Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 11, pp. 2217-2232, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00301-7

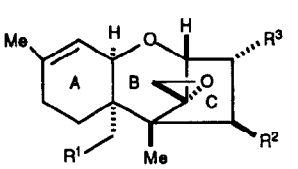
Synthetic Studies on the Trichothecene Family from D-Glucose

Jun Ishihara,[1] Rie Nonaka, Yuki Terasawa, Kin-ichi Tadano,* and Seiichiro Ogawa

Department of Applied Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223, Japan

Abstract: Base-catalyzed intramolecular cyclization of D-glucose-derived substrate **10** provided a diastereomeric mixture of bicyclic β-hydroxyl diesters ***6R*** and ***6S***. Further functionalization of the mixture afforded an enantiomerically pure bicyclic lactone **4**. A double alkylation of **4** provided **3** stereoselectively. Dieckmann cyclization of a lactone-ester **2**, which was prepared from **3**, followed by protection of a hemiacetal hydroxyl group provided smoothly a tricyclic compound **1**.

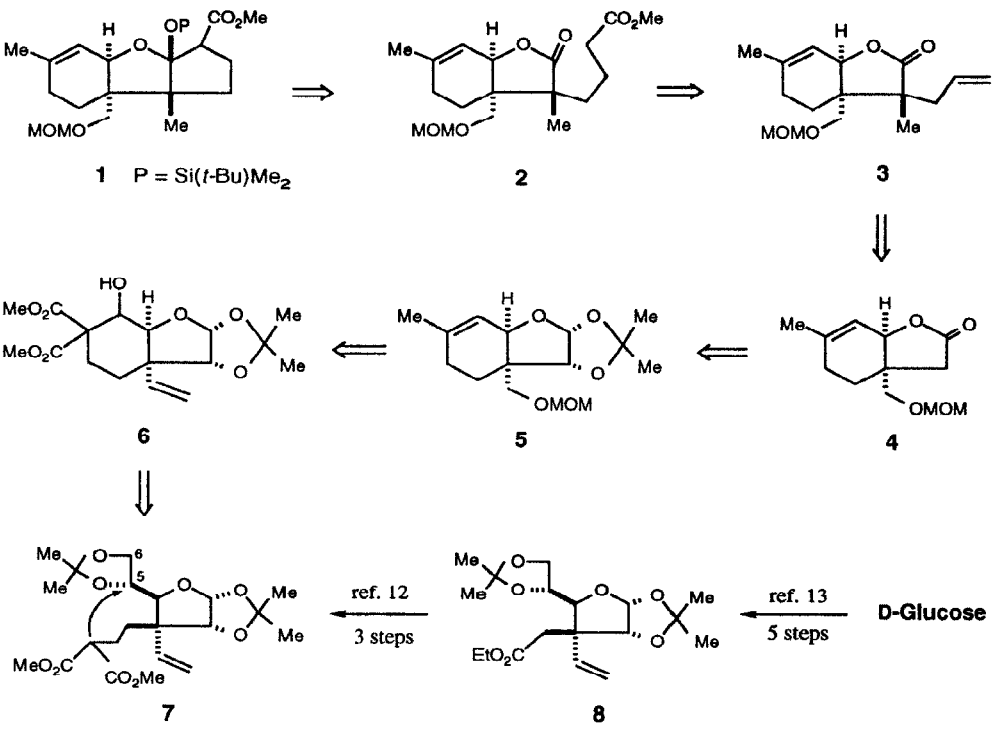
The trichothecenes are a family of structurally related sesquiterpenes isolated from various species of fungi.[2] Since the isolation of trichothecin (Fig. 1) , a prototype of the trichothecenes, by Freeman and Morrison in 1948 from the fungus *Trichothecium roseum*,[3] a number of trichothecenes were isolated and structurally characterized. The common framework of the trichothecene family, which consists of the A/B/C ring system including an exo-epoxide, is depicted in Fig. 1. The representatives of the trichothecenes shown in Fig.1 mainly differ from the oxidation states of one of the bridgehead substituents (R^1) and of the substituents in the C-ring (R^2 and/or R^3). Many of the trichothecene family exhibit significant biological activities such as antifungal, antibacterial, antiviral, and insecticidal properties.[4] Also, some of this family inhibit the growth of tumor cells.[5] A wide range of these biological activities and their structural uniqueness make the trichothecenes quite attractive synthetic targets, and a number of reports have been published so far for their chemical synthesis.[6] Total syntheses of the representative trichothecenes including those of verrucarol,[7] calonectrin,[8] and anguidine[9] were achieved in racemic form or enantio-enriched form. For several years, we have also been concerned with the enantiospecific total synthesis of the trichothecene family. We describe herein our recent results on our synthetic approach to this class of sesquiterpenes starting from D-glucose. [10]



trichothecin : R^1 = H, R^2 = OC(O)CH=CHMe, R^3 = H **trichodermin** : R^1 = H, R^2 =OAc, R^3 = H
trichodermol : R^1 = H, R^2 =OH, R^3 = H
verrucarol : R^1 = OH, R^2 =OH, R^3 = H **calonectrin** : R^1 = OAc, R^2 = H, R^3 = OAc
anguidine : R^1 = OAc, R^2 = OAc, R^3 = OH

Fig. 1

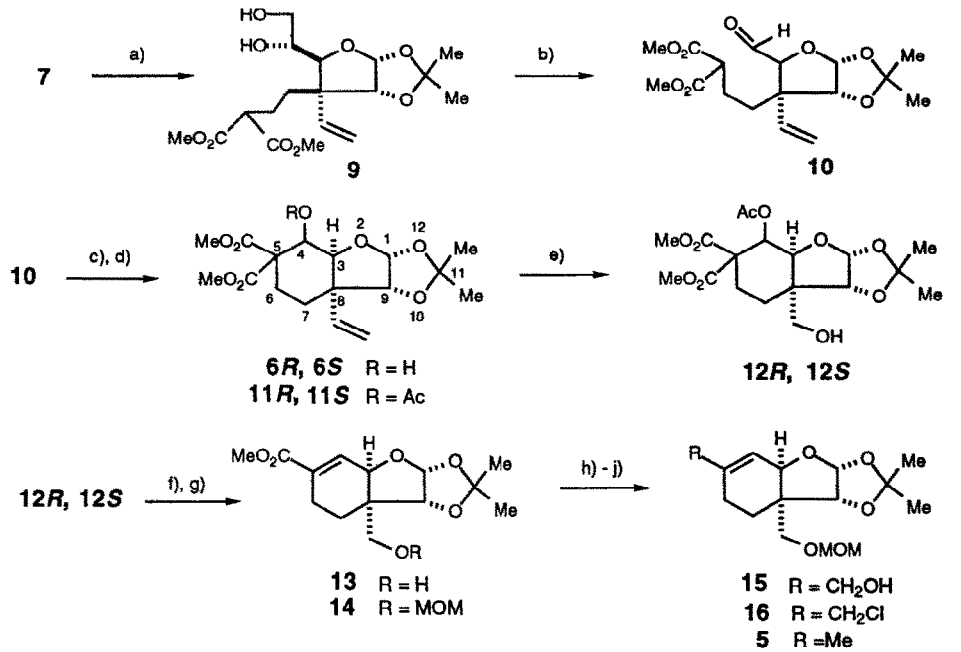
We envisaged that a tricyclic framework such as **1** depicted in Scheme 1 would serve as a pivotal synthetic intermediate for the total synthesis of the trichothecenes, especially for those of verrucarol, calonectrin, and anguidine. Introduction of hydroxyl group(s) appropriately in the right ring (= the cyclopentane carboxylate part) of **1** would provide some versatile intermediates which may serve as clues to the total syntheses of these trichothecenes. It was expected that this target compound **1** would be obtained by a Dieckmann cyclization of a bicyclic compound **2**, which in turn would be derived from **3** by a carbon-elongation of the allyl group. The α,α-disubstituted lactone **3** would be prepared by a sequential alkylation of a bicyclic lactone **4**.[11] It seems to be likely that the lactone **4** would be derived from a highly substituted perhydrobenzofuran derivative **6** via a hexahydrobenzofuran derivative such as compound **5**. Therefore, our initial concern was focused on the efficient construction of compound **6**, of which the left ring could be modified to the A ring of the trichothecenes (*i. e.* **6** to **5**). To achieve this left ring construction, we envisioned a base-catalyzed intramolecular cyclization of an aldehyde-diester **10** (Scheme 2). The substrate **10** would be readily prepared from our previously reported a pentasubstituted tetrahydrofuran derivative **7**. A C-C bond would be formed between the malonyl methine carbon and the aldehyde carbonyl generated by oxidative cleavage of the C-5 and C-6 in **7**. The preparation of the starting material **7**[12] for the present approach was achieved via the Claisen rearrangement product **8**, which in turn was prepared from D-glucose stereoselectively.[13,14] Recently, it was reported that compound **7** also served as a synthetic intermediate in our total syntheses of the sex attracting insect pheromones, (-)-anastrephin and (-)-epianastrephin.[12]



