) *m*/*z* 304 (M^+), 286, 268, 197, 159, 119, 107 (base); HRMS (EI) found *m*/*z* 304.2404 (M^+), $C_{20}H_{32}O_2$ requires 304.2402. **5**: oil; $[\alpha]^{23}_D$ −42.0 (*c* 0.84, $CHCl_3$); ^1H NMR (400 MHz) δ 0.97 (3H, s), 1.33 (3H, s), 1.34 (6H, s), 1.56 (3H, s), 1.76−1.89 (1H, m), 2.03 (1H, dd, J = 13.2, 5.8 Hz), 2.30 (1H, dd, 13.6, 7.0 Hz), 2.77 (1H, t, J = 7.0 Hz), 2.99

(1H, td, J = 11.0, 6.6 Hz), 5.71 (1H, d, J = 15.0 Hz), 5.89 (1H, d, J = 10.6 Hz), 6.46 (1H, dd, J = 15.0, 10.6 Hz); ^{13}C NMR (100 MHz) δ 17.7 (CH_3), 19.1 (CH_3), 23.1 (CH_2), 23.5 (CH_3), 25.6 (CH_2), 30.1 (CH_3), 30.1 (CH_3), 36.2 (CH_2), 40.1 (CH_2), 41.4 (CH_2), 43.6 (C), 44.1 (C), 57.8 (CH), 60.2 (C), 61.1 (C), 71.0 (C), 122.1 (CH), 126.9 (C), 139.4 (CH), 140.0 (C); MS (EI) m/z 286 $[M - H_2O]^+$, 268, 197, 159, 119, 107 (base); HRMS (EI) found m/z 286.2293 $[M - H_2O]^+$, $C_{20}H_{30}O_2$ requires 286.2296.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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