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A new synthetic approach to the lactol moiety of halichoblelide

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ABSTRACT

A stereoselective approach to the γ-lactol moiety of halichoblelide is described starting from commercially available (*R*)-3-butyn-2-ol. The key step is the hydroboration of a chiral protected 1,2-butadien-3-ol and its addition to furfural.

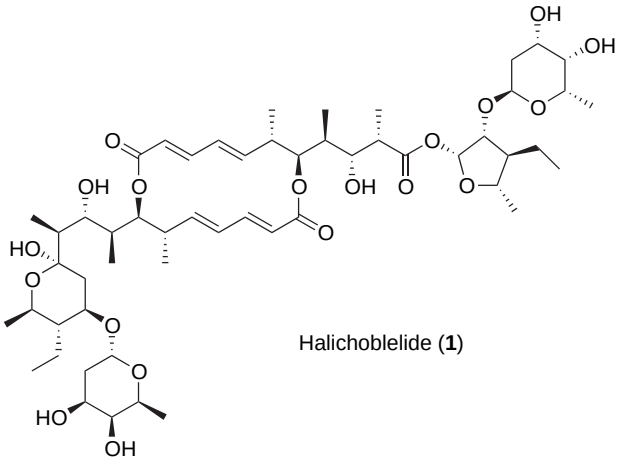
1. Introduction

In 2002, Numata and co-workers isolated halichoblelide (**1**),[1] a new cytotoxic macrodiolide obtained from a strain of *Streptomyces hygroscopicus* OUPS-N92, which inhabits the gastrointestinal tract of the fish *Halichoeres bleekeri* (Fig. 1).

The biological activity test of **1** revealed potent cytotoxicity against the murine cell line P388 (ED_{50} 0.63 μg/ml) and 39 human cancer cell lines (mean log GI_{50} −5.25).

Some years later, Kuwahara and co-workers embarked on the total synthesis of halichoblelide and reported the synthesis of the glycosyl lactol moiety (**2**) incorporated in **1**.[2] In fact, substructure **2** is the only synthetic fragment of halichoblelide described in the literature (Fig. 2).

Very recently, we developed a new stereoselective approach to 2-vinyl-1,3-diols based on the hydroboration of protected 2,3-alkadien-1-ols, followed by the addition of an aldehyde.[3] The *syn*,*syn* configuration observed in the products can be explained in terms of a transient (*E*)-alkenylborane generated in the hydroboration step. We envisaged that our methodology could be applied in the synthesis of the lactol moiety of **2** (**3** in Scheme 1). Thus, lactol **3** could be obtained from lactone **4**, which could be easily prepared from a *syn*,*syn*-2-vinyl-1,3-diol **5**.



Halichoblelide (**1**)

Fig. 1. Structure of halichoblelide (**1**).

2. Results and discussion

We took advantage of our experience in the synthesis of 2-vinyl-1,3-diols to prepare diol **5** (Scheme 2). Thus, we protected quantitatively the commercially available (*R*)-3-butyn-2-ol as *tert*-butyldimethylsilyl ether (**6**). We homologated the protected alkyne with formaldehyde under Ma's conditions,[4] to afford allene **7** in 82% yield.

At this point allene **7** was hydroborated with dicyclohexylborane and added to an aromatic aldehyde to yield the desired

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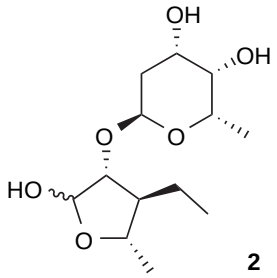
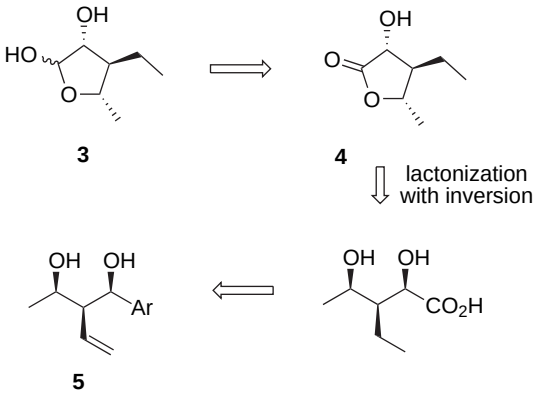
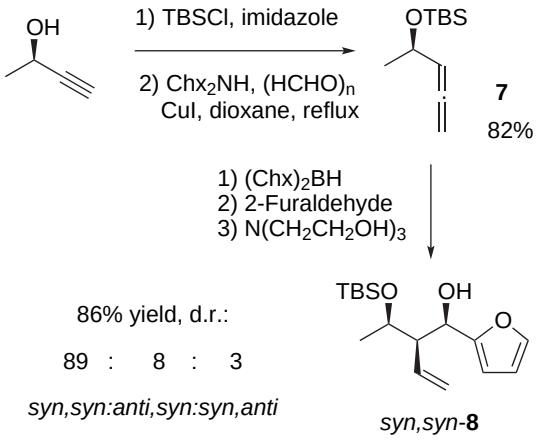


Fig. 2. Glycosyl lactol **2**.



