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Stereochemical revision of communiols D and H through synthesis

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Abstract—Based on the previously revised stereochemistries for communiols A–C, the *ent*-8-*epi*- and *ent*-6-*epi*-stereoisomers of the original structures proposed for communiols D and H, respectively, were synthesized as highly probable candidates for their genuine structures by using the Sharpless asymmetric dihydroxylation as the source of chirality. Complete accord in spectral properties between each synthetic candidate and the corresponding natural material as well as the fact that communiols A–D and H were all isolated from the same fungal source, led us to the conclusion that the stereochemistries of communiols D and H should also be revised to their (3*S*,5*S*,7*R*,8*S*,11*R*)- and (5*S*,7*R*,8*S*)-forms, respectively.

1. Introduction

In the course of their search for antimicrobial substances produced by coprophilous (dung-colonizing) fungi, Gloer and co-workers isolated four novel polyketide motabolites (communiols A–D, Fig. 1) from horse dung-colonizing *Podospora communis*, and determined their structures by spectroscopic methods including extensive 2D NMR experiments.[1] Quite recently, they also reported the isolation and structural determination of communiol H together with three other structurally-related cyclopentanoids (communiols E–G) from cultures of the same fungus.[2] Communiols A–C (**3**–**5**) showed significant antimicrobial activity against *Bacillus subtilis* and *Staphylococcus aureus*, while communiols D (**1**) and H (**2**) exhibited no such activity. The 2,4-disubstituted tetrahydrofuran substructure incorporated in **3**–**5** is relatively rare as a structural unit of natural products and displays a characteristic difference in substitution pattern from 2,5-disubstituted tetrahydrofurans frequently found in annonaceous acetogenins[3] or ionophores.[4] The 3,7-disubstituted 2,8-dioxabicyclo[3.3.0]-octane structure contained in communiol D (**1**) is also rare, although some related structural units analogous to but different in substitution and/or oxidation patterns from the bicyclic portion of **1** have been found in many natural products such as clerodane diterpenoids and fungal metabolites.[5] The structural uniqueness of communiols A–C (**3**–**5**), coupled with their interesting biological activity, prompted us to undertake the synthesis of **3**–**5**, which recently culminated in their stereochemical revision as described in our previous paper,[6] wherein the genuine stereochemistries of communiols A, B and C were concluded to be represented by structures *ent*-8-*epi*-**3**, *ent*-8-*epi*-**4** and *ent*-6-*epi*-**5**, respectively (Fig. 2). The corrected stereochemistries of **3**–**5**, as well as our presumption that the structurally-related metabolites (communiols D and H) of the same microbial origin should have the same stereochemical arrangement as communiols A–C, led us to

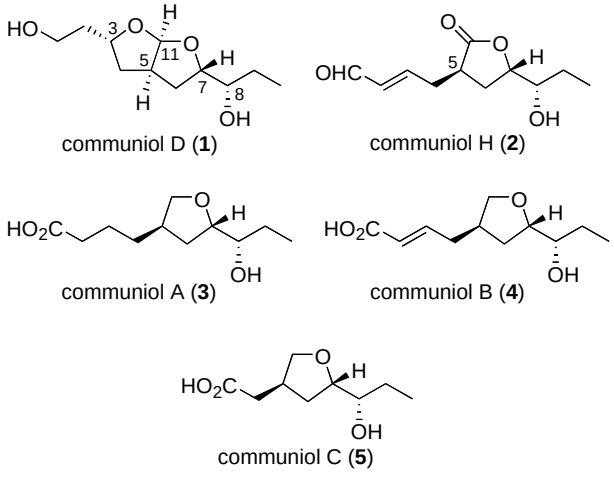

Figure 1. Originally proposed stereochemistries for communiols A–D and H.

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suppose that the genuine stereochemistries of communiols D and H might be exhibited by structures *ent*-8-*epi*-**1** and *ent*-8-*epi*-**2**, respectively (see Scheme 1). Herein, we describe the enantioselective synthesis of the newly proposed stereoisomers for communiols D and H, which eventually enabled us to revise their stereochemistries as shown later in this paper.

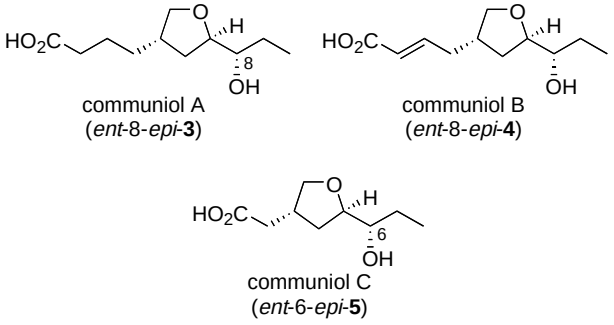
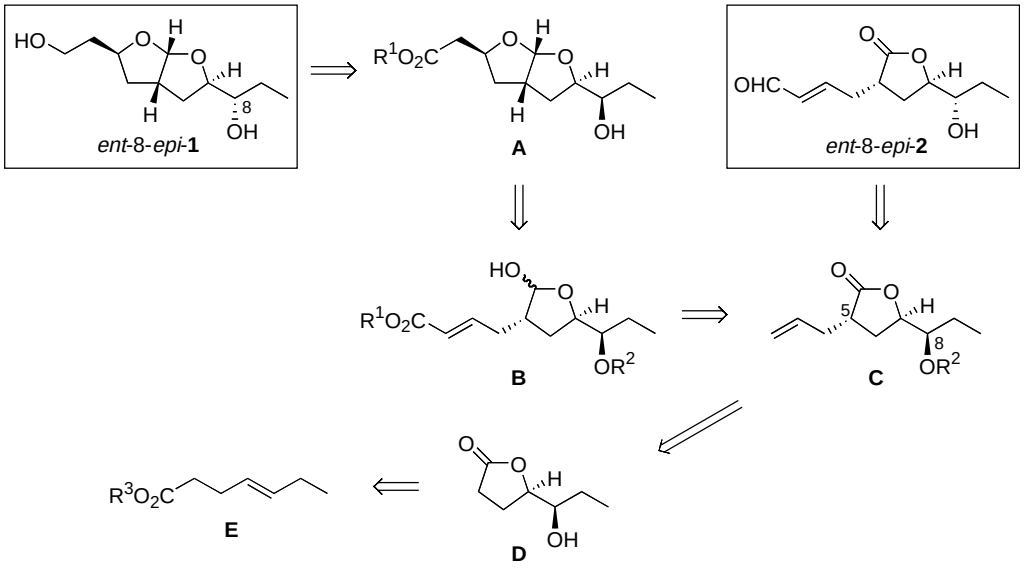


Figure 2. Revised stereochemistries for communiols A–C.

