Synthetic Studies of Azadirachtin. Synthesis of the Cyclic Acetal Intermediate in the Naturally Occurring Form

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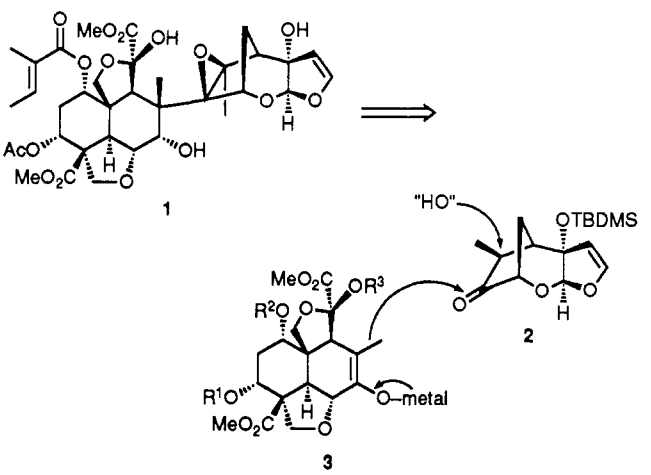
A stereoselective synthesis of the novel acetal unit **2**, a potential intermediate for the total synthesis of (−)-azadirachtin (**1**), has been achieved for the first time. The synthesis consists of three principal parts. First, a synthetic route capable of providing the optically active cyclopentanone derivative **7** in large quantities was developed, starting with (−)-ethyl lactate. Second, **11**, having a quaternary carbon atom, was synthesized in a highly stereoselective manner by a novel use of Sharpless asymmetric epoxidation. Third, after appropriate manipulation of the several functional groups, the novel acetal unit **2** was successfully constructed in the naturally occurring form.

Azadirachtin (**1**)[2] is a highly oxygenated terpenoid isolated from the neem tree *Azadirachta indica*, possessing strong insect antifeedant and ecdysis inhibitory activity. A few years ago we started synthetic studies on **1** in order to understand the structure–activity relationship and hopefully to find a simpler analogue with comparable biological activity. The recent paper[3] by Ley and coworkers describing a synthesis of the simple skeleton related to the azadirachtin acetal unit in racemic form prompted us to report our results. We describe here the first synthesis of the novel acetal unit **2**, a potential intermediate for the total synthesis of (−)-azadirachtin (**1**), starting with (−)-ethyl lactate. The synthesis would serve to confirm the absolute configuration of (−)-**1**, whose direct evidence has never been mentioned.[2] In considering the steric environment, **2** is expected to be transformed into **1** by a route utilizing hydroxylation followed by condensation with **3** as key steps[4] (Scheme I).

Scheme I



Results and Discussion

The synthesis of **2** started with the optically active aldehyde **4**, which is readily available from (−)-ethyl lactate.[5] Previously we had found that treatment of aldehydes with the ylide derived from (3-(ethoxycarbonyl)propyl)triphenylphosphonium bromide and potassium *tert*-butoxide in THF provides cis olefins in a highly selective manner.[6] By the use of this Wittig reagent the requisite cis olefin for the Claisen rearrangement was obtained stereospecifically (>98%) without any racemization and was converted to the cis allylic alcohol **5** by treatment with aqueous acetic acid. The optical purity was determined by the MTPA method at this stage. Claisen rearrangement of **5** provided diester **6** in a highly stereoselective manner (>98%) concerning the allylic asymmetric carbon. The optical purity was again determined by the MTPA method at the stage of **9**, and the absolute configuration was confirmed by conversion to the known compound **13**.[7] Diester **6** was then transformed into the cyclopentanone derivative **7** by Dieckmann consensation followed by the decarboethoxylation. Under the Dieckmann conditions, as expected, epimerization of the methyl group occurred, leading to the thermodynamically more stable **7** as the major product (trans:cis = 7:1). The stereochemistry of the trans isomer was unequivocally determined by ^{1}H NMR spectroscopy at the stage of **8**. Existence of the β-methyl group is essential for the later stereoselective hydroxylation (**12** → **15**).

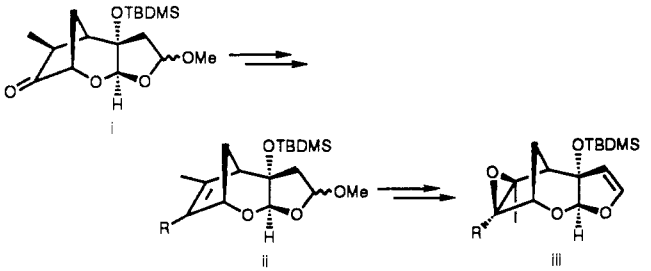
It was found that stereoselective synthesis of the quarternary carbon atom in **12** by simple alkylation of the corresponding ketones such as **8** and **14** was extremely difficult. For example, vinylation of **8** and/or benzyloxymethylation of **14** did not provide the desired product selectively. A solution to this problem was realized as follows. Sharpless asymmetric epoxidation[8] of the allylic

(1) Present address: Columbia University.

(2) (a) Kraus, W.; Bokel, M.; Klenk, A.; Pöhnl, H. *Tetrahedron Lett.* **1985**, *26*, 6435. (b) Broughton, H. B.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J.; Morgan, E. D. *J. Chem. Soc., Chem. Commun.* **1986**, 46.

(3) (a) Ley, S. V.; Santafianos, D.; Blaney, W. M.; Simmonds, M. S. *Tetrahedron Lett.* **1987**, *28*, 221. (b) Bilton, J. N.; Jones, P. S.; Ley, S. V.; Robinson, N. G.; Sheppard, R. N. *Tetrahedron Lett.* **1988**, *29*, 1849.

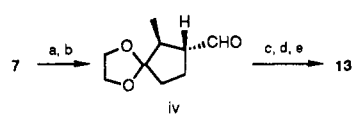
(4) Alternatively the present approach would allow for protection of the enol ether as an acetal as shown below.



(5) Hiyama, T.; Nishide, K.; Kobayashi, K. *Tetrahedron Lett.* **1984**, *25*, 569.

(6) Iseki, K.; Shinoda, M.; Ishiyama, C.; Hayashi, Y.; Yamada, S.; Shibasaki, M. *Chem. Lett.* **1986**, 559.

(7) Suzuki, T.; Sato, E.; Unno, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1988**, 724. Compound **13** was synthesized as follows.



[a] (a) $HOCH_2CH_2OH$, TsOH, benzene reflux, 82%; (b) OsO_4, NMO then $NaIO_4$, 98%; (c) $Ph_3P{=}CHCOOEt$, benzene reflux, 87%; (d) DIBAH; (e) $FeCl_3$–SiO_2, 58% (two steps).

