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Synthesis of the glycosyl lactol moiety of halichoblelide

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Abstract—The enantioselective synthesis of the 2-deoxy-α-L-fucosyl lactol moiety of halichoblelide, a potent cytotoxin isolated from an actinomycete of marine origin, was achieved using a diastereoselective addition of a dithianyl anion to a chiral aldehyde intermediate and a stereoselective glycosidation of a hydroxy lactone intermediate derived from the addition product with a protected L-fucal as the key steps.

1. Introduction

In the course of screening for antitumor and/or cytotoxic substances produced by microorganisms of marine origin, Numata and co-workers isolated a novel macrodiolide together with a cytotoxic tricyclic macrolactam (halichomycin)[1] from a strain of *Streptomyces hygroscopicus* OUPS-N92 inhabiting the gastrointestinal tract of the marine fish *Halichoeres bleekeri*.[2] The polyketidic macrodiolide (**1**), named halichoblelide (Fig. 1), exhibited potent cytotoxicity against the murine P388 cell line (ED_{50} 0.63 μg/ml) and 39 human cancer cell lines (mean log GI_{50} −5.25).[3] The structure of **1** including its relative stereochemistry was elucidated by extensive spectroscopic analyses of **1** and its degradation products, while its absolute stereochemistry was assigned on the basis of the NMR analysis of the MTPA esters of a degradation product coupled with the application of the CD exciton chirality method to the bis-*p*-bromobenzoate derivatives of the other degradation products.[1] The characteristic structure of **1** was reminiscent of our recent synthetic targets elaiophylin (**2**) and pteridic acids A (**3**) and B (11-*epi*-**3**),[4–6] which were also isolated from *Streptomyces* species and share many structural features with **1** (Fig. 2). Our successful total synthesis of pteridic acids A and B[5,6] and partial synthesis of elaiophylin[4] as well as the interesting biological activity of **1** prompted us to embark on the total synthesis of the structurally-related natural product **1**. As part of our studies directed toward the total synthesis of **1**, we describe herein the synthesis of the glycosyl lactol structure incorporated in **1** (boxed in broken line in Fig. 1).

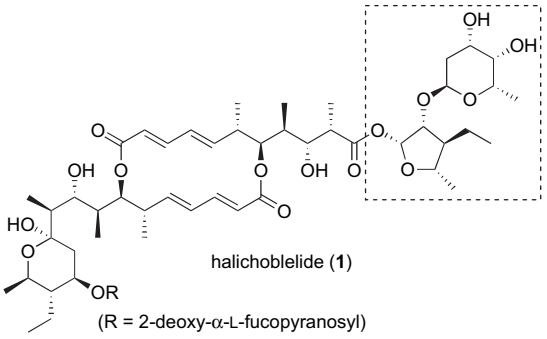

Figure 1. Structure of halichoblelide.

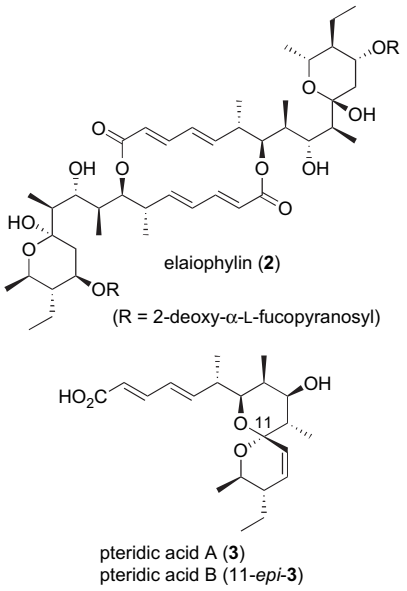

Figure 2. Natural products structurally-related to halichoblelide.