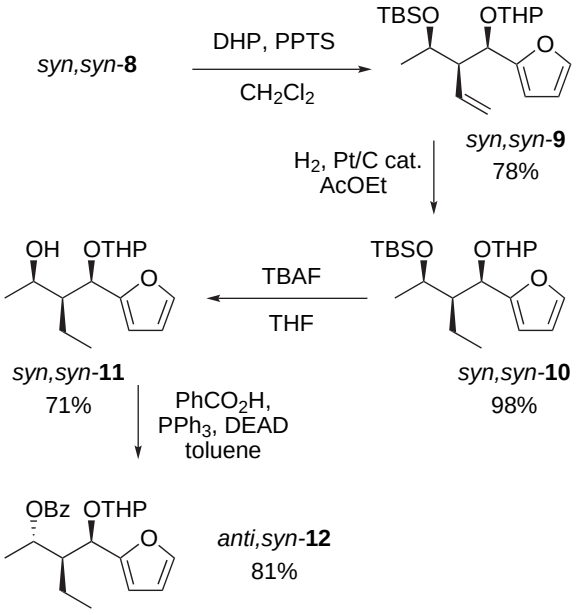
Scheme 1. Retrosynthetic analysis of lactol **3**.



Scheme 2. Synthesis of alcohol **8**.

protected 2-vinyl-1,3-diol. Furfural was considered as a good candidate because it can be easily oxidized to a carboxyl group. Under these conditions we obtained diol **8** in good yield and with high stereoselectivity. The major isomer *syn*,*syn*-**8** was easily isolated from the mixture of stereoisomers (86% yield).

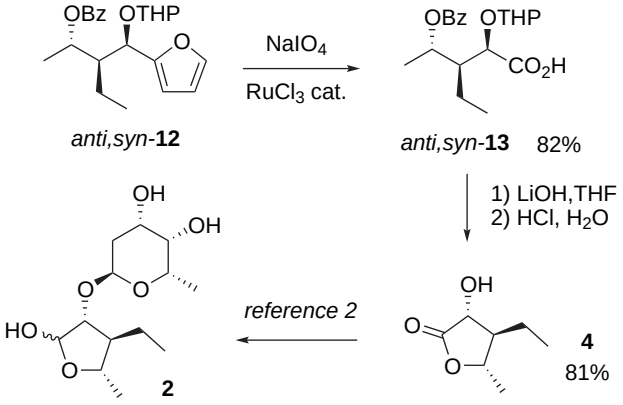
Protection of the free hydroxyl group of *syn*,*syn*-**8** as a tetrahydropyranyl (THP) yielded the corresponding adduct (*syn*,*syn*-**9**) in 78% yield (Scheme 3). The alternative protection of this alcohol as an acetate was troublesome since the acetyl migrated during the later TBS deprotection step. Hydrogenation of the olefin *syn*,*syn*-**9** was achieved almost quantitatively with Pt/C as catalyst, to afford *syn*,*syn*-**10**. Deprotection of TBS yielded the monoprotected diol *syn*,*syn*-**11**. After oxidation of the furan to a carboxyl group, we planned to activate the free hydroxyl group and cyclize to the lactone by an S_N2 process. However, any attempt to activate this alcohol as a sulfonate was unsuccessful, since the transient sulfonate



Scheme 3. Synthesis of benzoate *anti*,*syn*-**12**.

always decomposed. Alternatively, the inversion was performed easily prior the lactonization step by a Mitsunobu reaction.[5] Under these conditions, benzoate *anti*,*syn*-**12** was obtained in 81% yield. We checked that the assumed inversion had indeed occurred, by comparison with the non-inverted benzoate (prepared from *syn*,*syn*-**11** with benzoyl chloride).

