Use of aldolases in the synthesis of non-carbohydrate natural products. Stereoselective synthesis of aspicilin C-3—C-9 fragment

Robert Chênevert, Michèle Lavoie, and Mohammed Dasser

Abstract: The C-3—C-9 main fragment of aspicilin was prepared via a fructose 1,6-diphosphate aldolase reaction. The same fragment was also synthesized by chemical transformation starting from D-arabinose.

Key words: aldolase, aspicilin, arabinose, synthesis.

Résumé : Le fragment principal (C-3 à C-9) de l'aspiciline a été préparé via une réaction de l'aldolase du fructose 1,6-diphosphate. Le même fragment a été obtenu par une série de réactions non-enzymatiques à partir du D-arabinose.

Mots clés : aldolase, aspiciline, arabinose, synthèse.

Introduction

The development of methods for stereoselective C—C bond formation using the aldol reaction is a major focus of interest in organic synthesis. Both chemical (1) and enzymatic (2) aldol reactions with high level of asymmetric induction have recently been developed. The use of aldolases in the synthesis of carbohydrates and close analogs (azasugars, cyclitols) has been amply demonstrated (2, 3). However, the application of aldolases for the synthesis of natural products other than sugars has received very little attention. The synthesis of brevicomin, an insect pheromone, represents a rare example of this strategy (4). More recently, Shimagaki et al. (5) reported the synthesis of the C-11—C-16 fragment of pentamycin using an aldolase catalyzed reaction as the key step. The most prominent and easily available representative of these enzymes is fructose-1,6-diphosphate aldolase (FDP aldolase). This aldolase catalyzes the reversible aldol reaction of dihydroxyacetone phosphate (DHAP) and a broad range of aldehydes with the formation of a C—C bond having the D-*threo* (3*S*, 4*R*) configuration.

In this paper, we describe a FDP aldolase catalyzed stereoselective C—C bond formation leading to the main (C-3—C-9) fragment of (+)-aspicilin. (+)-Aspicilin (**1**) is a 18-membered lactone isolated from the lichen *Aspicilia gibbosa* (6). Several different nonenzymatic approaches for the synthesis of (−) or (+)-aspicilin have been reported (7).

Received June 15, 1996.

R. Chênevert,[1] M. Lavoie, and M. Dasser. Département de chimie, Faculté des sciences et de génie, Université Laval, Québec, QC G1K 7P4, Canada.

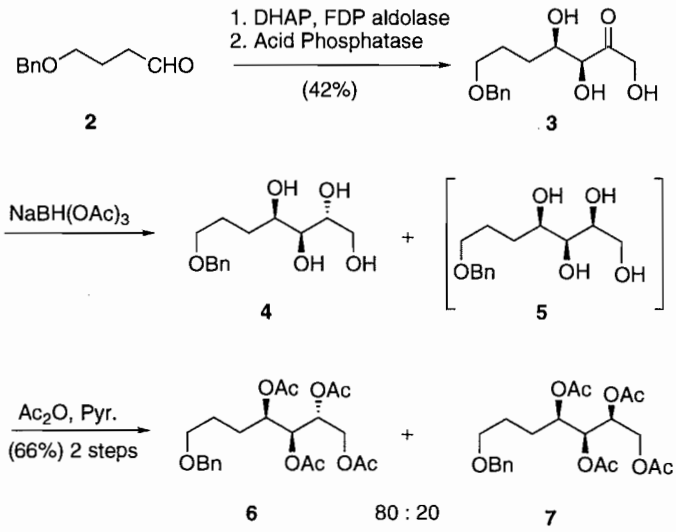
[1] Author to whom correspondence may be addressed. Telephone: (418) 656–3283. Fax: (418) 656–7916. E-mail: robert.chenevert@chm.ulaval.ca

