Synthesis of Enantiomerically Pure 2,5-Disubstituted 3-Oxygenated Tetrahydrofurans

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Abstract: The synthesis of enantiomerically pure 2,5-disubstituted 3-oxygenated tetrahydrofurans has been achieved from cheap and commercially available L-malic acid. This method was used to prepare an advanced intermediate toward CMI-977, a promising candidate for the treatment of chronic asthma.

Key words: furan, tetrahydrofuran, singlet oxygen, butenolide, oxacycles, natural products

The 2,5-disubstituted 3-oxygenated tetrahydrofuran moiety is present in a plethora of natural products, some of which are depicted in Figure 1. Dihydroxytetrahydrofurans **1**[1] and **2**[2] are marine natural products that were isolated from *Notheia anomala*, a brown algae found along the southern Australian coast. Because of their antiparasitic properties these compounds have attracted the attention of many synthetic chemists.[3] *trans*-Kumausyne (**3**)[4] and (–)-kumausallene (**4**)[5] are halogenated secondary metabolites isolated from the Japanese red algae, *Laurencia nipponica* and several synthetic approaches toward these molecules can be found in the literature.[6] The significance of (+)-muscarine (**5**) has led to a growing demand, which at present cannot be covered from the current natural resources, such as fungi of the genera *Amanita*,[7] *Clitocybe*,[8] and *Inocybe*[9] alone. Therefore, methods for the enantioselective synthesis of this alkaloid and its diastereomers have received considerable attention from the scientific community.[10] CMI-977, renamed later as LDP-977 is a promising candidate for chronic asthma.[11] Its 2,5-disubstituted tetrahydrofuran ring might be obtained by removal of the hydroxy group of the corresponding 2,5-disubstituted 3-oxygenated tetrahydrofuran.

We wish to report a new method for the synthesis of chiral 2,5-disubstituted 3-oxygenated tetrahydrofurans such as of compounds **7** and **8** (Scheme 1). Compound **7** is interesting because it can be considered as an advanced synthetic intermediate of CMI-977 containing the *trans*-juxtapositioned ring. Our synthesis is outlined retrosynthetically in Scheme 1.

We anticipated that the relatively inexpensive and readily available chiral pool material L-malic acid could lead to chiral furan **9** containing the 4-fluorophenyl ether moiety, setting the stage for the synthesis of compounds **7** and **8**

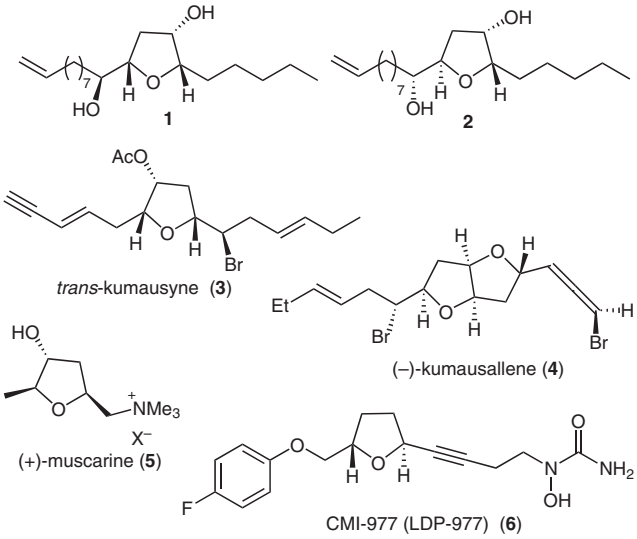
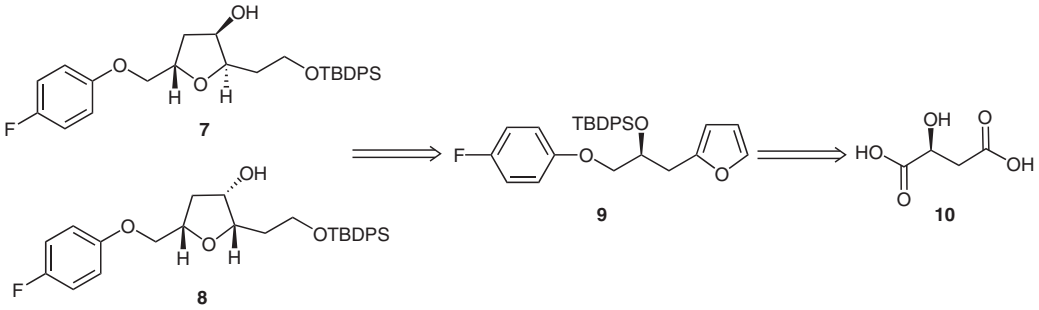


Figure 1 2,5-Disubstituted tetrahydrofuran-containing natural products



Scheme 1 Retrosynthetic analysis of 2,5-disubstituted 3-oxygenated tetrahydrofurans **7** and **8**

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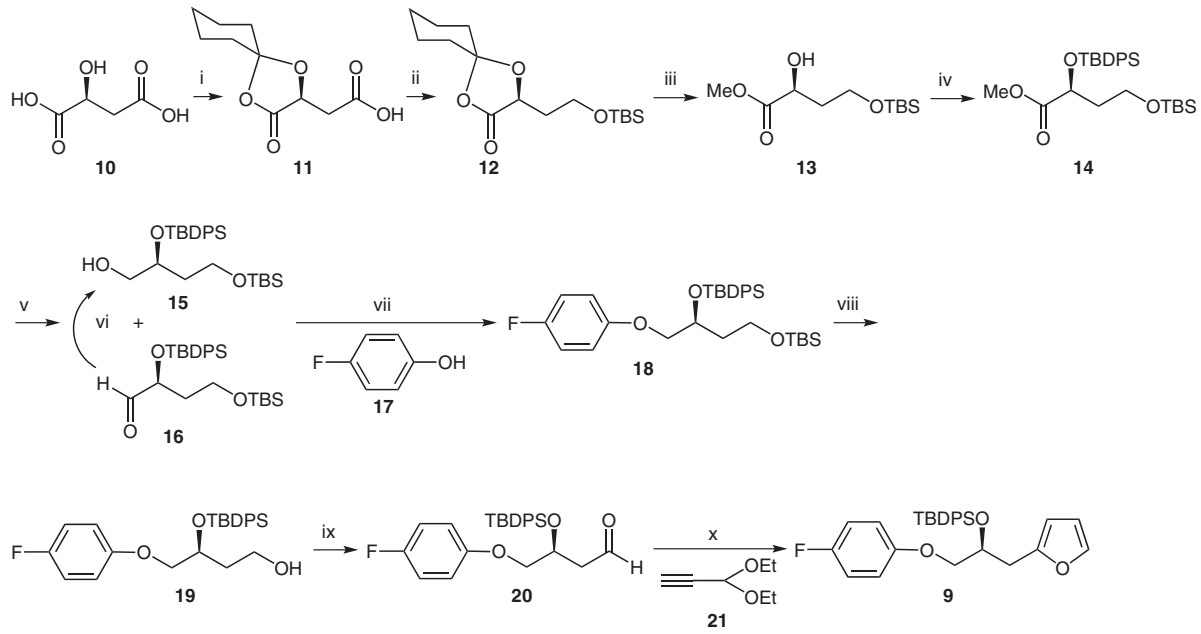
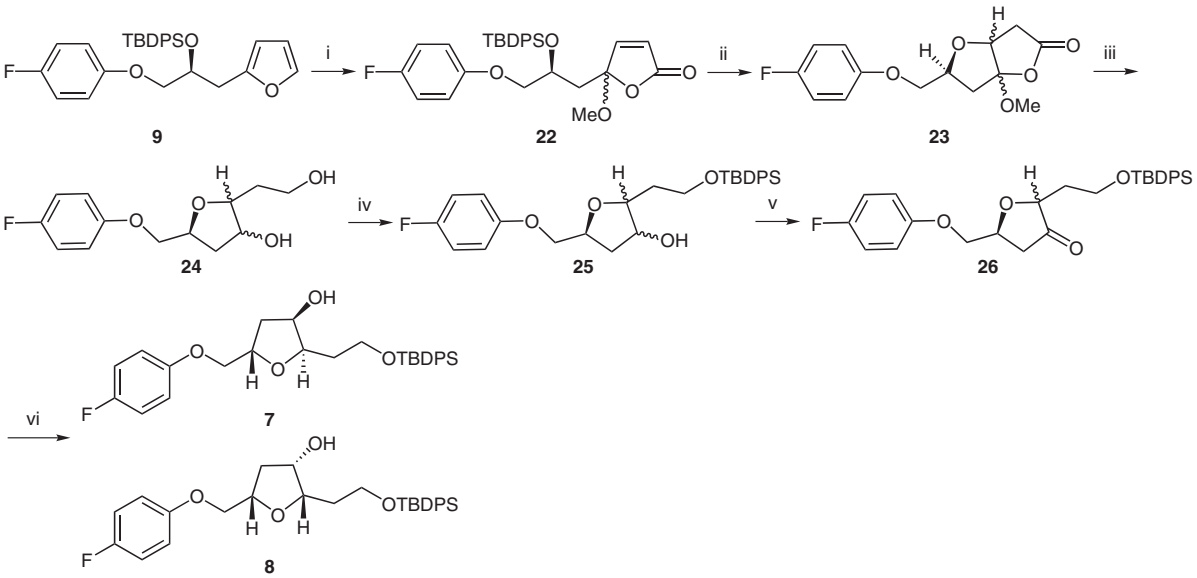