Scheme 1

RESULTS AND DISCUSSION

The isopropylidene group in the side chain of **7** was selectively removed by acid hydrolysis to give diol **9** (Scheme 2). Oxidative cleavage of the glycol in **9** with sodium periodate in aqueous MeOH, and subsequent brief exposure of the resulting crude aldehyde **10** to a catalytic amount of sodium methoxide in MeOH resulted in a smooth carbocyclization[15] providing a 5 : 3 diastereomeric mixture of **6*R*** and **6*S*** in 94% yield for two steps. Although these diastereomers were separated cleanly in a 7 gram scale experiment, we could not determine the stereochemistry of the newly introduced stereogenic center (C-4) in either **6*R*** or **6*S*** unambiguously. The mixture was then acetylated to give a diastereomeric mixture of **11*R*** and **11*S***. The acetoxy group in both **11*R*** and **11*S*** was expected to be a leaving group for introduction of C-C double bond in a later stage. Prior to introduction of the C-C double bond in the cyclohexane ring, it was required at this stage to convert the vinyl group to a hydroxymethyl group. Ozonolysis of the mixture of **11*R*** and **11*S*** followed by reduction with sodium borohydride provided a mixture of **12*R*** and **12*S*** quantitatively. The mixture was then subjected to a modified Krapcho's thermal dealkoxycarbonylation[16] accompanied by β-elimination of the acetoxy groups to provide a bicyclic α,β-unsaturated ester **13** in 47% yield. The mixture of **12*R*** and **12*S*** was also recovered (45%) and reused for the demethoxycarbonylation. Methoxymethylation of the primary hydroxyl group in **13** gave the MOM ether **14**. Conversion of the ester functionality in **14** to a methyl group was carried out next. This was efficiently achieved by a radical reduction of the allylic chloride **16**, which was prepared from **14** by isobutylaluminum hydride reduction

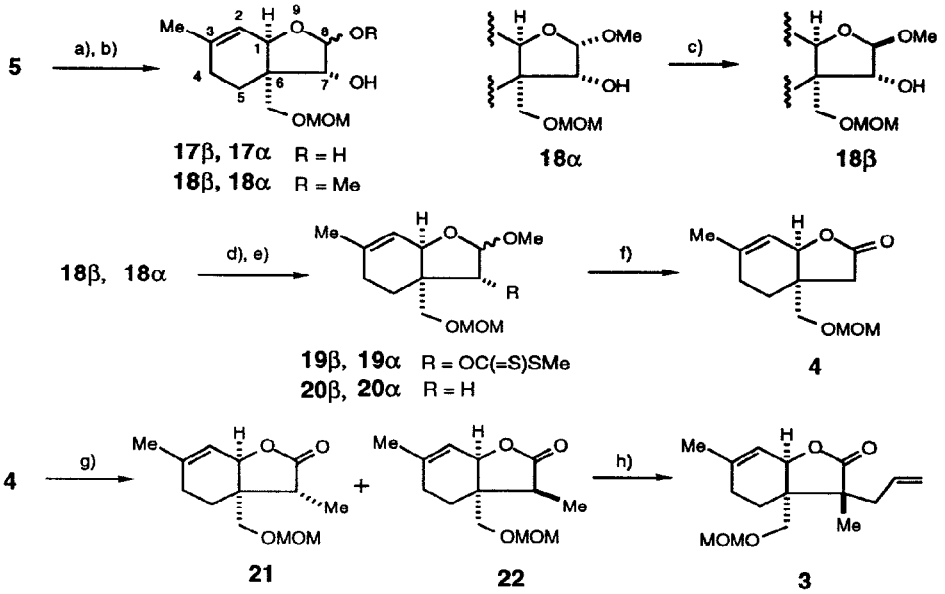


reagents and conditions: a) 60% aq. AcOH / rt (99%); b) $NaIO_4$ / aq. MeOH / rt ; c) MeONa / MeOH / 0 °C (**6*R* + 6*S***, 94%); d) Ac_2O / pyr. / rt (**11*R* + 11*S***, 92%); e) O_3 / MeOH : CH_2Cl_2 (1:3) / -78 °C; then $NaBH_4$ (**12*R* + 12*S***, 98%); f) DMSO : H_2O (10:1) / NaCl / 160 °C (47% for **13**, 45% recovery of the mixture of **12*R* + 12*S***); g) MOMCl / *i*-Pr_2EtN / rt (83%); h) Dibal-H / CH_2Cl_2 / -78 °C (100%); i) Ph_3P / CCl_4 / benzene / reflux (88%); j) *n*-Bu_3SnH /AIBN / toluene / reflux (100%).

Scheme 2

followed by treatment of the resulting allylic alcohol **15** with triphenylphosphine and carbon tetrachloride in refluxing benzene. The conversion of **14** to **16** was achieved in 88% yield. Radical dechlorination of **16** was effected smoothly under standard conditions to give **5** quantitatively.

Next, we explored the construction of another quaternary center (*i. e.* at C-7) adjacent to the bridgehead carbon of **5** (Scheme 3). Hydrolysis of **5** with 60% aqueous trifluoroacetic acid gave a 5:1 inseparable hemiacetal mixture of **17** in 63% yield, and **5** was recovered in part (25%). We tentatively assigned the configuration of the hemiacetal carbons to be β and α for the major and minor product, respectively. Exposure of the mixture of **17β** and **17α** to MeOH in the presence of *p*-TsOH gave methyl glycosides **18β** and **18α**, which were cleanly separated by careful chromatography on silica gel in 60% and 12% yield, respectively. The configuration of each C-8 in **18β** or **18α** was determined based on the *J* value of each C-8 proton in their ^{1}H NMR spectrum. Furthermore, the α-anomer **18α** was partially converted to the β-anomer **18β** by repeated exposure to MeOH in the presence of *p*-TsOH. The hydroxyl group in the major β-isomer **18β** was esterified to give the xanthate **19β** in 96% yield. Radical removal of the xanthate ester in **19β** proceeded smoothly to give deoxygenated product **20β**. Jones oxidation of **20β** provided the bicyclic lactone **4** in 76% yield, and **20β** was also recovered (15%). Analogously, the minor α-isomer **18α** was also converted to **4**. Surprisingly, radical removal of the xanthate group introduced to **18α**, i. e. **19α**, was problematic giving a complex mixture, from which 26% yield of the deoxygenated product was obtained.[17] Next we investigated the sequential alkylation at the α-carbon of the lactone **4** using methyl iodide and allyl bromide as electrophiles.

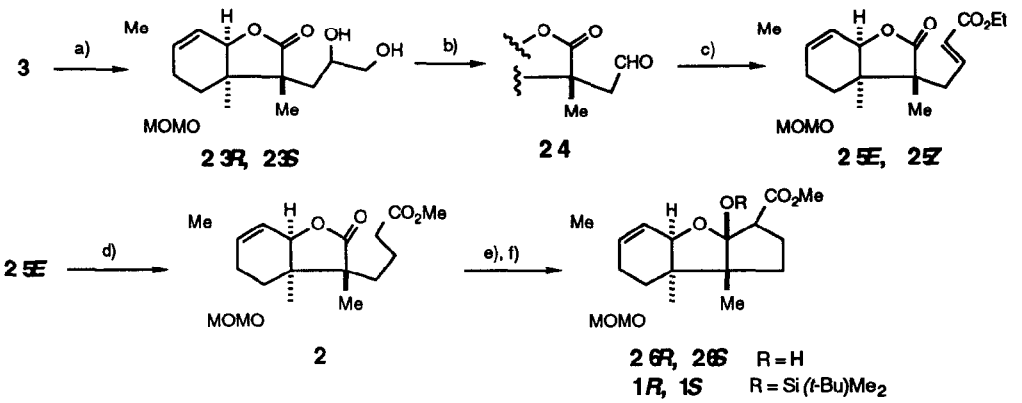


reagents and conditions: a) 60% aq. CF_3COOH / 0 °C (63% for the mixture of **17β** and **17α**, 25% recovery of **5**); b) MeOH / *p*-TsOH (0.5 eq.) / rt (15 h) (60% for **18β**, 12% for **18α**); c) MeOH / *p*-TsOH (0.5 eq.) / rt (3 h) (49% of **18β**, 33% of **18α**); d) imidazole / NaH / THF / rt, then CS_2 / rt, then MeI / rt (30 min) (96% for **19β**); e) AIBN / *n*-Bu_3SnH / benzene/ reflux (90% for **20β**); f) Jones reagent / acetone / 0 °C (76% for **4**, 15% recovery of **20β**); g) LDA / THF / -78 °C, then MeI / -78 °C to 0 °C (combined yield of 96%, **21** : **22** = 15:1); h) LDA / THF / -78 °C. then allyl bromide / -78 °C to 0 °C (89%).

Scheme 3

Lithium diisopropylamide (LDA) induced enolate generated from **4** was trapped with methyl iodide to give an inseparable mixture of **21** and **22** in a ratio of nearly 15:1 (^{1}H NMR analysis) in a combined yield of 96%.[18] The structure of the major product **21** was ascertained by n. O. e. difference experiments as shown in Fig. 2. As anticipated, the electrophile attacked preferentially from the less hindered α-side of the intermediary bicyclic enolate. This phenomenon was the same in the case of the second alkylation, which was achieved by treatment of the mixture of **21** and **22** with LDA followed by addition of allyl bromide. The doubly alkylated product **3** was obtained as a sole product in 89% yield. Again, the stereochemistry of the newly introduced quaternary center in **3** was confirmed by n. O. e. experiments as shown in Fig. 2.

Then we converted the allyl group in **3** to a four-carbon ester functionality, i.e. compound **2**, as follows (Scheme 4). Regioselective cis-dihydroxylation of the side chain double bond in **3** was efficiently achieved by oxidation with a catalytic amount of osmium tetroxide in the presence of 4-methylmorpholine N-oxide.[19] The diastereomeric diols **23*R*** and **23*S*** were obtained as an approximately 1 : 1 inseparable mixture in a combined yield of 84%. $NaIO_4$-oxidation of the mixture of **23*R*** and **23*S*** gave aldehyde **24**, which was treated with (ethoxycarbonyl)methylenetriphenylphosphorane to give the *E* and *Z*-α,β-unsaturated esters **25*E*** and **25*Z*** in 75% and 6% yield, respectively. The geometry of the α,β-unsaturated ester in each **25*E*** or **25*Z*** was assigned by ^{1}H NMR analysis. The double bond of the unsaturated ester in the major product **25*E*** was chemoselectively reduced with magnesium metal in MeOH[20] to give the saturated ester **2** in 86% yield. Finally, the crucial Dieckmann cyclization of the substrate **2** was examined under several basic conditions.[21]



reagents and conditions:a) OsO_4 in *t*-BuOH / NMO / aq. acetone, then 10% aq. $NaHSO_3$ / rt (**23*R*** + **23*S***, 84%); b) $NaIO_4$ / aq. MeOH / rt; c) Ph_3P=CHCOOEt / benzene / reflux (**25*E***, 75% and **25*Z***, 6%); d) Mg / MeOH / rt / ultrasonication (86%); e) KHMDS / THF / -78 °C (**26*R*** + **26*S***, 70%); f) TBDMSOTf / 2,6-lutidine / rt (**1*R*** + **1*S***, 74%).

