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Enantioselective Total Synthesis and Stereochemical Revision of Communiols E and F

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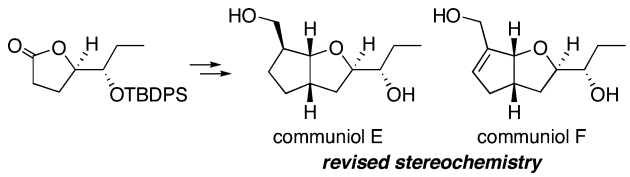

The enantioselective total synthesis of candidate structures for communiols E and F, novel bicyclic polyketides of fungal origin, was accomplished using a Lewis acid-mediated ring closure reaction of an allylsilane intermediate as the key step. Comparison of the spectral data of the synthetic materials with those of natural communiols E and F, coupled with biosynthetic considerations, led to the conclusion that the stereochemistry of communiols E and F should be (2*S*,5*S*,7*R*,8*S*,11*R*)- and (5*S*,7*R*,8*S*,11*R*)-forms, respectively.

In the course of screening for bioactive metabolites from coprophilous (dung-colonizing) fungi, Gloer and co-workers isolated novel bicyclic polyketides, communiols E and F, along with biosynthetically related monocyclic polyketides (communiols G and H) from the culture broth of the horse dung-inhabiting fungus *Podospora communis*, and proposed their structures as **1b** and **2b**, respectively (Figure 1). [1] Their stereochemical assignment for communiols E and F was based mainly on the following three grounds: (1) strong NOESY correlations between 2-H and 7-H, and 5-H and 11-H to support the relative stereochemical assignment among the stereogenic centers on the bicyclic system, (2) the similarity of the 7-H−8-H vicinal coupling constant ($J = 3.6$ Hz) to that observed for analogous polyketides (communiols A−D)[2] of the same microbial origin to rationalize the threo stereochemistry between the C7 and C8 positions (the C7−C8 threo relative stereochemistry of communiols A−D had previously been deduced on the basis of Born's empirical rule),[2,3] and (3) the biogenetically acceptable presumption that the absolute configuration at the C8-position

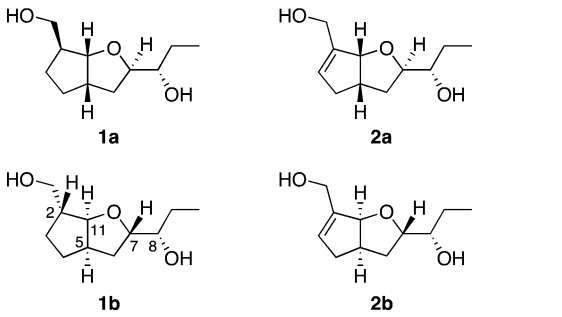

FIGURE 1. Newly proposed stereochemistry for communiols E and F (**1a** and **2a**, respectively) and their original stereochemistry (**1b** and **2b**, respectively).

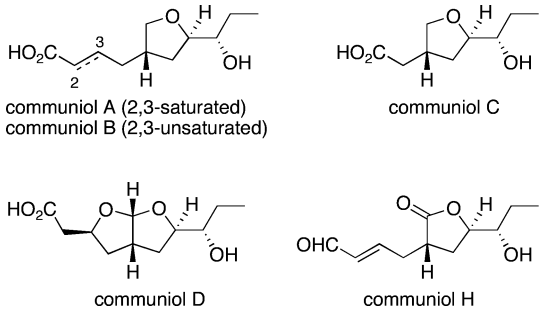

FIGURE 2. Revised stereochemistry for communiols A−D and H.

of communiols E and F should be the same as that of communiol A, which in turn was unambiguously determined to be *S* by the modified Mosher method.[4] Our previous synthetic studies on optically active forms of communiols A−D and H, however, enabled us to conclude that the relative stereochemical assignment between the C7 and C8 positions by Gloer et al. was incorrect, and that the stereochemistry of communiols A−D and H should all be altered as shown in Figure 2.[5,6] This stereochemical revision led us to suppose that the genuine stereochemistry for communiols E and F should also be altered to structures **1a** (*ent*-8-*epi*-**1b**) and **2a** (*ent*-8-*epi*-**2b**), respectively. In this note, we describe the enantioselective total synthesis of **1a** and **2a**, which culminated in the stereochemical revison of communiols E and F.