Scheme 2 *Reagents and conditions*: (i) cyclohexanone, $BF_3{\cdot}OEt_2$, Et_2O, 0 °C (78%); (ii) a) $BH_3{\cdot}SMe_2$, $B(OMe)_3$, THF, 0 °C to r.t., b) TBSCl, imidazole, DMAP, THF, r.t. (87%, 2 steps); (iii) NaOMe, MeOH, r.t. (97%); (iv) TBDPSCl, imidazole, DMAP, DMF, r.t. (95%); (v) DIBAL-H, CH_2Cl_2, –78 °C (**15**, 73%; **16**,17%); (vi) $NaBH_4$, MeOH, 0 °C (99%); (vii) PPh_3, DIAD, **17**, THF, r.t. (68%); (viii) AcOH–THF–H_2O (3:1:1), r.t. (80%); (ix) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to r.t. (87%); (x) a) **21**, *n*-BuLi, THF, –78 to 0 °C (86%), b) H_2, Lindlar catalyst, MeOH, r.t. (70%).

using a methodology we developed in our laboratories and for which we coined the furan approach to oxacyclic system.[12]

Accordingly, compound **9** was prepared as shown in Scheme 2. Reaction of L-malic acid (**10**) with cyclohexanone in the presence of a Lewis acid,[13] gave the protected acid **11** in 78% yield. Reduction of the latter with borane dimethyl sulfide complex[14] afforded a rather labile alcohol, which was protected as *tert*-butyldimethylsilyl ether without further purification to give **12** in 87% yield (2 steps). Removal of the cyclohexylidene protecting group with sodium methoxide afforded hydroxy ester **13** in 97% yield. The hydroxy group of **13** was protected as *tert*-butyldiphenylsilyl ether affording **14** in 95% yield. Reaction of ester **14** with DIBAL-H gave the desired alcohol **15** in 73% yield, together with aldehyde **16** (17%), which could be easily transformed into alcohol **15** by reduction with sodium borohydride in methanol in quantitative yield. Mitsunobu reaction[15] of alcohol **15** with readily available 4-fluorophenol (**17**) gave ether **18** in 68% yield. Selective



Scheme 3 *Reagents and conditions*: (i) a) O_2, hv, Rose Bengal, MeOH–CH_2Cl_2, b) Ac_2O, pyridine, r.t. (82%, 2 steps); (ii) TBAF, THF, r.t. (82%); (iii) $BF_3{\cdot}OEt_2$, $LiAlH_4$, Et_2O, r.t. (96%); (iv) TBDPSCl, imidazole, DMAP, DMF, r.t. (52%); (v) TPAP, NMO, molecular sieves, CH_2Cl_2, r.t. (80%); (vi) L-Selectride, THF, –78 °C (**7**, 56%; **8**, 43%).

removal of the TBS protecting group of **18** afforded alcohol **19** (80%), which underwent Swern oxidation to give aldehyde **20** in 87% yield. Aldehyde **20** was easily transformed into furan **9** in two steps (60% yield) using our previously described method.[16]

With furan **9** in hand, the stage was set for the crucial oxidation step using singlet oxygen (Scheme 3).

Furan **9** was subjected to singlet oxygen oxidation, followed by treatment with acetic anhydride in pyridine to afford butenolide **22** in 82% overall yield. Treatment of **22** with TBAF led to the bycyclic compound **23** through an intramolecular Michael addition (82% yield). On reaction with $LiAlH_4$ in the presence of $BF_3{\cdot}OEt_2$, **23** afforded a 96% yield of unseparable diastereoisomeric alcohols **24**. Selective protection of the primary hydroxy group of **24**, followed by TPAP oxidation afforded diastereoisomeric ketones **26**, which could not be separated by column chromatography. Stereoselective reduction of ketones **26** by L-Selectride afforded easily separable trisubstituted tetrahydrofurans **7** and **8** in 56% and 43% yield, respectively. The stereochemistry of **7** and **8** was established from the NOE correlations of the corresponding acetates **27** and **28** (Figure 2).

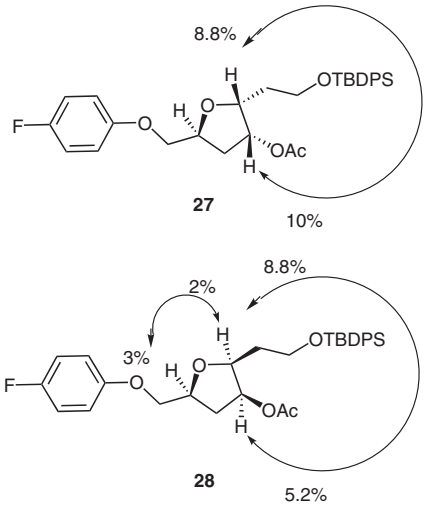


Figure 2 NOE correlation for **27** and **28**

In conclusion, we have demonstrated that the synthesis of enantiomerically pure 2,5-disubstituted 3-oxygenated tetrahydrofurans could be achieved from cheap and commercially available L-malic acid and using the furan approach. The application of this method for the synthesis of CMI-977 as well as some of the biologiacally active compounds depicted in Figure 1 is currently under way in our laboratories.

Solvents were purified and dried by standard procedures before use. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker ARX-400 spectrometer (400 MHz for ^{1}H NMR, 100.61 MHz for ^{13}C NMR) using TMS as internal standard (chemical shifts in δ values, *J* in Hz). Mass spectrometry was carried out with a Hewlett-Packard 5988A spectrometer. Flash chromatography (FC) was performed on silica gel (Merck 60, 230–400 mesh); analytical TLC was performed on plates precoated with silica gel (Merck 60 F_{254}, 0.25 mm).

(*S*)-2-(3-Oxo-1,4-dioxaspiro[4.5]decan-2-yl)acetic Acid (11)

To a solution of **10** (10.2 g, 76 mmol) in Et_2O (100 mL) cooled to 0 °C was added first $BF_3{\cdot}OEt_2$ (14 mL, 110.2 mmol) and then distilled cyclohexanone (8.7 mL, 83.6 mmol). The mixture was stirred at 0 °C for 1 h and then at r.t. for 19 h. The reaction mixture was quenched with aq 10% NaOAc (150 mL), the solution was stirred for 20 min, and then extracted with EtOAc (4 × 100 mL). The combined organic phases were dried (Na_2SO_4), filtered and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel using 20% EtOAc–hexane, then 50% EtOAc–hexane affording **11** as a white crystalline solid; yield: 12.6 g (78%); mp 108.4 °C; R_f = 0.78 (EtOAc); $[\alpha]_D^{23}$ +24.8 (*c* = 0.43, $CHCl_3$).

IR (NaCl, neat): 3035, 2943, 2866, 1793, 1724 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71 (dd, *J* = 3.9, 6.5 Hz, 1 H, H-2), 2.98 (dd, *J* = 3.9, 17.2 Hz, 1 H, H-1′), 2.83 (dd, *J* = 6.5, 17.2 Hz, 1 H, H-1′), 1.83 (m, 2 H, CH_{eq}-6, CH_{eq}-10), 1.6–1.77 (m, 6 H, CH_{ax}-6, CH_{ax}-10, CH_2-7, CH_2-9), 1.44 (m 2 H, CH_2-8).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.46 (C-2′), 171.92 (C-3), 112.21 (C-5), 70.01 (CH-2), 36.19 (CH_2-1′), 36.15, 35.33 (CH_2-6, CH_2-10), 24.40 (CH_2-8), 22.93 (CH_2-7, CH_2-9).

MS (ESI$^+$): *m*/*z* (%) = 237.07 ([M + Na]$^+$, 100), 215.09 ([M]$^+$, 12), 201.04 (13), 179.01 (21), 157.01 (27).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{10}H_{14}O_5$ + Na: 237.0739; found: 237.0733.

