Asymmetric Synthesis of the C_3-C_8 Fragment of Leucotrienes and Analogues

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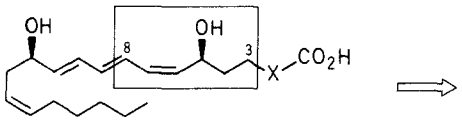
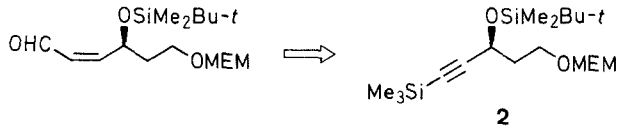
An asymmetric synthesis of the C_3-C_8 fragment of leukotrienes and analogues using the aldol-type condensation of chiral sulfinyl ester is described. Thus, starting from (3*S*)-3-*tert*-butyldimethylsiloxy-1-(2-methoxyethoxymethoxy)-5-trimethylsilyl-4-pentyne, the corresponding methyl (2*Z*,4*S*)-hexenoate, methyl (4*R*)-hexanoate, (2*Z*,4*S*)- and (2*E*,4*S*)-2-hexenal derivatives were prepared. Several molecules prepared during this work were shown to be important intermediates in the synthesis of various natural products.

Leukotriene B_4 (LTB_4, **1a**) is an important metabolite of the 5-lipoxygenase arachidonic acid peroxidation pathway and is implicated as a mediator of inflammation.



1a X = CH_2, LTB_4
b X = $(CH_2)_2$, HOMO LTB_4
c X = SCH_2, THIA-3-HOMO LTB_4



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Our retrosynthetic analysis of LTB_4 lead us to consider that the C_3-C_8 chiral fragment could be prepared from the optically active synthon **2** readily accessible by an asymmetric aldol type condensation of chiral sulfinyl ester to propargylic aldehyde (Scheme 1). The presence of a primary hydroxylic group on carbon 3 should allow also the synthesis of the analogues **1b** and **1c**. Moreover, **2** is a convenient precursor of other natural products (Scheme 2).

The key step of the synthesis is the asymmetric aldol type condensation of *tert*-butyl (+)-(*R*)-*p*-tolylsulfinylacetate **(5)** to the propargylic aldehyde **4**, (Scheme **1**) a well documented reaction[1-3] giving after cleavage of the sulfoxide the *S*-configuration at the created chiral hydroxylic center. An 85% enantiomeric excess (ee) was determined after desulfurization by NMR in presence of a chiral europium complex. The molecule **2** was finally obtained after protection of the hydroxylic function, reduction of the ester with diisobutylaluminum hydride (DIBAL-H) and protection of the resulting hydroxy group.

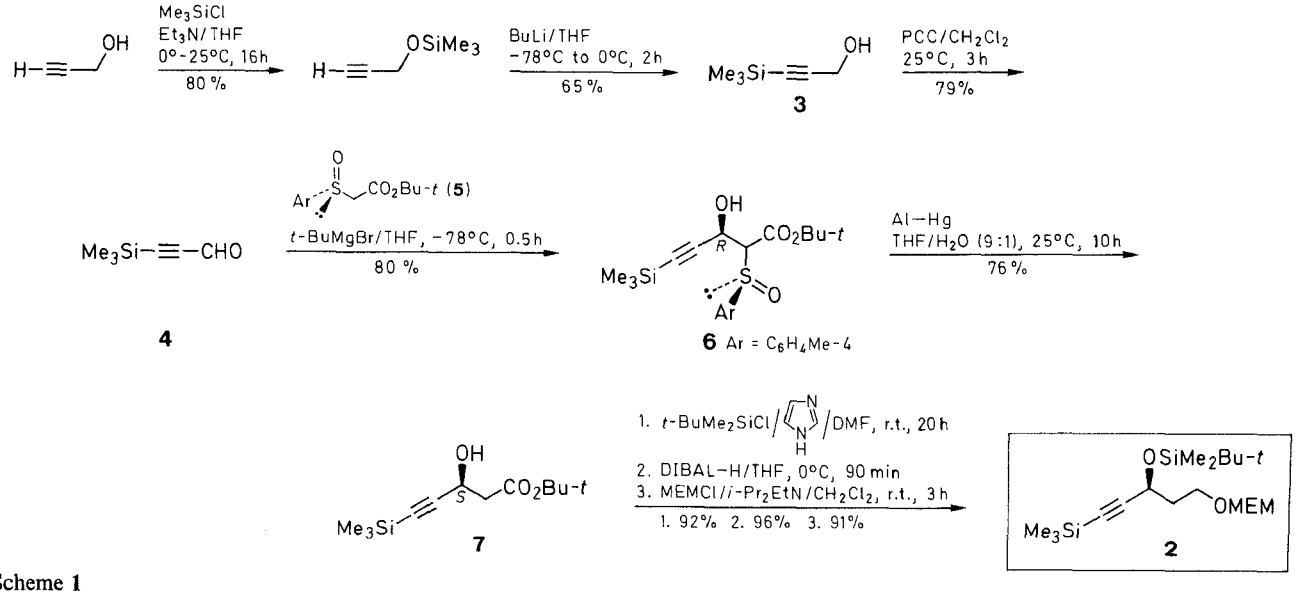
Compound **2** was then easily desilylated[4] in high yield to give the intermediate **8** which is a common intermediate to several kinds of natural products (Scheme **2**).