The endgame of this synthesis was the oxidation of the furan moiety with sodium periodate under Ru catalysis[6] to afford acid *anti*,*syn*-**13** in 82% yield (Scheme 4). Deprotection of benzoate under basic conditions followed by acidic treatment caused the hydrolysis of THP group with concomitant cyclization to the final lactone **4** in 81% yield. Transformation of **4** into glycosyl lactol **2** in three steps has been previously reported.[2]



Scheme 4. Oxidation of furane **12** and lactone formation.

The NMR spectroscopic data of lactone **4** were fully consistent with those in the literature.[2] Furthermore, the Mosher ester of **4** indicated a single enantiomer.[7]

3. Conclusion

Lactone **4**, an intermediate in the synthetic approach to halichoblelide, has been synthesized stereoselectively from commercially available (*R*)-3-butyn-2-ol. In the context of natural product synthesis, this approach constitutes the first application of our recently described methodology of hydroboration–addition of

allenes to aldehydes.[3] Although the *syn*,*syn* stereochemistry arising from this type of addition does not fit with that present in **4**, an inversion was successfully performed by a Mitsunobu reaction.

4. Experimental

4.1. General materials and methods

All reactions containing moisture or air sensitive reagents were performed in oven-dried glassware under nitrogen. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Mercury 400 spectrometer. Chemical shifts (δ) are quoted in parts per million and referenced to internal TMS for ^{1}H NMR and to $CDCl_3$ (δ 77.0) for ^{13}C NMR. Column chromatography was performed on silica gel (Merck 230–400 mesh). HRMS analyses were recorded on an Agilent LC/MSD-TOF mass spectrometer. IR spectra (wave numbers in cm^{-1}) were recorded on a NICOLET 6700 FT-IR spectrometer. Specific rotations were measured at room temperature in a Perkin–Elmer 241 MC polarimeter.

4.2. Synthesis of (*R*)-3-*tert*-butyldimethylsilyloxy-1-butyne (6)

A solution of *tert*-butyldimethylsilyl chloride (9.30 g, 62.5 mmol) in anhyd THF (40 mL) was added dropwise, under nitrogen atmosphere, to a stirred solution of commercially available (*R*)-3-butyn-2-ol (2.42 mL, 40 mmol) and imidazole (6.30 g, 92.4 mmol) at room temperature. The reaction mixture was stirred for 6 h. After this time, the mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum to yield the corresponding pure (+)-**6** (7.37 g, 40 mmol).

*4.2.1. Compound (+)-**6**[8].* Colourless oil; R_f (hexane/AcOEt 98:2): 0.60; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.12 (3H, s, $SiCH_3$), 0.13 (3H, s, $SiCH_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.42 (3H, d, J=6.6 Hz, C*H*$_3$CH), 2.36 (1H, d, J=2.0 Hz, C≡CH), 4.51 (1H, qd, J=6.6, 2.0 Hz, CHOTBS); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −3.89, −3.55, 19.3, 26.4, 26.9, 59.9, 72.3, 87.5; IR (film): 3312, 2963, 2225, 1435; $[\alpha]_D^{25}$ +54.6 (*c* 1.00, $CHCl_3$).

4.3. Synthesis of (*R*)-3-*tert*-butyldimethylsilyloxy-1,2-butadiene (7)

A solution of dicyclohexylamine (8.95 mL, 45.0 mmol) and (+)-**6** (5.60 g, 25.5 mmol) in anhyd dioxane (5 mL) was added dropwise, under nitrogen atmosphere, to a stirred solution of paraformaldehyde (1.88 g, 62.5 mmol) and CuI (2.38 g, 12.5 mmol) in anhyd dioxane (50 mL). The reaction mixture was refluxed for 4 h. Then, solvents were directly eliminated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane/AcOEt 98:2) to give 4.12 g (82%) of (+)-**7**.

*4.3.1. Compound (+)-**7**[9].* Colourless oil; R_f (hexane/AcOEt 98:2): 0.45; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.07 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.26 (3H, d, J=6.4 Hz, C*H*$_3$CH), 4.37 (1H, m, C*H*OTBS), 4.76 (2H, m, C=CH_2), 5.16 (1H, q, J=6.4 Hz, C*H*=C); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.9, −4.5, 18.2, 24.5, 25.9, 67.2, 76.3, 96.2, 206.9; IR (film): 3030, 2976, 1447, 1376, 842, 733; $[\alpha]_D^{25}$ +15.7 (*c* 1.00, $CHCl_3$).