(8) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

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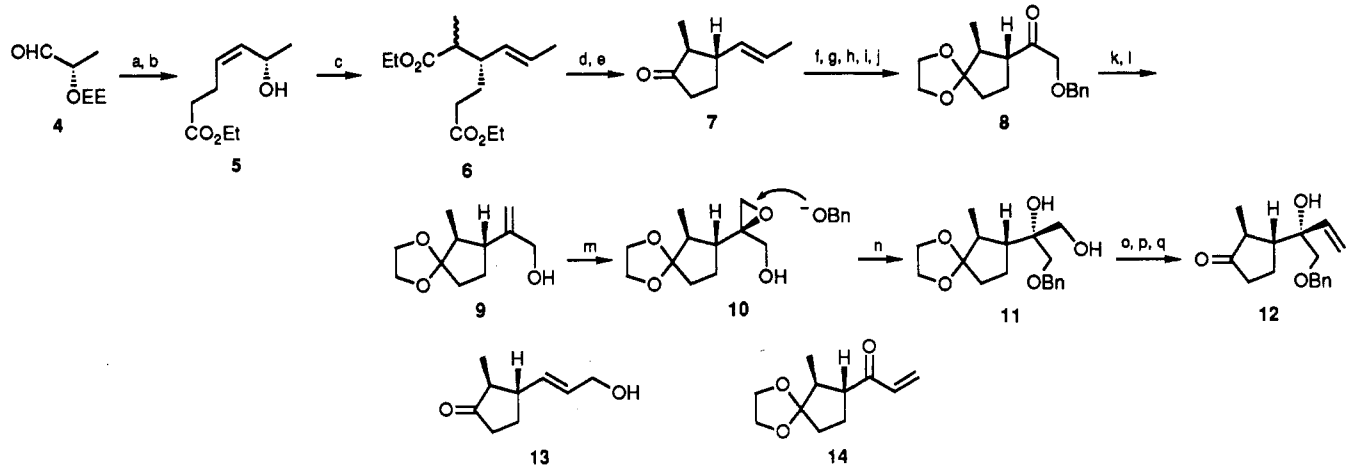
Scheme II[a]



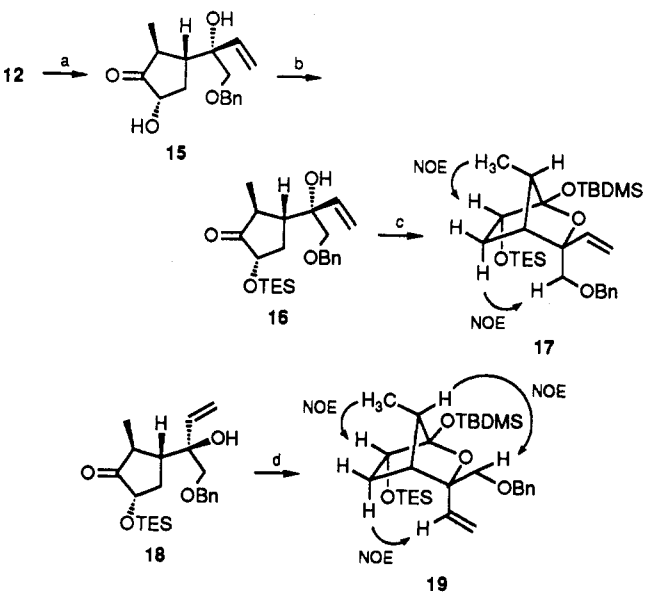
[a] (a) $Br^-Ph_3P^+(CH_2)_3CO_2Et$, ^tBuOK, THF, −78 °C to room temperature, 94%; (b) AcOH–H_2O–THF (3:1:1), 100%; (c) $EtC(OEt)_3$, $EtCO_2H$, xylene, 140 °C, 91%; (d) KH, THF, 89%; (e) NaCl, H_2O, DMSO, 130 °C, 100%; (f) $HOCH_2CH_2OH$, TsOH, benzene, reflux, 84%; (g) OsO_4–NMO, 99%; (h) $NaIO_4$, 95%; (i) $BnOCH_2SnBu_3$, BuLi, −78 °C, 83%; (j) CrO_3·2Py, MS4A, 94%; (k) H_2, Pd/C; (l) $Br^-Ph_3P^+Me$, ^tBuOK, 78% in two steps; (m) TBHP, (−)-DET, $Ti(^iPrO)_4$, MS4A, CH_2Cl_2, −20 °C, 96%; (n) BnOH, KH, THF, 91%; (o) SO_3·Py, DMSO, Et_3N, 93%; (p) $Br^-Ph_3P^+Me$, ^tBuOK, 50 °C, 89%; (q) $FeCl_3$·SiO_2, acetone, 100%.

alcohol **9**, derived from **7** via a seven-step sequence of reactions, afforded the β-epoxide **10** in a highly stereoselective manner (α:β = 1:14) (Scheme II). Subsequent oxirane ring opening by potassium benzyloxide proceeded regiospecifically to provide the diol **11** as a sole product in 91% yield. Under the oxirane opening conditions, of course, we had to consider the Payne rearrangement.[9] However, the epoxide derived via the Payne rearrangement was identical with **10**, thereby leading to **11**.

Hydroxylation of **12**, derived from **11** via a three-step sequence of reactions, with Vedejs' reagent MoOPh,[10] provided the α-alcohol **15** preferentially (α:β = 2.6:1)[11] (Scheme III). The stereochemistry of **15** was unequivocally determined from the ^1H NMR spectra (COSY and NOE) of **17** and **19**, which were obtained as follows. α-Alcohols **15** was protected as a triethylsilyl ether and was then treated with TBDMSOTf and 2,6-lutidine in CH_2Cl_2, giving **17** in 75% yield. Likewise, **18** was converted to **19** in 78% yield.

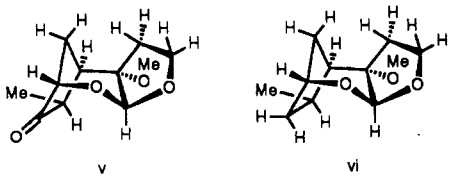
At this stage, on the basis of the molecular model studies as well as MM2 calculations,[12] we thought that conversion of the carbonyl group to other functionalities such as ketal, cyanohydrin derivative, and alcohol (sp^2 carbon → sp^3 carbon) would make formation of the fused ring cyclic acetal much easier. Toward this end, protection of **16** as a ketal was first attempted under several reaction conditions, giving none of the desired product. On the other hand, **16** was easily converted to **20** (Scheme IV). However, after appropriate manipulation of the several functional groups, treatment of the aldehyde **21** with CF_3CO-OH in toluene at 23 °C afforded **22** as a major product. This result clearly indicated that conversion of the carbonyl group to the β-alcohol would set the stage for cyclization. Treatment of **15** with Evans' reducing agent $Me_4NBH(OAc)_3$[13] afforded the β-alcohol **23** is a highly selective manner (β:α > 99:1). The stereochemistry of **23** was unequivocally determined by comparison of its ^1H NMR spectra (COSY and NOE) with those of the α-isomer obtainable by $NaBH_4$ reduction. Then the dialdehyde **24** was obtained via a four-step sequence of reactions. Selective desilylation under the acidic conditions (AcOH–H_2O–THF, 3:1:1, 60 °C) provided the desired acetal **25** (3:1 diastereomeric mixture at the hemiacetal carbon), which was transformed into the enol-ether **26** by Ley's procedure.[3] NOE was observed between the acetal proton and the methyl proton connected with silicon in **26**, indicating that the stereochemistry of the newly formed asymmetric carbon has the desired *S* configuration. Finally, PDC oxidation of **26** provided the potential intermediate **2**.

Scheme III[a]



[a] (a) LDA, THF, −78 °C then MoOPH, −30 °C, 40%; (b) TESCl, Et_3N, CH_2Cl_2, 0 °C, 99%; (c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 75%; (d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 78%.

