Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 781–790

TETRAHEDRON: *ASYMMETRY*

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

Frank Bien and Thomas Ziegler *

Institute of Organic Chemistry, University of Cologne, Greinstraße 4, D-50939 Cologne, Germany

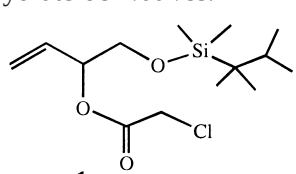
Received 15 December 1997; accepted 4 February 1998

Abstract

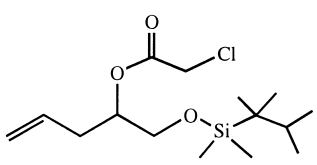
1-Dimethylthexylsiloxy-2-chloroacetoxy-4-pentene **2** and 1-dimethylthexylsiloxy-3-chloroacetoxy-4-pentene **3** were saponified with *Pseudomonas* lipase to give (*R*)-1-dimethylthexylsiloxy-4-pentene-2-ol (ee=99%) and (*S*)-**2** (ee=99%) and (*S*)-1-dimethylthexylsiloxy-4-pentene-3-ol (ee=99%) and (*R*)-**3** (ee=98%), respectively. All enantiomers were chemically transformed into the corresponding enatiomerically 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-*a*-D-mannopyranosyl trichloroacetimidate afforded the corresponding mannopyranosides.

1. Introduction

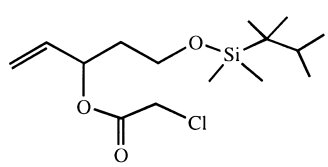
In the preceding paper,[1] partially blocked enantiomerically pure 3-butene-1,2-diol derivatives for direct glycosylation reactions were efficiently prepared from **1** using Schneiders approach[2] via lipase-catalyzed saponification. Since the thus-obtained 3-butene-1-hydroxy-2-yl glycopyranosides[1] 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]