(*S*)-3-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-1,4-dioxaspiro[4.5]decan-2-one (12)

To a solution of **11** (5.8 g, 27.2 mmol) in anhyd THF (40 mL) cooled to 0 °C was added $BH_3{\cdot}SMe_2$ (3.9 mL, 40.8 mmol), followed by $B(OMe)_3$ (4.6 mL, 40.8 mmol). The mixture was stirred for 19 h, before adding MeOH (30 mL) at 0 °C. The mixture was stirred for an additional 1 h, the solvent was evaporated, and the residue was dissolved again in MeOH (30 mL) at 0 °C and the mixture stirred for 1 h. Solvent evaporation afforded the expected alcohol that was used in the next reaction without further purification. It was dissolved in THF (55 mL), imidazole (3.7 g, 54 mmol), catalytic amount of DMAP, and TBSCl (4.1 g, 29.7 mmol) were added and the mixture was stirred at r.t. for 20 h. The solvent was evaporated and H_2O (40 mL) was added and the product extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was chromatographed on silica gel using 5% EtOAc–hexane affording **12** as a colorless oil; yield: 7.36 g (87%); R_f = 0.79 (30% EtOAc–hexane); $[\alpha]_D^{23}$ +26.5 (*c* = 0.78, $CHCl_3$).

IR (NaCl, neat): 2943, 2862, 1799 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.51 (m, 1 H, H-3), 3.81 (m, 1 H, H-2′), 3.73 (m, 1 H, H-2′), 2.07 (m, 1 H, H-1′), 1.83 (m, 3 H, CH_{2eq}-6, CH_{2eq}-10, H-1′), 1.6–1.77 (m, 6 H, CH_{ax}-6, CH_{ax}-10, CH_2-7, CH_2-9), 1.44 (m 2 H, CH_2-8), 0.87 (s, 9 H, *t*-C_4H_9), 0.03 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.66 (C-2), 111.18 (C-5), 70.29 (CH-3), 58.24 (CH_2-2′), 36.67 (CH_2-1′), 35.36, 34.85 (CH_2-6, CH_2-10), 25.80 [SiC(CH_3)$_3$], 24.40 (CH_2-8), 22.99, 22.94 (CH_2-7, CH_2-9), 18.21 [Si*C*(CH_3)$_3$], –5.48 [$Si(CH_3)_2$].

MS (ESI$^+$): *m*/*z* (%) = 337.18 ([M + Na]$^+$, 76), 315.2 ([M]$^+$, 100).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{16}H_{31}O_4Si$: 315.1992; found: 315.1975.

(*S*)-Methyl 4-(*tert*-Butyldimethylsilyloxy)-2-hydroxybutanoate (13)

To a solution of **12** (7.3 g, 23.0 mmol) in MeOH (100 mL) cooled at 0 °C was added a solution of NaOMe in MeOH (25%) and the mixture was stirred for 15 min under the same conditions. MeOH (100 mL) was added, followed by Amberlist till pH 6. The resin was filtered and the solvent was evaporated. The residue was chromatographed on silica gel using 20% EtOAc–hexane affording **13** as a colorless oil; yield: 5.53 g (97%); R_f = 0.63 (30% EtOAc–hexane); $[\alpha]_D^{23}$ –37.5 (*c* = 0.5, $CHCl_3$).

IR (NaCl, neat): 3487, 2951, 2862, 1740 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.33 (m, 1 H, H-2), 3.78 (m, 2 H, H-4), 3.73 (s, 3 H, CH_3O), 2.00 (m, 1 H, H-3), 1.85 (m, 3 H, H-3), 0.85 (9 H, s, *t*-C_4H_9), 0.03 [6 H, s, $Si(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.24 (C-1), 68.79 (CH-2), 59.74 (CH_2-4), 52.23 (CH_3O), 36.16 (CH_2-3), 25.80 [SiC(*C*H_3)$_3$], 18.21 [Si*C*$(CH_3)_3$], –5.58 [$Si(CH_3)_2$].

MS (ESI$^+$): *m*/*z* (%) = 271.14 ([M + Na]$^+$, 100), 249.15 ([M + 1]$^+$, 34).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{11}H_{24}O_4Si$ + Na: 271.1336; found: 271.1336.

(*S*)-Methyl 4-(*tert*-Butyldimethylsilyloxy)-2-(*tert*-butyldiphenylsilyloxy)butanoate (14)

To a solution of **13** (5.0 g, 20.3 mmol) in DMF (20 mL) was added imidazole (3.32 g, 48.8 mmol), a catalytic amount of DMAP, and TBDPSCl (6.8 mL, 26.4 mmol), and the mixture was stirred at r.t. for 6 d. EtOAc (50 mL) was added and the solution was washed with H_2O (4 × 30 mL). The organic phase was dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was chromatographed on silica gel using 5% EtOAc–hexane affording **14** as a colorless oil; yield: 9.36 g (95%); R_f = 0.81 (30% EtOAc–hexane); $[\alpha]_D^{23}$ –28.2 (*c* = 0.6, $CHCl_3$).

IR (NaCl, neat): 2951, 2889, 2858, 1751 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (m, 4 H, CH_o-Ph), 7.39 (m, 6 H, $CH_{p,m}$-Ph), 4.37 (t, *J* = 5.8 Hz, 1 H, H-2), 3.73 (t, *J* = 6.5 Hz, 2 H, H-4), 3.42 (s, 3 H, CH_3O), 1.94 (m, 2 H, H-3), 1.09 (s, 9 H, *t*-C_4H_9-TBDPS), 0.85 (s, 9 H, *t*-C_4H_9-TBS), 0.03 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.47 (C-1), 135.79 (CH_o-Ph), 133.29 (C-Ph), 129.73, (CH_m-Ph), 127.58 (CH_p-Ph), 69.89 (CH-2), 58.76 (CH_2-4), 51.30 (CH_3O), 38.09 (CH_2-3), 26.89 [C(*C*H_3)$_3$-TBS], 25.92 [C(*C*H_3)$_3$-TBDPS], 19.43 [*C*$(CH_3)_3$-TBDPS], 18.27 [*C*$(CH_3)_3$-TBS], –5.28 [$Si(CH_3)_2$].

MS (ESI$^+$): *m*/*z* (%) = 509.25 ([M + Na]$^+$, 100), 487.27 ([M + 1]$^+$, 36), 201.04 (32), 169.08 (22).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{27}H_{43}O_4Si_2$: 487.2700; found: 487.2694.

(*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-(*tert*-butyldiphenylsilyloxy)butan-1-ol (15) and (*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-(*tert*-butyldiphenylsilyloxy)butanal (16)

To a solution of **14** (4.80 g, 9.87 mmol) in CH_2Cl_2 (35 mL) cooled to –78 °C, was added a solution of DIBAL-H in hexane (1 M, 14.8 mL, 14.8 mmol) and the mixture was stirred for 90 min at –78 °C. Then, *t*-BuOMe (17 mL) and H_2O (1 mL) were added and the mixture was stirred for 15 min whence a translucent gel was obtained. Aq 4 M NaOH (1 mL) and H_2O (1 mL) were then added. The mixture was stirred till a white precipitate was formed and Na_2SO_4 (0.5 g) was added. The solid was filtered and the solution was evaporated and the residue was chromatographed on silica gel using 3% EtOAc–hexane, then 5% EtOAc–hexane affording **15** and **16**.

15

Yield: 3.29 g (73%); colorless oil; R_f = 0.28 (10% EtOAc–hexane); $[\alpha]_D^{23}$ +8.28 (*c* = 1.13, $CHCl_3$).

IR (NaCl, neat): 3425, 3066, 2939, 2889, 2862 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (m, 4 H, CH_o-Ph), 7.46 (m, 6 H, $CH_{p,m}$-Ph), 4.06 (m, 1 H, H-2), 3.82 (m, 1 H, H-4), 3.60 (m, 3 H, H-4, H-1), 2.95 (s, 1 H, OH), 1.85 (m, 2 H, H-3), 1.15 (s, 9 H, *t*-C_4H_9-TBDPS), 0.95 (s, 9 H, *t*-C_4H_9-TBS), 0.03 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.79 (CH_o-Ph), 133.91 (C-Ph), 129.88 (CH_m-Ph), 127.72 (CH_p-Ph), 71.92 (CH-2), 66.09 (CH_2-1), 59.43 (CH_2-4), 37.13 (CH_2-3), 26.71 [C(*C*H_3)$_3$-TBS], 25.98 [C(*C*H_3)$_3$-TBDPS], 19.43 [*C*$(CH_3)_3$-TBDPS], 18.26 [*C*$(CH_3)_3$-TBS], –5.28 [$Si(CH_3)_2$].

MS (ESI$^+$): *m*/*z* (%) = 481.26 ([M + Na]$^+$, 96), 459.27 ([M + 1]$^+$, 100), 381.23 (19), 203.12 (13), 171.09 (19).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{26}H_{43}O_3Si_2$: 459.2751; found: 459.2745.