Keywords: Halichoblelide; Enantioselective synthesis; Glycosidation; Cytotoxic.
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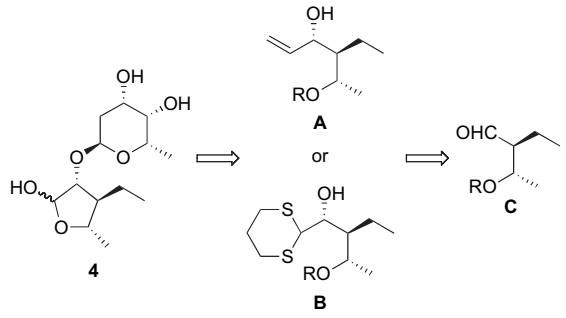
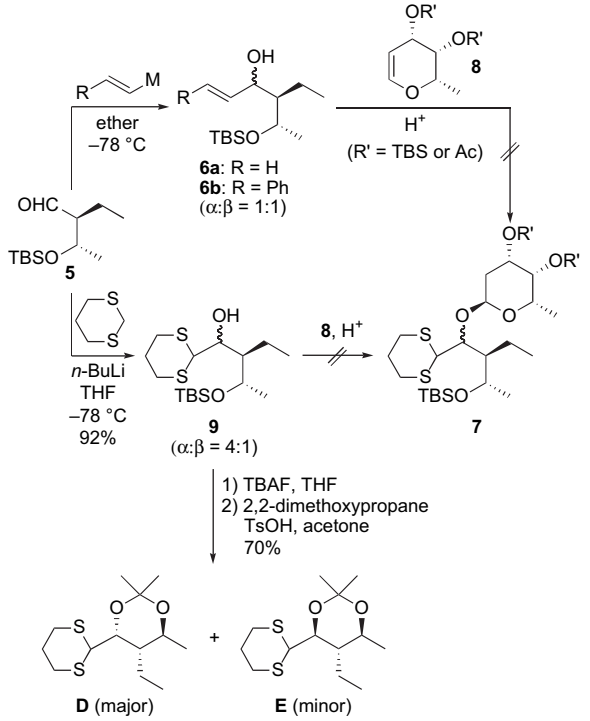
Our initial retrosynthetic analysis of the targeted glycosyl lactol **4** is shown in Scheme 1. This lactol **4** was considered to be obtainable from olefinic intermediate **A** or dithioacetal intermediate **B** via glycosidation followed by oxidative or hydrolytic liberation of the masked aldehyde and subsequent deprotection accompanied by spontaneous lactol formation. Intermediates **A** and **B** would readily be prepared by diastereoselective nucleophilic addition of a vinyl anion and a dithianyl anion, respectively, to aldehyde **C**. As described later in detail, however, this synthetic plan required a slight modification due to difficulties encountered in the glycosidation step.



Scheme 1. Initial synthetic plan for the glycosyl lactol moiety (**4**) of halichoblelide.