Results and discussion

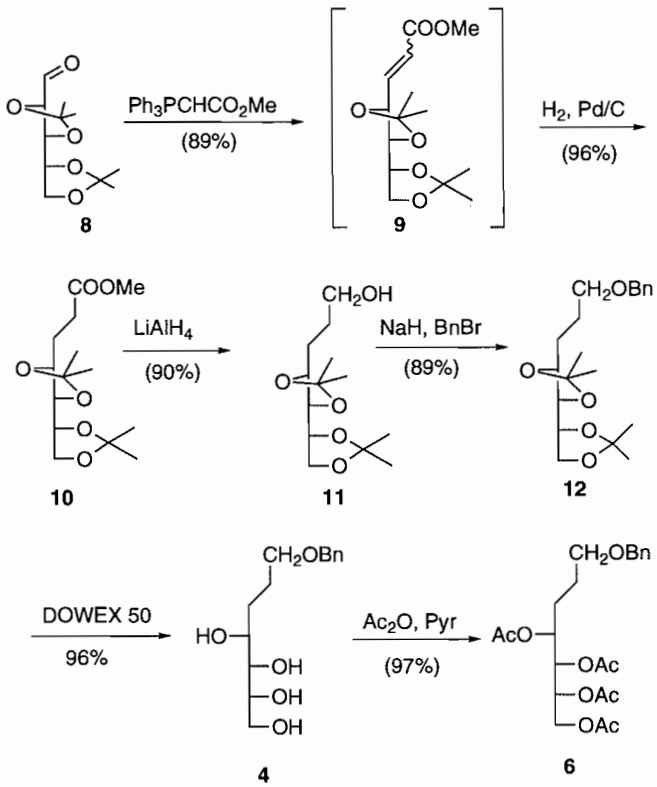
The reaction of aldehyde **2** (7*c*) with DHAP in the presence of FDP aldolase in water/DMF (10/1), followed by hydrolysis in situ of the intermediate phosphate ester with acid phosphatase, afforded ketotriol **3** in 42% overall yield (Scheme 1). Ketotriol **3** was reduced by using a variety of reagents and conditions. Sodium or lithium borohydride gave low diastereoselectivity. Evans et al. (8) reported that reduction of acyclic β-hydroxyketones with tetramethylammonium triacetoxyborohydride consistently affords 1,3-*anti* diols with high diastereoselectivity. The proposed mechanism involves a ligand exchange of acetate for substrate alcohol by the triacetoxyborohydride; the resultant intermediate, presumably an alkoxydiacetoxyborohydride, reduces the ketone by intramolecular hydride delivery (8). Reduction of **3** with triacetoxyborohydrides gave the desired 1,3-*anti* diastereoisomer **4** as the dominant product along with some 1,3–*syn* diastereoisomer **5** (1,3-*anti* **4**/1,3-*syn* **5** ~ 4/1). The separation of these diastereoisomers by flash chromatography provided the desired *anti*-**4** in a pure form but the minor *syn*-**5** isomer was still contaminated. A sample of the mixture **4**–**5** was acylated by acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine (DMAP) and the resulting diastereomeric esters **6**–**7** were separated by flash chromatography. The nature of the triacetoxy borohydrides (sodium or tetramethylammonium triacetoxyborohydride, tetramethylammonium borohydride in acetic acid) did not significantly affect the stereoselectivity of this reduction. The lower diastereoselectivity of our reduction reaction can be explained by the presence of three additional oxygen atoms interfering with the formation of the intermediate alkoxydiacetoxyborohydride. Presumably, several directed reduction reactions compete with opposite stereochemical preferences.

Compounds **4** and **6** are presumed to have the 2*R*,3*S*,4*R* absolute configuration. To prove this configuration beyond any doubt, we synthesized authentic (2*R*,3*S*,4*R*)-**4** and -**6** by chemical transformation starting from D-arabinose (Scheme 2).

