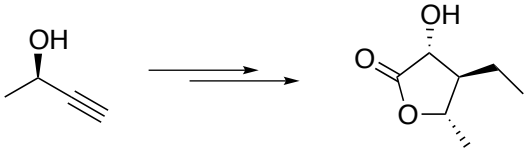
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

A new synthetic approach to the lactol moiety of halichoblelide

Leave this area blank for abstract info.

David Santos, Xavier Ariza*, Jordi Garcia* and Carolina Sánchez
Departament de Química Orgànica, Fac. de Química, Institut de Biomedicina de la UB (IBUB), Universitat de Barcelona, C/Martí i Franquès 1-11, 08028-Barcelona, Spain



Tetrahedron
journal homepage: www.elsevier.com

A new synthetic approach to the lactol moiety of halichoblelide

David Santos[a] , Xavier Ariza[a,] ∗, Jordi Garcia [a,] ∗ and Carolina Sánchez[a]

[a] *Departament de Química Orgànica, Fac. de Química, Institut de Biomedicina de la UB (IBUB), Universitat de Barcelona, C/Martí i Franquès 1-11, 08028-Barcelona, Spain*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Keyword_1 Hydroboration
Keyword_2 Allene
Keyword_3 1,3-Diol
Keyword_4 Stereoselective synthesis
Keyword_5 Natural product

ABSTRACT

A stereoselective approach to the γ-lactol moiety of halichoblelide is described starting from commercially available (*R*)-1-butyn-3-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 macrolactam obtained from a strain of *Streptomyces hygroscopicus* OUPS-N92, which inhabits the gastrointestinal tract of the fish *Halichoeres bleekeri*.

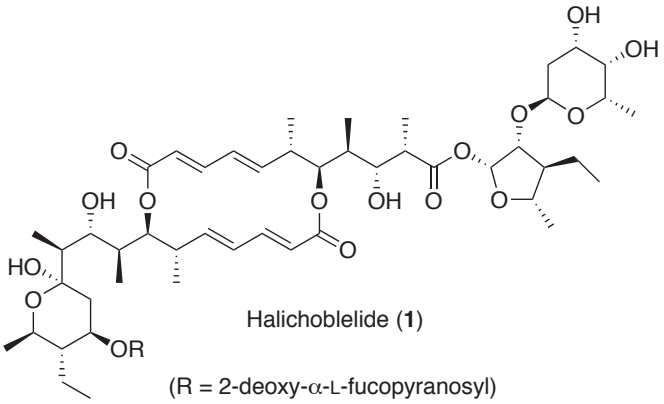


Figure 1. Structure of halichoblelide (**1**)

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 *et al.* 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.

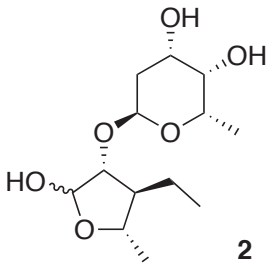


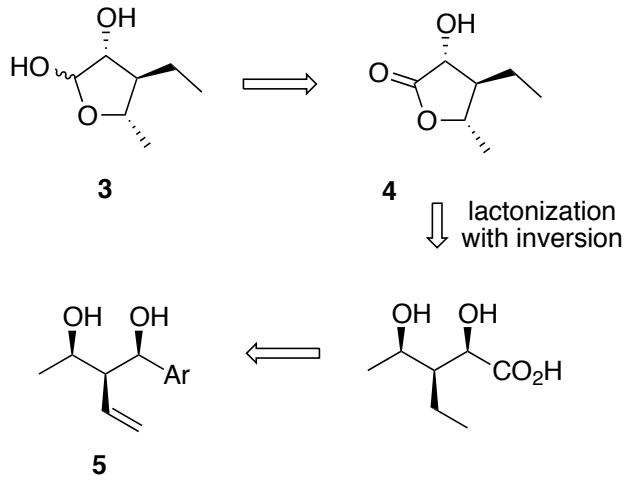
Figure 2. Glycosyl lactol **2**

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

∗ Corresponding author. Tel.: +34-93-403-9114; fax: +34-93-339-7878; e-mail: xariza@ub.edu

∗ Corresponding author. Tel.: +0-000-403-4819; fax: +34-93-339-7878; e-mail: jordigarciagomez@ub.edu

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**.