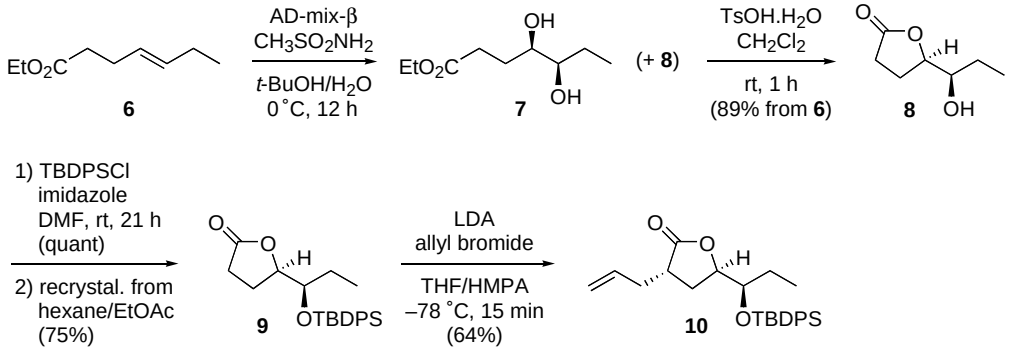
Our retrosynthetic analysis of *ent*-8-*epi*-**1** and *ent*-8-*epi*-**2** is depicted in Scheme 1. The 2,8-dioxabicyclo[3.3.0]octane structural unit in *ent*-8-*epi*-**1** was considered to be installable by the intramolecular Michael addition of lactol **B** into **A**, which, in turn, would readily be converted into the target molecule through inversion of the stereochemistry of the C8–OH and subsequent reduction of the ester group. The intermediate **B** would be obtainable from lactone **C** via elongation of the C5-side chain and reduction of the lactone moiety. Retrosynthetic dissection of the allyl substituent of **C** would lead to known hydroxy lactone **D**, which had previously been prepared from D-glutamic acid in modest yields through four steps.[7] In order to prepare **D**, we adopted the Sharpless asymmetric dihydroxylation of olefinic ester **E** followed by lactonization of the resulting diol, due to its simple experimental operation as compared to the previous procedure. In the synthetic plan presented in Scheme 1, we need to invert the original (*R*)-stereochemistry of the hydroxyl group in **D** (*threo* isomer) at the final stage of the synthesis, which might be avoidable by using *erythro*-**D** possessing the opposite absolute configuration at the OH-bearing stereogenic center. The preparation of the epimeric lactone (*erythro*-**D**) would demand the asymmetric dihydroxylation of the (*Z*)-isomer of olefin **E**. However, utilization of the (*Z*)-isomer as the substrate for the Sharpless asymmetric dihydroxylation was considered to be inappropriate based on a general rule that (*Z*)-olefinic substrates give only modest enantioselectivities on exposure to the asymmetric dihydroxylation conditions, while the (*E*)-olefins can be converted into the corresponding diols with constantly high enantioselectivities.[8] This consideration made us choose **D** as our synthetic intermediate, despite the additional stereoinversion process required at a later stage of the synthesis. As for *ent*-8-*epi*-**2**, transformation of the common intermediate **C** into the target aldehyde seemed to be effected straightforwardly through the inversion of the C8-stereochemistry of **C** and chain-elongation at its C5-side chain.

2. Results and discussion

Our synthesis of the common synthetic intermediate **C** (**10**, in Scheme 2) began with the Sharpless asymmetric dihydroxylation[8,9] of known olefinic ester **6**[10,11] using AD-mix-β as the chiral catalyst. Exposure of the resulting crude product consisting of diol **7** and its lactonization product **8** to acidic conditions brought about complete conversion of **7** into **8**, whose ^{1}H NMR spectrum was in good agreement with that reported for an authentic sample of **8** previously prepared from D-glutamic acid.[7] The absolute stereochemistry of **8** was confirmed by comparison of its specific rotation value ($[\alpha]_D^{22}$ −41.3 (*c* 2.25, CH_2Cl_2)) with the literature value ($[\alpha]_D^{22}$ −46.2 (*c* 2.25, CH_2Cl_2)),[7] and the enantiomeric excess of **8** was estimated to be 96% by analyzing the ^{1}H NMR spectra of the corresponding (*R*)- and (*S*)-MTPA esters.[12] The protection of the hydroxyl group of **8** as its TBDPS ether proceeded uneventfully to



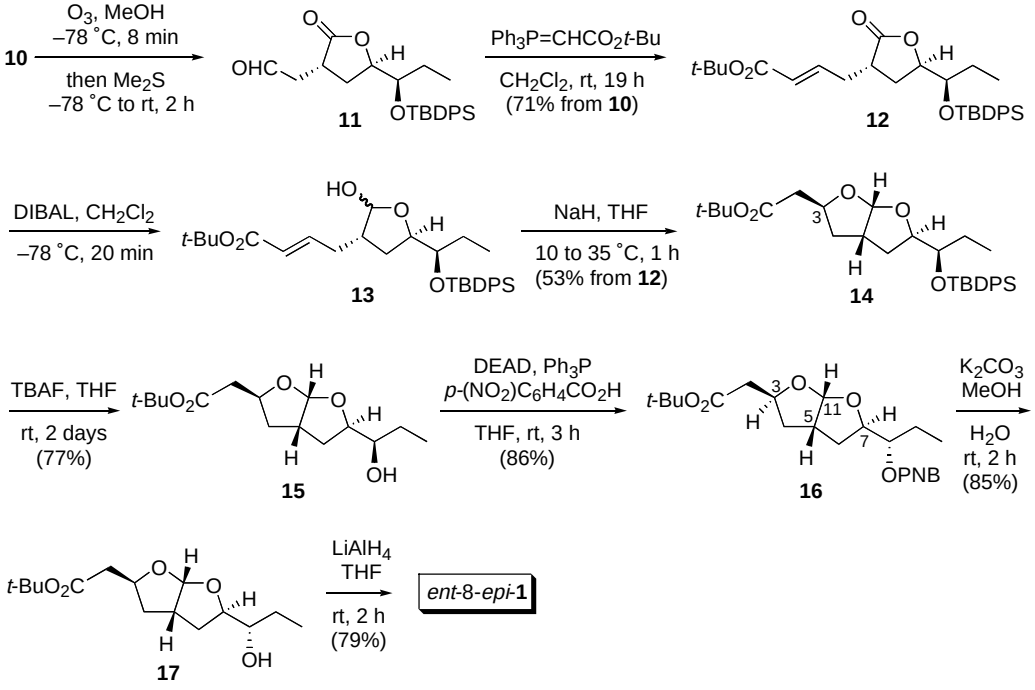
Scheme 1. Retrosynthetic analysis of *ent*-8-*epi*-**1** and *ent*-8-*epi*-**2**.