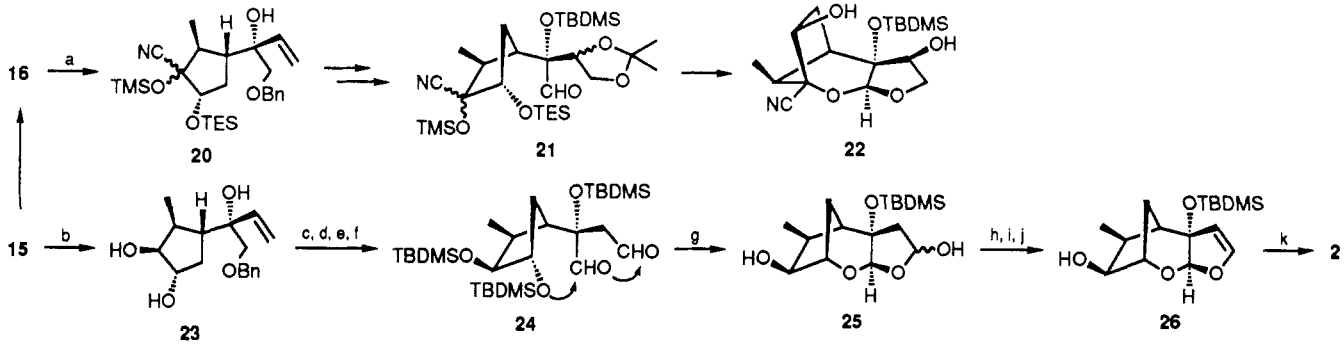
(9) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.
(10) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944.
(11) Hydroxylation of **7** did not give satisfactory results.
(12) Allinger's MM2(85) calculations of the steric energy were carried out, showing v (47.5 kcal) and vi (46.5 kcal).



v vi

(13) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939.

Scheme IV[a]



[a] (a) TMSCN, KCN·18-crown-6, CH_2Cl_2, 0 °C, 91%; (b) $Me_4NBH(OAc)_3$, AcOH, MeCN, room temperature, 83%; (c) TBDMSOTf, 2,6-lutidine, 50 °C, 91%; (d) BH_3·THF then Me_3NO, diglyme, 61%; (e) H_2, Pd/C, 90%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to room temperature; (g) AcOH–H_2O–THF (3:3:1), 60 °C, 60% in two steps; (h) PhSH, BF_3·Et_2O, 83%; (i) mCPBA, $NaHCO_3$; (j) toluene, reflux, 38% in two steps; (k) PDC, DMF, 40 °C, 98%.

In conclusion, the novel acetal unit **2** has been synthesized stereoselectively by a route utilizing **5** → **6**, **9** → **10** → **11**, and **24** → **25** as key steps. Although the synthesis of **2** is rather lengthy, it will pave the way for further progress. Biological evaluation of **2** and related compounds and the total synthesis of azadirachtin (**1**) are currently in progress.

Experimental Section

^1H NMR spectra were recorded at 100 or 270 MHz.

In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned. Solvents were distilled before use as follows: tetrahydrofuran (THF) from sodium benzophenone ketyl; dichloromethane (CH_2Cl_2), benzene, toluene, xylene, hexane, dimethyl sulfoxide (DMSO), and *N,N*-dimethylformamide (DMF) from calcium hydride; acetonitrile from phosphorus pentoxide. Flash chromatography was performed by use of silica gel (Merck Kieselgel 60, 230–400 mesh).

Satisfactory IR, ^1H NMR, and MS data were obtained on all intermediates described herein using chromatographically homogeneous samples.

Ethyl (6*S*)-6-Hydroxy-4(*Z*)-heptenoate (5). To a stirred suspension of (3-(ethoxycarbonyl)propyl)triphenylphosphonium bromide (5.30 g, 11.6 mmol) in THF (45 mL) was added potassium *tert*-butoxide (1.30 g, 11.6 mmol) at −78 °C, and the whole reaction mixture was stirred for 1 h. A solution of **4** (1.13 g, 7.7 mmol) in THF (7.7 mL) was then added dropwise to the ylide solution. After being stirred at −78 °C for 1 h, the reaction mixture was allowed to warm to 23 °C for 1 day. The reaction was quenched with saturated aqueous NH_4Cl, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane–ether, 5:1) to give the olefin (1.78 g, 94%) as a colorless oil. To a stirred solution of the olefin (1.78 g, 7.3 mmol) in THF (2 mL) and water (2 mL) was added acetic acid (6 mL) at 0 °C. After being stirred at 23 °C for 1 h, the reaction mixture was concentrated in vacuo to give **5** (1.30 g, 100%) as a colorless oil. An analytically pure sample was obtained by distillation (bp 95–97 °C/0.1 mmHg): ^1H NMR ($CDCl_3$) δ 5.49 (ddt, J = 11.0, 8.4, 1.1 Hz, 1 H), 5.37m (dddd, J = 11.0, 8.4, 5.9, 0.7 Hz, 1 H), 4.63 (ddq, J = 8.4, 0.7, 6.2 Hz, 1 H), 4.13 (q, J = 7.2 Hz, 2 H), 2.10–2.70 (m, 5 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.24 (d, J = 6.2 Hz, 3 H); IR (neat) 3450, 1740, 1660 cm^{-1}; MS m/z 154 ($M^+ - H_2O$), 126, 81, 43 (base peak); HR-MS ($M^+ - H_2O$) calcd for $C_9H_{16}O_3$ 154.0994, found 154.0984; $[\alpha]^{20}_D$ −7.7° (*c* 1.09, $CHCl_3$).

Diethyl (2*RS*,3*S*)-2-Methyl-3-[1(*E*)-propenyl]hexanedioate (6). To a stirred solution of **5** (1.04 g, 6.0 mmol) in xylene (24 mL) was added triethyl orthopropionate (3.6 mL, 17.9 mmol) and propionic acid (0.025 mL, 0.3 mmol) at 23 °C. After being stirred at 140 °C for 3 h, the reaction mixture was concentrated in vacuo. The crude product was purified by flash chromatography (hexane–ethyl acetate, 6:1) to give **6** (1.41 g, 91%) as a diastereomeric mixture: ^1H NMR ($CDCl_3$) δ 4.90–5.70 (m, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 4.08 (q, J = 7.2 Hz, 2 H), 1.60–1.70 (m, 3 H), 1.00–1.30 (m, 9 H); IR (neat) 1740 cm^{-1}; MS m/z 256 (M^+), 211 ($M^+ - OC_2H_5$), 182, 155, 136, 109, 95, 85 (base peak), 67. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.38; H, 9.42.

(2*S*,3*S*)-2-Methyl-3-[1(*E*)-propenyl]cyclopentanone (7). Potassium hydride (12.20 g, 35% wt dispersion in mineral oil, 107 mmol) was washed with hexane and suspended in THF (130 mL). To this suspension was added **6** (9.14 g, 35.7 mmol) in THF (180 mL) at 0 °C. After being warmed to 23 °C over 30 min, the reaction was quenched with acetic acid (20 mL) and water (60 mL) at 0 °C, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (hexane–ether, 3:1) to give the corresponding β-keto ester (6.69 g, 89%) as a colorless oil. To a stirred solution of the β-keto ester (6.58 g, 31.3 mmol) in DMSO (32 mL) and water (1.7 mL) was added sodium chloride (2.02 g, 34.5 mmol). The reaction mixture was degassed by three freeze–pump–thaw cycles and then stirred at 130 °C for 3 h. After being cooled, the reaction mixture was diluted with ether, washed with water and brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (ether) to give **7** (4.34 g, 100%) as a colorless oil. An analytically pure sample was obtained by distillation (bp 76–77 °C/10 mmHg): ^1H NMR ($CDCl_3$) δ 5.20–5.70 (m, 2 H), 1.70 (d, J = 5.1 Hz, 3 H), 1.04 (d, J = 6.8 Hz, 3 H); IR (neat) 1750 cm^{-1}; MS m/z 138 (M^+), 123, 109, 95, 81, 67 (base peak), 55; HR-MS (M^+) calcd for $C_9H_{14}O$ 138.1044, found 138.1031; $[\alpha]^{20}_D$ +109.2° (*c* 0.82, $CHCl_3$).