Our retrosynthetic analysis of **1a** and **2a** is shown in Scheme 1. For the construction of the 2-oxabicyclo[3.3.0]octane framework incorporated in **1a** and **2a**, we planned to utilize a Lewis acid-mediated cyclization of **4** containing a lactol functionality as the electrophilic site and an allylsilane moiety as the nucleophilic site. The bicyclic product **3** would be convertible into either **1a** or **2a** via oxidative cleavage of the double bond. The lactol **4** would be readily obtainable from **5** through diastereoselective trans alkylation and subsequent reduction of the lactone group.

(1) Che, Y.; Araujo, A. R.; Gloer, J. B.; Scott, J. A.; Malloch, D. *J. Nat. Prod.* **2005**, *68*, 435−438.

(2) Che, Y.; Gloer, J. B.; Scott, J. A.; Malloch, D. *Tetrahedron Lett.* **2004**, *45*, 6891−6894.

(3) (a) Born, L.; Lieb, F.; Lorentzen, J. P.; Moeschler, H.; Nonfon, M.; Söllner, R.; Wendisch, D. *Planta Med.* **1990**, *56*, 312−316. (b) Chávez, D. C.; Acevedo, L. A.; Mata, R. *J. Nat. Prod.* **1998**, *61*, 419−421. (c) Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, S.; Kakinuma, K.; Singh, S.; Singh, M.; Gupta, Y. K.; Sahai, M. *Chem. Pharm. Bull.* **1994**, *42*, 1175−1184.

(4) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(5) (a) Kuwahara, S.; Enomoto, M. *Tetrahedron Lett.* **2005**, *46*, 6297−6300. (b) Enomoto, M.; Nakahata, T.; Kuwahara, S. *Tetrahedron* **2006**, *62*, 1102−1109.

(6) For the synthesis of ent-communiols A−C which led to the same stereochemical revision as our studies, see the following: Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2005**, *46*, 8199−8202.

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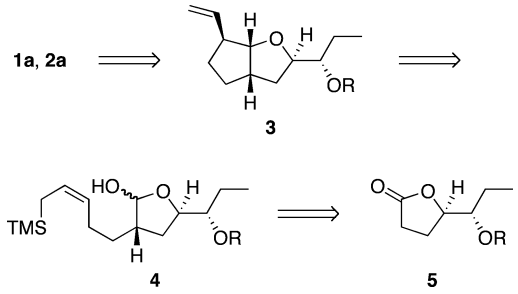
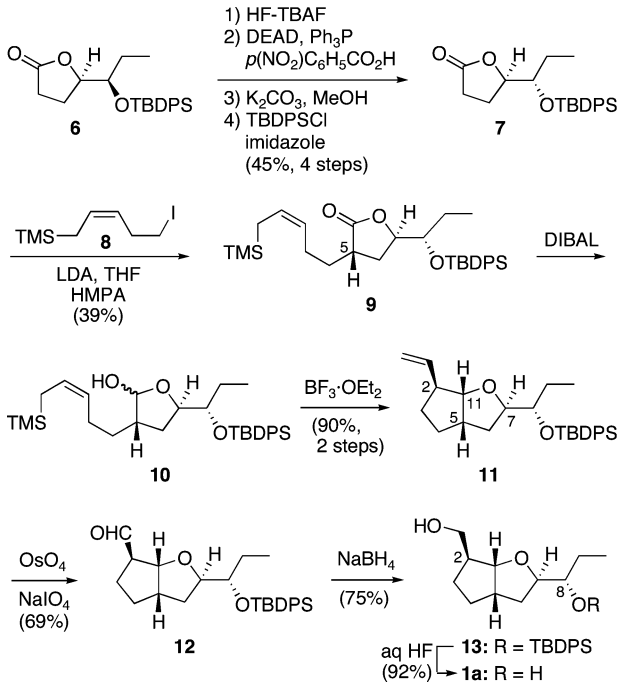
SCHEME 1. Retrosynthetic Analysis of 1a and 2a

