Pergamon

Tetrahedron 55 (1999) 14369–14380

TETRAHEDRON

Efficient Construction of 8-Membered Ring Framework of Vinigrol through SmI_2-Induced Coupling Cyclization

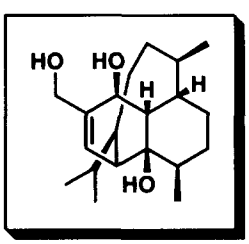
Fuyuhiko Matsuda,*† Makoto Kito, Toshinari Sakai, Naoko Okada, Masaaki Miyashita, and Haruhisa Shirahama

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

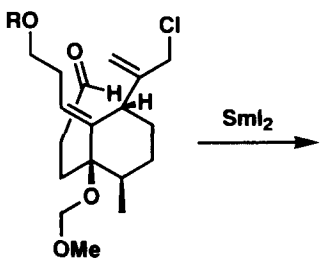
Received 13 August 1999; accepted 7 October 1999

Abstract: The 8-membered ring framework of vinigrol, a unique tricyclic diterpene isolated as a novel antihypertensive compound from a culture of *Virgaria nigra*, was efficiently synthesized employing an SmI_2-induced intramolecular coupling. It is particularly noteworthy that the 8-membered carbocycle was cyclized in *quantitative yields under non-high-dilution conditions.*

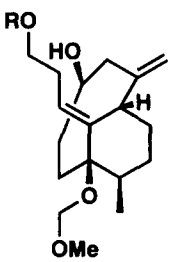
Vinigrol (**1**), a unique tricyclic diterpene, was isolated from a culture broth of the fungal strain identified as *Virgaria nigra* by Ando and co-workers in 1987. They also reported the antihypertensive and platelet aggregation inhibitory properties of **1**.[1] In addition, in 1991, it was found that **1** is a tumor necrosis factor (TNF) antagonist.[2] Therefore, **1** may be used to control conditions attributable to TNF, such as endotoxic shock, inflammation, infection, cachexia, and the progression from the AIDS-related complex to AIDS. Its remarkable physiological activity and unusual structure distinguish the molecule as a very interesting target for total synthesis.[3]



Vinigrol (**1**)



2a R=Bn
2b R=MPM



3a R=Bn
3b R=MPM

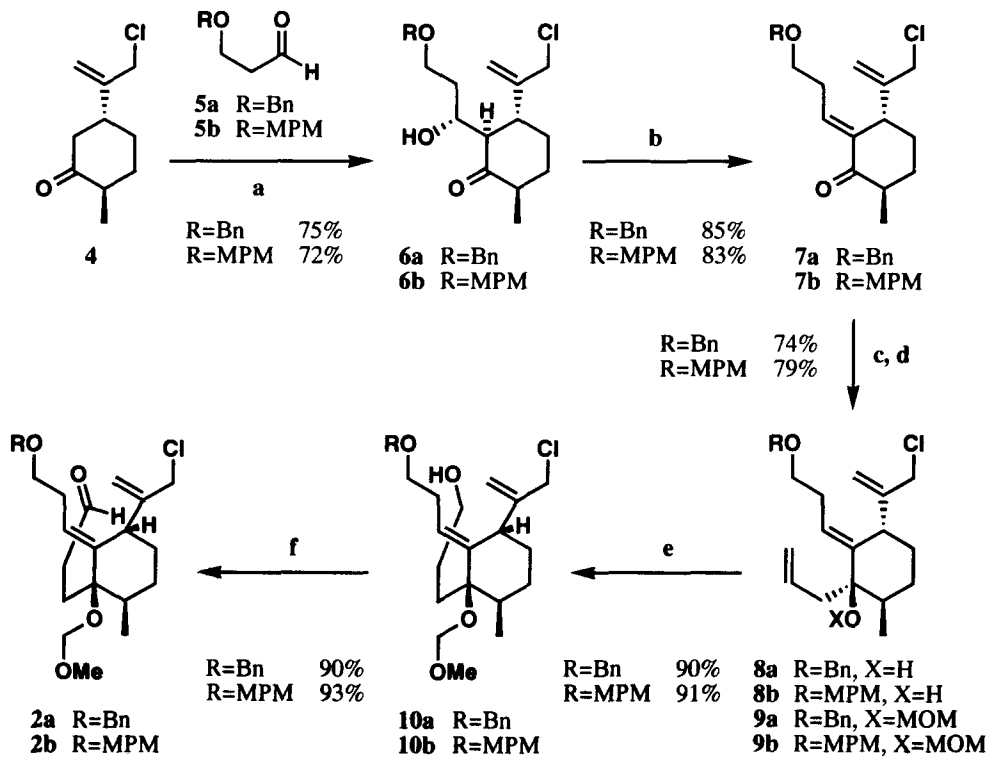
† Present address: Division of Material Science, Graduate School of Environmental Earth Science, Hokkaido University, Sapporo 060-0810, Japan. E-mail: fmatsuda@ees.hokudai.ac.jp

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00885-6

The diterpene features a complicated fused ring system involving an 8-membered ring. Naturally occurring compounds having medium ring frameworks have historically attracted much attention because of their potential biological activity and the synthetic challenge posed by the required formation of the ring itself.[4] While various types of annulation methods for the construction of the medium rings have evolved, the development of a general and efficient method for preparing medium-sized carbocycles by simple cyclization of acyclic precursors *via* carbon-carbon bond formation reaction has not proven as easy. In conjunction with our program directed toward the total synthesis of **1**, we found that treatment of the aldehydes **2a** and **2b** with samarium iodide (SmI_2)[4-7] cleanly allowed the 8-membered ring closing reaction to form the cyclooctanols **3a** and **3b** relevant to the 8-6 fused ring system of the diterpene.[8] Particularly impressive is the fact that the medium carbocycle was cyclized in *quantitative yields under non-high-dilution conditions*. In this paper we describe the 8-membered ring closure reaction through the intramolecular reductive coupling induced by SmI_2.

First, the aldehydes **2a** and **2b** were synthesized starting with (+)-chlorodihydrocarvone (**4**) as summarized in Scheme 1. Chlorodihydrocarvone (**4**) was readily prepared in multi-gram quantities from commercially

Scheme 1[a]

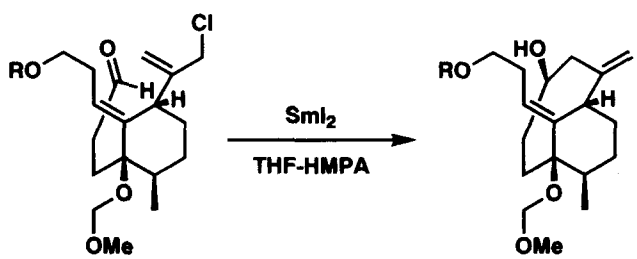


[a]Key: (a) (1) LDA, THF, –78 °C, (2) **5a** or **5b**, –78 °C; (b) $FC_5H_5NMe \cdot OTs$, Et_3N, CH_2Cl_2, reflux; (c) $CH_2{=}CHCH_2MgBr$, ether, –78 °C; (d) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, 25 °C; (e) (1) $ThexylBH_2$, THF, 0 °C, (2) 30% H_2O_2, 25 °C; (f) Dess-Martin Periodinane, Py, CH_2Cl_2, 25 °C.

available (+)-dihydrocarvone according to the known method.[9] The stereoselective aldol reactions of the Li-enolate generated from **4** with 3-benzyloxypropanal (**5a**)[10] or 3-(4-methoxyphenylmethoxy)propanal (**5b**) afforded the hydroxy ketones **6a** and **6b**. Treatment of **6a** and **6b** with 2-fluoro-1-methylpyridinium tosylate gave the (*E*)-α-enones **7a** and **7b**. The 1,2-addition of CH_2=$CHCH_2MgBr$ to **7a** and **7b** took place in a stereoselective manner, and the β-alcohols **8a** and **8b** were obtained as major isomers along with the α-epimers (β:α = 5:1). After protection of the hydroxyl groups of **8a** and **8b** as the MOM ethers, regioselective hydroboration-oxidation of the terminal olefin moieties of the MOM ethers **9a** and **9b** by thexylborane followed by Dess-Martin oxidation of the resulting alcohols **10a** and **10b** provided **2a** and **2b**. Remarkably, the allyl chloride groups of these synthetic intermediates were stable to the projected reactions such as the Grignard reaction or hydroboration. From a synthetic point of view, it is important that the 8-membered ring was formed with high efficiency using the stable allyl chloride functionality through the reductive coupling promoted by SmI_2 as mentioned below.

