

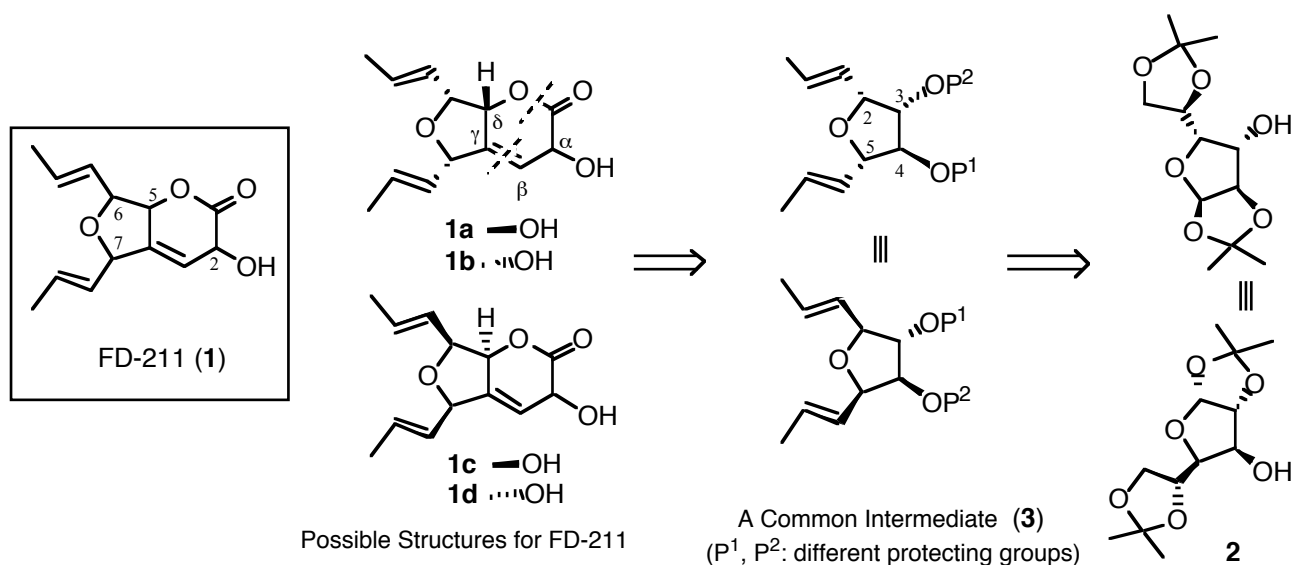
SYNTHESIS OF AN ENANTIOMERIC 2,5-DI-(*E*)-PROPENYL-TETRAHYDROFURAN-3,4-DIOL DERIVATIVE

Eiju Suzuki, Ken-ichi Takao, and Kin-ichi Tadano*

Department of Applied Chemistry, Keio University, Hiyoshi,
Yokohama 223-8522, Japan

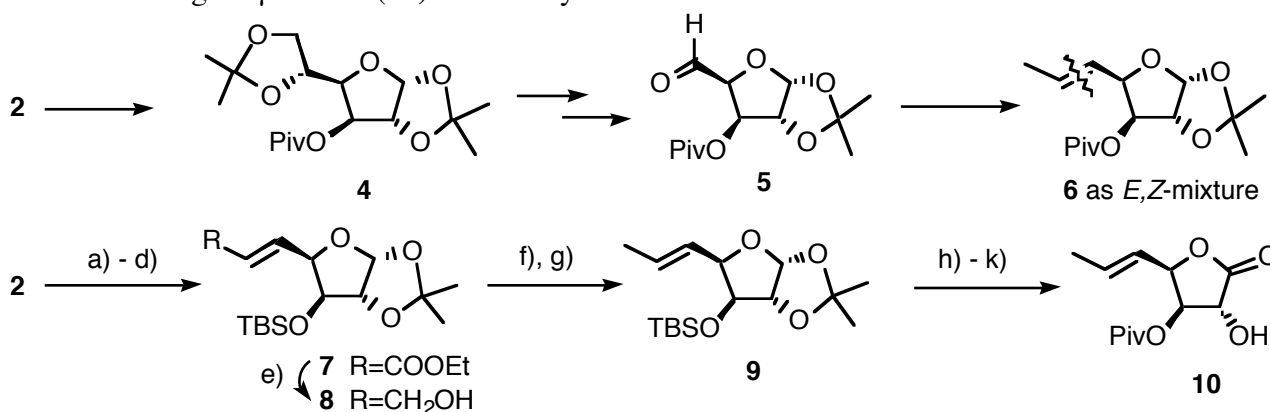
Abstract For total synthesis of a novel bioactive δ -lactone antibiotic FD-211, a key intermediate, a 2,5-di-(*E*)-propenyltetrahydrofuran-3,4-diol derivative, was synthesized from diacetone D-glucose.