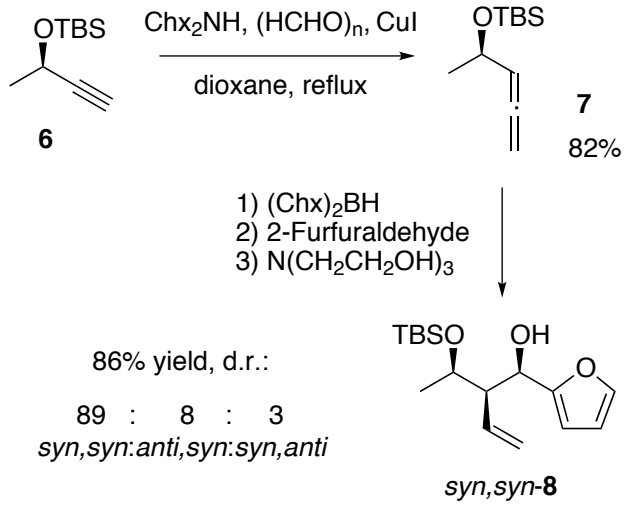


Scheme 1. Retrosynthetic analysis of lactol **3**

2. Results and discussion

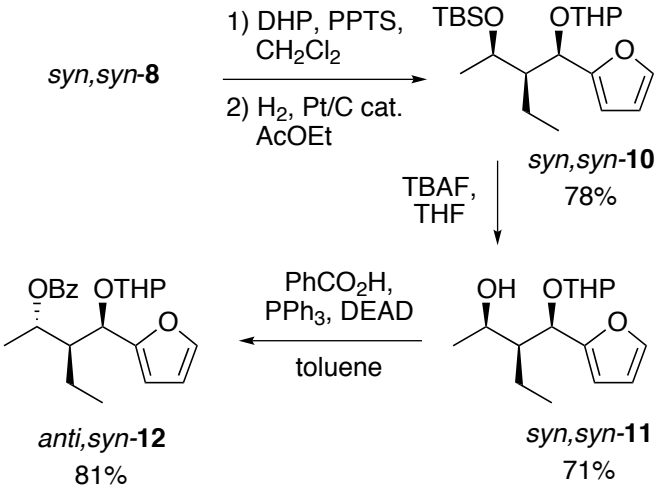
We took advantage of our experience in the synthesis of 2-vinyl-1,3-diols to prepare diol **5** (Scheme 2). Thus, we protected quantitatively the commercially available (*R*)-1-butyn-3-ol as *tert*-butyldimethylsilyl ether (**6**). We homologated the protected alkyne with formaldehyde under Ma's conditions,[4]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



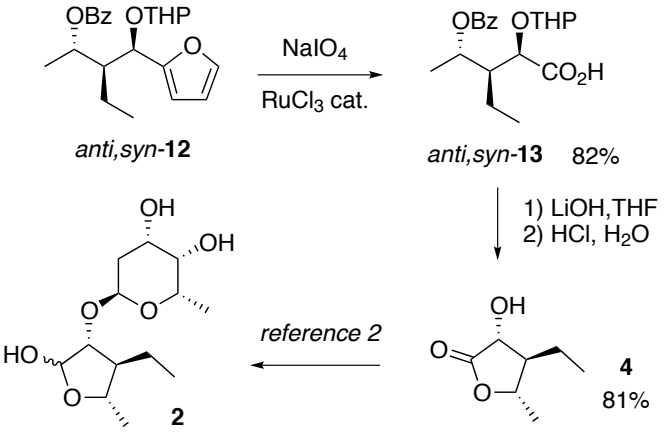
Scheme 2. Synthesis of alcohol **8**

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 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 sulphonate was unsuccessful, as, the transient sulphonate 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).



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

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. 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 the literature.[2] Furthermore, the Mosher ester of **4** indicated a single enantiomer.[8]

3. Conclusion

Lactone **4**, an intermediate in the synthetic approach to halichoblelide, has been synthesized stereoselectively from commercially available (*R*)-1-butyn-3-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 anh. 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), imidazole (6.30 g, 92.4 mmol) at room temperature. The reaction mixture was stirred for 6 hours. 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 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to yield the corresponding pure (+)-**6** (7.37 g, 40 mmol).

