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

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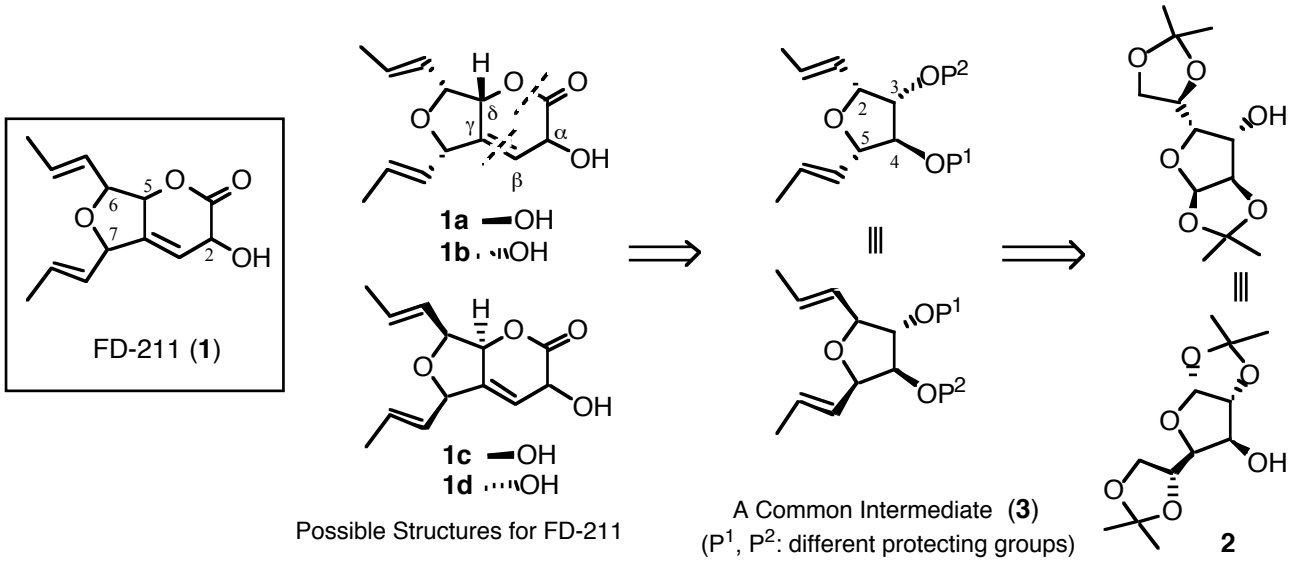
Abstract For total synthesis of a novel bioactive δ-lactone antibiotic FD-211, a key intermediate, a 2,5-di-(*E*)-propenyltetrahydrofuran-3,4-diol derivative, was synthesized from diacetone D-glucose.

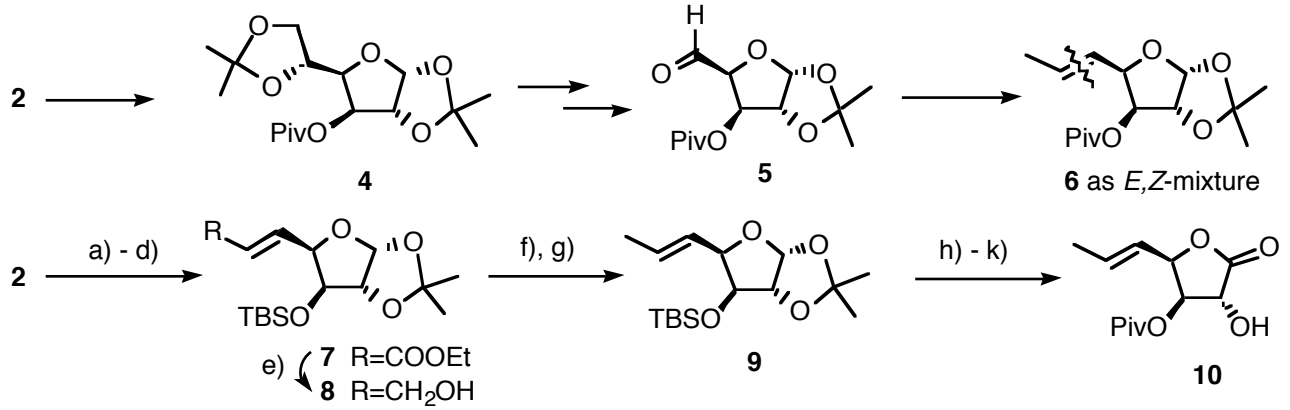
During a screening program for low molecular compounds effective against multidrug-resistant tumor cells, a novel antibiotic FD-211 (**1**) was isolated from the fermentation broth of *Myceliophthora lutea* TF-0409 by the research group of Taisho Pharmaceutical Co., Ltd.[1] Compound (**1**) showed a broad spectrum activity against cultured tumor cell lines including adriamycin-resistant HL-60 cells.[1] The ^{1}H and ^{13}C 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-positions[1] (**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