(2*S*,3*S*)-2-Methyl-3-[1(*E*)-propenyl]cyclopentanone Ethylene Acetal. To a stirred solution of **7** (4.34 g, 31.4 mmol) in benzene (30 mL) and ethylene glycol (5.3 mL, 95 mmol) was added *p*-toluenesulfonic acid monohydrate (19 mg, 0.1 mmol) at 23 °C. The mixture was refluxed for 7 h by using a Dean–Stark water separator. After being cooled to 23 °C, the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane–ether, 7:1) to give the corresponding ketal (4.78 g, 84%) as a colorless oil. An analytically pure sample was obtained by distillation (bp 55–58 °C/2 mmHg): ^1H NMR ($CDCl_3$) δ 5.10–5.70 (m, 2 H), 3.91 (m, 4 H), 1.00–2.40 (m, 6 H), 1.66 (d, J = 4.9 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H); IR (neat) 2990, 2900, 1450 cm^{-1}; MS m/z 182 (M^+), 163, 153, 139, 99 (base peak), 86; $[\alpha]^{21}_D$ − 28.3° (*c* 0.84, $CHCl_3$). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.36; H, 10.13.

(2*S*,3*R*)-3-(2-(Benzyloxy)-1-hydroxyethyl)-2-methylcyclopentanone Ethylene Acetal. To a stirred solution of the olefin (201 mg, 1.11 mmol) and *N*-methylmorpholine *N*-oxide monohydrate (221 mg, 1.56 mmol) in acetone (3.3 mL) and water (0.7 mL) was added osmium tetraoxide (0.28 mL, 1% w/v solution in *tert*-butyl alcohol, 0.01 mmol) at 0 °C. After being stirred at 23 °C for 2 h, the reaction was quenched with 33% aqueous Na_2SO_3 and was stirred at 23 °C for 1 h. The reaction mixture was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated to give the corresponding diol (236 mg, 99%) as a colorless oil. The crude diol was dissolved in dioxane (4.5 mL) and water (0.5 mL). To this solution was added

sodium periodate (413 mg, 1.93 mmol) at 0 °C. After being stirred at 23 °C for 1 h, the reaction mixture was diluted with water, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (ether) to give the corresponding aldehyde (177 mg, 95%) as a colorless oil. To a stirred solution of tri-*n*-butyl(benzyloxy)-methylstannane (11.40 g, 27.8 mmol) in THF (27 mL) was added *n*-butyllithium (18 mL, 1.40 M solution in hexane, 25.2 mmol) dropwise at −78 °C, and the solution was stirred at −78 °C for 10 min. To this solution was added a solution of the aldehyde (1.43 g, 8.4 mmol) in THF (9 mL) dropwise at −78 °C. After being stirred at −78 °C for 1 h, the reaction was quenched with saturated $NaHCO_3$, extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane–ethyl acetate, 3:1, silica gel was pretreated with 1% triethylamine–hexane) to give the corresponding alcohol (2.03 g, 83%) as a diastereomeric mixture: ^1H NMR ($CDCl_3$) δ 7.33 (s, 5 H), 4.55 (s, 2 H), 3.91 (m, 4 H), 3.20–3.70 (m, 3 H), 1.01 and 0.92 (d and d, J = 6.8 Hz and 6.9 Hz, 3 H); IR (neat) 3500 cm^{-1}; MS m/z 292 (M^+), 201 ($M^+ - CH_2Ph$), 171 ($M^+ - OCH_2Ph$), 141, 99 (base peak), 91; HR-MS (M^+) calcd for $C_{17}H_{24}O_4$ 292.1674, found 292.1671.

(2*S*,3*R*)-3-[(Benzyloxy)acetyl]-2-methylcyclopentanone Ethylene Acetal (8). To a stirred solution of pyridine (1.15 mL, 14.2 mmol) in CH_2Cl_2 (17 mL) was added chromium trioxide (686 mg, 6.9 mmol) at 0 °C. After being stirred at 23 °C for 20 min, powdered molecular sieves, 4A (0.35 g), was added, and the mixture was stirred at 23 °C for an additional 10 min. To this solution was added a solution of the alcohol (263 mg, 0.90 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. After being stirred at 23 °C for 30 min, the reaction mixture was diluted with ether, filtered through a short pad of Florisil, and concentrated. The residue was purified by flash chromatography (hexane–ethyl acetate, 5:1) to give 8 (224 mg, 94%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.35 (s, 5 H), 4.60 (s, 2 H), 4.13 (s, 2 H), 3.91 (m, 4 H), 2.75–2.90 (m, 1 H), 2.72 (dq, J = 10.5, 6.6 Hz, 1 H), 1.50–2.10 (m, 4 H), 0.90 (d, J = 6.6 Hz, 3 H); IR (neat) 1730 cm^{-1}; MS m/z 199 ($M^+ - CH_2Ph$), 184, 141, 99 (base peak), 91; HR-MS ($M^+ - CH_2Ph$) calcd for $C_{10}H_{15}O_4$ 199.0970, found 199.0944; $[\alpha]^{21}_D$ −43.7° (*c* 1.49, MeOH).

(2*S*,3*R*)-3-[1-(Hydroxymethyl)ethenyl]-2-methylcyclopentanone Ethylene Acetal (9). A solution of 8 (66 mg, 0.23 mmol) in ethanol (2 mL) was stirred with 10% Pd/C (13 mg, 0.01 mmol) under hydrogen atmosphere at 23 °C for 2.5 days. After filtration through a pad of Celite, the filtrate was concentrated to give the corresponding ketol as a colorless oil, which was used without further purification. To a stirred suspension of methyltriphenylphosphonium bromide (247 mg, 0.69 mmol) in THF (2 mL) was added a solution of potassium *tert*-butoxide (83 mg, 0.68 mmol) in THF (2 mL) at 23 °C. The reaction mixture was stirred at the same temperature for 15 min, and then a solution of the crude ketol in THF (2 mL) was added at 23 °C. After being stirred at 23 °C for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane–ether, 1:2, silica gel was pretreated with 1% triethylamine–hexane) to give 9 (35 mg, 78% in two steps) as a colorless oil: ^1H NMR (C_6D_6) δ 5.20 (dt, J = 1.5, 1.5 Hz, 1 H), 4.98 (dt, J = 0.8, 1.5 Hz, 1 H), 3.97 (dd, J = 1.5, 1.5 Hz, 2 H), 3.60 (m, 4 H), 1.40–2.60 (m, 6 H), 1.15 (d, J = 6.4 Hz, 3 H); IR (neat) 3450, 1650 cm^{-1}; MS, m/z 198 (M^+), 169 ($M^+ - CH_2OH$), 141, 99 (base peak), 86, 55; HR-MS (M^+) calcd for $C_{11}H_{18}O_3$ 198.1255, found 198.1241; $[\alpha]^{19}_D$ −54.7° (*c* 1.12, $CHCl_3$).