After carboxylation of the acetylenic anion with methyl chloroformate, followed by reduction of the triple bond to a *cis* double bond, we obtained the optically active molecule **10** which could be easily transformed into functionalized chiral butenolides.[5]

Complete hydrogenation of the triple bond in compound **9** gave **11**, precursor of six-membered functionalized chiral lactones which could be used for insect pheromone syntheses.[6]

A synthetic intermediate similar to **8** was already used by Nicolaou in the synthesis of (12*S*,14*E*,10*E*)-12-hydroxy-5,8,14,10-eicosatetraenoic acid (12-HETE).[4]

Finally formylation of the molecule **8** gave compound **12** which was semi-hydrogenated to the *cis*-isomer **13**, precursor of LTB_4 and analogues, or the *trans* isomer **14**, precursor of all-*trans* LTB_4. It is interesting to remark that hydrogenation of compound **9** with Lindlar catalyst



Scheme 1

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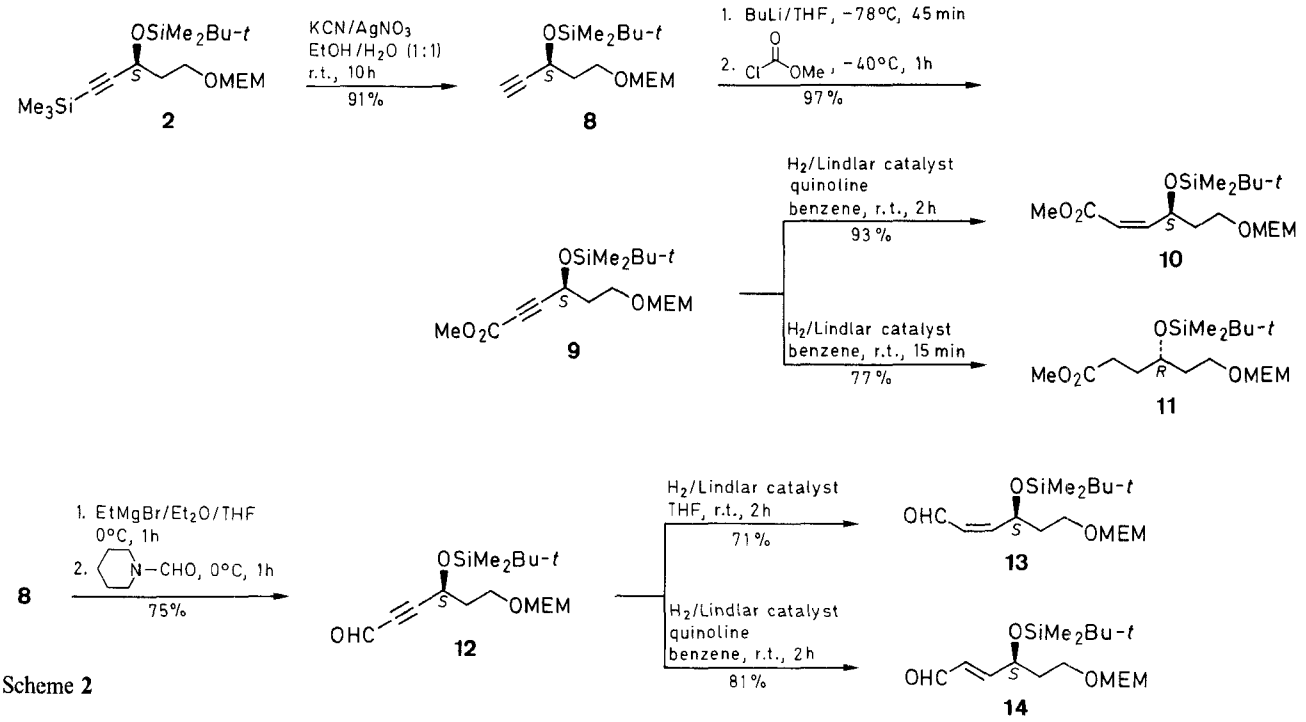