When the aldehydes **2a** and **2b** were treated with SmI_2 at room temperature in the presence of HMPA, the 8-membered ring-closure reaction instantaneously took place between the allyl chloride and the aldehyde groups, with the cyclooctanols **3a** and **3b** relevant to the 8-6 fused ring system of vinigrol (**1**) as the only detectable products (Scheme 2). *The quantitative yields* of **3a** and **3b** are remarkable in view of the difficulties normally encountered during the cyclization of 8-membered rings. Even at –78 °C, the reaction sufficiently proceeded, providing good yields of the 8-membered ring products. The addition of HMPA was essential for the SmI_2-promoted intramolecular coupling.[11] The reaction in the absence of HMPA produced a substantial decrease in product yield (15%). It is particularly noteworthy that the 8-membered rings were constructed *under non-high-dilution conditions*. Amazingly, the ready formation of the 8-membered carbocycles can be accomplished by adding a 0.1 M solution of SmI_2 (2.5 equiv) in THF-HMPA to a 2.0 M solution of **2a** or **2b** at once. The reaction was completed soon after the addition of SmI_2, *operationally quite simple!*

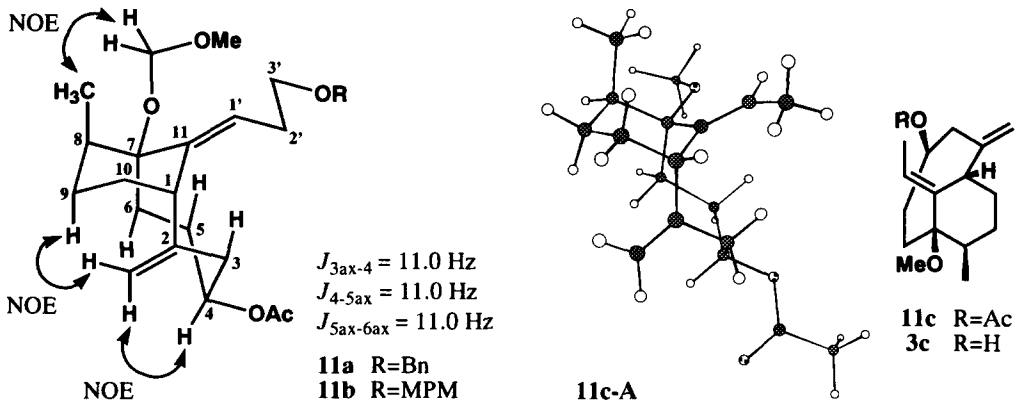
Scheme 2



2a R=Bn	25 °C, R=Bn	99%	**3a** R=Bn
2b R=MPM	25 °C, R=MPM	98%	**3b** R=MPM
	0 °C, R=Bn	93%	
	0 °C, R=MPM	94%	
	–78 °C, R=Bn	87%	
	–78 °C, R=MPM	85%	

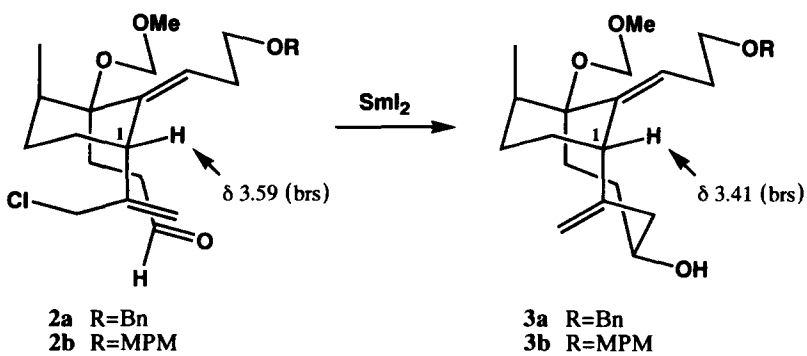
The structures of **3a** and **3b** were confirmed by 2D-COSY and 2D-NOESY experiments on the acetates **11a** and **11b** prepared from **3a** and **3b** through acetylation (Ac_2O, Py, 25 °C, 95% for **11a**, 97% for **11b**). The stereochemical assignments to **11a** and **11b** definitely follow from inspection of the selected key coupling constants ($J_{3ax\text{-}4}$, $J_{4\text{-}5ax}$, and $J_{5ax\text{-}6ax}$) and NOEs as depicted in Figure 1 (bicyclo[1.3.5]undecane numbering). The assignments also rested on an MM2 calculation preformed on the model compound **11c**. According to the MM2 calculation, **11c-A** is the global minimum-energy conformer.[12] The MM2 ground-state structure of **11c-A** is compatible with observed ^{1}H-NMR spectral data shown in Figure 1.

Figure 1



A conformational preorganization was observed in the 8-membered ring-closing reaction of the aldehydes **2a** and **2b** as illustrated in Scheme 3. This is a typical case of the 1,3-allylic strain ($A^{1,3}$ strain) involving a methylenecyclohexane ring system.[13] The ^{1}H-NMR spectra of the open chain aldehydes **2a** and **2b** showed that the allylic methine protons at C_1 were broad singlets, and the ^{1}H-NMR spectra of the cyclized 8-membered ring

Scheme 3



alcohols **3a** and **3b** showed that the allylic methine protons at C_1 were also broad singlets. Obviously, the cyclohexane rings of the open chain aldehydes **2a** and **2b** adopt chair conformations similar to those of the cyclohexane rings of the cyclized 8-membered ring alcohols **3a** and **3b**.[12] That conformation is the one that has the axial substituents and thus relieves a particularly serious $A^{1,3}$ strain.[13,14] Therefore, the favorable orientation of the two ends towards cyclization through such a conformation greatly facilitates 8-membered ring formation.