Scheme 2. Synthesis of common synthetic intermediate **10**.

afford **9** quantitatively. Quite fortunately, and expectedly to some extent, the TBDPS ether **9** was obtained as crystals, which enabled us to enrich the enantiomeric excess of **9** to 100% by a single recrystallization of the crystalline product from hexane/ethyl acetate. The optical integrity of **9** was checked by inspection of the ^{1}H NMR spectra of the corresponding (*R*)- and (*S*)-MTPA esters, which, in turn, were prepared by treatment of the optically enriched silyl ether **9** with TBAF and subsequent (*R*)- and (*S*)-MTPA esterifications of the resulting alcohol **8** ($[\alpha]_D^{22}$ −46.8 (*c* 0.24, CH_2Cl_2)). The protected lactone **9** was then subjected to well-documented trans-selective alkylation with allyl bromide,[13,14] which afforded an 8.3:1 mixture of desired product **10** and the corresponding cis-allylation product in 90% combined yield.[15] Careful chromatographic purification of the mixture, then, furnished diastereomerically pure trans-lactone **10** in 64% isolated yield.

Having secured a sufficient amount of the common synthetic intermediate **10**, we next turned our attention to its elaboration into *ent*-8-*epi*-**1** (Scheme 3), which we considered as the genuine structure for communiol D. Ozonolysis of **10** gave aldehyde **11**, which without purification was subjected to Wittig olefination conditions to afford *t*-butyl ester **12**. Chemoselective reduction of the lactone carbonyl of **12** was achieved by using DIBAL in CH_2Cl_2 to give lactol **13** as an inseparable 2.8:1 mixture of epimers.[15] Upon exposure to NaH in THF, the lactol **13** cyclized intramolecularly into a 6.3:1 mixture of desired bis-THF derivative **14** and its C3-epimer in 53% combined yield from **12**.[15] The preferential formation of the *exo*-stereoisomer **14** could readily be rationalized by considering thermodynamic stability among possible cyclization products (Fig. 3). Of the two possible alkoxide intermediates, **13**α and **13**β, the β-alkoxide intermediate (**13**β) could not cyclize into **14**β due to its extremely strained trans-fused bicyclo[3.3.0]octane system. The intramolecular Michael cyclization of the other alkoxide **13**α, which should also arise from **13**β through an open-chain intermediate, would produce two bis-THF intermediates, *exo*-**14**α and *endo*-**14**α, and higher thermodynamic stability of *exo*-**14**α possessing the C3-substituent on the convex face of the bicyclic system should have driven the equilibrium via retro-Michael reaction from less stable *endo*-**14**α with



Scheme 3. Synthesis of *ent*-8-*epi*-**1**, the newly proposed structure for communiol D.

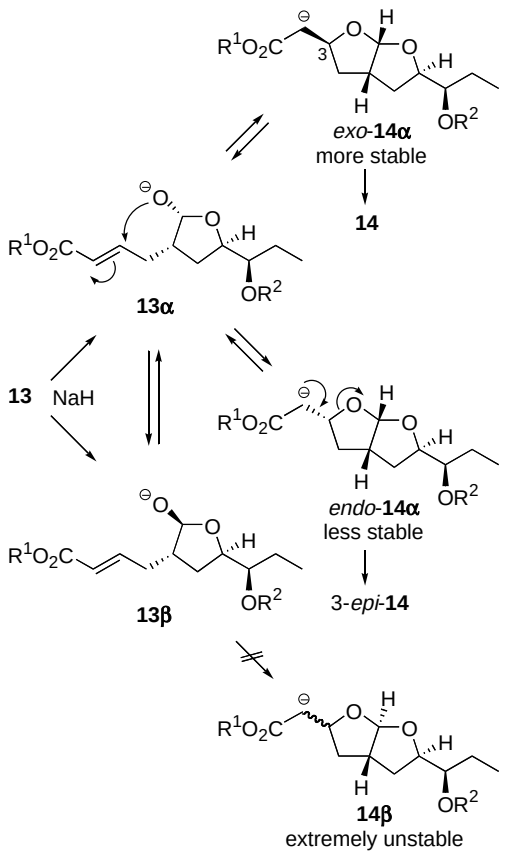


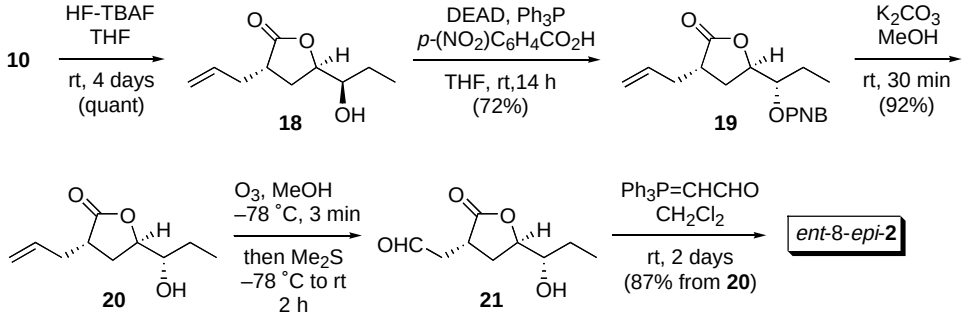
Figure 3. Preferential formation of **14**.

the C3-side chain on the concave face to more stable *exo*-**14α** leading eventually to **14** after aqueous workup. Since the separation of the epimers was difficult at this stage, **14** was subjected, as the mixture, to deprotection of the silyl group followed by the Mitsunobu inversion[16] of the C8-stereochemistry of the resulting alcohol **15** to give diastereomerically pure **16** after simple chromatographic purification. The stereochemistry of **16** was confirmed by observing diagnostic NOE correlations between C3-H and C7-H, and C5-H and C11-H. Finally, methanolysis of the PNB-ester to **17** and subsequent reduction of the *t*-butyl ester group afforded *ent*-8-*epi*-**1**. Direct comparison of the ^{1}H and ^{13}C NMR spectra of *ent*-8-*epi*-**1** with those of natural communiol D assured that these two samples were, as expected, identical, and the optical rotation value of *ent*-8-*epi*-**1** ($[\alpha]_D^{22}$ +3.0 (*c* 0.22, CH_2Cl_2)) also exhibited good agreement with that of natural communiol D ($[\alpha]_D$ +2.7 (*c* 0.3, CH_2Cl_2)).[1] On the basis of these facts, we concluded that the stereochemistry of communiol D, including its absolute configuration, should be represented by *ent*-8-*epi*-**1**.