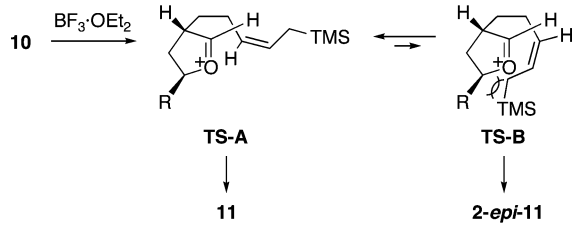


SCHEME 2. Synthesis of Communiol E (1a)



As shown in Scheme 2, our synthesis of the newly proposed candidate structure for communiol E (**1a**) began with a four-step inversion of the stereochemistry at the chiral center on the side chain of known lactone **6** to afford its epimer **7**. The starting lactone **6**, in turn, was prepared in enantiomerically pure form from ethyl (*E*)-4-heptenoate according to our previously reported three-step procedure consisting of the Sharpless asymmetric dihydroxylation, acid-catalyzed lactonization, and protection followed by recrystallization.[5b] The trans-selective alkylation of **7** with known silylated iodoalkene **8**[7] gave a 15.2:1 mixture of **9** and its C5-epimer in 44% yield along with recovered starting lactone **7** (16%).[8,9] After isolation of **9** by repeated silica gel column chromatography (39% isolated yield), the lactone was reduced with DIBAL to lactol **10**, which was then exposed to $BF_3{\cdot}OEt_2$ in CH_2Cl_2 to induce the formation of the bicyclic ring system in an intramolecular manner.[10] Fortunately, the C2-vinyl substituent of the cyclization product **11** preferred the desired exo orientation (**11**/2-*epi*-**11** = 6.4:1), as determined by observation of NOE correlations between 2-H and 7-H, and

SCHEME 3. Preferential Formation of 11



5-H and 11-H. This desirable diastereoselectivity could be explained by considering the thermodynamic stability of two types of transition states, **TS-A** and **TS-B**, leading to **11** and 2-*epi*-**11**, respectively (Scheme 3). The reaction must have taken place mainly through the less sterically demanding transition state **TS-A** rather than **TS-B** wherein severe steric repulsion between the side-chain moiety and the ring portion was anticipated, giving the desired product **11** preferentially. The double bond of **11** was cleaved by the Lemieux-Johnson reaction, and the resulting aldehyde **12** was reduced to alcohol **13**. The C2-epimer of **13** originating from the incomplete stereoselectivity in the formation of **11** (6.4:1, as mentioned above) was readily removed at this stage by SiO_2 chromatography. Finally, removal of the silyl protecting group of **13** with aq HF furnished the target bicyclic diol **1a**. Direct comparison of the ^1H and ^{13}C NMR spectra of **1a** with those of natural communiol E indicated them to be identical, which enabled us to confirm that the relative stereochemistry of communiol E should be represented by structure **1a**. Quite curiously, however, the specific rotation value of **1a** ($[\alpha]^{22}_D$ −8.3 (*c* 0.12, CH_2Cl_2)) was far different from that reported for natural communiol E ($[\alpha]_D$ +129 (*c* 0.075, CH_2Cl_2)).[1] Although this discrepancy prevented us from straightforwardly assigning the absolute stereochemistry of communiol E, the fact that structurally related metabolites of the same microbial origin (communiols A−D and H, see Figure 2) all had (*S*)-absolute configuration in common at the side chain asymmetric center (C8-position in **1a**)[1,2,5,6] strongly supported the stereochemical assignment of communiol E as **1a**, including its absolute configuration.

