Total Synthesis of (−)-Verrucarol[1]

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We have achieved the total synthesis of (−)-verrucarol, a trichothecene sesquiterpenoid obtained as a hydrolysis product of the naturally occurring verrucarin A. Our total synthesis began with the previously reported enantiomerically pure bicyclic α-methylated γ-lactone, which was prepared from D-glucose. The key steps for the total synthesis were (1) aldol-like carbon−carbon bond formation applied to the starting lactone using a four-carbon aldehyde as an electrophile for introduction of the quaternary stereogenic carbon sharing the B and C-rings of the trichothecene skeleton, (2) Dieckmann cyclization of the derived ϵ-ester lactone for construction of the C-ring equivalent, (3) Barton's decarboxylative oxygenation for conversion of a carboxylic acid functionality in the Dieckmann cyclization product into a hydroxyl group, (4) skeletal enlargement strategy for the crucial trichothecene skeleton construction, and (5) the final stereoselective formation of the *exo*-epoxy ring at the methylene carbon in the bridge constituting the B and C-rings.

Introduction

The trichothecenes are a family of structurally related sesquiterpenoids isolated from various species of fungi.[3−8] The biogenetical origin of these sesquiterpenes is assumed to be *trans,cis*-farnesol, which is transformed into a bisabolane, then into a cuparane nucleus, and finally into a trichothecane skeleton.[9,10] Since the isolation of trichothecin (**1**) (Figure 1), the first natural product of the trichothecenes, by Freeman and Morrison in 1948 from the fungus *Trichothecium roseum*,[11,12] numerous trichothecenes have been isolated from various sources. A large number of the trichothecenes comprise a common 2-oxatricyclo[7.2.1.0^{3,8}]dodec-4-ene core structure (the A/B/C-ring system) represented by **1**, trichodermin (**2**), and its alkaline hydrolysis product trichodermol (roridin C) (**3**).[13,14] However, some trichothecenes lacking this tricyclic framework such as trichodiene (**4**), the biogenetic precursor of the trichothecenes, were found in nature.[15,16] In some cases, the hydroxyl group(s) in the core tricyclic framework are esterified or macrolactonized.[4,6,8,17,18] In general, the trichothecenes possess an *exo*-epoxy ring at the methylene bridge constituting the B- and C-rings. Other naturally occurring representative trichothecenes, calonectrin (**5**),[19] anguidine (diacetoxyscirpenol) (**6**),[20,21]

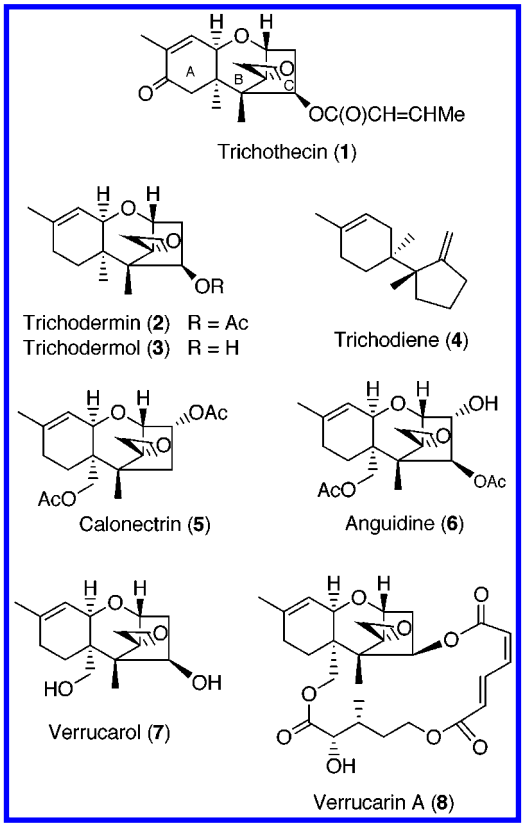

Figure 1.

(1) This paper is dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.
(2) Present address: Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo Japan.
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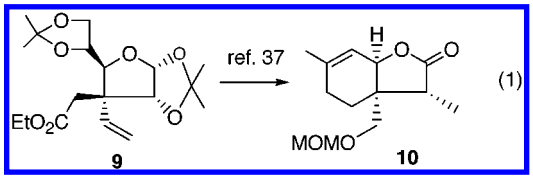
and verrucarol (**7**),[22] are shown in Figure 1, and these natural products differ from each other in the oxidation levels and/or positions of the substituents in the C-ring. In addition to these structural characteristics, many of the trichothecenes exhibit significant biological activities such as antifungal, antibacterial, antiviral, antitumor, and insecticidal properties.[5,7] The biological importance and structural uniqueness of the trichothecenes have rendered these sesquiterpenoids attractive and challenging synthetic targets for 30 years.[23] Total syntheses of **2**,[24] **3**,[25] and **4**[26] were achieved early in the history of the trichothecene synthesis. In the early 1980s, total (formal) syntheses of more oxygenated trichothecenes such as **5**,[27] **6**,[28] and **7**[29] were accomplished. A number of synthetic efforts for the trichothecene family have been also disclosed so far.[30] Most of the previous total syntheses and synthetic efforts of the trichothecene family were carried out in racemic forms; however, a few enantioselective approaches were also explored.[31] Furthermore, some synthetic routes to the tether parts (the macrodilactone part) of the macrocyclic trichothecenes were also investigated.[32] We describe herein our total synthesis of the naturally derived (−)-verrucarol (**7**) in detail.[33] The target compound **7** was isolated as an alkaline hydrolysis product of the macrocyclic trichothecene, varrucarrin A (**8**), by Tamm and co-workers in 1962.[34,35] The structure of **8** was determined on the basis of spectroscopic analysis, and its absolute stereochemistry (thence that of **7**) was later confirmed by X-ray crystallography of the *p*-iodobenzenesulfonate ester of **8**.[36] The enantioselective total synthesis of **7** has not been reported hitherto.

Our total synthesis of **7** started with the previously reported enantiomerically pure α-methylated bicyclic γ-lactone **10**,[37] which was prepared from the highly functionalized tetrahydrofuran derivative **9** (eq 1).[38−40]



Our retrosynthetic analysis for **7** from **10** is illustrated in Scheme 1. In the later stage of the total synthesis, the *exo*-epoxide part in **7** would be introduced via the hydroxyl-directed stereoselective epoxidation of a partially protected trichothecene **A**. The *exo*-methylene derivative **A** could be obtained by methylenation of a tricyclic ketone **B**. For construction of the trichothecene skeleton consisting in **B**, we envisaged the base-mediated ring-enlargement strategy applied to a 6,5,5-membered intermediate **C**, which possesses a leaving group (X such as a mesyloxy) and a vicinal hemiketal hydroxyl group.

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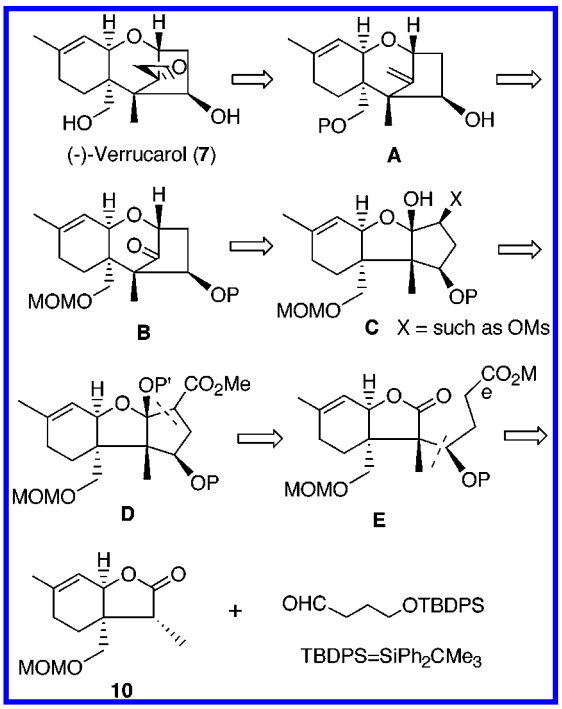
(37) Ishihara, J.; Nonaka, R.; Terasawa, Y.; Tadano, K.; Ogawa, S.*Tetrahedron: Asymmetry* **1994**, *5*, 2217.
(38) The starting compound **10** was prepared from **9** in overall yields of 10−15% in 19 steps. Compound **9**[39] was prepared from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose ("diacetone glucose") in an overall yield of 38% in four steps.
(39) Tadano, K.; Idogaki, Y.; Yamada, H.; Suami, T. *J. Org. Chem*. **1987**, *52*, 1201.
(40) The utility of **9** as an enantiomerically pure starting material for natural products synthesis, see: Takao, K.; Ochiai, H.; Yoshida, K.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *J. Org. Chem*. **1995**, *60*, 8179, and references therein.

Scheme 1

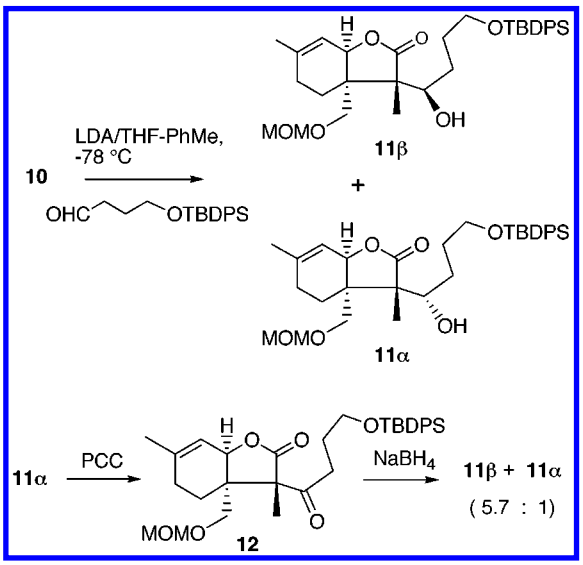


A similar skeletal rearrangement protocol was initially disclosed by Trost and McDougal in their racemic verrucarol synthesis.[29d] For the preparation of the tricyclic intermediate **C**, we expected that the Barton methodology[41] could be workable for a cyclopentyl carboxylic ester **D** (a synthetic equivalent to the C-ring). Namely, transformation of the ester functionality in **D** by means of the radically induced decarboxylative oxygenation would provide a hydroxyl group, which in turn is convertible to a leaving group. This intermediate **D** could be prepared by the Dieckmann cyclization of a bicyclic lactone **E** carrying a four-carbon γ-hydroxy ester tether. The intermediate **E** might be obtained via the aldol reaction of the starting compound **10** coupled with a protected 4-hydroxybutanal, which follows by functionalization of the introduced side chain.