4.4. Synthesis (1*R*,2*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-1-(furan-2-yl)-3-buten-1-ol (8)

A solution of (+)-**7** (4.12 g, 20.8 mmol) in anhyd CH_2Cl_2 (20 mL) was added dropwise to a stirred suspension of dicyclohexylborane (4.43 g, 24.9 mmol) at 0 °C, in anhyd CH_2Cl_2 (20 mL) in a dry flask under nitrogen atmosphere. After 10 min at 0 °C the reaction was stirred at room temperature for 2 h, until it became homogeneous. Then it was cooled down to −78 °C and 2-furaldehyde (2.06 mL, 5.6 mmol) was added. The solution was kept cold during 10 min and then stirred at room temperature for 2 h. Then, a solution of triethanolamine (5.2 mL, 44.4 mmol) in CH_2Cl_2 (10 mL) was added and stirred for 1 h. The volatiles were removed under vacuum. Purification by column chromatography on silica gel (hexane/AcOEt 95:5) afforded 5.28 g (86%) of product *syn*,*syn*-**8**, *anti*,*syn*-**8** and *syn*,*anti*-**8** in a ratio 89:8:3.

*4.4.1. Compound (+)-syn,syn-**8**.* Colourless oil; R_f (hexane/AcOEt 98:2): 0.15; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.00 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.09 (3H, d, J=6.4 Hz, C*H*$_3$CHOTBS), 2.43 (1H, ddd, J=9.6, 7.6, 2.2 Hz, C*H*CH=CH_2), 2.63 (1H, d, J=2.4 Hz, OH), 3.84 (1H, qd, J=6.4, 2.0 Hz, CHOTBS), 4.82 (1H, dd, J=7.6, 2.4 Hz, C*H*OH), 5.17 (1H, dd, J=17.4, 2.2 Hz, CH=C*H*$_2$), 5.34 (1H, dd, J=10.2, 2.2 Hz, CH=C*H*$_2$), 6.00 (1H, dt, J=17.4, 10.2 Hz, C*H*=CH_2), 6.29 (1H, d, J=3.2 Hz, Ar*H*), 6.33 (1H, dd, J=3.2, 1.8 Hz, Ar*H*), 7.37 (1H, dd, J=1.8, 0.8 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.1, −3.7, 17.9, 22.6, 25.8, 56.7, 68.7, 69.1, 107.5, 110.1, 120.8, 133.8, 141.8, 154.8; IR (film): 3400–3200, 3041, 2990, 1959, 1452, 1375, 1148; HRMS (ESI$^+$) calcd for $C_{16}H_{28}NaO_3Si$ $[M+Na]^+$ 319.1700, found 319.1696; $[\alpha]_D^{25}$ +49.9 (*c* 1.00, $CHCl_3$).

*4.4.2. Compound (+)-anti,syn-**8**.* Colourless oil; R_f (hexane/AcOEt 98:2): 0.20; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.09 (6H, s, $SiCH_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.27 (3H, d, J=6.4 Hz, C*H*$_3$CHOTBS), 2.45 (1H, ddd, J=8.8, 4.8, 3.0 Hz, C*H*CH=CH_2), 3.68 (1H, d, J=3.0 Hz, OH), 4.07 (1H, qd, J=6.4, 2.0 Hz, CHOTBS), 5.02 (1H, m, J=17.6, 2.0 Hz, CH=C*H*$_2$), 5.13 (1H, dd, J=10.0, 2.0 Hz, CH=C*H*$_2$), 5.16 (1H, t, J=3.0 Hz, C*H*OH) 5.95 (1H, dt, J=17.6, 10.0 Hz, C*H*=CH_2), 6.23 (1H, d, J=3.2 Hz, Ar*H*), 6.30 (1H, dd, J=3.2, 2.0 Hz, Ar*H*), 7.36 (1H, dd, J=2.0, 0.8 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.3, 17.9, 22.0, 25.7, 54.7, 67.8, 71.2, 106.2, 110.4, 118.2, 135.5, 141.2, 155.7; IR (film): 3447, 3117, 3076, 2929, 1255; HRMS (ESI$^+$) calcd for $C_{16}H_{28}NaO_3Si$ $[M+Na]^+$ 319.1700, found 319.1697; $[\alpha]_D^{25}$ +9.45 (*c* 1.00, $CHCl_3$).