During a screening program for low molecular compounds effective against multidrug-resistant tumor cells, a novel antibiotic FD-211 (**1**) was isolated from the fermentation broth of *Myceliophthora lutea* TF-0409 by the research group of Taisho Pharmaceutical Co., Ltd.¹ Compound (**1**) showed a broad spectrum activity against cultured tumor cell lines including adriamycin-resistant HL-60 cells.¹ The ¹H and ¹³C NMR data verify that **1** consists of a β,γ -unsaturated δ -lactone ring sharing a 2,5-disubstituted tetrahydrofuran ring at the γ - and δ -positions¹ (**Scheme 1**). The coupling constants of both propenyl olefin protons indicate that their geometrical structures are both *E*, and the NOE measurements also reveal that the substituents at C5, C6 and C7 dispose in all *cis* relationships. The stereochemistry of C2 bearing a hydroxyl group remains unclear. The absolute stereochemistry of **1** is not yet determined. We have concerned to confirm the structure of **1** by an enantiomeric total synthesis. For this object, we chose diacetone D-glucose (**2**) as a chiral pool. For access to all of the possible stereoisomers (**1a-1d**), we regard a suitably protected 2,5-di-(*E*)-propenyltetrahydrofuran-3,4-diol derivative (**3**) as a common intermediate. In this communication, we describe a stereoselective access to this key intermediate (**3**).



Scheme 1

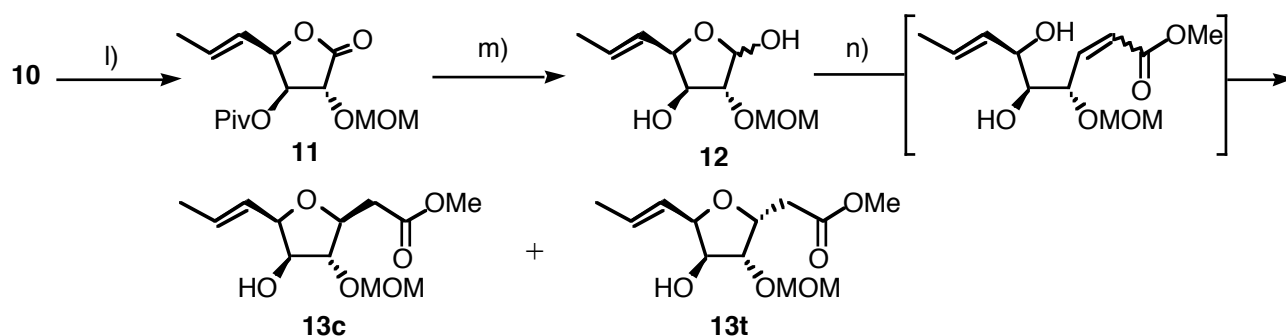
We first examined a direct introduction of a propenyl group (the left-arm) into 1,5-dialdose (**5**), prepared from **2** via a known 3-*O*-pivaloyl (Piv) ester (**4**)² (**Scheme 2**). Olefination of **5** by the Takai procedure³ (CrCl₂, MeCHI₂, DMF/THF) resulted in the formation of the 5-eno-heptose derivative (**6**) as an inseparable *E,Z* mixture without remarkable stereoselectivity (*E/Z* = *ca.* 2.6:1). Fortunately, the desired *E*-propenyl side chain was introduced stereoselectively as follows. Hydrolysis of the side chain ketal in **2**, cleavage of the resulting diol by a periodate oxidation followed by the Horner-Emmons olefination with triethyl phosphonoacetate, and protection of C3 hydroxyl group as the *tert*-butyldimethylsilyl (TBS) ether gave the (*E*)- α,β -unsaturated ester (**7**) in a high overall yield. Reduction of **7** with diisobutylaluminium hydride (DIBAL-H) afforded allyl alcohol (**8**)^{4,5}. Mesylation of **8** and successive LiAlH₄ reduction provided the desired (*E*)-olefin (**9**)⁶ in a high yield. Exchange of the C3 TBS group in **9** to a Piv group, hydrolysis of the ketal followed by chemoselective oxidation of the resulting hemiacetal with *N*-iodosuccinimide⁷ gave γ -lactone (**10**)⁸ efficiently.