Results and Discussion

We had previously found that the alkylation of **10** with allyl bromide proceeded with complete stereoselectivity, affording a single alkylation product in which the allyl group is disposed at the less sterically congested α-side.[37] Being encouraged by this observation, we executed the aldol-like reaction of the enolate generated from **10** with 4-(*tert*-butyldiphenylsilyloxy)butanal.[42] The introduction of the four-carbon side chain at the α-carbon of the γ-lactone **10** was best achieved by deprotonation with lithium diisopropylamide (LDA) at −78 °C in a mixture of THF and toluene (v/v, 5:7) followed by addition of the aldehyde. As a result, two aldol adducts, **11**β (50% yield) and **11**α (50%), were obtained after separation on silica gel (Scheme 2). The stereochemistry of the newly introduced contiguous stereocenters in **11**β and **11**α could not be determined unambiguously at this stage by ^{1}H NMR analysis. However, the stereochemistry was established

Scheme 2



as depicted at a later stage. Both adducts were diastereomers relative to the stereogenic carbinol carbon in each side chain. As anticipated, the aldehyde attacked exclusively from the less sterically congested convex-face of the enolate generated from **10**. Discouragingly, we could not improve the stereoselectivity in the formation of the desired **11**β after extensive examinations using a variety of bases and solvents. Lithium or potassium bis(trimethylsilyl)amide (LiHMDS or KHMDS) did not give any aldol adducts. Addition of HMPA to the LDA-mediated conditions (HMPA:THF = 1:10) did not effect the reaction and **10** was recovered intact. We expected the stereochemical bias in this aldol-like carbon−carbon bond formation, which may arise from the chelation-controlled transition state between the enolate oxygen and the aldehyde carbonyl or between the aldehyde carbonyl and one of the (methoxy)methoxy oxygens. These factors may work to some extent for the stereoselective introduction of the stereogenic carbinol center. Meanwhile, we examined the stereochemical inversion of **11**α into **11**β by an oxidation−reduction strategy. To our delight, sodium borohydride reduction of **12**, prepared from **11**α (PCC), afforded a mixture of **11**β and **11**α with predominant formation of the desired former (74% yield of **11**β and 13% of **11**α).

Next, our synthetic effort was directed to the construction of the C-ring equivalent via the Dieckmann cyclization of ester−lactone such as **17** (**E** in Scheme 1, P = MOM). Thus, the side chain in the aldol adduct **11**β was modified as follows (Scheme 3). Desilylation of **11**β with tetrabutylammonium fluoride (TBAF) (81%) followed by selective acylation of the resulting diol **13** with pivaloyl chloride (PivCl) provided mono ester **14** (87%). The secondary hydroxyl group in **14** was protected as the methoxymethyl (MOM) ether, giving **15** (83%). On the other hand, *O*-alkylation of **11**β with MOMCl proceeded quite slowly, and the corresponding MOM ether was obtained less effectively. Deacylation of **15** and successive Jones' oxidation of the primary hydroxyl group in the resulting **16** afforded carboxylic acid, which immediately was esterified with CH_2N_2 to give the substrate **17** for the Dieckmann cyclization (72%). As we had experienced in our previous model studies,[37] potassium bis(trimethylsilyl)amide (KHMDS) was the best base of choice for the Dieckmann cyclization. In the presence of

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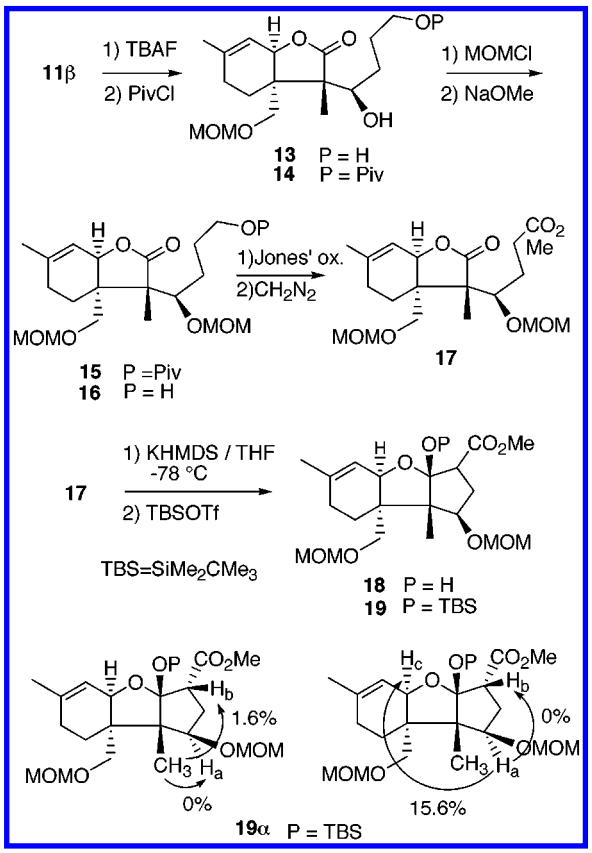
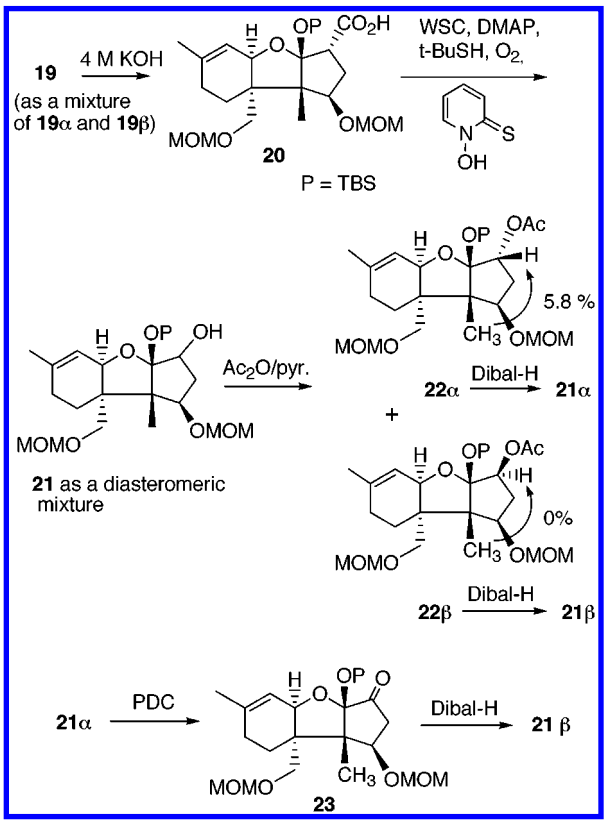
Scheme 3



Scheme 4

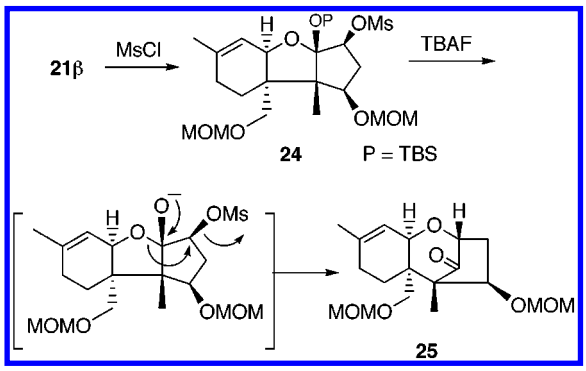


1.5 molar equiv of this base (used as solution in toluene) at −78 °C, the substrate **17** underwent smooth cyclization, and the cyclized product **18** (**D** in Scheme 1, P = MOM, P′ = H) was obtained as a 5:3 inseparable diastereomeric mixture after quenching by a THF solution including camphorsulfonic acid (82%). To avoid the retro-Dieckmann cyclization, the hemiketal hydroxyl groups in the mixture **18** were immediately protected with (*tert*-butyldimethyl)silyl trifluoromethanesulfonate (TBSOTf) to give the TBS ethers **19**α (52%) and **19***β* (29%), which were separated by chromatography on silica gel. The structure of the major isomer **19**α was determined by the ^{1}H NMR spectroscopic analysis including NOE difference experiments as shown in Scheme 3. A NOE (1.6%) was observed between H_b and the angular Me, but no NOEs were observed between the angular methyl and H_a or between H_a and H_b. Furthermore, a significant increase (15.6%) of NOE was observed between H_a and H_c. At this stage, we were able to confirm the stereochemistry of the quaternary carbon and the carbinol carbon in the aldol adduct **11***β*.

We next investigated the conversion of the ester functionality in the Dieckmann cyclization products **19**α,*β* into a hydroxyl group. In our previous studies using a model compound[37] which lacks a hydroxyl group in the C-ring equivalent, we noticed that a Baeyer−Villiger oxidative rearrangement strategy for insertion of an oxygen between the cyclopentyl ring carbon and a methyl ketone side chain did not proceed. Namely, the ester in the Dieckmann cyclization product was straightforwardly converted into a methyl ketone via (1) reduction to an aldehyde, (2) a Grignard addition with MeMgBr, and (3) PCC oxidation. Subjection of the resulting methyl ketone to *m*-chloroperbenzoic acid (*m*-CPBA) resulted in complete recovery of the starting substrate. To overcome this difficulty, we took advantage of Barton−Crich's decarboxylative oxygenation strategy for conversion of the ester functionality into a hydroxyl group.[41,43] Therefore, the diastereomeric mixture of **19** was saponified with aqueous KOH and the carboxylic acid **20** was obtained as a single product (81%) (Scheme 4). That both **19**α and **19***β* afforded the same carboxylic acid **20** was confirmed by the alkaline hydrolysis of each diastereomer. The structure of **20** was not determined unambiguously, but we tentatively assigned it to be the α-anomer as depicted on the basis of the similarity of the ^{1}H NMR spectra of **19**α and **20**. The carboxylic acid **20** was subjected to the decarboxylative oxygenation conditions reported by Barton and co-workers.[41] The initially formed thiohydroxamic ester was decarboxylated to leave a methylene radical on the cyclopentyl ring which was then trapped by a molecular oxygen. Reductive workup in the presence of *t*-BuSH finally provide a hydroxylated product (**21**) as an inseparable diastereomeric mixture. These diastereomers were readily separated as their acetates **22**α (58%) and **22***β* (40%) after acetylation. We first expected that the attack of molecular oxygen on the methylene radical, generated from the thiohydroxamic ester intermediate, occurred favorably from the less sterically congested convex side of the right-half bicyclic ring, providing **21***β* stereoselectively. However, no specified stereoselectivity was observed in the present case. The structural determination of **22**α and **22***β* was achieved on the basis of the ^{1}H NMR spectral analysis, including

(43) Some recent applications of the Barton's radically induced decarboxylation for natural products synthesis: Corey, E. J.; Hong, B.-c. *J. Am. Chem. Soc.* **1994**, *116*, 3149; Hatakeyama, S.; Kawamura, M.; Takano, S. *J. Am. Chem. Soc.* **1994**, *116*, 4081; Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 6120; Trost, B. M.; Higuchi, R. I. *J. Am. Chem. Soc.* **1996**, *118*, 10094. Stamos, D. P.; Chen, S. S.; Kishi, Y. *J. Org. Chem.* **1997**, *62*, 7552.