Scheme 4

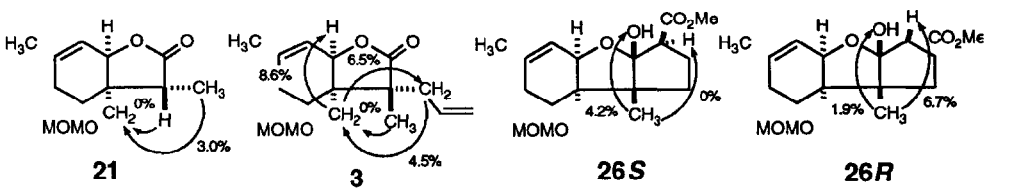


Fig. 2

We were pleased to find that the desired Dieckmann cyclization proceeded smoothly by brief exposure of **2** to potassium bis(trimethylsilyl)amide at -78 °C. A diastereomeric mixture of the tricyclic products **26*R*** and **26*S*** was obtained in a combined yield of 70%. The ratio of this inseparable diastereomeric mixture (**26*R*** : **26*S***) was estimated to be approximately 4:5 (^{1}H NMR analysis). And the structure of each cyclization product **26*S*** or **26*R*** was determined to be those as depicted in Fig. 2 based on n. O. e. experiments of the mixture. Protection of the hemiacetal hydroxyl groups in the mixture of **26*S*** and **26*R*** with a (*t*-butyl)dimethylsilyl group provided an inseparable mixture of the silyl ethers **1*R*** and **1*S*** in 74% yield.[22]

In conclusion, we have found a synthetic route to the promising intermediates such as compounds **3** and **1** for total synthesis of the trichothecene sesquiterpenes. Our present approach to these synthetic intermediates features the efficient intramolecular cyclizations of compounds **10** and **2** under basic conditions. Further functionalization of the right ring in **1** is now under extensive investigation.

EXPERIMENTAL

Melting points are uncorrected. Specific rotations were measured using a JASCO Model DIP-4 or JASCO DIP-370 digital polarimeter in a 10 mm cell. IR spectra were recorded using a JASCO IR-810 (neat) or BIO-RAD DEGILAB FTS-65 ($CHCl_3$) spectrometer. ^{1}H NMR spectra were recorded using a JEOL GX-270 (270 MHz) spectrometer in $CDCl_3$ solution with tetramethysilane as an internal standard. High-resolution mass spectra (HRMS) were taken using a Hitachi M-80 mass spectrometer. Microanalyses were carried out by staffs of the Analytical Center in our university.

Thin-layer chromatography (TLC) was performed with a glass plate coated Kieselgel 60 GF_{254} (Merck). Crude reaction mixtures or extractive materials were chromatographed on silicagel 60 K070 (Katayama Chemicals).

Reagents and solvents were removed by concentration in vacuo using an evaporator with bath at 35-45 °C. Solvents were dried (drying reagent in parenthesis) and distilled prior to use: tetrahydrofuran=THF ($LiAlH_4$, then Na/benzophenone ketyl), CH_2Cl_2 (CaH_2), dimethyl sulfoxide= DMSO (CaH_2), and pyridine (NaOH).

(2*R*,3*R*,4*R*,5*S*)-5-[(*R*)-1,2-Dihydroxyethyl]-2,3-(isopropylidenedioxy)-4-[3-bis(methoxycarbonyl)-propyl]-4-vinyltetrahydrofuran (9). A solution of **7** (34.4 g, 80.3 mmol) in 60% aqueous AcOH (400 mL) was stirred at rt for 24 h and concentrated in the aid of toluene and EtOH. The residue was purified by column chromatography on silica gel (toluene/acetone, 5:1) to give 30.9 g (99%) of **9** as a colorless oil: TLC, R_f 0.16 (EtOAc/hexane, 1:1); $[\alpha]^{24}_D$ +42.1 (*c* 1.25, $CHCl_3$); IR (neat) 3425, 2990, 2950, 1750, 1735, 1720, 1640, 1460, 1440, 1375, 1240, 1160 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.32, 1.53 (2 s, 3 H x 2), 1.23-1.50, 1.73-1.83, 1.96-2.02 (3 m, 2 H, 1 H, 1 H), 2.74 (s, 2 H), 3.36 (t, *J* = 7.3 Hz, 1 H), 3.76 (s, 6 H), 3.60-4.04 (m, 4 H), 4.51 (d, *J* = 3.7 Hz, 1 H), 5.30 (dd, *J* = 1.3, 17.6 Hz, 1 H), 5.31 (dd, *J* = 1.3, 11.7 Hz, 1H), 5.74 (d, *J* = 3.7 Hz, 1H), 6.04 (dd, *J* = 11.7, 17.6 Hz, 1 H). HRMS calcd for $C_{17}H_{25}O_9$ (M^+- CH_3) *m/z* 373.1497, found 373.1496.

Mixture of (1*R*,3*S*, 4*R* and *S*, 8*R*, 9*R*)-5,5-Bis(methoxycarbonyl)-11, 11-dimethyl-8-vinyl-2,10,12-trioxatricyclo[7.3.0.0^{3,8}]dodecan-4-ol (6*R* and 6*S*). To a cold (0 °C) stirred solution of **9** (30.9 g, 79.6 mmol) in MeOH (250 mL) was added an aqueous solution (165 mL) of $NaIO_4$ (20.4

g, 95.4 mmol) dropwise. The mixture was stirred at rt for 30 min, and the resulting solids were removed by filtration and washed well with MeOH. The combined filtrate and washings were concentrated. The residue was partitioned between EtOAc (500 mL) and H_2O (500 mL), and the aqueous layer was extracted with EtOAc (500 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give crude **10**, which was used for next step without purification.

To a cold (0 °C) stirred solution of the crude **10** obtained above in MeOH (300 mL) was added MeONa (1.0 M solution in MeOH, 8.0 mL, 8.0 mmol). The mixture was stirred at 0 °C for 30 min, 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 (EtOAc/hexane, 1:3) to give 26.6 g (94% combined yield) of the 5:3 diastereomeric mixture of **6*R*** and **6*S***, which was used for next step without separation, as white crystals. In a separate experiment starting from 6.88 g of **9**, the two diastereomers were cleanly separated by repeated chromatography on silica gel to give 3.46 g (55%) of **6*R*** (tentatively) and 2.31 g (36%) of **6*S***. **6*R*** as white crystals, mp 165.0-167.0 °C: R_f 0.59 (EtOAc/hexane, 1:1); $[\alpha]^{24}_D$ +9.3 (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 3500, 3030, 2950, 1720, 1640, 1460, 1440, 1425, 1390, 1315, 1300, 1250, 1170, 1140, 1080 cm^{-1}; ^1H NMR (270 MHz) δ 1.28, 1.54 (2 s, 3 H x 2), 1.74-1.85, 1.96-2.06, 2.13-2.20 (3m, 2 H, 1 H, 1 H), 3.69, 3.73 (2 s, 3 H x 2), 4.11 (d, *J* = 2.9 Hz, 1 H), 4.32 (d, *J* = 3.4 Hz, 1 H), 4.89 (d, *J* = 2.9 Hz, 1 H), 5.26 (dd, *J* = 1.0, 17.4 Hz, 1 H), 5.30 (dd, *J* = 1.0, 11.2 Hz, 1 H), 5.63 (d, *J* = 3.4 Hz, 1 H), 6.02 (dd, *J* = 11.2, 17.4 Hz, 1 H). Anal. Calcd for $C_{17}H_{24}O_8$: C, 57.30; H, 6.79. Found: C, 57.40; H, 6.53. **6*S*** as white crystals, mp 73.5-75.0 °C: TLC, R_f 0.52 (EtOAc/hexane, 1:1); $[\alpha]^{24}_D$ + 85.5 (*c* 0.90, $CHCl_3$); IR ($CHCl_3$) 3560, 3090, 3025, 2955, 1735, 1640, 1440, 1380, 1255, 1225 cm^{-1}; ^1H NMR (270 MHz) δ 1.29, 1.53 (2 s, 3 H x 2), 1.57-1.81, 2.26-2.33 (2 m, 3 H, 1 H), 3.75, 3.81 (2 s, 3 H x 2), 4.15 (d, *J* = 3.4 Hz, 1 H), 4.19 (d, *J* = 2.2 Hz, 1 H), 4.39 (d, *J* = 2.2 Hz, 1 H), 5.28 (d, *J* = 17.9 Hz, 1 H), 5.40 (d, *J* = 11.1 Hz, 1 H), 5.70 (d, *J* = 3.4 Hz, 1 H), 5.84 (dd, *J* = 11.1, 17.9 Hz, 1 H). Anal. Calcd for $C_{17}H_{24}O_8$: C, 57.30; H, 6.79. Found: C, 57.58; H, 6.72.