The candidate structure for communiol F (**2a**), which corresponds to 2,3-dehydrocommuniol E, was synthesized as shown in Scheme 4. The aldehydic intermediate **12** used for the synthesis of **1a** was subjected to α-selenylation with $PhSeNEt_2$,[11] and the resulting α-selenoaldehyde **14** was treated in situ with aq $NaIO_4$ to give α,*β*-unsaturated aldehyde **15**. Reduction of **15** to allylic alcohol **16** with DIBAL and subsequent deprotection of its TBDPS-protecting group afforded the target compound **2a**. The ^1H and ^{13}C NMR spectral data of **2a** were identical with those of natural communiol F. In this case also,

(7) (a) Schinzer, D.; Allagiannis, C.; Wichmann, S. *Tetrahedron* **1988**, *44*, 3851−3868. (b) Frank, K. E.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 655−666.

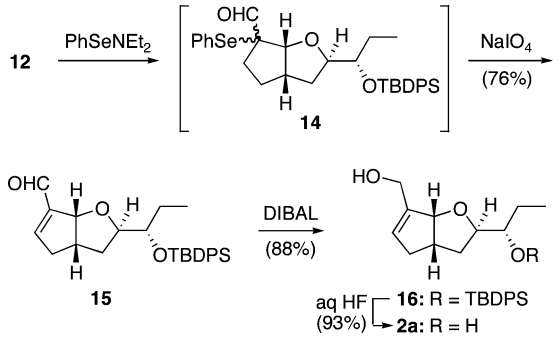
(8) For examples of the *trans*-selective alkylation of *γ*-substituted-*γ*-butyrolactones, see the following: (a) Sells, T. B.; Nair, V. *Tetrahedron* **1994**, *50*, 117−138. (b) Davidson, A. H.; Moloney, B. A. *J. Chem. Soc., Chem. Commun.* **1989**, 445−446.

(9) The modest chemical yield of this conversion is ascribable, in part, to the formation of a conjugated diene through *β*-elimination of **8**, in which the lithium enolate generated from **7** functioned as a base. Attempts to improve the yield of this step by using a zinc enolate of **7** (to reduce the basicity of the nucleophile) or a more reactive alkylating agent [$TMSCH_2CH{=}CH(CH_2)_2OTf$] were unsuccessful. For successful application of these methodologies, see the following: (a) Kuwahara, S.; Hamade, S.; Leal, W. S.; Ishikawa, J.; Kadama, O. *Tetrahedron* **2000**, *56*, 8111−8117. (b) Uenishi, J.; Tatsumi, Y.; Kobayashi, N.; Yonemitsu, O. *Tetrahedron Lett.* **1995**, *36*, 5909−5912.

(10) (a) Schmitt, A.; Rei*β*ig, H.-U. *Eur. J. Org, Chem.* **2000**, 3893−3901. (b) Lee, T. V.; Roden, F. S.; Yeoh, H. T−L. *Tetrahedron Lett.* **1990**, *31*, 2063−2066.

(11) (a) Jefson, M.; Meinwald, J. *Tetrahedron Lett.* **1981**, *22*, 3561−3564. (b) Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54*, 4345−4349.

SCHEME 4. Synthesis of Commuiol F (2a)



however, the specific rotation of **2a** ($[\alpha]^{22}_D$ +21 (*c* 0.21, CH_2Cl_2)) disagreed with that of natural communiol F ($[\alpha]_D$ +137 (*c* 0.058, CH_2Cl_2)).[1] Despite this disagreement, the same argument on biogenetic similarity as described for communiol E led us to the conclusion that the stereochemistry of communiol F should also be revised to **2a**.