1



2



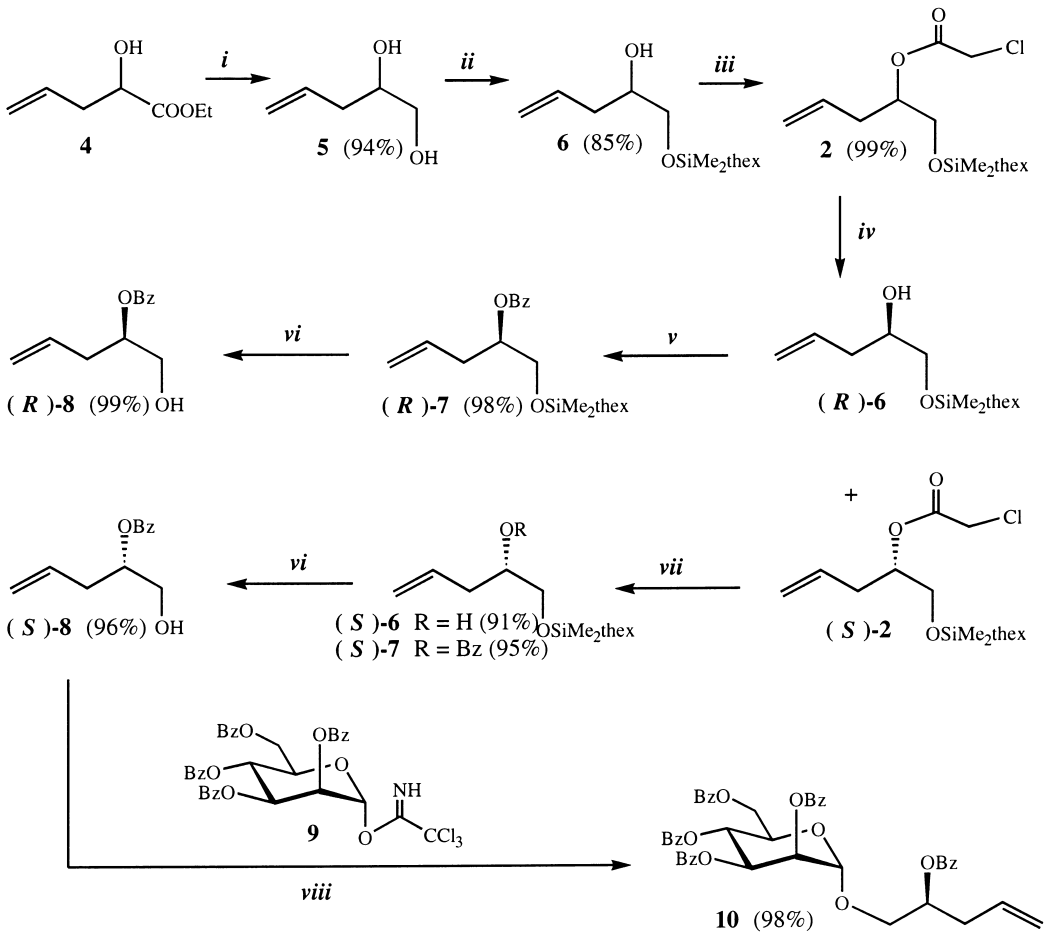
3

* Corresponding author. E-mail: Thomas.Ziegler@Uni-Koeln.de

0957-4166/98/$19.00
PII: S0957-4166(98)00052-4

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 promoted[9] allylation of ethyl glyoxylate. Next, reduction of **4** with $NaBH_4$ 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, chloroacetylation[1] 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) $NaBH_4$, dioxane–EtOH, 25°C. (ii) Cl–$SiMe_2$thex, imidazole, CH_2Cl_2, 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, Et_3N, 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 diamine[13] since removal of the chloroacetyl group by *Candida* lipase[1] 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.

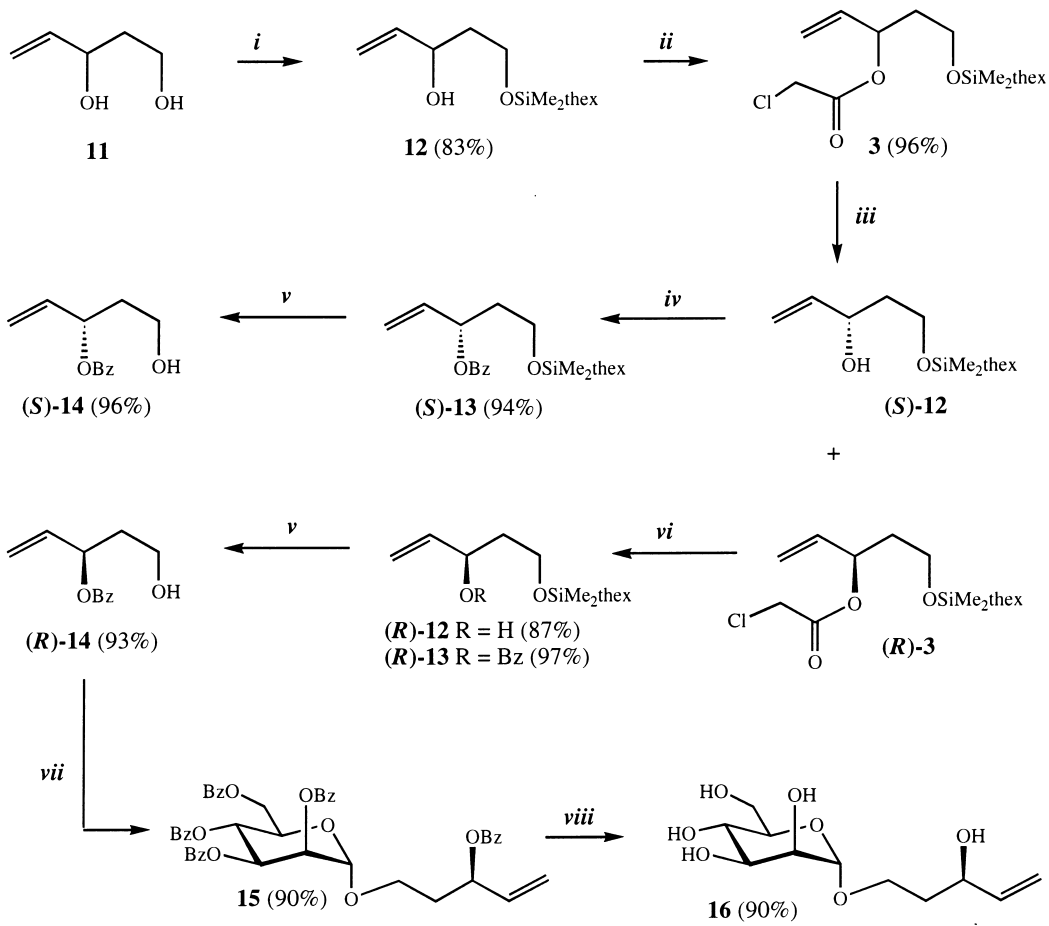
Direct glycosylation was further exemplified for compound (*S*)-**8**. Mannosylation proceeded smoothly with mannosyl imidate[14] **9** to give crystalline **10** in 98% yield. The crystal structure[15] of the latter showed unambiguously the (*S*)-configuration at C-2 of the aglycon.