16

Yield: 1.71 g (17%); colorless oil; R_f = 0.56 (10% EtOAc–hexane); $[\alpha]_D^{23}$ +10.5 (*c* = 0.84, $CHCl_3$)].

^1H NMR (400 MHz, $CDCl_3$): δ = 9.64 (s, 1 H, H-1), 7.69 (m, 4 H, CH_o-Ph), 7.41 (m, 6 H, $CH_{p,m}$-Ph), 4.22 (m, 1 H, H-2), 3.94 (m, 1 H, H-4), 3.68 (m, 1 H, H-4), 2.01 (m, 1 H, H-3), 1.81 (m, 1 H, H-3), 1.18 (s, 9 H, *t*-C_4H_9-TBDPS), 0.92 (s, 9 H, *t*-C_4H_9-TBS), 0.08 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.41 (C=O), 135.83 (CH_o-Ph), 133.26 (C-Ph), 130.03 (CH_m-Ph), 127.83 (CH_p-Ph), 75.82 (CH-2), 57.75 (CH_2-4), 37.01 (CH_2-3), 26.71 [C(*C*H_3)$_3$-TBS], 25.98 [C(*C*H_3)$_3$-TBDPS], 19.43 [*C*$(CH_3)_3$-TBDPS], 18.26 [*C*$(CH_3)_3$-TBS], –5.28 [$Si(CH_3)_2$].

*Reduction of Aldehyde **16** to Alcohol **15***: To aldehyde **16** (5.7 g, 12.5 mmol) in MeOH (30 mL) at 0 °C was added $NaBH_4$ (709 mg, 18.75 mmol) and the mixture stirred for 15 min, then quenched with H_2O (30 mL). Extraction with EtOAc (4 × 30 mL) and evaporation of the solvent gave a residue that was identical to alcohol **15**.

(*S*)-5-[(4-Fluorophenoxy)methyl]-2,2,9,9,10,10-hexamethyl-3,3-diphenyl-4,8-dioxa-3,9-disilaundecane (18)

To a solution of **15** (3.70 g, 8 mmol) in THF (40 mL) was added PPh_3 (3.14 g, 12 mmol), 4-fluorophenol (**17**; 1.34 g, 12 mmol), and DIAD (2.4 mL, 12 mmol). The mixture was stirred for 19 h at r.t. and with sonication. The solvent was evaporated and the residue chromatographed on silica gel using 5% EtOAc–hexane affording **18** as a colorless oil; yield: 3.03 g (68%); R_f = 0.79 (10% EtOAc–hexane); $[\alpha]_D^{23}$ –16.9 (*c* = 1.05, $CHCl_3$).

IR (NaCl, neat): 2935, 2862, 2357, 1508, 1466 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (m, 4 H, CH_o-Ph), 7.43 (m, 6 H, $CH_{p,m}$-Ph), 6.88 (m, 2 H, H-3′), 6.57 (m, 2 H, H-2′), 4.29 (m, 1 H, H-2), 3.82 (m, 4 H, H-1, H-4), 1.90 (m, 2 H, H-3), 1.15(s, 9 H, *t*-C_4H_9-TBDPS), 0.95 (s, 9 H, *t*-C_4H_9-TBS), 0.03 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.25, 155.89 (d, *J* = 236.9 Hz, C-Ph-4′), 154.76, 154.74 (d, *J* = 3.2 Hz, C-Ph-1′), 135.71 (*C*H_o-Ph-TBDPS), 133.86 (*C*-Ph-TBDPS), 129.69 (CH_m-Ph), 127.75 (*C*H_p-Ph-TBDPS), 115.65, 115.49 (d, *J* = 23.3 Hz, CH-Ph-H3′), 115.23, 115.16 (d, *J* = 8.3 Hz, CH-Ph-H2′), 72.12 (CH_2-1), 69.45 (CH-2), 59.46 (CH_2-4), 37.51 (CH_2-3), 26.81 [C(*C*H_3)$_3$-TBS], 25.96 [C(*C*H_3)$_3$-TBDPS], 19.49 [*C*$(CH_3)_3$-TBDPS], –5.28 [Si $(CH_3)_2$].

MS (ESI$^+$): *m*/*z* (%) = 575.28 ([M + Na]$^+$, 44), 553.3 ([M + 1]$^+$, 100), 475.25 ([M – Ph]$^+$, 13), 341.23 (23), 319.25 (67), 203.13 (19).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{32}H_{46}FO_3Si_2$: 553.2970; found: 553.2964.

(*S*)-3-(*tert*-Butyldiphenylsilyloxy)-4-(4-fluorophenoxy)butan-1-ol (19)

A solution of **18** (3.7 g, 6.7 mmol) in a mixture of AcOH–THF–H_2O (3:1:1, 116 mL) was stirred for 16 h. Afterwards, sat. aq $NaHCO_3$ (150 mL) was added. Then, solid $NaHCO_3$ was added till pH 7. The aqueous layer was extracted with EtOAc (5 × 40 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed by rotary evaporation. The residue was chromatographed on silica gel using 10% EtOAc–hexane, then 50% EtOAc–hexane affording **19** as a colorless oil; yield: 2.34 g (80%); R_f = 0.44 (30% EtOAc–hexane); $[\alpha]_D^{21}$ –33.5 (*c* = 0.5, $CHCl_3$).

IR (NaCl, neat): 3386, 2935, 2889, 2862 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (m, 4 H, CH_o-Ph), 7.41 (m, 6 H, $CH_{p,m}$-Ph), 6.86 (m, 2 H, H-3′), 6.52 (m, 2 H, H-2′), 4.24 (m, 1 H, H-3), 3.80 (m, 4 H, H-1, H-4), 1.89 (m, 2 H, H-2), 1.07 (s, 9 H, *t*-C_4H_9-TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.23, 155.87 (d, *J* = 238.0 Hz, C-Ph-4′), 154.29, 154.27 (d, *J* = 2.8 Hz, C-Ph-1′), 135.71 (*C*H_o-Ph-TBDPS), 133.86 (*C*-Ph-TBDPS), 129.69 (CH_m-Ph), 127.75 (*C*H_p-Ph-TBDPS), 115.69, 115.46 (d, *J* = 22.9 Hz, CH-Ph-3′), 115.13, 115.05 (d, *J* = 8.1 Hz, CH-Ph-2′), 71.16 (CH_2-4), 69.65 (CH-3), 59.40 (CH_2-1), 36.32 (CH_2-2), 25.76 [C(*C*H_3)$_3$-TBDPS], 19.49 [*C*(CH_3)$_3$-TBDPS].

MS (ESI$^+$): *m*/*z* (%) = 461.19 ([M + Na]$^+$, 61), 439.21 ([M + 1]$^+$, 40), 361.17 (([M – Ph]$^+$, 100), 315.17 (16), 301.13 (13), 283.12 (56).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{26}H_{32}FO_3Si$: 439.2105; found: 439.2095.

(*S*)-3-(*tert*-Butyldiphenylsilyloxy)-4-(4-fluorophenoxy)butanal (20)

To a solution of $(COCl)_2$ (2 M in CH_2Cl_2, 5.25 mL, 10.5 mmol) in CH_2Cl_2 (5 mL) cooled to –78 °C was added a solution of DMSO (1.48 mL, 20.9 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at –78 °C for 1 h. A solution of **19** (2.3 g, 5.25 mmol) in CH_2Cl_2 (15 mL) was added and stirred for 4 h. Et_3N (4.5 mL) was added and the stirring was continued for 15 min at –78 °C and 30 min at 0 °C. The reaction mixture was quenched with H_2O (50 mL) and stirred for 20 min at r.t. The organic layer was washed with aq 2% HCl (3 × 30 mL), H_2O (30 mL), sat. aq $NaHCO_3$ (2 × 30 mL), H_2O (30 mL), and finally with brine (30 mL). Drying (Na_2SO_4), filtering, and solvent evaporation afforded aldehyde **20** as a brown oil; yield: 2 g (87%); R_f = 0.70 (30% EtOAc–hexane); $[\alpha]_D^{21}$ –20.4 (*c* = 0.43, $CHCl_3$).