Scheme 5



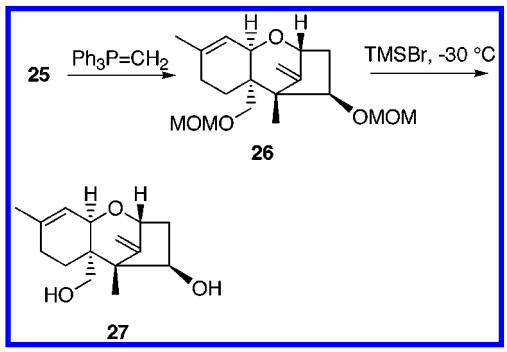
NOE experiments. As shown in Scheme 4, significant signal enhancement was observed at the ring proton bearing the acetoxyl group in **22**α when the angular methyl was irradiated. This phenomenon was not observed in the case of **22***β*. At a later stage, we recognized that the isomer **21***β* was solely effective for the crucial ring enlargement. Therefore, we looked into the stereochemical conversion of **21**α into **21***β*. Fortunately, oxidation of **21**α, prepared from **22**α by Dibal-H reduction, with PDC and successive reduction of the resulting ketone **23** with Dibal-H provided **21***β* almost exclusively (>20:1, 68%). The ^{1}H NMR analysis of the reduction mixture revealed the predominant formation of **21***β*, and a trace amount of **21**α could be removed after acetylation. The fact that the hydride delivery to **23** occurred from the (seemingly) more hindered α-side can be explained by the neighboring bulky (*tert*-butyldimethylsilyl)oxy group effectively shielding the *β*-side from the attack of the hydride.

The key skeletal rearrangement for the construction of the trichothecene framework was next investigated. The hydroxyl group in **21***β* was mesylated to introduce a leaving group (99%) (Scheme 5). The mesylate **24** was treated with TBAF for desilylation. The expected ring enlargement occurred simultaneously with removal of the mesyloxy group as depicted. The desired trichothecene skeleton was constructed to afford **25** in a yield of 97%. The stereochemistry of the methine carbon bearing the mesyloxy group was crucial for this smooth ring enlargement. We examined similar ring enlargement for the α-mesylate prepared from **21**α, which did not give any skeletal rearrangement product.

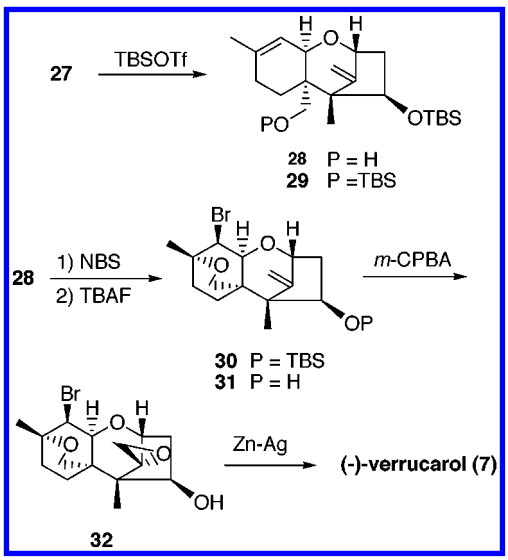
The final stage of the total synthesis was stereoselective introduction of the *exo*-epoxy group at the carbonyl carbon in **25**. It was apparent from the previous total syntheses[29] that the aimed stereoselective epoxidation of the *exo*-methylene group in **26**, prepared by usual Wittig methylenation (73%), was only possible when the hydroxyl group in the C-ring was unprotected (Scheme 6). Thus, the MOM groups in **26** were deprotected with bromotrimethylsilane at −30 °C. The resulting diol **27** (78%) was the naturally derived trichothecene known to be 12,13-deoxyverrucarol, which was isolated by Breitenstein and Tamm as an alkaline hydrolysis product of the antibiotic verrucarin K.[44] The spectral data of the synthetic **27** were in good accordance with those of the naturally derived product, including the sign and magnitude of the optical rotations. Thus, our present work confirmed the absolute stereochemistry of natural (−)-12,13-deoxyverrucarol (**27**) as depicted.

(44) Breitenstein, W.; Tamm, Ch. *Helv. Chim. Acta* **1977**, *60*, 1522.

Scheme 6



Scheme 7



The conversion of **27** into (−)-verrucarol (**7**) was as follows. To avoid undesired epoxidation of the A-ring carbon−carbon double bond, the protection of the primary hydroxyl group in **27** was required. Intramolecular bromoetherification of the diol **27** with *N*-bromosuccinimide (NBS) in acetone afforded the bromo ether **31** (58%).[29a,g] On the other hand, we examined the regioselective silylation of the primary hydroxyl in **27** with TBSOTf. As a result, mono-*O*-silyl derivative **28** (40%) and di-*O*-silyl derivative **29** (39%) were obtained without significant selectivity. Contrary to our expectation, the primary hydroxyl group was difficult to protect preferentially. Compound **28** was subjected to the intramolecular bromo ether formation conditions, giving **30**, which was then desilylated to give **31** (96% yield). *m*-CPBA epoxidation of **31** gave **32** stereoselectively (91%).[29a,g] Finally, reduction of **32** with a zinc−silver couple[45] in EtOH provided (−)-verrucarol **7** (81%) (Scheme 7).[29e] The comparison of properties (mp, TLC, ^{1}H, ^{13}C NMR, and IR) of the synthetic **7** with those of a natural specimen verified its identity.

In summary, the total synthesis of (−)-verrucarol, which was derived from the naturally occurring verrucarin A, was accomplished. Our enantioselective total synthesis commenced with the enantiomerically pure bicyclic α-methylated *γ*-lactone, which had been prepared from D-glucose. The key steps for the total synthesis were (1) the aldol-like four-carbon side chain elongation at the

(45) Denis, J. M.; Girard, C.; Conia, J. M. *Synthesis* **1972**, 549. Tokoroyama, T.; Matsuo, K.; Kanazawa, R. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3383.

α-carbon of the starting lactone, (2) Dieckmann cyclization for the construction of the C-ring equivalent, (3) the Barton's decarboxylative oxygenation for conversion of a carboxylic functionality in the cyclization product into a hydroxyl group, (4) the skeletal enlargement for the trichothecene skeleton construction, and (5) the final stereoselective *exo*-epoxy formation.

Experimental Section

Melting points are uncorrected. Specific rotations were measured in a 10 mm cell. ^{1}H NMR spectra were recorded at 270 or 400 MHz in $CDCl_3$ solution with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 67.5 MHz, 75 Hz, or 100 MHz in $CDCl_3$ solution. Thin-layer chromatography (TLC) was performed with a glass plate coated with Kieselgel 60 GF_{254} (Merck). The crude reaction mixtures and extractive materials were purified by chromatography on silica gel 60 K070 (Katayama Chemicals). Unless otherwise described, reactions were carried out at ambient temperature. Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed from reaction mixture or combined organic extracts by concentration under reduced pressure using an evaporator with a water bath at 35−45 °C. Solvents were dried (drying reagent in brackets) and distilled prior to use: tetrahydrofuran (THF) [$LiAlH_4$, then Na/benzophenone ketyl], *N*,*N*-dimethylforamide (DMF) [CaH_2], CH_2Cl_2 [CaH_2], benzene [CaH_2], dimethyl sulfoxide (DMSO) [CaH_2], pyridine [NaOH], and toluene [CaH_2].

(1*R*,6*R*,7*S*)-7-[(1*R* and 1*S*)-4-[(*tert*-Butyldiphenylsilyloxy)-1-hydroxybutyl]-3,7-dimethyl-6-(methoxymethoxy)methyl-9-oxabicyclo[4.3.0]non-2-en-8-one (11*β*) and (11α). The reaction was carried out under Ar. To a cold (0 °C) stirred solution of diisopropylamine (2.13 mL, 15.2 mmol) in THF (7 mL) was added *n*-BuLi (1.58 M solution in hexanes, 9.61 mL, 15.2 mmol). The solution was stirred at 0 °C for 1 h and then cooled to −78 °C. To this was added a solution of **10** (730 mg, 3.04 mmol) in a mixture of THF (7 mL) and toluene (14 mL). The resulting solution was stirred at −78 °C for 30 min, then a solution of 4-(*tert*-butyldiphenylsilyl)oxybutanal[42] (8.16 g, 25.0 mmol) in a mixture of THF and toluene (each 10 mL) was added. After 15 min of stirring at −78 °C, the solution was diluted with saturated aqueous NH_4Cl (5 mL) and poured into EtOAc (300 mL). The whole was washed with saturated aqueous NH_4Cl (150 mL) and saturated brine (150 mL × 2). The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15, 1:9, 1:7, then 1:5) to give 860 mg (50%) of **11***β* and 861 mg (50%) of **11**α. **11**α as a colorless oil: TLC, R_f 0.44 (EtOAc/hexane, 1:3); $[\alpha]^{22}_D$ −10.7 (*c* 0.99, $CHCl_3$); IR (neat) 3450, 2960, 1760, 1675 cm^{-1}; ^{1}H NMR (270 MHz) *δ* 1.05 (s, 9 H), 1.13 (s, 3 H), 1.69−1.84 (m, 3 H), 1.92−2.14 (m, 5 H), 1.75 (s, 3 H), 3.36 (s, 3 H), 3.51, 3.97 (ABq, *J* = 9.9 Hz, 1 H × 2), 3.60−3.76, 3.91−4.02 (2 m, 2 H × 2), 4.56, 4.62 (ABq, *J* = 6.6 Hz, 1 H × 2), 4.86 (d, *J* = 4.4 Hz, 1 H), 5.57−5.59 (m, 1 H), 7.32−7.47, 7.60−7.69 (2 m, total 10 H); ^{13}C NMR (100 MHz) *δ* 15.5, 19.1, 23.4, 24.0, 26.7, 29.2, 30.2, 45.5, 55.7, 64.6, 64.9, 75.3, 75.9, 117.5, 127.7, 127.8, 129.8, 132.8, 133.0, 135.6, 141.1, 179.1. **11***β* as a colorless oil: TLC, R_f 0.35 (EtOAc/hexane, 1:3); $[\alpha]^{22}_D$ +3.7 (*c* 1.33, $CHCl_3$); IR (neat) 3450, 2930, 1765, 1675 cm^{-1}; ^{1}H NMR (270 MHz) *δ* 1.04 (s, 9 H), 1.18 (s, 3 H), 1.54−1.71 (m, 1 H), 1.80−2.09 (m, 7 H), 1.77 (s, 3 H), 3.38 (s, 3 H), 3.60, 3.73 (ABq, *J* = 11.0 Hz, 1 H × 2), 3.55−3.77 (m, 3 H), 4.07−4.15 (m, 1 H), 4.51 (d, *J* = 5.1 Hz, 1 H), 4.59, 4.63 (ABq, *J* = 6.6 Hz, 1 H × 2), 5.56−5.64 (m, 1 H), 7.33−7.47, 7.62−7.72 (2 m, total 10 H); ^{13}C NMR (100 MHz) *δ* 11.8, 19.1, 22.9, 23.4, 26.6, 26.8, 29.2, 29.4, 45.6, 56.1, 56.8, 64.0, 65.0, 70.3, 73.8, 76.7, 116.4, 127.6, 129.6, 133.7, 135.5, 135.6, 142.4, 178.9.