Scheme 2

in benzene gave a *cis* double bond in presence of quinoline and a saturated compound without quinoline. Moreover, hydrogenation of the propargylic aldehyde **12** with the Lindlar catalyst gave a *cis* double bond (aldehyde **13**) in tetrahydrofuran without quinoline and a *trans* double bond (aldehyde **14**) in benzene in presence of quinoline.

The total synthesis of LTB_4 and all-*trans* LTB_4 from the intermediates **13** and **14** will shortly be reported.

All new compounds were characterized by full spectroscopic data as well as by microanalyses.

***tert*-Butyl (3*R*)-3-Hydroxy-2-(*p*-tolylsulfinyl)-5-trimethylsilyl-4-pentynoate (6):**

To a solution of sulfinyl ester **5** (15 g, 49 mmol) in THF is added at −78 °C a solution of *t*-BuMgBr [prepared from *t*-BuBr (134 g, 980 mmol, 20 equiv) and Mg (23.8 g, 980 mmol) in Et_2O (600 mL)]. After stirring at −78° for 30 min, the aldehyde **4** (24.7 g, 196 mmol, 4 equiv) in THF (100 mL) is dropwise added. The mixture is then added at −78 °C for 2 h. After adding a 5% HCl solution (300 mL) at −78 °C, the organic phase is separated and the aqueous layer extracted with Et_2O (2 × 300 mL). The organic phases are washed with H_2O (2 × 200 mL), then with sat. aq NaCl, dried (Na_2SO_4) and the solvent evaporated. The product is purified by flash chromatography (Et_2O/hexane: 20/80); yield: 15.1 g (39.4 mmol, 80%), yellow solid.

R_f = 0.27–0.37, mixture of diastereoisomers (Et_2O/hexane, 7:3).

IR (CCl_4): ν = 3600–3000 (OH), 2200 (C≡C), 1720 cm^{-1} (C=O).

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.17 [s, 9H, $(CH_3)_3Si$], 1.45 [s, 9H, $(CH_3)_3CO$], 2.43 (s, 3H, $CH_3C_6H_4$), 3.55 (d, 1H, J = 5.36 Hz, H_2), 4.56 (d, 1H, J = 5.36 Hz, H_3), 7.5 (AA'BB', 4H, J_{AB} = 8.04 Hz, $\Delta\nu$ = 52 Hz, H_{arom}).

^{13}C-NMR (50 MHz, $CDCl_3$/TMS): δ = 0.4 [$(CH_3)_3Si$], 21.4 (CH_3Ar), 27.7, 27.9 [$(CH_3)_3CO$ in two diastereoisomers], 60.58, 60.84 (C_2 in the two diastereoisomers), 75.1, 75.6 (C_3), 83.87 [$(CH_3)_3CO$], 92.28 (C_5), 101.98 (C_4), 124, 129, 138, 142 (C_{arom}), 165.5 (CO_2)

***tert*-Butyl (3*S*)-3-Hydroxy-5-trimethylsilyl-4-pentynoate (7):**

The crude product **6** (2 g, 5.2 mmol) in THF/H_2O (9:1, 500 mL) is treated with small amounts of aluminum amalgam (15.4 g, 570 mmol, 100 equiv). After stirring for 20 min, the mixture temperature must be maintained at 20 °C by cooling with an ice bath. After stirring at r.t. for 14 h, the mixture is filtered and washed with Et_2O (200 mL). The organic solution is dried (Na_2SO_4) and evaporated. The product is purified by flash chromatography (Et_2O/hexane, 30:70); yield: 9.7 g (3.9 mmol, 76%); R_f = 0.27 (Et_2O/hexane, 20:80); $[\alpha]_D$ −10.5° (c = 2, $CHCl_3$).

