Asymmetric Synthesis of 4-Deoxyverrucarol via Two Types of Ring Expansion Reactions

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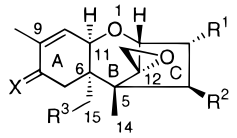
Asymmetric synthesis of a trichothecane analogue, 4-deoxyverrucarol (**2**), was carried out through two types of ring expansion reactions. First, synthesis of the racemate of **2** was investigated. Thus, 1-[1-(*tert*-butyldimethylsiloxy)-ethyl]-1-methoxycarbonyl-2-hexen-4-one (**10**), prepared by Diels−Alder reaction, was converted into the cyclopropylidene **15**. The cyclobutanone (±)-**18** was obtained from **15** via dihydroxylation, followed by successive treatments with SO_2Cl_2 in the presence of imidazole and Florisil. After transformation of (±)-**18** into the vinylcyclobutanol (±)-**19**, the second ring expansion reaction was performed with $Pd(OAc)_2$ to provide the cyclopentanone (±)-**20**. The product was converted into the racemate of 4-deoxyverrucarol (**2**) through the cyclohexenone (±)-**22**, but the diastereoselectivity during the introduction of the double bond was unsatisfactory. The selectivity was improved in the case of the asymmetric synthesis. The optically active cyclobutanone (+)-**18** was prepared via AD reaction of **15** with 73% ee. After the transformation of (+)-**18** into the cyclohexanone (−)-**30** through the palladium-mediated ring expansion reaction, (−)-**30** was subjected to the diastereoselective deprotonation reaction using the chiral amide. The key synthetic intermediate (−)-**25** of 4-deoxyverrucarol (**2**) was synthesized in an optically pure form by taking advantage of a kind of kinetic resolution that occurred during the deprotonation step.

Introduction

Trichothecanes are a group of tricyclic sesquiterpenes isolated from various species of fungi.[1] In general, these compounds comprise an A/B/C ring system and an *exo*-epoxy ring as the common features (Figure 1). Members of this class exhibit significant biological activities such as antifungal, antiviral, and antibacterial actions, and also some members of this family inhibit tumor cells.[2] Recently, Iida and Tomioka have reported that trichothecinol A (**1**) exhibited not only potent inhibitory effect against the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) but also tumor promotion effect in the absence of TPA.[3] Therefore, trichothecanes are expected to serve as a potential tool in disclosing the mechanism of carcinogenesis. These biological activities and unique structural features have stimulated many organic chemists to make significant contributions for the synthesis of this class of compounds.[4]



trichothecinol A (**1**)	X = O, R^1 = OH, R^2 = OCOCH=CH_3 , R^3 = H
4-deoxyverrucarol (**2**)	X = H_2, R^1 = R^2 = H, R^3 = OH
verrucarol (**3**)	X = H_2, R^1 = H, R^2 = R^3 = OH
scirpene (**4**)	X = H_2, R^1 = R^2 = R^3 = H

Figure 1.

Synthesis of 4-deoxyverrucarol (**2**) has been carried out from verrucarol (**3**) and analogues for studies on the preparation and development of monoclonal antibodies for trichothecanes.[5] A new route to 4-deoxyverrucarol (**2**) via a series of ring expansion reactions[6] of small ring compounds has been planned by us as shown in Scheme 1. The potential intermediate **5** would be synthesized through palladium-mediated ring expansion reaction of vinylcyclobutanol, the precursor **6** of which could be

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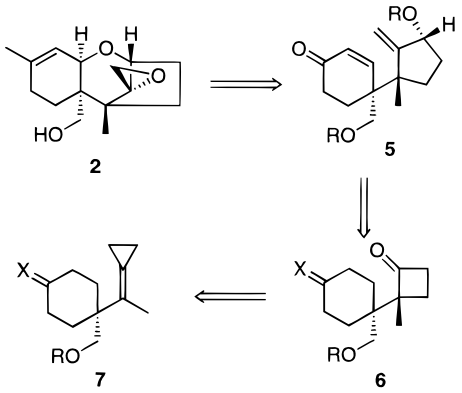
Scheme 1



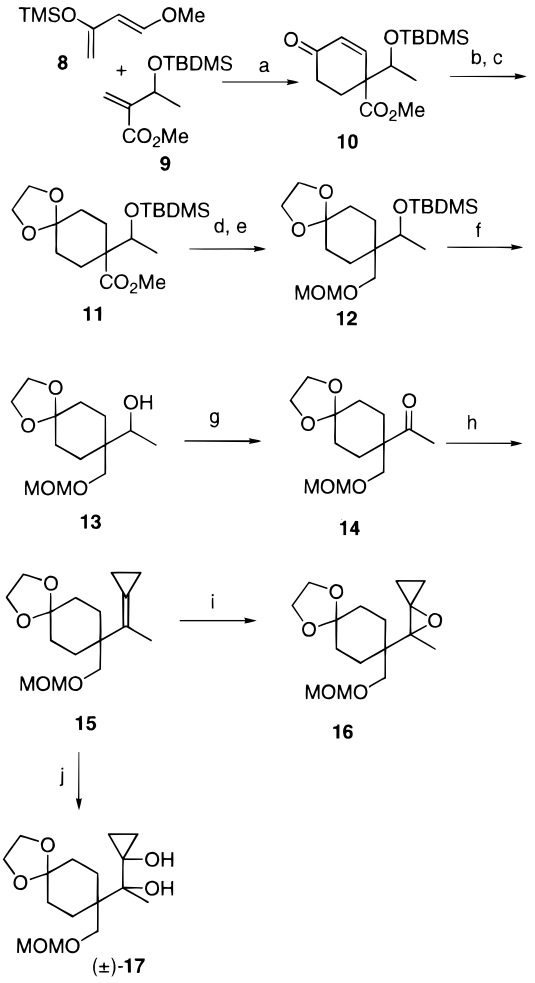
prepared from the cyclopropylidene **7**. We would like to describe an asymmetric synthesis of **2** according to this strategy.[7]

Results and Discussion

Synthesis of Racemic Compounds. The synthesis was first investigated utilizing racemic compounds. The construction of the contiguous quaternary carbons is one of the most difficult problems in trichothecane synthesis. Recently, we reported a synthesis of (±)-scirpene (**4**),[8] in which the A ring was constructed through Birch reduction and [3,3]-sigmatropic reaction. However, unsatisfactory stereocontrol was observed. To overcome the difficulty, a Diels−Alder reaction was adopted to build up one of the two quaternary carbons. Thus, the cycloaddition of the silyloxydiene **8**[9] and the methylenebutyric ester **9**[10] provided the unsaturated ketone **10** (ratio of diastereomers 2.6:1) corresponding to the A-ring part of trichothecanes (Scheme 2). Successive hydrogenation of **10** and acetalization gave the ester **11**. Because the A-ring part of the ester **11** had no chiral center, the necessity to handle diastereomers was avoided. Next, the ester **11** was reduced with DIBALH, and the resulting alcohol was protected as the MOM ether **12**. Desilylation of **12**, followed by Swern oxidation of **13**, afforded the ketone **14**. Wittig reaction of **14** with cyclopropylidene−triphenylphosphorane[11] afforded the cyclopropylidene **15**, but the reaction proceeded in low yield, presumably as a result of the bulkiness of the substrate. Treatment of the cyclopropylidene **15** with *m*-CPBA gave the corresponding epoxide **16.** However, the acidic treatment of the epoxide **16** did not produce the desired cyclobutanone. Therefore, **15** was transformed into the diol (±)-**17**, and its 1,2-rearrangement was investigated under various conditions. The results are shown in Table 1.

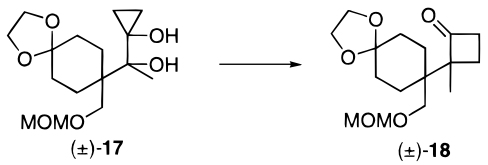
Reaction of (±)-**17** with PPTS resulted in nonproductive decomposition of the substrate (entry 1). Treatment with MsCl−pyridine or $SOCl_2$−Et_3N gave no desired product (entries 2 and 3). Therefore, a direct formation of the cyclic sulfate,[12] which was expected to be more reactive than the cyclic sulfite, was examined. When (±)-**17** was treated with SO_2Cl_2 and imidazole,[13] the consumption of (±)-**17** resulted in a complicated decomposition of the product (entry 4). However, formation of the cyclic sulfate, followed by treatment with silica gel, afforded the cyclobutanone (±)-**18** in a high yield (entry 5). Furthermore, reaction of (±)-**17** with SO_2Cl_2 and

Scheme 2[a]



[a] Key: (a) 180 °C (96%); (b) H_2, Pd−C×b0; (c) ethylene glycol, PPTS (90%); (d) DIBALH; (e) MOMCl, *i*-Pr_2NEt (96%); (f) TBAF (97%); (g) $(COCl)_2$, DMSO, Et_3N (93%); (h) cyclopropyltriphenylphosphonium bromide, NaH (27%; 99% based on recovered **14**); (i) *m*-CPBA, $NaHCO_3$ (96%); (j) OsO_4, DABCO, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$ (85%).