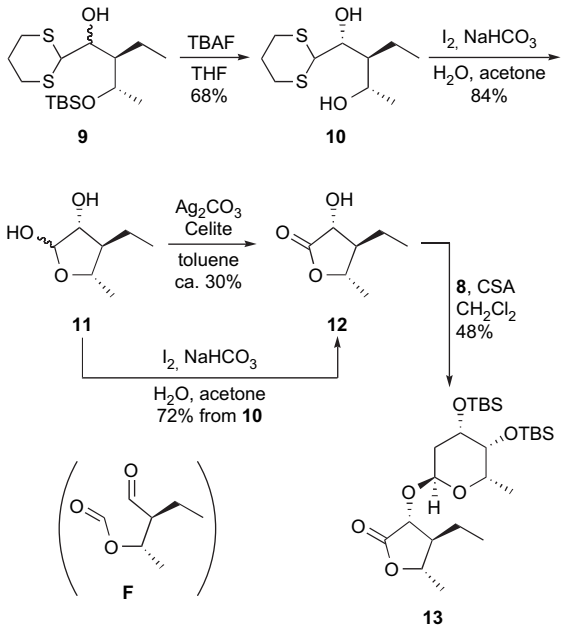
2. Results and discussion

Our synthesis of **4** began with the addition of vinylmagnesium chloride to aldehyde **5**, which was obtained from methyl (*S*)-3-hydroxybutanoate in four steps,[7] to give alcohol **6a** in 98% yield (Scheme 2). The addition reaction was, however, found to be nonstereoselective, giving **6a** as an inseparable 1:1 diastereomeric mixture contrary to our expectation based on the Felkin–Anh transition state model. The use of 2-phenylvinyllithium as nucleophile to obtain **6b** did not bring any improvement (1:1 diastereomeric ratio, 60% yield). Moreover, all attempts to convert **6a** and **6b** into glycoside **7** (R′=TBS or Ac) by Kinoshita's glycosidation method using glycal **8** (R′=TBS or Ac) as glycosyl donor under acidic conditions (CSA or PPTS in CH_2Cl_2 in the presence or absence of 4 Å molecular sieves) were unsuccessful, resulting in the recovery of the starting alcohols or the formation of unidentified products at elevated reaction temperatures.[8] First of all, in order to enhance the diastereoselectivity of the nucleophilic addition reaction to **5**, the use of a sterically more demanding nucleophile, 2-lithio-1,3-dithiane, was next examined. In this case, the diastereoselectivity was considerably high, furnishing **9** as an inseparable 4:1 diastereomeric mixture with the desired α-epimer predominating. The stereochemistries of the major and the minor epimers were assigned on the basis of the ^{13}C NMR chemical shifts of the corresponding acetonide derivatives, **D** and **E**, prepared from **9** by desilylation and subsequent treatment of the resulting epimeric mixture of diols with 2,2-dimethoxypropane in the presence of TsOH. In the case of the major isomer **D**, the quaternary carbon and the two methyl carbons of the acetonide moiety resonated at δ 101.3, 25.4, and 23.6 ppm, respectively, while in the minor isomer **E**, the corresponding signals were observed at δ 98.3, 30.0, and 19.6 ppm, respectively. These data enabled us to unambiguously assign the stereochemistries of **D** and **E** as depicted in Scheme 2 according to the Rychnovsky rule,[9] and therefore the absolute configuration of the hydroxyl-bearing position of the major epimer of **9** as *R* (α-configuration). Glycosidation of **9** to form **7** was then attempted according to Kinoshita's procedure mentioned above. In this case also, however, no glycosidation product was obtained, resulting only in the same results obtained for **6a** and **6b**.



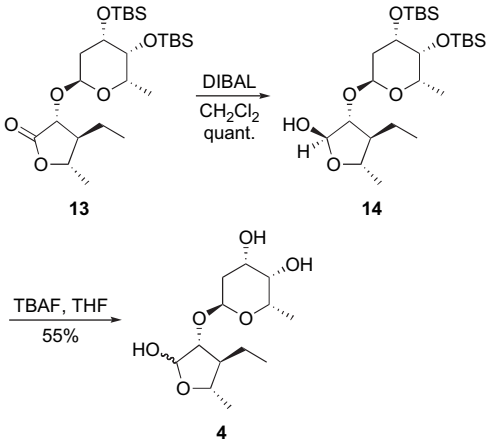
Scheme 2.

Taking into account the steric congestion around the secondary hydroxyl group of **9** brought on by the considerably bulky dithiane moiety, we decided to unmask the dithiane group prior to the glycosidation reaction. Before the removal of the dithiane moiety, the TBS group of **9** was deprotected with TBAF to give the corresponding mixture of diols (Scheme 3), and, quite fortunately, the undesired β-configured alcohol was removed at this stage by SiO_2 column chromatography, furnishing the desired α-epimer **10** in 68% isolated yield. Treatment of **10** with I_2 in H_2O/acetone in the presence of $NaHCO_3$ smoothly afforded lactol **11** as a 1:1 epimeric mixture. Despite some successful precedents for similar transformations, the oxidation of **11** with Ag_2CO_3/Celite in toluene to form lactone **12** proved to be problematic,[10,11] giving oxidative cleavage product **F** (ca. 30% yield) together with the desired lactone **12** (ca. 30% yield).[12] On the other hand, the oxidation of **11** with iodine proceeded smoothly to give **12** in 72% overall yield from **10**. The glycosidation of the lactone **12** thus obtained with the L-fucal derivative **8** (R′=TBS) by Kinoshita's protocol[8] proceeded in a moderate yield of 48% to provide **13** as the only glycosidation product; the anomeric hydrogen of **13** was observed at δ 4.97 as a doublet with J=2.0 Hz in its ^1H NMR spectrum, in good agreement with data reported previously for analogous 2-deoxy-α-L-fucopyranosides.[13,14]



Scheme 3.

Reduction of lactone **13** with DIBAL quantitatively gave crystalline lactol **14** as nearly a single stereoisomer (β-OH/α-OH, >95:<5) (Scheme 4). The ^{13}C NMR signal for the hemiacetal carbon of **14** appeared at 101.8 ppm, and the ^{1}H NMR coupling constant between the hydrogen on the hemiacetal carbon and the adjacent vicinal hydrogen was 1.5 Hz, which matched typical values usually observed in 1,2-*trans*-2-*O*-alkylfuranoses.[15] Finally, deprotection of the TBS groups with TBAF furnished the target molecule **4** as an epimeric mixture (β-OH/α-OH, 1.8:1) in 55% yield.[16] For successful isolation of **4**, Kishi's workup procedure for water-soluble compounds was quite helpful.[17]



Scheme 4.