Mixture of (1*R*,3*S*,4*R* and *S*, 8*R*, 9*R*)-4-Acetoxy-5,5-bis(methoxycarbonyl)-11,11-dimethyl-8-vinyl-2,10,12-trioxatricyclo[7.3.0.0^{3,8}]dodecane (11*R* and 11*S*). To a solution of the mixture of **6*R*** and **6*S*** obtained above (24.0 g, 67.3 mmol) in pyridine (180 mL) was added acetic anhydride (180 mL). The mixture was stirred at rt for 64 h and concentrated in the aid of toluene and EtOH. The residue was purified by column chromatography on silica gel (toluene/acetone, 20:1) to give 24.7 g (92%) of mixture of **11*R*** and **11*S***, which was used for next step without separation, as white crystals.

Pure **11*R*** and **11*S*** were prepared from diastereomerically homogeneous **6*R*** and **6*S*** by acetylation described for the mixture. Compound **11*R*** (tentatively) was obtained as white crystals, mp 143.0-145.0 °C: TLC, R_f 0.56 (toluene/acetone, 6:1); $[\alpha]^{24}_D$ +16.7 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2995, 2960, 2850, 1755, 1640, 1460, 1440, 1380, 1310, 1280, 1225, 1210, 1180, 1165 cm^{-1}; ^1H NMR (270 MHz) δ 1.27, 1.51 (2 s, 3 H x 2), 1.51-1.65, 1.86-2.06, 2.34-2.39 (3 m, 1 H, 2 H, 1 H), 1.97 (s, 3 H), 3.68, 3.72 (2 s, 3 H x 2), 4.09 (d, *J* = 3.3 Hz, 1 H), 4.19 (d, *J* = 3.3 Hz, 1 H), 5.24 (dd, *J* = 0.7, 17.9 Hz, 1 H), 5.28 (dd, *J* = 0.7, 10.5 Hz, 1 H), 5.64 (d, *J* = 3.3 Hz, 1 H), 5.79 (ddd, *J* = 0.7, 10.5, 17.9 Hz, 1 H), 6.06 (d, *J* = 3.3 Hz, 1 H). Anal. Calcd for $C_{19}H_{26}O_9$: C, 57.28; H, 6.58. Found: C, 57.29; H, 6.57. Compound **11*S*** as white crystals, mp 157.0-159.0 °C; TLC, R_f 0.49 (toluene/acetone, 6:1); $[\alpha]^{24}_D$ +67.0 (*c* 1.00, $CHCl_3$); IR (neat) 3000, 2970, 1735, 1640, 1435, 1370, 1295, 1255, 1230, 1165, 1135, 1110, 1075 cm^{-1}; ^1H NMR (270 MHz) δ 1.28, 1.48 (2 s, 3 H x 2), 1.63-1.98, 2.32-2.42 (2 m, 3 H, 1 H), 2.14 (s, 3 H), 3.71, 3.78 (2 s, 3 H x 2), 4.15 (d, *J* =

3.5 Hz, 1 H), 4.40 (d, J = 2.2 Hz, 1 H), 5.41 (d, J = 17.8 Hz, 1 H), 5.44 (d, J = 11.1 Hz, 1 H), 5.52 (d, J = 2.2 Hz, 1 H), 5.72 (d, J = 3.5 Hz, 1 H), 5.87 (dd, J = 11.1, 17.8 Hz, 1 H). Anal. Calcd for $C_{19}H_{26}O_9$: C, 57.28; H, 6.58. Found: C, 57.57; H, 6.42.

Mixture of (1*R*,3*S*,4*R* and *S*,8*R*,9*R*)-4-Acetoxy-8-(hydroxymethyl)-5,5-bis(methoxycarbonyl)-11,11-dimethyl-2,10,12-trioxatricyclo[7.3.0.0^{3,8}]dodecane (12*R* and 12*S*). To a cold (-78 °C) solution of the mixture of **11*R*** and **11*S*** (11.2 g, 28.1 mmol) in a mixture of CH_2Cl_2 (50 mL) and MeOH (150 mL) was bubbled ozone (ca. 3% in O_2) for 3 h. To the mixture was bubbled dry O_2 at -78 °C for 1 h. Then to the mixture was added $NaBH_4$ (3.18 g, 84.1 mmol) at -78 °C. The mixture was gradually warmed to rt in a period of 2.5 h, while two portions of $NaBH_4$ (1.06 g and 0.532 g) were added after 1.5 and 2 hrs. The mixture was neutralized with Amberlite IR-120 [H+] at 0 °C. 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 (toluene/acetone, 5:1) to give 11.1 g (98%) of the mixture of **12*R*** and **12*S***, which was used for next step without separation, as white crystals.

Pure **12*R*** and **12*S*** were obtained from diastereomerically homogeneous **11*R*** and **11*S*** as described for the mixture. Compound **12*R*** as white crystals, mp 145.5-147.0 °C: TLC, R_f 0.10 (EtOAc/hexane, 1:2); $[\alpha]^{24}_D$ -6.9 (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 3470, 2985, 2895, 1750, 1725, 1455, 1375, 1310, 1275, 1220, 1170, 1065 cm^{-1}; ^1H NMR (270 MHz) δ 1.30, 1.52 (2 s, 3 H x 2), 1.46-1.69, 1.88-2.09, 2.26-2.41 (3 m, 1 H, 1 H, 2 H), 2.04 (s, 3 H), 3.69, 3.72 (2 s, 3 H x 2), 3.82 (dd, J = 4.5, 11.6 Hz, 2 H), 4.21 (d, J = 3.5 Hz, 1 H), 4.26 (d, J = 3.5 Hz, 1 H), 5.64 (d, J = 3.5 Hz, 1 H), 6.07 (d, J = 3.5 Hz, 1 H). Anal. Calcd for $C_{18}H_{26}O_{10}$: C, 53.73; H, 6.51. Found: C, 53.65; H, 6.45. Compound **12*S*** as a colorless oil: TLC, R_f 0.13 (EtOAc/hexane, 2:3); $[\alpha]^{24}_D$ +51.7 (*c* 1.03, $CHCl_3$); IR (neat) 3480, 2930, 2900, 1755, 1460, 1395, 1315, 1255, 1190, 1160, 1135, 1100, 1055 cm^{-1}; ^1H NMR (270 MHz) δ 1.30, 1.48 (2 s, 3 H x 2), 1.66-1.83, 2.36-2.42 (2 m, 2H, 2 H), 2.13 (s, 3 H), 3.71, 3.77(2 s, 3 H x 2), 3.69-3.89 (m, 2 H), 4.23-4.27 (m, 2 H), 5.49 (d, J = 2.2 Hz, 1 H), 5.70 (d, J = 3.7 Hz, 1 H). HRMS calcd for $C_{17}H_{23}O_9$ (M^+- OCH_3) *m/z* 371.1341, found 371.1345.

(1*R*,3*R*,8*R*,9*R*)-8-(Hydroxymethyl)-5-(methoxycarbonyl)-11,11-dimethyl-2,10,12-trioxatricyclo-[7.3.0.0^{3,8}]dodec-4-ene (13). A solution of the mixture of **12*R*** and **12*S*** (20.3 g, 50.4 mmol) in a mixture of DMSO (300 mL) and H_2O (30 mL) in the presence of NaCl (11.8 g, 202 mmol) was heated from 110 to 160 °C for a period of 3 h and kept at 160 °C for 30 min with stirring. After being cooled to rt, the solution was diluted with saturated aqueous $NaHCO_3$ (600 mL). The solution was extracted with CH_2Cl_2 (500 mL x 3). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (toluene/acetone, 1:3) to give 6.70 g (47%) of **13** as a colorless oil, and 8.90 g (45%) of the mixture of **12*R*** and **12*S*** was recovered. The recovered mixture of **12*R*** and **12*S*** was resubjected to the demethoxycarbonylation under the same conditions. After four recycles, total amount of 10.8 g (75%) of **13** was obtained, and 0.60 g (3%) of the mixture of **12*R*** and **12*S*** was recovered. Compound **13**: TLC, R_f 0.44 (EtOAc/hexane, 1:1); $[\alpha]^{24}_D$ +62.4 (*c* 1.33, $CHCl_3$); IR (neat) 3500, 2990, 2950, 1720, 1650, 1440, 1380, 1370, 1310, 1260, 1220, 1170, 1140 cm^{-1}; ^1H NMR (270 MHz) δ 1.35, 1.58 (2 s, 3 H x 2), 1.22-1.34, 1.77-1.90, 2.17-2.37, 2.45-2.57 (4 m, 1 H x 4), 3.54-3.74 (m,

2 H), 3.76 (s, 3 H), 4.39 (d, J = 4.4 Hz, 2 H), 5.90 (d, J = 3.7 Hz, 1 H), 6.94-6.96 (m, 1 H). HRMS calcd for $C_{14}H_{20}O_6$ (M^+) m/z 284.1258, found 284.1246.

(1*R*,3*R*,8*R*,9*R*)-5-(Methoxycarbonyl)-8-[(methoxymethoxy)methyl]-11,11-dimethyl-2,10,12-trioxatri-cyclo[7.3.0.0^{3,8}]dodec-4-ene (14). To a cold (0°C) stirred solution of **13** (8.24 g, 29.0 mml) in CH_2Cl_2 (120 mL) were added diisopropylethylamine (DIPEA) (20.2 mL, 116.0 mmol) and chloromethyl methyl ether (MOMCl) (4.40 mL, 57.9 mmol). The mixture was stirred at rt for 1h, and DIPEA (10.1 mL, 58.0 mmol) and MOMCl (2.20 mL, 29.0 mmol) were added. The mixture was stirred at rt for an additional 30 min and diluted with 0.2 M aqueous HCl (500 mL). The whole was extracted with CH_2Cl_2 (500 mL x 3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (hexane; then EtOAc/hexane, 1:5) to give 7.89 g (83%) of **14** as white crystals, mp 123.0-124.0 °C: TLC, R_f 0.55 (EtOAc/hexane, 1:2); $[\alpha]^{29}_D$ +43.7 (c 1.10, $CHCl_3$); IR (neat) 3020, 2990, 2950, 2930, 2890, 1730, 1680, 1620, 1440, 1380, 1320, 1280, 1250, 1180, 1150, 1100, 1020 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.34, 1.55 (2 s, 3 H x 2), 1,21-1.31, 1.95-2.02, 2.26-2.35, 2.48-2.58 (4 m, 1 H x 4), 3.38 (s, 3 H), 3.31, 3.67 (ABq, J = 9.6 Hz, 1 H x 2), 3.76 (s, 3 H), 4.14 (d, J = 4.8 Hz, 1 H), 4.38 (d, J = 3.7 Hz, 1 H), 4.61, 4.66 (ABq, J = 6.6 Hz, 1 H x 2), 5.89 (d, J = 3.7 Hz, 1 H), 6.91-6.93 (m, 1 H). Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.52; H, 7.37. Found: C, 58.51; H, 7.27.

