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Chemoenzymatic synthesis of glycosylated enantiomerically pure 4-pentene 1,2- and 1,3-diol derivatives

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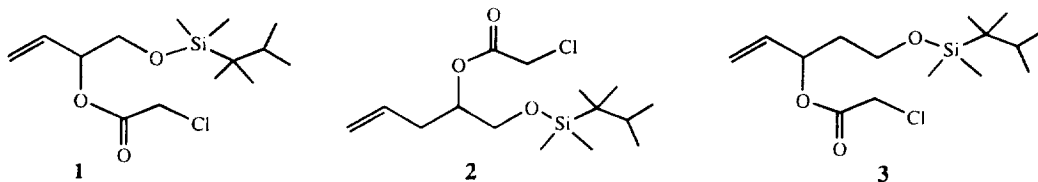
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Abstract

1-Dimethylhexylsiloxy-2-chloroacetoxy-4-pentene **2** and 1-dimethylhexylsiloxy-3-chloroacetoxy-4-pentene **3** were saponified with *Pseudomonas* lipase to give (*R*)-1-dimethylhexylsiloxy-4-pentene-2-ol (ee=99%) and (*S*)-**2** (ee=99%) and (*S*)-1-dimethylhexylsiloxy-4-pentene-3-ol (ee=99%) and (*R*)-**3** (ee=98%), respectively. All enantiomers were chemically transformed into the corresponding enantiomerically pure 2-benzoyloxy-4-pentene-1-ols **8** and 3-benzoyloxy-4-pentene-1-ols **14**, respectively. Mannosylation of (*R*)-**8** and (*S*)-**14** with 2,3,4,6-tetra-*O*-benzoyl- α -D-mannopyranosyl trichloroacetimidate afforded the corresponding mannosylated mannopyranosides. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

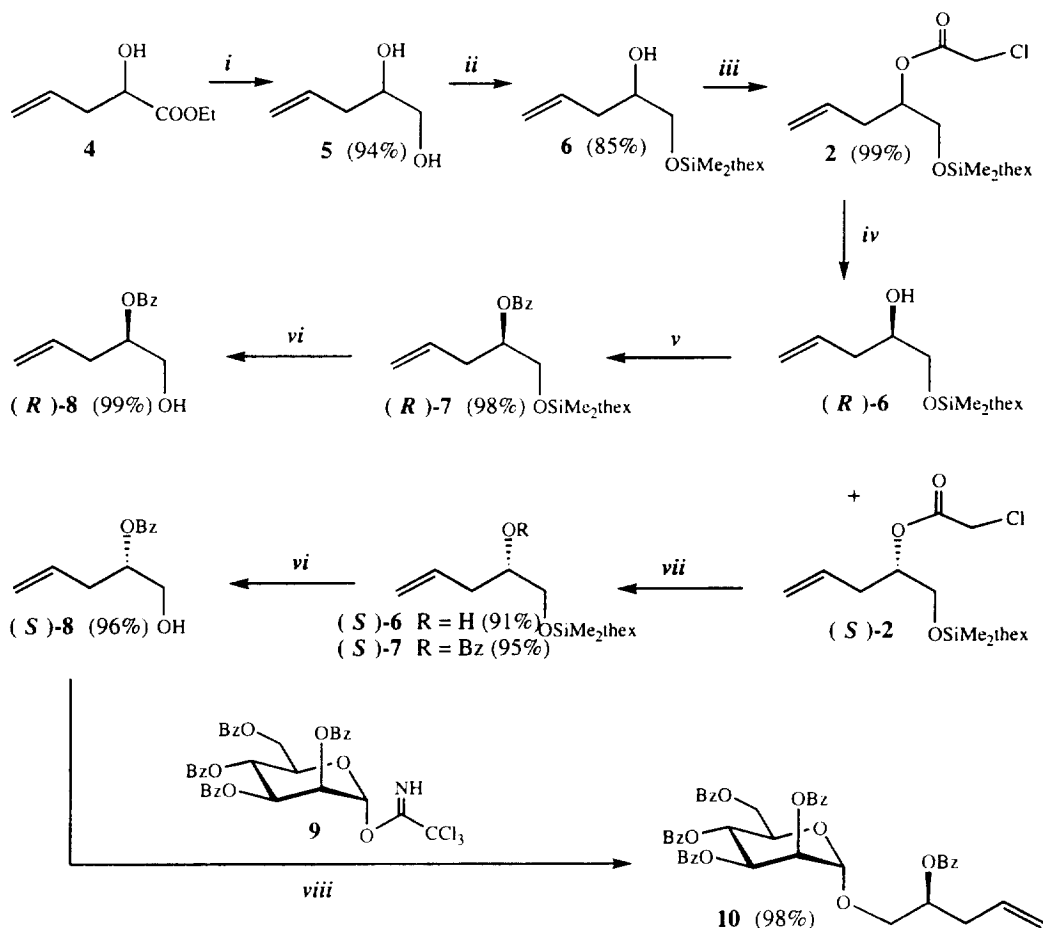
In the preceding paper,¹ partially blocked enantiomerically pure 3-butene-1,2-diol derivatives for direct glycosylation reactions were efficiently prepared from **1** using Schneiders approach² via lipase-catalyzed saponification. Since the thus-obtained 3-butene-1-hydroxy-2-yl glycopyranosides¹ are thought to be suitable precursors for aldolase-catalyzed preparation of novel disaccharides,³ the enzymatic resolution of racemic alkenediols was extended here to the 4-pentene-1,2- and 1,3-diol derivatives **2** and **3**, respectively. Furthermore, optically active 4-pentene-1,3-diols were previously used as starting materials for the synthesis of various deoxysugars^{4–6} and thus are ideal building blocks for the preparation of carbohydrate derivatives.^{7,8}



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2. Results and discussion

Racemic 4-pentene-1,2-diol derivative **2** was conveniently prepared from ethyl 2-hydroxy-4-pentenoate **4** which, in term, was easily accessible in 56% yield via Sn–Al promoted⁹ allylation of ethyl glyoxylate. Next, reduction of **4** with NaBH₄ in dioxane afforded diol **5** (94%) which was regioselectively silylated at the primary alcohol to give **6** (85%; Scheme 1). Alternative preparations^{10–12} of racemic **5** and **6** were less efficient. Finally, chloroacetylation¹ of compound **6** with chloroacetic anhydride furnished racemic **2** in 99% yield. Since *Pseudomonas* lipase-catalyzed saponification of **1** was previously found to be more efficient than saponification with other enzymes,¹ *Pseudomonas* lipase was also used here for kinetic resolutions of **2** and **3**. Thus, enzyme-catalyzed saponification of **2** was accomplished on a 13 g scale exactly as previously described for compound **1**.^{1,16} Alcohol (*R*)-**6** (45%, ee=99%) and unreacted (*S*)-**2** (45%, ee=99%) were obtained. Although (*R*)-**6** can be directly used for glycosylation reactions at its secondary hydroxyl, further manipulations of the blocking groups of the latter were performed as follows.