In summary, on the basis of our previous synthetic studies on communiols A−D and H, which culminated in their stereochemical revision, we proposed the most probable stereochemistry for communiols E and F, and synthesized the candidate structures (**1a** and **2a**). The complete agreement of **1a** and **2a** with natural communiols E and F, respectively, in ^{1}H and ^{13}C NMR, coupled with the fact that structurally related communiols A−D and H isolated from the same microbial origin have (*S*)-absolute configuration in common at the side chain asymmetric center, strongly suggested that the originally proposed structures for cummuniols E and F (**1b** and **2b**, respectively) should be revised to **1a** and **2a**, respectively.

Experimental Section

(2*S*,4*R*,5*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2-[(*Z*)-5-trimethylsilyl-3-pentenyl]-4-heptanolide (9). To a stirred solution of LDA [prepared by treating a solution of *i*Pr$_2$NH (22 μL, 0.16 mmol) and HMPA (50 μL) in THF (0.50 mL) with *n*BuLi (1.6 M in hexane, 90 μL, 0.14 mmol) at −10 °C] was added a solution of **7** (50.2 mg, 0.131 mmol) in THF (0.50 mL) at −65 °C. After 15 min, a solution of **8** (70.4 mg, 0.262 mmol) in THF (0.30 mL) was added, and the resulting mixture was stirred for 1 h at −78 °C. The reaction was quenched with saturated aq NH_4Cl, and the mixture was extracted with Et_2O. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc, 50:1−4:1) to give a 15.2:1 mixture of **9** and its cis isomer (31.8 mg, 44%) along with recovered starting lactone **7** (16%). Repeated SiO_2 column chromatography (hexane/EtOAc, 40:1) of the mixture afforded 26.5 mg (39%) of pure **9** as a colorless oil: $[\alpha]^{22}_D$ −19 (*c* 0.27, $CHCl_3$). IR (film) ν_{max}: 3020 (w), 1770 (s), 1110 (s), 700 (vs). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (9H, s), 0.68 (3H, t, *J* = 7.4 Hz), 1.03 (9H, s), 1.36−1.52 (5H, m), 1.80−1.93 (2H, m), 2.02−2.13 (2H, m), 2.47 (1H, ddd, *J* = 12.6, 9.3, 4.1 Hz), 2.54−2.61 (1H, m), 3.81−3.89 (1H, m), 4.45 (1H, dt, *J* = 8.2, 4.1 Hz), 5.21 (1H, dt, *J* = 10.7, 7.4 Hz), 5.45 (1H, dt, *J* = 10.7, 8.8 Hz), 7.35−7.47 (6H, m), 7.64−7.70 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ −1.8 (3C), 9.1, 18.6, 19.4, 24.7, 26.2, 27.0 (3C), 28.0, 31.4, 39.0, 74.9, 79.1, 125.6, 127.0, 127.5 (2C), 127.7 (2C), 129.7, 129.9, 132.8, 134.2, 135.8 (2C), 136.0 (2C), 179.6. HRMS (FAB): *m*/*z* calcd for $C_{31}H_{47}O_3Si_2$ ($[M + H]^+$), 523.3064; found, 523.3068.