3. Conclusion

In summary, the stereoselective synthesis of the 2-deoxy-α-L-fucopyranosyl lactol moiety (**4**) of halichoblelide (**1**) was accomplished in seven steps from aldehyde **5** using the diastereoselective addition of 2-lithio-1,3-dithiane to **5** and the stereoselective glycosidation of hydroxy lactone intermediate **12** with L-fucal derivative **8** as the key steps. Efforts toward the total synthesis of **1** are currently in progress.

4. Experimental

4.1. General

IR spectra were recorded as films by a Jasco IR Report-100 spectrometer unless otherwise stated. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian Gemini 2000 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) or a Varian UNITY plus-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C). Optical rotation values were measured with a Jasco DIP-371 polarimeter, and mass spectra were obtained with a Jeol JMS-700 spectrometer operated in the FAB mode. Merck silica gel 60 (70–230 mesh) was used for silica gel column chromatography.

4.1.1. (2*S*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-ethylbutanal (5). This aldehyde was prepared in four steps from methyl (*S*)-3-hydroxybutanoate according to the procedure reported for the preparation of the corresponding (2*R*,3*R*)-enantiomer from methyl (*R*)-3-hydroxybutanoate.[7] $[\alpha]_D^{22}$ +23.9 (*c* 2.65, $CHCl_3$); IR *ν* 2710 (w), 1726 (s), 1254 (s), 833 (vs), 774 (vs); ^{1}H NMR (300 MHz) *δ* 0.04 (3H, s), 0.05 (3H, s), 0.85 (9H, s), 0.89 (3H, t, *J*=7.4 Hz), 1.20 (3H, d, *J*=6.3 Hz), 1.46–1.60 (1H, m), 1.63–1.80 (1H, m), 2.03–2.12 (1H, m), 4.06 (1H, dq, *J*=5.1, 6.3 Hz), 9.68 (1H, d, *J*=3.9 Hz); ^{13}C NMR (75 MHz) *δ* −5.2, −4.3, 11.7, 17.8, 19.4, 22.2, 25.6, 61.0, 68.8, 205.8; HRMS (FAB) *m/z* calcd for $C_{12}H_{27}O_2Si$ ([M+H]$^+$) 231.1780, found 231.1787.

4.1.2. (1*R*/*S*,2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-(1,3-dithian-2-yl)-2-ethyl-1-butanol (9). To a stirred solution of 1,3-dithiane (600 mg, 5.16 mmol) in THF (20 ml) was added dropwise a solution of butyllithium (1.6 M in hexane, 3.0 ml, 4.8 mmol) at −78 °C. After 1 h, a solution of **5** (820 mg, 3.60 mmol) in THF (20 ml) was added dropwise, and the resulting mixture was gradually warmed to room temperature over 12 h. The reaction mixture was quenched with satd NH_4Cl aq and 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/EtOAc=10:1) to give 1.15 g (92%) of **9** as a pale yellow oil. $[\alpha]_D^{22}$ +4.1 (*c* 1.00, $CHCl_3$); IR *ν* 3471 (w), 1254 (s), 833 (vs), 753 (vs); ^{1}H NMR (500 MHz) *δ* 0.09 (6H×0.2, s), 0.10 (6H×0.8, s), 0.88 (9H×0.8, s), 0.89 (9H×0.2, s), 0.93–0.98 (3H, m), 1.28 (3H×0.2, d, *J*=5.6 Hz), 1.29 (3H×0.8, d, *J*=5.6 Hz), 1.39–1.48 (1H×0.2, m), 1.50–1.58 (3H×0.8 and 1H×0.2, m), 1.78–1.83 (1H×0.2, m), 1.85–1.98 (1H, m), 2.06–2.14 (1H, m), 2.75–2.96 (4H, m), 3.75 (1H×0.2, d, *J*=3.4 Hz), 3.84–3.88 (1H×0.2, m), 4.07 (1H×0.2, quint, *J*=5.6 Hz), 4.15 (1H×0.8, d, *J*=10.3 Hz), 4.20 (1H, s, OH), 4.21–4.27 (1H×0.8, m), 4.26 (1H×0.8, d, *J*=10.3 Hz); ^{13}C NMR (125 MHz) *δ* (for the major epimer) −5.3, −4.2, 12.0, 16.6, 17.8, 22.0, 25.7, 25.9, 28.9, 29.3, 46.5, 50.1, 69.6, 71.7; HRMS (FAB) *m/z* calcd for $C_{16}H_{35}O_2SiS_2$ ([M+H]$^+$) 351.1848, found 351.1852.