Scheme 1. (i) NaBH₄, dioxane–EtOH, 25°C. (ii) Cl–SiMe₂thex, imidazole, CH₂Cl₂, 0°C. (iii) Chloroacetic anhydride, pyridine, 0°C. (iv) *Pseudomonas* lipase, phosphate buffer (pH 7), 45% (*S*)-**2** (ee=99%), 45% (*R*)-**6** (ee=99%). (v) BzCl, pyridine, rt. (vi) 3% HF in MeCN, rt. (vii) (1) ethylenediamine, Et₃N, MeOH, pyridine; (2) (v). (viii) Cat. TMSOTf, MeCN, –30°C

Benzoylation of (*R*)-**6** first gave (*R*)-**7** (98%), protodesilylation of which with HF in MeCN afforded

enantiomerically pure (*R*)-**8** (99%). Similarly, (*S*)-**2** was chemically dechloroacetylated, to first give (*S*)-**6**. Here, deacylation was performed most efficiently with ethylene diamine¹³ since removal of the chloroacetyl group by *Candida* lipase¹ which was found to be optimal for compound **1** gave lower yields with **2**. Next, (*S*)-**6** was first benzoylated and the resulting (*S*)-**7** was once again desilylated with HF to afford (*S*)-**8**. Thus, both enantiomers of regioselectively blocked 4-pentene-1,2-diol derivatives **6** and **8** were easily available on a multigram scale.

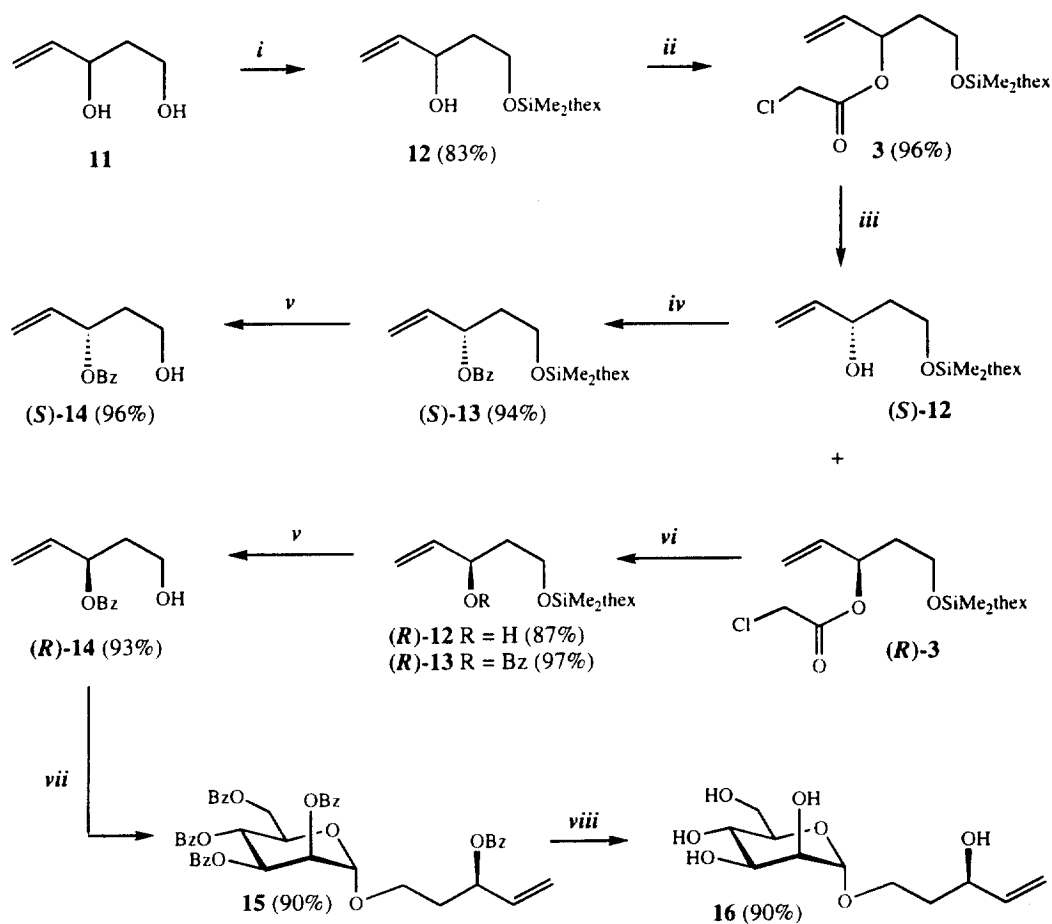
Direct glycosylation was further exemplified for compound (*S*)-**8**. Mannosylation proceeded smoothly with mannosyl imidate¹⁴ **9** to give crystalline **10** in 98% yield. The crystal structure¹⁵ of the latter showed unambiguously the (*S*)-configuration at C-2 of the aglycon.

Enzymatic resolution of racemic 4-pentene-1,3-diol derivative **3** was performed according to that of compound **2**. First, known ethyl 3-hydroxy-4-pentenoate¹⁶ was converted into diol **11**, regioselective silylation of which furnished **12** (83%; Scheme 2). Next, chloroacetylation of the remaining hydroxyl gave racemic **3**; *Pseudomonas* lipase-catalyzed saponification of the latter then afforded (*S*)-**12** (44%, ee=99%) and (*R*)-**3** (49%, ee=98%), respectively on a 21 g scale. Similar to the aforementioned 4-pentene-1,2-diol derivatives, (*S*)-**12** was converted via (*S*)-**13** into (*S*)-**14** and (*R*)-**3** was converted via (*R*)-**12** and (*R*)-**13** into (*R*)-**14**, respectively. For the dechloroacetylation of (*R*)-**3**, *Candida cylindracea* lipase-catalyzed deacylation was superior to chemical procedures. Mannosylation of the (*R*)-**14** with mannosyl imidate **9** then afforded crystalline glycoside **15** (90%), the crystal structure of which¹⁵ proved the (*R*)-configuration of the aglycon of compound **15**. Finally, Zemplén deacylation of **15** furnished the free 3-hydroxy-4-pentene-1-yl mannopyranoside **16** (90%) which is a suitable precursor for aldolase-catalyzed preparation of novel saccharides as previously described for similar derivatives.^{3,17}