PCC Oxidation of 11α and Reduction of the Resulting Ketone 12 with $NaBH_4$. Stereoselective Formation of 11*β*. (1*R*,6*R*,7*S*)-7-[4-(*tert*-Butyldiphenylsilyloxy)-1-oxobutyl]-3,7-dimethyl-6-(methoxymethoxy)methyl-9-oxabicyclo[4.3.0]non-2-en-8-one (12). To a stirred solution of **11**α (359 mg, 0.63 mmol) in CH_2Cl_2 (7 mL) were added molecular sieves (4A powder, 364 mg) and PCC (564 mg, 2.53 mmol). The mixture was stirred for 90 min then silica gel (500 mg) was added. The solvent was removed by concentration, and the residue was transferred to a short silica gel column, which was eluted with excess Et_2O. The ethereal eluate was concentrated to give **12** (358 mg) as a colorless oil, which was used in the next step without further purification. **12**: TLC, R_f 0.53 (EtOAc/hexane, 1:3); IR (neat) 2930, 2860, 1770, 1700 cm^{-1}; ^{1}H NMR (270 MHz) *δ* 1.05 (s, 9 H), 1.46 (s, 3 H), 1.17−2.17 (m, 6 H), 1.75 (s, 3 H), 2.70−2.82 (m, 2 H), 3.26 (s, 3 H), 3.23, 3.43 (ABq, *J* = 9.9 Hz, 1 H × 2), 3.67 (t, *J* = 6.2 Hz, 2 H), 4.41 (s, 2 H), 4.64 (d, *J* = 5.1 Hz, 1 H), 5.58−5.66 (m, 1 H), 7.33−7.48, 7.60−7.69 (2 m, total 10 H).

To a cold (0 °C) stirred solution of **12** (358 mg) in MeOH (7 mL) was added $NaBH_4$ (72 mg, 1.90 mmol). After the mixture was stirred for 2 h, additional $NaBH_4$ (23 mg, 0.61 mmol) was added. The mixture was stirred for an additional 45 min, diluted with saturated aqueous NH_4Cl (5 mL), and extracted with $CHCl_3$ (5 mL × 3). The combined organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:9, 1:7, then 1:5) to give 265 mg (74% for 2 steps) of **11***β* and 46 mg (13%) of **11**α.

(1*R*,6*R*,7*S*)-7-[(1*R*)-1,4-Dihydroxybutyl]-3,7-dimethyl-6-(methoxymethoxy)methyl-9-oxabicyclo[4.3.0]non-2-en-8-one (13). To a cold (0 °C) stirred solution of **11***β* (1.63 g, 2.88 mmol) in THF (20 mL) was added TBAF (1.0 M solution in THF, 3.74 mL, 3.74 mmol). The solution was stirred for 20 min and the solvent was removed by concentration. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:3) to give **13** (0.766 g, 81%) as a colorless oil: TLC, R_f 0.21 (acetone/toluene, 1:3); $[\alpha]^{21}_D$ +2.0 (*c* 0.49, $CHCl_3$); IR (neat) 3450, 2950, 1750, 1675 cm^{-1}; ^{1}H NMR (270 MHz) *δ* 1.20 (s, 3 H), 1.64−2.07 (m, 8 H), 1.78 (s, 3 H), 2.17−2.39 (br, 1 H), 3.40 (s, 3 H), 3.62−3.72 (m, 2 H), 3.64, 3.70 (ABq, *J* = 10.6 Hz, 1 H × 2), 3.80−4.02 (br, 1 H), 4.12−4.16 (m, 1 H), 4.56 (d, *J* = 5.1 Hz, 1 H), 4.63, 4.66 (ABq, *J* = 6.6 Hz, 1 H × 2), 5.61−5.63 (m, 1 H); ^{13}C NMR (75 MHz) *δ* 11.6, 22.9, 23.4, 26.6, 29.5, 29.9, 45.7, 56.2, 56.9, 62.9, 65.1, 70.2, 73.8, 97.0, 116.3, 142.5, 178.7.

(1*R*,6*R*,7*S*)-7-[(1*R*)-1-Hydroxy-4-(pivaloyloxy)butyl]-3,7-dimethyl-6-(methoxymethoxy)methyl-9-oxabicyclo-[4.3.0]non-2-en-8-one (14) . To a cold (0 °C) stirred solution of **13** (1.14 g, 3.46 mmol) in pyridine (15 mL) was added pivaloyl chloride (0.63 mL, 5.19 mmol). The solution was stirred for 70 min, then EtOH (1 mL) was added. This was diluted with H_2O (50 mL). The whole was extracted with $CHCl_3$ (50 mL × 3), and the combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:15) to give **14** (1.24 g, 87%) as a colorless oil: TLC, R_f 0.58 (acetone/toluene, 1:3); $[\alpha]^{23}_D$ +4.0 (*c* 0.83, $CHCl_3$); IR (neat) 3475, 2930, 1765, 1730, 1680 cm^{-1}; ^{1}H NMR (270 MHz) *δ* 1.19 (s, 3 H), 1.19 (s, 9 H), 1.55−2.09 (m, 8 H), 1.77 (s, 3 H), 3.40 (s, 3 H), 3.54 (dd, *J* = 1.1, 2.6 Hz, 1 H), 3.65, 3.72 (ABq, *J* = 10.6 Hz, 1 H × 2), 4.05−4.16 (m, 3 H), 4.55 (d, *J* = 5.1 Hz, 1 H), 4.62, 4.65 (ABq, *J* = 6.6 Hz, 1 H × 2), 5.61−5.63 (m, 1 H); ^{13}C NMR (75 MHz) *δ* 11.3, 22.9, 23.3, 25.7, 26.6, 27.2, 28.5, 45.7, 56.2, 56.9, 63.9, 65.1, 69.1, 73.6, 97.0, 116.3, 142.5, 178.4, 178.6; HRMS calcd for $C_{22}H_{36}O_7$ (M^+) *m*/*z* 412.2461, found 412.2467.

(1*R*,6*R*,7*S*)-7-[(1*R*)-1-(Methoxymethoxy)-4-(pivaloyloxy)-butyl]-3,7-dimethyl-6-(methoxymethoxy)methyl-9-oxabicyclo[4.3.0]non-2-en-8-one (15). To a cold (0 °C) stirred solution of **14** (1.20 g, 2.90 mmol) in $CHCl_3$ (12 mL) were added diisopropylethylamine (5.05 mL, 29.0 mmol) and MOMCl (1.10 mL, 14.5 mmol). The solution was heated under reflux for 4.5 h and then diluted with 0.2 M HCl solution (50 mL). This was extracted with $CHCl_3$ (40 mL × 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give **15** (1.10 g, 83%) as a colorless oil: TLC, R_f 0.59 (EtOH/toluene, 1:6); $[\alpha]^{23}_D$ +17.1 (*c* 1.09, $CHCl_3$); IR (neat) 2970, 2930, 1760, 1725, 1680 cm^{-1}; ^{1}H NMR (270 MHz) *δ* 1.12 (s, 3 H), 1.20 (s, 9 H), 1.25−1.38 (m, 1 H), 1.58−1.73 (m, 2 H), 1.76 (s, 3 H), 1.85−2.23 (m, 5 H), 3.36 (s, 3 H), 3.38 (s, 3 H), 3.48, 3.83

(ABq, J = 10.3 Hz, 1 H × 2), 3.78 (dd, J = 3.3, 6.2 Hz, 1 H), 4.07 (t, J = 6.2 Hz, 2 H), 4.59 (s, 2 H), 4.60, 4.65 (ABq, J = 6.6 Hz, 1 H × 2), 5.52−5.58 (m, 1 H); ^{13}C NMR (100 MHz) δ 16.6, 23.4, 23.5, 26.4, 27.2, 28.4, 38.7, 45.1, 56.0, 56.1, 56.3, 64.0, 65.2, 75.8, 86.6, 97.0, 116.6, 142.0, 178.4, 181.6.; HRMS calcd for $C_{24}H_{39}O_8$ (M^+ − H) m/z 455.2645, found 455.2633.

(1*R*,6*R*,7*S*)-7-[(1*R*)-4-Hydroxy-1-(methoxymethoxy)butyl]-3,7-dimethyl-6-(methoxymethoxy)methyl-9-oxabicyclo[4.3.0]non-2-en-8-one (16). To a cold (0 °C) stirred solution of **15** (1.08 g, 2.36 mmol) in MeOH (12 mL) was added MeONa (1.0 M solution in MeOH, 4.72 mL, 4.72 mmol). The solution was stirred for 16 h and neutralized with Amberlite IR-120 [H^+]. The resin was removed by filtration and washed well with MeOH. The combined filtrate and washings were concentrated. The residue was purified by column chromatography on silica gel (EtOH/toluene, 1:8) to give **16** (0.88 g, 100%) as a colorless oil: TLC, R_f 0.45 (EtOH/toluene, 1:6); $[\alpha]^{25}_D$ +21.9 (*c* 1.01, $CHCl_3$); IR (neat) 3480, 2930, 2880, 1755, 1675 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.14 (s, 3 H), 1.26−1.37 (m, 1 H), 1.54−2.06 (m, 6 H), 1.76 (s, 3 H), 2.09−2.26 (m, 1 H), 3.37 (s, 3 H), 3.40 (s, 3 H), 3.46, 3.88 (ABq, J = 10.3 Hz, 1 H × 2), 3.66 (td, J = 6.2, 1.5 Hz, 2 H), 3.82 (dd, J = 3.7, 6.2 Hz, 1 H), 4.58−4.68 (m, 5 H), 5.54−5.56 (m, 1 H); ^{13}C NMR (100 MHz) δ 16.6, 23.4, 23.5, 26.4, 27.9, 31.9, 45.2, 56.0, 56.1, 56.4, 62.3, 65.3, 75.8, 86.5, 97.1, 116.6, 142.0, 181.7; HRMS calcd for $C_{19}H_{32}O_7$(M^+) m/z 372.2149, found 372.2182.