(2*S*,3*R*)-3-[(1*R*)-1-(Hydroxymethyl)-1,2-epoxyethyl]-2-methylcyclopentanone Ethylene Acetal (10). To a mixture of D-(−)-diethyl tartrate (33 mg, 0.16 mmol), powdered molecular sieves, 4A (40 mg), and CH_2Cl_2 (2 mL) was added titanium(IV) isopropoxide (0.026 mL, 0.087 mmol) at 0 °C. After the mixture was cooled to −20 °C, *tert*-butyl hydroperoxide (0.88 mL, 6.0 M in CH_2Cl_2, 5.3 mmol) was added, and the mixture was stirred at the same temperature for 10 min. With vigorous stirring, 9 (81 mg, 0.42 mmol) in CH_2Cl_2 (3 mL) was added dropwise to the reaction mixture. After being stirred at −20 °C for 5 h, the reaction was quenched with water (0.5 mL), allowed to warm to 23 °C, and then stirred for 30 min. The solution prepared by adding NaCl (0.1 g) to a solution of NaOH (0.3 g) in water (0.8 mL) was then added. After being stirred vigorously for 30 min, the reaction mixture was extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane–ether, 1:4, silica gel was pretreated with 1% triethylamine–hexane) to give 10 (83 mg, 96%) as a colorless oil: ^1H NMR (C_6D_6) δ 3.49 (m, 6 H), 2.59 (d, J = 4.8 Hz 1 H), 2.44 (d, J = 4.8 Hz, 1 H), 1.80–2.00 (m, 2 H), 1.65–1.80 (m, 2 H), 1.50–1.65 (m, 2 H), 1.30–1.50 (m, 1 H), 1.12 (d, J = 6.6 Hz, 3 H); IR (neat) 3450 cm^{-1}; MS, m/z 214 (M^+), 183 ($M^+ - CH_2OH$), 141, 99 (base peak), 86, 55; HR-MS (M^+) calcd for $C_{11}H_{18}O_4$ 214.1205, found 214.1207; $[\alpha]^{20}_D$ −10.4° (*c* 1.05, $CHCl_3$).

(2*S*,3*R*)-3-[(1*R*)-2-(Benzyloxy)-1-hydroxy-1-(hydroxymethyl)ethyl]-2-methylcyclopentanone Ethylene Acetal (11). Potassium hydride (614 mg, 35 wt % dispersion in mineral oil, 5.37 mmol) was washed with hexane and was suspended in THF (5 mL). To this suspension was added benzyl alcohol (0.9 mL, 8.70 mmol) at 0 °C, and the reaction mixture was stirred at 23 °C for 20 min. A solution of 10 (115 mg, 0.54 mmol) in THF (5 mL) was added dropwise at 0 °C. After being stirred at 23 °C for 32 h, the reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (hexane–ether, 1:5 → ether, silica gel was pretreated with 1% triethylamine–hexane) to give 11 (157 mg, 91%) as a colorless oil: ^1H NMR (C_6D_6) δ 7.20 (m, 5 H), 4.30 (d, J = 11.9 Hz, 1 H), 4.22 (d, J = 11.9 Hz, 1 H), 3.76 (d, J = 11.0 Hz, 1 H), 3.67 (d, J = 11.0 Hz, 1 H), 3.57 (d, J = 9.0 Hz, 1 H), 3.44 (d, J = 9.0 Hz, 1 H), 3.30–3.50 (m, 4 H), 2.10–2.30 (m, 2 H), 1.60–1.80 (m, 4 H), 1.15 (d, J = 7.0 Hz, 3 H); IR (neat) 3450 cm^{-1}; MS m/z 304 ($M^+ - H_2O$), 291, 201 ($M^+ - CH_2OCH_2Ph$), 141, 99, 91 (base peak); HR-MS ($M^+ - H_2O$) calcd for $C_{18}H_{24}O_4$ 304.1674, found 304.1674; $[\alpha]^{19}_D$ −12.0° (*c* 0.97, MeOH).

(2*S*,3*R*)-3-[(1*S*)-1-[(Benzyloxy)methyl]-1-hydroxy-2-propenyl]-2-methylcyclopentanone Ethylene Acetal. To a stirred solution of 11 (157 mg, 0.49 mmol) in DMSO (4 mL, 56 mmol) containing triethylamine (1.3 mL, 9.3 mmol) was added sulfur trioxide pyridine complex (789 mg, 5.0 mmol) in DMSO (4 mL, 56 mmol) at 23 °C. After being stirred at the same temperature for 1 h, the reaction was quenched with water at 0 °C, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane–ether, 1:3, silica gel was pretreated with 1% triethylamine–hexane) to give the corresponding aldehyde (145 mg, 93%) as a colorless oil. To a stirred suspension of methyltriphenylphosphonium bromide (168 mg, 0.47 mmol) in THF (1 mL) was added a solution of potassium *tert*-butoxide (55 mg, 0.45 mmol) in THF (1 mL) at 23 °C. The reaction mixture was stirred at the same temperature for 20 min. To this solution was added a solution of the aldehyde (50 mg, 0.16 mmol) in THF (2 mL) at 23 °C. After being stirred at 50 °C for 48 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 23 °C, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane–ether, 1:1, silica gel was pretreated with 1% triethylamine–hexane) to give the corresponding olefin (44 mg, 89%) as a colorless oil: ^1H NMR (C_6D_6) δ 7.20 (m, 5 H), 6.14 (dd, J = 17.9, 10.3 Hz, 1 H), 5.66 (dd, J = 17.9, 2.4 Hz, 1 H), 5.23 (dd, J = 10.3, 2.4 Hz, 1 H), 4.38 (d, J = 12.2 Hz, 1 H), 4.24 (d, J = 12.2 Hz, 1 H), 3.43 (m, 6 H), 1.12 (d, J = 7.1 Hz, 3 H); IR (neat) 3500, 1645 cm^{-1}; MS m/z 318 (M^+), 300 ($M^+ - H_2O$), 291 ($M^+ - C_2H_3$) 227 ($M^+ - CH_2Ph$), 197 ($M^+ - CH_2OCH_2Ph$), 141 (base peak), 99, 91, 55; HR-MS (M^+) calcd for $C_{19}H_{28}O_4$ 318.1830, found 318.1816; $[\alpha]^{23}_D$ +8.5° (*c* 1.05, MeOH).

(2*S*,3*R*)-3-[(1*S*)-1-[(Benzyloxy)methyl]-1-hydroxy-2-propenyl]-2-methylcyclopentanone (12). To a stirred solution of the ketal (104 mg, 0.33 mmol) in acetone (3.5 mL) was added iron(III) chloride dispersed on silica gel (8 wt %, 7 mg) at 23 °C. After being stirred at 23 °C for 5 h, the reaction mixture was filtered through a pad of Florisil and concentrated. The crude product was purified by flash chromatography (ether) to give 12 (90 mg, 100%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.33 (b s, 5 H), 5.90 (dd, J = 17.3, 10.5 Hz, 1 H), 5.3. (dd, J = 17.3, 1.7 Hz, 1 H), 5.25 (dd, J = 10.5, 1.7 Hz, 1 H), 4.56 (s, 2 H), 3.49 (s, 2 H), 1.50–2.60 (m, 7 H), 1.10 (d, J = 7.6 Hz, 3 H); IR (neat) 3500, 1740, 1645 cm^{-1}; MS m/z 274 (M^+), 153 ($M^+ - CH_2OCH_2Ph$), 91 (base peak), 55; HR-MS (M^+) calcd for $C_{17}H_{22}O_3$ 274.1570, found 274.1582; $[\alpha]^{20}_D$ +46.1° (*c* 1.53, $CHCl_3$).