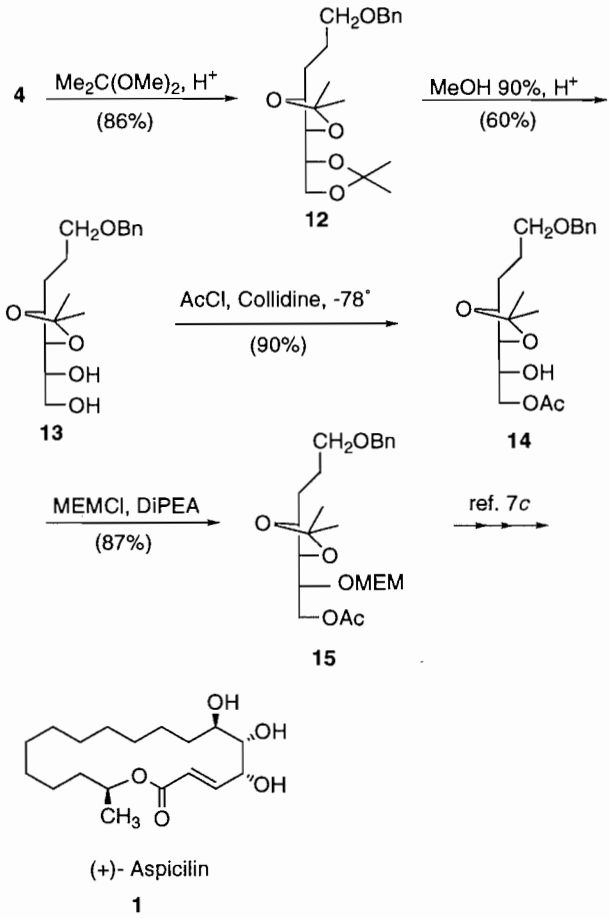
Scheme 1.



Scheme 2.



Scheme 3.

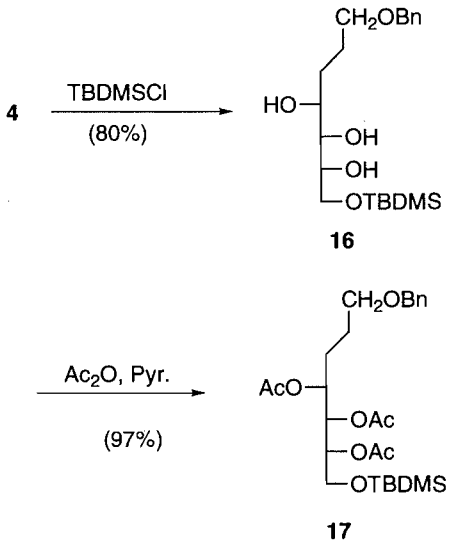


D-Arabinose was transformed into di-*O*-isopropylidene-D-arabinose **8** in a three-step sequence according to known procedures (9). The Wittig reaction of **8** with (carbomethoxymethylene)triphenylphosphorane in benzene afforded **9** as a mixture in which the *trans* isomer was predominant (*E*/*Z* ratio = 6). Catalytic hydrogenation of ester mixture **9** furnished the dihydro derivative **10**. Ester **10** was reduced with $LiAlH_4$ in ether to afford alcohol **11**. Alcohol **11** was benzylated with benzyl bromide in the presence of NaH to give **12**. Deprotection of isopropylidenes in **12** was achieved satisfactorily using acidic resin in water at 60°C to give tetraol **4**. A sample of tetraol **4** was acetylated with acetic anhydride in pyridine in the presence of DMAP. Compounds **4** and **6** prepared from D-arabinose were identical in all respects with the samples obtained via the enzymatic addition–reduction sequence. This correlation proved that the aldolase catalyzed reaction provided an addition product with a 3*S*,4*R* configuration and that the subsequent reduction gave the 2*R*,3*S*,4*R* tetraol **4** as the major product.

Compound **15** corresponding to the C-3—C-9 fragment of aspicilin was easily prepared in a few steps from tetraol **4** (from the enzymatic condensation) or from **12** (from arabinose). Compound **4** was treated with dimethoxypropane in acidic medium to give **12** (Scheme 3). Selective deprotection of **12** was achieved by treatment with methanol in the presence of an acidic resin (Dowex 50W-X8) (10). The primary alcohol of **13** was selectively acylated with acetyl chloride in the presence of collidine at −78°C in CH_2Cl_2 (11). Mono-alcohol **14** was converted into the corresponding 2-methoxyethoxymethyl (MEM) ether **15** in high yield by reaction with MEMCl in the presence of *N*,*N*-diisopropylethylamine (DiPEA). This sequence constitutes a formal synthesis of aspicilin since the transformation of **15** into aspicilin has been reported by Solladié et al. (7*c*).