3. Experimental

3.1. General

Optical rotations were performed with a Perkin–Elmer polarimeter 241 LC. Melting points were determined with a Büchi SMP-20 apparatus. The NMR data were obtained from spectra measured in CDCl₃ solutions for blocked compounds (with Me₄Si as an internal standard) and D₂O for deblocked compounds (with MeOH as an internal standard) at 25°C with a Bruker AC 250 F, a Bruker CXP 300 and a Bruker ARX 500 spectrometer. ¹H NMR signals assignments were made by first-order analysis of the spectra. ¹³C NMR assignments were made by mutual comparison of spectra, by DEPT spectra, by comparison with spectra of related compounds and ¹H–¹³C correlated spectra. GC for determination of the enantiomeric excess: (a) Carlo Erba HRGC 5300 Mega Series with FID, Carlo Mega Series integrator, 0.4–0.6 bar hydrogen, column 20 m, Bondex-un-Et-105 (β-cyclodextrin); (b) Fisons HRGC 8560 with FID, Mega Series 2 integrator, 0.4–0.6 bar hydrogen, column 20 m, Bondex-un-a-5,6-Et-57 (α-cyclodextrin). Mass spectrometry was performed with a Finnigan mass spectrometer MAT 95 in FAB mode. GC–MS was performed with a Hewlett–Packard 5890 GC, 0.4 bar hydrogen, column 30 m, HP-5 MS and Finnigan MAT 95 mass spectrometer, CI, methane 0.5 torr. Thin-layer chromatography (TLC) was performed on precoated plastic sheets, Polygram SIL UV₂₅₄, 40×80 mm (Macherey–Nagel) using appropriately adjusted mixtures of CCl₄–acetone or petroleum ether–ethyl acetate for development. Detection was effected with UV light, where applicable, iodine and by charring with 5% H₂SO₄ in EtOH. Preparative column chromatography was performed with glass columns of different sizes packed with silica gel S, grain size 0.032–0.063 mm (Riedel de Haen).



Scheme 2. (i) Cl–SiMe₂thex, imidazole, CH₂Cl₂, 0°C. (ii) Chloroacetic anhydride, pyridine, 0°C. (iii) *Pseudomonas* lipase, phosphate buffer pH 7, 49% (*R*)-**3** (ee=98%), 44% (*S*)-**12** (ee=99%). (iv) BzCl, pyridine, rt. (v) 3% HF in MeCN, rt. (vi) (1) CC lipase, phosphate buffer (pH 7.0); (2) (v). (vii) **9**, cat. TMSOTf, MeCN, –30°C. (viii) cat. NaOMe, MeOH, rt

3.2. Ethyl 2-hydroxy-4-pentenoate **4**

A 50% solution of ethyl glyoxylate in toluene (50 g, 0.15 mol) and allyl bromide (16.9 ml, 0.2 mol) was dissolved in petroleum ether (50 ml). Water (25 ml), Sn dust (9.97 g, 0.084 mol), Al powder (4.72 g, 0.175 mol) and a catalytic amount of aq. HBr were added to the solution and the reaction mixture was stirred for 1 h at room temperature and filtered through a layer of Celite. The solid residue was extracted twice with petroleum ether and the combined organic layers were washed with 2 M aq. HCl and NaHCO₃ solution dried (Na₂SO₄) and concentrated. The residue was purified by Kugelrohr distillation, to give **4** (11.78 g, 56%); bp: 100°C/15 mmHg (Kugelrohr oven temperature); ¹H NMR (500 MHz): δ=1.30 (t, 3H, OCH₂CH₃, *J*=7.2 Hz), 2.42–2.47 (m, 1H, 3-H_b), 2.56–2.61 (m, 1H, 3-H_a), 2.60 (d, 1H, OH, *J*=4.6 Hz), 4.20–4.30 (m, 3H, 2-H, OCH₂CH₃), 5.13–5.18 (m, 2H, 5-H_{cis}, 5-H_{trans}), 5.81 (ddt, 1H, 4-H, *J*_{3a,4}=*J*_{3b,4}=7.0 Hz, *J*_{4,5cis}=10.1 Hz, *J*_{4,5trans}=17.1 Hz); ¹³C NMR (125 MHz): δ=14.2 (OCH₂CH₃), 38.7 (C-3), 61.7 (OCH₂CH₃), 70.0 (C-2), 118.7 (C-5), 132.5 (C-4), 174.5 (C-1). GC–MS, CI, m/z: 144 (M)⁺, 126 (M–H₂O)⁺, 99 (M–OCH₂CH₃)⁺, 71 (M–COOCH₂CH₃)⁺.

3.3. 4-Pentene-1,2-diol **5**

A solution of **4** (1.50 g, 10.40 mmol) in dioxane:EtOH (10:1, 55 ml) was treated with NaBH₄ (474 mg, 12.50 mmol) for 22 h at room temperature. After removal of the solvent, the residue was coevaporated twice with MeOH and redissolved in MeOH. Ion-exchange resin (Dowex 50 WX8, H⁺) was added until the solution became neutral. Filtration of the mixture, concentration of the filtrate and chromatography (CHCl₃:MeOH=3:1) of the residue afforded **5** (997 mg, 94%). ¹H NMR (500 MHz): δ=2.21–2.29 (m, 2H, 3-H_a, 3-H_b), 2.95 (s, 2H, 2×OH), 3.47 (dd, 1H, 1-H_b, *J*_{1b,2}=7.4 Hz, *J*_{1a,1b}=11.3 Hz), 3.66 (dd, 1H, 1-H_a, *J*_{1a,2}=2.9 Hz), 3.75–3.79 (m, 1H, 2-H), 5.12–5.16 (m, 2H, 5-H_{cis}, 5-H_{trans}), 5.82 (ddt, 1H, 4-H, *J*_{3,4}=7.1 Hz, *J*_{4,5cis}=10.1 Hz, *J*_{4,5trans}=17.1 Hz); ¹³C NMR (125 MHz): δ=37.8 (C-3), 66.2 (C-1), 71.3 (C-2), 118.1 (C-5), 134.1 (C-3); GC-MS (CI) *m/z*: 102 (M)⁺, 85 (M-OH)⁺, 67 (C₅H₇)⁺.