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-pentenoate[16] 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 which[15] 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 $CDCl_3$ solutions for blocked compounds (with Me_4Si as an internal standard) and D_2O 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. ^{13}C NMR assignments were made by mutual comparison of spectra, by DEPT spectra, by comparison with spectra of related compounds and ^1H–^{13}C 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 UV_{254}, 40×80 mm (Macherey–Nagel) using appropriately adjusted mixtures of CCl_4–acetone or petroleum ether–ethyl acetate for development. Detection was effected with UV light, where applicable, iodine and by charring with 5% H_2SO_4 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–SiMe$_2$thex, imidazole, CH_2Cl_2, 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 $NaHCO_3$ solution dried (Na_2SO_4) and concentrated. The residue was purified by Kugelrohr distillation, to give **4** (11.78 g, 56%); bp: 100°C/15 mmHg (Kugelrohr oven temperature); ^{1}H NMR (500 MHz): δ=1.30 (t, 3H, OCH_2CH_3, 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, OCH_2CH_3), 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); ^{13}C NMR (125 MHz): δ=14.2 (OCH_2CH_3), 38.7 (C-3), 61.7 (OCH_2CH_3), 70.0 (C-2), 118.7 (C-5), 132.5 (C-4), 174.5 (C-1). GC–MS, CI, m/z: 144 $(M)^+$, 126 $(M-H_2O)^+$, 99 $(M-OCH_2CH_3)^+$, 71 $(M-COOCH_2CH_3)^+$.

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

A solution of **4** (1.50g, 10.40 mmol) in dioxane:EtOH (10:1, 55 ml) was treated with $NaBH_4$ (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 ($CHCl_3$:MeOH=3:1) of the residue afforded **5** (997 mg, 94%). ^{1}H 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); ^{13}C 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 $(C_5H_7)^+$.

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

Thexyldimethylsilylchloride (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 CH_2Cl_2 (80 ml). After stirring for 1 h at room temperature, the mixture was diluted with CH_2Cl_2, washed with aq. $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated. Chromatography of the residue (petroleum ether:ethyl acetate=20:1) afforded **6** (9.06 g, 82%); ^{1}H NMR (500 MHz): δ=0.11 (s, 6H, $Si(CH_3)_2$), 0.86 (s, 6H, $Si(CH_3)_2C(CH_3)_2$), 0.89 (d, 6H, $Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$, J=6.9 Hz), 1.63 (quint, 1H, $Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$), 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); ^{13}C NMR (125 MHz): δ=−3.5, −3.4 ($Si(CH_3)_2$), 18.5 ($Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$), 20.3 ($Si(CH_3)_2C(CH_3)_2$), 25.1 ($Si(CH_3)_2C(CH_3)_2$), 34.2 ($Si(CH_3)_2C(CH_3)_2C$), 37.6 (C-2), 66.3 (C-1), 71.1 (C-2), 117.4 (C-5), 134.5 (C-4); anal. calcd for $C_{13}H_{28}O_2Si$ (244.5): C, 63.88; H, 11.54; found: C, 63.87; H; 11.58.