We next set about the synthesis of *ent*-8-*epi*-**2**, which we presumed to be the real structure of communiol H (Scheme 4). Deprotection of **10** and subsequent inversion of the stereochemistry of the resulting alcohol **18** yielded **19**. Methanolytic removal of its PNB group afforded **20**, the double bond of which was then cleaved by ozonolysis to give aldehyde **21**. Two-carbon elongation of **21** by the Wittig reaction furnished the target molecule, *ent*-8-*epi*-**2**. The ^{1}H and ^{13}C NMR data of *ent*-8-*epi*-**2** were completely identical with those of natural communiol H,[17] which enabled us to revise the relative stereochemistry of communiol C to the 7,8-*erythro*-form of its original structure proposed by Gloer et al. As in the cases of communiols A and B, however, the specific rotation value of synthetic *ent*-8-*epi*-**2** ($[\alpha]_D^{22}$ −12.9 (*c* 0.135, CH_2Cl_2)) was inconsistent with the reported value for natural communiol H ($[\alpha]_D$ −70 (*c* 0.1, CH_2Cl_2)), although they shared the same minus sign. Actually, our synthetic *ent*-8-*epi*-**2** seems to contain a minute amount of dienal (less than 5%, as judged by ^{1}H NMR) generated by an additional two-carbon elongation toward the initially formed enal *ent*-8-*epi*-**2**, but this large difference in specific rotation value seems to be inexplicable by the contamination of such a slight amount of analogous compound. Despite this ambiguity, the complete agreement in ^{1}H and ^{13}C NMR data between synthetic *ent*-8-*epi*-**2** and natural communiol H as well as the consideration of biogenetic similarity among the metabolites isolated from the same fungal source led us to the conclusion that the genuine stereochemistry of communiol H should be depicted as *ent*-8-*epi*-**2**.

3. Conclusion

In summary, the enantioselective total synthesis of *ent*-8-*epi*-**1** and *ent*-8-*epi*-**2**, which we presumed as the genuine structures of communiols D and H, respectively, was accomplished starting from known olefinic ester **6** in 12 and 9 steps, respectively, by using the Sharpless asymmetric dihydroxylation as the source of chirality. The ^{1}H and ^{13}C NMR data of *ent*-8-*epi*-**1** and *ent*-8-*epi*-**2** were identical with those of natural communiols D and H, respectively, and



Scheme 4. Synthesis of *ent*-8-*epi*-**2**, the newly proposed structure for communiol H.

furthermore, the specific rotation value of *ent*-8-*epi*-**1** exhibited good agreement with that of natural communiol D, which allowed us to revise the stereochemistry of communiol D to 3*S*, 5*S*, 7*R*, 8*S* and 11*R*. With regard to communiol H, despite considerable discrepancy in specific rotation value, the complete accord in spectral properties between *ent*-8-*epi*-**2** and natural communiol H as well as the fact that communiol H was isolated together with communils A–D from the same fungal source, strongly supported that genuine structure of commuiols H should be *ent*-8-*epi*-**2**.

4. Experimental

4.1. General

IR spectra were measured as films by a Jasco IR Report-100 spectrometer. ^{1}H NMR spectra (300 or 500 MHz) and ^{13}C NMR spectra (75 or 125 MHz) were recorded with TMS as an internal standard in $CDCl_3$ by a Varian Gemini 2000 spectrometer or a Varian UNITYplus-500 spectrometer. Optical rotation values were measured with a Horiba Septa-300 polarimeter, and mass spectra were obtained with a Jeol JMS-700 spectrometer. Merck silica gel 60 (70–230 mesh) was used for silica gel column chromatography.

4.1.1. (4*R*,5*R*)-5-Hydroxy-4-heptanolide (8). To a stirred mixture of AD-mix-β (53.3 g) and $MeSO_2NH_2$ (3.62 g, 38.0 mmol) in water–*t*-BuOH (1/1, 430 ml) was added a solution **6** (5.94 g, 38.0 mmol) in water–*t*-BuOH (1/1, 30 ml) at 0 °C. After 12 h, $Na_2S_2O_3$ was added, and the resulting mixture was stirred for 3 h at rt. The mixture was extracted with ethyl acetate, and the extract was successively washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue containing **7** and **8** (1:1, as judged by ^{1}H NMR) was dissolved in CH_2Cl_2 (130 ml), and $TsOH\cdot H_2O$ (1.60 g) was added to the solution. The mixture was stirred for 1.5 h at rt, and then successively washed with satd $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/ethyl acetate, 3:1) to give 4.88 g (89% from **6**) of **8** as a colorless oil: $[\alpha]_D^{22}$ −41.3 (*c* 2.25, CH_2Cl_2); IR *ν* 3430 (m), 1765 (s), 1190 (s), 750 (s); ^{1}H NMR *δ* 1.03 (3H, t, *J*=7.5 Hz), 1.50–1.70 (2H, m), 1.96 (1H, d, *J*=4.5 Hz, OH), 2.06–2.20 (1H, m), 2.20–2.33 (1H, m), 2.48–2.70 (2H, m), 3.45–3.56 (1H, m), 4.45 (1H, dt, *J*=4.5, 7.5 Hz); ^{13}C NMR *δ* 9.9, 24.1, 26.0, 28.7, 75.0, 82.6, 177.2; HRMS (FAB) *m*/*z* calcd for $C_7H_{13}O_3$ ($[M+H]^+$) 145.0865, found 145.0869.

4.1.2. Determination of the enantiomeric excess of 8. According to the literature,[12] **8** (2.0 mg) was treated with 2 equiv of (*R*)- and (*S*)-MTPA chloride in pyridine to give (*S*)- and (*R*)-MTPA esters, respectively, which were analyzed, without purification, by ^{1}H NMR (500 MHz). The methoxy signal of the (*R*)-MTPA ester derived from **8** was observed at *δ* 3.51 as a singlet, while that from *ent*-**8** contained as an impurity appeared at *δ* 3.58 as a singlet, and each chemical shift was confirmed by the ^{1}H NMR spectrum of the (*S*)-MTPA ester. Calculation of the ratio of the two peak areas revealed the enantiomeric excess of **8** to be 96%.

4.1.3. (4*R*,5*R*)-5-(*t*-Butyldiphenylsilyloxy)-4-heptanolide (9). To a stirred solution of **8** (4.67 g, 32.4 mmol) in DMF (23 ml) was added imidazole (1.22 g, 18.0 mmol) and TBDPSCl (10.95 ml, 42.1 mmol) at rt. After 21 h, satd NH_4Cl aq was added, and the resulting mixture was extracted with ether. The extract was successively washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/ethyl acetate, 4:1) to give 12.4 g (quant) of **9** as a white crystalline solid, recystallization of which from hexane/ethyl acetate afforded 9.29 g (75%) of enantiomerically pure **9** as colorless prisms: mp 62.5–63 °C; $[\alpha]_D^{22}$ −23.2 (*c* 1.00, $CHCl_3$); IR (KBr) *ν* 3070 (w), 3050 (w), 1780 (s), 1585 (w); ^{1}H NMR *δ* 0.73 (3H, t, *J*=7.5 Hz), 1.05 (9H, s), 1.35–1.50 (1H, m), 1.58–1.74 (1H, m), 2.07–2.22 (2H, m), 2.40–2.65 (2H, m), 3.65 (1H, ddd, *J*=7.2, 4.8, 3.3 Hz), 4.54 (1H, dt, *J*=3.3, 6.9 Hz), 7.35–7.48 (6H, m), 7.67–7.74 (4H, m); ^{13}C NMR *δ* 9.5, 19.5, 23.2, 25.6, 27.0, 28.5, 76.1, 80.5, 127.5 (2C), 127.7 (2C), 129.7 (1C), 129.8 (1C), 133.2 (1C), 133.9 (1C), 135.8 (4C), 177.4; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{31}O_3Si$ ($[M+H]^+$) 383.2042, found 383.2046. Anal. Calcd for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.90. Found: C, 72.47; H, 7.63.