3.4. 1-Dimethylhexylsilyloxy-4-pentene-2-ol **6**

Hexyldimethylsilylchloride (9.3 ml, 47.4 mmol) was added at 0°C to a solution of **5** (4.60 g, 45.04 mmol) and imidazole (7.66 g, 112.5 mmol) in CH₂Cl₂ (80 ml). After stirring for 1 h at room temperature, the mixture was diluted with CH₂Cl₂, washed with aq. NaHCO₃ solution, dried (Na₂SO₄) and concentrated. Chromatography of the residue (petroleum ether:ethyl acetate=20:1) afforded **6** (9.06 g, 82%); ¹H NMR (500 MHz): δ=0.11 (s, 6H, Si(CH₃)₂), 0.86 (s, 6H, Si(CH₃)₂C(CH₃)₂), 0.89 (d, 6H, Si(CH₃)₂C(CH₃)₂CH(CH₃)₂, *J*=6.9 Hz), 1.63 (quint, 1H, Si(CH₃)₂C(CH₃)₂CH(CH₃)₂), 2.24 (t, 2H, 3-H_a, 3-H_b, *J*=6.8 Hz), 2.41 (d, 1H, OH, *J*=3.8 Hz), 3.44 (dd, 1H, 1-H_b, *J*_{1b,2}=7.0 Hz, *J*_{1a,1b}=10.0 Hz), 3.61 (dd, 1H, 1-H_a, *J*_{1a,2}=3.7 Hz), 3.68–3.73 (m, 1H, 2-H), 5.09 (d, 1H, 5-H_{cis}, *J*=10.8 Hz), 5.12 (d, 1H, 5-H_{trans}), 5.73 (ddt, 1H, 4-H, *J*_{4,5cis}=17.1 Hz); ¹³C NMR (125 MHz): δ=-3.5, -3.4 (Si(CH₃)₂), 18.5 (Si(CH₃)₂C(CH₃)₂CH(CH₃)₂), 20.3 (Si(CH₃)₂C(CH₃)₂), 25.1 (Si(CH₃)₂C(CH₃)₂), 34.2 (Si(CH₃)₂C(CH₃)₂C), 37.6 (C-2), 66.3 (C-1), 71.1 (C-2), 117.4 (C-5), 134.5 (C-4); anal. calcd for C₁₃H₂₈O₂Si (244.5): C, 63.88; H, 11.54; found: C, 63.87; H, 11.58.

3.5. 2-Chloroacetoxy-1-dimethylhexylsilyloxy-4-pentene **2**

A solution of **6** (10.54 g, 43.12 mmol) in pyridine:CH₂Cl₂ (1:13, 75 ml) was treated with chloroacetic anhydride (7.74 g, 45.27 mmol) at 0°C. After 90 min water was added and the mixture was diluted with CH₂Cl₂, washed with water, aq. 2 M HCl and NaHCO₃ solution, dried (Na₂SO₄) and concentrated. The residue was chromatographed (petroleum ether:ethyl acetate=20:1) to give **2** (13.70 g, 99%); ¹H NMR (500 MHz): δ=0.08 (s, 6H, Si(CH₃)₂), 0.83 (s, 6H, Si(CH₃)₂C(CH₃)₂), 0.87 (d, 6H, Si(CH₃)₂C(CH₃)₂CH(CH₃)₂, *J*=6.9 Hz), 1.61 (sept, 1H, Si(CH₃)₂C(CH₃)₂CH(CH₃)₂), 2.28–2.50 (m, 2H, 3-H_a, 3-H_b), 3.66 (m, 2H, 1-H_a, 1-H_b), 4.04 (s, 2H, CH₂Cl), 4.96–5.15 (m, 3H, 2-H, 5-H_{cis}, 5-H_{trans}), 5.75 (ddt, 1H, 4-H, *J*_{3a,4}=*J*_{3b,4}=7.1 Hz, *J*_{4,5cis}=10.1 Hz, *J*_{4,5trans}=17.1 Hz); ¹³C NMR (125 MHz): δ=-3.6 (Si(CH₃)₂), 18.5 (Si(CH₃)₂C(CH₃)₂CH(CH₃)₂), 20.2 (Si(CH₃)₂C(CH₃)₂), 25.1 (Si(CH₃)₂C), 34.2 (Si(CH₃)₂C(CH₃)₂CH(CH₃)₂), 34.9 (C-3), 41.0 (CH₂Cl), 63.1 (C-1), 75.8 (C-2), 118.3 (C-5), 132.9 (C-4), 166.9 (CO); anal. calcd for C₁₅H₂₉ClO₃Si (320.9): C, 56.14; H, 9.11; Cl, 11.05; found: C, 55.99; H, 9.18; Cl, 11.03.

3.6. Kinetic resolution of compound **2**

Racemic **2** (13.00 g, 40.51 mmol) was added to a suspension of *Pseudomonas* lipase (Amano PS) (400 mg) in 0.1 M aq. phosphate buffer (pH 7.0; 100 ml). The mixture was vigorously stirred, with the

pH maintained at 7.0 by addition of aq. 1.0 M NaOH. After 18 h, the reaction had consumed 19.798 ml of base. NaCl (40 g) was added and the solution was extracted several times with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄) and concentrated. Chromatography (petroleum ether:ethyl acetate=25:1) of the residue afforded first (*S*)-(2) (5.82 g, 45%, ee=99%), [α]_D²⁰=−2.3 (*c*=1.7, CHCl₃).

Eluted next was (*R*)-(6) (4.45 g, 45%, ee=99%); [α]_D²⁰=−1.7 (*c*=2.1, CHCl₃).

3.7. (*S*)-1-Thexydimethylsilyloxy-4-pentene-2-ol (*S*)-(6)

A solution of (*S*)-2 (5.65 g, 17.61 mmol) in pyridine:methanol (1.5:1, 100 ml) was treated with ethylenediamine (2.4 ml, 35.74 mmol) and triethylamine (12 ml) for 15 h at room temperature. The mixture was diluted with CH₂Cl₂, washed with water, aq. 2 M HCl and NaHCO₃ solution, dried (Na₂SO₄) and concentrated. Chromatography (petroleum ether:ethyl acetate=20:1) of the residue afforded (*S*)-6 (3.92 g, 91%); [α]_D²⁰=+0.9 (*c*=3.0, CHCl₃).