3.5. 2-Chloracetoxy-1-dimethylthexylsilyloxy-4-pentene **2**

A solution of **6** (10.54 g, 43.12 mmol) in pyridine:CH_2Cl_2 (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 CH_2Cl_2, washed with water, aq. 2 M HCl and $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated. The residue was chromatographed (petroleum ether:ethyl acetate=20:1) to give **2** (13.70 g, 99%); ^{1}H NMR (500 MHz): δ=0.08 (s, 6H, $Si(CH_3)_2$), 0.83 (s, 6H, $Si(CH_3)_2C(CH_3)_2$), 0.87 (d, 6H, $Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$, J=6.9 Hz), 1.61 (sept, 1H, $Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$), 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, CH_2Cl), 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); ^{13}C NMR (125 MHz): δ=−3.6 ($Si(CH_3)_2$), 18.5 ($Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$), 20.2 ($Si(CH_3)_2C(CH_3)_2$), 25.1 ($Si(CH_3)_2C$), 34.2 ($Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$), 34.9 (C-3), 41.0 ($CH_2Cl$), 63.1 (C-1), 75.8 (C-2), 118,3 (C-5), 132.9 (C-4), 166.9 (CO); anal. calcd for $C_{15}H_{29}ClO_3Si$ (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 CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. Chromatography (petroleum ether:ethyl acetate=25:1) of the residue afforded first (*S*)-(**2**) (5.82 g, 45%, ee=99%), $[\alpha]_D^{20}=-2.3$ (*c*=1.7, $CHCl_3$).

Eluted next was (*R*)-(**6**) (4.45 g, 45%, ee=99%); $[\alpha]_D^{20}=-1.7$ (*c*=2.1, $CHCl_3$).

*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 CH_2Cl_2, washed with water, aq. 2 M HCl and $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated. Chromatography (petroleum ether:ethyl acetate=20:1) of the residue afforded (*S*)-**6** (3.92 g, 91%); $[\alpha]_D^{20}=+0.9$ (*c*=3.0, $CHCl_3$).

*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 CH_2Cl_2. The combined organic layers were washed with water, aq. 2 M HCl and $NaHCO_3$ solution. After drying (Na_2SO_4) the solvent was removed and chromatography (petroleum ether:ethyl acetate=20:1) of the residue afforded (*R*)-**7** (5.87 g, 98%); $[\alpha]_D^{20}=+9.0$ (*c*=1.7, $CHCl_3$); ^{1}H NMR (500 MHz): δ=0.07 (s, 6H, $Si(CH_3)_2$), 0.83 (s, 6H, $Si(CH_3)_2C\mathit{H}$), 0.85, 0.86 (2d, 6H, $Si(CH_3)_2C(CH_3)_2CH(C\mathit{H}_3)_2$, *J*=6.8 Hz), 1.60 (quint, 1H, $Si(CH_3)_2C(CH_3)_2C\mathit{H}$), 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, C_6H_5); ^{13}C NMR (125 MHz): δ=−3.6 ($Si(CH_3)_2$), 18.4, 18.5 ($Si(CH_3)_2C(CH_3)_2CH(\mathit{C}H_3)_2$), 20.2, 20.3 ($Si(CH_3)_2C(\mathit{C}H_3)_2$), 25.1 ($Si(CH_3)_2\mathit{C}$), 34.2 ($Si(CH_3)_2C(CH_3)_2\mathit{C}H$), 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 $C_{20}H_{32}O_3Si$ (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%); $[\alpha]_D^{20}=-9.1$ (*c*=2.4, $CHCl_3$).