Compound (+)-**6**:[7] 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-RMN ($CDCl_3$, 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; $[\alpha]_D$= +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 anh. 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 anh. dioxane (50 mL). The reaction mixture was refluxed for 4 hours. Then, solvents were directly eliminated under reduced pressure. The crude was purified by flash chromatography on silica gel (Hexane/AcOEt 98:2) to give 4.12 g (82%) of (+)-**7.**

Compound (+)-**7**: 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 RMN ($CDCl_3$, 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; $[\alpha]_D$= +15.7 (*c* 1.00, $CHCl_3$).

*4.4. Synthesis (1R,2R)-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 anh. CH_2Cl_2 (20 mL) was added dropwise to a stirred suspension of dicyclohexylborane (4.43 g, 24.9 mmol) at 0 ^{o}C, in anh. CH_2Cl_2 (20 mL) in a dry flask under nitrogen atmosphere. After 10 min at 0 ^{o}C the reaction was allowed to heat to room temperature and the mixture was stirred for 2 hours, until it became homogeneous. Then it was cooled down to –78 ^{o}C and 2-furaldehyde (2.06 mL, 5.6 mmol) was added. The solution was kept cold during 10 min and then allowed to heat to room temperature and stirred for 2 hours. Then, a solution of triethanolamine (5.2 mL, 44.4 mmol) in CH_2Cl_2 (10 mL) was added and stirred for 1 hour. The volatiles were removed under vacuum. Purification by column chromatography on silica gel (Hexane/AcOEt 95:5) afforded 5.277 g (86 %) of product *syn,syn*-**8,** *anti,syn*-**8,** and *syn,anti*-**8** in a ratio 89:8:3.

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, cd, *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-RMN ($CDCl_3$, 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; $[\alpha]_D$= +49.9 (*c* 1.00, $CHCl_3$).

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, cd, *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-RMN ($CDCl_3$, 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; $[\alpha]_D$= +9.45 (*c* 1.00, $CHCl_3$).

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, cd, *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-RMN ($CDCl_3$, 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] $[\alpha]_D$= +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** (5.277 g, 17.8 mmol) and pyridinium *p*-toluensulphonate (0.129 g, 0.5 mmol) in anh. CH_2Cl_2 (50 mL) under nitrogen atmosphere. The reaction mixture was refluxed for 14 hours. 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 (3x10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to yield the corresponding crude that was purified by flash chromatography on silica gel (Hexane/AcOEt 95:5) to afford 5.303 g (78%) of product *syn,syn*-**9** as a 1:1 mixture of diastereomers.

Compound syn,syn-**9**: colourless oil; R_f (Hexane/AcOEt 90:10): 0.60; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 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, C*H*$_3$CHOTBS), 1.07 (1.5H, d, *J*=6.4 Hz, C*H*$_3$CHOTBS), 1.37-1.80 (6H, m, $(CH_2)_3$), 2.55 (1H, td, *J*=9.6, 2.0 Hz, C*H*CH=CH_2), 3.29 (0.5H, m, OC*H*$_2$CH$_2$), 3.46-3.58 (2H, m, CHOTBS and OC*H*$_2$CH$_2$), 3.87 (0.5H, td, *J*=11.2, 2.8 Hz, OC*H*$_2$CH$_2$), 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=C*H*$_2$), 5.86-5.99 (1H, m, C*H*=CH_2), 6.26-6.32 (2H, m, Ar*H*), 7.37 (0.5H, s, Ar*H*), 7.39 (0.5H, s, Ar*H*); ^{13}C-RMN ($CDCl_3$, 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** (5.085 g, 13.4 mmol) in AcOEt (20 mL). The mixture was shaken under hydrogen (1 atmosphere) until TLC showed complete conversion. The suspension was filtered through a short pad of Celite® and solvent was directly eliminated under reduce pressure to yield 5.010 g of *syn,syn*-**10** (98%) as a 1:1 mixture of diastereomers.