(2*S*,3*R*,5*S*)-3-[(1*S*)-1-[(Benzyloxy)methyl]-1-hydroxy-2-propenyl]-5-hydroxy-2-methylcyclopentanone (15). To a stirred solution of diisopropylamine (0.2 mL, 1.5 mmol) in THF (5 mL) was added to a solution of *n*-butyllithium (0.87 mL, 1.4 M in hexane, 1.2 mmol) at −78 °C. After being stirred at −78 °C for 10 min, a solution of **12** (139 mg, 0.51 mmol) in THF (5 mL) was added. The reaction mixture was stirred at −78 °C for 30 min and then warmed to −30 °C. To the enolate solution was added oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) (443 mg, 1.0 mmol) at −30 °C. After being stirred at −30 °C for 10 min, the reaction was quenched with saturated aqueous Na_2SO_3 (3 mL), warmed to 23 °C, extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane–ether, 1:2) to give the desired α-alcohol **15** (more polar isomer, 59 mg, 40%) as a colorless solid together with the β-alcohol (less polar isomer, 22 mg, 15%) and the starting material **12** (17 mg, 12%). The spectral data of **15** were as follows: mp 122–123 °C; ^1H NMR ($CDCl_3$) δ 7.33 (b s, 5 H), 5.90 (dd, *J* = 17.3, 10.5 Hz, 1 H), 5.38 (dd, *J* = 17.3, 1.7 Hz, 1 H), 5.26 (dd, *J* = 10.5, 1.7 Hz, 1 H), 4.56 (s, 2 H), 4.12 (dd, *J* = 11.5, 8.5 Hz, 1 H), 3.46 (s, 2 H), 1.14 (d, *J* = 7.1 Hz, 3 H); IR ($CHCl_3$) 3600, 3500, 1750, 1645 cm^{-1}; MS *m/z* 169 ($M^+ - CH_2OCH_2Ph$), 151, 123, 91 (base peak), 55; HR-MS ($M^+ - CH_2OCH_2Ph$) calcd for $C_9H_{13}O_3$ 169.0865, found 169.0876; $[\alpha]^{24}_D$ +30.6° (*c* 0.55, $CHCl_3$).

(3*S*,4*R*,6*S*,7*S*)-3-[(Benzyloxy)methyl]-1-[(*tert*-butyldimethylsilyl)oxy]-3-ethenyl-7-methyl-6-[(triethylsilyl)oxy]-2-oxabicyclo[2.2.1]heptane (17). To a stirred solution of **15** (116 mg, 0.40 mmol) in CH_2Cl_2 (2 mL) and triethylamine (0.56 mL, 4.0 mmol) was added chlorotriethylsilane (0.10 mL, 0.60 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (hexane–ether, 2:1) to give **16** (159 mg, 99%) as a colorless oil. To a stirred solution of **16** (9.0 mg, 0.022 mmol) in CH_2Cl_2 (0.2 mL) and 2,6-lutidine (11 μL, 0.094 mmol) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (11 μL, 0.048 mmol) at 0 °C. After being stirred at 0 °C for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane–ether, 20:1) to give **17** (8.6 mg, 75%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.31 (b s, 5 H), 6.07 (dd, *J* = 17.2, 11.0 Hz, 1 H), 5.34 (dd, *J* = 17.2, 1.8 Hz, 1 H), 5.17 (dd, *J* = 11.0, 1.8 Hz, 1 H), 4.60 (d, *J* = 12.3 Hz, 1 H), 4.44 (d, *J* = 12.3 Hz, 1 H), 4.00 (d, *J* = 9.3 Hz, 1 H), 3.94 (dd, *J* = 8.5, 2.5 Hz, 1 H), 3.54 (d, *J* = 9.3 Hz, 1 H), 2.18 (dq, *J* = 3.0, 7.3 Hz, 1 H), 2.08 (ddd, *J* = 14.0, 8.5, 4.5 Hz, 1 H), 2.02 (ddd, *J* = 4.5, 3.0, 2.5 Hz, 1 H), 1.57 (ddd, *J* = 14.0, 2.5, 2.5 Hz, 1 H), 0.95 (d, *J* = 7.3 Hz, 3 H), 0.94 (t, *J* = 8.0 Hz, 9 H), 0.89 (s, 9 H), 0.56 (q, *J* = 8.0 Hz, 6 H), 0.17 (s, 3 H), 0.15 (s, 3 H); IR (neat) 1640 cm^{-1}; MS *m/z* 518 (M^+), 295, 223, 91 (base peak), 73; HR-MS (M^+) calcd for $C_{29}H_{50}O_4Si_2$ 518.3246, found 518.3228.

(3*R*,4*R*,6*S*,7*S*)-3-[(Benzyloxy)methyl]-1-[(*tert*-butyldimethylsilyl)oxy]-3-ethenyl-7-methyl-6-[(triethylsilyl)oxy]-2-oxabicyclo[2.2.1]heptane (19). To a stirred solution of **18** (26 mg, 0.064 mmol) in CH_2Cl_2 (0.5 mL) and 2,6-lutidine (30 μL, 0.26 mmol) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (19 μL, 0.08 mmol) at 0 °C. After being stirred at 0 °C for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane–ether, 30:1) to give **19** (26 mg, 78%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.32 (m, 5 H), 5.98 (dd, *J* = 17.2, 11.0 Hz, 1 H), 5.70 (dd, *J* = 17.2, 2.6 Hz, 1 H), 5.23 (dd, *J* = 11.0, 2.6 Hz, 1 H), 4.55 (d, *J* = 12.1 Hz, 1 H), 4.46 (d, *J* = 12.1 Hz, 1 H), 3.94 (dd, *J* = 9.9, 2.6 Hz, 1 H), 3.66 (d, *J* = 9.2 Hz, 1 H), 3.30 (d, *J* = 9.2 Hz, 1 H), 2.23 (dq, *J* = 1.9, 8.1 Hz, 1 H), 2.05 (ddd, *J* = 4.9, 2.6, 1.9 Hz, 1 H), 1.97 (ddd, *J* = 13.0, 9.9, 4.9 Hz, 1 H), 1.67 (dd, *J* = 13.0, 2.6, 2.6 Hz, 1 H), 0.94 (d, *J* = 8.1 Hz, 3 H), 0.94 (t, *J* = 8.0 Hz, 9 H), 0.88 (s, 9 H), 0.55 (q, *J* = 8.0 Hz, 6 H), 0.14 (s, 3 H), 0.10 (s, 3 H); IR (neat) 1640 cm^{-1}; MS *m/z* 518 (M^+), 295, 223, 115, 91 (base peak), 73; HR-MR (M^+) calcd for $C_{29}H_{50}O_4Si_2$ 518.3247, found 518.3216.