(1*R*,3*R*,8*R*,9*R*)-5-(Hydroxymethyl)-8-[(methoxymethoxy)methyl]-11,11-dimethyl-2,10,12-trioxa-tricyclo[7.3.0.0^{3,8}]dodec-4-ene (15). The following reaction was carried out under Ar. To a cold (-78 °C) stirred solution of **14** (7.89 g, 24.0 mmol) in CH_2Cl_2 (150 mL) was added diisobutylaluminum hydride (1.02 M solution in toluene, 70.7 mL, 72.1 mmol). The mixture was stirred at -78 °C for 30 min and quenched with H_2O (15 mL). After the mixture was stirred at 0 °C for 15 min, the resulting gels were removed by filtration through a pad of Celite, washed well with CH_2Cl_2. The combined filtrate and washings were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (toluene/acetone, 5:1) to give 7.22 g (100%) of **15** as a colorless oil: TLC, R_f 0.24 (toluene/acetone, 1:2); $[\alpha]^{24}_D$ +55.7 (c 1.11, $CHCl_3$); IR (neat) 3450, 2990, 2930, 2880, 1670, 1650, 1445, 1380, 1370, 1310, 1260, 1220, 1160, 1150, 1110, 1045 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.34, 1.54 (2 s, 3 H x 2), 1.24-1.31, 1.91-2.16 (2 m, 1 H, 3 H), 3.39 (s, 3 H), 3.35, 3.68 (ABq, J = 9.5 Hz, 1 H), 4.07 (s, 3 H), 4.36 (d, J = 3.8 Hz, 1 H), 4.62, 4.67 (ABq, J = 6.6 Hz, 1 H x 2), 5.85 (br d, J = 3.7 Hz, 1 H), 5.89 (d, J = 3.8 Hz, 1 H). HRMS calcd for $C_{14}H_{21}O_6$ (M^+- CH_3) m/z 285.1337, found 285.1361.

(1*R*,3*R*,8*R*,9*R*)-5-(Chloromethyl)-8-[(methoxymethoxy)methyl]-11,11-dimethyl-2,10,12-trioxatri-cyclo[7.3.0.0^{3,8}]dodec-4-ene (16). To a solution of **15** (7.22 g, 24.0 mmol) in benzene (140 mL) were added triphenylphosphine (12.6 g, 48.0 mmol) and carbon tetrachloride (23.2 mL, 240 mmol). The mixture was refluxed for 8 h and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to give 6.70 g (88%) of **16** as a colorless oil: TLC, R_f 0.74 (toluene/acetone, 5:1); $[\alpha]^{24}_D$ +49.8 (c 1.03; $CHCl_3$); IR (neat) 2950, 2900, 2850, 1460, 1400, 1390, 1325, 1230, 1190, 1165, 1130, 1065 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.34, 1.54 (2 s, 3 H x 2), 1.26-1.30, 1.94-2.36 (2 m, 1 H, 3 H), 3.39 (s, 3 H), 3.33, 3.68 (ABq, J = 9.5 Hz, 1 H x 2), 4.02 (s, 2 H), 4.06 (d, J = 5.5 Hz, 1 H), 4.36 (d, J = 3.8 Hz, 1 H), 4.63, 4.67 (ABq, J = 6.6 Hz, 1 H x 2), 5.89 (d, J = 3.8 Hz, 1 H), 5.92 (br d, J = 5.5 Hz, 1 H).

(1*R*,3*R*,8*R*,9*R*)-8-[(Methoxymethoxy)methyl]-5,11,11-trimethyl-2,10,12-trioxa-tricyclo[7.3.0.0^{3,8}]-dodec-4-ene (5). The following reaction was carried out under Ar. To a solution of **16** (1.11 g, 3.48 mmol) and 2,2'-azobis(isobutyronitrile) (AIBN) (0.286 g, 1.74 mmol) in toluene (35 mL) was added tributyltin hydride (0.29 mL, 10.8 mmol) dropwise under reflux. Then, the mixture was refluxed for 30 min and concentrated. The residue was purified by column chromatography on silica gel [toluene, then (toluene/acetone, 10:1)] to give 1.07 g (100%) of **5** as a colorless oil: TLC, R_f 0.36 (EtOAc/hexane, 1:5); $[\alpha]^{24}_D$ +28.1 (*c* 0.67, $CHCl_3$); IR (neat) 2950, 2930, 2870, 1670, 1440, 1380, 1305, 1260, 1215, 1170, 1150, 1010 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.33, 1.53 (2 s, 3 H x 2), 1.74 (s, 3 H), 1.25-1.40, 1.50-1.73, 1.85-2.20 (3 m, 1 H, 1 H, 2 H), 3.39 (s, 3 H), 3.34, 3.65 (ABq, *J* = 9.5 Hz, 1 H x 2), 4.00 (d, *J* = 4.8 Hz, 1 H), 4.34 (d, *J* = 3.9 Hz, 1 H), 4.63, 4.67 (ABq, *J* = 9.5 Hz, 1 H x 2), 5.56-5.58 (m, 1 H), 5.89 (d, *J* = 3.9 Hz, 1 H).

Mixture of (1*R*, 6*R*, 7*R*, 8*R* and *S*)-7,8-Dihydroxy-6-[(methoxymethoxy)methyl]-3-methyl-9-oxa-bicyclo[4.3.0]non-2-ene (17β and 17α). A solution of **5** (1.09 g, 3.83 mmol) in 60% aqueous trifluoro-acetic acid (20 mL) was stirred at 0 °C for 11 h. The solution was neutralized with 10 M aqueous NaOH (16 mL), diluted with H_2O (50 mL), and extracted with CH_2Cl_2 (50 mL x 3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel [(EtOAc/hexane, 1:10), toluene, then (toluene/EtOH, 10:1)] to give 0.593 g (63%) of 1:6 mixture of **17α** and **17β** and 0.277 g (25%) of **5** was recovered. The inseparable mixture of **17α** and **17β** as a colorless oil: TLC, R_f 0.18 (EtOAc/hexane, 1:1); IR (neat) 3420, 2930, 1665, 1445, 1380, 1260, 1220 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.71 (s, 3 H x 1/7), 1.73 (s, 3 H x 6/7), 1.22-1.86 (m, 4 H), 3.40 (s, 3 H x 1/7), 3.41 (s, 3 H x 6/7), 3.55, 3.65 (ABq, *J* = 9.9 Hz, 1 H x 2), 3.46-3.50 (m, 1 H), 3.98 (d, *J* = 4.4 Hz, 1 H), 4.25 (d, *J* = 4.8 Hz, 1 H), 4.42-4.45 (m, 1 H), 4.67 (s, 2 H), 5.42-5.54 (m, 1 H), 5.55-5.45 (m, 1 H).

(1*R*,6*R*,7*R*,8*R* and *S*)-7-Hydroxy-8-methoxy-6-[(methoxymethoxy)methyl]-3-methyl-9-oxabicyclo-[4.3.0]non-2-ene (18β and 18α). A solution of the mixture of **17β** and **17α** (2.04 g, 8.35 mmol) in MeOH (40 mL) was stirred at rt for 15 h in the presence of pyridinium *p*-toluenesulfonate (1.05 g, 4.18 mmol). The solution was neutralized with saturated aqueous $NaHCO_3$ (100 mL), and the whole was extracted with CH_2Cl_2 (100 mL x 3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified carefully by column chromatography on silica gel (EtOAc/hexane, 1:4) to give 1.29 g (60%) of **18β** and 0.264 g (12%) of **18α**. Compound **18β** as a colorless oil: TLC, R_f 0. 47 (EtOAc/hexane, 1:1): $[\alpha]^{21}_D$ -71.2 (*c* 1.33, $CHCl_3$); IR (neat) 3425, 2910, 1685, 1460, 1395, 1230, 1210, 1160, 1120, 1060 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.72 (s, 3 H), 1.65-2.02 (m, 4 H), 3.15-3.16 (m, 1 H), 3.40, 3.42 (2 s, 3 H x 2), 3.56, 3.61 (ABq, *J* = 9.9 Hz, 1H x 2), 3.90 (br s, 1 H), 4.11- 4.13 (m, 1 H), 4.64 (s, 2 H), 4.84 (d, *J* = 1.8 Hz, 1 H), 5.54-5.55 (m, 1 H). HRMS calcd for $C_{12}H_{19}O_4$ (M^+- OCH_3) *m/z* 227.1282, found 227.1288. Compound **18α** as a colorless oil: TLC, R_f 0.48 (EtOAc/hexane, 1:1): $[\alpha]^{20}_D$ +65.6 (*c* 1.47, $CHCl_3$); IR (neat) 3470, 2920, 1670, 1470, 1445, 1380, 1305, 1260, 1220, 1170, 1150, 1110, 1045 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.74 (s, 3 H), 1.39-1.50, 1.55-2.07 (2 m, 1H, 3 H), 3.09 (br d, *J* = 5.8 Hz, 1 H), 3.38, 3.50 (2 s, 3 H x 2), 3.44, 3.67 (ABq, *J* = 9.5 Hz, 1 H x 2), 3.96 (t, *J* = 5.1 Hz, 1 H), 4.11 (d, *J* = 4.4 Hz, 1 H), 4.62, 4.66 (ABq, *J* = 6.6 Hz, 1 H x 2), 5.04 (d, *J* = 4.4 Hz, 1 H), 5.53-5.55 (m, 1 H). HRMS calcd $C_{12}H_{19}O_4$ (M^+- OCH_3) *m/z* 227.1282, found 227.1303.