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

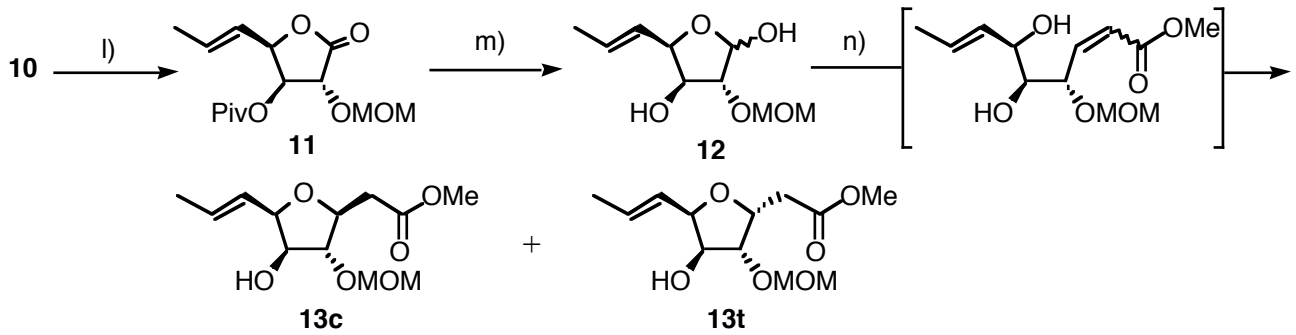
We first examined a direct introduction of a propenyl group (the left-arm) into 1,5-dialdose (**5**), prepared from **2** *via* a known 3-*O*-pivaloyl (Piv) ester (**4**)[2] (**Scheme 2**). Olefination of **5** by the Takai procedure[3] ($CrCl_2$, $MeCHI_2$, DMF/THF) resulted in the formation of the 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 $LiAlH_4$ 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*-iodosuccinimide[7] gave γ-lactone (**10**)[8] efficiently.



Reagents and conditions: a) 70% aq. AcOH; b) $NaIO_4$, MeOH:H_2O=1:1; c) $(EtO)_2P(O)CH_2COOEt$, NaH, THF; d) TBSCl, imid., DMF (74% from **2**); e) DIBAL-H, CH_2Cl_2, -78 °C (quant.); f) MsCl, Et_3N, CH_2Cl_2, -18 °C; g) $LiAlH_4$, THF, 0 °C (91%); h) *n*-Bu_4NF, THF; i) PivCl, DMAP, pyr.; j) 60% aq. CF_3COOH; k) *N*-iodosuccinimide, *n*-Bu_4NI, CH_2Cl_2 (96% from **9**).