In summary, the 8-6 fused ring system of vinigrol (**1**), an unusual tricyclic diterpene, was efficiently constructed using the SmI_2-induced intramolecular reductive coupling. This synthesis described here is noteworthy for the high efficiency with which the 8-membered ring is assembled. Particularly impressive is the fact that *the quantitative formation of the 8-membered carbocycles can be accomplished under non-high-dilution conditions*. The protocol should be applicable to the construction of various medium-sized rings.[15]

Experimental Section

General Methods. Melting points are uncorrected. Optical rotations were measured on a JASCO DIP-360 digital polarimeter. IR spectra were recorded on a Shimadzu FTIR-8200A spectrometer using a NaCl cell. ^{1}H- and ^{13}C-NMR spectra were recorded on a JNM-FX-400 (400 and 100 MHz) spectrometer. Chemical shifts were reported in ppm down-field from the peak of Me_4Si used as the internal standard. Splitting patterns are designated as "s, d, t, q, and m"; these symbols indicate "singlet, doublet, triplet, quartet, and multiplet," respectively. Mass spectra were obtained on a JEOL JMS-DX-303 spectrometer. All reactions were carried out under an Ar atmosphere. Tetrahydrofuran (THF) and ether were distilled from Na metal / benzophenone ketyl. Dichloromethane (CH_2Cl_2) and hexamethylphosphoramide (HMPA) were distilled from CaH_2. (2*R*,5*R*)-5-(1-Chloromethylethenyl)-2-methylcyclohexanone (**4**), 3-benzyloxypropanal (**5a**) and 3-(4-methoxyphenylmethoxy)propanal (**5b**) were prepared according to known procedures.[9,10] All other commercially obtained reagents were used as received. Analytical and preparative TLC were carried out using pre-coated silica gel plates (Macherey-Nagel DC-Fertigplatten SIL G-25 UV254). The silica gel used for column chromatographies was Merck Kieselgel 60 Art 7734.

(2*R*,5*R*)-5-(1-Chloromethylethenyl)-2-methylcyclohexanone 4. According to known procedure,[9] the title compound was synthesized from (+)-(2*R*,5*R*)-5-isopropenyl-2-methylcyclohexanone (dihydrocarvone) in 55% yield as colorless crystals: mp 36 – 37 °C; $[\alpha]^{25}_D$ +6.11° (*c* 0.655, $CHCl_3$); IR ($CHCl_3$) 3020, 2970, 2935, 2860, 1715, 1645, 1450, 1425, 1410, 1375, 1365, 1320, 1260, 1220, 1185, 1140, 1085, 1055, 1020, 915 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, d, *J* = 6.4 Hz), 1.41 (1H, dq, *J* = 3.3, 13.2 Hz), 1.68 (1H, dq, *J* = 3.3, 13.2 Hz), 2.05 (1H, ddq, *J* = 2.3, 13.2, 3.3 Hz), 2.15 (1H, ddt, *J* = 5.8, 13.2, 3.3 Hz), 2.28 (1H, t, *J* = 13.2 Hz), 2.39 (1H, ddq, *J* = 5.8, 13.2, 6.4 Hz), 2.51 – 2.66 (2H, m), 4.08 (2H, brs), 5.05, 5.23 (each 1H, brs); EI-MS m/z 186 (M^+). Anal. Calcd for $C_{10}H_{15}ClO$: C, 64.34; H, 8.10; Cl, 18.99. Found: C, 64.52; H, 7.98; Cl, 19.07.

3-Benzyloxypropanal 5a. The title compound was prepared in three steps according to known procedure[10] by starting with $HOCH_2CH_2CH_2OH$ and C_6H_5CHO in 77% yield as a colorless oil: IR (neat) 3020, 2960, 2930, 2860, 2735, 1725, 1610, 1515, 1445, 1365, 1300, 1265, 1250, 1220, 1175, 1090, 1035, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.69 (2H, dt, *J* = 2.0, 6.1 Hz), 3.78 (2H, t, *J* = 6.1 Hz), 4.53 (2H, brs), 7.22 – 7.37 (5H, m), 9.78 (1H, t, *J* = 2.0 Hz); EI-MS m/z 164 (M^+). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.26; H,

7.22.

3-(4-Methoxyphenylmethoxy)propanal 5b. Following known procedure,[10] the title compound was prepared in three steps from $HOCH_2CH_2CH_2OH$ and *p*-$MeOC_6H_4CHO$ in 74% yield as a colorless oil: IR (neat) 3020, 2960, 2930, 2860, 2735, 1610, 1515, 1445, 1365, 1300, 1250, 1220, 1175, 1090, 1035, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.69 (2H, dt, *J* = 2.0, 6.1 Hz), 3.78 (2H, t, *J* = 6.1 Hz), 3.80 (3H, s), 4.46 (2H, brs), 6.88, 7.25 (each 2H, d, J = 8.7 Hz), 9.78 (1H, t, *J* = 2.0 Hz); EI-MS m/z 194 (M^+). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.91; H, 7.33.

(2*R*,3*R*,6*R*)-3-[1-(Chloromethyl)ethenyl]-2-[(*R*)-1-hydroxy-3-benzyloxypropyl]-6-methylcyclohexanone 6a. To a solution of *i*-Pr_2NH (1.65 mL, 11.8 mmol) in THF (85 mL) cooled at –78 °C was added dropwise a 1.60 M hexane solution of *n*-BuLi (7.02 mL, 11.2 mmol) over 20 min. After stirring at –78 °C for 30 min, a solution of **4** (2.00 g, 10.7 mmol) in THF (10 mL) was added dropwise over 15 min. Stirring was continued at –78 °C for 30 min, and a solution of **5a** (2.11 g, 12.8 mmol) in THF (10 mL) was added dropwise over 15 min. After stirring at –78 °C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was then allowed to warm to room temperature and extracted with ether. The combined ethereal extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane, 20:80) to afford **6a** (2.82 g, 75%) as a colorless oil: $[\alpha]^{25}_D$ +18.4° (*c* 0.980, $CHCl_3$); IR (neat) 3530, 3080, 2965, 2930, 2860, 1720, 1700, 1610, 1585, 1515, 1455, 1445, 1410, 1375, 1300, 1270, 1250, 1210, 1175, 1095, 1035, 910, 820, 750, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.98 (3H, d, *J* = 6.3 Hz), 1.38 (1H, dq, *J* = 3.8, 12.9 Hz), 1.71 – 1.91 (2H, m), 1.95 – 2.19 (3H, m), 2.40 – 2.56 (1H, m), 2.44 (1H, brd, *J* = 12.2 Hz), 2.77 (1H, dt, *J* = 3.8, 12.2 Hz), 3.14 (1H, d, *J* = 11.2 Hz), 3.53 (2H, t, *J* = 5.6 Hz), 3.62 – 3.72 (1H, m), 4.07 (1H, dd, *J* = 0.8, 12.0 Hz), 4.12 (1H, dd, *J* = 1.0, 12.0 Hz), 4.52 (2H, s), 5.13, 5.36 (each 1H, brs), 7.22 – 7.37 (5H, m); EI-MS m/z 350 (M^+), 332 (M^+–H_2O), 315 (M^+–Cl), 242 (M^+–$C_6H_5CH_2OH$); High-Resolution EI-MS m/z 350.1650 (M^+, calcd for $C_{20}H_{27}ClO_3$ 350.1649). Anal. Calcd for $C_{20}H_{27}ClO_3$: C, 68.46; H, 7.76; Cl, 10.10. Found: C, 68.38; H, 7.83; Cl, 9.98.