(1*R*,6*R*,7*R*,8*R*)-8-Methoxy-6-[(methoxymethoxy)methyl]-3-methyl-7-[(methyldithiocarbonyl)oxy]-9-oxabicyclo[4.3.0]non-2-ene (19β). The following reaction was carried out under Ar. To a cold (0 °C) stirred suspension of imidazole (949 mg, 13.9 mmol) and sodium hydride (60% emulsion in mineral oil, 930 mg, 23.3 mmol) in THF (10 mL) was added a solution of **18β** (1.20 g, 4.65 mmol) in THF (12 mL). After the mixture was stirred at rt for 30 min, carbon disulfide (1.40 mL, 23.3 mmol) was added at 0 °C. The mixture was stirred at rt for 1 h, then methyl iodide (1.45 mL, 23.3 mmol) was added. The mixture was stirred at rt for an additional 30 min, quenched with EtOH (1 mL), and diluted with H_2O (50 mL). The whole was extracted with CH_2Cl_2 (50 mL x 3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel [toluene, then (EtOAc/toluene, 1:80)] to give 1.56 g (96%) of **19β** as a colorless oil: TLC, R_f 0.58 (EtOAc/hexane, 1:3); IR (neat) 2920, 2880, 1715, 1670, 1440, 1375, 1320, 1210, 1150, 1105, 1065 cm^{-1}; ^1H NMR (270 MHz) δ 1.74 (s, 3 H), 1.92-2.06 (m, 4 H), 2.59 (s, 3 H), 3.34, 3.40 (2 s, 3 H x 2), 3.35-3.59 (m, 2 H), 4.25-4.27 (m, 1 H), 4.59 (s, 2 H), 4.94 (d, J = 1.1 Hz, 1 H), 5.55-5.57 (m, 1 H), 5.81 (d, J = 1.1 Hz, 1 H).

The 8*S* isomer (19α). By using the analogous reaction conditions and workup, compound **18α** (59.5 mg) was converted to 67.5 mg (84%) of **19α** as a colorless oil: TLC, R_f 0.66 (EtOAc/hexane, 1:3); IR (neat) 2920, 2880, 2830, 1670, 1440, 1380, 1315, 1205, 1140, 1130, 1105 cm^{-1}; ^1H NMR (270 MHz) δ 1.75 (s, 3 H), 1.52-1.58, 2.01-2.12 (2 m, 1 H, 3 H), 2.59 (s, 3 H), 3.36, 3.38 (2 s, 3 H x 2), 3.59 (s, 2 H), 4.25-4.27 (m, 1 H), 4.59, 4.64 (ABq, J = 6.2 Hz, 1 H x 2), 5.20 (d, J = 4.7 Hz, 1 H), 5.53-5.55 (m, 1 H), 5.64 (d, J = 4.7 Hz, 1 H).

(1*R*,6*R*,8*R*)-8-Methoxy-6-[(methoxymethoxy)methyl]-3-methyl-9-oxabicyclo[4.3.0]non-2-ene (20β). The following reaction was carried out under Ar. To a refluxing solution of **19β** (1.56 g, 4.48 mmol) and AIBN (368 mg, 2.24 mmol) in benzene (26 mL) was added tributyltin hydride (2.41 mL, 8.96 mmol) dropwise for 10 min. The mixture was refluxed for an additional 30 min and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:12) to give 972 mg (90%) of **20β** as a colorless oil: TLC, R_f 0.45 (EtOAc/hexane, 1:3); $[\alpha]^{23}_D$ -90.6 (*c* 0.57, $CHCl_3$); IR (neat) 2990, 2920, 2880, 2830, 1670, 1465, 1445, 1375, 1360, 1320, 1210, 1195, 1170, 1145, 1110 cm^{-1}; ^1H NMR (270 MHz) δ 1.73 (s, 3 H), 1.76-1.98 (m, 5 H), 2.12 (dd, J = 6.2, 13.6 Hz, 1 H), 3.35, 3.36 (2 s, 3 H x 2), 3.29, 3.41 (ABq, J = 9.3 Hz, 1 H x 2), 4.13-4.14 (m, 1 H), 4.62 (s, 2 H), 5.01 (dd, J = 3.3, 6.2 Hz, 1 H), 5.47-5.49 (m, 1 H).

The 8*S* isomer (20α). By using the analogous reaction conditions and workup, compound **19α** (55.9 mg) was converted to 10.3 mg (26%) of **20α** as a colorless oil: TLC, R_f 0.53 (EtOAc/hexane, 1:3); IR (neat) 2920, 1670, 1470, 1440, 1380, 1325, 1310, 1290, 1250, 1205, 1150, 1100, 1070 cm^{-1}; ^1H NMR (270 MHz) δ 1.74 (s, 3 H), 1.46-1.60, 1.76-1.97 (2 m, 2 H, 2 H), 2.02 (d, J = 4.4 Hz, 2 H), 3.35, 3.37 (2 s, 3 H x 2), 3.35, 3.47 (ABq, J = 10.6 Hz, 1 H x 2), 4.01-4.03 (m, 1 H), 4.61 (s, 2 H), 5.04 (t, J = 4.4 Hz, 1 H), 5.57-5.59 (m, 1 H).

(1*R*,6*R*)-6-[(Methoxymethoxy)methyl]-3-methyl-9-oxabicyclo[4.3.0]non-2-en-8-one (4). From 20β. To a cold (0 °C) stirred solution of **20β** (972 mg, 4.01 mmol) in acetone (20 mL) was added Jones reagent (5.30 mL, 12.0 mmol) dropwise. The mixture was stirred at 0 °C for 30 min, quenched with 2-propanol (2 mL), and diluted with H_2O (50 mL). The whole was extracted with CH_2Cl_2 (50 mL x 3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by

column chromatography on silica gel (EtOAc/hexane, 1:4) to give 712 mg (76%) of **4** and 150 mg (15%) of **20β** was recovered. Compound **4** as a colorless oil: TLC, R_f 0.19 (EtOAc/hexane, 1:4); $[\alpha]^{23}_D$ -10.6 (*c* 1.19, $CHCl_3$); IR (neat) 2920, 1770, 1670, 1440, 1415, 1375, 1360, 1325, 1300, 1270, 1240, 1230, 1195, 1145, 1105 cm^{-1}; ^1H NMR (270 MHz) δ 1.69-1.75 (m, 2 H), 1.77 (s, 3 H), 2.01-2.06 (m, 2 H), 2.39, 2.61 (ABq, *J* = 17.4 Hz, 1 H x 2), 3.36 (s, 3 H), 3.42, 3.47 (ABq, *J* = 9.5 Hz, 1 H x 2), 4.63 (s, 2 H), 4.66-4.68 (m, 1 H), 5.54-5.57 (m, 1 H); HRMS calcd for $C_{12}H_{18}O_4$ (M^+) *m/z* 226.1203, found 226.1189.

As analogously described for **20β**, **20α** (9.2 mg) was converted to 7.2 mg (84%) of **4**.

Mixture of (1*R*,6*R*,7*R*)-6-[(Methoxymethoxy)methyl]-3,7-dimethyl-9-oxabicyclo-[4.3.0]non-2-en-8-one (21) and its 7-epimer (22). The following reaction was carried out under Ar. To a cold (0 °C) stirred solution of diisopropylamine (2.08 mL, 12.9 mmol) in THF (10 mL) was added *n*-butyllithium (1.6 M solution in hexane, 8.03 mL, 12.9 mmol). The mixture was stirred at 0 °C for 1 h, and a solution of **4** (1.17 g, 5.17 mmol) in THF (12 mL) was added at -78 °C. After the mixture was stirred at -78 °C for 30 min, methyl iodide (1.61 mL, 25.9 mmol) was added. The mixture was stirred at -78 °C for 30 min then at 0 °C for 1 h, and quenched with saturated aqueous NH_4Cl (50 mL). The whole was extracted with CH_2Cl_2 (50 mL x 3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to give 1.20 g (96%) of **21**, which was contaminated by ca. 6% of the 7*S* isomer **22** judging from the ^1H NMR spectrum, as a colorless oil: TLC, R_f 0.32 (EtOAc/hexane, 1:3); $[\alpha]^{23}_D$ +15.9 (*c* 1.02, $CHCl_3$); IR (neat) 2920, 1765, 1670, 1440, 1380, 1340, 1300, 1240, 1200, 1145, 1105 cm^{-1}; ^1H NMR (270 MHz) for **21** δ 1.15 (d, *J* = 7.4 Hz, 3 H), 1.57-1.85 (m, 2 H), 1.73 (s, 3 H), 2.01-2.13 (m, 2H), 2.58 (q, *J* = 7.4 Hz, 1 H), 3.36 (s, 3 H), 3.35, 3.46 (ABq, *J* = 10.1 Hz, 1 H x 2), 4.61 (s, 2 H), 4.79-4.80 (m, 1 H), 5.46-5.47 (m, 1 H). HRMS calcd for $C_{13}H_{20}O_4$ (M^+) *m/z* 240.1360, found 240.1344.