(1*R*,6*R*,7*S*)-7-[(1*R*)-3-(Methoxycarbonyl)-1-(methoxymethoxy)propyl]-3,7-dimethyl-6-(methoxymethoxy)methyl-9-oxabicyclo[4.3.0]non-2-en-8-one (17). To a cold (0 °C) stirred solution of **16** (912 mg, 2.46 mmol) in acetone (15 mL) was added Jones reagent (2.67 M solution, 1.38 mL, 3.69 mmol). The solution was stirred at 0 °C for 2 h, and 2-propanol (5 mL) was added and then diluted with H_2O (100 mL). This was extracted with $CHCl_3$ (50 mL × 3). The combined extracts were dried and concentrated. The residue was dissolved in a mixture of $CHCl_3$ (5 mL) and Et_2O (10 mL). At 0 °C with stirring, an ethereal solution of diazomethane was added to the solution until the yellow color persisted. The solution was stirred at 0 °C for 10 min and gradually warmed to ambient temperature. The solvents were removed by concentration. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give **17** (713 mg, 72%) as a colorless oil: TLC, R_f 0.60 (EtOAc/hexane, 1:1); $[\alpha]^{25}_D$ +36.6 (*c* 1.01, $CHCl_3$); IR (neat) 2925, 2850, 1760, 1740, 1680 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.14 (s, 3 H), 1.26−1.37 (m, 1 H), 1.76 (s, 3 H), 1.88−2.06 (m, 4 H), 2.28−2.48, 2.54−2.66 (2m, 2H, 1 H), 3.36 (s, 3 H), 3.40 (s, 3 H), 3.50, 3.86 (ABq, J = 10.6 Hz, 1 H × 2), 3.67 (s, 3 H), 3.76 (dd, J = 2.8, 7.9 Hz, 1 H), 4.57−4.66 (m, 5 H), 5.54−5.56 (m, 1 H); ^{13}C NMR (67.5 MHz) δ 16.7, 23.3, 23.4, 26.3, 26.8, 32.4, 45.2, 56.0, 56.2, 65.0, 75.8, 86.6, 97.0, 97.6, 116.6, 142.0, 173.6, 181.5; HRMS calcd for $C_{20}H_{32}O_8$ (M^+) m/z 400.2097, found 400.2092.

Mixture of (1*R*,3*R*,8*R*,9*S*,10*R*,12*R* and -12*S*)-1-Hydroxy-12-(methoxycarbonyl)-10-(methoxymethoxy)-8-[(methoxymethoxy)methyl]-5,9-dimethyl-2-oxatricyclo[7.3.0.0^{3,8}]-dodec-4-ene (18). The following reaction was carried out under Ar. To a cold (−78 °C) solution of potassium bis(trimethylsilazide) (0.5 M solution in toluene, 5.34 mL, 2.67 mmol) in THF (10 mL) was added a THF (15 mL) solution of **17** (713 mg, 1.78 mmol). The solution was stirred at −78 °C for 15 min and diluted with a THF (5 mL) solution of DL-10-camphorsulfonic acid (1.24 g, 5.34 mmol). The resulting solution was stirred at −78 °C for 5 min and then diluted with saturated aqueous NH_4Cl (300 mL). This was extracted with $CHCl_3$ (150 mL × 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give an inseparable (5:3,^{1}H NMR analysis) diastereomeric mixture of **18** (585 mg, 82%) as a colorless oil: TLC, R_f 0.58 (EtOAc/hexane, 1:1); IR (neat) 3450, 2950, 2925, 2880, 1735, 1675 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.11, 1.73 (2s, each 3H × 4/9), 1.15, 1.72 (2s, each 3H × 5/9), 1.81−2.26, 2.41−2.53 (2m, 5H, 1 H), 2.95 (dd, J = 8.2, 11.9 Hz, 1 H × 4/9), 3.11 (dd, J = 7.7, 9.9 Hz, 1 H × 5/9), 3.35, 3.40 (2s, each 3 H × 4/9), 3.36, 3.38 (2s, each 3 H × 5/9), 3.42−3.49 (m, 2 H), 3.73, 3.74 (2s, 3 H × 4/9, 3 H × 5/9), 3.79 (s, 1 H × 5/9), 3.86 (d, J = 4.8 Hz, 1 H × 5/9), 3.95 (d, J = 4.4 Hz, 1 H × 4/9), 4.06 (dd, J = 6.2, 11.0 Hz, 1 H × 4/9), 4.30 (dd, J = 5.9, 7.7 Hz, 1 H × 5/9), 4.39 (s, 1 H × 4/9), 4.54, 4.58 (ABq, J = 6.6 Hz, each 1 H × 4/9), 4.55, 4.59 (ABq, J = 6.4 Hz, each 1 H × 5/9), 4.66, 4.70 (ABq, J = 6.6 Hz, each 1 H × 5/9), 4.69, 4.74 (ABq, J = 6.6 Hz, each 1 H × 4/9), 5.53−5.55 (m, 1 H); ^{13}C NMR (67.5 MHz) δ 9.8, 10.6, 21.5, 23.4, 23.6, 27.0, 27.1, 31.2, 32.2, 45.4, 45.7, 50.7, 51.3, 51.9, 52.0, 55.2, 55.7, 59.7, 60.4, 66.1, 66.7, 75.0, 76.8, 77.2, 78.0, 78.3, 96.0, 96.4, 96.7, 110.7, 112.6, 118.5, 119.3, 139.4, 140.2, 171.0, 173.1; HRMS calcd for $C_{20}H_{31}O_8$ (M^+ − H) m/z 399.2019, found 399.2002.

(1*S*,3*R*,8*R*,9*S*,10*R*,12*R* and -12*S*)-1-(*tert*-Butyldimethylsilyloxy)-12-(methoxycarbonyl)-10-(methoxymethoxy)-8-[(methoxymethoxy)methyl]-5,9-dimethyl-2-oxatricyclo-[7.3.0.0^{3,8}]dodec-4-ene (19*β* and 19α). The following reaction was best achieved in a 100∼150 mg scale and was carried out under Ar. To a cold (0 °C) solution of the diastereomeric mixture **18** obtained above (109 mg, 0.27 mmol) in CH_2Cl_2 (2 mL) were added 2,6-lutidine (0.25 mL, 2.17 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.25 mL, 1.09 mmol). The mixture was stirred at 0 °C for 1 h, diluted with EtOAc (10 mL), and washed with saturated aqueous $NaHCO_3$ (5 mL) and saturated brine (5 mL × 2). The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to give a diastereomeric mixture **19** (105 mg, 75%). In a separate experiment using 41.5 mg of the mixture **18**, two diasteremers **19**α and **19***β* were obtained in homogeneous form after repeated chromatography on silica gel (EtOAc/hexane, 1:11) in 52% (27.8 mg) and 29% (15.3 mg) yields, respectively. **19**α as a colorless oil: TLC, R_f 0.42 (EtOAc/hexane, 1:5); $[\alpha]^{27}_D$ −62.1 (*c* 1.06, $CHCl_3$); IR (neat) 2950, 2930, 2880, 2850, 1740, 1680 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.04, 0.19 (2s, 3 H × 2), 0.88 (s, 9 H), 1.07 (s, 3 H), 1.69 (s, 3 H), 1.73−2.10 (m, 5 H), 2.38 (ddd, J = 1.4, 6.2, 12.8 Hz, 1 H), 2.96 (d, J = 9.2 Hz, 1 H), 3.34 (s, 3 H), 3.37 (s, 2 H), 3.38 (s, 3 H), 3.66 (s, 3 H), 3.84 (d, J = 4.8 Hz, 1 H), 4.37 (dd, J = 6.2, 11.0 Hz, 1 H), 4.53, 4.56 (ABq, J = 6.6 Hz, 1 H × 2), 4.68, 4.77 (ABq, J = 6.6 Hz, 1 H × 2), 5.40−5.46 (m, 1 H); ^{13}C NMR (67.5 Hz) δ −3.5, −3.1, 11.0, 18.1, 21.1, 23.3, 25.9, 27.1, 32.8, 44.6, 51.1, 54.3, 55.2, 55.7, 61.1, 66.4, 76.2, 79.6, 96.6, 96.8, 113.7, 118.8, 138.8, 172.6; HRMS calcd for $C_{26}H_{45}O_8Si$ (M^+ − H) m/z 513.2883, found 513.2875. **19***β* as a colorless oil: TLC, R_f 0.55 (EtOAc/hexane, 1:3); $[\alpha]^{27}_D$ −5.4 (*c* 1.12, $CHCl_3$); IR (neat) 2945, 2920, 2875, 2845, 1735, 1670 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.05, 0.08 (2s, 3 H × 2), 0.84 (s, 9 H), 1.15 (s, 3 H), 1.71 (s, 3 H),1.73−2.43 (m, 6 H), 2.95 (dd, J = 8.1, 10.6 Hz, 1 H), 3.34, 3.37 (2s, 3 H × 2), 3.39 (s, 2 H), 3.65 (s, 3 H), 3.92 (d, J = 4.8 Hz, 1 H), 4.08 (dd, J = 7.0, 10.3 Hz, 1 H), 4.53, 4.56 (ABq, J = 6.6 Hz, 1 H × 2), 4.67, 4.71 (ABq, J = 7.0 Hz, 1 H × 2), 5.49−5.55 (m, 1 H); ^{13}C NMR (67.5 Hz) δ −3.2, −2.1, 10.3, 18.2, 20.6, 23.4, 26.1, 27.0, 34.3, 45.2, 51.5, 54.1, 55.3, 55.7, 60.7, 66.5, 75.4, 78.7, 96.4, 96.8, 114.2, 118.8, 139.5, 172.2; HRMS calcd for $C_{25}H_{43}O_8Si$ (M^+ − CH_3) m/z 499.2727, found 499.2729.

(1*S*,3*R*,8*R*,9*S*,10*R*,12*R*)-1-(*tert*-Butyldimethylsilyloxy)-10-(methoxymethoxy)-8-[(methoxymethoxy)methyl]-5,9-dimethyl-2-oxatricyclo[7.3.0.0^{3,8}]dodec-4-en-12-carboxylic Acid (20). To a solution of the mixture of **19**α and **19***β* (ca. 5:3, 472 mg, 0.92 mmol) in MeOH (4 mL) was added aqueous KOH solution (4 M, 4 mL). The solution was heated at 80 °C for 6 h and, after cooling to ambient temperature, neutralized with 1 M aqueous HCl solution. This was diluted with H_2O (20 mL) and extracted with $CHCl_3$ (20 mL × 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:8) to give **20** (372 mg, 81%) as colorless crystals: mp 108−110 °C; TLC, R_f 0.28 (EtOAc/hexane, 1:2); IR (neat) 2950, 2930, 2850, 1735, 1715 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.06 (s, 3 H), 0.18 (s, 3 H), 0.87 (s, 9 H), 1.09 (s, 3 H), 1.71 (s, 3 H), 1.75−2.21 (m, 5 H), 2.31−2.44 (m, 1 H), 3.00 (dd, J = 2.4, 10.4 Hz, 1 H), 3.34, 3.37 (2s, 3 H × 2), 3.40 (s, 2 H), 4.01 (d, J = 4.9 Hz, 1 H), 4.29 (dd, J = 6.7, 9.8 Hz, 1 H), 4.53, 4.56 (ABq, J = 6.7 Hz, 1 H × 2), 4.66, 4.74 (ABq, J = 6.7 Hz, 1 H × 2), 5.50−5.54 (m, 1 H); ^{13}C NMR (100 Hz) δ −3.4, −3.1, 11.0, 18.0, 21.0,

23.3, 25.8, 26.0, 27.0, 33.3, 44.6, 54.1, 55.3, 55.7, 61.2, 66.4, 76.6, 79.5, 96.6, 96.8, 113.4, 118.8, 139.0, 177.1. Anal. Calcd for $C_{25}H_{43}O_8Si$: C, 60.09; H, 8.67. Found: C, 59.67; H, 8.86.