*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 CH_2Cl_2, washed with water and aq. $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated. Chromatography (CCl_4:acetone=8:1) of the residue afforded (*R*)-**8** (3.29 g, 99%); $[\alpha]_D^{20}=+8.7$ (*c*=2.0, $CHCl_3$); ^{1}H 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, C_6H_5); ^{13}C 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 $C_{12}H_{14}O_3$ (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-mannopyranose[14] (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}H NMR (300 MHz): δ=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}C NMR (75.5 MHz): δ=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 $C_{36}H_{28}NO_{10}Cl_3$ (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}H NMR (500 MHz): δ=2.59–2.66 (t, 2H, 3^1-H_a, 3^1-H_b), 3.82 (dd, 1H, 1^1-H_b, $J_{11b,21}$=4.0 Hz, $J_{11a,11b}$=10.6 Hz), 4.07 (dd, 1H, 1^1-H_a, $J_{11a,21}$=6.1 Hz), 4.40–4.46 (m, 2H, 5^2-H, 6^2-H_b), 4.66–4.69 (m, 1H, 6^2-H_a), 5.15 (dd, 1H, 5^1-H_{cis}, $J_{41,51cis}$=10.3 Hz, $J_{51cis,51trans}$=1.3 Hz), 5.17 (d, 1H, 1^2-H, $J_{12,22}$=1.5 Hz). 5.23 (dd, 1H, 5^1-H_{trans}, $J_{41,51trans}$=17.1 Hz), 5.46–5.50 (m, 1H, 2^1-H), 5.76 (dd, 1H, 2^2-H, $J_{22,32}$=3.1 Hz), 5.85 (dd, 1H, 3^2-H, $J_{32,42}$=10.1 Hz), 5.87–5.93 (m, 1H, 4^1-H), 6.08 (t, 1H, 4^2-H); ^{13}C NMR (125 MHz): δ=35.6 (C-3^1), 62.7 (C-6^2), 66.7 (C-4^2), 68.4 (C-1^1), 69.0 (C-5^2), 70.0 (C-3^2), 70.2 (C-2^2), 71.9 (C-2^1), 97.5 (C-1^2), 118.8 (C-5^1), 133.5 (C-4^1); anal. calcd for $C_{46}H_{40}O_{12}$ (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 **11**[4] (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}H NMR (250 MHz): δ=0.12 (s, 6H, $Si(CH_3)_2$), 0.85 (s, 6H, $Si(CH_3)_2C(CH_3)_2$), 0.89 (d, 6H, $Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$, *J*=6.9 Hz), 1.54–1.85 (m, 3H, $Si(CH_3)_2C(CH_3)_2CH$), 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}, $J_{4,5cis}$=10.4 Hz, $J_{3,5cis}$=$J_{5cis,5trans}$=1.6 Hz), 5.24 (dt, 1H, 5-H_{trans}, $J_{4,5trans}$=17.2 Hz), 5.88 (ddd, 1H, 4-H, $J_{3,4}$=5.4 Hz); ^{13}C NMR (62.9 MHz):

δ=−3.6 ($Si(CH_3)_2$), 18.5 ($Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$), 20.2 ($Si(CH_3)_2C(CH_3)_2$), 25.0 ($Si(CH_3)_2C$), 34.1 ($Si(CH_3)_2C(CH_3)_2CH$), 38.3 (C-2), 61.6 (C-1), 72.5 (C-3), 114.1 (C-5), 140.7 (C-4); anal. calcd for $C_{13}H_{28}O_2Si$ (244.5): C, 63.88; H, 11.54; found: C, 63.64; H, 11.66.

*3.15. 3-Chloroacetoxy-1-dimethylthexylsilyloxy-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 CH_2Cl_2 (100 ml) and the mixture was stirred for 2 h at 0°C. The mixture was diluted with CH_2Cl_2, washed with aq. 2 M HCl and $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated. Chromatography (petroleum ether:ethyl acetate=15:1) of the residue afforded **3** (21.39 g, 96%); ^{1}H NMR (250 MHz): δ=0.07 (s, 6H, $Si(CH_3)_2$), 0.84 (s, 6H, $Si(CH_3)_2C(CH_3)_2$), 0.88 (d, 6H, $Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$, J=6.9 Hz), 1.61 (quint, 1H, $Si(CH_3)_2C(CH_3)_2CH$), 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, CH_2Cl), 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); ^{13}C NMR (62.9 MHz): δ=−3.5 ($Si(CH_3)_2$), 18.6 ($Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$), 20.4 ($Si(CH_3)_2C(CH_3)_2$), 25.1 ($Si(CH_3)_2C$), 34.2 ($Si(CH_3)_2C(CH_3)_2CH$), 37.1 (C-2), 41.6 ($CH_2Cl$), 58.5 (C-1), 74.3 (C-3), 117.7 (C-5), 135.5 (C-4), 166.4 (CO); anal. calcd for $C_{15}H_{29}ClO_3Si$ (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, $CHCl_3$).

Eluted next was (*S*)-**12** (7.05 g, 44%, ee=99%); $[\alpha]_D^{20}$=+8.6 (*c*=2.45, $CHCl_3$).

*3.17. (*R*)-1-Dimethylthexylsilyloxy-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 CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvent was removed. Chromatography of the residue afforded (*R*)-**12** (6.66 g, 87%); $[\alpha]_D^{20}$=−8.6 (*c*=2.8, $CHCl_3$).