Compound **4** has also been transformed in two steps into **17**, another compound corresponding to the C-3—C-9 fragment of aspicilin with orthogonal protection (Scheme 4). The primary alcohol of **4** was selectively protected by reaction with

Scheme 4.



tert-butyldimethylsilyl chloride (TBDMSCl) followed by acylation of the remaining alcohol functionalities in compound **16** with acetic anhydride.

In conclusion, we have completed a formal synthesis of (+)-aspicilin via an aldolase-catalyzed condensation. The main C-3—C-9 fragment was obtained in six steps and 10% overall yield. The same fragment was also prepared from D-arabinose in 10 steps and 22% overall yield. The synthesis of this fragment from D-arabinose not only provides unambiguous establishment of the relative and absolute stereochemistry of the intermediate but also provides an alternative pathway for the formal synthesis of (+)-aspicilin. The present work demonstrates that the aldolase-catalyzed condensation is an efficient process in the asymmetric synthesis of natural products other than carbohydrates. Applications of this strategy for the stereospecific synthesis of other non-carbohydrate natural products are underway.

Experimental section

Aldolase (D-fructose-1,6–biphosphate-D-glyceraldehyde-3-phosphate-lyase; EC 4.1.2.13, from rabbit muscle) and acid phosphatase (from wheat germ, EC 3.1.3.2) were purchased from Sigma Chem. Co. Melting points are uncorrected. NMR spectra were recorded at 300 MHz (^{1}H), 75.44 MHz (^{13}C).

(3*S*,4*R*)-7-Benzyloxy-1,3,4-trihydroxyheptan-2-one (3)
Aldehyde **2** (166.2 mg, 0.94 mmol) was added to a solution of DHAP (12) (180.0 mg, 1.06 mmol) in 10 mL of water containing 10% DMF under nitrogen atmosphere and the pH was adjusted to 6.8 with 1 N NaOH. Aldolase was added (8.6 mg, 102 U) and the mixture was shaken at room temperature. After 24 h, the pH was readjusted to 6.8, additional aldolase (7.8 mg, 92 U) and DHAP (98 mg, 0.58 mmol) were added, and the mixture was stirred for another 45 h. The pH was then set at 4.8 with 1 N HCl, the acid phosphatase (40 mg, 16 U) was added, and the mixture was stirred at room temperature for 12 h. Additional phosphatase (40 mg, 16 U) was added and the mixture was stirred for 12 h. The pH was then raised to 7 with 1 N NaOH. The solution was freeze-dried, the residue was taken up in ethyl acetate, and the solution was filtered and evaporated. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 19:1 as eluant) to afford **3** as an oil (106 mg, 42%). $[\alpha]_D^{23}$ +14.0 (*c* 3.1, $CHCl_3$); IR (neat): 3650–3000, 2980–2800, 1720, 1490, 1140–1000 cm^{-1}; ^{1}H NMR ($CDCl_3$): 7.31 (m, 5H), 4.51 (d, J = 19 Hz, 1H), 4.48 (s, 2H), 4.34 (d, J = 19 Hz, 1H), 4.14 (s, 1H), 3.91 (m, 1H), 3.89 (br s, 3H), 3.71 (m, 2H), 1.59–1.71 (m, 4H); ^{13}C NMR ($CDCl_3$): 211.87, 137.70, 128.37, 127.73, 77.82, 72.98, 72.03, 70.12, 66.56, 30.47, 26.05. MS (CI, isobutane) *m/e* (rel. intensity): 269 (MH^+, 25), 91 (100).