Table 1



entry	conditions	yield (%)
1	PPTS, 80 °C, 1 h	0
2	MsCl, pyridine, rt, 48 h	0
3	$SOCl_2$, Et_3N, rt, 24 h	0
4	SO_2Cl_2, imidazole, rt, 1 h	0
5	SO_2Cl_2, imidazole, rt, 1 h then silica gel, rt, 19 h	88
6	SO_2Cl_2, imidazole, rt, 1 h then Florisil, rt, 14 h	91

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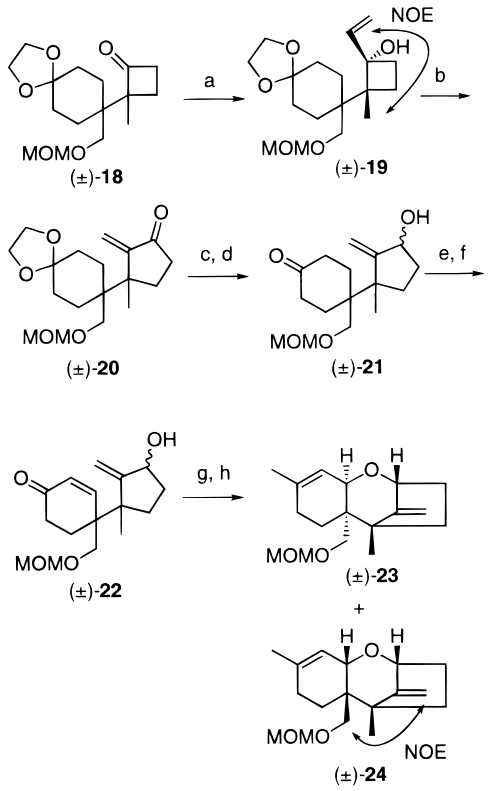
Scheme 3[a]



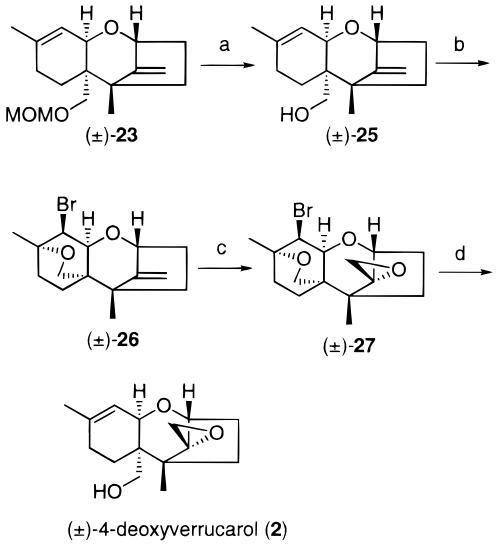
[a] Key: (a) vinylmagnesium bromide, $CeCl_3$ (97%); (b) $Pd(OAc)_2$ (90%); (c) DIBALH; (d) 10% HCl (92%); (e) TMSCl, Et_3N, 100 °C; (f) $Pd(OAc)_2$ (79%); (g) MeLi; (h) CSA (**23**, 23%; **24**, 30%).

imidazole, followed by addition of Florisil, gave the most effective outcome (entry 6). These results would suggest that the role of silica gel and Florisil is to promote the rearrangement of cyclic sulfate intermediate.

Next, the construction of the skeletal structure of trichothecanes via the ring expansion reaction as the second key step was performed as shown in Scheme 3. The cyclobutanone (±)-**18** was stereoselectively converted into the vinylcyclobutanol (±)-**19** by treatment with vinylmagnesium bromide in the presence of $CeCl_3$.[14] The stereochemistry of (±)-**19** was determined by the observation of the definite NOE between the methyl group and a vinyl hydrogen. The ring expansion reaction of (±)-**19** was achieved by using a stoichiometric amount of $Pd(OAc)_2$ to give the cyclopentanone (±)-**20** in a high yield. Reduction of (±)-**20**, followed by treatment with 10% HCl, provided a 5.2:1 mixture of the hydroxyketones **21**. Silyl enolization[15] of (±)-**21**, followed by application of Saegusa's method,[16] furnished enones (±)-**22** as an inseparable mixture of four diastereoisomers. Analysis of the ^{1}H NMR spectrum of the mixture suggested that the mixture is composed of stereoisomers at the quaternary stereogenic center of the cyclohexenone in the ratio of 1.3:1. The mixture thus obtained was treated with MeLi, and the resulting diols were subjected to cyclization under acidic conditions to give a 1:1.3 mixture of the tricyclic compounds (±)-**23** and (±)-**24**.

The stereochemistry of these tricyclic compounds was determined as follows. Namely, it is apparent that only

Scheme 4[a]



[a] Key: (a) CSA, $LiBF_4$ (50%); (b) NBS (67%); (c) *m*-CPBA, $NaHCO_3$ (73%); (d) Zn, NH_4Cl (85%).

the cis relationship between the hydroxy group at the C-3 position and the A-ring part permits cyclization to form the B ring. These two compounds were expected to be diastereomers at C-6 and C-11 positions. The configuration of (±)-**23** was assigned mainly on the basis of its conversion into the known compound as shown in Scheme 4. On the other hand, the structure **24** of the diastereoisomer was supported by the NOE observation between the *exo*-methylene and the methylene of the C-15 position. Deprotection of (±)-**24** failed because of its instability under acidic conditions.

The MOM group of (±)-**23** was deprotected to give (±)-15-hydroxytrichothec-9,12-diene (**25**), whose (+)-enantiomer had been synthesized by Gilbert with 45% ee.[4i] The stereoselective introduction of the *exo*-epoxy group at the C-12 and -13 positions was performed by the application of Schlessinger's procedure.[4a] Thus, intramolecular bromoetherification with NBS afforded the bromoether (±)-**26**, which on treatment with *m*-CPBA stereoselectively provided the epoxide (±)-**27**. Finally, reductive ring opening of (±)-**27** with zinc and NH_4Cl[17] produced (±)-4-deoxyverrucarol (**2**). The spectral data of the synthetic compound were consistent with those reported by Schuda.[5]

Thus, the total synthesis of (±)-4-deoxyverrucarol (**2**) was accomplished. This route must be efficient, if introduction of the double bond into the A-ring part could be carried out diastereoselectively. The selectivity was improved in the case of asymmetric synthesis (vide infra).

Asymmetric Synthesis. Asymmetric dihydroxylation of **15**, followed by 1,2-rearrangement of the resulting **17**, would lead to the optically active cyclobutanone **18**. It was expected that the desired diastereoselective introduction of the double bond into the cyclohexane part would be performed by deprotonation using chiral base.

Thus, the asymmetric dihydroxylation of the cyclopropylidene **15** was examined (Scheme 5). $(DHQ)_2PHAL$ is one of the most widely used ligands because of the high ability for enantioselective dihydroxylation of almost all

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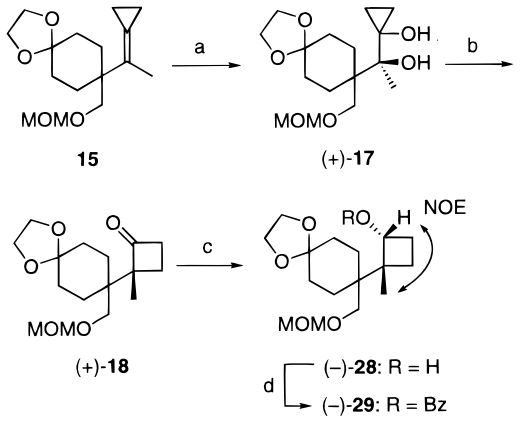
Scheme 5[a]



[a] Key: (a) OsO_4, $(DHQ)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$ (79%): (b) SO_2Cl_2, imidazole then Florisil, −40 °C (74%; 73% ee); (c) $NaBH_4$ (87%); (d) BzCl, Et_3N, DMAP (95%).