IR (CCl_4): ν = 3600–3300 (OH), 2180 (C≡C), 1710 cm^{-1} (C=O).

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.17 [s, 9H, $(CH_3)_3Si$], 1.48 [s, 9H, $(CH_3)_3CO$], 2.65 (d, 2H, J = 6.2 Hz, H2), 3.2 (d, 1H, J = 6.3 Hz, OH), 4.7 (q, 1H, J = 6.2 Hz, H3).

The ee is determined by ^{1}H-NMR in presence of tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato] europium(III) (ratio: 0.8) from the splitting of the *tert*-butyl signal ($\Delta\delta$ = 12 Hz): ee = 85%. Compound **7** (85% ee) was used in the next step without further purification. An enantiomerically pure sample could be obtained by recrystallization.

All the compounds prepared below, **2**, **8**–**14**, have the same enantiomeric purity (85%).

(3*S*)-3-*tert*-Butyldimethylsiloxy-1-(2-methoxyethoxymethoxy)-5-trimethylsilyl-4-pentyne (2):

1. Compound **7** (6.2 g, 25.6 mmol) is dissolved in DMF (100 mL) in the presence of imidazole (6.92 g, 101.6 mmol, 4 equiv) and *t*-$BuMe_2SiCl$ (8.42 g, 55.9 mmol, 2.2 equiv). After stirring at r.t. for 20 h, the mixture is hydrolyzed with a solution of NH_4Cl (500 mL) and extracted with Et_2O (3 × 200 mL). The organic layers are washed with sat. aq NaCl (500 mL), dried (Na_2SO_4) and evaporated. The crude product is purified by chromatography (Et_2O/hexane, 3:97); yield: 8.4 g (23.6 mmol, 92%); $[\alpha]_D$ −40° (c = 1.2, $CHCl_3$)

IR ($CHCl_3$): ν = 2160, 1710 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS, 200 MHz): δ = 0.16, [s, 15H, $(CH_3)_3Si$], 0.9 (s, 9H, *t*-BuSi), 2.6 (AB part of ABX, 2H, J_{AB} = 15 Hz, J_{AX} = 8 Hz, J_{BX} = 5 Hz, $\Delta\nu$ = 54 Hz, H2), 4.8 (X part, 1H, J_{AX} = 8 Hz, J_{BX} = 5 Hz, H3).

2. To the preceeding silylated product (5 g, 14 mmol) in THF (100 mL) is dropwise added at 0 °C a DIBAL-H solution (1 M in toluene, 42 mL, 42 mmol, 3 equiv). After stirring at 0 °C for 90 min, the mixture is treated at 0 °C with MeOH (2.5 mL), then with EtOAc (250 mL) and sat aq sodium tartrate (250 mL). After separation the

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aqueous phase is extracted with EtOAc (2 × 250 mL). The organic layers are washed with sat. aq NaCl (300 mL), dried and evaporated. The product is then purified by chromatography (EtOAc/hexane, 1:9); yield: 3.85 g (13.43 mmol, 96%); R_f = 0.3 (EtOAc/hexane; 10:90); $[\alpha]_D^{22}$ −49° (*c* = 0.5, $CHCl_3$).

IR ($CHCl_3$): ν = 3600–3300, 2100 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS, 200 MHz): δ = 0.15, 0.17 [2 s, 15 H, $(CH_3)_2Si$, $(CH_3)_3Si$], 0.9 (s, 9 H, *t*-BuSi), 1.9 (m, 2 H, H_2), 3.8 (m, 2 H, H1), 4.62 (X from ABX, 1 H, J_{AX} = 6.5 Hz, J_{BX} = 5 Hz, H3).

^{13}C-NMR (50 MHz, $CDCl_3$/TMS): δ = −4.5, −3.8 [$(CH_3)_2Si$], −0.2 [$(CH_3)_3Si$], 18.6 [$(CH_3)_3\underline{C}Si$], 26 [$(\underline{C}H_3)_3CSi$], 40. 8 (C_2), 60.44 (C_1), 63 (C_3), 90.33 (C_5, 107.2 (C_4).