*3.18. (*R*)-3-Benzoyloxy-1-dimethylthexylsiloxy-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 CH_2Cl_2, washed with water, aq. 2 M HCl and $NaHCO_3$ solution, dried (Na_2SO_4) 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, $CHCl_3$); ^{1}H NMR (250 MHz): δ=0.05, 0.06 (s, 6H, $Si(CH_3)_2$), 0.83 (s, 6H, $Si(CH_3)_2C(CH_3)_2$), 0.87 (d,

6H, $Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$, J=6.9 Hz), 1.60 (sept, 1H, $Si(CH_3)_2C(CH_3)_2CH$), 186–2.10 (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, C_6H_5); ^{13}C NMR (62.9 MHz): δ=−3.5 ($Si(CH_3)_2$), 18.5 ($Si(CH_3)_2C(CH_3)_2CH(CH_3)_2$), 20.3 ($Si(CH_3)_2C(CH_3)_2$), 25.1 ($Si(CH_3)_2C$), 34.2 ($Si(CH_3)_2C(CH_3)_2CH$), 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 $C_{20}H_{32}O_3Si$ (348.6): C, 68.92; H, 9.25; found: C, 69.14 H, 9.22.

*3.19. (S)-3-Benzoyloxy-1-dimethylthexylsiloxy-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, $CHCl_3$).

*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, $CHCl_3$); ^{1}H NMR (250 MHz): δ=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, C_6H_5); ^{13}C NMR (62.9 MHz): δ=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 $C_{12}H_{14}O_3$ (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, $CHCl_3$).

*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 μl, 1.0 mmol) in CH_2Cl_2 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 CH_2Cl_2 (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 CH_2Cl_2 and washed with aq. 2 M HCl and $NaHCO_3$ solution. The dried (Na_2SO_4) 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, $CHCl_3$); ^{1}H NMR (500 MHz): δ=2.18–2.28 (m, 2H, 2^1-H_a, 2^1-H_b), 3.67–3.70 (m, 1H, 1^1-H_b), 3.99–4.04 (m, 1H, 1^1-H_a), 4.26 (dd, 1H, 6^2-H_b, $J_{52,62b}$=4.1 Hz, $J_{62a,62a}$=12.2 Hz), 4.35 (ddd, 1H, 5^2-H, $J_{42,52}$=10.1 Hz, $J_{52,62a}$=2.6, $J_{52,62b}$=3.7 Hz), 4.48 (dd, 1H, 6^2-H_a), 5.09 (d, 1H, 1^2-H, $J_{12,21}$=1.4 Hz), 5.29 (d, 1H, 5^1-H_{cis}, $J_{41,51cis}$=10.5 Hz), 5.45 (d, 1H, 5^1-H_{trans}, $J_{41,51trans}$=17.2 Hz), 5.71 (dd, 1H, 2^2-H, $J_{22,32}$=3.2 Hz), 5.82–5.85 (m, 1H, 3^1-H), 5.92 (dd, 1H, 3^2-H), 5.96–6.03 (m, 1H, 4^1-H), 6.11 (t, 1H, 4^2-H); ^{13}C NMR (125 MHz): δ=34.2 (C-2^1), 62.5 (C-6^2), 64.4 (C-1^1), 66.6 (C-4^2), 68.8 (C-5^2), 70.2 (C-3^2), 70.4 (C-2^2), 71.9 (C-3^1), 97.7 (C-1^2), 117.1 (C-5^1), 136.1 (C-4^1); anal. calcd for $C_{46}H_{40}O_{12}$ (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**