(2*R*,3a*S*,6*S*,6a*R*)-2-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)propyl]-5-vinylhexahydrocyclopenta[*b*]furan (11). To a stirred solution of **9** (42.3 mg, 81 μmol) in CH_2Cl_2 (1 mL) was added dropwise a solution of DIBAL (0.94 M in hexane, 95 μL, 89 μmol) at −78 °C. After 10 min, the reaction was quenched with saturated aq Rochelle's salt, and the mixture was stirred for 1 h at room temperature before being extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give **10** (49.6 mg) as a colorless oil, which was then dissolved in CH_2Cl_2 (1 mL). To the solution was added BF_3·OEt_2 (12 μL, 97 μmol) at −78 °C, and the resulting mixture was gradually warmed to −15 °C over a period of 45 min before being quenched with a suspension of $NaHCO_3$ in MeOH. The reaction mixture was filtered through a pad of Celite, and the filter cake was washed with EtOAc. The combined filtrate and washings were concentrated in vacuo, and the residue was chromatographed over SiO_2 (hexane/EtOAc, 10:1) to give 31.5 mg (90% from **9**) of a 6.4:1 mixture of **11** and its epimer as a colorless oil: $[\alpha]^{22}_D$ −35.4 (*c* 1.28, $CHCl_3$). IR (film) ν_{max}: 3070 (m), 1640 (w), 1110 (s), 700 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (3H, t, *J* = 7.5 Hz), 1.05 (9H, s), 1.22−1.51 (4H, m), 1.56 (1H, ddd, *J* = 12.1, 5.5, 2.2 Hz), 1.74−1.91 (2H, m), 1.93 (1H, dt, *J* = 12.4, 8.7 Hz), 2.42−2.63 (2H, m), 3.76 (1H, dt, *J* = 5.4, 5.1 Hz), 3.94 (1H, ddd, *J* = 9.0, 5.1, 4.5 Hz), 4.11 (1H, dd, *J* = 6.9, 3.8 Hz), 4.96 (1H, d, *J* = 10.4 Hz), 5.01 (1H, d, *J* = 18.3 Hz), 5.78 (1H, ddd, *J* = 18.3, 10.4, 6.9 Hz), 7.33−7.43 (6H, m), 7.67−7.73 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 19.4, 26.8, 27.0 (3C), 30.8, 31.6, 34.4, 42.2, 50.4, 75.5, 80.6, 89.5, 113.8, 127.40 (2C), 127.43 (2C), 129.46, 129.47, 134.4, 134.8, 136.1 (2C), 136.2 (2C), 140.4. HRMS (FAB): *m*/*z* calcd for $C_{28}H_{38}O_2SiNa$ ($[M + Na]^+$), 457.2539; found, 457.2540.

(*S*)-1-[(2*R*,3a*S*,6*S*,6a*R*)-6-Hydroxymethylhexahydrocyclopenta-[*b*]furan-2-yl]-1-propanol (1a). To a stirred solution of **13** (5.7 mg 13 μmol) in CH_3CN (0.175 mL) was added 40% aq HF (75 μL) at 0 °C. After 8.5 h, the reaction was quenched with saturated aq $NaHCO_3$, and the mixture was extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (EtOAc only) to give 2.4 mg (92%) of **1a** as a colorless oil: $[\alpha]^{22}_D$ −8.3 (*c* 0.12, CH_2Cl_2). IR (film) ν_{max}: 3410 (s), 2940 (vs), 2875 (s), 1455 (m), 1045 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, t, *J* = 7.4 Hz), 1.20−1.39 (2H, m), 1.42 (2H, qui, *J* = 7.3 Hz), 1.52 (1H, br dd, *J* = 12.6, 5.6 Hz), 1.58 (1H, br s, OH), 1.78−1.88 (1H, m), 1.89−2.00 (2H, m), 2.02−2.11 (1H, m), 2.10 (1H, br s, OH), 2.69 (1H, qui, *J* = 7.4 Hz), 3.56−3.70 (2H, m), 3.72−3.81 (1H, m), 3.93 (1H, ddd, *J* = 9.9, 5.4, 3.4 Hz), 4.34 (1H, dd, *J* = 7.2, 4.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.5, 25.8, 28.5, 31.2, 31.8, 43.0, 49.9, 65.2, 72.8, 80.9, 88.1. HRMS (FAB): *m*/*z* calcd for $C_{11}H_{21}O_3$ ($[M + H]^+$), 201.1491; found, 201.1493.