4.1.4. Determination of the enentiomeric excess of 9. A solution of the optically enriched silyl ether **9** (1.00 g, 2.61 mmol) in THF (5 ml) was added to a stirred solution of TBAF–HF in THF (prepared by adding several drops of 40% aq HF to 4 ml of 1 M TBAF in THF, pH ca. 7, checked by a pH-test paper). The mixture was stirred for 2 days at rt, diluted with satd $NaHCO_3$ aq and then extracted with ethyl acetate. The extract was successively washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/ethyl acetate, 5:1) to give 269 mg (71%) of **8** as a colorless oil ($[\alpha]_D^{22}$ −46.8 (*c* 0.24, CH_2Cl_2)). The enantiomeric excess of **8** just obtained from enriched **9** was determined to be 100% by the same protocol as described above.

4.1.5. (2*S*,4*R*,5*R*)-2-Allyl-5-(*t*-butyldiphenylsilyloxy)-4-heptanolide (10). To a stirred solution of LDA, prepared by treating a solution of diisopropylamine (0.263 ml, 1.88 mmol) and HMPA (0.311 ml, 1.79 mmol) in THF (7 ml) with butyllithium (1.6 M in hexane, 1.12 ml, 1.79 mmol) at −10 °C, was added dropwise a solution of **9** (684 mg, 1.79 mmol) in THF (7 ml) at −78 °C. After 20 min, a solution of allyl bromide (0.155 ml, 1.79 mmol) in THF (3 ml) was added, and the resulting mixture was stirred for 20 min at −78 °C. After the addition of satd NH_4Cl aq, the mixture was extracted with ether. The extract was successively washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/ethyl acetate, 20:1) to give 680 mg (90%) of a mixture of **10** and its cis-allylation epimer in a ratio of 8.3:1.[15] Repeated SiO_2-column chromatography of the mixture yielded 481 mg (64%) of pure **10** as a colorless oil: $[\alpha]_D^{22}$ −10.9 (*c* 1.00, $CHCl_3$); IR *ν* 3080 (w), 3050 (w), 1770 (s), 1110 (s), 705 (s); ^{1}H NMR *δ* 0.70 (3H, t, *J*=7.5 Hz), 1.04 (9H, s), 1.39 (1H, ddq, *J*=13.8, 5.4, 7.5 Hz), 1.59–1.74 (1H, m), 1.94 (1H, dt, *J*=13.2, 8.1 Hz), 2.16–2.33 (2H, m), 2.51–2.61 (1H, m), 2.78–2.89 (1H, m), 3.63 (1H, ddd, *J*=7.8, 5.1, 3.3 Hz), 4.48 (1H, ddd, *J*=8.1, 3.9, 3.3 Hz), 5.10 (1H, br d, *J*=11.1 Hz), 5.11 (1H,

dm, J=15.9 Hz), 5.67–5.81 (1H, m), 7.35–7.48 (6H, m), 7.65–7.72 (4H, m); ^{13}C NMR δ 9.6, 19.5, 25.7, 27.0, 28.9, 35.5, 39.1, 76.6, 78.4, 117.7, 127.5 (2C), 127.7 (2C), 129.7 (1C), 129.9 (1C), 133.1 (1C), 133.9 (1C), 134.5, 135.81 (2C), 135.83 (2C), 179.1; HRMS (FAB) *m/z* calcd for $C_{26}H_{35}O_3Si$ ($[M+H]^+$) 423.2355, found 423.2358.

4.1.6. (2*S*,4*R*,5*R*)-2-[3-(*t*-Butoxycarbonyl)-2-propenyl]-5-(*t*-butyldiphenylsilyloxy)4-heptanolide (12). Ozone was bubbled into a stirred solution of **10** (1.00 g, 2.34 mmol) in methanol (10 ml) for 8 min at −78 °C. After the addition of Me_2S (1.7 ml), the mixture was allowed to gradually warm to rt and concentrated in vacuo to give 1.22 g of crude aldehyde **11** as a pale yellow oil, which was then dissolved in CH_2Cl_2 (2.5 ml). To this solution was added $Ph_3P{=}CHCO_2t$-Bu (980 mg, 2.82 mmol), and the mixture was stirred for 19 h at rt, diluted with water and extracted with ethyl acetate. The extract was successively washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/ethyl acetate, 15:1) to give 877 mg (71% from **10**) of **12** as a colorless oil: $[\alpha]_D^{22}$ −3.54 (*c* 1.00, $CHCl_3$); IR ν 3060 (w), 3045 (w), 1770 (s), 1710 (s), 1655 (m); ^{1}H NMR δ 0.71 (3H, t, J=7.4 Hz), 1.04 (9H, s), 1.35–1.46 (1H, m), 1.50 (9H, s), 1.62–1.74 (1H, m), 1.90 (1H, dt, J=12.9, 9.0 Hz), 2.21–2.34 (2H, m), 2.67–2.77 (1H, m), 2.83–2.95 (1H, m), 3.62 (1H, ddd, J=8.4, 4.8, 2.7 Hz), 4.50 (1H, ddd, J=9.0, 3.6, 2.7 Hz), 5.80 (1H, d, J=15.6 Hz), 6.74 (1H, dt, J=15.6, 7.5 Hz), 7.36–7.46 (6H, m), 7.64–7.71 (4H, m); ^{13}C NMR δ 9.6, 19.5, 25.8, 27.0, 28.1, 29.3, 33.7, 38.6, 76.6, 78.3, 80.5, 125.7, 127.6 (2C), 127.8 (2C), 129.8 (1C), 130.0 (1C), 133.0 (1C), 133.8 (1C), 135.78 (2C), 135.82 (2C), 143.1, 165.4, 178.4; HRMS (FAB) *m/z* calcd for $C_{31}H_{42}O_5SiNa$ ($[M+Na]^+$) 545.2699, found 545.2703.