*4.4.3. Compound (+)-syn,anti-**8**.* Colourless oil; R_f (hexane/AcOEt 98:2): 0.23; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.10 (3H, s, $SiCH_3$), 0.13 (3H, s, $SiCH_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.22 (3H, d, J=6.4 Hz, C*H*$_3$CHOTBS), 2.69 (1H, td, J=9.2, 2.8, C*H*CH=CH_2), 4.04 (1H, d, J=3.4 Hz, OH), 4.18 (1H, qd, J=6.4, 2.8 Hz, CHOTBS), 4.84 (1H, d, J=9.4, 3.4 Hz, C*H*OH), 4.97 (1H, m, J=17.4, 1.8 Hz, CH=C*H*$_2$), 5.00 (1H, dd, J=10.4, 1.8 Hz, CH=C*H*$_2$), 5.56 (1H, ddd, J=17.4, 10.4, 9.4 Hz, C*H*=CH_2), 6.22 (1H, d, J=3.2 Hz, Ar*H*), 6.28 (1H, dd, J=3.2, 1.6 Hz, Ar*H*), 7.35 (1H, dd, J=1.6, 0.8 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.0, −4.4, 17.9, 19.6, 25.8, 54.4, 68.6, 70.6, 107.1, 109.8, 118.3, 134.4, 141.8, 155.8; IR (film): 3451, 2956, 2929, 2857, 1472, 1375, 1255, 1158, 1008, 808, 776; HRMS (ESI$^+$) calcd for $C_{16}H_{28}NaO_3Si$ $[M+Na]^+$ 319.1700, found 319.1697;[3] $[\alpha]_D^{25}$ +27.3 (*c* 1.00, $CHCl_3$).

4.5. Synthesis of *syn*,*syn*-9

A solution of 3,4-dihydro-2*H*-pyran (4.77 mL, 55.8 mmol) was added to a stirred solution of *syn*,*syn*-**8** (5.28 g, 17.8 mmol) and pyridinium *p*-toluenesulfonate (0.13 g, 0.5 mmol) in anhyd CH_2Cl_2 (50 mL) under nitrogen atmosphere. The reaction mixture was refluxed for 14 h. Then, the mixture was quenched with a saturated aqueous solution of NaCl (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum to yield the corresponding crude residue that was purified by flash chromatography on silica gel (hexane/AcOEt 95:5) to afford 5.30 g (78%) of product *syn*,*syn*-**9** as a 1:1 mixture of diastereomers.

*4.5.1. Compound syn,syn-**9**.* Colourless oil; R_f (hexane/AcOEt 90:10): 0.60; ^{1}H NMR ($CDCl_3$, 400 MHz): δ −0.07 (1.5H, s, $SiCH_3$), −0.08 (1.5H, s, $SiCH_3$), −0.05 (1.5H, s, $SiCH_3$), −0.04 (1.5H, s, $SiCH_3$) 0.90 (9H, s, $SiC(CH_3)_3$), 1.05 (1.5H, d, J=6.4 Hz, CH_3CHOTBS), 1.07 (1.5H, d, J=6.4 Hz, CH_3CHOTBS), 1.37–1.80 (6H, m, $(CH_2)_3$), 2.55 (1H, td, J=9.6, 2.0 Hz, CHCH=CH_2), 3.29 (0.5H, m, OCH_2CH_2), 3.46–3.58 (2H, m, CHOTBS and OCH_2CH_2), 3.87 (0.5H, td, J=11.2, 2.8 Hz, OCH_2CH_2), 4.49 (0.5H, t, J=2.8 Hz, OCHO), 4.66–4.68 (1H, m, OCHO and CHOTHP), 4.82 (0.5H, d, J=9.6 Hz, CHOTHP), 5.14–5.26 (2H, m, CH=CH_2), 5.86–5.99 (1H, m, CH=CH_2), 6.26–6.32 (2H, m, ArH), 7.37 (0.5H, s, ArH), 7.39 (0.5H, s, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.1, −3.8, −3.7, 18.1, 18.6, 19.0, 22.4, 22.5, 25.4, 25.7, 25.9, 29.8, 30.3, 55.7, 56.4, 61.0, 61.6, 67.5, 67.6, 69.4, 73.4, 93.6, 99.7, 107.9, 109.8, 109.9, 110.0, 118.2, 119.0, 135.0, 135.7, 141.6, 142.3, 152.9, 154.9; IR (film): 3028, 2912, 2878, 1462, 1371, 1233; HRMS (ESI$^+$) calcd for $C_{21}H_{36}NaO_4Si$ [M+Na]$^+$ 403.2275, found 403.2278.

4.6. Synthesis of *syn,syn*-10

Platinum on carbon (5 wt %, 100 mg, 0.010 mmol) was added to a solution of *syn,syn*-**9** (5.09 g, 13.4 mmol) in AcOEt (20 mL). The mixture was shaken under hydrogen (1 atm) until TLC showed complete conversion. The suspension was filtered through a short pad of Celite® and solvent was directly eliminated under reduced pressure to yield 5.01 g of *syn,syn*-**10** (98%) as a 1:1 mixture of diastereomers.