(2*R*,3a*S*,6a*R*)-2-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)propyl]-3,-3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-6-carbaldehyde (15). To a stirred and ice-cooled solution of **12** (10.2 mg, 23.4 μmol) in THF (0.25 mL) was added a solution of $PhSeNEt_2$ [prepared by treating a solution of PhSeCl (9.0 mg, 47 μmol) in hexane (0.25 mL) with Et_2NH (10 μL, 94 μmol) at 0 °C for 15 min], and the mixture was stirred at room temperature for 4 h until compound **12** was completely consumed (TLC analysis). Water (0.2 mL) and $NaIO_4$ (22.5 mg, 0.105 mmol) were then added, and the resulting mixture was stirred at room temperature for 7 h, during which time 10.4 mg (49 μmol) and 20.0 mg (94 μmol) of additional $NaIO_4$ were added to bring the oxidative elimination to completion. The reaction was quenched with saturated aq $Na_2S_2O_3$ and extracted with EtOAc. The extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc, 7:1) to give 7.8 mg (76%) of **15** as a colorless oil: $[\alpha]^{22}_D$ −31 (*c* 0.17, $CHCl_3$). IR (film) ν_{max}: 3070 (w), 3050 (w), 1690 (s), 1110 (m), 740 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (3H, t, *J* = 7.5 Hz), 1.05 (9H, s), 1.35−1.62 (3H, m), 2.00 (1H, dt, *J* = 12.5, 9.1 Hz), 2.31 (1H, dm, *J* = 19.8 Hz), 2.80 (1H, ddd, *J* = 19.8, 8.5, 2.6 Hz), 2.88−2.99 (1H, m), 3.73 (1H, dt, *J* = 9.5, 5.1 Hz), 3.79 (1H, q, *J* = 5.1 Hz), 5.18 (1H, dd, *J* = 7.1, 1.7 Hz), 6.89 (1H, t, *J* = 2.6 Hz), 7.32−7.44 (6H, m), 7.66−7.74 (4H, m), 9.78 (1H, s). ^{13}C NMR (300 MHz, $CDCl_3$): δ 9.3, 19.6, 27.1 (3C), 27.2, 35.4, 40.1, 40.3,

75.2, 79.5, 84.1, 127.4 (4C), 129.4 (2C), 134.1, 134.6, 136.06 (2C), 136.14 (2C), 145.4, 153.2, 189.1. HRMS (FAB): *m*/*z* calcd for $C_{27}H_{34}O_3SiNa$ ($[M + Na]^+$), 457.2175; found, 457.2181.

(*S*)-1-[(2*R*,3a*S*,6a*R*)-6-Hydroxymethyl-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-yl]-1-propanol (2a). To a stirred solution **16** (9.7 mg 0.022 mmol) in CH_3CN (0.37 mL) was added 40% aq HF (0.17 mL) at 0 °C. After 10 h, the reaction was quenched with saturated aq $NaHCO_3$ and extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (EtOAc only) to give 4.1 mg (93%) of **2a** as a colorless oil: $[\alpha]^{22}_D$ +21 (*c* 0.21, CH_2Cl_2). IR (film) ν_{max}: 3735 (s), 3400 (br s), 1700 (w), 1505 (m), 1035 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, t, J = 7.4 Hz), 1.42 (2H, qui, J = 7.1 Hz), 1.51 (1H, ddd, J = 12.6, 5.0, 1.5 Hz), 2.04 (1H, dt, J = 12.6, 9.6 Hz), 2.15 (1H, br d, 17.7 Hz), 1.95−2.26 (2H, br, OH), 2.67 (1H, br dd, J = 17.7, 8.6 Hz), 2.94−3.06 (1H, m), 3.71−3.80 (2H, m), 4.21−4.34 (2H, m), 5.16 (1H, br d, J = 7.3 Hz), 5.80 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.2, 26.0, 33.1, 39.3, 39.7, 60.9, 72.4, 79.4, 89.2, 130.5, 141.1; HRMS (FAB): *m*/*z* calcd for $C_{11}H_{19}O_3$ ($[M + H]^+$), 199.1334; found, 199.1336.

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Supporting Information Available: Experimental procedures for compounds **7**, **12**, **13**, and **16**, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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