4.1.7. *t*-Butyl [(2*S*,3a*S*,5*R*,6a*R*)5-((*R*)-1-(*t*-butyldiphenylsilyloxy)propyl)hexahydrofuro[2,3-*b*]furan-2-yl]acetate (14). To a stirred solution of **12** (169 mg, 0.322 mmol) in CH_2Cl_2 (3 ml) was added dropwise a solution of DIBAL (0.94 M in hexane, 0.377 ml, 0.355 mmol) at −78 °C. After 20 min, the reaction mixture was quenched with a saturated potassium sodium tartrate aqueous solution, stirred for an additional 1.5 h at ambient temperature, and extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give 185 mg of a 2.8:1 epimeric mixture of lactols **13** as a pale yellow oil,[15] which was then dissolved in THF (3 ml). To the solution was added NaH (0.355 mmol) at −10 °C, and the mixture was stirred for 1 h at 35 °C. The reaction mixture was poured into satd NH_4Cl aq at 0 °C and extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/ethyl acetate, 7:1) to give 89.0 mg (53% from **12**) of a 6.3:1 mixture[15] of **14** and its C3-epimer as a colorless oil: $[\alpha]_D^{22}$ +15.8 (*c* 1.00, $CHCl_3$); IR ν 3060 (w), 3045 (w), 1730 (s), 1150 (m), 1110 (s), 1015 (m); ^{1}H NMR δ 0.74 (3H, t, J=7.4 Hz), 1.05 (9H, s), 1.28–1.40 (1H, m), 1.51–1.75 (3H, m), 1.82–1.90 (1H, m), 1.96–2.08 (1H, m), 2.29 (1H, dd, J=15.3, 7.8 Hz), 2.62 (1H, dd, J=15.3, 6.0 Hz), 2.84–2.94 (1H, m), 3.58 (1H, dt, J=3.9, 6.0 Hz), 4.20 (1H, ddd, J=8.1, 6.6, 4.2 Hz), 4.27–4.37 (1H, m), 5.70 (1H, d, J=4.9 Hz), 7.32–7.45 (6H, m), 7.66–7.74 (4H, m); ^{13}C NMR δ 10.0, 19.5, 25.7, 27.1, 28.1, 33.5, 38.9, 41.5, 42.8, 75.3, 76.4, 80.7, 81.1, 109.0, 127.38 (2C), 127.44 (2C), 129.4 (1C), 129.5 (1C), 134.0 (1C), 134.6 (1C), 135.9 (2C), 136.0 (2C), 170.2; HRMS (FAB) *m/z* calcd for $C_{31}H_{44}O_5SiNa$ ($[M+Na]^+$) 547.2856, found 547.2857.

4.1.8. *t*-Butyl [(2*S*,3a*S*,5*R*,6a*R*)-5-((*R*)-1-hydroxypropyl)-hexahydrofuro[2,3-*b*]furan-2yl]acetate (15). To a stirred solution of **14** (112 mg, 0.214 mmol) in THF (0.5 ml) was added a solution of TBAF (1 M in THF, 0.641 ml, 0.641 mmol) at rt. After 2 days, the reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_4 (hexane/ethyl acetate, 4:1) to give 47.0 mg (77%) of a 6.3:1 mixture of **15** and its C3-epimer as a colorless oil: $[\alpha]_D^{22}$ −0.92 (*c* 0.50, $CHCl_3$); IR ν 3050 (br w), 1730 (s), 1150 (s), 1020 (s); ^{1}H NMR δ 1.00 (3H, t, J=7.4 Hz), 1.40–1.55 (2H, m), 1.45 (9H, s), 1.70–1.85 (2H, m), 1.89–2.02 (2H, m), 2.14 (1H, d, J=4.0 Hz, OH), 2.32 (1H, dd, J=15.6, 7.5 Hz), 2.64 (1H, dd, J=15.6, 6.0 Hz), 2.95–3.04 (1H, m), 3.24–3.33 (1H, m), 4.06 (1H, dt, J=9.6, 5.7 Hz), 4.39–4.49 (1H, m), 5.75 (1H, d, J=4.8 Hz); ^{13}C NMR δ 10.1, 26.7, 28.1, 34.8, 38.7, 41.5, 43.2, 75.2, 75.9, 80.8, 82.8, 108.8, 170.1; HRMS (FAB) *m/z* calcd for $C_{15}H_{27}O_5$ ($[M+H]^+$) 287.1859, found 287.1861.

4.1.9. *t*-Butyl [(2*S*,3a*S*,5*R*,6a*R*)-5-((*S*)1-(*p*-nitrobenzoyloxy)propyl)hexahydrofuro[2,3-*b*]furan-2-yl]acetate (16). To a stirred solution of **15** (47.2 mg, 0.165 mmol), Ph_3P (130 mg, 0.494 mmol) and *p*-nitrobenzoic acid (83 mg, 0.494 mmol) in THF (2 ml) was added diethylazodicarboxylate (90 μl, 0.494 mmol) at 0 °C, and the mixture was stirred for 3 h at rt. The reaction mixture was quenched with satd $NaHCO_3$ aq and extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/ethyl acetate, 5:1) to give 62.0 mg (86%) of **16** as a pale yellow oil: $[\alpha]_D^{22}$ −16.8 (*c* 1.02, $CHCl_3$); IR ν 3110 (w), 1720 (s), 1525 (m), 1270 (s); ^{1}H NMR δ 0.98 (3H, t, J=7.5 Hz), 1.45 (9H, s), 1.72–1.91 (4H, m), 1.98 (1H, ddd, J=12.0, 5.4, 1.8 Hz), 2.08 (1H, dt, J=12.9, 9.2 Hz), 2.32 (1H, dd, J=15.6, 7.5 Hz), 2.65 (1H, dd, J=15.6, 6.0 Hz), 2.93–3.04 (1H, m), 4.34 (1H, dt, J=9.3, 5.7 Hz), 4.39–4.49 (1H, m), 5.16 (1H, dt, J=8.4, 4.8 Hz), 5.72 (1H, d, J=4.9 Hz), 8.21 (2H, d, J=9.0 Hz), 8.30 (2H, d, J=8.7 Hz); ^{13}C NMR δ 9.6, 23.9, 28.0, 34.2, 38.6, 41.4, 42.5, 75.8, 77.7, 80.1, 80.9, 109.0, 123.6, 130.8, 135.8, 150.7, 164.3, 170.3; HRMS (FAB) *m/z* calcd for $C_{22}H_{29}O_8NNa$ ($[M+Na]^+$) 458.1791, found 458.1794.

4.1.10. *t*-Butyl [(2*S*,3a*S*,5*R*,6a*R*)-5-((*S*)-1-hydroxypropyl)hexahydrofuro[2,3-*b*]furan-2-yl]acetate (17). To a stirred solution of **16** (20 mg, 0.047 mmol) in methanol (1 ml) was added 1 M K_2CO_3 aq (1 ml, 1 mmol) at 0 °C, and the mixture was stirred at rt for 2 h. After the addition of satd NH_4Cl aq, the reaction mixture was extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/ethyl acetate, 1:1) to give 11 mg (85%) of **17** as a colorless oil: $[\alpha]_D^{22}$ −5.73 (*c* 0.565, $CHCl_3$); IR ν 3470 (br m), 1725 (s), 1150 (s), 1010 (s), 755 (s); ^{1}H NMR δ 0.99 (3H, t, J=7.4 Hz), 1.34–1.46

(2H, m), 1.45 (9H, s), 1.62 (1H, ddd, J=12.9, 6.3, 2.1 Hz), 1.80 (1H, dt, J=12.6, 9.3 Hz), 1.98 (1H, ddd, J=12.9, 5.4, 2.1 Hz), 2.01 (1H, br s, OH), 2.11 (1H, dt, J=12.6, 9.9 Hz), 2.32 (1H, dd, J=15.3, 6.9 Hz), 2.63 (1H, dd, J=15.3, 6.0 Hz), 2.92–3.02 (1H, m), 3.73–3.80 (1H, m), 4.13 (1H, ddd, J=9.9, 5.7, 3.3 Hz), 4.39–4.49 (1H, m), 5.75 (1H, d, J=4.9 Hz); ^{13}C NMR δ 10.2, 25.4, 28.0, 30.9, 38.8, 41.6, 42.8, 72.3, 76.1, 80.8, 82.4, 108.7, 170.3; HRMS (FAB) m/z calcd for $C_{15}H_{27}O_5$ ($[M+H]^+$) 287.1858, found 287.1860.