*4.6.1. Compound syn,syn-**10**.* Colourless oil; R_f (hexane/AcOEt 90:10): 0.65; ^{1}H NMR ($CDCl_3$, 400 MHz): δ −0.06 (1.5H, s, $SiCH_3$), −0.05 (1.5H, s, $SiCH_3$), −0.03 (1.5H, s, $SiCH_3$), −0.02 (1.5H, s, $SiCH_3$), 0.86 (4.5H, s, $SiC(CH_3)_3$), 0.88 (4.5H, s, $SiC(CH_3)_3$), 0.98 (1.5H, t, J=7.6 Hz, CH_3CH_2), 1.04 (1.5H, t, J=7.6 Hz, CH_3CH_2), 1.13 (1.5H, d, J=6.4 Hz, CH_3CHOTBS), 1.16 (1.5H, d, J=6.0 Hz, CH_3CHOTBS), 1.45–1.80 (9H, m, $(CH_2)_3$ and $CHCH_2CH_3$), 3.25 (0.5H, m, OCH_2CH_2), 3.49–3.56 (1H, m, OCH_2CH_2), 3.62–3.71 (1H, m, CHOTBS), 3.89 (0.5H, ddd, J=11.2, 9.2, 4.0 Hz, OCH_2CH_2), 4.45 (0.5H, t, J=3.2 Hz, OCHO), 4.64 (0.5H, d, J=7.6 Hz, CHOTHP), 4.74 (0.5H, t, J=3.2 Hz, OCHO), 4.79 (0.5H, d, J=8.4 Hz, CHOTHP), 6.22–6.25 (1H, m, ArH), 6.29–6.31 (1H, m, ArH), 7.34 (0.5H, m, ArH), 7.37 (0.5H, m, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.0, −3.9, 13.7, 14.2, 18.1, 18.9, 19.2, 19.2, 19.3, 21.6, 22.0, 25.4, 25.6, 25.9, 30.5, 30.6, 51.1, 51.2, 61.8, 61.8, 68.1, 68.3, 71.6, 75.1, 94.5, 99.9, 107.2, 109.2, 109.7, 109.9, 141.2, 142.0; IR (film): 3013, 2967, 2923, 1467, 1375, 1239; HRMS (ESI$^+$) calcd for $C_{21}H_{38}NaO_4Si$ [M+Na]$^+$ 405.2432, found 405.2432.

4.7. Synthesis of *syn,syn*-11

A solution of *syn,syn*-**10** (5.01 g, 13.1 mmol), TBAF·3H_2O (20.68 g, 65.5 mmol) in anhyd THF (50 mL), under nitrogen atmosphere was stirred at room temperature for 24 h. Then, the mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum to yield the corresponding crude residue *syn,syn*-**11**. Purification by column chromatography using silica gel (hexane/AcOEt 80:20) gave 2.50 g of a 1:1 mixture of diastereomers (71%).

*4.7.1. Compound syn,syn-**11**.* Colourless oil; R_f (hexane/AcOEt 80:20): 0.25; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.84 (1.5H, t, J=7.2 Hz, CH_3CH_2), 0.93 (1.5H, t, J=7.6 Hz, CH_3CH_2), 1.16 (1.5H, d, J=6.4 Hz, CH_3CH), 1.20 (1.5H, d, J=6.4 Hz, CH_3CH), 1.41–1.81 (9H, m, $(CH_2)_3$ and $CHCH_2CH_3$) 2.49 (1H, bs, OH), 3.30 (0.5H, dt, J=11.6, 4.8 Hz, OCH_2CH_2), 3.49 (0.5H, dt, J=12.0, 4.8 Hz, OCH_2CH_2), 3.61 (0.5H, ddd, J=11.6, 8.8, 3.2 Hz, OCH_2CH_2), 3.89 (0.5H, m, OCH_2CH_2), 3.92 (0.5H, m, CHOH), 4.03 (0.5H, qd, J=6.4, 2.0 Hz, CHOH), 4.49 (0.5H, dd, J=5.2, 2.8 Hz, OCHO), 4.70 (0.5H, d, J=5.2 Hz, CHOTHP), 4.75 (0.5H, t, J=3.6 Hz, OCHO), 4.94 (0.5H, d, J=5.2 Hz, CHOTHP), 6.23 (0.5H, d, J=3.2 Hz, ArH), 6.28 (0.5H, d, J=3.2 Hz, ArH), 6.30 (0.5H, dd, J=3.2, 1.8 Hz, ArH), 6.32 (0.5H, dd, J=3.2, 1.6 Hz, ArH), 7.34 (0.5H, dd, J=1.8, 0.8 Hz, ArH), 7.37 (0.5H, dd, J=1.6, 0.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 14.1, 16.8, 17.7, 19.2, 20.0, 21.1, 21.3, 25.2, 30.6, 30.7, 50.4, 50.5, 62.2, 63.2, 67.7, 69.2, 74.2, 75.2, 96.6, 99.2, 107.3, 107.9, 110.1, 110.1, 141.4, 142.0, 153.7, 154.9; IR (film): 3400–3200, 3024, 2956, 1442, 1370, 1212, 1155; HRMS (ESI$^+$) calcd for $C_{15}H_{24}NaO_4$ [M+Na]$^+$ 291.1567, found 291.1565.