(2*R*,3*R*,6*R*)-3-[1-(Chloromethyl)ethenyl]-2-[(*R*)-1-hydroxy-3-(4-methoxyphenylmethoxy)propyl]-6-methylcyclohexanone 6b. Following the procedure previously described, the cross aldol reaction of the Li-enolate generated from **4** with **5b** furnished **6b** in 72% yield as a colorless oil: $[\alpha]^{25}_D$ +27.9° (*c* 0.700, $CHCl_3$); IR (neat) 3530, 3080, 2965, 2930, 2860, 1700, 1610, 1585, 1515, 1455, 1445, 1410, 1375, 1300, 1250, 1210, 1175, 1095, 1035, 910, 820, 750, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.98 (3H, d, *J* = 6.4 Hz), 1.38 (1H, dq, *J* = 3.8, 12.9 Hz), 1.71 – 1.91 (2H, m), 1.95 – 2.19 (3H, m), 2.40 – 2.56 (3H, m), 2.77 (1H, dt, *J* = 3.8, 12.2 Hz), 3.14 (1H, d, *J* = 11.2 Hz), 3.53 (2H, t, *J* = 5.6 Hz), 3.62 – 3.72 (1H, m), 3.80 (3H, s), 4.07 (1H, dd, *J* = 0.8, 12.0 Hz), 4.12 (1H, dd, *J* = 1.0, 12.0 Hz), 4.45 (2H, s), 5.13, 5.36 (each 1H, brs), 6.86, 7.22 (each 2H, d, *J* = 8.6 Hz); EI-MS m/z 380 (M^+), 362 (M^+–H_2O), 345 (M^+–Cl), 242 (M^+–$MeOC_6H_4CH_2OH$); High-Resolution EI-MS m/z 380.1743 (M^+, calcd for $C_{21}H_{29}ClO_4$ 380.1754). Anal. Calcd for $C_{21}H_{29}ClO_4$: C, 66.22; H, 7.67; Cl, 9.31. Found: C, 66.35; H, 7.55; Cl, 9.42.

(3*R*,6*R*)-3-[1-(Chloromethyl)ethenyl]-2-[(*E*)-3-benzyloxypropylidene]-6-methylcyclohexanone 7a. A solution of **6a** (2.07 g, 5.88 mmol) and Et_3N (4.91 mL, 35.2 mmol) in CH_2Cl_2 (200 mL) was warmed to 50 °C, and 2-fluoro-1-methylpyridinium *p*-toluenesulfonate (5.00 g, 17.6 mmol) was added. After stirring at 50 °C for 2 h, the reaction mixture was cooled to room temperature, saturated aqueous NH_4Cl was added and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by silica gel column chromatography

(AcOEt/hexane, 10:90) gave **7a** (1.67 g, 85%) as a colorless oil: $[\alpha]^{25}_D$ –105° (*c* 1.620, $CHCl_3$); IR (neat) 3005, 2960, 2935, 2865, 1710, 1685, 1610, 1585, 1515, 1460, 1445, 1360, 1300, 1275, 1250, 1175, 1095, 1035, 995, 920, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.14 (3H, d, *J* = 7.3 Hz), 1.42 – 1.53 (1H, m), 1.67 – 1.77 (1H, m), 1.86 – 2.11 (2H, m), 2.22 – 2.53 (3H, m), 3.50 – 3.58 (2H, m), 3.83 (1H, brs), 4.08, 4.18 (each, 1H, d, *J* = 11.9 Hz), 4.50 (2H, s), 4.84, 5.20 (each, 1H, brs), 6.72 (1H, dt, *J* = 1.3, 6.6 Hz), 7.22 – 7.37 (5H, m); EI-MS m/z 332 (M^+), 297 (M^+–Cl); High-Resolution EI-MS m/z 332.1551 (M^+, calcd for $C_{20}H_{25}ClO_2$ 332.1543). Anal. Calcd for $C_{20}H_{25}ClO_2$: C, 72.17; H, 7.57; Cl, 10.65. Found: C, 72.31; H, 7.49; Cl, 10.77.

(3*R*,6*R*)-3-[1-(Chloromethyl)ethenyl]-2-[(*E*)-3-(4-methoxyphenylmethoxy)propylidene]-6-methylcyclohexanone 7b. According to the protocol previously described, **7b** was synthesized from **6b** in 83% yield as a colorless oil: $[\alpha]^{25}_D$ –90.0° (*c* 1.40, $CHCl_3$); IR (neat) 3005, 2960, 2935, 2865, 1685, 1610, 1585, 1515, 1460, 1445, 1360, 1300, 1250, 1175, 1095, 1035, 995, 920, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.14 (3H, d, *J* = 7.3 Hz), 1.42 – 1.53 (1H, m), 1.67 – 1.77 (1H, m), 1.86 – 2.11 (2H, m), 2.22 – 2.53 (3H, m), 3.50 – 3.58 (2H, m), 3.80 (3H, s), 3.83 (1H, brs), 4.08, 4.18 (each, 1H, d, *J* = 11.9 Hz), 4.43 (2H, s), 4.84, 5.20 (each, 1H, brs), 6.72 (1H, dt, *J* = 1.3, 6.6 Hz), 6.87, 7.24 (each 2H, d, *J* = 8.7 Hz); EI-MS m/z 362 (M^+); High-Resolution EI-MS m/z 362.1627 (M^+, calcd for $C_{21}H_{27}ClO_3$ 362.1649). Anal. Calcd for $C_{21}H_{27}ClO_3$: C, 69.51; H, 7.50; Cl, 9.77. Found: C, 69.40; H, 7.58; Cl, 9.62.

(1*R*,3*R*,6*R*)-1-Allyl-3-[1-(chloromethyl)ethenyl]-2-[(*E*)-3-benzyloxypropylidene]-6-methyl-1-cyclohexanol 8a. To a solution of **7a** (1.20 g, 3.60 mmol) in ether (50 mL) cooled at –78 °C was added a 1.00 M ether solution of CH_2=$CHCH_2MgBr$ (7.19 mL, 7.19 mmol). After stirring at –78 °C for 30 min, the mixture was quenched with saturated aqueous NH_4Cl, allowed to warm to room temperature, and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane, 15:85) to furnish **8a** (1.09 g, 81%) as a colorless oil: $[\alpha]^{25}_D$ –105° (*c* 0.410, $CHCl_3$); IR (neat) 3555, 3070, 2945, 2870, 1710, 1635, 1610, 1585, 1515, 1465, 1445, 1375, 1360, 1300, 1275, 1250, 1175, 1095, 1035, 1000, 915, 820, 755, 710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.90 (3H, d, *J* = 6.9 Hz), 1.37 – 1.46 (1H, m), 1.80 – 2.10 (4H, m), 2.35 (1H, dd, *J* = 7.9, 14.2 Hz), 2.42 – 2.68 (3H, m), 3.48 – 3.61 (2H, m), 3.70 (1H, brs), 3.98 (2H, brs), 4.53 (2H, s), 5.03 (1H, d, *J* = 16.8 Hz), 5.08 (1H, d, *J* = 10.3 Hz), 5.26 (1H, d, *J* = 2.0 Hz), 5.36 (1H, brs), 5.65 (1H, dddd, *J* = 6.5, 7.9, 10.3, 16.8 Hz), 5.83 (1H, t, *J* = 7.3 Hz), 7.22 – 7.37 (5H, m); EI-MS m/z 374 (M^+), 356 (M^+–H_2O), 333 (M^+–CH_2CH=CH_2); High-Resolution EI-MS m/z 374.2001 (M^+, calcd for $C_{23}H_{31}ClO_2$ 374.2012). Anal. Calcd for $C_{23}H_{31}ClO_2$: C, 73.68; H, 8.33; Cl, 9.46. Found: C, 73.53; H, 8.50; Cl, 9.52.