IR (NaCl, neat): 2931, 2858, 2357, 1723, 1504 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.77 (t, *J* = 2.2 Hz, 1 H, H-1), 7.67 (m, 4 H, CH_o-Ph), 7.39 (m, 6 H, $CH_{p,m}$-Ph), 6.87 (m, 2 H, H-3′), 6.56 (m, 2 H, H-2′), 4.50 (m, 1 H, H-3), 3.84 (m, 2 H, H-4), 2.69 (dd, *J* = 2.2, 6.1 Hz, 2 H, H-2), 1.04 (s, 9 H, *t*-C_4H_9-TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.67 (CH-1), 158.48, 156.11 (d, *J* = 234.5 Hz, C-Ph-4′), 154.24, 154.22 (d, *J* = 2.11 Hz, C-Ph-1′), 135.77 (*C*H_o-Ph-TBDPS), 133.39 (*C*-Ph-TBDPS), 129.89 (CH_m-Ph), 127.70 (*C*H_p-Ph-TBDPS), 115.79, 115.56 (d, *J* = 23.3 Hz, CH-Ph-3′), 115.33, 115.25 (d, *J* = 7.7 Hz, CH-Ph-2′), 71.26 (CH_2-4), 67.46 (CH-3), 48.36 (CH_2-2), 26.87 [C(*C*H_3)$_3$-TBDPS], 19.28 [*C*(CH_3)$_3$-TBDPS].

MS (ESI$^+$): *m*/*z* (%) = 459.17 ([M + Na]$^+$, 19), 359.15 (18), 259.09 (100).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{26}H_{29}FO_3Si$ + Na: 459.1768; found: 459.1762.

(*S*)-*tert*-Butyl[1-(4-fluorophenoxy)-3-(furan-2-yl)propan-2-yloxy]diphenylsilane (9)

To a solution of 3,3-diethoxyprop-1-yne (**21**; 770 μL, 5.37 mmol) in THF (5 mL) cooled to –78 °C was slowly added a solution of *n*-BuLi (2.5 M in hexane, 2.15 mL, 5.37 mmol). The mixture was stirred at 0 °C for 2 h. Then a solution of **20** (1.95 g, 4.47 mmol) in THF (5 mL) was added at –78 °C via cannula and the mixture was stirred at r.t. for 3 h. The reaction was quenched with H_2O (40 mL) and the mixture extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed by rotary evaporation. The residue was chromatographed on silica gel using 10% EtOAc–hexane, 20% EtOAc–hexane, then 50% EtOAc–hexane to afford the expected propargylic alcohol (2.17 g, 86%). The latter (1.38 g, 2.39 mmol) was dissolved in MeOH (50 mL) and Lindlar catalyst (200 mg) was added. The mixture was stirred in H_2 atmosphere at r.t. for 5 days, and fresh catalyst (200 mg) was added every 24 h. After filtration, the filtrate was evaporated and the residue dissolved in CH_2Cl_2 (30 mL), and washed with aq 1 M HCl (3 × 10 mL). Drying (Na_2SO_4), filtering, and solvent evaporation afforded a residue, which was chromatographed on silica gel using 3% EtOAc–hexane, 5% EtOAc–hexane, then 10% EtOAc–hexane affording **9** as a yellow oil; yield: 721 mg (70%); R_f = 0.56 (20% EtOAc–hexane); $[\alpha]_D^{24}$ –22 (*c* = 1.07, $CHCl_3$)].

IR (NaCl, neat): 2931, 2858, 2357 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (m, 4 H, CH_o-Ph), 7.40 (m, 6 H, $CH_{p,m}$-Ph), 7.32 (m, 1 H, H-5), 6.90 (m, 2 H, H-3″), 6.61 (m, 2 H, H-2″), 6.31 (m, 1 H, H-4), 6.03 (m, 1 H, H-3), 4.36 (dd, *J* = 5.5, 10.9 Hz, 1 H, H-2′), 3.82 (d, *J* = 5.0 Hz, 2 H, H-3′), 2.99 (t, *J* = 6.7 Hz, 2 H, H-1′), 1.07 (s, 9 H, *t*-C_4H_9-TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.32, 155.95 (d, *J* = 238 Hz, C-Ph-4′), 154.71, 154.69 (d, *J* = 2.11 Hz, C-Ph-1″), 141.17 (CH-5), 135.86 (*C*H_o-Ph-TBDPS), 133.99 (*C*-Ph-TBDPS), 129.70 (*C*H_m-Ph-TBDPS), 127.50 (*C*H_p-Ph-TBDPS), 115.68, 115.45 (d, *J* = 23.3 Hz, CH-Ph-H3′) 115.36, 115.28 (d, *J* = 7.7 Hz, CH-Ph-H2′), 110.27 (CH, C-4), 71.21 (CH_2-3′), 70.59 (CH-2′), 33.10 (CH_2-1′), 37.51 (CH_2-3), 110.27 (CH-4), 107.34 (CH-3), 71.19 (CH_2-3′), 70.59 (CH-2′), 33.09 (CH_2-1′), 26.85 [C(*C*H_3)$_3$-TBDPS], 19.27 [*C*(CH_3)$_3$-TBDPS].

MS (ESI$^+$): *m*/*z* (%) = 497.19 ([M + Na]$^+$, 31), 475.21 ([M + 1]$^+$, 11), 397.16 ([M – Ph]$^+$, 43), 391.28 (100), 355.13 (21), 337.13 (25), 291.19 (20).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{29}H_{31}FO_3Si$ + Na: 497.1924; found: 497.1919.

(*S*)-5-[2-(*tert*-Butyldiphenylsilyloxy)-3-(4-fluorophenoxy)propyl]-5-methoxyfuran-2(5*H*)-one (22)

A solution of **9** (301 mg, 0.63 mmol) and Rose Bengal (13 mg) in MeOH (5 mL) in CH_2Cl_2 (7 mL) was cooled to –78 °C in O_2 atmosphere and stirred for 30 min while irradiating with a 200 W lamp. The solution was allowed to reach r.t. and the solvent evaporated. The resulting residue was chromatographed on silica gel using 80% EtOAc–hexane to remove the Rose Bengal. Solvent evaporation afforded a residue (379 mg), which was dissolved in pyridine (938 μL). Ac_2O (330 μL) was added dropwise at 0 °C followed by a catalytic amount of DMAP. The mixture was stirred at r.t. for 14 h. MeOH (3 mL) was added and the stirring continued for 1 h. The solvent was removed by rotary evaporation and the residue dissolved in *t*-BuOMe (50 mL). The organic layer was washed with $CuSO_4$ (3 × 30 mL), dried (Na_2SO_4), and filtered, affording **22** as an orange oil; yield: 269 mg (82%); R_f = 0.13 (20% EtOAc–hexane).

IR (NaCl, neat): 3062, 2939, 2858, 2357, 1774 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (diastereoisomeric mixture) = 7.59 (m, 8 H, CH_o-Ph), 7.28 (m, 12 H, $CH_{p,m}$-Ph), 6.94 (d, *J* = 5.5 Hz, 1 H, H-4), 6.90 (d, *J* = 5.5 Hz, 1 H, H-4), 6.77 (m, 4 H, H-3″), 6.46 (m, 4 H, H-2″), 5.99 (d, *J* = 5.5 Hz, 1 H, H-3), 5.94 (d, *J* = 5.5 Hz, 1 H, H-3), 3.80 (m, 4 H, H-3′), 3.66 (m, 2 H, H-2′), 3.02 (s, 3 H, CH_3O), 3.01 (s, 3 H, CH_3O), 2.11 (m, 4 H, H-1′), 0.97 (s, 18 H, *t*-C_4H_9-TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ (diastereoisomeric mixture) = 169.45 (C-2), 169.41 (C-2), 158.32, 155.95 (d, *J* = 238.7 Hz, C-Ph-4″), 154.71, 154.69 (d, *J* = 2.11 Hz, C-Ph-1″), 153.77 (CH-4), 153.75 (CH-4), 135.89 (*CH*$_o$-Ph-TBDPS), 133.72 (*C*-Ph-TBDPS), 129.70 (*CH*$_m$-Ph-TBDPS), 127.71 (*CH*$_p$-Ph-TBDPS), 124.06 (CH-3), 115.68, 115.45 (d, *J* = 23 Hz, CH-Ph-3″), 115.66, 115.43 (d, *J* = 23.1 Hz, CH-Ph-3″), 115.33, 115.25, (d, *J* = 7.9 Hz, CH-Ph-3″), 115.28, 115.20 (d, *J* = 7.7 Hz, CH-Ph-3″), 109.64 (C-5), 109.51 (C-5), 71.92 (CH_2-3′), 71.76 (CH_2-3′), 68.28 (CH-2′), 68.27 (CH-2′), 50.95 (CH_3O), 50.86 (CH_3O), 42.45 (CH_2-1′), 41.86 (CH_2-1′), 26.83 [C(*C*H$_3$)$_3$-TBDPS], 19.30 [*C*(CH$_3$)$_3$-TBDPS].

MS (ESI$^+$): *m*/*z* (%) = 543.20 ([M + Na]$^+$, 43), 505.22 ([M – CH_3]$^+$, 50), 443.17 ([M – Ph]$^+$, 100), 429.15 (23), 321.25, (30).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{30}H_{33}FO_5Si$ + Na: 543.1979; found: 543.1973.