(2*R*,3*S*,4*R*)-7-Benzyloxy-1,2,3,4-tetrahydroxyheptane (4)
To a solution of sodium triacetoxyborohydride (127 mg, 0.60 mmol) in anhydrous acetic acid (4 mL) at 10°C was added dropwise a solution of **3** (40 mg, 0.15 mmol) in acetic acid (10 mL). The solution was stirred for 3 h at 10°C. Ice water (5 mL) was added and the solvent were eliminated by freeze-drying. Flash chromatography on silica gel (CH_2Cl_2/MeOH, 9:1) gave diastereoisomer **4** (24.4 mg, 60%) as a white solid along with a fraction of impure **5**. Compound **4**: mp 114.5–115.5°C (recrystallized from AcOEt:EtOH, 9/1); $[\alpha]_D^{23}$ +5.9 (*c* 0.7, MeOH); IR (neat): 3300–3600, 3000–3100, 2850–2990, 1100–1300 cm^{-1}; ^{1}H NMR (CD_3OD): 7.31 (m, 5H), 4.55 (s, 2H), 3.58–3.83 (m, 6H), 3.4 (dd, J_1 = 8.0 Hz, J_2 = 2.2 Hz, 1H), 1.5–1.8 (m, 4H); ^{13}C NMR (CD_3OD): 129.44, 128.96, 128.72, 74.71, 73.96, 73.28, 71.56, 71.41, 65.16, 31.46, 27.93. MS (CI, isobutane) *m/e* (rel. intensity): 271 (MH^+, 17.5), 145 (100). Anal. calcd. for $C_{14}H_{22}O_5$: C 62.20, H 8.20; found: C 62.22, H 8.39.

(2*R*,3*S*,4*R*) and (2*S*,3*S*,4*R*)-7-Benzyloxy-1,2,3,4-tetraacetoxyheptane (6 and 7)
The crude reduction product (40 mg, 0.15 mmol, mixture of **4** and **5**), DMAP (10 mg), and acetic anhydride (2 mL) were dissolved in pyridine (4 mL) and the solution was stirred for 36 h at room temperature. CH_2Cl_2 (75 mL) was added and the resulting organic layer was washed with 1 N HCl (3 × 30 mL), saturated aqueous $NaHCO_3$ (2 × 30 mL), brine (2 × 30 mL), and then dried over $MgSO_4$ and evaporated. Flash chromatography on silica gel (ether/petroleum ether, 3:2) gave diastereoisomer **6** (34 mg) and diastereoisomer **7** (9 mg). Total yield: 66%; compound **6**: mp 50–51°C; $[\alpha]_D$ + 13.8 (*c* 0.8, $CHCl_3$); IR (neat): 2990–3100, 2850–2980, 1740, 1490, 1100–1300 cm^{-1}; ^{1}H NMR ($CDCl_3$): 7.31 (m, 5H), 5.31 (dd, J_1 = 8 Hz, J_2 = 3 Hz, 1H), 5.17–5.25 (m, 2H), 4.47 (s, 2H), 4.24 (dd, J_1 = 12 Hz, J_2 = 3 Hz, 1H), 4.13 (dd, J_1 = 12 Hz, J_2 = 6 Hz, 1H), 3.46 (m, 2H), 2.11 (s, 3H), 2.04 (s, 9H), 1.61 (m, 4H); ^{13}C NMR ($CDCl_3$): 170.59, 170.39, 169.91, 169.82, 138.48, 128.35, 127.58, 72.83, 70.41, 69.51, 68.48, 61.97, 27.69, 25.50, 20.82, 20.68, 20.62. MS (CI, isobutane) *m/e* (rel. intensity): 439 (MH^+, 41), 289 (72), 229 (100). Anal. calcd. for $C_{22}H_{30}O_9$: C 60.26, H 6.89; found: C 60.44, H 6.90.