(1*S*,2*S*,3*S*,4*R*)-4-[(1*S*)-1-[(Benzyloxy)methyl]-1-hydroxy-2-propenyl]-3-methylcyclopentane-1,2-diol (23). To a stirred solution of tetramethylammonium triacetoxyborohydride (574 mg, 2.18 mmol) in acetonitrile (1.5 mL) and acetic acid (1.5 mL) was added a solution of **15** (125 mg, 0.43 mmol) in acetonitrile (4 mL) at −40 °C. The reaction mixture was stirred at −40 °C for 15 min and was warmed to 23 °C. After being stirred at 23 °C for an additional 1 h, the reaction was quenched by the addition of 0.5 N aqueous sodium potassium tartrate (5.6 mL, 2.80 mmol) with vigorous stirring for 30 min. The mixture was extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (ethyl acetate) to give **23** (104 mg, 83%) as a colorless solid: mp 122–123 °C; ^1H NMR ($CDCl_3$) δ 7.31 (b s, 5 H), 5.87 (dd, *J* = 17.2, 10.2 Hz, 1 H), 5.36 (dd, *J* = 17.2, 2.0 Hz, 1 H), 5.25 (dd, *J* = 10.2, 2.0 Hz, 1 H), 4.55 (s, 2 H), 3.70–4.00 (m, 2 H), 3.41 (s, 2 H), 0.96 (d, *J* = 7.8 Hz, 3 H); IR ($CHCl_3$) 3570, 3440, 1640 cm^{-1}; MS *m/z* 171 ($M^+ - CH_2OCH_2Ph$), 153, 135, 91 (base peak); HR-MS ($M^+ - CH_2OCH_2Ph$) calcd for $C_9H_{15}O_3$ 171.1021, Found 171.1013; $[\alpha]^{24}_D$ +22.3° (*c* 1.46, $CHCl_3$).

(1*S*,2*S*,3*S*,4*R*)-4-[(1*S*)-1-[(Benzyloxy)methyl]-1-[(*tert*-butyldimethylsilyl)oxy]-2-propenyl]-1,2-bis[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclopentane. To a stirred solution of **23** (101 mg, 0.35 mmol) in CH_2Cl_2 (3.5 mL) and 2,6-lutidine (1.6 mL, 13.7 mmol) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.8 mL, 3.1 mmol) at 23 °C. The reaction mixture was warmed to 50 °C and stirred at the same temperature for 1 day. After being cooled to 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (hexane–ether, 100:1) to give the corresponding olefin (200 mg, 91%) as a colorless oil; ^1H NMR ($CDCl_3$) δ 7.33 (m, 5 H), 5.91 (dd, *J* = 17.5, 11.1 Hz, 1 H), 5.29 (dd, *J* = 17.5, 2.0 Hz, 1 H), 5.14 (dd, *J* = 11.1, 2.0 Hz, 1 H), 4.54 (d, *J* = 11.7 Hz, 1 H), 4.42 (d, *J* = 11.7 Hz, 1 H), 3.60–3.90 (m, 2 H), 3.41 (d, *J* = 8.8 Hz, 1 H), 3.37 (d, *J* = 8.8 Hz, 1 H), 1.30–2.00 (m, 4 H), 0.80–1.00 (m, 30 H), 0.00–0.20 (m, 18 H); IR ($CHCl_3$) 1640 cm^{-1}; MS *m/z* 577 ($M^+ - C_4H_9$), 513 ($M^+ - CH_2OCH_2Ph$), 147, 91 (base peak), 73; HR-MS ($M^+ - C_4H_9$) calcd for $C_{31}H_{57}O_4Si_3$ 577.3565, found 577.3574; $[\alpha]^{22}_D$ +25.9° (*c* 0.65, $CHCl_3$).

(1*S*,2*S*,3*S*,4*R*)-4-[(1*S*)-1-[(Benzyloxy)methyl]-1-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxypropyl]-1,2-bis[(*tert*-butyldimethylsilyl)oxy]-3-methylcyclopentane. To a stirred solution of the olefin (197 mg, 0.31 mmol) in THF (3 mL) containing triethylamine (0.043 mL, 0.31 mmol) was added BH_3·THF complex (0.6 mL, 2.0 M in THF, 3.20 mmol) at 0 °C, and stirring was continued at 0 °C for 5 h. Diglyme (4.5 mL) and trimethylamine *N*-oxide (704 mg, 9.39 mmol) was added at 0 °C. The reaction mixture was heated to 140 °C and stirred at the same temperature for 3 h. After the reaction mixture was cooled at 23 °C, water was added. The reaction mixture was extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane–ether, 4:1) to give the corresponding alcohol (123 mg, 61%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.33 (b s, 5 H), 4.56 (d, *J* = 11.4 Hz, 1 H), 4.40 (d, *J* = 11.4 Hz, 1 H), 3.60–4.00 (m, 4 H), 3.41 (s, 2 H), 0.80–1.00 (m, 30 H), 0.00–0.10 (m, 18 H); IR ($CHCl_3$) 3450 cm^{-1}; MS *m/z* 531 ($M^+ - CH_2OCH_2Ph$), 513, 147, 91 (base peak), 73; HR-MS ($M^+ - CH_2OCH_2Ph$) calcd for $C_{27}H_{59}O_4Si_3$ 531.3721, found 531.3722; $[\alpha]^{21}_D$ +7.2° (*c* 1.17, $CHCl_3$).

(1*S*,2*S*,3*S*,4*R*)-1,2-Bis[(*tert*-butyldimethylsilyl)oxy]-4-[(1*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-1-(hydroxymethyl)propyl]-3-methylcyclopentane. A solution of the alcohol (22 mg, 0.043 mmol) in ethanol (2 mL) was stirred with 10% Pd/C (2 mg, 0.002 mmol) under hydrogen atmosphere at 23 °C for 1 day. After filtration through a pad of Celite, the filtrate was concentrated. The residue was purified by flash chromatography (ether) to give the corresponding alcohol (17 mg, 90%) as a viscous oil: ^1H NMR ($CDCl_3$) δ 3.60–4.00 (m, 4 H), 3.53 (s, 2 H), 0.80–1.00 (m, 30 H), 0.00–0.20 (m, 18 H); IR ($CHCl_3$) 3350 cm^{-1}; MS *m/z* 531 ($M^+ - CH_2OH$), 513, 147, 73 (base peak); HR-MS ($M^+ - CH_2OH$) calcd for $C_{27}H_{59}O_4Si_3$ 531.3721, found 531.3712; $[\alpha]^{20}_D$ +30.0° (*c* 0.78, $CHCl_3$).

(1*R*,2*R*,6*S*,8*S*,9*S*,10*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-10-methyl-5,7-dioxatricyclo[6.2.1.0^{2,6}]undecane-4,9-diol (25). To a stirred solution of oxalyl chloride (0.11 mL, 1.3 mmol) in CH_2Cl_2 (0.9 mL) was added DMSO (0.18 mL, 2.5 mmol) at −78