(1*R*,6*R*,7*R*)-7-Allyl-6-[(methoxymethoxy)methyl]-3,7-dimethyl-9-oxabicyclo-[4.3.0]non-2-en-8-one (3). The following reaction was carried out under Ar. To a cold (0 °C) solution of diisopropylamine (3.21 mL, 20.0 mmol) in THF (8 mL) was added *n*-buthyllithium (1.6 M solution in hexane, 12.4 mL, 20.0 mmol). After being stirred at 0 °C for 1 h, a solution of the 15:1 diastereomeric mixture of **21** and **22** (1.20 g, 4.99 mmol) in THF (12 mL) was added at -78 °C. The mixture was stirred at -78 °C for 30 min, and then allyl bromide (3.02 mL, 34.9 mmol) was added. The mixture was stirred at -78 °C for 30 min then at 0 °C for 2 h, and quenched with saturated aqueous NH_4Cl (50 mL). The whole was extracted with CH_2Cl_2 (50 mL x 3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to give 1.25 g (89%) of **3** as a colorless oil: TLC, R_f 0.52 (EtOAc/hexane, 1:3); $[\alpha]^{21}_D$ +2.5 (*c* 0.61, $CHCl_3$); IR (neat) 2980, 2930, 2910, 1765, 1675, 1640, 1485, 1440, 1380, 1340, 1325, 1295, 1240, 1200, 1150 cm^{-1}; ^1H NMR (270 MHz) δ 1.19 (s, 3 H), 1.76 (s, 3 H), 1.96-2.13 (m, 4 H), 2.33 (dd, *J* = 7.4, 14.0 Hz, 1 H), 2.57 (dd, *J* = 6.6, 14.0 Hz, 1 H), 3.40 (s, 3 H), 3.43, 3.60 (ABq, *J* = 10.3 Hz, 1 H x 2), 4.37 (d, *J* = 5.1 Hz, 1 H), 4.59, 4.62 (ABq, *J* = 6.6 Hz, 1 H x 2), 5.10-5.16 (m, 2 H), 5.58-5.60 (m, 1 H), 5.78-5.94 (m, 1 H). HRMS calcd for $C_{16}H_{24}O_4$ (M^+) *m/z* 280.1672, found 280.1657. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.55; H, 8.37.

Mixture of (1*R*,6*R*,7*R*)-7-[(2*R* and *S*)-2,3-(Dihydroxypropyl)]-6-[(methoxymethoxy)methyl]-3,7-di-methyl-9-oxabicyclo[4.3.0]non-2-en-8-one (23*R* and 23*S*). To a cold (0 °C) stirred solution of **3** (450 mg, 1.61 mmol) in 50% aqueous acetone (9 mL) were added 4-methylmorpholine N-oxide (226 mg, 1.93 mmol) and osmium tetroxide (0.05 M solution in *t*-BuOH, 3.22 mL, 0.61 mmol). The mixture was stirred at rt for 3 h, and 10% aqueous $NaHSO_3$ (25 mL) was added. The mixture was stirred at rt for 30 min, and the whole was extracted with CH_2Cl_2 (25 mL x 3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (acetone, toluene, 1:2) to give 425 mg (84%) of inseparable mixture of **23*R*** and **23*S*** as a colorless oil: TLC, R_f 0.19 (acetone/toluene, 1:2); IR (neat) 3420, 2920, 1750, 1670, 1440, 1380, 1240 cm^{-1}; ^1H NMR (270 MHz) δ 1.27 (s, 3 H x 9/19), 1.37 (s, 3 H x 10/19), 1.77 (s, 3 H), 1.31-1.37, 1.57-2.10 (2 m, total 6 H), 2.22-2.37 (br, 1 H), 2.86 (br s, 1 H x 9/19), 3.01 (br s, 1 H x 10/19), 3.37 (s, 3 H x 10/19), 3.39 (s, 3 H x 9/19), 3.40-3.62 (m, 4 H), 3.84-3.94 (m, 1 H x 9/19), 3.96-4.08 (m, 1 H x 10/19), 4.37 (br d, J = 5.1 Hz, 1 H x 9/19), 4.49 (br d, J = 4.8 Hz, 1 H x 10/19), 4.54-4.63 (m, 2 H), 5.58-5.63 (m, 1 H). HRMS calcd for $C_{16}H_{26}O_6$ (M^+) *m/z* 314.1727, found 314.1739.

(1*R*,6*R*,7*R*)-7-[(2*E* and *Z*)-3-(Ethoxycarbonyl)-2-propenyl]-6-[(methoxymethoxy)methyl]-3,7-di-methyl-9-oxabicyclo[4.3.0]non-2-en-8-one (25*E* and 25*Z*). To a cold (0 °C) stirred solution of the mixture of **23*R*** and **23*S*** (414 mg, 1.32 mmol) in MeOH (4.5 mL) was an aqueous solution (3 mL) of $NaIO_4$ (338 mg, 1.58 mmol). The mixture was stirred at rt for 15 min, and the resulting precipitates were removed by filtration, washed well with CH_2Cl_2. The combined filtrate and washings were concentrated. The residue was partitioned between CH_2Cl_2 (25 mL) and H_2O (25 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL x 2). The combined organic layers were dried (Na_2SO_4) and concentrated to give 326 mg of crude aldehyde **24**, which was used for next step, as a colorless oil: IR (neat) 2920, 2750, 1760, 1715, 1670, 1440, 1380, 1290 cm^{-1}; ^1H NMR (270 MHz) δ 1.38 (s, 3 H), 1.78 (s, 3 H), 1.58-2.18 (m, 4 H), 2.64 (d, J = 2.9 Hz, 2 H), 3.38 (s, 3 H), 3.34, 3.51 (ABq, J = 10.7 Hz, 1 H x 2), 4.42 (br d, J = 4.9 Hz, 1 H), 4.54 (s, 2 H), 5.56-5.70 (m, 1 H), 9.81 (t, J = 2.9 Hz, 1 H).

To a stirred solution of the crude aldehyde **24** (326 mg) in benzene (8 mL) was added (ethoxycarbonyl)-methylenetriphenylphosphorane (690 mg, 1.98 mmol). The mixture was refluxed for 1 h and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give 349 mg (75%) of **25*E*** and 27 mg (6%) of **25*Z***. Compound **25*E*** as a colorless oil: TLC, R_f 0.42 (EtOAc/hexane, 1:2); $[\alpha]^{26}_D$ +25.8 (*c* 0.72, $CHCl_3$); IR (neat) 2980, 2905, 1760, 1710, 1670, 1650, 1440, 1380, 1270 cm^{-1}; ^1H NMR (270 MHz) δ 1.22 (s, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.77 (s, 3 H), 1.25-1.40, 1.98-2.09 (2 m, 1 H, 3 H), 2.51 (ddd, J = 1.1, 8.2, 14.3 Hz, 1 H), 2.65 (ddd, J = 1.1, 7.2, 14.3 Hz, 1 H), 3.40 (s, 3 H), 3.46, 3.53 (ABq, J = 10.3 Hz, 1 H x 2), 4.18 (q, J = 7.2 Hz, 2 H), 4.34 (d, J = 5.1 Hz, 1 H), 4.57, 4.61 (ABq, J = 6.6 Hz, 1 H x 2), 5.59-5.62 (m, 1 H), 5.89 (d, J = 15.6 Hz, 1 H), 6.98 (ddd, J = 7.2, 8.2, 15.6 Hz, 1 H). HRMS calcd for $C_{19}H_{28}O_6$ (M^+) *m/z* 352.1884, found 352.1912. Compound **25*Z*** as a colorless oil: TLC, R_f 0.49 (EtOAc/hexane, 1:2); $[\alpha]^{26}_D$ +3.6 (*c* 0.77, $CHCl_3$); IR (neat) 2905, 1765, 1730, 1670, 1650, 1435, 1380, 1360, 1200 cm^{-1}; ^1H NMR (270 MHz) δ 1.24 (s, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.77 (s, 3 H), 1.33-1.42, 1.97-2.13 (2 m, 1 H, 3 H), 3.07 (ddd, J = 1.1, 7.3, 15.6 Hz, 1 H), 3.22 (ddd, J = 1.1, 7.3, 15.6 Hz, 1 H), 3.39 (s, 3 H), 3.48, 3.56 (ABq, J = 10.3 Hz, 1 H x 2), 4.15 (q, J = 7.2 Hz, 2 H), 4.42 (d, J = 4.8 Hz, 1 H), 4.59, 4.64 (ABq, J = 6.9 Hz, 1 H x 2), 5.59-5.62 (m, 1 H), 5.92 (dt, J = 1.8, 11.4 Hz, 1 H), 6.41 (dt, J = 7.3, 11.4 Hz).

(1*R*,6*R*,7*R*)-7-[3-(Methoxycarbonyl)propyl]-6-[(methoxymethoxy)methyl]-3,7-dimethyl-9-oxa-bicyclo[4.3.0]non-2-en-8-one (2). The following reaction was carried out under Ar. A solution of **25*E*** (380 mg, 1.08 mmol) in MeOH (8 mL) was ultrasonicated in the presence of magnesium metal (79 mg, 3.3 mmol) at rt for 7 h. The mixture was 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 (EtOAc/hexane, 1:4) to give 317 mg (86%) of **2** as a colorless oil: TLC, R_f 0.42 (EtOAc/hexane, 1:2); $[\alpha]^{26}_D$ -4.5 (*c* 0.54, $CHCl_3$); IR (neat) 2980, 2950, 1760, 1730, 1670, 1440, 1370 cm^{-1}; ^1H NMR (270 MHz) δ 1.21 (s, 3 H), 1.76 (s, 3 H), 1.24-1.40, 1.62-1.89, 1.98-2.09 (3 m, 1 H, 4 H, 3 H), 2.29-2.37 (m, 2 H), 3.37 (s, 3 H), 3.41, 3.56 (ABq, J = 10.0 Hz, 1 H x 2), 3.66 (s, 3 H), 4.33 (d, J = 4.3 Hz, 1 H), 4.56, 4.60 (ABq, J = 6.6 Hz, 1 H), 5.57-5.60 (m, 1 H). HRMS calcd for $C_{18}H_{28}O_6$ (M^+) *m/z* 340.1883, found 340.1864.