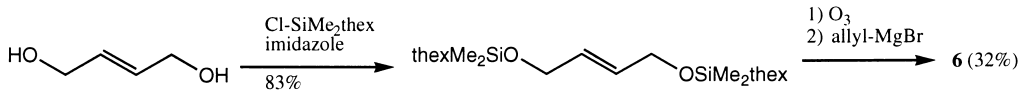
A solution of **15** (6.70 g, 8.95 mmol) in MeOH:toluene (5:1, 120 ml) and methanolic 1 M NaOMe (300 ml, 0.30 mmol) was kept for 7 days at room temperature. The mixture was neutralized by addition of ion-exchange resin (Dowex 50 WX8, H^+), filtered and concentrated. Chromatography ($CHCl_3$:MeOH 3: 1) of the residue afforded **16** (2.13 g, 90%); $[\alpha]_D^{20}$=+65 (*c*=1.0, CH_3OH); ^{1}H 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, 1^1-H_a, 3^2-H, 4^2-H, 5^2-H, 6^2-H_a, 6^2-H_b), 3.84 (dd, 1H, 2^2-H, $J_{12,22}$=1.3 Hz, $J_{22,32}$=3.1 Hz), 4.16–4.20 (m, 1H, 3^1-H), 4.76 (d, 1H, 1^2-H), 5.09 (d, 1H, 5^1-H_{cis}, $J_{41,51cis}$=10.3 Hz), 5.17 (d, 1H, 5^1-H_{trans}, $J_{41,51trans}$=17.2 Hz), 5.81 (ddd, 1H, 4^1-H, $J_{31,41}$=6.4 Hz); ^{13}C NMR (125 MHz): δ=35.7 (C-2^1), 61.2 (C-6^2), 64.4 (C-1^1), 67.0 (C-4^2), 70.2 (C-2^2), 70.4 (C-3^2), 70.9 (C-3^1), 73.0 (C-5^2), 100.0 (C-1^2), 115.6 (C-5^1), 140.2 (C-4^1); FAB-MS: 287 $(M+Na)^+$.

Acknowledgements

We thank Dr. P. Fischer, Institute of Organic Chemistry, University of Stuttgart, Dr. H. Schmickler and Dr. R. Tappe, Institute of Organic Chemistry, University of Cologne for performing the NMR spectra and Dr. J. Opitz, University of Stuttgart for the elemental analyses. This work was financially supported by the Bundesministerium für Bildung und Forschung (BMBF) and the Fonds der Chemischen Industrie. Support by the Bayer AG and Boehringer Mannheim GmbH is also gratefully acknowledged.

References

1. Ziegler, T.; Bien, F.; Jurisch, C., *Tetrahedron: Asymmetry*, **1997**, *9*, 765–780
2. Goergens, U.; Schneider, M. P., *J. Chem. Soc., Chem. Commun.*, **1991**, 1066–1068.
3. Petersen, M.; Zannetti, M. T.; Fessner, W.-D., *Topics Curr. Chem.*, **1997**, *186*, 87–117.
4. Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E., *J. Org. Chem.*, **1987**, *52*, 4191–4202.
5. Kim, Y. G.; Cha, J. K., *Tetrahedron Lett.*, **1988**, *29*, 2011–2014.
6. Tamura, Y.; Hojo, M.; Kawamura, S.; Sawada, S.; Yoshida, Z., *J. Org. Chem.*, **1987**, *52*, 4062–4072.
7. Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, P. D., *J. Org. Chem.*, **1990**, *55*, 4117–4126.
8. Braun, M.; Gräf, S., *Liebigs Ann.*, **1993**, 1091–1098.
9. Nokami, J.; Otera, J.; Sudo, T.; Okawara, R., *Organometallics*, **1983**, 191–193.
10. Lolkema, L. M. D.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N., *Tetrahedron*, **1994**, *50*, 7115–7128.
11. Andrey, O.; Landais, Y.; Planchenault, D., *Tetrahedron Lett.*, **1993**, *34*, 2927–2930.
12. Compound **6** was prepared alternatively from 2-butene-1,4-diol by silylation, ozonolysis and Grignard reaction as outlined above.



13. Cook, A. F.; Maickuk, D. T., *J. Org. Chem.*, **1970**, *35*, 1940–1943.
14. Nicolaev, A. V.; Inanova, I. A.; Shibaef, V. N.; Kochetkov, N. K., *Carbohydr. Res.*, **1990**, *204*, 65–78.
15. Bien, F., Dissertation, University of Stuttgart, 1997; X-ray data are available from the Cambridge Crystallographic Database.
16. Smith, A. B.; Levenberg, P. A., *Synthesis*, **1981**, 567–570.
17. Wong, C.-H.; Moris-Varas, F.; Hung, S.-C.; Marron, T. G.; Lin, C.-C.; Gong, K. W.; Weitz-Schmidt, G., *J. Am. Chem. Soc.*, **1997**, *119*, 8152–8158.