4.8. Synthesis of *anti,syn*-12

A solution of DEAD (0.95 mL, 5.18 mmol) in anhyd toluene was added dropwise to a stirred suspension of *syn,syn*-**11** (0.88 g, 2.59 mmol), benzoic acid (0.63 g, 5.18 mmol) and triphenylphosphine (1.36 g, 5.18 mmol) in anhyd toluene (20 mL) at −78 °C, in a dry flask under nitrogen atmosphere. After 30 min at −78 °C, the reaction mixture was stirred at 0 °C for 3 h. Then, the reaction was quenched with *tert*-butyl dimethyl ether (10 mL) and washed with an aqueous solution of $NaHCO_3$ 1 M (3×10 mL). The layers were separated and the organic layer was washed again with a saturated aqueous solution of NaCl (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum to yield the corresponding crude residue. Purification by column chromatography using silica gel (hexane/AcOEt 98:2) afforded 0.79 g (81%) of *anti,syn*-**12**.

*4.8.1. Compound anti,syn-**12**.* Colourless oil; R_f (hexane/AcOEt 98:2): 0.53; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.00 (1.5H, t, J=7.6 Hz, CH_3CH_2), 1.05 (1.5H, t, J=7.6 Hz, CH_3CH_2), 1.21 (1.5H, d, J=6.2 Hz, CH_3CHOBz), 1.23 (1.5H, d, J=6.2 Hz, CH_3CHOBz), 1.44–1.84 (8H, m, $(CH_2)_3$ and CH_2CH_3), 2.18 (0.5H, q, J=6.2 Hz, CHCHOTHP), 2.24 (0.5H, q, J=6.4 Hz, CHCHOTHP), 3.27 (0.5H, m, OCH_2CH_2), 3.40 (0.5H, dt, J=10.4, 4.4 Hz, OCH_2CH_2), 3.61 (0.5H, ddd, J=11.2, 8.8, 2.8 Hz, OCH_2CH_2), 3.79 (0.5H, m, OCH_2CH_2), 4.47 (0.5H, t, J=3.6 Hz, OCHO), 4.71 (0.5H, t, J=3.6 Hz, OCHO), 4.77 (0.5H, d, J=6.0 Hz, CHOTHP), 4.87 (0.5H, d, J=6.4 Hz, CHOTHP), 5.14 (0.5H, quint, J=6.4 Hz, CHOBz), 5.21 (0.5H, quint, J=6.4 Hz, CHOBz), 6.29 (0.5H, m, ArH), 6.32 (1.5H, m, ArH), 7.36–7.45 (3H, m, ArH), 7.54 (1H, m, ArH), 8.02 (2H, m, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.9, 13.2, 16.7, 17.1, 19.2, 19.4, 19.6, 19.9, 25.3, 25.4, 30.5, 30.5, 48.5, 48.7, 62.1, 62.3, 71.3, 71.4, 71.6, 74.0, 95.3, 99.6, 107.0, 108.6, 110.0, 110.2, 128.2, 128.3, 129.5, 132.6, 132.7, 141.3, 142.1, 153.4, 155.0, 165.8; IR (film): 3023, 2967, 1984, 1723, 1443, 1381, 1275, 1212; HRMS (ESI$^+$) calcd for $C_{22}H_{28}NaO_5$ [M+Na]$^+$ 395.1829, found 395.1827.