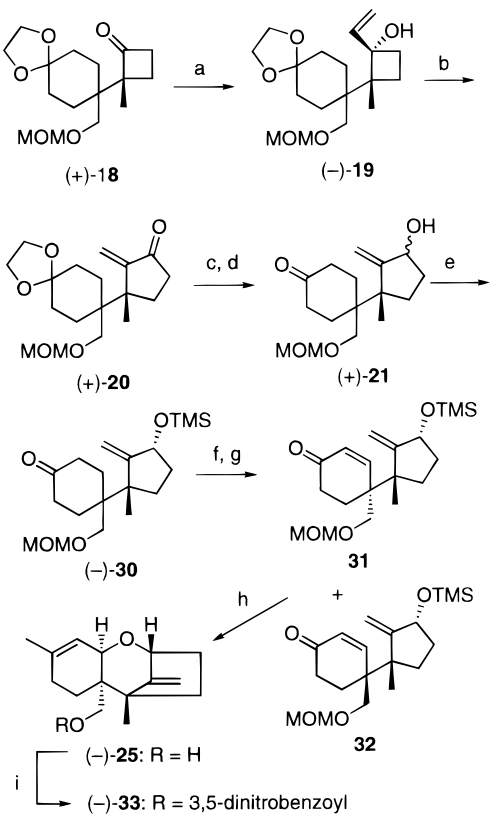
classes of olefins, which include tetrasubstituted olefins.[18] However, AD-mix α, including the ligand $(DHQ)_2PHAL$, did not have any characteristic influence on the reaction of the cyclopropylidene **15** at all. The ligand would not be suitable for the tetrasubstituted olefin because the A-ring part is presumably too hindered to permit access of OsO_4 and $(DHQ)_2PHAL$ to the double bond. In contrast, OsO_4 and $(DHQ)_2PYR$, which is known as a better ligand for oxidation of olefins having bulky alkyl substituents,[19] reacted with **15** to afford the optically active diol (+)-**17**, whose absolute configuration was predicted on the basis of theory.[18] Conversion of (+)-**17** into benzoyl or MTPA ester was attempted to evaluate the optical purity but failed.

Compound (+)-**17** was subjected to the 1,2-rearrangement through the direct formation of the cyclic sulfate intermediate. When the reaction was carried out at −40 °C, the enantiomeric purity of (+)-**18** was 73% ee. It is expected that the rearrangement would proceed via the inversion at the stereogenic center.[20]

The enantiomeric excess was evaluated after conversion of (+)-**18** into the benzoyl ester (−)-**29**. Namely, the cyclobutanone was reduced with $NaBH_4$ to afford the *cis*-cyclobutanol (−)-**28**. The stereochemistry of (−)-**28** was established by NOE between the methyl group and the methine hydrogen on the cyclobutane ring. The benzoyl ester (−)-**29**, obtained from (−)-**28**, was subjected to a chiral HPLC analysis.

Grignard reaction of (+)-**18** provided (−)-**19**, which was applied to the palladium-mediated ring expansion reaction (Scheme 6). The enantiomeric excess (73% ee) of the product (+)-**20**, determined directly by chiral HPLC, indicates no loss of the optical purity during the ring expansion reaction. Successive DIBALH reduction and deprotection afforded the allyl alcohol (+)-**21** as an inseparable mixture of diastereomers. The major diastereomer of (+)-**21** was isolated as TMS ether (−)-**30**, which was then subjected to the deprotonation reaction using lithium (*S,S*)-α,α-bis(phenylethyl)amide.[21] The reaction was executed at −98 °C, and the resulting silyl enol ether was immediately used for the next step after separation from the chiral amine through Florisil column chromatography. The Saegusa reaction[16] proceeded smoothly to give the cyclohexenones **31** and **32** as an inseparable mixture in the ratio of 2:1. When lithium (*R,R*)-α,α-bis(phenylethyl)amide was used for the above transformation, a mixture of **31** and **32** was formed in the ratio of 1:4. Reaction of the mixture, obtained by the use of the (*S,S*)-amine, with MeLi followed by addition of 50% HF afforded (−)-**25**. No formation of other diastereoisomers was observed.

Scheme 6[a]



[a] Key; (a) vinylmagnesium bromide, $CeCl_3$ (86%); (b) $Pd(OAc)_2$ (82%, 73% ee); (c) DIBALH; (d) 10% HCl (87%); (e) TMSCl, imidazole (79%); (f) (*S,S*)-α,α-bis(phenethyl)amine, BuLi, −98 °C then TMSCl, Et_3N; (g) $Pd(OAc)_2$ (88%); (h) MeLi then 50% HF (49); (i) 3,5-dinitrobenzoyl chloride, Et_3N, DMAP (95%, >98% ee).

The 98% ee enantiomeric purity of the synthetic (−)-**25** was determined by the chiral HPLC analysis of (−)-**33**, derived from (−)-**25**. The enhancement of the optical purity could be attributed to an enantiomeric enrichment during the conversion. Recrystallization of (−)-**25** gave the enantiomerically pure compound (>99% ee). The specific rotation of the synthetic compound **38**, $[\alpha]_D$ −147 (*c* 0.42, $CHCl_3$), [45% ee of its antipode, lit.[4i] $[\alpha]_D$ +33 (*c* 0.3, $CHCl_3$)] supports that its absolute stereochemistry must be the same as natural trichothecanes. Because (−)-**25** is convertible into 4-deoxyverrucarol (**2**) as described as above, its formal asymmetric synthesis has been achieved.

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Experimental Section

General Procedure. All reactions were carried out under a positive atmosphere of nitrogen in dried glassware unless indicated otherwise. Dehydrated THF, Et_2O, and CH_2Cl_2 were purchased, and other solvents were distilled prior to use. DME was freshly distilled from CaH_2 and $LiAlH_4$, and DMF, DMSO, *o*-dichlorobenzene, toluene, and MeCN were distilled form CaH_2 and stored over 4 Å molecular sieves. Eluants for HPLC were purchased. Silica gel column chromatography was carried out by using Merck Kieselgel 60 Art. 7734, Merck Kieselgel 60 Art. 9385, or Cica silica gel 60 (spherical). Reactions and chromatography fractions were analyzed by employing precoated silica gel 60 F254 plates (Merck). Shimadzu LC-10AD was employed for HPLC, equipped with Shimadzu SPD-10A as a UV detector at 254 nm. CHIRAL CEL OJ or OB-H (0.46 cm $\phi \times$ 25 cm, Daicel Chemical) was used as a HPLC column.

1-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-methoxycarbonyl-2-hexen-4-one (10). A solution of **9** (27.2 g, 0.111 mol) and **8** (25 mL, 0.13 mol) in *o*-dichlorobenzene (80 mL) was heated for 14 h at 180 °C. The solvent was distilled off, and the residue was diluted with Et_2O. The mixture was washed with 10% HCl, saturated $NaHCO_3$, and saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (92:8 v/v) to give the cyclohexenone **10** (33.4 g, 72:28 diastereomers mixture, 96%) as a colorless oil: IR (neat) 1740, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.86 (9H, s), 1.12 (2.16H, d, J = 6.3 Hz), 1.10 (0.84H, d, J = 6.3 Hz), 1.98−2.14 (1H, m), 2.26−2.38 (1H, m), 2.41−2.57 (2H, m), 3.72 (3H, s), 4.19−4.31 (1H, m), 6.03 (0.28H, d, J = 10.5 Hz), 6.10 (0.72H, d, J = 10.5 Hz), 6.82 (0.28H, dd, J = 1.5 and 10.5 Hz), 6.97 (0.72H, dd, J = 1.5 and 10.5 Hz); MS m/z 297 (M^+ − Me). Anal. Calcd for $C_{16}H_{28}O_4Si$: C, 61.50; H, 9.03. Found: C, 61.41; H, 8.86.

1-[1-(*tert*-Butyldimethylsiloxy)ethyl]-1-methoxycarbonyl-4-cyclohexanone Ethylene Acetal (11). To a solution of **10** (30.0 g, 96.0 mmol) in MeOH (400 mL) was added 10% Pd−C (300 mg). The suspension was stirred under H_2 for 13 h at room temperature and filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in benzene (300 mL), and ethylene glycol (20 mL, 0.36 mol) and PPTS (0.40 g, 1.6 mmol) were added. The mixture was refluxed for 5 h with removal of water. The resulting mixture was cooled, diluted with water, and extracted with Et_2O, and the combined extracts were washed with saturated $NaHCO_3$ and saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (85:15 v/v) to give the ketal **11** (31.0 g, 90%) as a colorless oil: IR (neat) 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.02 (3H, s), 0.86 (9H, s), 1.07 (3H, d, J = 6.3 Hz), 1.51−1.70 (6H, m), 1.99−2.08 (1H, m), 2.09−2.18 (1H, m), 3.66 (3H, s), 3.80 (1H, q, J = 6.3 Hz), 3.91 (4H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −4.1, 17.8, 19.0, 25.7, 27.2, 27.4, 32.1, 52.5, 52.6, 64.2, 73.6, 108.7, 175.3; MS m/z 343 (M^+ − Me); HRMS calcd for $C_{17}H_{31}O_5Si$ 343.1939, found 343.1921.