3. The preceeding alcohol (3.75 g, 13.1 mmol) in CH_2Cl_2 (200 mL) with 2-methoxyethoxymethyl chloride (45 mL, 39 mmol, 3 equiv) and *i*-Pr_2EtN (6.85 mL, 39 mmol, 3 equiv) is stirred at r.t. for 3 h. Then NH_4Cl (5 g/10 mL of H_2O) is added to the mixture. After extraction with Et_2O (100 mL) and filtration over silica gel (Et_2O as eluent), the solvent is evaporated and the product purified by chromatography (EtOAc/hexane; 9:91); yield: 4.8 g (12.8 mmol, 98%); R_f = 0.34 (EtOAc, hexane; 10:90); $[\alpha]_D^{22}$ −22° (*c* = 1, $CHCl_3$).

IR ($CHCl_3$): ν = 2180 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.16 [s, 15 H, $(CH_3)_2Si$, $(CH_3)_3Si$], 0.9 (s, 9 H, *t*-BuSi), 1.96 (m, 2 H, H2), 3.4 (s, 3 H, H9), 3.54 and 3.72 (m, 6 H, H7, H8, H1), 4.52 (X part of ABX, 1 H, J_{AX} = J_{BX} = 6.5 Hz, H3).

(3*S*)-3-*tert*-Butyldimethylsiloxy-1-(2-methoxyethoxymethoxy)-4-pentyne (8):

Compound **2** (4 g, 10.7 mmol) is treated with KCN (4.9 g, 75 mmol, 7 equiv) and $AgNO_3$ (7.27 g, 42.8 mmol, 4 equiv) in $EtOH/H_2O$ (1:1, 80 mL). After stirring for 10 h at r.t., and evaporation of EtOH, H_2O is added (100 mL) and extracted with Et_2O (3 × 75 mL). The organic layers are washed with sat. aq NaCl (150 mL), dried and evaporated. The product is purified by chromatography (EtOAc/hexane, 1:9); yield: 2.94 g (9.72 mmol, 91%); R_f = 0.46 (EtOAc/hexane, 2:5); $[\alpha]_D$ −16° (*c* = 0.5, $CHCl_3$).

IR ($CHCl_3$): ν = 3310 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$/TMS: δ = 0.15, 0.16 [2s, 6 H, $(CH_3)_2CSi$], 0.9 (s, 9 H, *t*-Bu$C(CH_3)_2Si$), 1.97 (m, 2 H, H_2), 2.4 (d, 1 H, J_{5-3} = 2.1 Hz, H_5), 3.4 (s, 3 H, H9), 3.56–3.76 (m, 6 H, H1, H7, H8), 4.54 (X part of ABX, 1 H, J_{AX} = J_{BX} = 6.4 Hz splitted by J_{5-3} = 2.1 Hz, H3), 4.71 (s, 2 H, H6).

^{13}C-NMR (50 MHz, $CDCl_3$/TMS): δ = −4.6, −4.1 [$(CH_3)_2CSi$], 18.61 [$(\underline{C}H_3)_3CSi$], 26.2 [$(CH_3)_3\underline{C}Si$], 39.13 (C_2), 59.4 (C_3), 60.24 (C_9), 64.26 (C_1), 67.22 (C_8), 72.27 (C_7), 72.92 (C_6), 96.0 (C_4).

Methyl-(4*S*)-4-*tert*-Butyldimethylsyloxy-6-(2-methoxyethoxymethoxy)-2-hexynoate (9):

Compound **8** (300 mg, 1 mmol) in THF (20 mL) is treated at −78 °C with BuLi (1.5 M in hexane, 1 mL) methyl chloroformate (155 mL, 2 mmol, 2 equiv) is added and the mixture is stirred at −40 °C for 1 h. Hydrolysis with sat. aq NH_4Cl (0.5 g in 10 mL of H_2O), Et_2O extraction (50 mL), solvent evaporation and chromatography (silica gel, EtOAc/hexane, 15:85) gave the ester **9**; yield: 350 mg (0.97 mmol, 97%); oily product; R_f = 0.32 (EtOAc/hexane, 2:8); $[\alpha]_D$ −17° (*c* = 1, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.11, 0.16 (2 s, 6 H, $(CH_3)_2Si$), 0.9 (s, 9 H, *t*-BuSi), 2.01 (m, 2 H, H5), 3.4 (s, 3 H, H10), 3.52, 3.72 (2 m, 6 H, H6, H8, H9), 3.77 (s, 3 H, CO_2Me), 4.65 (X part of ABX, 1 H, J_{AX} = J_{BX} = 6.5 Hz, H4), 4.7 (AB, 2 H, H7).