(1*R*,3*R*,6*R*)-1-Allyl-3-[1-(chloromethyl)ethenyl]-2-[(*E*)-3-(4-methoxyphenylmethoxy)propylidene]-6-methyl-1-cyclohexanol 8b. The Grignard reaction of **7b** with CH_2=$CHCH_2MgBr$ in accord with the procedure previously described furnished **8b** in 85% yield as a colorless oil: $[\alpha]^{25}_D$ –123° (*c* 1.91, $CHCl_3$); IR (neat) 3555, 3070, 2945, 2870, 1635, 1610, 1585, 1515, 1465, 1445, 1375, 1360, 1300, 1250, 1175, 1095, 1035, 1000, 915, 820, 755, 710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.90 (3H, d, *J* = 6.9 Hz), 1.37 – 1.46 (1H, m), 1.80 – 2.10 (4H, m), 2.35 (1H, dd, *J* = 7.9, 14.2 Hz), 2.42 – 2.68 (3H, m), 3.48 – 3.61 (2H, m), 3.70 (1H, brs), 3.80 (3H, s), 3.98 (2H, brs), 4.46 (2H, s), 5.03 (1H, d, *J* = 16.8 Hz), 5.08 (1H, d, *J* = 10.3 Hz), 5.26 (1H, d, *J* = 2.0 Hz), 5.36 (1H, brs), 5.65 (1H, dddd, *J* = 6.5, 7.9, 10.3, 16.8 Hz), 5.83 (1H, t, *J* = 7.3 Hz), 6.87, 7.27 (each 2H, d, *J* = 8.6 Hz); EI-MS m/z 404 (M^+), 386 (M^+–H_2O), 363 (M^+–CH_2CH=CH_2); High-Resolution EI-MS m/z 404.2109 (M^+, calcd for $C_{24}H_{33}ClO_3$ 404.2118). Anal. Calcd for $C_{24}H_{33}ClO_3$: C, 73.68; H, 8.33; Cl, 9.46. Found: C, 73.53; H, 8.50; Cl, 9.52.

(1*R*,3*R*,6*R*)-1-Allyl-3-[1-(chloromethyl)ethenyl]-2-[(*E*)-3-benzyloxypropylidene]-1-(methoxymethoxy)-6-methylcyclohexane 9a. To a solution of **8a** (300 mg, 0.800 mmol), *i*-Pr_2NEt (1.69 mL, 9.68 mmol) and DMAP (15.0 mg, 0.123 mmol) in CH_2Cl_2 (5.0 mL) was added $MeOCH_2Cl$ (0.682 mL, 8.00 mmol) at room temperature. The mixture was stirred at room temperature for 96 h, poured into saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The combined layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (AcOEt/hexane, 5:95) afforded **9a** (304 mg, 91%) as a colorless oil: $[\alpha]^{25}_D$ –176° (*c* 0.850, $CHCl_3$); IR (neat) 3075, 2935, 2860, 1720, 1640, 1610, 1585, 1515, 1465, 1445, 1360, 1300, 1265, 1250, 1215, 1175, 1145, 1095, 1035, 920, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.94 (3H, d, *J* = 6.6 Hz), 1.42 – 1.52 (1H, m), 1.68 – 1.79 (2H, m), 1.82 – 1.94 (2H, m), 2.35 – 2.51 (2H, m), 2.60 (1H, dd, *J* = 7.4, 15.5 Hz), 2.76 (1H, dd, *J* = 5.8, 15.5 Hz), 3.38 (3H, s), 3.44 – 3.52 (2H, m), 4.03, 4.06 (each 1H, d, *J* = 11.5 Hz), 4.50 (2H, s), 4.56, 4.76 (each 1H, d, *J* = 6.8 Hz), 4.96 (1H, dd, *J* = 1.6, 10.2 Hz), 5.00 (1H, dd, *J* = 1.6, 17.5 Hz), 5.11, 5.27 (each 1H, brs), 5.67 (1H, dddd, *J* = 5.8, 7.4, 10.2, 17.5 Hz), 5.86 (1H, t, *J* = 7.3 Hz), 7.22 – 7.37 (5H, m); EI-MS m/z 418 (M^+), 377 (M^+–CH_2CH=CH_2), 357 (M^+–OCH_2OMe); High-Resolution EI-MS m/z 418.2275 (M^+, calcd for $C_{25}H_{35}ClO_3$ 418.2275). Anal. Calcd for $C_{25}H_{35}ClO_3$: C, 71.66; H, 8.42; Cl, 8.46. Found: C, 71.78; H, 8.33; Cl, 8.51.

(1*R*,3*R*,6*R*)-1-Allyl-3-[1-(chloromethyl)ethenyl]-2-[(*E*)-3-(4-methoxyphenylmethoxy)propylidene]-1-(methoxymethoxy)-6-methylcyclohexane 9b. According to the method previously described, **9b** was driven from **8b** in 93% yield as a colorless oil: $[\alpha]^{25}_D$ –219° (*c* 1.66, $CHCl_3$); IR (neat) 3075, 2935, 2860, 1640, 1610, 1585, 1515, 1465, 1445, 1360, 1300, 1250, 1215, 1175, 1145, 1095, 1035, 920, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.94 (3H, d, *J* = 6.6 Hz), 1.42 – 1.52 (1H, m), 1.68 – 1.79 (2H, m), 1.82 – 1.94 (2H, m), 2.35 – 2.51 (2H, m), 2.60 (1H, dd, *J* = 7.4, 15.5 Hz), 2.76 (1H, dd, *J* = 5.8, 15.5 Hz), 3.38 (3H, s), 3.44 – 3.52 (3H, m), 3.80 (3H, s), 4.03, 4.06 (each 1H, d, *J* = 11.5 Hz), 4.43 (2H, s), 4.56, 4.76 (each 1H, d, *J* = 6.8 Hz), 4.96 (1H, dd, *J* = 1.6, 10.2 Hz), 5.00 (1H, dd, *J* = 1.6, 17.5 Hz), 5.11, 5.27 (each 1H, brs), 5.67 (1H, dddd, *J* = 5.8, 7.4, 10.2, 17.5 Hz), 5.86 (1H, t, *J* = 7.3 Hz), 6.87, 7.25 (each 2H, d, *J* = 8.7 Hz); EI-MS m/z 448 (M^+), 407 (M^+–CH_2CH=CH_2), 387 (M^+–OCH_2OMe); High-Resolution EI-MS m/z 448.2375 (M^+, calcd for $C_{26}H_{37}ClO_4$ 448.2380). Anal. Calcd for $C_{26}H_{37}ClO_4$: C, 69.55; H, 8.31; Cl, 7.90. Found: C, 69.46; H, 8.20; Cl, 8.05.

(1*R*,3*R*,6*R*)-3-[1-(Chloromethyl)ethenyl]-2-[(*E*)-3-benzyloxypropylidene]-1-(methoxymethoxy)-6-methylcyclohexane Propanol 10a. To a solution of Me_2C=CMe_2 (80.0 μL, 0.674 mmol) in THF (1.0 mL) at –10 °C was added BH_3·SMe_2 (60.0 μL, 0.632 mmol). After stirring at –10 °C for 1 h, the resulting mixture was added to a solution of **9a** (100 mg, 0.239 mmol) in THF (4.0 mL) at –10 °C. The mixture was stirred at –10 °C for 1 h, treated with a 3 N aqueous solution of NaOH and a 35% aqueous solution of H_2O_2, and allowed to warm to room temperature. After stirring at room temperature for 5 h, the mixture was extracted with ether, and the combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated and silica gel column chromatography (AcOEt/hexane, 30:70) gave **10a** (93.9 mg, 90%) as a colorless oil: $[\alpha]^{25}_D$ –67.8° (*c* 1.050, $CHCl_3$); IR (neat) 3440, 3005, 2950, 2935, 2875, 1710, 1610, 1585, 1515, 1465, 1445, 1360, 1300, 1270, 1250, 1215, 1175, 1150, 1090, 1035, 920, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.90 (3H, d, *J* = 6.6 Hz), 1.18 – 1.30 (2H, m), 1.43 – 1.65 (2H, m), 1.72 – 1.95 (5H, m), 2.37 – 2.54 (2H, m), 3.39 (3H, s), 3.44 – 3.57 (5H, m), 4.07, 4.51 (each 2H, brs), 4.63, 4.69 (each 1H, d, *J* = 6.9 Hz), 5.15, 5.30 (each 1H, brs), 5.85 (1H, t, *J* = 7.3 Hz), 7.22 – 7.37 (5H, m); EI-MS m/z 436 (M^+), 375 (M^+–OCH_2OMe); High-Resolution EI-MS m/z 436.2401 (M^+, calcd for $C_{25}H_{37}ClO_4$ 436.2380). Anal. Calcd

for $C_{25}H_{37}ClO_4$: C, 68.71; H, 8.53; Cl, 8.11. Found: C, 68.66; H, 8.65; Cl, 7.98.