1-[1-(*tert*-Butyldimethylsiloxy)ethyl]-1-(methoxymethoxy)methyl-4-cyclohexanone Ethylene Acetal (12). To a stirred solution of **11** (25.8 g, 72.0 mmol) in CH_2Cl_2 (400 mL) was added a solution of DIBALH (170 mL, 0.96 M solution in hexane, 0.17 mol) dropwise over 30 min at −78 °C. The reaction mixture was stirred for 1.5 h at the same temperature. The reaction mixture was quenched with MeOH (10 mL), and the temperature was raised to room temperature. To the resulting solution was added aqueous 10% NaOH (200 mL), and the stirring was continued for 1 h at the same temperature. The resulting mixture was extracted with Et_2O, and the organic layer was washed with saturated NaCl. The combined extracts were evaporated, and the residue was dissolved in CH_2Cl_2 (350 mL). *i*-Pr_2NEt (28 mL, 0.16 mol) and MOMCl (11 mL, 0.14 mol) were added at 0 °C, and the stirring was continued for 12 h at room temperature. The reaction mixture was quenched with water and extracted with Et_2O. The combined extracts were washed with saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (93:7 v/v) to give the ether **12** (26.0 g, 96%) as a colorless oil: IR (neat) 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 1.11 (3H, d, J = 6.6 Hz), 1.50−1.69 (8H, m), 3.35 (3H, s), 3.46 (1H, d, J = 9.9 Hz), 3.60 (1H, d, J = 9.9 Hz), 3.79 (1H, q, J = 6.6 Hz), 3.94 (4H, s), 4.58 (1H, d, J = 6.6 Hz), 4.61 (1H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, −4.0, 18.0, 18.3, 25.9, 26.0, 26.7, 30.6, 40.5, 55.2, 64.2, 67.9, 71.8, 96.9, 109.1; MS m/z 359 (M^+ − Me); HRMS calcd for $C_{18}H_{35}O_5Si$ 359.2252, found 359.2293.

1-(1-Hydroxyethyl)-1-(methoxymethoxy)methyl-4-cyclohexane Ethylene Acetal (13). A mixture of **12** (26.0 g, 69.4 mmol) and a solution of TBAF (150 mL, 1.0 M in THF, 0.15 mol) was stirred for 20 h at 50 °C. The reaction mixture was cooled, diluted with water, and extracted with AcOEt. The combined extracts were washed with saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (70:30 v/v) to give the alcohol **13** (17.6 g, 97%) as a colorless oil: IR (neat) 3500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, d, J = 6.6 Hz), 1.13−1.50 (8H, m), 2.84−2.91 (1H, m), 3.01 (3H, s), 3.18 (1H, d, J = 9.9 Hz), 3.30 (1H, d, J = 9.9 Hz), 3.35−3.44 (1H, m), 3.58 (4H, s), 4.27 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1, 26.0, 26.4, 29.6, 29.7, 38.7, 54.5, 63.5, 69.2, 71.3, 96.0, 108.1; MS m/z 260 (M^+). Anal. Calcd for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 59.91; H, 9.20.

1-Acetyl-1-(methoxymethoxy)methyl-4-cyclohexanone Ethylene Acetal (14). To a stirred solution of DMSO (5.8 mL, 82 mmol) in CH_2Cl_2 (330 mL) was added oxalyl chloride (5.8 mL, 66 mmol) dropwise at −78 °C. After 10 min, a solution of **13** (7.09 g, 27.2 mmol) in CH_2Cl_2 (20 mL) was added, and the stirring was continued for 30 min at the same temperature. Et_3N (22 mL, 0.16 mol) was added, and the temperature was raised to 0 °C over 20 min. The reaction mixture was quenched with 10% NaOH (100 mL) and extracted with AcOEt. The combined extracts were washed with saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (70:30 v/v) to give the ketone **14** (6.53 g, 93%) as a colorless oil: IR 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.51−1.74 (6H, m), 2.06−2.21 (2H, m), 2.21 (3H, s), 3.31 (3H, s), 3.57 (2H, s), 3.93 (4H, s), 4.56 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 27.9, 31.3, 51.5, 55.3, 64.3, 73.1, 96.6, 108.5, 211.6; MS m/z 258 (M^+); HRMS calcd for $C_{13}H_{22}O_5$ 258.1466, found 258.1499.

1-(1-Cyclopropylideneethyl)-1-(methoxymethoxy)methyl-4-cyclohexanone Ethylene Acetal (15). A suspension of cyclopropyltriphenylphosphonium bromide (9.9 g, 26 mmol) and NaH (0.84 g, 60% oil suspension, 21 mmol) in DME (80 mL) was stirred for 9 h at 56 °C. A solution of **14** (2.66 g, 10.3 mmol) in DME (20 mL) was added dropwise at the same temperature, and the stirring was continued for 12 h at 95 °C (bath temperature). The reaction mixture was quenched with water and extracted with AcOEt. The combined extracts were washed with saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (96:4 v/v) to give the cyclopropylidene derivative **15** (0.797 g, 27%) as a colorless oil. Further elution with hexane−AcOEt (85:15 v/v) gave the recovered substrate **14** (1.92 g, 72%). **15**: IR (neat) 1160, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (2H, dd, J = 5.7 and 8.7 Hz), 1.23 (2H, ddd, J = 1.5, 5.7, and 8.7 Hz), 1.49−1.73 (6H, m), 1.85 (3H, t, J = 1.5 Hz), 2.01−2.13 (2H, m), 3.29 (3H, s), 3.36 (2H, s), 3.88−3.98 (4H, m), 4.54 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.2, 6.1, 18.5, 29.0, 31.4, 43.1, 54.9, 64.2, 64.3, 74.6, 96.6, 109.2, 119.0, 124.7; MS m/z 282 (M^+); HRMS calcd for $C_{16}H_{26}O_4$ 282.1803, found 282.1815.

1-(2-Methyl-1-oxaspiropent-2-yl)-1-(methoxymethoxy)-meththyl-4-cyclohexanone Ethylene Acetal (16). To a stirred solution of **15** (38.0 mg, 0.135 mmol) in CH_2Cl_2 (3 mL) was added $NaHCO_3$ (0.12 g, 1.4 mmol) and *m*-CPBA (35 mg, 0.16 mmol) at room temperature,and the mixture was stirred for 2 h at the same temperature. The reaction mixture was quenched with aqueous 10% $Na_2S_2O_3$ (5 mL) and further stirred for 1 h. The resulting mixture was extracted with Et_2O, and the extract was washed with saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (85:15 v/v) to give the epoxide **16** (38.7 mg, 96%) as a colorless oil: IR (neat) 1150, 1100, 1040 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 0.68−0.86 (2H, m), 1.06−1.17 (1H, m), 1.18−1.29 (1H, m), 1.45 (3H, s), 1.53−1.95 (8H, m), 3.30 (3H, s), 3.49 (1H, d, J = 9.6 Hz), 3.61 (1H, d, J = 9.6 Hz), 3.93 (4H, s), 4.57 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.1, 6.2, 18.4, 25.3, 27.0, 30.7, 30.8, 39.7, 55.2, 61.8, 64.3, 67.1, 69.5, 96.8, 108.7; MS *m/z* 298 (M^+); HRMS calcd for $C_{16}H_{26}O_5$ 298.1779, found 298.1766.

(±)-1-[1-Hydroxy-1-(1-hydroxycyclopropyl)ethyl]-1-(methoxymethoxy)methyl-4-cyclohexanone Ethylene Acetal (17). To a well stirred solution of **15** (324 mg, 1.15 mmol), DABCO (7 mg, 0.06 mmol), $K_3Fe(CN)_6$ (1.1 g, 3.5 mmol), and K_2CO_3 (0.47 g, 3.5 mmol) in *t*-BuOH−water (1:1 v/v, 12 mL) was added OsO_4 (aqueous 2% w/v, 0.15 mL, 0.012 mmol) at room temperature, and the stirring was continued for 20 h at the same temperature. To the reaction mixture was added 10% $Na_2S_2O_3$ (10 mL), and stirring was continued for 1 h. The resulting mixture was extracted with AcOEt, and the combined extracts were succesively washed with 10% NaOH and saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (70:30 v/v) to give (±)-**17** (309 mg, 85%) as a colorless oil: IR (neat) 3420 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.42−0.53 (1H, m), 0.68−0.78 (2H, m), 0.97−1.10 (1H, m), 1.31 (3H, s), 1.57−1.71 (4H, m), 1.79−1.95 (4H, m), 2.52 (1H, br s), 3.40 (3H, s), 3.47 (1H, br s), 3.84 (1H, d, J = 10.5 Hz), 3.89 (1H, d, J = 10.5 Hz), 3.95 (4H, s), 4.67 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6, 12.6, 20.8, 24.6, 26.4, 30.4, 30.7, 43.2, 56.0, 60.7, 64.2, 67.6, 76.3, 96.8, 108.5; MS *m/z* 298 ($M^+ - H_2O$); HRMS calcd for $C_{16}H_{26}O_5$ 298.1779, found 298.1786.