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, C*H*$_3$CH$_2$), 1.04 (1.5H, t, *J*=7.6 Hz, C*H*$_3$CH$_2$), 1.13 (1.5H, d, *J*=6.4 Hz, C*H*$_3$CHOTBS), 1.16 (1.5H, d, *J*=6.0 Hz, C*H*$_3$CHOTBS), 1.45-1.80 (9H, m, $(CH_2)_3$ and C*H*C*H*$_2$CH$_3$), 3.25 (0.5H, m, OC*H*$_2$CH$_2$), 3.49-3.56 (1H, m, OC*H*$_2$CH$_2$), 3.62-3.71 (1H, m, CHOTBS), 3.89 (0.5H, ddd, *J*=11.2, 9.2, 4.0 Hz, OC*H*$_2$CH$_2$), 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, Ar*H*), 6.29-6.31 (1H, m, Ar*H*), 7.34 (0.5H, m, Ar*H*), 7.37 (0.5H, m, Ar*H*); ^{13}C-RMN ($CDCl_3$, 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** (5.010 g, 13.1 mmol), TBAF·3H_2O (20.677 g, 65.5 mmol) in anh. THF (50 mL), under nitrogen atmosphere was stirred at room temperature for 24 hours. 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 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to yield the corresponding crude *syn,syn*-**11**. Purification by column chromatography using silica gel (Hexane:AcOEt 80:20) gave 2.496 g of a 1:1 mixture of diastereomers (71%).

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, C*H*$_3$CH$_2$), 0.93 (1.5H, t, *J*=7.6 Hz, C*H*$_3$CH$_2$), 1.16 (1.5H, d, *J*=6.4 Hz, C*H*$_3$CH), 1.20 (1.5H, d, *J*=6.4 Hz, C*H*$_3$CH), 1.41-1.81 (9H, m, $(CH_2)_3$ and C*H*C*H*$_2$CH$_3$) 2.49 (1H, sa, OH), 3.30 (0.5H, dt, *J*=11.6, 4.8 Hz, OC*H*$_2$CH$_2$), 3.49 (0.5H, dt, *J*=12.0, 4.8 Hz, OC*H*$_2$CH$_2$), 3.61 (0.5H, ddd, *J*=11.6, 8.8, 3.2 Hz, OC*H*$_2$CH$_2$), 3.89 (0.5H, m, OC*H*$_2$CH$_2$), 3.92 (0.5H, m, C*H*OH), 4.03 (0.5H, qd, *J*=6.4, 2.0 Hz, C*H*OH), 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, Ar*H*), 6.28 (0.5H, d, *J*=3.2 Hz, Ar*H*), 6.30 (0.5H, dd, *J*=3.2, 1.8 Hz, Ar*H*), 6.32 (0.5H, dd, *J*=3.2, 1.6 Hz, Ar*H*), 7.34 (0.5H, dd, *J*=1.8, 0.8 Hz, Ar*H*), 7.37 (0.5H, dd, *J*=1.6, 0.8 Hz, Ar*H*); ^{13}C-RMN ($CDCl_3$, 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 anh. toluene was added dropwise to a stirred suspension of *syn,syn*-**11** (0.880 g, 2.59 mmol), benzoic acid (0.630 g, 5.18 mmol) and triphenylphosphine (1.360 g, 5.18 mmol) in anh. toluene (20 mL) at -78 ^{o}C, in a dry flask under nitrogen atmosphere. After 30 min at -78 ºC, the reaction was allowed to heat 0 ºC and the mixture was stirred for 3 hours. Then, the reaction was quenched with *tert*-butyl dimethyl ether (10 mL) and washed with a solution of $NaHCO_3$ 1M (3x10 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 $MgSO_4$ and concentrated under vacuum to yield the corresponding crude. Purification by column chromatography using silica gel (Hexane:AcOEt 98:2) afforded 0.784 g (81%) of *anti*,*syn*-**12**.