4.1.11. (*S*)-1-[(2*R*,3a*S*,5*S*,6a*R*)-5-(2-Hydroxyethyl)hexahydrofuro[2,3-*b*]furan2-yl]-1-propanol (*ent*-8-*epi*-1). To a stirred suspension of $LiAlH_4$ (3.5 mg, 0.092 mmol) in THF (0.5 ml) was added dropwise a solution of **17** (11 mg, 0.039 mmol) in THF (0.5 ml) at 0 °C, and the mixture was stirred for 1 h at rt. To the mixture was successively added ethyl acetate and a large amount of SiO_2. The resulting slurry was stirred for 30 min and filtered through a pad of Celite. The filter cake was washed with 2-propanol, and the combined filtrate and washings were concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/ethyl acetate, 1:5) to give 6.7 mg (79%) of *ent*-8-*epi*-**1** as a colorless oil: $[\alpha]_D^{22}$ +3.0 (c 0.22, CH_2Cl_2); IR ν 3395 (br s), 1090 (m), 1005 (s); ^{1}H NMR δ 0.99 (3H, t, J=7.5 Hz), 1.36–1.46 (2H, m), 1.62 (1H, ddd, J=12.9, 6.5, 2.1 Hz), 1.72 (1H, ddt, J=14.3, 8.4, 6.0 Hz), 1.76–1.88 (2H, m), 1.89 (1H, ddd, J=13.0, 5.9, 2.5 Hz), 1.99 (1H, br s, OH), 2.13 (1H, dt, J=12.6, 9.9 Hz), 2.29 (1H, br s, OH), 2.91–3.02 (1H, m), 3.72–3.83 (3H, m), 4.13 (1H, ddd, J=9.9, 6.0, 3.3 Hz), 4.24–4.34 (1H, m), 5.78 (1H, d, J=4.9 Hz); ^{13}C NMR δ 10.4, 25.4, 31.1, 37.7, 39.4, 42.6, 60.9, 72.4, 79.1, 82.6, 108.9; HRMS (FAB) m/z calcd for $C_{11}H_{21}O_4$ ($[M+H]^+$) 217.1440, found 217.1444.

4.1.12. (2*S*,4*R*,5*R*)-2-Allyl-5-hydroxy-4-heptanolide (18). To a stirred solution of TBAF–HF in THF (prepared by adding a few drops of 40% aq HF to 0.71 ml of 1 M TBAF in THF, pH ca. 7, checked by a pH-test paper) was added a solution of **10** (200 mg, 0.473 mmol) in THF (1.0 ml) at rt. After 4 days, the reaction mixture was quenched with satd $NaHCO_3$ aq and extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/ethyl acetate, 1:1) to give 88 mg (quant) of **18** as a colorless oil: $[\alpha]_D^{22}$ −15.4 (c 1.00, $CHCl_3$); IR ν 3440 (br m), 3075 (w), 1755 (s), 1180 (m); ^{1}H NMR δ 1.02 (3H, t, J=7.4 Hz), 1.51–1.69 (2H, m), 1.84 (1H, d, J=6.0 Hz, OH), 2.06 (1H, ddd, J=13.2, 8.4, 7.2 Hz), 2.22–2.35 (2H, m), 2.52–2.62 (1H, m), 2.80–2.91 (1H, m), 3.45–3.54 (1H, m), 4.41 (1H, dt, J=8.4, 4.4 Hz), 5.14 (1H, dt, J=17.1, 2.1 Hz), 5.16 (1H, d, J=10.2 Hz), 5.78 (1H, ddt, J=17.1, 10.2, 6.9 Hz); ^{13}C NMR δ 10.0, 26.2, 29.5, 35.3, 39.1, 75.3, 80.5, 118.0, 134.3, 179.1; HRMS (FAB) m/z calcd for $C_{10}H_{17}O_3$ ($[M+H]^+$) 185.1178, found 185.1178.

4.1.13. (2*S*,4*R*,5*S*)-2-Allyl-5-(*p*-nitrobenzoyloxy)-4-heptanolide (19). To a stirred solution of **18** (90.0 mg, 0.473 mmol), Ph_3P (186 mg, 0.710 mmol) and *p*-nitrobenzoic acid (119 mg, 0.710 mmol) in THF (4 ml) was added diethylazodicarboxylate (0.129 ml, 0.710 mmol) at 0 °C, and the mixture was stirred for 14 h at rt. The reaction mixture was quenched with satd $NaHCO_3$ aq and extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/ethyl acetate, 7:1) to give 114 mg (72%) of **19** as a pale yellow oil: $[\alpha]_D^{22}$ +4.54 (c 1.15, $CHCl_3$); IR ν 3080 (w), 1770 (s), 1725 (s), 1525 (s), 1265 (s); ^{1}H NMR δ 1.02 (3H, t, J=7.4 Hz), 1.83 (2H, qui, J=7.5 Hz), 2.13 (1H, ddd, J=13.5, 8.4, 7.8 Hz), 2.26–2.40 (2H, m), 2.52–2.62 (1H, m), 2.74–2.86 (1H, m), 4.66 (1H, dt, J=8.4, 5.1 Hz), 5.15 (1H, dm, J=9.6 Hz), 5.16 (1H, dm, J=17.1 Hz), 5.29 (1H, dt, J=5.1, 6.5 Hz), 5.77 (1H, ddt, J=17.1, 9.6, 6.9 Hz), 8.17–8.22 (2H, m), 8.29–8.34 (2H, m); ^{13}C NMR δ 9.6, 23.3, 28.1, 35.1, 38.5, 76.6, 77.7, 118.4, 123.7, 130.8, 133.9, 135.0, 150.8. 164.1, 177.9; HRMS (FAB) m/z calcd for $C_{17}H_{20}O_6N$ ($[M+H]^+$) 334.1290, found 334.1291.