(1*R*,3*R*,6*R*)-3-[1-(Chloromethyl)etheny]-2-[(*E*)-3-(4-methoxyphenylmethoxy)propylidene]-1-(methoxymethoxy)-6-methylcyclohexane Propanol 10b. Hydroboration-oxidation of **9b** using the procedure previously described gave **10b** in 91% yield as a colorless oil: $[\alpha]^{25}_D$ −51.0° (*c* 0.590, $CHCl_3$); IR (neat) 3440, 3005, 2950, 2935, 2875, 1610, 1585, 1515, 1465, 1445, 1360, 1300, 1250, 1215, 1175, 1150, 1090, 1035, 920, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.90 (3H, d, *J* = 6.6 Hz), 1.18 – 1.30 (2H, m), 1.43 – 1.65 (2H, m), 1.72 – 1.95 (5H, m), 2.37 – 2.54 (2H, m), 3.39 (3H, s), 3.44 – 3.57 (5H, m), 3.80 (3H, s), 4.07, 4.44 (each 2H, brs), 4.63, 4.69 (each 1H, d, *J* = 6.9 Hz), 5.15, 5.30 (each 1H, brs), 5.84 (1H, t, *J* = 7.3 Hz), 6.87, 7.26 (each 2H, d, *J* = 8.6 Hz); EI-MS m/z 466 (M^+), 405 (M^+–OCH_2OMe); High-Resolution EI-MS m/z 466.2491 (M^+, calcd for $C_{26}H_{39}ClO_5$ 466.2486). Anal. Calcd for $C_{26}H_{39}ClO_5$: C, 66.86; H, 8.42; Cl, 7.59. Found: C, 67.01; H, 8.31; Cl, 7.66.

(1*R*,3*R*,6*R*)-3-[1-(Chloromethyl)etheny]-2-[(*E*)-3-benzyloxypropylidene]-1-(methoxymethoxy)-6-methylcyclohexane Propanal 2a. To a solution of **10a** (34.3 mg, 78.4 μmol) and pyridine (0.100 mL, 1.24 mmol) in CH_2Cl_2 (2.0 mL) was added Dess-Martin periodinane (82.9 mg, 0.196 mmol) at room temperature. After stirring at room temperature for 1 h, saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ were added, and the resulting mixture was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane, 15:85) to afford **2a** (30.8 mg, 90%) as a colorless oil: $[\alpha]^{25}_D$ −87.5° (*c* 0.535, $CHCl_3$); IR (neat) 3005, 2935, 2880, 2720, 1720, 1610, 1585, 1515, 1465, 1445, 1410, 1390, 1360, 1300, 1275, 1250, 1215, 1175, 1145, 1095, 1035, 920, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, d, *J* = 6.6 Hz), 1.40 – 1.51 (1H, m), 1.77 – 2.01 (3H, m), 2.04 – 2.20 (2H, m), 2.37 – 2.59 (3H, m), 3.37 (3H, s), 3.48 – 3.56 (2H, m), 3.59 (1H, brs), 4.01 (2H, brs), 4.51, 4.64 (each 2H, s), 5.16, 5.30 (each 1H, brs), 5.87 (1H, t, *J* = 7.3 Hz), 7.22 – 7.37 (5H, m), 9.63 (1H, brs); EI-MS m/z 436 (M^+), 398 (M^+–HCl), 389 (M^+–CH_2OMe), 373 (M^+–OCH_2OMe); High-Resolution EI-MS m/z 434.2201 (M^+, calcd for $C_{25}H_{35}ClO_4$ 434.2224). Anal. Calcd for $C_{25}H_{35}ClO_4$: C, 69.03; H, 8.11; Cl, 8.15. Found: C, 68.91; H, 8.21; Cl, 8.02.

(1*R*,3*R*,6*R*)-3-[1-(Chloromethyl)ethenyl]-2-[(*E*)-3-(4-methoxyphenylmethoxy)propylidene]-1-(methoxymethoxy)-6-methylcyclohexane Propanal 2b. Following the procedure previously described, Dess-Martin oxidation of **10b** afforded **2b** in 93% yield as a colorless oil: $[\alpha]^{25}_D$ −77.3° (*c* 0.535, $CHCl_3$); IR (neat) 3005, 2935, 2880, 2720, 1720, 1610, 1585, 1515, 1465, 1445, 1410, 1390, 1360, 1300, 1250, 1215, 1175, 1145, 1095, 1035, 920, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, d, *J* = 6.6 Hz), 1.40 – 1.51 (1H, m), 1.77 – 2.01 (3H, m), 2.04 – 2.20 (2H, m), 2.37 – 2.59 (3H, m), 3.37 (3H, s), 3.48 – 3.56 (2H, m), 3.59 (1H, brs), 3.80 (3H, s), 4.01 (2H, brs), 4.44, 4.64 (each 2H, s), 5.16, 5.30 (each 1H, brs), 5.87 (1H, t, *J* = 7.3 Hz), 6.86, 7.25 (each 2H, d, *J* = 7.4 Hz), 9.63 (1H, brs); EI-MS m/z 466 (M^+), 428 (M^+–HCl), 419 (M^+–CH_2OMe), 403 (M^+–OCH_2OMe); High-Resolution EI-MS m/z 464.2301 (M^+, calcd for $C_{26}H_{37}ClO_5$ 464.2329). Anal. Calcd for $C_{26}H_{37}ClO_5$: C, 67.15; H, 8.02; Cl, 7.62. Found: C, 67.27; H, 7.88; Cl, 7.73.

Preparation of THF solution of SmI_2-HMPA. To a slurry of Sm metal powder (2.00 g, 13.3 mmol) in THF (100 mL) at room temperature was added CH_2I_2 (0.900 mL, 11.2 mmol). The mixture was stirred at ambient temperature for 3 h. At this time, HMPA (15.5 mL, 89.7 mmol) was added, and the initially blue solution turned deep purple. The resulting solution was used directly to effect the following reductive coupling cyclizations.