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, C*H*$_3$CH$_2$), 1.05 (1.5H, t, *J*=7.6 Hz, C*H*$_3$CH$_2$), 1.21 (1.5H, d, *J*=6.2 Hz, C*H*$_3$CHOBz), 1.23 (1.5H, d, *J*=6.2 Hz, C*H*$_3$CHOBz), 1.44-1.84 (8H, m, $(CH_2)_3$ and CH_2CH$_3$), 2.18 (0.5H, q, *J*=6.2 Hz, C*H*CHOTHP), 2.24 (0.5H, q, *J*=6.4 Hz, C*H*CHOTHP), 3.27 (0.5H, m, OC*H*$_2$CH$_2$), 3.40 (0.5H, dt, *J*=10.4, 4.4 Hz, OC*H*$_2$CH$_2$), 3.61 (0.5H, ddd, *J*=11.2, 8.8, 2.8 Hz, OC*H*$_2$CH$_2$), 3.79 (0.5H, m, OC*H*$_2$CH$_2$), 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, quin, *J*=6.4 Hz, CHOBz), 5.21 (0.5H, quin, *J*=6.4 Hz, CHOBz), 6.29 (0.5H, m, Ar*H*), 6.32 (1.5H, m, Ar*H*), 7.36-7.45 (3H, m, Ar*H*), 7.54 (1H, m, Ar*H*), 8.02 (2H, m, Ar*H*); ^{13}C-RMN ($CDCl_3$, 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 $C_{22}H_{28}NaO_5$ $[M+Na]^+$ 295.1829, founded 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** (0.063 g, 0.176 mmol) and $NaIO_4$ (0.190 g, 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. Water was added and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were dried over $MgSO_4$ 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.

Compound anti,syn-**13**: colourless oil; R_f (CH_2Cl_2:MeOH 95:5): 0.35; ^{1}H-RMN ($CDCl_3$, 400 MHz): δ 0.99 (1.5H, t, *J*=7.2 Hz, C*H*$_3$CH$_2$), 1.03 (1.5H, t, *J*=7.6 Hz, C*H*$_3$CH$_2$), 1.40 (1.5H, d, *J*=6.0 Hz, C*H*$_3$CHOBz), 1.44 (1.5H, d, *J*=6.4 Hz, C*H*$_3$CHOBz), 1.52-1.83 (8H, m, (CH$_2$)$_3$ and C*H*$_2$CH$_3$), 2.27 (0.5H, m, C*H*CH$_2$CH$_3$), 2.42 (0.5H, m, C*H*CH$_2$CH$_3$), 3.25 (0.5H, m, OC*H*$_2$CH$_2$), 3.53 (0.5H, ddd, *J*=11.6, 10.8, 3.2 Hz, OC*H*$_2$CH$_2$), 3.63 (0.5H, m, OC*H*$_2$CH$_2$), 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, sa, OH); ^{13}C-RMN ($CDCl_3$, 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 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 hours until TLC showed complete conversion. Then, the mixture was acidified with HCl 37% and later, refluxed during 6 hours. The reaction was quenched with saturated aqueous NaCl. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure. The crude was purified by flash chromatography (Hexane:AcOEt 85:15) gave 17 mg of **4** (0.117 mmol, 81%).

Compound **4**: colourless oil; R_f (Hexane:AcOEt 70:30): 0.10; ^{1}H-RMN ($CDCl_3$, 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 RMN ($CDCl_3$, 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; $[\alpha]_D$= -0.4 (*c* 1.00, $CHCl_3$).

Acknowledgements

This study was supported by the Ministerio de Educación y Ciencia (CTQ2006-13249 and CTQ2009-09692). We thank the *Generalitat de Catalunya* for a doctorate studentship to C.S.

References and notes

1. Yamada, T.; Minoura, K.; Numata A. *Tetrahedron Lett.* **2002**, *43*, 1721–1724.
2. Satoh, Y.; Nakahata, T.; Kuwahara, S. *Tetrahedron* **2007**, *63*, 11733–11737.
3. Sánchez, C.; Ariza, X.; Cornellà, J.; Farràs, J.; Garcia, J.; Ortiz, J. *Chem. Eur. J.* **2010**, *16*, 11535–11538.
4. Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763–1765.
5. (a) Mitsunobu, O. ; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382; (b) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551–2651.
6. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem*. **1981**, *46*, 3936–3938.
7. (a) Cotterill, A. S.; Gill, M.; Gimenez, A.; Milanovic, N. M. *J. Chem. Soc. Perkin Trans. 1*, **1994**, 3269–3276; (b) Robinson, J. E.; Brimble, M. A. *Org. Biomol. Chem.*, **2007**, *5*, 2572–2582.
8. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.*, **1969**, *34*, 2543–2549.

Supplementary Material

^{1}H-NMR and ^{13}C-NMR spectra for all compounds. Supplementary data related to this article can be found online at doi:xxxx.