Reagents and conditions: a) 70% aq. AcOH; b) NaIO₄, MeOH:H₂O=1:1; c) (EtO)₂P(O)CH₂COOEt, NaH, THF; d) TBSCl, imid., DMF (74% from **2**); e) DIBAL-H, CH₂Cl₂, -78 °C (quant.); f) MsCl, Et₃N, CH₂Cl₂, -18 °C; g) LiAlH₄, THF, 0 °C (91%); h) *n*-Bu₄NF, THF; i) PivCl, DMAP, pyr.; j) 60% aq. CF₃COOH; k) *N*-iodosuccinimide, *n*-Bu₄NI, CH₂Cl₂ (96% from **9**).

Scheme 2

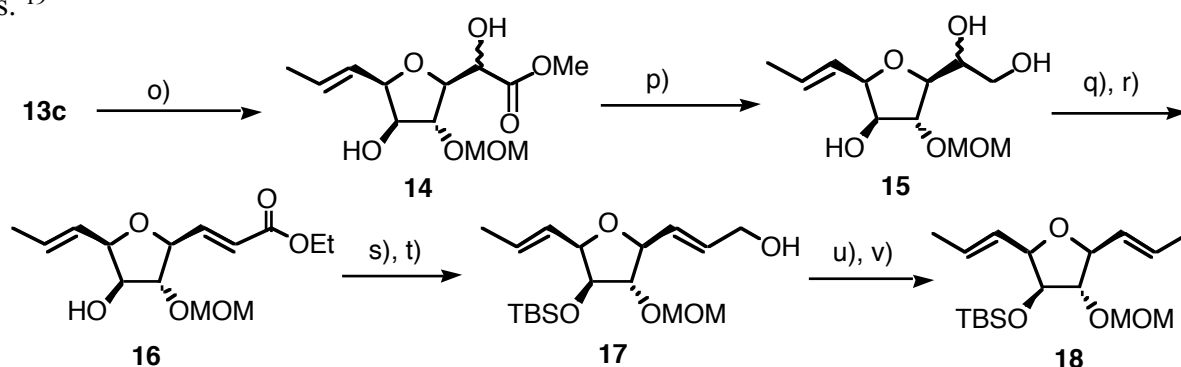
We next explored the introduction of another propenyl group (the right-arm). We envisaged the tandem Wittig reaction and 1,4-conjugate addition at the anomeric position for the aimed *C*-glycosidation. This approach worked as expected (**Scheme 3**). The hydroxyl group in γ -lactone (**10**) was protected as the methoxymethyl (MOM) ether, then reduction with DIBAL-H of the resulting **11** provided lactol (**12**) as a result of concomitant removal of the pivaloyl group. The Wittig olefination of **12** with (methoxycarbonyl)methylenetriphenylphosphorane provided 2,5-*cis*- (**13c**)⁹ and 2,5-*trans*-substituted tetrahydrofuran-3,4-diol (**13t**)¹⁰ in 65% and 20% yields, respectively.¹¹⁻¹³ This reaction proceeded through the 1,4-conjugate addition of the ϵ -hydroxyl group in a ring-opened Wittig adduct(s) to the β -carbon of the unsaturated ester. Conversion of the (methoxycarbonyl)methyl moiety in **13c** to an (*E*)-propenyl group (the right-arm) was achieved as follows (**Scheme 4**). The enolate derived from ester (**13c**) was exposed to the Davis' oxaziridine [racemic *trans*-2-phenylsulfonyl-3-phenyloxaziridine]¹⁴ affording α -hydroxylated esters (**14**) as an inseparable diastereomeric mixture. The ratio of the mixture was approximately 1 to 3 (¹H NMR analysis). We did not undertake their stereochemical assignment.



Reagents and conditions: l) MOMCl, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , reflux (68%); m) DIBAL-H, CH_2Cl_2 , -78°C (84%); n) $\text{Ph}_3\text{P}=\text{CHCOOMe}$, MeCN, reflux [**13c** (65%) + **13t** (20%)].