3.8. (*R*)-2-Benzoyloxy-1-dimethylthexylsilyloxy-4-pentene (*R*)-(7)

Benzoyl chloride (2.4 ml, 20.69 mmol) was added to a solution of (*R*)-6 (4.20 g, 17.18 mmol) in pyridine (40 ml) and the mixture was stirred for 3 h at room temperature. Water (2 ml) was added and the mixture was extracted with CH₂Cl₂. The combined organic layers were washed with water, aq. 2 M HCl and NaHCO₃ solution. After drying (Na₂SO₄) the solvent was removed and chromatography (petroleum ether:ethyl acetate=20:1) of the residue afforded (*R*)-7 (5.87 g, 98%); [α]_D²⁰=+9.0 (*c*=1.7, CHCl₃); ¹H NMR (500 MHz): δ =0.07 (s, 6H, Si(CH₃)₂), 0.83 (s, 6H, Si(CH₃)₂CH), 0.85, 0.86 (2d, 6H, Si(CH₃)₂C(CH₃)₂CH(CH₃)₂, *J*=6.8 Hz), 1.60 (quint, 1H, Si(CH₃)₂C(CH₃)₂CH), 2.45–2.51 (m, 1H, 3-H_b), 2.53–2.59 (m, 1H, 3-H_a), 3.76–3.77 (m, 2H, 1-H_a, 1-H_b), 5.07 (dd, 1H, 5-H_{cis}, *J*_{4,5cis}=10.1 Hz, *J*_{5cis,5trans}=1.2 Hz), 5.13 (dd, 1H, 5-H_{trans}, *J*_{4,5trans}=17.1 Hz), 5.16–5.20 (m, 1H, 2-H), 5.84 (ddt, 1H, 4-H, *J*_{3a,4}=*J*_{3b,4}=7.1 Hz, *J*_{4,5cis}=10.0 Hz), 7.42–8.05 (m, 5H, C₆H₅); ¹³C NMR (125 MHz): δ =−3.6 (Si(CH₃)₂), 18.4, 18.5 (Si(CH₃)₂C(CH₃)₂CH(CH₃)₂), 20.2, 20.3 (Si(CH₃)₂C(CH₃)₂), 25.1 (Si(CH₃)₂C), 34.2 (Si(CH₃)₂C(CH₃)₂CH), 35.1 (C-3), 63.3 (C-1), 74.2 (C-2), 117.9 (C-5), 133.5 (C-4), 166.1 (CO); anal. calcd for C₂₀H₃₂O₃Si (348.6): C, 68.92; H, 9.25; found: C, 68.67; H, 9.36.

3.9. (*S*)-2-Benzoyloxy-1-dimethylthexylsilyloxy-4-pentene (*S*)-(7)

Treatment of (*S*)-6 (3.70 g, 15.14 mmol) as described for compound (*R*)-6 afforded (*S*)-7 (5.21 g, 99%); [α]_D²⁰=−9.1 (*c*=2.4, CHCl₃).

3.10. (*R*)-2-Benzoyloxy-4-pentene-1-ol (*R*)-(8)

40% aq. HF (4 ml) was added to a solution of (*R*)-7 (5.60 g, 16.07 mmol) in MeCN (80 ml). After stirring at room temperature for 1.5 h, the reaction mixture was diluted with CH₂Cl₂, washed with water and aq. NaHCO₃ solution, dried (Na₂SO₄) and concentrated. Chromatography (CCl₄:acetone=8:1) of the residue afforded (*R*)-8 (3.29 g, 99%); [α]_D²⁰=+8.7 (*c*=2.0, CHCl₃); ¹H NMR (500 MHz): δ =2.27 (t, 1H, OH, *J*=6.1 Hz), 2.52 (t, 2H, 3-H_a, 3-H_b, *J*=6.7 Hz), 3.79 (ddt, 1-H_b, *J*_{1b,2}=6.0 Hz, *J*_{1a,1b}=12.1 Hz), 3.84 (ddd, 1H, 1-H_a, *J*_{1a,2}=3.6 Hz), 5.10 (d, 1H, 5-H_{cis}, *J*_{4,5cis}=10.1 Hz), 5.15–5.19 (m, 1H, 5-H_{trans}), 5.19–5.22 (m, 1H, 2-H), 5.84 (ddt, 1H, 4-H), 7.42–8.05 (m, 5H, C₆H₅); ¹³C NMR (125 MHz): δ =35.3 (C-3), 64.3 (C-1), 75.2 (C-2), 118.4 (C-5), 133.2 (C-4), 166.7 (CO); anal. calcd for C₁₂H₁₄O₃ (206.2): C, 69.89; H, 6.84; found: C, 69.71; H, 6.88.

3.11. (*S*)-2-Benzoyloxy-4-pentene-1-ol (*S*)-(8)

Treatment of (*S*)-7 (900 mg, 2.58 mmol) as described for compound (*R*)-7 afforded (*S*)-8 (516 mg, 97%); $[\alpha]_D^{20} = -9.7$ ($c=2.1$, CHCl_3).

3.12. 2,3,4,6-Tetra-*O*-benzoyl- α -D-mannopyranosyl trichloroacetimidate 9

DBU (500 μl , 3.40 mmol) was added to a solution of trichloroacetonitrile (6.7 ml, 67 mmol) and 2,3,4,6-tetra-*O*-benzoyl-D-mannopyranose¹⁴ (20.0 g, 33.5 mmol) in CH_2Cl_2 (150 ml) and the mixture was stirred for 2 h at 0°C. The mixture was concentrated and the residue was chromatographed (petroleum ether:ethyl acetate=2:1 with 1% Et_3N) to afford 9 (18.62 g, 75%); $[\alpha]_D^{20} = -37$ ($c=1.5$, CHCl_3); $^1\text{H NMR}$ (300 MHz): $\delta=4.62$ (dd, 1H, 6- H_b , $J_{5,6b}=4.1$ Hz, $J_{6a,6b}=12.2$ Hz), 4.61–4.67 (m, 1H, 5-H), 4.74 (dd, 1H, 6- H_a ; $J_{5,6a}=2.4$ Hz), 5.95 (dd, 1H, 2-H, $J_{1,2}=1.9$ Hz, $J_{2,3}=3.3$ Hz), 5.99 (dd, 1H, 3-H, $J_{3,4}=9.9$ Hz), 6.24 (1H, 4-H, $J_{4,5}=10.0$ Hz), 6.58 (d, 1H, 1-H), 7.24–8.11 (m, 20H, C_6H_5), 8.87 (s, 1H, CNHCCl_3); $^{13}\text{C NMR}$ (75.5 MHz): $\delta=62.4$ (C-6), 66.1 (C-4), 68.9 (C-3), 69.8 (C-2), 71.6 (C-5), 90.6 (CNHCCl_3), 94.7 (C-1), 159.9 (CNHCCl_3), 165.1, 165.4, 165.5, 166.0 (CO); anal. calcd for $\text{C}_{36}\text{H}_{28}\text{NO}_{10}\text{Cl}_3$ (741.0): C, 58.43; H, 3.81; N, 1.89; Cl, 14.35; found: C, 58.49; H, 3.95; N, 1.64; Cl, 14.54.