(±)-1-(Methoxymethoxy)methyl-1-(1-methyl-2-oxocyclobutyl)-4-cyclohexanone Ethylene Acetal (18). (entry 6; Table 1) To a stirred solution of (±)-**17** (72.2 mg, 0.228 mmol) and imidazole (0.18 g, 2.6 mmol) in CH_2Cl_2 (20 mL) was added SO_2Cl_2 (0.050 mL, 0.69 mmol) at 0 °C, and the mixture was stirred for 1 h at the same temperature. Florisil (1.0 g) was added at room temperature, and the stirring was further continued for 14 h at the same temperature. The reaction mixture was filtered through silica gel in vacuo, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel with hexane−AcOEt (85:15 v/v) to give (±)-**18** (61.7 mg, 91%) as a colorless oil: IR (neat) 1770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (3H, s), 1.43−1.74 (7H, m), 1.80−1.99 (2H, m), 2.37 (1H, ddd, J = 6.9, 10.5 and 12.3 Hz), 2.82 (1H, ddd, J = 6.0, 10.5 and 18.0 Hz), 2.99 (1H, ddd, J = 6.9, 10.2 and 18.0 Hz), 3.36 (3H, s), 3.57 (1H, d, J = 10.5 Hz), 3.68 (1H, d, J = 10.5 Hz), 3.93 (4H, br s), 4.57 (1H, d, J = 6.6 Hz), 4.60 (1H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 22.2, 25.5, 26.0, 30.5, 38.9, 42.3, 55.4, 64.2, 67.8, 70.4, 96.8, 108.4, 215.7; MS *m/z* 298 (M^+). Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.41; H, 8.78.

(±)-(1*S,2*R**)-2-{8-(Methoxymethoxy)methyl-1,4-dioxaspiro[4.5]dec-8-yl}-2-methyl-1-vinylcyclobutanol (19).** To a stirred suspension of $CeCl_3$ (2.2 g, 8.8 mmol) in THF (170 mL) was added a solution of vinylmagnesium bromide (23 mL, 0.80 M in THF, 18 mmol) at −78 °C. After 1 h of stirring, a solution of (±)-**18** (1.32 g, 4.42 mmol) in THF (30 mL) was added dropwise to the reaction mixture at the same temperature, and the temperature was then raised to room temperature in 30 min. The reaction mixture was quenched with saturated NH_4Cl (1 mL) followed by addition of saturated $NaHCO_3$ (1 mL) and $MgSO_4$ (3 g). The resulting mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with hexane−AcOEt (85:15 v/v) to give (±)-**19** (1.40 g, 97%) as a colorless oil: IR (neat) 3430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, s), 1.24−1.35 (1H, m), 1.38−1.47 (1H, m), 1.48−1.70 (5H, m), 1.75−1.86 (1H, m), 1.87−2.03 (1H, m), 2.16−2.28 (1H, m), 2.34−2.51 (2H, m), 3.39 (3H, s), 3.40 (1H, d, J = 10.2 Hz), 3.78 (1H, d, J = 10.2 Hz), 3.85−3.90 (4H, m), 4.19 (1H, s), 4.62 (1H, d, J = 7.2 Hz), 4.65 (1H, d, J = 7.2 Hz), 5.04 (1H, dd, J = 1.8 and 10.5 Hz), 5.16 (1H, dd, J = 1.8 and 17.4 Hz), 6.08 (1H, dd, J = 10.5 and 17.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 24.8, 26.4, 27.3, 29.3, 30.7, 30.9, 31.2, 40.4, 51.6, 56.0, 64.2, 67.0, 82.0, 96.9, 108.4, 112.1, 142.7; MS *m/z* 326 (M^+); HRMS calcd for $C_{18}H_{30}O_5$ 326.2092, found 326.3071.

(±)-1-(1-Methyl-2-methylene-3-oxocyclopropyl)-1-(methoxymethoxy)methyl-4-cyclohexanone Ethylene Acetal (20). To a stirred solution of (±)-**19** (1.28 g, 3.92 mmol) in THF (150 mL) under Ar was added $Pd(OAc)_2$ (1.3 g, 5.8 mmol) at room temperature, and the stirring was continued for 8 h at the same temperature. The reaction mixture was passed through a short pad of silica gel with Et_2O as eluant. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel with hexane−AcOEt (90:10 v/v) to give (±)-**20** (1.15 g, 90%) as colorless prisms: mp 53−54 °C (petroleum ether); IR ($CHCl_3$) 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, s), 1.44−1.80 (9H, m), 2.28−2.36 (2H, m), 2.37−2.54 (1H, m), 3.34 (3H, s), 3.51 (1H, d, J = 10.8 Hz), 3.66 (1H, d, J = 10.8 Hz), 3.93 (4H, br s), 4.52 (1H, d, J = 6.6 Hz), 4.55 (1H, d, J = 6.6 Hz), 5.27 (1H, d, J = 0.9 Hz), 6.13 (1H, d, J = 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 25.4, 26.2, 30.4, 30.6, 30.8, 36.0, 40.9, 48.7, 55.7, 64.2, 67.7, 96.9, 108.4, 119.4, 153.0, 208.6; MS *m/z* 324 (M^+). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found 66.63; H, 8.67.

(±)-1-(3-Hydroxy-1-methyl-2-methylenecyclopentyl)-1-(methoxymethoxy)methyl-4-cyclohexane (21). To a stirred solution of (±)-**20** (375 mg, 1.16 mmol) in THF (30 mL) was dropwise added a solution of DIBALH (1.8 mL, 0.94 M in hexane, 1.7 mmol) at −78 °C, and the mixture was stirred for 2 h at the same temperature. The reaction mixture was quenched with MeOH (2 mL) and the temperature was raised to room temperature. To the mixture was added 10% HCl (10 mL), and stirring was continued for 2.5 h at the same temperature. The reaction mixture was quenched with 10% NaOH (20 mL) and extracted with AcOEt. The combined extracts were washed with saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (60:40 v/v) to give (±)-**21** (*cis:trans* = 84:16, 300 mg, 92%) as a colorless oil: IR (neat) 3450, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (2.52H, s), 1.21 (0.48H, s), 1.37−1.47 (1H, m), 1.67−1.86 (2.16H, m), 1.88−2.13 (3.84H, m), 2.25−2.64 (7H, m), 3.38 (0.48H, s), 3.39 (2.52H, s), 3.66 (0.16H, d, J = 10.5 Hz), 3.74 (0.16H, d, J = 10.5 Hz), 3.79 (0.84H, d, J = 10.5 Hz), 3.86 (0.84H, d, J = 10.5 Hz), 4.62 (0.32H, s), 4.63 (1.68H, s), 5.03 (0.16H, d, J = 2.7 Hz), 5.10 (0.84H, s), 5.22 (0.16H, d, J = 2.7 Hz), 5.35 (0.84H, s); MS *m/z* 282 (M^+ − MeOH); HRMS calcd for $C_{15}H_{22}O_3$ 250.1568, found 250.1577.

(±)-1-(3-Hydroxy-1-methyl-2-methylenecyclopropyl)-1-(methoxymethoxy)methyl-2-cyclohexen-4-one Ethylene Acetal (22). To a stirred solution of (±)-**21** (98.9 mg, 0.350 mmol) and Et_3N (2 mL, 14 mmol) in DMF (15 mL) was added TMSCl (1 m, 0.8 mmol) at room temperature, and the stirring was continued for 5 h at 100 °C. The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with hexane. The combined extracts were washed with saturated NaCl. The residue upon workup was dissolved in MeCN (15 mL). $Pd(OAc)_2$ (0.12 g, 0.53 mmol) was added at room temperature, and the mixture was stirred for 24 h at the same temperature under Ar. The reaction mixture was passed through a short pad of Florisil with hexane−AcOEt (70:30 v/v) as elueant. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel with hexane−AcOEt (50:50 v/v) to give (±)-**22** (77.6 mg, diastereoisomeric ratio 47:37:8:8, 79%) as a colorless oil: IR (neat) 3400, 1670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (0.37H, s), 1.20 (2.47H, s), 1.25 (0.16H, s), 1.38−1.57 (2H, m), 1.67−1.81 (1H, m), 1.81−2.51 (4H, m), 2.61−2.77 (1H, m), 3.33 (0.08H, s), 3.34 (0.08H, s), 3.35 (2.47H, s), 3.36 (0.37H, s), 3.60−3.85 (2H, m), 4.29−4.43 (0.53H, m), 4.44−4.50 (0.47H, m), 4.53−4.64 (2H, m), 5.03 (0.08H, d, J = 2.4 Hz), 5.21 (0.37H, s), 5.29 (0.08H, d, J = 2.4 Hz), 5.21 (0.47H, s), 5.29 (0.08H, d, J = 2.4 Hz), 5.30 (0.08H, d, J = 2.4 Hz), 5.36 (0.47H, s), 5.41 (0.37H, s), 6.06−6.15 (1H, m), 6.69 (0.08H, dd, J = 1.2 and 10.2 Hz), 6.84 (0.08H, dd, J = 1.2 and 10.2 Hz), 6.92 (0.37H, dd, J = 1.2 and 10.5 Hz), 6.97 (0.47H, dd, J = 1.5 and 10.5 Hz); MS *m/z* 279 (M^+ − H); HRMS calcd for $C_{16}H_{23}O_4$ 279.1595, found 279.1567.