(1*R*,3*R*,8*R*,9*S*,10*R*,12*S* and -12*R*)-12-Acetoxy-1-(*tert*-butyldimethylsilyloxy)-10-(methoxymethoxy)-8-[(methoxymethoxy)methyl]-5,9-dimethyl-2-oxatricyclo[7.3.0.0^{3,8}]-dodec-4-ene (22*β*) and (22α). To a solution of **20** (305 mg, 0.61 mmol) in CH_2Cl_2 (48 mL) were added 4-(dimethylamino)-pyridine (372 mg, 3.04 mmol), 1-ethyl-3-(3-(dimethylamino)-propyl)carbodiimide hydrochloride (504 mg, 3.04 mmol), 2-mercaptopyridine *N*-oxide (542 mg, 4.26 mmol), and *tert*-butylmercaptan (1.37 mL, 12.2 mmol). To the resulting solution was bubbled a stream of dry oxygen for 14.5 h with stirring. This was diluted with 0.2 M aqueous HCl solution (150 mL) and extracted with CH_2Cl_2 (60 mL × 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:9 to 1:6) to give an inseparable diastereomeric mixture of **21***β* and **21**α which was used for acetylation.

The diastereomeric mixture of **21** obtained above (237 mg) was stirred with acetic anhydride (2 mL) in pyridine (2 mL) for 10 h and the solution was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:9 to 1:6) to give diastereomerically homogeneous **22***β* (103 mg, 40%) and **22**α (150 mg, 58%) contaminated with a small amount of unacetylated **21**. Pure **22**α was obtained by rechromatography on silica gel. **22**α as a colorless oil: TLC, R_f 0.32 (EtOAc/hexane, 1:4); $[\alpha]^{29}_D$ −53.2 (*c* 1.02, $CHCl_3$);IR (neat) 2955, 2930, 2890, 2860, 1745 cm^{-1}; ^{1}H NMR (270 MHz) *δ* 0.05, 0.06 (2s, 3 H × 2), 0.84 (s, 9 H), 1.06 (s, 3 H), 1.71 (s, 3 H), 1.75−2.06 (m, 5 H), 2.11 (s, 3 H), 2.24 (dt, *J* = 13.9, 8.4 Hz, 1 H), 3.34, 3.36 (2s, 3 H × 2), 3.41, 3.45 (ABq, *J* = 10.3 Hz, 1 H × 2), 3.97 (d, *J* = 4.0 Hz, 1 H), 4.21 (t, *J* = 8.1 Hz, 1 H), 4.53, 4.57 (ABq, *J* = 6.2 Hz, 1 H × 2), 4.63, 4.68 (ABq, *J* = 6.6 Hz, 1 H × 2), 4.87 (dd, *J* = 4.4, 8.4 Hz, 1 H), 5.58−5.60 (m, 1 H). **22***β* as a colorless oil: TLC, R_f 0.39 (EtOAc/hexane, 1:4); $[\alpha]^{31}_D$ −13.7 (*c* 1.06, $CHCl_3$); IR (neat) 2960, 2930, 2890, 2860, 1740, 1680 cm^{-1}; ^{1}H NMR (270 MHz) *δ* 0.01 (s, 6 H), 0.90 (s, 9 H), 1.15 (s, 3 H), 1.70 (s, 3 H), 1.64−2.17 (m, 5 H), 2.05 (s, 3 H), 2.66 (ddd, *J* = 7.0, 8.1, 14.7 Hz, 1 H), 3.35 (s, 6 H), 3.44 (s, 2 H), 3.83 (d, *J* = 4.0 Hz, 1 H), 4.14 (dd, *J* = 6.2, 8.1 Hz, 1 H), 4.53, 4.58 (ABq, *J* = 6.6 Hz, 1 H × 2), 4.62, 4.67 (ABq, *J* = 7.0 Hz, 1 H × 2), 4.70 (dd, *J* = 3.7, 6.6 Hz, 1 H), 5.48−5.50 (m, 1 H); ^{13}C NMR (100 Hz) *δ* −3.7, −2.9, 10.6, 18.2, 20.7, 21.5, 23.5, 25.9, 26.9, 38.0, 46.0, 55.4, 55.7, 60.3, 67.2, 76.8, 76.9, 96.1, 96.7, 112.6, 119.6, 138.5, 170.3.

(1*R*,3*R*, 8*R*,9*S*,10*R*,12*R*)-1-(*tert*-Butyldimethylsilyloxy)-10-(methoxymethoxy)-8-[(methoxymethoxy)methyl]-5,9-dimethyl-2-oxatricyclo[7.3.0.0^{3,8}]dodec-4-en-12-ol (21α). The following reaction was carried out under Ar. To a cold (−78 °C) stirred solution of **22**α (28.5 mg, 0.055 mmol) in CH_2Cl_2 (1 mL) was added diisobutylaluminum hydride (1.0 M solution in hexane, 0.16 mL, 0.16 mmol). The mixture was stirred at −78 °C for 45 min, quenched with H_2O (0.1 mL), and warmed gradually. The resulting gels were removed by filtration through a Celite pad and washed well with EtOAc. The combined filtrate and washings were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to give **21**α (25.9 mg, 99%) as a colorless oil: TLC, R_f 0.39 (EtOAc/hexane, 1:3); $[\alpha]^{27}_D$ −45.5 (*c* 1.00, $CHCl_3$); IR (neat) 3510, 2955, 2930, 2890, 2850, 1680 cm^{-1}; ^{1}H NMR (270 MHz) *δ* 0.04, 0.12 (2s, 3 H × 2), 0.86 (s, 9 H), 1.04 (s, 3 H), 1.73 (s, 3 H), 1.78−2.21 (m, 6 H), 2.95 (d, *J* = 3.7 Hz, 1 H), 3.33, 3.36 (2s, 3 H × 2), 3.40 (s, 2 H), 3.74 (dd, *J* = 3.7, 6.2 Hz, 1 H), 3.96 (d, *J* = 4.8 Hz, 1 H), 4.16 (dd, *J* = 6.2, 11.0 Hz, 1 H), 4.52, 4.56 (ABq, *J* = 6.2 Hz, 1 H × 2), 4.64, 4.68 (ABq, *J* = 6.6 Hz, 1 H × 2), 5.52−5.54 (m, 1 H); ^{13}C NMR (75 MHz) *δ* −4.0, −3.2, 10.7, 17.9, 21.2, 23.4, 25.7, 27.1, 38.2, 45.5, 55.3, 55.7, 60.6, 66.5, 76.2, 76.8, 78.1, 96.2, 96.8, 112.6, 118.3, 139.9; HRMS calcd for $C_{24}H_{44}O_7Si$ (M^+) *m*/*z* 472.2856, found 472.2850.

(1*R*,3*R*, 8*R*,9*S*,10*R*,12*S*)-1-(*tert*-Butyldimethylsilyloxy)-10-(methoxymethoxy)-8-[(methoxymethoxy)methyl]-5,9-dimethyl-2-oxatricyclo[7.3.0.0^{3,8}]dodec-4-en-12-ol (21*β*). Compound **22***β* (51.1 mg, 0.099 mmol) was converted into **21***β* as described in the preparation of **21**α using diisobutylaluminum hydride (1.0 M solution, 0.295 mL) at −78 °C for 25 min. Purification of crude product by column chromatography on silica gel (EtOAc/hexane, 1:5) gave **21***β* (45.3 mg, 97%) as a colorless oil: TLC, R_f 0.39 (EtOAc/hexane, 1:3); $[\alpha]^{24}_D$ -54.1 (*c* 0.86, $CHCl_3$); IR (neat) 3500, 2960, 2930, 2890, 2850, 1680 cm^{-1}; ^{1}H NMR (270 MHz) *δ* 0.07, 0.17 (2s, 3 H × 2), 0.92 (s, 9 H), 1.14 (s, 3 H), 1.71 (s, 3 H), 1.78−2.13 (m, 5 H), 2.18 (d, *J* = 2.9 Hz, 1 H), 2.44 (ddd, *J* = 6.2, 8.1, 14.3 Hz, 1 H), 3.35, 3.38 (2s, 3 H × 2), 3.44 (s, 2 H), 3.73−3.84 (m, 2 H), 4.18 (dd, *J* = 6.2, 8.1 Hz, 1 H), 4.54, 4.58 (ABq, *J* = 6.6 Hz, 1 H × 2), 4.66, 4.70 (ABq, *J* = 6.6 Hz, 1 H × 2), 5.46−5.53 (m, 1 H); ^{13}C NMR (75 MHz) *δ* −3.6, −3.1, 11.5, 18.2, 20.9, 23.4, 26.0, 27.0, 39.0, 45.8, 55.4, 55.7, 60.0, 67.1, 75.6, 77.4, 96.0, 96.8, 114.1, 119.3, 138.9; HRMS calcd for $C_{24}H_{45}O_7Si$ (M^+ + H) *m*/*z* 473.2935, found 473.2943.

PDC Oxidation of 21α followed by Dibal-H Reduction of the Resulting Ketone 23. Stereoselective Formation of 21*β*. (1*R*,3*R*,8*R*,9*S*,10*R*)-1-(*tert*-Butyldimethylsilyloxy)-10-(methoxymethoxy)-8-[(methoxymethoxy)methyl]-5,9-dimethyl-2-oxatricyclo[7.3.0.0^{3,8}]dodec-4-en-12-one (23). To a solution of **21**α (23.6 mg, 0.050 mmol) in CH_2Cl_2 (1 mL) was added pyridinium dichromate (PDC) (94 mg, 0.25 mmol) and molecular sieves (4A powder, 94 mg). The mixture was stirred at ambient temperature for 8 h and 94 mg of each PDC and molecular sieves was added. The mixture was stirred for an additional 3 h, then the solvent was removed by concentration. The residue was transferred to a short silica gel column. The column was eluted with excess Et_2O. The ethereal eluate was concentrated to give **23** (23.5 mg, 100%) as a colorless oil: $[\alpha]^{24}_D$ −25.6 (*c* 0.68, $CHCl_3$); IR (neat) 2930, 2890, 2850, 1765, 1680 cm^{-1}; ^{1}H NMR (270 MHz) *δ* 0.10, 0.17 (2s, 3 H × 2), 0.84 (s, 9 H), 1.10 (s, 3 H), 1.71 (s, 3 H), 1.86−2.20 (m, 4 H), 2.37 (dd, *J* = 9.5, 19.1 Hz, 1 H), 2.93 (dd, *J* = 7.5, 18.8 Hz, 1 H), 3.36, 3.38 (2s, 3 H × 2), 3.46, 3.51 (ABq, *J* = 10.3 Hz, 1 H × 2), 4.09 (d, *J* = 4.4 Hz, 1 H), 4.22 (dd, *J* = 7.7, 9.5 Hz, 1 H), 4.56, 4.59 (ABq, *J* = 6.6 Hz, 1 H × 2), 4.67, 4.74 (ABq, *J* = 7.0 Hz, 1 H × 2), 5.53−5.55 (m, 1 H); ^{13}C NMR (75 MHz) *δ* −3.4, 9.1, 18.5, 21.1, 23.5, 25.8, 26.6, 29.7, 41.4, 46.0, 55.4, 56.0, 60.7, 67.1, 74.2, 77.4, 78.6, 96.7, 96.8, 108.5, 119.7, 138.5, 206.7; HRMS calcd for $C_{24}H_{42}O_7Si$ (M^+) *m*/*z* 470.2700, found 470.2715.