3.13. (*S*)-2-Benzoyloxy-4-pentene-1-yl 2,3,4,6-tetra-*O*-benzoyl- α -D-mannopyranoside 10

A solution of TMSOTf (91 μl , 0.5 mmol) in CH_2Cl_2 (10 ml) was added at -30°C to a solution of (*S*)-8 (969 mg, 4.70 mmol) and 9 (3.60 g, 4.86 mmol) in CH_2Cl_2 (50 ml). After stirring for 50 min, the mixture was neutralized with pyridine, filtered, washed with aq. 2 M HCl and NaHCO_3 solution, dried (Na_2SO_4) and concentrated. Chromatography (CCl_4 :acetone=15:1) of the residue afforded 10 (3.63 g, 98%), which was crystallized from petroleum ether–acetone; mp: 114–116°C; $[\alpha]_D^{20} = -27$ ($c=1.2$, CHCl_3); $^1\text{H NMR}$ (500 MHz): $\delta=2.59$ –2.66 (t, 2H, 3¹- H_a , 3¹- H_b), 3.82 (dd, 1H, 1¹- H_b , $J_{11b,21}=4.0$ Hz, $J_{11a,11b}=10.6$ Hz), 4.07 (dd, 1H, 1¹- H_a , $J_{11a,21}=6.1$ Hz), 4.40–4.46 (m, 2H, 5²-H, 6²- H_b), 4.66–4.69 (m, 1H, 6²- H_a), 5.15 (dd, 1H, 5¹- H_{cis} , $J_{41,51\text{cis}}=10.3$ Hz, $J_{51\text{cis},51\text{trans}}=1.3$ Hz), 5.17 (d, 1H, 1²-H, $J_{12,22}=1.5$ Hz), 5.23 (dd, 1H, 5¹- H_{trans} , $J_{41,51\text{trans}}=17.1$ Hz), 5.46–5.50 (m, 1H, 2¹-H), 5.76 (dd, 1H, 2²-H, $J_{22,32}=3.1$ Hz), 5.85 (dd, 1H, 3²-H, $J_{32,42}=10.1$ Hz), 5.87–5.93 (m, 1H, 4¹-H), 6.08 (t, 1H, 4²-H); $^{13}\text{C NMR}$ (125 MHz): $\delta=35.6$ (C-3¹), 62.7 (C-6²), 66.7 (C-4²), 68.4 (C-1¹), 69.0 (C-5²), 70.0 (C-3²), 70.2 (C-2²), 71.9 (C-2¹), 97.5 (C-1²), 118.8 (C-5¹), 133.5 (C-4¹); anal. calcd for $\text{C}_{46}\text{H}_{40}\text{O}_{12}$ (784.8): C, 70.40; H, 5.14; found: C, 70.37; H, 5.17.

3.14. 1-Dimethylthexylsilyloxy-4-pentene-3-ol 12

Thexyldimethylsilyl chloride (17.1 ml, 87.14 mmol) was added at 0°C to a solution of 11⁴ (8.70 g, 85.18 mmol) and imidazole (14.50 g, 213.0 mmol) in CH_2Cl_2 (100 ml). The mixture was stirred for 1 h, diluted with CH_2Cl_2 , washed with aq. NaHCO_3 solution, dried (Na_2SO_4) and concentrated. Chromatography (petroleum ether:ethyl acetate=15:1) of the residue afforded 12 (17.27 g, 83%); $^1\text{H NMR}$ (250 MHz): $\delta=0.12$ (s, 6H, $\text{Si}(\text{CH}_3)_2$), 0.85 (s, 6H, $\text{Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_2$), 0.89 (d, 6H, $\text{Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_2\text{CH}(\text{CH}_3)_2$, $J=6.9$ Hz), 1.54–1.85 (m, 3H, $\text{Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_2\text{CH}$), 2- H_a , 2- H_b), 3.33 (d, 1H, OH, $J=3.5$ Hz), 3.78 (ddd, 1H, 1- H_b , $J_{1b,2a}=4.6$ Hz, $J_{1b,2b}=7.2$ Hz, $J_{1a,1b}=10.2$ Hz), 3.88 (ddd, 1H, 1- H_a , $J_{1a,2a}=4.6$ Hz), 4.31–4.40 (m, 1H, 3-H), 5.11 (dt, 1H, 5- H_{cis} , $J_{4,5\text{cis}}=10.4$ Hz, $J_{3,5\text{cis}}=J_{5\text{cis},5\text{trans}}=1.6$ Hz), 5.24 (dt, 1H, 5- H_{trans} , $J_{4,5\text{trans}}=17.2$ Hz), 5.88 (ddd, 1H, 4-H, $J_{3,4}=5.4$ Hz); $^{13}\text{C NMR}$ (62.9 MHz):

$\delta = -3.6$ (Si(CH₃)₂), 18.5 (Si(CH₃)₂C(CH₃)₂CH(CH₃)₂), 20.2 (Si(CH₃)₂C(CH₃)₂), 25.0 (Si(CH₃)₂C), 34.1 (Si(CH₃)₂C(CH₃)₂CH), 38.3 (C-2), 61.6 (C-1), 72.5 (C-3), 114.1 (C-5), 140.7 (C-4); anal. calcd for C₁₃H₂₈O₂Si (244.5): C, 63.88; H, 11.54; found: C, 63.64; H, 11.66.