(±)-(2*R,5*S**,6*S**,11*S**)-15-(Methoxymethoxy)methyltrichothec-9,12-diene (24) and (±)-(2R*,5S*,6R*,11R*)-15-(Methoxymethoxy)methyltrichothec-9,12-diene (23).** To a stirred solution of (±)-**22** (77.6 mg, 0.277 mmol) in THF (30 mL) was added a solution of MeLi (3 mL, 1.04 M in Et_2O, 3.1 mmol) at −78 °C, and the stirring was continued for 1 h at the same temperature. The reaction mixture was quenched with MeOH (1 mL) and water. The mixture was extracted with AcOEt. The residue upon workup was dissolved in CH_2Cl_2 (30 mL) and stirred. To the solution was added CSA (40 mg, 0.17 mmol) at room temperature, and the stirring was continued for 2 h at the same temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (97:3 v/v) to successively give (±)-**24** (23.2 mg, 30%) and (±)-**23** (17.9 mg, 23%) as colorless oil.

(±)-**23**: IR (neat) 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (3H, s), 1.38 (1H, ddd, J = 5.4, 12.7 and 1.35 Hz), 1.55−1.64 (1H, m), 1.69 (3H, br s), 1.71−2.00 (5H, m), 2.39 (1H, ddd, J = 4.5, 9.3 and 13.5 Hz), 3.28 (1H, d, J = 10.5 Hz), 3.36 (3H, s), 3.53 (1H, d, J = 10.5 Hz), 3.77 (1H, br d, J = 5.4 Hz), 4.30 (1H, d, J = 4.5 Hz), 4.55 (1H, d, J = 6.6 Hz), 4.58 (1H, d, J = 6.6 Hz), 4.61 (1H, s), 4.96 (1H, s), 5.40 (1H, br d, J = 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 20.2, 23.4, 27.3, 28.4, 32.8, 43.4, 47.8, 55.6, 67.0, 68.3, 80.0, 97.2, 102.9, 120.0, 140.3, 155.7; MS m/z 278 (M^+); HRMS calcd for $C_{16}H_{26}O_3$ 278.1880, found 278.1909.

(±)-**24**: IR (neat) 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.20−1.31 (1H, m), 1.48−1.61 (1H, m), 1.65−1.84 (3H, m), 1.70 (3H, br s), 1.84−2.05 (3H, m), 2.31 (1H, ddd, J = 4, 8, 9.6 and 13.8 Hz), 3.10 (1H, d, J = 10.5 Hz), 3.34 (1H, d, J = 10.5 Hz), 3.36 (3H, s), 4.37 (1H, d, J = 3.0 Hz), 4.53 (1H, d, J = 6.6 Hz), 4.56 (1H, d, J = 6.6 Hz), 4.85 (1H, s), 5.02 (1H, s), 5.36−5.41 (1H, dr d, J = 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 21.7, 23.6, 28.1, 31.5, 32.2, 46.0, 46.3, 56.0, 68.3, 69.0, 80.4, 97.3, 105.0, 121.3, 139.0, 155.3; MS m/z 247 (M^+ − MeO); HRMS calcd for $C_{16}H_{23}O_2$ 247.1697, found 247.1649.

(±)-(2*R,5*S**,6*R**,11*R**)-15-Hydroxytrichothec-9,12-diene (25).** To a stirred solution of (±)-**23** (30.0 mg, 0.108 mmol) in 10% MeOH (5.5 mL) was added CSA (30 mg, 0.13 mmol), and the reaction mixture was refluxed for 3.5 h. CSA (30 mg, 0.13 mmol) was added again, and the solution was refluxed for 6.5 h. After addition of $LiBF_4$ (60 mg, 0.64 mmol), the mixture was refluxed for 4 h. The reaction mixture was quenched with saturated $NaHCO_3$. MeOH was evaporated off, and the resulting mixture was diluted with water and extracted with Et_2O. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (97:3 v/v) to give (±)-**25** (12.7 mg, 50%) as colorless needles: mp 61−62 °C (hexane−AcOEt); IR ($CHCl_3$) 3430 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, s), 1.41 (1H, ddd, J = 5.4, 12.6, and 13.5 Hz), 1.55−1.67 (2H, m), 1.70 (3H, br s), 1.71−1.94 (3H, m), 1.99−2.07 (2H, m), 2.30 (1H, ddd, J = 4.8, 9.0, and 13.5 Hz), 3.49 (1H, d, J = 12.0 Hz), 3.70 (1H, br d, J = 5.4 Hz), 3.73 (1H, d, J = 12.0 Hz), 4.30 (1H, d, J = 4.8 Hz), 4.62 (1H, s), 4.97 (1H, s), 5.42 (1H, br d, J = 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 19.9, 23.4, 27.3, 28.7, 32.7, 44.2, 47.8, 63.2, 66.9, 79.9, 103.1, 119.9, 140.7, 155.6; MS m/z 234 (M^+); HRMS calcd for $C_{15}H_{22}O_2$ 234.1619, found 234.1613.

(±)-(1*S,2*S**,5*R**,7*S**,8*S**,9*S**)-8-Bromo-2,9-dimethyl-14-methylene-6,10-dioxatetracyclo[7.2.2.0^{1,7}.1^{2,5}]tetradecane (26).** To a stirred solution of (±)-**25** (12.7 mg, 0.05442 mmol) in acetone (2 mL) was added NBS (14 mg, 0.081 mmol) at 0 °C ,and stirring was continued for 30 min. NBS (14 mg, 0.081 mmol) was added again, and the stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with Et_2O and washed with saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (96:4 v/v) to give (±)-**26** (11.6 mg, 67%) as colorless needles: mp 74−75 °C (hexane−AcOEt): IR ($CHCl_3$) 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, s), 1.27 (3H, s), 1.25−1.42 (2H, m), 1.64−1.88 (3H, m), 1.89−2.00 (2H, m), 2.05−2.23 (2H, m), 3.70 (1H, d, J = 1.2 Hz), 4.01 (1H, dd, J = 2.7 and 8.7 Hz), 4.25 (1H, dd, J = 1.5 and 8.7 Hz), 4.49 (1H, d, J = 4.5 Hz), 4.62 (1H, s), 5.02 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 18.3, 24.2, 27.6, 27.9, 31.6, 40.4, 45.0, 55.7, 67.0, 68.0, 73.2, 80.6, 103.6, 153.3; MS m/z 312 (M^+); HRMS calcd for $C_{15}H_{21}O_2Br$ 312.0724, found 312.0724.

(±)-(1S*,2S*,5R*,7S*,8S*,9S*,14R*)-8-Bromo-14,14-(epoxymethano)-2,9-dimethyl-6,10-dioxatetracyclo[7.2.2.0^{1,7}.0^{2,5}]tetradecane (27). To a stirred solution of (±)-**26** (11.6 mg, 0.0370 mmol) in CH_2Cl_2 (2 mL) were added $NaHCO_3$ (80 mg, 0.96 mmol) and *m*-CPBA (40 mg, 80% active, 0.185 mmol) at room temperature, and the stirring was continued for 16 h at the same temperature. The reaction mixture was quenched with 10% $Na_2S_2O_3$ (5 mL) and extracted with Et_2O. The combined extracts were washed with saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (95:5 v/v) to give (±)-**27** (8.9 mg, 73%) as colorless prisms: mp 62−63 °C (hexane−AcOEt); IR ($CHCl_3$) 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.69 (3H, s), 1.29 (3H, s), 1.47−1.64 (2H, m), 1.68−1.82 (1H, m), 1.86−2.14 (4H, m), 2.23 (1H, dd, J = 10.2 and 13.8 Hz), 2.85 (1H, d, J = 3.9 Hz), 3.18 (1H, d, J = 3.9 Hz), 3.68 (1H, dd, J = 2.4 and 9.3 Hz), 3.71 (1H, dd, J = 2.4 and 9.3 Hz), 3.87 (1H, d, J = 4.5 Hz), 3.99 (1H, dd, J = 2.4 and 8.7 Hz), 4.29 (1H, dd, J = 1.8 and 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 18.9, 24.4, 26.4, 28.0, 30.8, 40.7, 42.6, 48.8, 55.1, 65.8, 66.8, 68.1, 73.7, 80.9; MS m/z 328 (M^+); HRMS calcd for $C_{15}H_{21}O_3Br$ 328.0673, found 328.0668.