Scheme 2

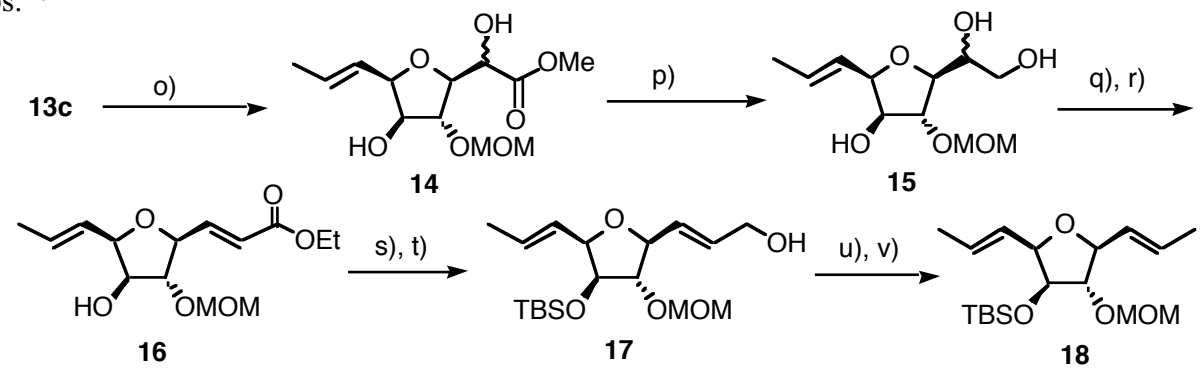
We next explored the introduction of another propenyl group (the right-arm). We envisaged the tandem Wittig reaction and 1,4-conjugate addition at the anomeric position for the aimed *C*-glycosidation. This approach worked as expected (**Scheme 3**). The hydroxyl group in γ-lactone (**10**) was protected 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*Pr_2NEt, CH_2Cl_2, reflux (68%); m) DIBAL-H, CH_2Cl_2, -78 °C (84%); n) Ph_3P=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 conditions[17] 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) $KN(TMS)_2$, then Davis' oxaziridine, THF, -78 °C (63%); p) $LiAlH_4$, THF (86%); q) $NaIO_4$, MeOH:H_2O=1:1; r) $(EtO)_2P(O)CH_2COOEt$, 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 P^1=MOM and P^2=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

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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, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) 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);^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{15}H_{27}O_4Si$ (M^+-Me) *m/z* 299.1678, found 299.1672.

7. S. Hanessian, D. H. Wong, and M. Therien, *Synthesis*, **1981**, 394.

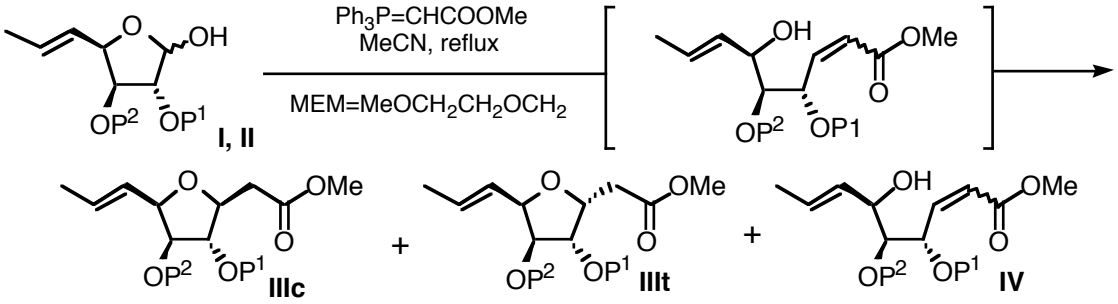
8. Compound **10**: Mp 74-75 °; $[\alpha]_D^{22}$ +148.2 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.74 (dd, 1H, *J* =1.5, 6.6 Hz), 3.65 (br s, 1H), 4.58-4.65 (m, 1H), 5.18-5.25 (m, 2H), 5.32-5.43(m, 1H), 5.87 (dq, 1H, *J* =15.1, 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 27.0, 38.7, 70.2, 75.8, 79.6, 122.6, 134.8, 173.5, 177.7; HRMS calcd for $C_{12}H_{18}O_5$ (M^+) *m/z* 242.1154, found 242.1159.

9. Compound **13c**: $[\alpha]_D^{22}$ -44.7 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz,$CDCl_3$) 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$C_{12}H_{20}O_6$ (M^+) *m/z* 260.1260, found 260.1259.

10. Compound **13t**: $[\alpha]_D^{22}$ -40.5 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{12}H_{20}O_6$ (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 (P^1) or nor MEM ether (or OH) at C3 (P^2) 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% (*E* 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**: $[\alpha]_D^{22}$ -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 $C_{14}H_{22}O_6$ (M^+) *m/z* 286.1416, found 286.1418.

16. Compound **17**: $[\alpha]_D^{22}$ -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, 1 H, 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 $C_{18}H_{34}O_5Si$ (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**: $[\alpha]_D^{21}$ -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* =5.1Hz), 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 $C_{18}H_{34}O_4Si$ (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**) (P^1=P^2=H) was *not* a C_2 symmetrical compound (^1H and ^{13}C NMR analysis).