3.15. 3-Chloroacetoxy-1-dimethylhexylsilyloxy-4-pentene 3

Chloroacetic anhydride (13.08 g, 76.5 mmol) was added to a solution of **12** (16.97 g, 69.4 mmol) in pyridine (8.1 ml) and CH₂Cl₂ (100 ml) and the mixture was stirred for 2 h at 0°C. The mixture was diluted with CH₂Cl₂, washed with aq. 2 M HCl and NaHCO₃ solution, dried (Na₂SO₄) and concentrated. Chromatography (petroleum ether:ethyl acetate=15:1) of the residue afforded **3** (21.39 g, 96%); ¹H NMR (250 MHz): $\delta = 0.07$ (s, 6H, Si(CH₃)₂), 0.84 (s, 6H, Si(CH₃)₂C(CH₃)₂), 0.88 (d, 6H, Si(CH₃)₂C(CH₃)₂CH(CH₃)₂, $J = 6.9$ Hz), 1.61 (quint, 1H, Si(CH₃)₂C(CH₃)₂CH), 1.75–1.99 (m, 2H, 2-H_a, 2-H_b), 3.61–3.66 (m, 2H, 1-H_a, 1-H_b), 4.05 (s, 2H, CH₂Cl), 5.22 (dt, 1H, 5-H_{cis}, $J_{4,5cis} = 10.3$ Hz, $J_{3,5cis} = J_{5cis,5trans} = 1.1$ Hz), 5.30 (dt, 1H, 5-H_{trans} = 17.2 Hz, $J_{3,5trans} = 1.2$ Hz), 5.47 (q, 1H, 3-H, $J_{2a,3} = J_{2b,3} = J_{3,4} = 6.7$ Hz), 5.81 (ddd, 1H, 4-H); ¹³C NMR (62.9 MHz): $\delta = -3.5$ (Si(CH₃)₂), 18.6 (Si(CH₃)₂C(CH₃)₂CH(CH₃)₂), 20.4 (Si(CH₃)₂C(CH₃)₂), 25.1 (Si(CH₃)₂C), 34.2 (Si(CH₃)₂C(CH₃)₂CH), 37.1 (C-2), 41.6 (CH₂Cl), 58.5 (C-1), 74.3 (C-3), 117.7 (C-5), 135.5 (C-4), 166.4 (CO); anal. calcd for C₁₅H₂₉ClO₃Si (320.9): C, 56.14; H, 9.11; Cl, 11.05; found: C, 56.18; H, 9.20; Cl, 10.85.

3.16. Kinetic resolution of compound 3

A suspension of racemic **3** (21.00 g, 65.43 mmol) in aq. 0.1 M phosphate buffer (pH 7.0; 120 ml) was treated with *Pseudomonas* lipase (400 mg) as described for compound **2**. The reaction was stopped after 37.821 ml of aq. 1 M NaOH solution had been consumed in 13 h and 40 min. Chromatography (petroleum ether:ethyl acetate=20:1) afforded first (*R*)-**3** (10.33 g, 49%, ee=98%); $[\alpha]_D^{20} = +19.6$ ($c = 3.0$, CHCl₃).

Eluted next was (*S*)-**12** (7.05 g, 44%, ee=99%); $[\alpha]_D^{20} = +8.6$ ($c = 2.45$, CHCl₃).

3.17. (*R*)-1-Dimethylhexylsilyloxy-4-pentene-3-ol (*R*)-(**12**)

Compound (*R*)-**3** (10 g, 31.16 mmol) was added to a stirred suspension of *Candida cylindracea* lipase (400 mg) in aq. 0.1 M phosphate buffer (pH 7.0; 120 ml) and the pH was maintained by addition of aq. NaOH solution. After 116 h, the reaction mixture had consumed 30.944 ml of 1 M NaOH. NaCl (50 g) was added and the mixture was extracted several times with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄) and the solvent was removed. Chromatography of the residue afforded (*R*)-**12** (6.66 g, 87%); $[\alpha]_D^{20} = -8.6$ ($c = 2.8$, CHCl₃).

3.18. (*R*)-3-Benzoyloxy-1-dimethylhexylsilyloxy-4-pentene (*R*)-(**13**)

Compound (*R*)-**12** (6.50 g, 26.59 mmol) and benzoyl chloride (3.4 ml, 29.31 mmol) were dissolved in pyridine (40 ml) and stirred for 3 h at room temperature. After the addition of water (2 ml), the solvent was removed followed by coevaporation with toluene. The residue was redissolved in CH₂Cl₂, washed with water, aq. 2 M HCl and NaHCO₃ solution, dried (Na₂SO₄) and concentrated. Chromatography of the residue (petroleum ether:ethyl acetate=20:1) afforded (*R*)-**13** (9.00 g, 97%); $[\alpha]_D^{20} = -1.2$ ($c = 1.2$, CHCl₃); ¹H NMR (250 MHz): $\delta = 0.05$, 0.06 (s, 6H, Si(CH₃)₂), 0.83 (s, 6H, Si(CH₃)₂C(CH₃)₂), 0.87 (d,

6H, Si(CH₃)₂C(CH₃)₂CH(CH₃)₂, $J=6.9$ Hz), 1.60 (sept, 1H, Si(CH₃)₂C(CH₃)₂CH), 1.86–2.10 (m, 2H, 2-H_a, 2-H_b), 3.69–3.74 (m, 2H, 1-H_a, 1-H_b), 5.20 (dt, 1H, 5-H_{cis}, $J_{4,5cis}=10.5$ Hz, $J_{3,5cis}=J_{5cis,5trans}=1.1$ Hz), 5.33 (dt, 1H, 5-H_{trans}, $J_{4,5trans}=17.3$ Hz, $J_{3,5trans}=1.2$ Hz), 5.59–5.67 (m, 1H, 3-H), 5.92 (ddd, 1H, 4-H, $J_{3,4}=6.3$ Hz), 7.41–8.08 (m, 5H, C₆H₅); ¹³C NMR (62.9 MHz): $\delta=-3.5$ (Si(CH₃)₂), 18.5 (Si(CH₃)₂C(CH₃)₂CH(CH₃)₂), 20.3 (Si(CH₃)₂C(CH₃)₂), 25.1 (Si(CH₃)₂C), 34.2 (Si(CH₃)₂C(CH₃)₂CH), 37.4 (C-2), 58.8 (C-1), 72.1 (C-3), 116.6 (C-5), 136.5 (C-4), 165.7 (CO); anal. calcd for C₂₀H₃₂O₃Si (348.6): C, 68.92; H, 9.25; found: C, 69.14 H, 9.22.

3.19. (S)-3-Benzoyloxy-1-dimethylthexylsiloxo-4-pentene (S)-(13)

Treatment of (S)-12 (6.60 g, 27.00 mmol) as described for compound (R)-13 afforded (S)-13 (8.83 g, 94%); $[\alpha]_D^{20}=+0.9$ ($c=2.4$, CHCl₃).