4.1.3. NMR data for compounds D and E. Compound **D**: ^{1}H NMR (300 MHz) δ 0.93 (3H, t, J=7.4 Hz), 1.27 (3H, d, J=6.3 Hz), 1.38 (6H, s), 1.46–1.54 (1H, m), 1.57–1.70 (2H, m), 1.82–1.97 (1H, m), 2.06–2.17 (1H, m), 2.81–2.89 (4H, m), 3.69 (1H, quint, J=6.3 Hz), 3.98 (1H, dd, J=11.1, 3.6 Hz), 4.11 (1H, d, J=11.1 Hz); ^{13}C NMR (75 MHz) δ 11.5, 19.1, 22.7, 23.6, 25.4, 25.8, 29.1, 29.3, 45.6, 47.2, 69.5, 70.3, 101.3. *Compound* ***E***: ^{1}H NMR (500 MHz) δ 0.94 (3H, t, J=7.6 Hz), 1.21 (3H, d, J=5.9 Hz), 1.35–1.41 (2H, m), 1.44 (3H, s), 1.46 (3H, s), 1.60–1.66 (1H, m), 1.97–2.11 (2H, m), 2.75 (1H, ddd, J=13.2, 9.8, 2.9 Hz), 2.88 (1H, ddd, J=13.2, 9.8, 2.9 Hz), 3.01–3.08 (2H, m), 3.84 (1H, dq, J=10.3, 5.9 Hz), 4.06 (1H, d, J=10.3 Hz), 4.12 (1H, br s); ^{13}C NMR (75 MHz) δ 10.4, 19.4, 19.5, 19.6, 25.9, 29.9, 30.0, 30.4, 42.9, 48.7, 68.0, 77.5, 98.3.

4.1.4. (1*R*,2*S*,3*S*)-1-(1,3-Dithian-2-yl)-2-ethyl-1,3-butanediol (10). To a stirred solution of **9** (1.15 g, 3.20 mmol) in THF (20 ml) was added dropwise a solution of TBAF (1.0 M in THF) at 0 °C. After 2 h, the reaction mixture was quenched with satd NH_4Cl aq and 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/EtOAc=1:1) to give 530 mg (68%) of **10** as a pale yellow oil. $[\alpha]_D^{22}$ +14 (*c* 0.80, ether); IR ν 3384 (m), 1023 (s), 908 (s), 730 (vs); ^{1}H NMR (500 MHz) δ 0.99 (3H, t, J=7.3 Hz), 1.33 (3H, d, J=6.3 Hz), 1.42–1.51 (1H, m), 1.56–1.66 (1H, m), 1.73–1.78 (1H, m), 1.96–2.04 (1H, m), 2.04–2.12 (1H, m), 2.71 (2H, ddd, J=14.2, 8.3, 2.4 Hz), 2.89 (1H, ddd, J=14.2, 8.3, 2.4 Hz), 2.98 (1H, ddd, J=14.2, 8.3, 2.4 Hz), 2.94–3.05 (1H, br s, OH), 3.40–3.46 (1H, br s, OH), 3.90 (1H, d, J=9.8 Hz), 4.10–4.16 (1H, m), 4.32 (1H, d, J=9.8 Hz); ^{13}C NMR (125 MHz) δ 12.1, 16.8, 22.0, 25.3, 26.7, 27.3, 45.6, 48.3, 67.7, 70.2; HRMS (FAB) *m*/*z* calcd for $C_{10}H_{21}O_2S_2$ ([M+H]$^+$) 237.0983, found 237.0980.