(1*S*,4*R*,7*R*,8*R*)-11-[(*E*)-3-Benzyloxypropylidene]-7-(methoxymethoxy)-8-methyl-2-methylenebicyclo-[5.3.1]undecan-4-ol 3a. To a solution of **2a** (30.8 mg, 70.7 μmol) in THF (1.0 mL) at room temperature was added 0.10 M THF solution of SmI_2-HMPA (1.61 mL, 0.177 mmol). Soon after adding SmI_2, TLC analysis of the reaction mixture showed completed consumption of the starting ketone. The reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$, and the resulting mixture was extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane, 30:70) to give **3a** (28.0 mg, 99%) as a colorless oil: $[\alpha]^{25}_D$ –68.4° (*c* 0.370, $CHCl_3$); IR (neat) 3420, 3080, 2935, 2875, 1715, 1630, 1610, 1585, 1515, 1465, 1440, 1360, 1300, 1270, 1215, 1175, 1150, 1090, 1040, 920, 885, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.81 (3H, d, *J* = 6.8 Hz), 1.31 (1H, brd, *J* = 12.5 Hz), 1.45 (1H, brdq, *J* = 6.5, 11.1 Hz), 1.58 – 1.70 (4H, m), 1.73 (1H, brd, *J* = 14.3 Hz), 1.84 – 1.92 (2H, m), 1.95 – 2.04 (2H, m), 2.44 (1H, dq, *J* = 14.6, 7.3 Hz), 2.47 (1H, dd, *J* = 4.0, 11.1 Hz), 2.49 (1H, dq, *J* = 14.6, 7.3 Hz), 3.28 (3H, s), 3.41 (1H, brs), 3.50 – 3.65 (3H, m), 4.54 (2H, s), 4.49, 4.78 (each 1H, d, *J* = 7.3 Hz), 5.00 (2H, brs), 5.92 (1H, t, *J* = 7.3 Hz), 7.22 – 7.37 (5H, m); ^{13}C-NMR ($CDCl_3$) δ 14.5, 21.5, 25.5, 28.5, 28.8, 31.6, 36.8, 40.8, 43.2, 55.8, 70.0, 72.6, 72.8, 82.5, 89.2, 109.4, 123.8, 127.5, 127.6, 137.4, 138.5, 146.1; EI-MS m/z 400 (M^+), 382 (M^+–H_2O), 355 (M^+–CH_2OMe), 338 (M^+–$MeOCH_2OH$); High-Resolution EI-MS m/z 400.2608 (M^+, calcd for $C_{25}H_{36}O_4$ 400.2613). Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.08; H, 9.01.

(1*S*,4*R*,7*R*,8*R*)-11-[(*E*)-3-(4-Methoxyphenylmethoxy)propylidene]-7-(methoxymethoxy)-8-methyl-2-methylenebicyclo[5.3.1]undecan-4-ol 3b. In accord with the protocol previously discussed, **2b** was cyclized to produce **3b** in 98% yield as a colorless oil: $[\alpha]^{25}_D$ –88.6° (*c* 0.370, $CHCl_3$); IR (neat) 3420, 3080, 2935, 2875, 1630, 1610, 1585, 1515, 1465, 1440, 1360, 1300, 1215, 1175, 1150, 1090, 1040, 920, 885, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.81 (3H, d, *J* = 6.8 Hz), 1.31 (1H, brd, *J* = 12.5 Hz), 1.45 (1H, brdq, *J* = 6.5, 11.1 Hz), 1.58 – 1.70 (4H, m), 1.73 (1H, brd, *J* = 14.3 Hz), 1.84 – 1.92 (2H, m), 1.95 – 2.04 (2H, m), 2.44 (1H, dq, *J* = 14.6, 7.3 Hz), 2.47 (1H, dd, *J* = 4.0, 11.1 Hz), 2.49 (1H, dq, *J* = 14.6, 7.3 Hz), 3.28 (3H, s), 3.41 (1H, brs), 3.50 – 3.65 (3H, m), 3.80 (3H, s), 4.47 (2H, s), 4.49, 4.78 (each 1H, d, *J* = 7.3 Hz), 5.00 (2H, brs), 5.92 (1H, t, *J* = 7.3 Hz), 6.87, 7.28 (each, 2H, d, *J* = 8.7 Hz); ^{13}C-NMR ($CDCl_3$) δ 14.5, 21.5, 25.5, 28.5, 28.8, 31.6, 36.8, 40.8, 43.2, 55.3, 55.8, 70.0, 72.6, 72.8, 82.5, 89.2, 109.4, 113.7, 123.8, 129.2, 130.5, 137.4, 146.1, 159.0; EI-MS m/z 430 (M^+), 412 (M^+–H_2O), 385 (M^+–CH_2OMe), 368 (M^+–$MeOCH_2OH$); High-Resolution EI-MS m/z 430.2703 (M^+, calcd for $C_{26}H_{38}O_5$ 430.2719). Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.53; H, 8.89. Found: C, 72.41; H, 9.06.

(1*S*,4*R*,7*R*,8*R*)-11-[(*E*)-3-Benzyloxypropylidene]-7-(methoxymethoxy)-8-methyl-2-methylenebicyclo-[5.3.1]undecan-4-yl Acetate 11a. To a solution of **3a** (10.0 mg, 22.2 μmol) in pyridine (1.0 mL) was added Ac_2O (0.100 mL, 0.106 mmol) at room temperature. The mixture was stirred at room temperature for 24 h, poured into a mixture of ice and saturated aqueous $NaHCO_3$, and extracted with ether. The combined extracts were washed with saturated aqueous $CuSO_4$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (AcOEt/hexane, 10:90) gave **11a** (10.4 mg, 95%) as a colorless oil: $[\alpha]^{25}_D$ –57.6° (*c* 0.375, $CHCl_3$); IR ($CHCl_3$) 3015, 2935, 2875, 1730, 1635, 1610, 1515, 1465, 1440, 1380, 1365, 1300, 1275, 1250, 1215, 1175, 1150, 1090, 1035, 970, 920, 895, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.81 (3H, d, *J* = 6.8 Hz), 1.32 (1H, brd, *J* = 12.6 Hz), 1.54 (1H, brdq, *J* = 6.5, 11.0 Hz), 1.55 – 1.71 (3H, m), 1.78 (1H, brdd, *J* = 11.0, 15.2 Hz), 1.91 (1H, brdd, *J* = 6.5, 15.2 Hz), 1.96 (1H, t, *J* = 11.0 Hz), 2.00 (3H, s), 2.02 (1H, m), 2.44 (1H, dq, *J* = 14.6, 7.3 Hz), 2.47 (1H, dd, *J* = 4.4, 11.0 Hz), 2.51 (1H, dq, *J* = 14.6,

7.3 Hz), 3.37 (3H, s), 3.42 (1H, brs), 3.50 – 3.62 (2H, m), 4.54 (2H, s), 4.48 (1H, d, J = 7.3 Hz), 4.71 (1H, tt, J = 4.4, 11.0 Hz), 4.76 (1H, d, J = 7.3 Hz), 5.05, 5.10 (each 1H, brs), 5.94 (1H, t, J =7.3 Hz), 7.22 – 7.37 (5H, m); ^{13}C-NMR ($CDCl_3$) δ 14.4, 21.4, 21.6, 25.5, 27.7, 28.5, 28.9, 36.7, 39.1, 40.7, 55.8, 69.9, 72.6, 77.9, 82.4, 89.2, 110.5, 123.9, 127.5, 127.6, 137.4, 138.6, 145.4, 170.2; EI-MS m/z 442 (M^+), 410 (M^+–MeOH), 381 (M^+–OCH_2OMe); High-Resolution EI-MS m/z 442.2722 (M^+, calcd for $C_{27}H_{38}O_5$ 442.2719). Anal. Calcd for $C_{27}H_{38}O_5$: C, 73.27; H, 8.65. Found: C, 73.15; H, 8.76.