3.20. (R)-3-Benzoyloxy-4-pentene-1-ol (R)-(14)

Treatment of (R)-13 (8.85 g, 25.39 mmol) with aq. 40% HF (4.5 ml) in MeCN (150 ml) as described for compound (R)-8 afforded (R)-14 (4.89 g, 93%); $[\alpha]_D^{20}=-27$ ($c=1.8$, CHCl₃); ¹H NMR (250 MHz): $\delta=1.88-2.10$ (m, 2H, 2-H_a, 2-H_b), 2.17–2.22 (m, 1H, OH), 3.63–3.78 (m, 2H, 1-H_a, 1-H_b), 5.23 (dt, 1H, 5-H_{cis}, $J_{4,5cis}=10.5$ Hz, $J_{3,5cis}=J_{5cis,5trans}=1.0$ Hz), 5.38 (dt, 1H, 5-H_{trans}, $J_{4,5trans}=17.2$ Hz, $J_{3,5cis}=J_{5cis,5trans}=1.1$ Hz), 5.67–5.75 (m, 1H, 3-H), 5.96 (ddd, 1H, $J_{3,4}=6.1$ Hz), 7.41–8.08 (m, 5H, C₆H₅); ¹³C NMR (62.9 MHz): $\delta=37.5$ (C-2), 58.8 (C-1), 72.4 (C-3), 116.8 (C-5), 136.3 (C-4), 166.5 (CO); anal. calcd for C₁₂H₁₄O₃ (206.2): C, 69.89; H, 6.84; found: C, 69.67; H, 6.95.

3.21. (S)-3-Benzoyloxy-4-pentene-1-ol (S)-(14)

Treatment of (S)-13 (8.00 g, 22.95 mmol) as described for (R)-13 afforded (S)-14 (4.96 g, 96%); $[\alpha]_D^{20}=+26$ ($c=2.77$, CHCl₃).

3.22. (R)-3-Benzoyloxy-4-pentene-1-yl 2,3,4,6-tetra-O-benzoyl- α -D-mannopyranoside 15

A solution of TMSOTf (181 μ l, 1.0 mmol) in CH₂Cl₂ was added at -30°C to a solution of (R)-14 (2.0 g, 9.7 mmol) and **9** (8.15 g, 10.22 mmol) in CH₂Cl₂ (110 ml) containing molecular sieves 3 Å (5 g). After 1.5 h the reaction mixture was neutralized with pyridine, filtered through a layer of Celite, diluted with CH₂Cl₂ and washed with aq. 2 M HCl and NaHCO₃ solution. The dried (Na₂SO₄) solution was concentrated and the residue was crystallized from hexane–acetone to afford **15** (6.84 g, 90%); mp: 176–178°C; $[\alpha]_D^{20}=-18$ ($c=1.4$, CHCl₃); ¹H NMR (500 MHz): $\delta=2.18-2.28$ (m, 2H, 2¹-H_a, 2¹-H_b), 3.67–3.70 (m, 1H, 1¹-H_b), 3.99–4.04 (m, 1H, 1¹-H_a), 4.26 (dd, 1H, 6²-H_b, $J_{52,62b}=4.1$ Hz, $J_{62a,62a}=12.2$ Hz), 4.35 (ddd, 1H, 5²-H, $J_{42,52}=10.1$ Hz, $J_{52,62a}=2.6$, $J_{52,62b}=3.7$ Hz), 4.48 (dd, 1H, 6²-H_a), 5.09 (d, 1H, 1²-H, $J_{12,21}=1.4$ Hz), 5.29 (d, 1H, 5¹-H_{cis}, $J_{41,51cis}=10.5$ Hz), 5.45 (d, 1H, 5¹-H_{trans}, $J_{41,51trans}=17.2$ Hz), 5.71 (dd, 1H, 2²-H, $J_{22,32}=3.2$ Hz), 5.82–5.85 (m, 1H, 3¹-H), 5.92 (dd, 1H, 3²-H), 5.96–6.03 (m, 1H, 4¹-H), 6.11 (t, 1H, 4²-H); ¹³C NMR (125 MHz): $\delta=34.2$ (C-2¹), 62.5 (C-6²), 64.4 (C-1¹), 66.6 (C-4²), 68.8 (C-5²), 70.2 (C-3²), 70.4 (C-2²), 71.9 (C-3¹), 97.7 (C-1²), 117.1 (C-5¹), 136.1 (C-4¹); anal. calcd for C₄₆H₄₀O₁₂ (784.8): C, 70.40 H, 5.14; found: C, 70.49; H, 5.13.

3.23. (R)-3-Hydroxy-4-pentene-1-yl α -D-mannopyranoside **16**

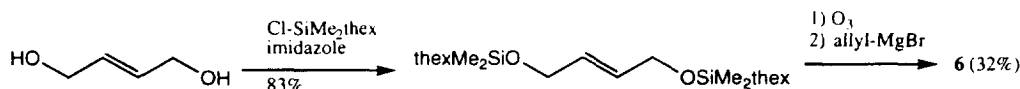
A solution of **15** (6.70 g, 8.95 mmol) in MeOH:toluene (5:1, 120 ml) and methanolic 1 M NaOMe (300 ml, 0.30 mmol) was kept for 7 days at room temperature. The mixture was neutralized by addition of ion-exchange resin (Dowex 50 WX8, H⁺), filtered and concentrated. Chromatography (CHCl₃:MeOH 3: 1) of the residue afforded **16** (2.13 g, 90%); [α]_D²⁰=+65 (c=1.0, CH₃OH); ¹H NMR (500 MHz): δ =1.72–1.79 (m, 2H, 2-H_a, 2-H_b), 3.48 (dt, 1H, $J_{11b,21a}=J_{11b,21b}=6.0$ Hz, $J_{11a,11b}=10.0$ Hz), 3.52–3.80 (m, 6H, 1¹-H_a, 3²-H, 4²-H, 5²-H, 6²-H_a, 6²-H_b), 3.84 (dd, 1H, 2²-H, $J_{12,22}=1.3$ Hz, $J_{22,32}=3.1$ Hz), 4.16–4.20 (m, 1H, 3¹-H), 4.76 (d, 1H, 1²-H), 5.09 (d, 1H, 5¹-H_{cis}, $J_{41,51cis}=10.3$ Hz), 5.17 (d, 1H, 5¹-H_{trans}, $J_{41,51trans}=17.2$ Hz), 5.81 (ddd, 1H, 4¹-H, $J_{31,41}=6.4$ Hz); ¹³C NMR (125 MHz): δ =35.7 (C-2¹), 61.2 (C-6²), 64.4 (C-1¹), 67.0 (C-4²), 70.2 (C-2²), 70.4 (C-3²), 70.9 (C-3¹), 73.0 (C-5²), 100.0 (C-1²), 115.6 (C-5¹), 140.2 (C-4¹); FAB-MS: 287 (M+Na)⁺.

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- Compound **6** was prepared alternatively from 2-butene-1,4-diol by silylation, ozonolysis and Grignard reaction as outlined above.



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