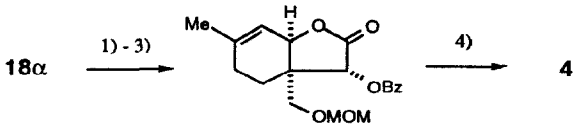
Mixture of (1*R*, 3*R*, 8*R*, 9*R*, 12*R* and *S*)-1-Hydroxy-12-(methoxycarbonyl)-8-[(methoxymethoxy)-methyl]-5,9-dimethyl-2-oxatricyclo[7.3.0.0^{3,8}]dodec-4-ene (26*R* and 26*S*). The following reaction was carried out under Ar. To a cold (-78 °C) stirred solution of potassium bis(trimethylsilyl)amide (0.5 M solution in toluene, 1.17 mL, 0.59 mmol) in THF (1.5 mL) was added a solution of **2** (100 mg, 0.29 mmol) in THF (1.5 mL). The mixture was stirred at -78 °C for 10 min, and quenched with saturated aqueous NH_4Cl (10 mL). This was extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give 69 mg (70%) of inseparable mixture of **26*R*** and **26*S*** as a colorless oil: TLC, R_f 0.43 (EtOAc/hexane, 1:2); IR (neat) 3450, 2950, 2880, 1760 (s), 1735, 1670, 1435, 1380, 1345, 1300, 1270 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.13 (s, 3 H x 5/9), 1.18 (s, 3 H x 4/9), 1.71 (s, 3 H x 4/9), 1.72 (s, 3 H x 5/9), 1.45-1.80, 1.89-2.35 (2 m, 1 H, 7 H), 2.93-3.12 (m, 1 H), 3.37-3.50 (m, total 5 H), 3.72 (s, 3 H x 5/9), 3.74 (s, 3 H x 4/9), 3.81 (d, J = 4.9 Hz, 1 H x 4/9), 3.86 (d, J = 4.9 Hz, 1 H x 5/9), 4.05 (s, 1 H x 4/9), 4.45 (s, 1 H x 5/9); 4.54-4.67 (m, 2 H), 5.00-5.54-5.56 (m, 1 H). HRMS calcd for $C_{18}H_{28}O_6$ (M^+) *m/z* 340.1883, found 340.1874.

Mixture of (1*S*, 3*R*, 8*R*, 9*R*, 12*R* and *S*)-1-(*t*-Butyldimethylsilyl)oxy-12-(methoxycarbonyl)-8-[(methoxymethoxy)methyl]-5,9-dimethyl-2-oxatricyclo[7.3.0.0^{3,8}]-dodec-4-ene (1*R* and 1*S*). The following reaction was carried out under Ar. To a cold (0 °C) stirred solution of the mixture of **26*R*** and **26*S*** (193 mg, 0.57 mmol) in CH_2Cl_2 (4 mL) were added *t*-butyldimethylsilyl trifluoromethanesulfonate (0.39 mL, 1.7 mmol) and 2,6-lutidine (0.37 mL, 3.4 mmol). The mixture was stirred at rt for 1 h, and diluted with EtOAc (10 mL). The whole was washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated brine (10 mL x 2). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to give 190 mg (74%) of inseparable mixture of **1*R*** and **1*S*** as a colorless oil: TLC, R_f 0.65 (EtOAc/hexane, 1:2); IR (neat) 2950, 2930, 2880, 2850, 1735, 1675, 1470, 1460, 1445, 1385, 1370, 1345, 1250, 1200 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.05, 0.18 (2 s, each 3 H x 5/9), 0.05, 0.17 (2 s, each 3 H x 4/9), 0.84 (s, 3 H x 4/9), 0.87 (s, 9 H x 5/9), 1.09 (s, 3 H x 5/9), 1.20 (s, 3 H x 4/9), 1.68 (s, 3 H), 1.45-1.55, 1.73-2.05, 2.10-2.40 (3 m, total 8 H), 2.93-3.00 , 3.00-3.08 (2 m, total 1 H), 3.28-3.48 (m, 2 H), 3.35 (s, 3 H x 5/9), 3.36 (s, 3

H x 5/9), 3.62 (s, 3 H x 4/9), 3.66 (s, 3 H x 5/9), 3.77-3.83 (m, 1 H), 4.52-4.60 (m, 2 H), 5.41-5.44 (m, 1 H x 5/9), 5.50-5.52 (m, 1 H x 4/9). HRMS calcd for $C_{24}H_{42}O_6Si$ (M^+) *m/z* 454.2748, found 454.2748.

REFERENCES AND NOTES

1. Present address: Department of Chemistry, Hokkaido University, Sapporo 060, Japan
2. A recent review: Grove, J. F. *Nat. Prod. Rep.* **1988**, 187.
3. Freeman, G. G.; Morrison, R. I. *Nature* **1948**, *162*, 30.
4. Ueno, Y. *Trichothecens-Chemical, Biological and Toxicological Aspects, Developments in Food Science-4* ; Elsevier: New York, 1983.
5. Doyle, T. W.; Bradner, W. T. In *Anticancer Agents Based on Natural Product Models*; Cassady, J. M.; Douros, J. D., Eds.; Academic: New York, 1980; p. 43.
6. A leading review: McDougal, P. G.; Schmuff, N. R. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Grisebach, H.; Kirby, G. W.; Tamm, Ch. Eds.; Springer-Verlag: New York, 1985; Vol. 47, p. 153.
7. a) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116. b) Trost, B. M.; McDougal, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 6110. c) Roush, W. R.; D'Ambra T. E. *J. Am. Chem. Soc.* **1983**, 105, 1058.
8. Kraus, G. A.; Roth, B.; Frazier, K.; Shimagaki, M. *J. Am. Chem. Soc.* **1982**, *104*, 1114.
9. Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *J. Am. Chem. Soc.* **1983**, *105*, 4472.
10. Other carbohydrate-based synthetic approaches toward trichothecenes: a) Fraser-Reid, B.; Tsang, R. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic: New York, 1989; Vol. 2, p. 123. b) Ferrier, R. J.; Hall, D. W.; Petersen, P. M. *Carbohydr. Res.* **1993**, *239*, 143.
11. Previously, the preparation of compound **4** in racemic form was reported: Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 658. We thank a referee for noticing us the valuable information on this precedent.
12. Tadano, K.; Isshiki, Y.; Minami, M.; Ogawa, S. *Tetrahedron Lett.* **1992**, *33*, 7899; idem, *J. Org. Chem.* **1993**, *58*, 6266.
13. Tadano, K.; Idogaki, Y.; Yamada, H.; Suami, T. *Chem. Lett.* **1985**, 1925; idem, *J. Org. Chem.* **1987**, *52*, 1201.
14. Natural products synthesis using **8** as a chiron: Tadano, K. In *Studies in Natural Products Chemistry*, Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1992; Vol. 10, p.405.
15. Our previous reports on the analogous cyclization strategy applied to carbohydrate-derived substrates for five- and six-membered carbocycles formation, see: a) Tadano, K.; Maeda, H.; Hoshino, M.; Iimura, Y.; Suami, T. *J. Org. Chem.* **1987**, *52*, 1946. b) Tadano, K.; Murata, T.; Kumagai, T.; Isshiki, Y.; Ogawa, S. *J. Carbohydr. Chem.* **1993**, *12*, 1187.
16. Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957.
17. We also investigated the transformation of **18α** into **4** by a different approach as follows: 1) BzCl / pyr. (91%); 2) 60% aqueous TFA (55%); 3) Jones oxidation (78%) (**18α** to **27**); and 4) SmI_2 / *i*-PrOH + HMPA (57%). The overall yield (22%) of **4** by this reaction sequence did not exceed significantly that obtained by the route via the radical deoxygenation of **19α**. For the SmI_2-mediated deoxygenation of α-acyloxy aldolactones, see: Hanessian, S.; Girard, C.; Chiara, J. L. *Tetrahedron Lett.* **1992**, *33*, 573.



27

18. On the α-methylation of the racemic lactone **4**, Colvin and co-workers reported that they isolated racemic **21** (presumably) as a sole product in 75% yield (see, ref. 11) In our case, the base (LDA) was same as used in the precedent, but the reaction temperature (-78 °C to 0 °C) and solvent (THF) of our conditions were different (vs. reflux, ether). Although our conditions provided the mixture of **21** and **22** (15:1), the second alkylation of the mixture with allyl bromide resulted in the sole formation of **3** in a good yield.

19. VanRheene, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

20. Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409.

21. The following conditions were examined for the Dieckmann cyclization of **2**: 1) NaH / THF / 0 °C to reflux (no cyclization occurred but the corresponding side chain carboxylic acid was obtained in 95% yield); 2) MeONa / MeOH / 0 °C to rt (quantitative recovery of **2**); 3) LDA / THF / -78 °C to rt (85% recovery of **2**); 4) LiHMDS / THF / -78 to 50 °C (81% recovery of **2**); Na HMDS / THF / -78 to 50 ° C (56% recovery of **2**).

22. The cyclization products, the mixture of ***26R*** and ***26S***, are prone to occur a retro-Dieckmann cyclization returning back to **2**. When the mixture of ***26R*** and ***26S*** was subjected to a standard O-benzylation conditions (NaH / DMF, then BnBr / rt / 40 min), only retro-Dieckmann reaction occurred to give **2** in 73% yield. However, the silyl ethers ***1R*** and ***1S*** are quite stable under basic conditions.

(*Received* 22 *August* 1994)