4.1.14. (2*S*,4*R*,5*S*)-2-Allyl-5-hydroxy-4-heptanolide (20). To a stirred solution of **19** (54.0 mg, 0.163 mmol) in methanol (0.5 ml) was added a catalytic amount of K_2CO_3 at 0 °C, and the mixture was stirred at rt for 30 min. The reaction mixture was filtered through a pad of Celite, and the filter cake was washed with ethyl acetate. The combined filtrate and washings were concentrated in vacuo, and the residue was chromatographed over SiO_2 (hexane/ethyl acetate, 4:1) to give 27.5 mg (92%) of **20** as a colorless oil: $[\alpha]_D^{22}$ −0.84 (c 0.56, $CHCl_3$); IR ν 3445 (br m), 3080 (w), 1750 (s), 1180 (m); ^{1}H NMR δ 1.02 (3H, t, J=7.5 Hz), 1.42–1.54 (2H, m), 1.93 (1H, ddd, J=13.2, 8.1, 6.9 Hz), 2.03 (1H, d, J=4.5 Hz, OH), 2.22–2.34 (1H, m), 2.40 (1H, ddd, J=13.2, 9.9, 5.1 Hz), 2.51–2.61 (1H, m), 2.78–2.89 (1H, m), 3.78–3.86 (1H, m), 4.41 (1H, ddd, J=8.1, 5.1, 3.3 Hz), 5.12 (1H, dm, J=10.2 Hz), 5.14 (1H, dm, J=16.8 Hz), 5.78 (1H, ddt, J=16.8, 10.2, 6.9 Hz); ^{13}C NMR δ 9.9, 25.1, 26.5, 35.3, 39.2, 73.4, 80.6, 118.0, 134.5, 179.4; HRMS (FAB) m/z calcd for $C_{10}H_{17}O_3$ ($[M+H]^+$) 185.1178, found 185.1178.

4.1.15. (2*S*,4*R*,5*S*)-2-(3-Formyl-2-propenyl)-5-hydroxy-4-heptanolide (*ent*-8-*epi*-2). Ozone was bubbled into a stirred solution of **20** (27.5 mg, 0.149 mmol) in methanol (1 ml) for 3 min at −78 °C. After the addition of Me_2S (0.3 ml), the mixture was allowed to gradually warm to rt and concentrated in vacuo. The residue was roughly chromatographed over SiO_2 (hexane/ethyl acetate, 3:1) to give 26.9 mg **21** as a colorless oil, which was immediately dissolved in CH_2Cl_2 (0.5 ml). To this solution was added Ph_3P=CHCHO (87.9 mg, 0.289 mmol), and the mixture was stirred for 2 days at rt. After concentration of the reaction mixture, the residue was chromatographed over SiO_2 (hexane/ethyl acetate, 1:5) to give 27.5 mg (87% from **20**) of *ent*-8-*epi*-**2** as a colorless oil (*ent*-8-*epi*-**2**/two carbon-homologated dienal=95:5): $[\alpha]_D^{22}$ −12.9 (c 0.135, CH_2Cl_2); IR ν 3445 (m), 2750 (w), 1760 (s), 1685 (s), 1170 (m), 975 (m), 805 (m), 745 (m); ^{1}H NMR δ 1.02 (3H, t, J=7.4 Hz), 1.43–1.55 (2H, m), 1.90 (1H, dt, J=13.2, 8.4 Hz), 2.01 (1H, d, J=3.9 Hz, OH), 2.50 (1H, ddd, J=13.2, 9.6, 3.6 Hz), 2.48–2.59 (1H, m), 2.85 (1H, dddd, J=15.0, 6.5, 5.5, 1.5 Hz), 2.95–3.06 (1H, m), 3.80–3.89 (1H, m), 4.45 (1H, dt, J=8.4, 3.5 Hz), 6.20 (1H, ddt, J=15.6, 8.0, 1.5 Hz), 6.84 (1H, dt, J=15.6, 7.1 Hz), 9.55 (1H, d, J=8.0 Hz); ^{13}C NMR δ 10.3, 25.7, 27.4, 34.4, 38.7, 73.8, 80.7, 135.1, 153.5, 178.4, 193.7; HRMS (EI) m/z calcd for $C_{11}H_{16}O_4$ (M^+) 212.1048, found 212.1041.

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References and notes

1. Che, Y.; Gloer, J. B.; Scott, J. A.; Malloch, D. *Tetrahedron Lett.* **2004**, *45*, 6891–6894.
2. Che, Y.; Araujo, A. R.; Gloer, J. B.; Scott, J. A.; Malloch, D. *J. Nat. Prod.* **2005**, *68*, 435–438.
3. Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303.
4. Wierenga, W. In ApSimon, J., Ed.; The Total Synthesis of Natural Products; Wiley: New York, 1981; Vol. 4, pp 263–351.
5. Lorenzo, E.; Alonso, F.; Yus, M. *Tetrahedron* **2000**, *56*, 1745–1757 and references cited therein.
6. Kuwahara, S.; Enomoto, M. *Tetrahedron Lett.* **2005**, *46*, 6297–6300.
7. Larchevêque, M.; Lalande, J. *Bull. Soc. Chim. Fr.* **1987**, 116–122.
8. Kolb, H. C.; VanNiewenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
9. Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035–6051.
10. Odinokov, V. N.; Vakhidov, R. R.; Shakhmaev, R. M.; Zorin, V. V. *Khim. Prir. Soedin.* **1996**, 936–939.
11. Bruyère, D.; Bouyssi, D.; Balme, G. *Tetrahedron* **2004**, *60*, 4007–4017.
12. Kuwahara, S.; Ishikawa, J.; Leal, W. S.; Hamade, S.; Kodama, O. *Synthesis* **2000**, 1930–1935.
13. Sells, T. B.; Nair, V. *Tetrahedron* **1994**, *50*, 117–138.
14. Bouchard, H.; Soulié, J.; Lallemand, J. Y. *Tetrahedron Lett.* **1991**, *32*, 5957–5958.
15. The ratio of **10** and its cis-isomer (8.3:1) was calculated from the peak areas of the proton signals (500 MHz ^{1}H NMR) assignable to 7-H (communiol numbering) of each epimer (δ 4.48 for **10**, and δ 4.37 for the cis-isomer). Comparison of the peak areas of the hemiacetalic proton signals of the epimeric mixture **13** (δ 4.95 and 5.25) indicated their ratio to be 2.8:1. The acetalic protons of **14** and its C3-epimer were observed at δ 5.70 and δ 5.58, respectively, which showed the ratio of them to be 6.3:1.
16. Mitsunobu, O. *Synthesis* **1981**, 1–28.
17. The ^{1}H and ^{13}C NMR data for *ent*-8-*epi*-**2** shown in the Section 4 were recorded with TMS as an internal standard in $CDCl_3$, while the published data for natural communiol H are reported to have been obtained by using the solvent signals (δ_H 7.24, δ_C 77.0) as internal standards.[2] This difference brought about subtle disagreement in the NMR chemical shifts between synthetic *ent*-8-*epi*-**2** and natural communiol H (see Section 4 and Ref. 2). However, we were able to make sure that the two samples were identical by regarding the chemical shifts due to C*H*Cl_3 and *C*DCl_3 in our measurements as 7.24 and 77.0 ppm, respectively.