Compound **23** (23.5 mg) was dissolved in CH_2Cl_2 (1 mL). To the solution was added diisobutylaluminum hydride (1 M solution in hexane, 0.099 mL) at −78 °C then the mixture was stirred at −78 °C for 20 min and quenched with H_2O (0.1 mL). The resulting gels were removed by filtration through a Celite pad and washed with EtOAc. The combined filtrate and washings were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8 to 1:6) to give an inseparable mixture of **21***β* and **21**α (16.1 mg, 68%) in a ratio of more than 20:1 (270 MHz ^{1}H NMR analysis).

(1*R*,3*R*,8*R*,9*S*,10*R*,12*S*)-1-(*tert*-Butyldimethylsilyloxy)-12-mesyloxy-10-(methoxymethoxy)-8-[(methoxymethoxy)-methyl]-5,9-dimethyl-2-oxatricyclo[7.3.0.0^{3,8}]dodec-4-ene (24). To a solution of **21***β* (45.3 mg, 0.096 mmol) in pyridine (1 mL) was added methanesulfonyl chloride (0.022 mL, 0.29 mmol). The mixture was stirred for 4 h and additional methanesulfonyl chloride (0.022 mL) was added after 3 h. The mixture was stirred for an additional 3 h and diluted with 5 mL of H_2O. This was extracted with $CHCl_3$ (5 mL × 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give **24** (52.4 mg, 99%) as a colorless oil: TLC, R_f 0.38 (EtOAc/hexane, 1:2); $[\alpha]^{21}_D$ −12.7 (*c* 0.81, $CHCl_3$); IR (neat) 2960, 2930, 2890, 2860, 1680 cm^{-1}; ^{1}H NMR (270 MHz) *δ* 0.04, 0.19 (2s, 3 H × 2), 0.91 (s, 9 H), 1.13 (s, 3 H), 1.70 (s, 3 H), 1.74−2.14 (m, 4 H), 2.25 (ddd, *J* = 3.7, 5.1, 15.0 Hz, 1 H), 2.47 (ddd, *J* = 5.5, 7.3, 15.0 Hz, 1 H), 3.03 (s, 3 H), 3.35, 3.37 (2s, 3 H × 2), 3.41, 3.47 (ABq, *J* = 10.6 Hz, 1 H × 2), 3.77 (d, *J* = 4.4 Hz, 1 H), 4.25 (dd, *J* = 5.1, 7.3 Hz, 1 H), 4.54, 4.57 (ABq, *J* = 6.6 Hz, 1 H × 2), 4.62−4.69 (m, 3 H), 5.45−5.52 (m, 1 H); ^{13}C NMR (75 Hz) *δ* −3.5, −3.0, 11.4, 18.2, 20.9, 23.4, 25.9, 27.0, 37.1, 39.4, 45.8, 55.4, 55.7, 60.5, 66.9,

76.3, 76.7, 82.9, 96.0, 96.7, 112.4, 118.8, 139.2; HRMS calcd for $C_{25}H_{46}O_9SiS$ (M^+) *m/z* 550.2632, found 550.2636.

(1*R*,3*R*,8*R*,9*S*,10*R*)-10-(Methoxymethoxy)-8-[(methoxymethoxy)methyl]-5,9-dimethyl-2-oxatricyclo[7.2.1.0^{3,8}]-dodec-4-en-12-one (25). To a solution of **24** (51.1 mg, 0.093 mmol) in THF (2 mL) was added TBAF (1.0 M solution in THF, 0.23 mL, 0.23 mmol) at 0 °C. The mixture was stirred at 0 °C for 40 min and then at ambient temperature for 1.5 h and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give **25** (30.8 mg, 97%) as a colorless oil: TLC, R_f 0.39 (EtOAc/hexane, 1:2); $[\alpha]^{26}_D$ −6.3 (*c* 0.82, $CHCl_3$); IR (neat) 2940, 2890, 1760, 1680 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.09 (s, 3 H), 1.53−1.68 (m, 2 H), 1.71 (s, 3 H), 1.83 (ddd, J = 3.3, 5.5, 15.8 Hz, 1 H), 1.91−2.08 (m, 2 H), 2.65 (dd, J = 8.4, 15.8 Hz, 1 H), 3.35, 3.36 (2s, 3 H × 2), 3.43, 3.55 (ABq, J = 10.6 Hz, 1 H × 2), 3.94 (d, J = 5.1 Hz, 1 H), 4.16 (d, J = 5.9 Hz, 1 H), 4.55, 4.58 (ABq, J = 6.6 Hz, 1 H × 2), 4.59, 4.67 (ABq, J = 6.6 Hz, 1 H × 2), 5.01 (dd, J = 3.3, 8.4 Hz, 1 H), 5.45−5.51 (m, 1 H); ^{13}C NMR (75 Hz) δ 8.0, 21.4, 23.2, 27.9, 33.5, 49.2, 55.45, 55.53, 55.6, 66.4, 68.1, 73.6, 76.7, 95.2, 96.9, 117.7, 141.0, 213.1; HRMS calcd for $C_{18}H_{28}O_6$ (M^+) *m/z* 340.1886, found 340.1865.

(1*R*,3*R*,8*R*,9*S*,10*R*)-10-(Methoxymethoxy)-8-[(methoxymethoxy)methyl]-5,9-dimethyl-12-methylene-2-oxatricyclo[7.2.1.0^{3,8}]dodec-4-ene (26). The following reaction was carried out under Ar. A THF solution of (methylene)-triphenylphosphorane was prepared as follows. To a suspension of methyltriphenylphosphonium bromide (265 mg, 0.74 mmol) in THF (1.6 mL) was added *n*-BuLi (1.66 M solution in hexane, 0.41 mL, 0.67 mmol) at − 78 °C. The mixture was stirred for 20 min, and the resulting solution was used as the Wittig reagent. To a solution of **25** (30.5 mg, 0.090 mmol) in THF (1 mL) was added the ylide solution prepared above (0.96 mL, 0.31 mmol). The resulting solution was heated at 60 °C with stirring for 1 h, and the ylide solution was added (0.54 mL). The solution was stirred at 60 °C for additional 1 h. The solution was cooled to ambient temperature and saturated aqueous NH_4Cl (5 mL) was added. The whole was extracted with $CHCl_3$ (5 mL × 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to give **26** (22.0 mg, 73%) as a colorless oil: TLC, R_f 0.50 (EtOAc/hexane, 1:2); $[\alpha]^{23}_D$ −79.7 (*c* 0.44, $CHCl_3$); IR (neat) 2930, 2890, 1680 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.15 (s, 3 H), 1.43−2.04 (m, 5 H), 1.68 (s, 3 H), 2.47 (dd, J = 7.3, 15.0 Hz, 1 H), 3.36 (s, 6 H), 3.40, 3.58 (ABq, J = 10.6 Hz, 1 H × 2), 3.77 (d, J = 5.5 Hz, 1 H), 4.40 (d, J = 5.5 Hz, 1 H), 4.57 (s, 2 H), 4.61, 4.67 (ABq, J = 7.0 Hz, 1 H × 2), 4.71 (s, 1 H), 4.75 (dd, J = 2.9, 7.3 Hz, 1 H), 5.11 (s, 1 H), 5.31−5.43 (m, 1 H); ^{13}C NMR (75 MHz) δ 11.5, 20.4, 23.3, 28.1, 38.3, 43.2, 52.1, 55.35, 55.42, 66.7, 68.5, 77.6, 78.9, 95.3, 97.0, 104.9, 119.0, 140.2, 153.1; HRMS calcd for $C_{19}H_{30}O_5$ (M^+) *m/z* 338.2093, found 338.2105.

(1*R*,3*R*,8*R*,9*S*,10*R*)-8-Hydroxymethyl-5,9-dimethyl-12-methylene-2-oxatricyclo[7.2.1.0^{3,8}]dodec-4-en-10-ol, (−)-12,13-Deoxyverrucarol (27). The following reaction was carried out under Ar. To a cold (−30 °C) solution of **26** (7.9 mg, 0.023 mmol) in CH_2Cl_2 (1 mL) were added bromotrimethylsilane (0.012 mL, 0.094 mmol) and molecular sieves (4A powder, 6.2 mg). The mixture was stirred at −30 °C for 5.5 h, and saturated aqueous $NaHCO_3$ (5 mL) was added. The whole was extracted with CH_2Cl_2 (5 mL × 6). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:6 to 1:3) to give **27** (4.5 mg, 78%) as amorphous solids: TLC, R_f 0.31 (acetone/toluene, 1:2); $[\alpha]^{26}_D$ −93.3 (c 0.18, $CHCl_3$); IR (neat) 3400, 2960, 2930, 2855, 1680 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.17 (s, 3 H), 1.40−2.06 (m, 7 H), 1.66 (s, 3 H), 2.55 (dd, J = 7.7, 15.4 Hz, 1 H), 3.58, 3.78 (ABq, J = 11.7 Hz, 1 H × 2), 3.70 (d, J = 5.5 Hz, 1 H), 4.39 (d, J = 5.1 Hz, 1 H), 4.71 (dd, J = 2.6, 7.7 Hz, 1 H), 4.72 (s, 1 H), 5.14 (s, 1 H), 5.38−5.45 (m, 1 H); ^{13}C NMR (75 MHz) δ 11.5, 20.3, 23.3, 28.2, 40.3, 43.9, 52.5, 63.0, 66.4, 73.4, 78.6, 105.6, 119.1, 140.5, 152.6; HRMS calcd for $C_{15}H_{22}O_3$ (M^+) *m/z* 250.1569, found 250.1564.