Methyl (2*Z*,4*S*)-4-*tert*-Butyldimethylsiloxy-6-(2-methoxyethoxymethoxy)-2-hexenoate (10):

The propargylic ester **9** (100 mg, 0.28 mmol) is dissolved in benzene (20 mL) in the presence of Lindlar catalyst (100 mg) and quinoline (10 µL) and H_2. After stirring for 2 h at r.t., the solution is filtrated on Celite, the solvent evaporated and the product purified by chromatography (silica gel, EtOAc/hexane, 15:85); yield: 96 mg (0.26 mmol, 93%), oil: $[\alpha]_D$ +7.5° (*c* = 1.5, $CHCl_3$).

IR ($CHCl_3$): ν = 1720 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.013, 0.055 (2 s, 6 H, $(CH_3)_2Si$), 0.88 (s, 9 H, *t*-BuSi), 1.8 (m, 2 H, H5), 3.4 (s, 3 H, H10), 3.54–3.71 (2 m, 6 H, H6, H8, H9), 3.72 (s, 3 H, CO_2Me), 4.7 (AB, 2 H, H7), 5.42 (m, 1 H, H4), 5.7 (dd, 1 H, J_{2-3} = 11.7 Hz, J_{2-4} = 1.4 Hz, H2), 6.2 (dd, 1 H, J_{3-2} = 11.7 Hz, J_{3-4} = 8 Hz, H3).

Methyl-(4*R*)-4-*tert*-Butyldimethylsiloxy-6-(2-methoxyethoxymethoxy)hexanoate (11):

The propargylic ester **9** (100 mg, 0.28 mmol) in benzene (20 mL) is treated with Lindlar catalyst (100 mg) and H_2. After stirring at r.t. for 15 min, the mixture is filtered on Celite, the solvent evaporated and the crude product purified by chromatography (silica gel, EtOAc/hexane, 2:8); yield: 89 mg (0.24 mmol, 87%), oil; R_f = 0.28 (EtOAc/hexane, 2:8).

IR ($CHCl_3$): ν = 1760 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.02 (s, 6 H, $(CH_3)_2Si$), 0.86 (s, 9 H, *t*-BuSi), 1.7–1.9 (m, 4 H, H3, H5), 2.4 (t, 2 H, *J* = 7 Hz, H2), 3.35 (s, 3 H, H10), 3.6–3.8 (m, 6 H, H6, H8, H9), 3.75 (s, 3 H, CO_2Me), 3.9 (m, 1 H, H4), 4.7 (s, 2 H, H7).

(4*S*)-4-*tert*-Butyldimethylsiloxy-6-(2-methoxyethoxymethoxy)-2-hexynal (12):

Compound **8** (1 g, 3.3 mmol) in THF (15 mL) is treated at 0 °C with a 1 M solution of EtMgBr in Et_2O (5 mL, 5 mmol, 1.5 equiv). After stirring for 1 h at 0 °C, *N*-formylpiperidine (0.57 g, 5 mmol, 1.5 equiv) in THF (5 mL) is added and stirring maintained for 1 h. After hydrolysis with a 5% HCl solution (10 mL) and Et_2O extraction (2 × 20 mL), the organic layers are washed with H_2O (2 × 20 mL) and with sat. aq NaCl (20 mL). After evaporation of the solvent, the crude product is purified by chromatography (silica gel, EtOAc/hexane, 15:85); yield: 820 mg (248 mmol, 75%); R_f = 0.31; (EtOAc/hexane, 2:8); $[\alpha]_D$ −15° (*c* = 1, $CHCl_3$).