(5*S*)-5-[(4-Fluorophenoxy)methyl]-6a-methoxytetrahydrofuro[3,2-*b*]furan-2(5*H*)-one (23)

To compound **22** (980 mg, 1.71 mmol) was added a 1 M solution of TBAF in THF (1.71 mL, 1.71 mmol) and the mixture was stirred for 9.5 h at r.t. The mixture was quenched with aq $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried (Na_2SO_4), filtered. The solvent was removed by rotary evaporation to give a residue, which was chromatographed on silica gel using 2% EtOAc–hexane then 5% EtOAc–hexane affording **23** as a diastereoisomeric mixture; yield: 381 mg (82%), yellow oil; R_f = 0.26 (20% EtOAc–hexane).

IR (NaCl, neat): 2943, 2357, 1790 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (diastereoisomeric mixture) = 7.01 (m, 4 H, H-3″), 6.88 (m, 4 H, H-2″), 4.58 (m, 4 H, H-7, H-5), 3.97 (m, 4 H, H-1′), 3.53 (s, 3 H, CH_3O), 3.50 (s, 3 H, CH_3O), 2.87 (m, 2 H, H-8), 2.67–2.57 (m, 4 H, H-4, H-8), 2.38 (m, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ (diastereoisomeric mixture) = 174.67, 174.45 (C=O), 158.71, 156.33 (d, *J* = 238.5 Hz, C-Ph-4″), 158.67, 156.30 (d, *J* = 238.5 Hz, C-Ph-4″), 154.62, 154.60 (d, *J* = 2.4 Hz, C-Ph-1″), 154.53, 154.51 (d, *J* = 2.4 Hz, C-Ph-1″), 116.01, 115.78 (d, *J* = 23.3 Hz, CH-Ph-3″), 115.98, 115.75 (d, *J* = 23.3 Hz, CH-Ph-3″), 115.63, 115.55, (d, *J* = 8.0 Hz, CH-Ph-2″), 81.07 (CH-5), 80.23 (CH-5), 77.73 (CH-7), 77.66 (CH-7), 70.01 (CH_2-1′), 69.94 (CH_2-1′), 53.42 (CH_3O), 52.98 (CH_3O), 36.31 (CH_2-8), 36.24 (CH_2-8), 35.83 (CH_2-4), 35.72 (CH_2-4).

MS (ESI$^+$): *m*/*z* (%) = 305.08 ([M + Na]$^+$, 28), 283.50 ([M + 1]$^+$, 41), 233.07 (13), 201.05 (100).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_{16}FO_5$: 283.0982; found: 283.0976.

(5*S*)-5-[(4-Fluorophenoxy)methyl]-2-(2-hydroxyethyl)tetrahydrofuran-3-ol (24)

To a solution of **23** (154 mg, 0.53 mmol) in Et_2O (20 mL) was added BF_3·OEt_2 (170 μL, 1.33 mmol). The mixture was stirred at r.t. for 40 min, cooled to 0 °C before adding slowly $LiAlH_4$ (101 mg, 2.7 mmol). The stirring was continued at r.t. for 45 min. The mixture was cooled again to 0 °C before adding some drops of H_2O and Na_2SO_4 (0.5 g). The mixture was filtered and the filtrate was evaporated affording **24** as a colorless oil; yield: 135 mg (96%); R_f = 0.09 (20% EtOAc–hexane).

IR (NaCl, neat): 3737, 3390, 2931, 2360 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (diastereoisomeric mixture) = 6.95 (m, 4 H, H-3″), 6.88 (m, 4 H, H-2″), 4.51 (s, 1 H, H-4), 4.35 (s, 1 H, H-4), 4.13–3.68 (m, 12 H, H-1, H-2, H-2′, C*H*$_2$OPh), 2.10–1.53 (m, 8 H, H-1′, H-5).

^{13}C NMR (100 MHz, $CDCl_3$): δ (diastereoisomeric mixture) = 158.76, 156.73 (d, *J* = 203.5 Hz, C-Ph-4″), 154.53, 154.51 (d, *J* = 2.4 Hz, C-Ph-1″), 115.90, 115.83 (d, *J* = 23.3 Hz, CH-Ph-3″), 115.75, 115.68, (d, *J* = 8.0 Hz, CH-Ph-2″), 85.57 (CH-2), 75.73 (CH-1), 72.93 (CH-4), 71.27 (*C*H$_2$OPh), 60.71 (CH_2-2′), 37.08 (CH_2), 35.94 (CH_2).

MS (ESI$^+$): *m*/*z* (%) = 279.10 ([M + Na]$^+$, 92), 257.12 ([M + 1]$^+$, 66), 233.07 (14), 201.05 (100).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{13}H_{18}FO_4$: 257.1189; found: 257.1184.

(5*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-5-[(4-fluorophenoxy)methyl]tetrahydrofuran-3-ol (25)

To a solution of **24** (130 mg, 0.51 mmol) in DMF (2 mL) was added imidazole (138 mg, 2 mmol), a catalytic amount of DMAP, and TBDPSCl (145 μL, 0.56 mmol) and the mixture was stirred at r.t. for 5 days. The reaction was quenched with EtOAc (5 mL) and the mixture was washed with H_2O (3 × 10 mL). After the usual treatment of the organic layer, the residue was chromatographed on silica gel using 3% EtOAc–hexane, then 10% EtOAc–hexane affording **25** as a colorless oil; yield: 137 mg (52% for two steps); R_f = 0.25 (30% EtOAc–hexane).

IR (NaCl, neat): 3494, 2953, 2862, 2360 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (diastereoisomeric mixture) = 7.68 (m, 8 H, CH$_o$-Ph), 7.40 (m, 12 H, CH$_{p,m}$-Ph), 6.95 (m, 4 H, H-3″), 6.88 (m, 4 H, H-2″), 4.45 (s, 2 H, H-4), 3.93–3.70 (m, 8 H, H-1, H-2, C*H*$_2$OPh), 3.54–3.46 (m, 4 H, C*H*$_2$OPh, H-2′), 2.15–2.05 (m, 4 H, H-5), 2.00–1.73 (m, 4 H, H-1′), 1.06 (s, 9 H, *t*-C_4H_9-TBDPS).

^{13}C NMR (100 MHz $CDCl_3$): δ (diastereoisomeric mixture) = 158.47, 156.10 (d, *J* = 239.5 Hz, C-Ph-4″), 154.97, 154.95 (d, *J* = 2.11 Hz, C-Ph-1″), 135.52 (*CH*$_o$-Ph-TBDPS), 133.02 (*C*-Ph-TBDPS), 129.83 (*CH*$_m$-Ph-TBDPS), 127.75 (*CH*$_p$-Ph-TBDPS), 115.78, 115.64 (d, *J* = 14.8 Hz, CH-Ph-H-3″) 115.56 (CH-Ph-H-2″), 85.07 (CH-2), 82.72 (CH-2), 75.84 (CH-1), 75.59 (CH-1), 72.80 (CH-4), 71.67 (*C*H$_2$OPh), 71.05 (*C*H$_2$OPh), 61.60 (CH_2-2′), 61.15 (CH_2-2′), 36.48 (CH_2-5), 36.34 (CH_2-5), 31.79 (CH_2-1′), 31.68 (CH_2-1′), 26.77 [C(*C*H$_3$)$_3$-TBDPS], 19.24 [*C*(CH$_3$)$_3$-TBDPS].

MS (ESI$^+$): *m*/*z* (%) = 517.22 ([M + Na]$^+$, 100), 495.24 ([M + 1]$^+$, 35), 417.19 ([M – Ph]$^+$, 21), 349.29 (3), 321.26 (10).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{29}H_{36}FO_4Si$: 495.2367; found: 495.2361.

(5*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-5-[(4-fluorophenoxy)methyl]dihydrofuran-3(2*H*)-one (26)

To a solution of **25** (125 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) were added 4 Å molecular sieves (153 mg), NMO (59 mg, 0.51 mmol), and a catalytic amount of TPAP and the mixture stirred at r.t. for 5 days. After solvent evaporation, the residue was chromatographed on silica gel using 3% EtOAc–hexane, then 30% EtOAc–hexane affording **26** as a colorless oil; yield: 100 mg (80%); R_f = 0.46 (30% EtOAc–hexane).