(1*S*,4*R*,7*R*,8*R*)-11-[(*E*)-3-(4-Methoxyphenylmethoxy)propylidene]-7-(methoxymethoxy)-8-methyl-2-methylenebicyclo[5.3.1]undecan-4-yl Acetate 11b. Acetylation of **3b** according to the procedure previously described gave **11b** in 97% yield as a colorless oil: $[\alpha]^{25}_D$ –66.4° (c 0.375, $CHCl_3$); IR ($CHCl_3$) 3015, 2935, 2875, 1730, 1635, 1610, 1515, 1465, 1440, 1380, 1365, 1300, 1250, 1215, 1175, 1150, 1090, 1035, 970, 920, 895, 820, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.81 (3H, d, J = 6.8 Hz), 1.32 (1H, brd, J = 12.6 Hz), 1.54 (1H, brdq, J = 6.5, 11.0 Hz), 1.55 – 1.71 (3H, m), 1.78 (1H, brdd, J = 11.0, 15.2 Hz), 1.91 (1H, brdd, J = 6.5, 15.2 Hz), 1.96 (1H, t, J = 11.0 Hz), 2.00 (3H, s), 2.02 (1H, m), 2.44 (1H, dq, J = 14.6, 7.3 Hz), 2.47 (1H, dd, J = 4.4, 11.0 Hz), 2.51 (1H, dq, J = 14.6, 7.3 Hz), 3.37 (3H, s), 3.42 (1H, brs), 3.50 – 3.62 (2H, m), 3.80 (3H, s), 4.47 (2H, s), 4.48 (1H, d, J = 7.3 Hz), 4.71 (1H, tt, J = 4.4, 11.0 Hz), 4.76 (1H, d, J = 7.3 Hz), 5.05, 5.10 (each 1H, brs), 5.94 (1H, t, J =7.3 Hz), 6.84, 7.28 (each, 2H, d, J = 8.8 Hz); ^{13}C-NMR ($CDCl_3$) δ 14.4, 21.4, 21.6, 25.5, 27.7, 28.5, 28.9, 36.7, 39.1, 40.7, 55.3, 55.8, 69.9, 72.6, 77.9, 82.4, 89.2, 110.5, 113.7, 123.9, 129.1, 130.6, 137.4, 145.4, 159.0, 170.2; EI-MS m/z 472 (M^+), 440 (M^+–MeOH), 411 (M^+–OCH_2OMe); High-Resolution EI-MS m/z 472.2830 (M^+, calcd for $C_{28}H_{40}O_6$ 472.2825). Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 70.98; H, 8.71.

Acknowledgment. The present work was supported by a Grant-in-Aid for Scientific Research on Priority Areas No. 8245203 from The Ministry of Education, Science, Sports and Culture of the Japanese Government. The authors are greatly indebted to Professor Dennis P. Curran (University of Pittsburgh) for helpful discussions.

References and Notes

(1) (a) Uchida, I.; Ando, T.; Fukami, N.; Yoshida, K.; Hashimoto, M.; Toda, T.; Koda, S.; Morimoto, Y. *J. Org. Chem.* **1987**, *52*, 5292. (b) Ando, T.; Tsurumi, Y.; Ohata, N.; Uchida, I.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 25. (c) Ando, T.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 31.

(2) Norris, D. B.; Depledge, P.; Jackson, A. P. PCT Int. Appl. WO 9107,953; *Chem. Abstr.* **1991**, *115*, 64776h.

(3) (a) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y. *J. Org. Chem.* **1993**, *58*, 2349. (b) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y.; Prangé, T. *J. Chem. Res. (S)* **1996**, 32. (c) Devaux, J.-F.; Hanna, I.; Lallemand, J.-Y. *J. Org. Chem.* **1997**, *62*, 5062. (d) Mehta, G.; Reddy, K. S. *Synlett* **1996**, 625.

(4) During the last decade, samarium(II) iodide (SmI_2) has become an exceedingly useful reagent for promoting reductive coupling reactions. For reviews, see: (a) Kagan, H. B. *New J. Chem.* **1990**, *14*, 453. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Molander, G. A.; Harris, R. H. *Chem. Rev.* **1996**, *96*, 307.

(5) The SmI_2-promoted Reformatsky reactions, ketyl-olefin reductive couplings, and pinacol couplings have been adapted to permit construction of medium ring molecules. See: (a) Tabuchi, T.; Kawamura, K.;

Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889. (b) Inanaga, J.; Yokoyama, Y.; Handa, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 6371. (c) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132. (d) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186. (e) Shiina, I.; Uoto, K.; Mori, N.; Kosugi, T.; Mukaiyama, T. *Chem. Lett.* **1995**, 181. (f) Swindell, C. S.; Fan, W. *Tetrahedron Lett.* **1996**, *37*, 2321.

(6) Recently, we described the new types of highly stereoselective reductive couplings mediated by SmI_2. See: (a) Kan, T.; Matsuda, F.; Yanagiya, M.; Shirahama, H. *Synlett* **1991**, 391. (b) Kito, M.; Sakai, T.; Yamada, K.; Matsuda, F.; Shirahama, H. *Synlett* **1993**, 158. (c) Kan, T.; Nara, S.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5111. (d) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532. (e) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900. (f) Kawatsura, M.; Hosaka, K.; Matsuda, F.; Shirahama, H. *Synlett* **1995**, 729. (g) Matsuda, F. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 987. (h) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373. (i) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 1057. (j) Kawatsura, M.; Kishi, E.; Kito, M.; Sakai, T.; Shirahama, H.; Matsuda, F. *Synlett* **1997**, 479.

(7) In this laboratory, the *cis*-decalin ring skeleton of vinigrol (**1**) was prepared with complete stereocontrol using the SmI_2-promoted ketyl-olefin coupling. See: Ref. 6i.

(8) For a preliminary account of part of this work, see: Kito, M.; Sakai, T.; Miyashita, M.; Shirahama, H.; Matsuda, F. *Synlett* **1997**, 219.

(9) Hegde, S. G.; Bechwith, D.; Doti, R.; Wolinsky, J. *J. Org. Chem.* **1985**, *50*, 894.

(10) Martinelli, M. J. *J. Org. Chem.* **1990**, *55*, 5065.

(11) Many SmI_2-induced reactions benefit from the presence of HMPA. See: (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763. (b) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485. (c) Otsubo, K.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1487. (d) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4437.

(12) The model acetate **11c** was subjected to a Monte Carlo conformational search procedure in MacroModel (Version 6.0) equipped with the MM2 force field. The calculations found the 5 conformers within 3 kcal/mol of the ground state. The structures of the bicyclo[1.3.5]undecane ring systems of the higher energy 4 conformers are closely related to that of the bicyclic ring system of the lowest energy conformer **11c-A**. Furthermore, the same MM2 calculations performed on the model alcohol **3c** (Figure 1) indicated that there are 2 conformers within 3 kcal/mol of the global minimum. The conformational features of the 2 conformers are the same as those of the 5 conformers of **11c**. We are grateful to Dr. Kazuhiko Nakatani (Kyoto University) for his help in performing the MM2 calculations.

(13) For a review of the 1,3-allylic strain ($A^{1,3}$ strain), see: Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(14) Furthermore, in each case of ^{1}H-NMR spectra of the synthetic intermediates **7** and **8** (R=Bn or MPM) bearing a similar methylenecyclohexane ring system to that of **2** (R=Bn or MPM), the peak due to the C_1 methine proton is always detected as a broad singlet.

(15) We have recently found that the introduction of a much smaller conformational constraint sufficiently enhances the ability of acyclic precursors to undergo such a type of SmI_2-promoted cyclization of medium rings (8- and 9-membered carbocycles) in general. See: Matsuda, F.; Sakai, T.; Okada, N.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 863.