(±)-4-Deoxyverrucarol (2). To a stirred solution of (±)-**27** (4.2 mg, 0.013 mmol) in THF (5 mL) and EtOH (1 mL) were added Zn powder (100 mg, 1.5 mmol) and NH_4Cl (70 mg, 1.3 mmol), and the mixture was heated at 60 °C for 9 h with vigorous stirring. The reaction mixture was cooled, diluted with Et_2O, and filtered through Celite. The filtrate was concentrated under reduced pressure. The residue upon evaporation was chromatographed on silica gel with hexane−AcOEt (90:10 v/v) to give (±)-4-deoxyverrucarol (**2**) (2.7 mg, 85%) as colorless prisms: mp 111−112 °C (hexane−AcOEt); IR ($CHCl_3$) 3450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, s), 1.20−1.32 (1H, m), 1.57−1.72 (1H, m), 1.73 (3H, s), 1.74−2.13 (6H, m), 2.24 (1H, ddd, J = 4.2, 9.3, and 13.8 Hz), 2.90 (1H, d, J = 3.9 Hz), 3.17 (1H, d, J = 3.9 Hz), 3.49 (1H, d, J = 12.0 Hz), 3.64−3.76 (3H, m), 5.41−5.48 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 20.7, 23.3, 26.2, 28.6, 32.0, 44.1, 45.3, 49.5, 63.0, 66.5, 66.9, 80.1, 119.5, 141.1; MS m/z 250 (M^+). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.77; H, 8.88.

(+)-(*S*)-1-[1-Hydroxy-1-(1-hydroxycyclopropyl)ethyl]-1-(methoxymethoxy)methyl-4-cyclohexanone Ethylene Acetal (17). To a well stirred solution of **15** (154 mg, 0.545 mmol), $(DHQ)_2PYR$ (24 mg, 0.027 mmol), $K_3Fe(CN)_6$ (0.53 g, 1.6 mmol), K_2CO_3 (0.22 g, 1.6 mmol), and $MeSO_2NH_2$ (0.15 g, 1.6 mmol) in *t*-BuOH−water (1:1 v/v; 6 mL) was added OsO_4 (aqueous 2% w/v, 0.07 mL, 0.005 mmol) at 0 °C, and stirring was continued for 8 h at the same temperature. To the reaction mixture was added 10% $Na_2S_2O_3$ (15 mL), and the stirring was continued for 1 h. The reaction mixture was extracted with AcOEt, and the combined extracts were washed with 10% NaOH and saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (70:30 v/v) to give (+)-**17** (137 mg, 79%) as a colorless oil: $[\alpha]^{24}_D$ +9.92 (*c* 2.24, $CHCl_3$). Spectral data were consistent with those of the corresponding racemate.

(+)-(*R*)-1-(Methoxymethoxy)methyl-1-(1-methyl-2-oxocyclobutyl)-4-cyclohexanone Ethylene Acetal (18). To a stirred solution of (+)-**17** (310 mg, 0.980 mmol) and imidazole (0.68 g, 10 mmol) in CH_2Cl_2 (20 mL) was added SO_2Cl_2 (0.15 mL, 2.0 mmol) at 0 °C, and the stirring was continued for 20 min at the same temperature. Florisil (4.4 g) was added at −78 °C, and the mixture was stirred for 1.5 h at the same temperature. The temperature was raised to −40 °C ,and the stirring was continued for 12 h. The reaction mixture was warmed to room temperature and further stirred for 4.5 h. The resulting mixture was quenched with MeOH (0.5 mL) and Et_3N (0.5 mL) and filtered through Florisil. The filtrate was

evaporated under reduced pressure. The residue was chromatographed on silica gel with hexane−AcOEt (85:15 v/v) to give (+)-**18** (216 mg, 73% ee, 74%) as a colorless oil: $[\alpha]^{24}_D$ +19.5 (*c* 1.36, $CHCl_3$). Spectral data were consistent with those of the corresponding racemate.

(−)-(1*R*,2*R*)-1-Benzoyloxy-2-{8-(methoxymethoxy)methyl-1,4-dioxaspiro[4.5]dec-8-yl}-2-methylcyclobutane (29). To a stirred solution of (+)-**18** (56.1 mg, 0.188 mmol) in MeOH (4 mL) was added $NaBH_4$ (50 mg, 1.3 mmol), and the stirring was continued for 1 h. Addition of the same amount of $NaBH_4$ and the same treatment was further repeated twice. The solvent was evaporated before addition of water. The mixture was extracted with AcOEt, and the extract was washed with saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (85:15 v/v) to give (−)-**28** (49.4 mg, 87%) as a colorless oil: $[\alpha]^{26}_D$ −2.53 (*c* 1.35, $CHCl_3$); IR (neat) 3430 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, s), 1.24−1.36 (1H, m), 1.37−1.80 (7H, m), 1.81−1.98 (1H, m), 2.10−2.34 (3H, m), 3.40 (3H, s), 3.56 (1H, d, J = 9.9 Hz), 3.83 (1H, d, J = 9.9 Hz), 3.91−3.98 (4H, m), 4.47 (2H, d, J = 2.7 Hz), 4.68 (2H, s); MS *m*/*z* 272 (M^+); HRMS calcd for $C_{16}H_{28}O_5$ 272.1624, found 272.1645.

To a stirred solution of (−)-**28** (13.1 mg, 0.0436 mmol), Et_3N (0.60 mL, 4.3 mmol), and DMAP (15 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) was added benzoyl chloride (0.10 mL, 0.86 mmol), and the reaction mixture was refluxed for 33 h. To the mixture was added 10% NaOH at 0 °C, and the resulting mixture was extracted with Et_2O. The extract was washed with 10% HCl, saturated $NaHCO_3$, and saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (90:10 v/v) to give (−)-**29** (16.8 mg, 95%) as colorless prisms: mp 88−89 °C (petroleum ether); $[\alpha]^{24}_D$ −15.3 (*c* 1.68, $CHCl_3$); IR (neat) 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, s), 1.38−1.51 (1H, m), 1.58−1.78 (4H, m), 1.79−2.02 (4H, m), 2.06−2.21 (1H, m), 2.39−2.52 (2H, m), 3.27 (3H, s), 3.58 (1H, d, J = 10.2 Hz), 3.64 (1H, d, J = 10.2 Hz), 3.84−3.98 (4H, m), 4.51 (2H, s), 5.23 (1H, t, J = 6.0 Hz), 7.45 (2H, t, J = 7.5 Hz), 7.56 (1H, tt, J = 1.5 and 7.5 Hz), 8.20 (2H, dd, J = 1.5 and 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 25.8, 25.9, 26.1, 26.5, 30.9, 39.4, 51.0, 55.4, 64.1, 64.2, 68.6, 79.3, 97.0, 108.9, 128.4, 130.2, 130.8, 132.9, 166.4; MS *m*/*z* 404 (M^+). Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.94. Found 68.31; H, 7.86.

The benzoate was applied on HPLC equipped with CHIRALCEL OJ (hexane−*i*-PrOH 9:1 v/v, 0.5 mL/min). The enantiomeric excess was determined as 73% ee from the chromatogram; t_R of (−)-**29**,17 min; t_R of (+)-**29**, 22 min.

(−)-(1*S*,2*R*)-2-{8-(Methoxymethoxy)methyl-1,4-dioxaspiro[4.5]dec-8-yl}-2-methyl-1-vinylcyclobutanol (19). To a stirred suspension of $CeCl_3$ (1.5 g, 6.0 mmol) in THF (50 mL) was added a solution of vinylmagnesium bromide (19 mL, 0.62 M in THF, 12 mmol) at −78 °C. After 1 h of stirring, a solution of (+)-**18** (607 mg, 2.03 mmol) in THF (30 mL) was added dropwise to the reaction mixture at the same temperature, and the temperature was then raised to room temperature in 30 min. The reaction mixture was quenched with saturated NH_4Cl (1 mL), and $MgSO_4$ (1.5 g) was added. The resulting mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with hexane−AcOEt (85:15 v/v) to give (−)-**19** (569 mg, 86%) as a colorless oil: $[\alpha]^{25}_D$ −17.7 (*c* 0.97, $CHCl_3$). Spectral data were consistent with those of the corresponding racemate.

(+)-(*R*)-1-(1-Methyl-2-methylene-3-oxocyclopropyl)-1-(methoxymethoxy)methyl-4-cyclohexanone Ethylene Acetal (20). The following reaction was carried out under Ar. To a stirred solution of (−)-**19** (472 mg, 1.45 mmol) in THF (200 mL) was added $Pd(OAc)_2$ (0.52 g, 2.3 mmol) at room temperature, and the stirring was continued for 8 h at the same temperature. The reaction mixture was passed through a short pad of silica gel with Et_2O as eluant. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel with hexane−AcOEt (90:10 v/v) to give (+)-**20** (386 mg, 82%) as a colorless oil.

(+)-**20** was applied on HPLC equipped with CHIRALCEL OJ (hexane−*i*-PrOH 9:1 v/v, 0.5 mL/min). The enantiomeric excess was calculated as 73% ee from the chromatogram; t_R of (+)-**20**, 37 min; t_R of (−)-**20**, 46 min.