IR (NaCl, neat): 3070, 2931, 2858, 1759, 1506 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (diastereoisomeric mixture) = 7.68 (m, 8 H, CH$_o$-Ph), 7.40 (m, 12 H, CH$_{p,m}$-Ph), 6.97 (m, 4 H, H-3″), 6.84 (m, 4 H, H-2″), 4.70 (m, 1 H, H-4), 4.55 (m, 1 H, H-4), 4.35 (dd, 1 H, *J* = 4.8, 7.1 Hz, H-2), 4.10 (m, 5 H, C*H*$_2$OPh, H-2), 3.91 (m, 2 H, H-2′), 3.79 (m, 2 H, H-2′), 2.60 (m, 4 H, H-5), 2.05 (m, 2 H, H-1′), 1.92 (m, 2 H, H-1′), 1.05 (s, 18 H, *t*-C_4H_9-TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ (diastereoisomeric mixture) = 215.31 (C=O), 214.67 (C=O), 158.70, 156.32 (d, *J* = 239.5 Hz, C-Ph-4″), 158.67, 156.30 (d, *J* = 238.7 Hz, C-Ph-4″), 154.67, 154.65 (d, *J* = 2.11 Hz, C-Ph-1″), 154.52, 154.50 (d, *J* = 2.11 Hz, C-Ph-

1″), 135.59 (CH_o-Ph-TBDPS), 133.54 (*C*-Ph-TBDPS), 129.88 (CH_m-Ph-TBDPS), 127.65 (CH_p-Ph-TBDPS), 115.97, 115.75 (d, *J* = 21.9 Hz, CH-Ph-H3′), 115.93, 115.70 (d, *J* = 23.3 Hz, CH-Ph-H3′), 115.62, 115.54 (d, *J* = 7.7 Hz, CH-Ph-H2′), 115.62, 115.54 (d, *J* = 7.7 Hz, CH-Ph-H2′), 78.27 (CH-2), 76.85 (CH-2), 74.04 (CH-4), 73.61 (CH-4), 71.50 (CH_2OPh), 70.26 (CH_2OPh), 59.59 (CH_2-2′), 59.57 (CH_2-2′), 39.08 (CH_2-5), 38.29 (CH_2-5), 34.28 (CH_2-1′), 34.00 (CH_2-1′), 26.79 [C(*C*H_3)$_3$-TBDPS], 19.16 [*C*(CH_3)$_3$-TBDPS].

MS (ESI$^+$): *m*/*z* (%) = 515.22 ([M + Na]$^+$, 74), 493.22 ([M + 1]$^+$, 100), 415.17 ([M – Ph]$^+$, 51), 209.63 (11).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{29}H_{34}FO_4Si$: 493.2210; found: 493.2205.

(2*S*,3*S*,5*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-5-[(4-fluorophenoxy)methyl]tetrahydrofuran-3-ol (8)

To a solution of **26** (43 mg, 0.09 mmol) in THF (2 mL) cooled to –78 °C was a added a 1 M solution of L-Selectride in THF (874 μL, 0.9 mmol) and the mixture was stirred for 2 h under the same conditions. Aq NH_4Cl (10 mL) was added and the stirring continued for 30 min at r.t. The aqueous layer was extracted with EtOAc (4 × 15 mL). After the usual treatment of the organic layer, the residue was chromatographed on silica gel using 3% EtOAc–hexane, then 15% EtOAc–hexane affording **7** and **8** as colorless oils.

8

Yield: 18.5 mg (43%); R_f = 0.42 (30% EtOAc–hexane); $[\alpha]_D^{22}$ +5.1 (*c* = 0.83, $CHCl_3$).

IR (NaCl, neat): 3435, 2933, 2858 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (m, 4 H, CH_o-Ph), 7.40 (m, 6 H, $CH_{p,m}$-Ph), 6.95 (m, 2 H, H-3″), 6.86 (m, 2 H, H-2″), 4.30 (m, 2 H, H-1, H-4), 4.02 (m, 2 H, CH_2OPh), 3.89 (m, 1 H, H-2), 3.81 (m, 1 H, H-2′), 3.74 (m, 1 H, H-2′), 2.44 (m, 1 H, H-5), 2.10 (m, 1 H, H-1′), 1.95 (m, 2 H, H-1′, H-5), 1.05 (s, 9 H, *t*-C_4H_9-TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.66, 156.28 (d, *J* = 237.3 Hz, C-Ph-4″), 154.70, 154.68 (d, *J* = 2.11 Hz, C-Ph-1″), 135.56 (CH_o-Ph-TBDPS), 133.06 (*C*-Ph-TBDPS), 129.81 (CH_m-Ph-TBDPS), 127.78 (CH_p-Ph-TBDPS), 115.90, 115.79 (d, *J* = 10.6 Hz, CH-Ph-H3′), 115.71, 115.67 (d, *J* = 4.2 Hz, CH-Ph-H2′), 82.72 (CH-2), 75.64 (CH-1), 72.02 (CH-4), 71.50 (CH_2OPh), 61.35 (CH_2-2′), 37.16 (CH_2-5), 31.73 (CH_2-1′), 26.80 [C(*C*H_3)$_3$-TBDPS), 19.06 [*C*(CH_3)$_3$-TBDPS].

MS (ESI$^+$): *m*/*z* (%) = 517.22 ([M + Na]$^+$, 100), 495.24 ([M + 1]$^+$, 35), 417.19 ([M – Ph]$^+$, 21), 349.29 (3), 321.26 (10).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{29}H_{36}FO_4Si$: 495.2367; found: 495.2361.

7

Yield: 25 mg (56%); colorless oil; R_f = 0.74 (30% EtOAc–hexane); $[\alpha]_D^{22}$ –39.9 (*c* = 0.95, $CHCl_3$).

IR (NaCl, neat): 3435, 2933, 2858 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (m, 4 H, CH_o-Ph), 7.41 (m, 6 H, $CH_{p,m}$-Ph), 6.94 (m, 2 H, H-3″), 6.85 (m, 2 H, H-2″), 4.61 (m, 1 H, H-1), 4.48 (m, 1 H, H-4), 4.06 (m, 1 H, H-2), 3.99 (m, 1 H, CH_2OPh), 3.93 (m, 1 H, CH_2OPh), 3.80 (m, 1 H, H-2′), 3.65 (m, 1 H, H-2′), 2.20 (m, 1 H, H-5), 2.12 (m, 2 H, H-1′, H-5), 1.96 (m, 1 H, H-1′), 1.06 (s, 9 H, *t*-C_4H_9-TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.50, 156.13 (d, *J* = 238.8 Hz, C-Ph-4″), 155.05, 155.03 (d, *J* = 2.8 Hz, C-Ph-1″), 135.55 (CH_o-Ph-TBDPS), 132.57 (*C*-Ph-TBDPS), 129.97 (CH_m-Ph-TBDPS), 127.80 (CH_p-Ph-TBDPS), 115.81, 115.68 (d, *J* = 12.7 Hz, CH-Ph-H3′) 115.60, 115.58 (d, *J* = 2.11 Hz, CH-Ph-H2′), 82.88 (CH-2), 75.55 (CH-1), 72.84 (CH-4), 71.09 (CH_2OPh), 61.18 (CH_2-2′), 36.94 (CH_2-5), 31.81 (CH_2-1′), 26.97 [C(*C*H_3)$_3$-TBDPS], 19.28 [*C*(CH_3)$_3$-TBDPS].

MS (ESI$^+$): *m*/*z* (%) = 517.22 ([M + Na]$^+$, 100), 495.24 ([M + 1]$^+$, 35), 417.19 ([M – Ph]$^+$, 21), 349.29 (3), 321.26 (10).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{29}H_{36}FO_4Si$: 495.2367; found: 495.2361.

(2*R*,3*R*,5*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-5-[(4-fluorophenoxy)methyl]tetrahydrofuran-3-yl Acetate (27) and (2*S*,3*S*,5*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-5-[(4-fluorophenoxy)methyl]tetrahydrofuran-3-yl Acetate (28)

To a solution of **7** or **8** (0.043 mmol) in pyridine (80 μL) was added Ac_2O (0.43 mmol) and the mixture was stirred overnight at r.t. MeOH (2 mL) was added and the stirring continued for 20 min. The solvent was evaporated and Et_2O (6 mL) was added. The organic layer was washed with aq $CuSO_4$ (4 × 8 mL), dried (Na_2SO_4), and the solvent was removed by rotary evaporation affording **27** or **28**.

27

Yield: 99%; yellow oil; R_f = 0.48 (30% EtOAc–hexane); $[\alpha]_D^{21}$ –1.52 (*c* = 1.28, $CHCl_3$).