4.1.5. (3*R*,4*R*,4*S*)-4-Ethyl-3-hydroxy-5-methyltetrahydro-2-furanone (12). To a stirred mixture of **10** (320 mg, 1.35 mmol) and $NaHCO_3$ (1.37 g, 16.2 mmol) in a mixture of acetone and water (5:1, 10 ml) was added iodine (2.06 g, 8.12 mmol) at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was quenched with $Na_2S_2O_3$ (powder) and extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated in vacuo to give crude **11** as an oil, which was taken up in a mixture of acetone and water (5:1, 10 ml). To the solution were added $NaHCO_3$ (1.37 g, 16.2 mmol) and iodine (2.06 g, 8.12 mmol) at 0 °C, and the mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with $Na_2S_2O_3$ (power) and extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc=1:1) to give 140 mg (72%) of **12** as a colorless oil. $[\alpha]_D^{22}$ 0.00 (*c* 4.50, $CHCl_3$); IR ν 3429 (w), 1764 (vs), 1111 (s), 1051 (s), 753 (s); ^{1}H NMR (500 MHz) δ 1.09 (3H, t, J=7.6 Hz), 1.47 (3H, d, J=6.3 Hz), 1.55–1.64 (1H, m), 1.64–1.74 (1H, m), 1.94–2.02 (1H, m), 2.70 (1H, d, J=2.4 Hz, OH), 4.13–4.20 (2H, m); ^{13}C NMR (125 MHz) δ 11.4, 19.6, 23.1, 52.3, 73.7, 78.3, 177.3; HRMS (FAB) *m*/*z* calcd for $C_7H_{13}O_3$ ([M+H]$^+$) 145.0864, found 145.0864.

4.1.6. (3*R*,4*R*,5*S*)-3-[(2*S*,4*S*,5*R*,6*S*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-6-methyltetrahydropyran-2-yloxy]-4-ethyl-5-methyltetrahydrofuran-2-one (13). To a stirred solution of **12** (300 mg, 2.08 mmol) and **8** (810 mg, 2.30 mmol) in CH_2Cl_2 (30 ml) was added a catalytic amount of camphorsulfonic acid at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was quenched with satd $NaHCO_3$ aq and extracted with ether. The extract was successively washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc=5:1) to give 501 mg (48%) of **13** as a white solid: mp 64.5–65.5 °C. $[\alpha]_D^{22}$ −63 (*c* 0.27, $CHCl_3$); IR ν 1784 (m), 1032 (vs), 1015 (s), 833 (vs), 777 (s); ^{1}H NMR (500 MHz) δ 0.06 (3H, s), 0.067 (3H, s), 0.071 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 0.91 (9H, s), 0.99 (3H, t, J=7.6 Hz), 1.17 (3H, d, J=6.8 Hz), 1.42 (3H, d, J=5.9 Hz), 1.56–1.67 (3H, m), 1.98–2.05 (1H, m), 2.09 (1H, dt, J=3.4, 12.2 Hz), 3.60 (1H, br s), 4.05–4.15 (2H, m), 4.17 (1H, d, J=9.8 Hz), 4.37 (1H, q, J=6.3 Hz), 4.97 (1H, d, J=2.0 Hz); ^{13}C NMR (125 MHz) δ −4.7, −4.6, −4.3, −3.8, 11.4, 17.7, 18.4, 18.6, 20.2, 22.9, 26.1, 26.2, 32.9, 51.2, 68.1, 68.7, 73.6, 77.1, 77.3, 99.2, 174.5; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{51}O_6Si_2$ ([M+H]$^+$) 503.3224, found 503.3220. Anal. Calcd for $C_{25}H_{50}O_6Si_2$: C, 59.72; H, 10.02. Found: C, 59.49; H, 9.96.