(1*R*,3*S*,4*S*,5*R*,8*R*,9*S*,10*R*)-4-Bromo-10-hydroxy-12-methylene-5,9-dimethyl-2,6-dioxatetracyclo[7.2.2.^{5,8}1.0^{3,8}]-tetradecane (31). To a solution of **27** (4.0 mg, 0.016 mmol) in acetone (1 mL) was added *N*-bromosuccinimide (4.3 mg, 0.024 mmol). The mixture was stirred at 0 °C for 15 min and diluted with saturated brine (10 mL). This was extracted with $CHCl_3$ (5 mL × 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel to give **31** (3.1 mg, 58%) as colorless crystals: mp 105−107 °C; TLC, R_f 0.30 (EtOAc/hexane, 3:2); $[\alpha]^{25}_D$ −55.7 (*c* 0.12, $CHCl_3$); IR (neat) 3440, 2970, 2930, 2875, 1680 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.93 (s, 3 H), 1.27 (s, 3 H), 1.32−1.48 (m, 1 H), 1.66 (ddd, J = 3.3, 5.1, 15.4 Hz, 1 H), 1.71−1.91 (m, 2 H), 2.11−2.28 (m, 1 H), 2.62 (dd, J = 7.3, 15.4 Hz, 1 H), 3.75 (s, 2 H), 3.83 (dd, J = 2.6, 8.8 Hz, 1 H), 4.23 (dd, J = 1.8, 8.8 Hz, 1 H), 4.30−4.40 (br, 1 H), 4.59 (d, J = 5.1 Hz, 1 H), 4.73 (s, 1 H), 5.20 (s, 1 H); ^{13}C NMR (75 MHz) δ 10.2, 18.4, 24.3, 27.8, 29.7, 40.3, 41.0, 55.0, 66.6, 67.6, 72.4, 73.2, 79.3, 106.4, 150.2; HRMS calcd for $C_{15}H_{21}O_3Br$ (M^+) *m/z* 328.0674, found 328.0678.

(1*R*,3*R*,8*R*,9*S*,10*R*)-10-(*tert*-Butyldimethylsilyloxy)-8-hydroxymethyl-5,9-dimethyl-12-methylene-2-oxatricyclo-[7.2.1.0^{3,8}]dodec-4-ene (28) and (1*R*,3*R*,8*R*,9*S*,10*R*)-10-(*tert*-Butyldimethylsilyloxy)-8-[(*tert*-butyldimethylsilyl-oxy)methyl]-5,9-dimethyl-12-methylene-2-oxatricyclo-[7.2.1.0^{3,8}]dodec-4-ene (29). The following reaction was carried out under Ar. To a cold (−78 °C) solution of **27** (10.8 mg, 0.043 mmol) in CH_2Cl_2 (1 mL) were added 2,6-lutidine (0.015 mL, 0.13 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (0.012 mL, 0.052 mmol). The mixture was stirred for 44 h while 2,6-lutidine (total 0.17 mL, 1.42 mmol) and TBSOTf (total 0.13 mL, 0.57 mmol) were added in 7 portions. The mixture was quenched with H_2O (0.1 mL), diluted with EtOAc (10 mL), and washed with saturated brine (5 mL × 2). The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel to give **28** (6.2 mg, 40%) and **29** (8.0 mg, 39%). **28** as a colorless oil: TLC, R_f 0.46 (EtOAc/hexane, 1:4); IR (neat) 3440, 2960, 2930, 2855, 1680 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.07, 0.08 (2s, 3 H × 2), 0.88 (s, 9 H), 1.08 (s, 3 H), 1.45−1.58 (m, 2 H), 1.63 (ddd, J = 2.9, 5.1, 14.7 Hz, 1 H), 1.69 (s, 3 H), 1.80−2.06 (m, 3 H), 2.41 (dd, J = 7.0, 15.0 Hz, 1 H), 3.56, 3.75 (ABq, J = 11.7 Hz, 1 H × 2), 3.65 (d, J = 5.9 Hz, 1 H), 4.35 (d, J = 5.1 Hz, 1 H), 4.63 (dd, J = 2.9, 7 3 Hz, 1 H), 4.65 (d, J = 0.7 Hz, 1 H), 5.08 (s, 1 H), 5.39−5.42 (m, 1 H). **29** as a colorless oil: TLC, R_f 0.85 (EtOAc/hexane, 1:2); IR (neat) 2960, 2930, 2860, 1680 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.00, 0.02, 0.06 (3s, 3H, 3 H, 6 H), 0.87, 0.89 (2s, 9 H × 2), 1.06 (s, 3 H), 1.23−1.48 (m, 1 H), 1.53−1.86 (m, 2 H), 1.66 (s, 3 H), 1.91−2.01 (m, 2 H), 2.39 (dd, J = 7.0, 15.0 Hz, 1 H), 3.42, 3.63 (ABq, J = 10.6 Hz, 1 H × 2), 3.57 (d, J = 5.9 Hz, 1 H), 4.21 (dd, J = 3.3, 6.2 Hz, 1 H), 4.33 (d, J = 5.5 Hz, 1 H), 4.55 (dd, J = 2.9, 7.0 Hz, 1 H), 4.63 (d, J = 0.9 Hz, 1 H), 5.06 (s, 1 H), 5.31−5.38 (m, 1 H).

To a solution of **29** (8.0 mg, 0.016 mmol) in THF (1 mL) was added TBAF (1.0 M solution in THF) in 3 portions (0.020 mL, 0.034 mL, 0.017 mL after 0, 1.3, and 4 h). The solution was stirred for total 5.5 h, then the solvent was removed by concentration. The residue was purified by column chromatography on silica gel to give (4.0 mg, 95%) of **27**.

Compound 31 from 28. To a solution of **28** (5.6 mg, 0.015 mmol) in acetone (1 mL) was added *N*-bromosuccinimide (4.2 mg, 0.023 mmol). The mixture was stirred at 0 °C for 10 min and diluted with EtOAc (10 mL). This was washed with saturated brine (5 mL × 2). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:25) to give **30** (6.4 mg); TLC, R_f 0.68 (EtOAc/hexane, 1:4); IR (neat) 2980, 2930, 2855, 1680 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.03, 0.04, (2s, 3 H × 2), 0.84 (s, 3 H), 0.85 (s, 9 H), 1.26 (s, 3 H), 1.32−1.45 (m, 1 H), 1.63−1.90 (m, 3 H), 2.10−2.26 (m, 1 H), 2.47 (dd, J = 7.0, 15.0 Hz, 1 H), 3.67−3.78 (m, 2 H), 3.82 (dd, J = 2.6, 8.8 Hz, 1 H), 4.22 (dd, J = 1.8, 8.4 Hz, 1 H), 4.32 (dd, J = 2.9, 7.0 Hz, 1 H), 4.55 (d, J = 5.1 Hz, 1 H), 4.66 (s, 1 H), 5.13 (s, 1 H).

To a solution of **30** (6.4 mg, 0.014 mmol) in THF (1 mL) was added TBAF (1.0 M solution in THF, 0.022 mL, 0.022 mmol). The mixture was stirred at 0 °C for 2 h and then at ambient temperature for 3 h and the solvent was removed by concentration. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6 to 1:1) to give **31** (4.5 mg, 96%).

Epoxidation of 31. Formation of Epoxide 32. To a solution of **31** (4.5 mg, 0.014 mmol) in CH_2Cl_2 (1 mL) were added *m*-chloroperbenzoic acid (5.1 mg, 0.021 mmol) and $NaHCO_3$ (4.0 mg, 0.048 mmol). The mixture was stirred for 16 h and diluted with 10% aqueous $NaHSO_3$ (5 mL) and then saturated aqueous $NaHCO_3$ (5 mL). This was extracted with $CHCl_3$ (5 mL × 3). The combined extracts were dried and concentrated. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:8 to 1:6) to give **32** (4.3 mg, 91%) as white crystals: mp 179−181 °C; TLC, R_f 0.29 (acetone/toluene. 1:4); $[\alpha]^{25}_D$ −41.0 (*c* 0.21, $CHCl_3$); IR (neat) 3490, 2930, 2875 cm^{-1}; ^1H NMR (270 MHz) δ 0.73 (s, 3 H), 1.28 (s, 3 H), 1.47−1.58 (m, 1 H), 1.71−2.28 (m, 4 H), 2.64 (dd, J = 7.3, 15.8 Hz, 1 H), 2.78 (d, J = 3.7 Hz, 1 H), 3.13 (d, J = 3.7 Hz, 1 H), 3.69−3.81 (m, 3 H), 3.98 (d, J = 5.5 Hz, 1 H), 4.23 (dd, J = 1.8, 8.8 Hz, 1 H), 4.27−4.38 (m, 1 H); ^{13}C NMR (100 MHz) δ 6.3, 19.0, 24.3, 27.8, 29.7, 40.2, 40.5, 46.4, 47.0, 54.3, 66.1, 67.7, 73.2, 73.5, 79.4; HRMS calcd for $C_{14}H_{18}O_4Br$ (M^+-CH_3) *m/z* 329.0388, found 329.0403.

(1*R*,3*R*,8*R*,9*S*,10*R*)-12-Epoxy-8-hydroxymethyl-5,9-dimethyl-2-oxatricyclo[7.2.1.0^{3,8}]dodec-4-en-10-ol, (−)-Verrucarol (7). A zinc−silver couple was prepared according to the literature method.[45] Compound **32** (4.2 mg, 0.012 mmol) was dissolved in a mixture of THF and EtOH (5:1, 1.2 mL), and the zinc−silver couple (5.1 mg), prepared from silver acetate (1 mg) and activated zinc (125 mg), was added. The mixture was refluxed for 83.5 h with stirring while each 10 mg of the zinc−silver couple was added for an interval of 20 h. The insoluble materials were removed by filtration through a Celite pad and washed with EtOAc. The combined filtrate and washings were concentrated. The residue was partitioned between $CHCl_3$ (5 mL) and saturated brine (10 mL). The aqueous layer was extracted with EtOAc (5 mL × 2). The combined organic layers were dried and concentrated. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:6 to 1:3) to give **7** (2.6 mg, 81%) as colorless crystals: mp 144−147 °C; TLC, R_f 0.10 (acetone/toluene, 1:3); $[\alpha]^{21}_D$ −40.6 (*c* 0.13, $CHCl_3$); IR (neat) 3420, 2965, 2935, 2855 cm^{-1}; ^1H NMR (400 MHz) δ 0.95 (s, 3 H), 1.69−2.11 (m, 7 H), 1.72 (s, 3 H), 2.58 (dd, J = 7.7, 15.8 Hz, 1 H), 2.86 (d, J = 3.7 Hz, 1 H), 3.11 (d, J = 3.7 Hz, 1 H), 3.57, 3.77 (ABq, J = 12.1 Hz, 1 H × 2), 3.62 (d, J = 5.5 Hz, 1 H), 3.82 (d, J = 5.5 Hz, 1 H), 4.62 (dd, J = 2.9, 7.3 Hz, 1 H), 5.41−5.46 (m, 1 H); ^{13}C NMR (100 MHz) δ 7.3, 20.9, 23.3, 28.2, 39.9, 43.8, 47.6, 48.9, 62.5, 65.7, 66.5, 74.5, 78.6, 118.7, 141.1; HRMS calcd for $C_{15}H_{22}O_4$ (M^+) *m/z* 266.1518, found 266.1520.

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Supporting Information Available: Copies of ^1H NMR spectra and of ^{13}C NMR spectra of **11**α, **11**β, **13**−**18**, **19**α, **19**β, **20**, **21**α, **21**β, **22**β, **23**−**27**, **31**, **32**, synthetic (−)-verrucarol (**7**), and naturally derived (−)-verrucarol and also ^1H NMR spectra of **12**, **22**α, and **28**−**30** (51 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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