Scheme 3

This mixture (**14**) was converted to vicinal diol (**15**). Periodate glycol cleavage of **15** followed by Horner-Emmons olefination of the resulting aldehyde gave α,β -unsaturated ester (**16**)¹⁵ as a sole (*E*)-isomer. Protection of the hydroxyl group in **16** as the TBS ether followed by DIBAL-H reduction afforded allylic alcohol (**17**).¹⁶ Mesylation of **17** and subsequent replacement of the mesyloxy group by a hydride proceeded under specified conditions¹⁷ providing the desired 2,5-di(*E*)-propenyltetrahydrofuran-3,4-diol derivative (**18**),¹⁸ in which two hydroxyl groups were protected by differentially removable groups.¹⁹



Reagents and conditions: o) $\text{KN}(\text{TMS})_2$, then Davis' oxaziridine, THF, -78°C (63%); p) LiAlH_4 , THF (86%); q) NaIO_4 , $\text{MeOH}:\text{H}_2\text{O}=1:1$; r) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOEt}$, NaH, THF (71% for 2 steps); s) TBSCl, imid., DMF; t) DIBAL-H, CH_2Cl_2 , -78°C (89% for 2 steps); u) MsCl , Et_3N , CH_2Cl_2 , -18°C ; v) NaBH_4 , cyclohexene, DMSO (67% for 2 steps).

Scheme 4

We have established a stereocontrolled synthetic route to the key intermediate (**18**), i.e., compound (**3**) with $\text{P}^1=\text{MOM}$ and $\text{P}^2=\text{TBS}$, for the enantiomeric total syntheses of FD-211 and its stereoisomers. Further synthetic endeavor to FD-211 and establishment of its undetermined absolute stereochemistry are in progress in our laboratory.

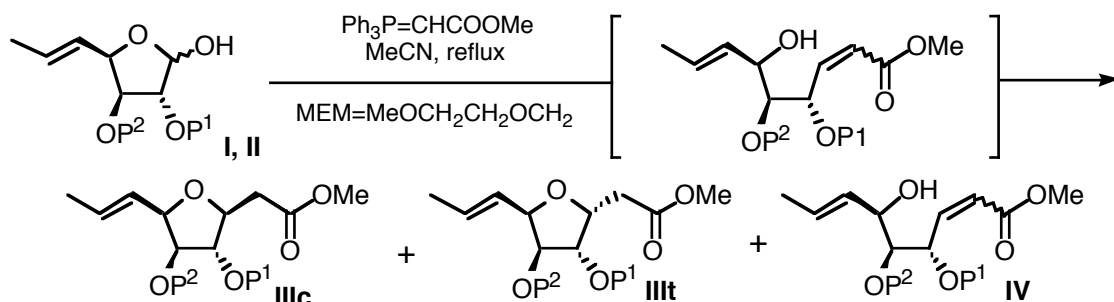
ACKNOWLEDGMENT

We are grateful to the staffs of the Applied Biology, Research Center of Taisho Pharmaceutical Co., Ltd. for providing the spectral data of **1** and useful discussion.