4.9. Synthesis of *anti,syn*-13

Ruthenium (III) chloride monohydrate (3 mg, 0.008 mmol) was added to a solution of *anti,syn*-**12** (63 mg, 0.176 mmol) and $NaIO_4$ (190 mg, 1.60 mmol) in CCl_4 (0.6 mL), CH_3CN (0.6 mL) and H_2O (1.0 mL) and the mixture was vigorously stirred until TLC showed complete conversion. Additional water was added and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude mixture by column chromatography using silica gel (CH_2Cl_2/MeOH 95:5) afforded 51 mg (82%) of *anti,syn*-**13** as 1:1 diastereomeric mixture.

*4.9.1. Compound anti,syn-**13**.* Colourless oil; R_f (CH_2Cl_2/MeOH 95:5): 0.35; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.99 (1.5H, t, J=7.2 Hz, CH_3CH_2), 1.03 (1.5H, t, J=7.6 Hz, CH_3CH_2), 1.40 (1.5H, d, J=6.0 Hz, CH_3CHOBz), 1.44 (1.5H, d, J=6.4 Hz, CH_3CHOBz), 1.52–1.83 (8H, m, $(CH_2)_3$ and CH_2CH_3), 2.27 (0.5H, m, CHCH$_2$CH$_3$), 2.42 (0.5H, m, CHCH$_2$CH$_3$), 3.25 (0.5H, m, OCH_2CH_2), 3.53 (0.5H, ddd, J=11.6, 10.8, 3.2 Hz, OCH_2CH_2), 3.63 (0.5H, m, OCH_2CH_2), 3.97 (0.5H, m,

OC*H*$_2$CH$_2$), 4.26 (0.5H, dd, *J*=8.0, 1.6 Hz, OCHO), 4.38 (0.5H, d, *J*=2.4 Hz, CHOTHP), 4.60 (0.5H, *J*=5.2, 2.8 Hz, OCHO), 4.71 (0.5H, d, *J*=2.4 Hz, CHOTHP), 5.17–5.24 (1H, m, CHOBz), 7.39–7.48 (2H, m, Ar*H*), 7.52–7.60 (1H, m, Ar*H*), 8.03–8.06 (2H, m, Ar*H*), 10.0–12.0 (1H, br s, OH); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 13.6, 13.7, 19.4, 19.9, 20.9, 21.2, 22.3, 26.0, 26.5, 31.7, 32.2, 48.5, 49.0, 64.3, 67.3, 72.6, 72.8, 72.9, 74.9, 99.5, 105.5, 129.6, 129.7, 130.9, 131.0, 134.1, 134.5, 167.3, 167.3, 175.5, 179.4; IR (film): 2939, 3028, 2912, 1725, 1698, 1439, 1376, 1266; HRMS (ESI$^+$) calcd for $C_{19}H_{26}NaO_6$ [M+Na]$^+$ 371.1829, found 373.1620.

4.10. Synthesis of 4

A solution of aqueous LiOH (2 mL, 8 M) was added dropwise to a stirred solution of *anti*,*syn*-**13** (51 mg, 0.144 mmol) in THF (1.88 g, 62.5 mmol). The reaction mixture was then refluxed for 12 h until TLC showed complete conversion. Then, the mixture was acidified with aqueous HCl 37% and later, refluxed during 6 h. The reaction was quenched with saturated aqueous NaCl. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography (hexane/AcOEt 85:15) gave 17 mg of **4** (0.117 mmol, 81%).

*4.10.1. Compound **4**.* Colourless oil; R_f (hexane/AcOEt 70:30): 0.10; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.08 (3H, t, *J*=7.6 Hz, C*H*$_3$CH$_2$), 1.45 (3H, d, *J*=6.4 Hz, C*H*$_3$CH), 1.55–1.74 (2H, m, C*H*$_2$CH$_3$), 1.94–2.02 (1H, m, C*H*CH$_2$), 2.70 (1H, d, *J*=2.4 Hz, OH), 4.17 (1H, q, *J*=6.4 Hz, CH$_3$C*H*), 4.18 (1H, d, *J*=10.4 Hz, C*H*OH); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 11.4, 19.6, 23.1, 52.3, 73.7, 78.4, 176.7; IR (film): 3360, 3936, 2872, 1766, 1444, 1031; HRMS (ESI$^+$) calcd for $C_7H_{12}NaO_3$ [M+Na]$^+$ 167.0679, found 167.0678; $[\alpha]_D^{25}$ −0.4 (*c* 1.00, CHCl$_3$).

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Supplementary data

^{1}H NMR and ^{13}C NMR spectra for all compounds. Supplementary data related to this article can be found in online version at doi:10.1016/j.tet.2011.05.055.

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