4.1.7. (2*R*/*S*,3*R*,4*S*,5*S*)-3-[(2*S*,4*S*,5*R*,6*S*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-6-methyltetrahydropyran-2-yloxy]-4-ethyl-5-methyltetrahydrofuran-2-ol (14). To a stirred solution of **13** (501 mg, 1.00 mmol) in CH_2Cl_2 (20 ml) was added dropwise a solution of DIBAL (1.0 M in hexane, 1.20 ml, 1.20 mmol) at −78 °C. After being stirred for 2 h at the same temperature, the reaction mixture was quenched with satd Rochelle's salt aq and extracted with ether. The extract was successively washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc=5:1) to give 501 mg (quant.) of **14** as a white solid: mp 95–96 °C. $[\alpha]_D^{22}$ −110 (*c* 0.20, $CHCl_3$); IR ν 3414 (w), 1254 (m), 1030 (vs), 840 (vs), 771 (s); ^{1}H NMR (300 MHz) δ 0.06 (3H, s), 0.065 (3H, s), 0.070 (3H, s), 0.10 (3H, s), 0.90 (9H, s), 0.91 (9H, s), 0.96 (3H, t, J=7.5 Hz), 1.16 (3H, d, J=6.3 Hz), 1.29 (3H, d, J=6.0 Hz), 1.45–1.64 (4H, m), 2.09 (1H, dt, J=3.6, 12.0 Hz), 2.56 (1H, d, J=2.7 Hz, OH), 3.55–3.59 (1H, m), 3.71 (1H, dd, J=4.8, 1.5 Hz), 3.85 (1H, br q, J=6.8 Hz), 3.98 (1H, dq, J=7.8, 6.3 Hz), 4.04 (1H, ddd, J=12.0, 4.5, 2.4 Hz), 4.95 (1H, br d, J=3.0 Hz), 5.29 (1H, dd, J=2.7, 1.5 Hz); ^{13}C NMR (75 MHz) δ −4.9, −4.7, −4.5, −3.9, 12.2, 17.7, 18.4, 18.5, 20.2, 23.8, 26.0, 26.1, 33.5, 53.9, 68.3, 68.5, 73.7, 78.6, 90.5, 98.9, 101.8; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{52}O_6Si_2Na$ ([M+Na]$^+$) 527.3201, found 527.3206. Anal. Calcd for $C_{25}H_{52}O_6Si_2$: C, 59.48; H, 10.38. Found: C, 59.43; H, 10.58.

4.1.8. (2*S*,3*S*,4*S*)-6-[(2*R*/*S*,3*R*,4*S*,5*S*)-4-Ethyl-2-hydroxy-5-methyltetrahydrofuran-3-yloxy]-2-methyltetrahydropyran-3,4-diol (4). To a stirred solution of **14** (20.0 mg, 39.6 μmol) in THF (3 ml) was added a solution of TBAF (1.0 M in THF, 0.24 ml, 0.24 mmol) at 0 °C, and the mixture was stirred at room temperature for 5 h. To the mixture were added $CaCO_3$ (140 mg), Dowex 50WX8-100 (420 mg), and MeOH (1 ml), and the mixture was stirred for 12 h. The mixture was filtered through a pad of Celite, and the filter cake

was washed with EtOAc. The combined filtrates were concentrated in vacuo, and the residue was purified by preparative TLC (Merck silica gel 60 F_{254}; layer thickness, 1 mm; $CHCl_3$/MeOH=10:1) to give 6.0 mg (55%) of **4** as a colorless oil. $[\alpha]_D^{22}$ −82 (*c* 0.45, $CHCl_3$); IR *ν* 3376 (s), 1642 (m), 1215 (m), 746 (vs); ^{1}H NMR (500 MHz, $CDCl_3$+D_2O) *δ* 0.98 (3H×0.64, t, *J*=7.3 Hz), 0.99 (3H×0.36, t, *J*=7.6 Hz), 1.25 (3H×0.36, d, *J*=6.8 Hz), 1.27 (3H×0.64, d, *J*=6.8 Hz), 1.31 (3H×0.64, d, *J*=7.3 Hz), 1.35 (3H×0.36, d, *J*=5.9 Hz), 1.44–1.64 (2H and 1H×0.64, m), 1.78–1.91 (2H, m), 1.96 (1H×0.36, dd, *J*=12.9, 5.1 Hz), 3.65 (1H, br s), 3.67–3.74 (2H×0.36, m), 3.80 (1H×0.64, d, *J*=3.9 Hz), 3.97 (1H×0.64, q, *J*=6.8 Hz), 3.97–4.06 (2H×0.64 and 1H×0.36, m), 4.12 (1H×0.36, q, *J*=6.8 Hz), 4.99 (1H×0.64, d, *J*=2.9 Hz), 5.01 (1H×0.36, d, *J*=3.4 Hz), 5.15 (1H×0.36, d, *J*=3.9 Hz), 5.31 (1H×0.64, br s); ^{13}C NMR (125 MHz) *δ* (β-isomer) 12.4, 16.7, 20.5, 24.1, 33.1, 53.8, 65.8, 66.2, 71.2, 79.1, 88.9, 97.3, 101.7; *δ* (α-isomer) 12.1, 16.8, 22.9, 24.0, 32.6, 49.2, 65.8, 66.5, 71.0, 77.6, 83.1, 95.8, 98.4; HRMS (FAB) *m*/*z* calcd for $C_{13}H_{24}O_6Na$ ($[M+Na]^+$) 299.1470, found 299.1465.

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