(+)-1-(3-Hydroxy-1-methyl-2-methylenecyclopentyl)-1-(methoxymethoxy)methyl-4-cyclohexanone (21). To a stirred solution of (+)-**20** (390 mg, 1.20 mmol) in THF (30 mL) was added a solution of DIBALH (3.8 mL, 0.94 M in hexane, 3.6 mmol) dropwise at −78 °C, and the stirring was continued for 1.5 h at the same temperature. The reaction mixture was quenched with MeOH (4 mL), and the temperature was raised to room temperature. To the mixture was added 10% HCl (10 mL), and the stirring was continued for 2.5 h at the same temperature. The resulting mixture was quenched with 10% NaOH (20 mL) and extracted with AcOEt. The combined extracts were washed with saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (60:40 v/v) to give (+)-**21** (*cis*:*trans* = 84:16, 294 mg, 87%) as a colorless oil: $[\alpha]^{25}_D$ +8.09 (*c* 1.11, $CHCl_3$). Spectral data were consistent with those of the corresponding racemate.

(−)-(1*R*,3*S*)-3-[1-(Methoxymethoxy)methyl-4-oxocyclohexyl]-3-methyl-2-methylene-1-trimethylsilyloxycyclopentane (30). To a stirred solution of (+)-**21** (294 mg, 1.04 mmol) and imidazole (0.35 g, 5.2 mmol) in DMF (10 mL) was added TMSCl (0.27 mL, 2.1 mmol) at 0 °C ,and the stirring was continued for 15 min at the same temperature. Saturated $NaHCO_3$ was added, and the mixture was extracted with Et_2O. The extract was washed with saturated NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt−NEt_3 (96:1:3 v/v) to give (−)-**30** (291 mg, 79%) as a colorless oil: $[\alpha]^{26}_D$ −6.87 (*c* 1.28, DME); IR (neat) 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.16 (9H, s), 1.09 (3H, s), 1.20−1.30 (1H, m), 1.42−1.63 (2H, m), 1.77−2.02 (4H, m), 2.26−2.43 (2H, m), 2.52 (1H, ddd, J = 6.6, 11.4 and 16.2 Hz), 3.19 (3H, s), 3.60 (1H, d, J = 10.5 Hz), 3.64 (1H, d, J = 10.5 Hz), 4.26 (1H, br d, J = 3.9 Hz), 4.46 (1H, d, J = 6.3 Hz), 4.48 (1H, d, J = 6.3 Hz), 4.94 (1H, s), 5.14 (1H, s); ^{13}C NMR (75 MHz, C_6D_6) δ 0.0, 25.9, 27.8, 28.2, 32.7, 35.0, 37.9, 40.4, 50.4, 55.1, 71.9, 78.6, 97.0, 112.5, 161.1, 210.8; MS *m*/*z* 354 (M^+). Anal. Calcd for $C_{19}H_{34}O_4Si$: C, 64.36; H, 9.67. Found: 64.25; H, 9.57.

(1*R*,3*S*)-3-[(1*S*)-1-(Methoxymethoxy)methyl-4-oxocyclohexyl]-3-methyl-2-methylene-1-trimethylsilyloxycyclopentane (31) and (1*S*,3*R*)-3-[(1*R*)-1-(Methoxymethoxy)methyl-4-oxocyclohexyl]-3-methyl-2-methylene-1-trimethylsilyloxycyclopentane (32). To a stirred solution of (*S*,*S*)-α,α-bis(phenylethyl)amine (0.37 g, 1.4 mmol) in THF (30 mL) was added BuLi (0.91 mL, 1.5 M in hexane, 0.91 mmol) at −98 °C, and the stirred reaction mixture was warmed to room temperature and recooled to −98 °C. TMSCl (0.91 mL, 7.2 mmol) and a solution of (−)-**30** (128 mg, 0.361 mmol) in THF (2 mL) were added to the mixture at the same temperature. After 30 min of stirring, Et_3N (4 mL) and then saturated $NaHCO_3$ were added. The mixture was warmed to room temperature and extracted with hexane. The extract was washed with saturated NaCl. The residue upon workup was chromatographed on Florisil with hexanes−Et_2O (98:2 v/v) to give crude silyl enol ether. The enol ether was immediately dissolved in MeCN (30 mL), and $Pd(OAc)_2$ (0.12 g, 0.54 mmol) was added. The mixture was stirred for 9 h under Ar. The solvent was evaporated, and the resulting residue was chromatographed on silica gel with hexane−AcOEt−NEt_3 (94:3:3 v/v) to give an inseparable mixture of **31** and **32** (66:34, 112 mg, 88%) as a colorless oil: $[\alpha]^{26}_D$ +30.0 (*c* 1.12, DME); IR (neat) 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.11 (9H, s), 1.14 (1.98H, s), 1.18 (1.02H, s), 1.38−1.48 (1H, m), 1.57−1.65 (2H, m), 2.08−2.31 (3H, m), 2.34−2.53 (1H, m), 2.58−2.86 (1H, m), 3.32 (1.98H, s), 3.35 (1.02H, s), 3.65 (0.66H, d, J = 10.2 Hz), 3.69 (0.34H, d, J = 10.2 Hz), 3.73 (0.34H, d, J = 10.2 Hz), 3.80 (0.66H, d, J = 10.2 Hz), 4.33−4.36 (0.66H, m), 4.36−4.40 (0.34H, m), 4.53−4.63 (2H, m), 4.62 (0.34H, s), 5.03 (0.34H, s), 5.10 (0.66H, s), 5.21 (0.66H, s), 5.23 (0.34H, s); 6.07 (0.66H, d, J = 10.2 Hz), 6.08 (0.34H, d, J = 10.2 Hz), 6.96 (0.66H, dd, J = 2.1 and 10.2 Hz), 7.02 (0.34H, d, J = 10.2 Hz); MS *m*/*z* 352 (M^+); HRMS calcd for $C_{19}H_{32}O_4Si$ 352.2068, found 352.2065.

(−)-(2*R*,5*S*,6*R*,11*R*)-15-Hydroxytrichothec-9,12-diene (25). To a stirred solution of the mixture of **31** and **32** (96.0 mg, 0.272 mmol) in THF (12 mL) was added MeLi (1.0 mL, 1.0 M in Et_2O, 1.0 mmol) at −78 °C, and the stirring was continued for 30 min. A 50% solution of HF (0.60 mL, 15 mmol) was slowly added to the reaction mixture, and the temperature was raised to room temperature. The mixture was stirred for 48 h at the same temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (97:3 v/v) to give (−)-**25** (31.0 mg, 98% ee, 49%) as a colorless solid, which was recrystallized from petroleum ether−AcOEt to give colorless prisms, mp 103−104 °C: $[\alpha]^{25}_D$ −147 (*c* 0.42, $CHCl_3$) [lit.[4i] (+)-**25** (45% ee), oil, $[\alpha]_D$ +33 (*c* 0.3, $CHCl_3$)]. Spectral data were consistent with those of the racemate.

(−)-(2*R*,5*S*,6*R*,11*R*)-15-(3,5-Dinitrobenzoyl)oxytrichothec-9,12-diene (33). To a stirred mixture of (−)-**25** (2.7 mg, 0.012 mmol), Et_3N (0.050 mL, 0.36 mmol), and DMAP (5 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) was added 3,5-dinitrobenzoyl chloride (15 mg, 0.065 mmol) at room temperature, and the stirring was continued for 30 min at the same temperature. After addition of 10% HCl, the mixture was extracted with Et_2O. The extract was washed with saturated $NaHCO_3$. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (95:5 v/v) to give (−)-**33** (4.9 mg, 95%) as a colorless oil: $[\alpha]^{25}_D$ −136 (*c* 0.26, $CHCl_3$); IR ($CHCl_3$) 1710, 1540, 1320 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, s), 1.46−1.55 (3H, m), 1.70 (3H, s), 1.75−2.15 (4H, m), 2.25 (1H, ddd, J = 4.8, 9.0, and 13.8 Hz), 3.84 (1H, d, J = 4.8 Hz), 4.30 (1H, d, J = 12.0 Hz), 4.37 (1H, d, J = 4.2 Hz), 4.47 (1H, d, J = 12.0 Hz), 4.73 (1H, s), 5.06 (1H, s), 5.47 (1H, br d, J = 5.1 Hz), 9.12 (2H, br s), 9.25 (1H, br s); MS *m*/*z* 428 (M^+); HRMS calcd for $C_{22}H_{24}N_2O_7$ 428.1582, found 428.1582.

(−)-**33** was subjected to HPLC equipped with CHIRALCEL OJ (hexanes−EtOH 7:3 v/v, 1.0 mL/min). The chromatogram showed >99% ee; t_R of (−)-**33**, 17 min; t_R of (+)-**33**, 36 min.

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Supporting Information Available: ^1H NMR spectra (300 MHz) for compounds, **2**, **11**, **12**, **14**−**17**, **19**, **21**−**28**, **31** + **32**, and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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