°C. After 20 min, a solution of the alcohol (48 mg, 0.085 mmol) in CH_2Cl_2 (1.8 mL) was added dropwise at −78 °C, and the reaction mixture was stirred at the same temperature for 20 min. After addition of triethylamine (0.6 mL, 4.3 mmol) at −78 °C, the reaction mixture was stirred at −78 °C for 20 min and warmed to 23 °C. The reaction was quenched with water at 0 °C, extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in ether, passed through a short silica gel column, and concentrated to give the crude dialdehyde **24**. To a stirred solution of the crude dialdehyde **24** in THF (0.2 mL) and water (0.2 mL) was added acetic acid (0.6 mL) at 0 °C. The reaction mixture was warmed to 60 °C and stirred at the same temperature for 12 h. After being cooled to 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (ethyl acetate) to give **25** (17 mg, 60% in two steps, mixture of diastereomers at hemiacetal position): ^1H NMR ($CDCl_3$) δ 5.70 (dd, J = 6.0, 5.0 Hz, $^3/_4$ H), 5.65 (dd, J = 5.5, 1.8 Hz, $^1/_4$ H), 4.98 (s, $^1/_4$ H), 4.75 (s, $^3/_4$ H), 4.36 (d, J = 7.6 Hz, $^3/_4$ H), 4.31 (d, J = 7.6 Hz, $^1/_4$ H), 4.00–4.10 (m, 1 H), 2.78 (dq, J = 7.6, 7.3 Hz, 1 H), 1.04 (d, J = 7.3 Hz, 3 H), 0.88 (s, 9 H), 0.12 (s, 6 H); IR ($CHCl_3$) 3600, 3400 cm^{-1}; MS m/z 330 (M^+), 329 ($M^+ - H$), 313 ($M^+ - OH$), 295, 273 ($M^+ - C_4H_9$), 225, 73 (base peak); HR-MS (M^+) calcd for $C_{16}H_{30}O_5Si$ 330.1862, found 330.1840; $[\alpha]^{20}_D$ +22.8° (c 0.68, $CHCl_3$).

(1*R*,2*R*,6*S*,8*S*,9*S*,10*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-10-methyl-5,7-dioxatricyclo[6.2.1.0^{2,6}]undec-3-en-9-ol (26). To a stirred solution of **25** (17 mg, 0.052 mmol) in CH_2Cl_2 (0.8 mL) was added thiophenol (6 μL, 0.058 mmol) and boron trifluoride diethyl etherate (13 μL, 0.11 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and warmed to 0 °C. After being stirred at 0 °C for 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexane–ether, 2:3) to give the corresponding thioether (18 mg, 83%) as a colorless oil. To a stirred solution of the thioether (18 mg, 0.043 mmol) and $NaHCO_3$ (8 mg, 0.095 mmol) in CH_2Cl_2 (0.4 mL) was added a solution of *m*-chloroperbenzoic acid (9 mg, 0.05 mmol) in CH_2Cl_2 (0.35 mL) at 0 °C. After being stirred at the same temperature for 10 min, the reaction was quenched with saturated aqueous Na_2SO_3, extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), passed through a short silica gel column, and concentrated to give the corresponding sulfoxide. The crude sulfoxide was dissolved in toluene (1 mL), and the solution was refluxed for 40 min. After being cooled to 23 °C, the reaction mixture was concentrated. The residue was purified by flash chromatography (hexane–ether, 1:1) to give **26** (5 mg, 38% in two steps) as a colorless solid: ^1H NMR (C_6D_6) δ 6.10 (d, J = 2.9 Hz, 1 H), 5.51 (s, 1 H), 4.61 (d, J = 2.9 Hz, 1 H), 3.90–4.00 (m, 2 H), 2.88 (dq, J = 7.0, 7.0 Hz, 1 H), 1.83 (ddd, J = 12.8, 6.5, 3.0 Hz, 1 H), 1.67 (d, J = 6.5 Hz, 1 H), 1.59 (d, J = 12.8 Hz, 1 H), 0.90–1.10 (m, 12 H), 0.10 (s, 3 H), 0.09 (s, 3 H); IR ($CHCl_3$) 3600, 3450, 1610 cm^{-1}; MS m/z 255 ($M^+ - C_4H_9$), 198, 157, 129, 97, 75 (base peak), 73; HR-MS ($M^+ - C_4H_9$) calcd for $C_{12}H_{19}O_4Si$ 255.1053, found 255.1062; $[\alpha]^{20}_D$ −145.8° (c 0.19, $CHCl_3$).

(1*R*,2*R*,6*S*,8*S*,10*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-10-methyl-5,7-dioxatricyclo[6.2.1.0^{2,6}]undec-3-en-9-one (2). To a stirred solution of **26** (4.5 mg, 0.013 mmol) in DMF (0.3 mL) was added pyridinium dichromate (50.8 mg, 0.14 mmol) at 0 °C. After being stirred at 40 °C for 90 min, the reaction mixture was diluted with ether, passed through a short silica gel column, and concentrated. The crude product was purified by flash chromatography (hexane–ether, 3:1) to give **2** (4.4 mg, 98%) as a colorless oil: ^1H NMR (C_6D_6) δ 6.02 (d, J = 2.9 Hz, 1 H), 5.52 (s, 1 H), 4.56 (d, J = 2.9 Hz, 1 H), 3.77 (d, J = 2.8 Hz, 1 H), 3.00 (dq, J = 2.5, 7.7 Hz, 1 H), 1.71 (d, J = 6.0 Hz, 1 H), 1.56 (dd, J = 14.1, 2.5 Hz, 1 H), 1.18 (ddd, J = 14.1, 6.0, 2.8 Hz, 1 H), 1.02 (d, J = 7.7 Hz, 3 H), 0.87 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); IR ($CHCl_3$) 1755, 1615 cm^{-1}; MS m/z 253 ($M^+ - C_4H_9$), 75 (base peak); HR-MS ($M^+ - C_4H_9$) calcd for $C_{12}H_{17}O_4Si$ 253.0896, found 253.0899; $[\alpha]^{20}_D$ − 110.2° (c 0.44, $CHCl_3$).

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Supplementary Material Available: ^1H NMR spectra of **2**, **5–12**, **15**, **23**, **25**, and **26** (13 pages). Ordering information is given on any current masthead page.

New Methodology for the Synthesis of Protected, Primary Pentadienylamines

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The utility of forming *N*-*tert*-butoxycarbonyl- (Boc) and *N*-phthalimido-protected primary 2(*E*),4(*E*)-pentadienylamines from aldehydes and ketones is described. When diethyl [(*E*)-4-[*N*-(*tert*-butoxycarbonyl)-amino]-2-buten-1-yl]phosphonate (**33*E***) is treated with sodium bis(trimethylsilyl)amide at −78 °C followed by aldehydes or ketones, the desired Boc-protected 2(*E*),4(*E*)-pentadienylamines are obtained in good yields. When diethyl [(*E*)-4-(*N*-phthalimido)-2-buten-1-yl]phosphonate (**17*E***) is subjected to similar conditions, the corresponding 2(*E*),4(*E*)-pentadienylphthalimides are obtained in good yields. In all cases, the 2*E*,4*E* isomer is the predominant isomer formed under these conditions and can be obtained in isomerically pure form from a simple recrystallization.

The 1-amino-2(*E*),4(*E*)-pentadiene system is found in a wide variety of natural products. The antibiotics aurodox[1] and efrotomycin,[2] for example, are two of the most prominent members of the elfamycins. Mocimycin (kirromycin), heneicomycin, and dihydromocimycin constitute the remaining members of this family of narrow-spectrum antibiotics.[3] Neooxazolomycin[4] and oxazolomycin[5] are

(1) Aurodox has also been called X-108 and goldinamycin. For an excellent review of the isolation, characterization, synthesis, and biological activity of aurodox, see: Maeher, H.; Leach, M.; Williams, T. H.; Blount, J. F. *Can. J. Chem.* **1980**, *58*, 501–526 and references cited therein.

(2) For references related to the isolation, characterization, and biological activity of efrotomycin, see: Dewey, R. S.; Arison, B. H.; Hannah, J.; Shih, D. H.; Albers-Schoenberg, G. *J. Antibiot.* **1985**, *38*, 1691–1698.

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