IR (NaCl, neat): 3050, 2956, 2929, 2854, 1740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (m, 4 H, CH_o-Ph), 7.36 (m, 6 H, $CH_{p,m}$-Ph), 6.92 (m, 2 H, H-3″), 6.82 (m, 2 H, H-2″), 5.32 (m, 1 H, H-3), 4.48 (m, 1 H, H-5), 4.30 (m, 1 H, H-2), 3.95 (m, 2 H, CH_2OPh), 3.76 (m, 2 H, H-2′), 2.18 (m, 2 H, H-4), 2.04 (s, 3 H, CH_3O), 1.83 (m, 2 H, H-1′), 1.03 (s, 9 H, *t*-C_4H_9-TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.38 (C=O), 158.56, 156.19 (d, *J* = 238.7 Hz, C-Ph-4″), 154.94, 154.92 (d, *J* = 2.11 Hz, C-Ph-1″), 135.56 (CH_o-Ph-TBDPS), 133.80 (*C*-Ph-TBDPS), 129.59 (CH_m-Ph-TBDPS), 127.64 (CH_p-Ph-TBDPS), 115.88, 115.66 (d, *J* = 21.8 Hz, CH-Ph-H3′), 115.65, 115.58 (d, *J* = 7.7 Hz, CH-Ph-H2′), 78.24 (CH-2), 75.76 (CH-3), 75.32 (CH-5), 70.89 (CH_2OPh), 60.92 (CH_2-2′), 35.66 (CH_2-1′), 32.25 (CH_2-4), 26.83 [C(*C*H_3)$_3$-TBDPS], 21.04 (CH_3O), 19.06 [*C*(CH_3)$_3$-TBDPS).

MS (ESI$^+$): *m*/*z* (%) = 559.22 ([M + Na]$^+$, 100), 537.25 ([M + 1]$^+$, 27), 459.20 ([M – Ph]$^+$, 6), 321.25 (37).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{31}H_{38}FO_5Si$: 537.2473; found: 537.2467.

28

Yield: 99%; yellow oil; R_f = 0.55 (30% EtOAc–hexane); $[\alpha]_D^{20}$ +7.25 (*c* = 1.01, $CHCl_3$).

IR (NaCl, neat): 3070, 3050, 2956, 2931, 2857, 1740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (m, 4 H, CH_o-Ph), 7.39 (m, 6 H, $CH_{p,m}$-Ph), 6.95 (m, 2 H, H-3″), 6.84 (m, 2 H, H-2″), 5.24 (m, 1 H, H-3), 4.24 (m, 1 H, H-5), 4.05 (m, 2 H, H-2, CH_2OPh), 3.89 (m, 1 H, CH_2OPh), 3.79 (m, 2 H, H-2′), 2.50 (m, 1 H, H-1′), 2.01 (s, 3 H, CH_3O), 1.88 (m, 3 H, H-4 H-1′), 1.04 (s, 9 H, *t*-C_4H_9-TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.38 (C=O), 158.52, 156.15 (d, *J* = 237.4 Hz, C-Ph-4″), 154.89, 154.86 (d, *J* = 2.11 Hz, C-Ph-1″), 135.55 (CH_o-Ph-TBDPS), 133.79 (*C*-Ph-TBDPS), 129.59 (CH_m-Ph-TBDPS), 127.63 (CH_p-Ph-TBDPS), 115.84, 115.63 (d, *J* = 21.2 Hz, CH-Ph-H3′), 115.61, 115.56 (d, *J* = 5.6 Hz, CH-Ph-H2′), 78.89 (CH-2), 75.41 (CH-3), 74.62 (CH-5), 71.11 (CH_2OPh), 60.92 (CH_2-2′), 36.25 (CH_2-1′), 32.03 (CH_2-4), 26.84 [C(*C*H_3)$_3$-TBDPS), 21.03 (CH_3O), 19.19 [*C*(CH_3)$_3$-TBDPS).

MS (ESI$^+$): *m*/*z* (%) = 559.23 ([M + Na]$^+$, 100), 537.24 ([M + 1]$^+$, 74), 459.20 ([M – Ph]$^+$, 56), 321.25 (16).

HRMS (ESI$^+$): *m*/*z* calcd for $C_{31}H_{38}FO_5Si$: 537.2473; found: 537.2467.

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References

(1) Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene, C.; Lacey, E.; Gill, J. H.; Friedl, T.; Wadsworth, D. *Tetrahedron* **1998**, *54*, 2227.

(2) Warren, R. G.; Wells, R. J.; Blount, J. F. *Aust. J. Chem.* **1980**, *33*, 891.

(3) (a) Gadikota, R. R.; Callam, C. S.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 9046. (b) Nesbitt, C. L.; McErlean, C. S. P. *Tetrahedron Lett.* **2009**, *50*, 6318; and references cited therein.

(4) Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, 1643.

(5) Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, 1639.

(6) (a) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378. (b) Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468. (c) Osumi, K.; Sugimura, H. *Tetrahedron Lett.* **1995**, *36*, 5789. (d) Lee, E.; Yoo, S.-K.; Cho, Y.-S.; Cheon, H.-S.; Chong, Y. H. *Tetrahedron Lett.* **1997**, *38*, 7757. (e) Boukouvalas, J.; Fortier, G.; Radu, I.-I. *J. Org. Chem.* **1998**, *63*, 916. (f) Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 3175. (g) Braddock, D. C.; Bhuva, R.; Millan, D. S.; Pérez-Fuentes, Y.; Roberts, C. A.; Sheppard, R. N.; Solanki, S.; Stokes, E. S. E.; White, A. J. P. *Org. Lett.* **2007**, *9*, 445.

(7) (a) Eugster, C. H. *Helv. Chim. Acta* **1956**, *39*, 1002. (b) Kögl, F.; Salemink, C. A.; Schouten, H.; Jellinek, F. *Recl. Trav. Chim. Pays Bas* **1957**, *76*, 109. (c) Eugster, C. H. *Naturwissenschaften* **1968**, *55*, 305. (d) Bollinger, H.; Eugster, C. H. *Helv. Chim. Acta* **1971**, *54*, 2704.

(8) Nitta, K.; Stadelmann, R. J.; Eugster, C. H. *Helv. Chim. Acta* **1977**, *60*, 1747.

(9) (a) Eugster, C. H.; Müller, G. *Helv. Chim. Acta* **1959**, *42*, 1189. (b) List, H. P.; Müller, H. *Arch. Pharm.* **1959**, *292*, 777. (c) Catalformo, P.; Eugster, C. H. *Helv. Chim. Acta* **1970**, *53*, 848. (d) Bollinger, H.; Eugster, C. H. *Helv. Chim. Acta* **1971**, *54*, 1332.

(10) (a) Popsavin, V.; Popsavin, M.; Radic, L.; Beric, O.; Cirin-Novta, V. *Tetrahedron Lett.* **1999**, *40*, 9305. (b) Kang, K. H.; Cha, M. Y.; Pae, A. N.; Choi, K. L.; Cho, Y. S.; Koh, H. Y.; Chung, B. Y. *Tetrahedron Lett.* **2000**, *41*, 8137. (c) Hartung, J.; Kneuer, R. *Tetrahedron: Asymmetry* **2003**, *14*, 3019.

(11) (a) Gurjar, M. K.; Murugaiah, A. M. S.; Radhakrishna, P.; Ramana, C. V.; Chorghade, M. S. *Tetrahedron: Asymmetry* **2003**, *14*, 1363. (b) Sharma, G. V. M.; Punna, S.; Rajendra Prasad, T.; Krishna, P. R.; Chorgade, M. S.; Ley, S. V. *Tetrahedron: Asymmetry* **2005**, *16*, 1113. (c) Sharma, G. V. M.; Punna, S.; Krishna, P. R.; Chorghade, M. S.; Ley, S. V. *Tetrahedron: Asymmetry* **2005**, *16*, 1125.

(12) (a) Fall, Y.; Vidal, B.; Alonso, D.; Gómez, G. *Tetrahedron Lett.* **2003**, *44*, 4467. (b) Pérez, M.; Canoa, P.; Gómez, G.; Terán, C.; Fall, Y. *Tetrahedron Lett.* **2004**, *45*, 5207. (c) Alonso, D.; Pérez, M.; Gómez, G.; Covelo, B.; Fall, Y. *Tetrahedron* **2005**, *61*, 2021. (d) Teijeira, M.; Suárez, P. L.; Gómez, G.; Terán, C.; Fall, Y. *Tetrahedron Lett.* **2005**, *46*, 5889. (e) García, I.; Gómez, G.; Teijeira, M.; Terán, C.; Fall, Y. *Tetrahedron Lett.* **2006**, *47*, 1333. (f) Canoa, P.; Pérez, M.; Covelo, B.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2007**, *48*, 3441.

(13) Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768.

(14) Hanessian, S.; Ugolini, A.; Dubé, D.; Glamyan, A. *Can. J. Chem.* **1984**, *62*, 2146.

(15) Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E.; Pavan Kumar, K. V. P. *Chem. Rev.* **2009**, *109*, 2551.

(16) Canoa, P.; Vega, N.; Pérez, M.; Gómez, G. *Tetrahedron Lett.* **2008**, *49*, 1149.