REFERENCES AND NOTES

1. O. Nozawa, T. Okazaki, N. Sakai, T. Komurasaki, K. Hanada, S. Morimoto, Z. -X. Chen, B. -M. He, and K. Mizoue, *J. Antibiot.*, 1995, **48**, 113.
2. A. Klausener, G. Beyer, H. Leismann, H. -D. Scharf, E. Müller, J. Runsink and H. Görner, *Tetrahedron*, 1989, **45**, 4989.
3. T. Okazoe, K. Takai, and K. Utimoto, *J. Am. Chem. Soc.*, 1987, **109**, 951.
4. We could improve this time our previous procedure for obtaining **8**. In the previous report,⁵ the Wittig (not Horner-Emmons) olefination of 1,2-*O*-isopropylidene- α -D-xylo-furano-5-ulose gave the α,β -unsaturated ester, i.e., the 3-OH form of **7**, as the *E,Z*-mixture without remarkable selectivity.
5. K. Tadano, K. Shimada, A. Miyake, J. Ishihara, and S. Ogawa, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 3798.
6. Compound **9**: $[\alpha]_D^{23}$ -40.2 (*c* 0.99, CHCl₃); ¹H NMR (270 MHz, CDCl₃) δ 0.06, 0.08 (2s, 3H x2), 0.90 (s, 9H), 1.32, 1.51 (2s, 3Hx2), 1.73 (dd, 3H, *J* = 1.5, 6.2 Hz), 4.04 (d, 1H, *J* = 2.6 Hz), 4.38 (d, 1H, *J* = 3.7 Hz), 4.53 (dd, 1H, *J* = 8.1, 2.6 Hz), 5.56 (ddq, 1H, *J* = 15.4, 8.1, 1.5 Hz), 5.82 (dq, 1H, *J* = 15.4, 6.2 Hz), 5.91 (d, 1H, *J* = 3.7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ -5.0, -4.9, 17.9, 18.2, 25.7, 26.3, 26.8, 77.8, 82.2, 85.9, 104.7, 111.3, 125.9, 130.9; HRMS calcd for C₁₅H₂₇O₄Si (M⁺-Me) *m/z* 299.1678, found 299.1672.
7. S. Hanessian, D. H. Wong, and M. Therien, *Synthesis*, **1981**, 394.
8. Compound **10**: Mp 74-75 °; $[\alpha]_D^{22}$ +148.2 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 1.20 (s, 9H), 1.74 (dd, 1H, *J* = 1.5, 6.6 Hz), 3.65 (br s, 1H), 4.58-4.65 (m, 1H), 5.18-5.25 (m, 2H), 5.32-5.43 (m, 1H), 5.87 (dq, 1H, *J* = 15.1, 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 17.8, 27.0, 38.7, 70.2, 75.8, 79.6, 122.6, 134.8, 173.5, 177.7; HRMS calcd for C₁₂H₁₈O₅ (M⁺) *m/z* 242.1154, found 242.1159.
9. Compound **13c**: $[\alpha]_D^{22}$ -44.7 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 1.77 (dd, 3H, *J* = 1.0, 6.6 Hz), 2.75 (dd, 1H, *J* = 5.6, 16.4 Hz), 2.82 (dd, 1H, *J* = 5.6, 16.4 Hz), 3.39 (s, 3H), 3.71 (s, 3H), 3.98-4.03 (m, 2H), 4.10 (dt, 1H, *J* = 3.7, 5.6 Hz), 4.37-4.41 (m, 1H), 4.69, 4.73 (ABq, 1Hx2, *J* = 6.8 Hz), 5.62 (ddq, 1H, *J* = 7.1, 15.4, 1.7 Hz), 5.90 (ddq, *J* = 6.6, 15.4, 1.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 18.0, 37.5, 51.8, 55.6, 77.5, 79.2, 82.3, 86.7, 96.1, 125.2, 131.3, 171.7; HRMS calcd for C₁₂H₂₀O₆ (M⁺) *m/z* 260.1260, found 260.1259.
10. Compound **13t**: $[\alpha]_D^{22}$ -40.5 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 1.76 (d, 3H, *J* = 6.6 Hz), 2.70 (d, 2H, *J* = 7.1 Hz), 3.37 (s, 3H), 3.69 (s, 3H), 4.12 (dd, 1H, *J* = 1.7, 3.4 Hz), 4.15 (dd, 1H, *J* = 1.7, 4.4 Hz), 4.54-4.58 (m, 1H), 4.64, 4.70 (ABq, 1Hx2, *J* = 6.8 Hz), 4.65-4.71 (m, 1H), 5.54 (ddq, 1H, *J* = 6.6, 15.4, 1.7 Hz), 5.92 (ddq, 1H, *J* = 6.6, 15.4, 1.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 18.0, 34.4, 51.6, 55.8, 75.8, 76.4, 80.8, 83.5, 96.7, 125.2, 131.1, 171.7; HRMS calcd for C₁₂H₂₀O₆ (M⁺) *m/z* 260.1260, found 260.1247.
11. Stereochemical assignment of **13c** and **13t** was achieved as follows. Deprotection of the MOM group in **13c** (6M HCl/MeOH=1:1) gave γ -hydroxy ester as a sole product. On the other hand, **13t** gave γ -lactone in a good yield under the same deprotection conditions. Thus, 2,3-*trans* for **13c** and 2,3-*cis* relationship for **13t** were confirmed.