IR ($CHCl_3$): ν = 1670, 2200 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.09, 0.14 (2 s, 6 H, $(CH_3)_2Si$), 0.89 (s, 9 H, *t*-BuSi), 2.01 (dd, 2 H, *J* = 6 Hz, *J* = 12.5 Hz, H5), 3.38 (s, 3 H, H10), 3.5, 3.75 (m, 6 H, H6, H8, H9), 4.69 (s, 2 H, H7), 4.72 (t, 1 H, *J* = 6 Hz, H4).

^{13}C-NMR (50 MHz, $CDCl_3$/TMS): δ = −4.5, −3.98 (Me_2Si), 18.5 (*t*-BuSi), 26.3 (*t*-BuSi), 39 (C_5), 59.66 (C_4), 60.5 (C_{10}), 64 (C_6), 67 (C_9), 72 (C_8), 85 (C_2), 95 (C_7), 97 (C_3).

(2*Z*4*S*) 4-*tert*-Butyldimethylsiloxy-6-(2-methoxyethoxymethoxy)-2-hexenal (13):

The propargylic aldehyde **12** (105 mg, 0.32 mmol) in THF (10 mL) is treated with Lindlar catalyst (50 mg) and H_2 for 2 h at r.t. After filtration on Celite and solvent evaporation, the crude product is purified by chromatography (silica gel, Et_2O/hexane, 4:6); yield: 76 mg (0.23 mmol, 71%), oil, R_f = 0.37 (Et_2O/hexane, 4:6); $[\alpha]_D$ +20° (*c* = 0.84, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.02, 0.06 (2 s, 6 H, Me_2Si), 0.88 (s, 9 H, *t*-BuSi), 1.8 (m, 2 H, H5), 3.37 (s, 3 H, H10), 3.55–3.66 (m, 6 H, H6, H9, H8), 4.68 (s, 3 H, H7), 5.2 (m, 1 H, H4), 5.9 (A part of ABX, J_{AB} = J_{3-2} = 11.4 Hz, J_{AX} = J_{2-4} = 1.08 Hz, J_{2-1} = 7.68 Hz, H2), 6.5 (B part of ABX, 1 H, J_{AB} = J_{3-2} = 11.4 Hz, J_{BX} = J_{3-4} = 8.7 Hz, H3), 10.1 (d, 1 H, J_{1-2} = 7.68 Hz, H1).

^{13}C-NMR (50 MHz, $CDCl_3$/TMS: δ = −4.96, −4.53 (Me_2Si), 18 (*t*-BuSi), 25.62 (*t*-BuSi), 38.09 (C_5), 58.9 (C_4), 63.4 (C_6), 65.6 (C_{10}), 66.8 (C_9), 71.65 (C_8), 95.5 (C_7), 128.1 (C_3), 153.9 (C_2), 190.9 (C_1).

(2*E*,4*S*) 4-*tert*-Butyldimethylsiloxy-6-(2-methoxyethoxymethyl)-2-hexenal (14):

The propargylic aldehyde **12** (120 mg, 0.36 mmol) in benzene (15 mL) is treated with Lindlar catalyst (60 mg), quinoline (10 µL) and H_2 for 2 h at r.t. After filtration on Celite and solvent evaporation, the crude product is purified by chromatography (silica gel, Et_2O/hexane, 5:5); yield: 97 mg (0.29 mmol, 81%), oil, R_f = 0.21 (Et_2O/hexane, 5:5). *E,Z* mixtures were also observed in a few cases with the same experimental conditions.

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^{1}H-NMR (200 MHz, $CDCl_3$/TMS): $\delta = 0.02$, 0.06 (2 s, 6 H, Me_2Si), 0.9 (s, 9 H, *t*-BuSi), 3.4 (s, 3 H, H10), 3.5–3.7 (m, 6 H, H6, H8, H9), 4.55 (m, 1 H, H4), 4.7 (s, 3 H, H7), 6.25 (A part of ABX, $J_{AB} = J_{3-2} = 15$ Hz, $J_{AX} = J_{2-4} = 1.1$ Hz, $J_{2-1} = 7.5$ Hz, H2), 6.85 (B part of ABX, $J_{AB} = J_{3-2} = 15$ Hz, $J_{BX} = J_{3-4} = 4.5$ Hz, H3), 9.6 (d, 1 H, $J_{1-2} = 7.5$ Hz, H1).

Financial support from L'OREAL is gratefully acknowledged.

Received: 12 November 1990; revised: 3 May 1991

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