12. We have also examined the effect of the protecting groups at C2 and/or C3 hydroxyl group on the stereoselectivity in the 1,4-conjugate addition of the Wittig adduct. Thus, we prepared two substrates (**I**) and (**II**) from **9**. As shown below, neither TBS ether at C2 (P¹) or nor MEM ether (or OH) at C3 (P²) improved the yields of the desired 2,5-*cis*-substituted tetrahydrofuran (**IIIc**).



run	compound	P ¹	P ²	reaction time	IIIc	IIIt	IV
1	I	TBS	MEM	23 h	17%	23%	59% (<i>E</i> only)
2	I	TBS	MEM	37 h	30%	53%	0%
3	II	TBS	H	12 h	complex mixture		

13. By exposure of **13t** to NaOMe (1.5 eq.) in MeOH at ambient temperature for 37 h, the desired **13c** was obtained in 39% yield (41% of **13t** was recovered).
14. F. A. Davis and B. -C. Chen, *Chem. Rev.*, 1992, **92**, 919; *Org. Synth.*, 1987, **66**, 203.
15. Compound **16**: $[\alpha]_{\text{D}}^{22}$ -16.9 (*c* 1.00, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 1.30 (t, 3H, *J* = 7.0 Hz), 1.79 (d, 3H, *J* = 6.6 Hz), 3.41 (s, 3H), 3.92 (dd, 1H, *J* = 2.2, 4.4 Hz), 4.09 (dd, 1H, *J* = 2.2, 4.0 Hz), 4.20 (q, 2H, *J* = 7.0 Hz), 4.41 (ddd, 1H, *J* = 1.8, 4.4, 5.1 Hz), 4.54-4.58 (m, 1H), 4.69, 4.74 (ABq, 1Hx2, *J* = 6.6 Hz), 5.59 (ddq, 1H, *J* = 6.6, 15.4, 1.8 Hz), 5.96 (ddq, 1H, *J* = 6.6, 15.4, 1.3 Hz), 6.12 (dd, 1H, *J* = 1.8, 15.8 Hz), 7.02 (dd, 1H, *J* = 5.1, 15.8 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 14.2, 18.0, 55.8, 60.5, 81.7, 82.1, 87.6, 96.4, 121.2, 125.0, 131.4, 145.4, 166.2; HRMS calcd for $\text{C}_{14}\text{H}_{22}\text{O}_6$ (M^+) *m/z* 286.1416, found 286.1418.
16. Compound **17**: $[\alpha]_{\text{D}}^{22}$ -26.3 (*c* 0.99, CHCl_3); ^1H NMR (270 MHz, CDCl_3) δ 0.04, 0.07 (2s, 3Hx2), 0.90 (s, 9H), 1.72 (dd, 3H, *J* = 1.5, 6.2 Hz), 3.37 (s, 3H), 3.83-3.85 (m, 1H), 4.05 (dd, 1H, *J* = 1.1, 3.3 Hz), 4.12 (d, 1H, *J* = 3.7 Hz), 4.26-4.30 (m, 1H), 4.34 (dd, 1H, *J* = 3.3, 6.1 Hz), 4.68 (s, 2H), 5.57-5.67 (m, 1H), 5.72-5.89 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ -5.1, -4.9, 17.9, 18.1, 25.6, 55.5, 63.0, 78.8, 83.3, 84.2, 87.9, 95.8, 127.2, 130.4, 130.8, 131.5; HRMS calcd for $\text{C}_{18}\text{H}_{34}\text{O}_5\text{Si}$ (M^+) *m/z* 358.2175, found 358.2174.
17. L. E. Overman and A. S. Thompson, *J. Am. Chem. Soc.*, 1988, **110**, 2248.
18. Compound **18**: $[\alpha]_{\text{D}}^{21}$ -17.6 (*c* 1.01, CHCl_3); ^1H NMR (270 MHz, CDCl_3) δ 0.05, 0.08 (2s, 3Hx2), 0.91 (s, 9H), 1.68 (d, 3H, *J* = 5.1 Hz), 1.71 (dd, 3H, *J* = 1.1, 6.2 Hz), 3.36 (s, 3H), 3.81-3.83 (m, 1H), 4.03 (dd, 1H, *J* = 1.5, 3.3 Hz), 4.19 (dd, 1H, *J* = 2.2, 7.7 Hz), 4.30 (dd, 1H, *J* = 3.3, 7.7 Hz), 4.68 (s, 2H), 5.58-5.83 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ -5.1, -4.9, 17.7, 17.9, 18.1, 25.6, 55.4, 78.9, 82.9, 84.9, 87.8, 95.7, 127.5, 128.4, 130.1, 130.7; HRMS calcd for $\text{C}_{18}\text{H}_{34}\text{O}_4\text{Si}$ (M^+) *m/z* 342.2226, found 342.2226.
19. The structure of **18** was confirmed by deprotection of both protecting groups (6M HCl in 99%). The resulting diol (**3**) (P¹=P²=H) was *not* a C₂ symmetrical compound (^1H and ^{13}C NMR analysis).