Diastereoisomer **7**: $[\alpha]_D^{23}$ +6.4 (*c* 0.4, $CHCl_3$); IR (neat): 3100–2990, 2850–2980, 1740, 1490, 1100–1300 cm^{-1}; ^{1}H NMR ($CDCl_3$): 7.32 (m, 5H), 5.30 (m, 3H), 4.48 (s, 2H), 4.35 (dd, J_1 = 12 Hz, J_2 = 6 Hz, 1H), 3.50 (m, 2H), 2.05 (m, 12H), 1.70 (m, 4H); ^{13}C NMR ($CDCl_3$): 170.15, 169.82, 138.27, 128.23, 127.55, 127.48, 72.78, 71.33, 69.44, 69.34, 61.85, 27.43, 25.16, 20.73, 20.57, 20.48, 20.23. MS (CI, isobutane)

m/e (rel. intensity): 439 (MH^+, 64), 229 (100); Anal. calcd. for $C_{22}H_{30}O_9$: C 60.26, H 6.89; found: C 60.30, H 7.11.

Methyl 2,3-dideoxy-4,5:6,7-di-O-isopropylidene-D-*arabino*-hept-2-enoate (9)

A solution of aldehyde **8** (1.730 g, 7.513 mmol) and carbomethoxymethylene triphenyl phosphorane (2.782 g, 8.32 mmol) in benzene (30 mL) was refluxed for 3 h. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (ethyl acetate/hexane 1:4) to give **9** as an oil (1.92 g, 89%). This compound was a *trans*/*cis* (6:1) mixture. *trans*-**9**: $[\alpha]_D^{25}$ −1.27 (*c* 2.62, $CHCl_3$) (lit. (13, 14) $[\alpha]_D^{19}$ −1.1 (*c* 3.0, ethanol); IR (neat): 2850–3000, 1735, 1660, 1375, 1385, 1000–1300 cm^{-1}; ^1H NMR ($CDCl_3$): 6.94 (dd, J_1 = 15.5 Hz, J_2 = 4.5 Hz, 1H), 6.1 (dd, J_1 = 15.5 Hz, J_2 = 1.6 Hz, 1H), 4.46 (m, 1H), 4.05 (m, 2H), 3.90 (m, 1H), 3.68 (s, 3H), 3.60 (t, *J* = 7.7 Hz, 1H), 1.35 (s, 3H), 1.33 (s, 6H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$): 166.48, 145.17, 120.86, 110.12, 109.71, 81.06, 78.79, 77.30, 67.37, 51.45, 26.79, 26.57, 26.52, 25,02.

Methyl 2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*arabino*-heptonate (10)

The *cis*/*trans* mixture of olefin **9** (600 mg, 2.1 mmol) was subjected to hydrogenation (18 h) at a 40 psi pressure (1 psi = 6.8-kPa) and room temperature in the presence of Pd/C (60 mg) in EtOH (30 mL). The suspension was then filtered and the solvent evaporated. The crude product was purified by flash chromatography (ethyl acetate/hexane 1:4) to give **10** (580 mg, 96%) as an oil; $[\alpha]_D^{23}$ +16.5 (*c* 2, $CHCl_3$); IR (neat): 3000–2850, 1730, 1300–1000, 1380, 1370 cm^{-1}; ^1H NMR ($CDCl_3$): 4.10 (dd, J_1 = 8.1 Hz, J_2 = 5.9 Hz, 1H), 3.95 (m, 1H), 3.89 (m, 2H), 3.64 (s, 3H), 3.52 (t, *J* = 7.7 Hz, 1H), 2.48 (m, 2H), 2.08 (m, 1H), 1.84 (m, 1H), 1.37 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$): 173.71, 109.61, 109.03, 81.09, 79.45, 67.74, 51.50, 30.49, 28.81, 27.24, 26.98, 26.70, 25.27. MS (CI, isobutane) *m/e* (rel. intensity): 289 (MH^+, 16), 231 (100), 129 (70).

5,6-Dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*lyxo*-heptitol (11)

To a suspension of $LiAlH_4$ (80 mg, 2.1 mmol) in 10 mL of ether was added dropwise a solution of ester **10** (1.32 mmol) in 5 mL of ether at 0°C. The mixture was stirred for 0.5 h at 0°C, then for 14 h at room temperature under dry atmosphere. The resulting mixture was cooled at 0°C and quenched with 1 N HCl (2 mL). Ether (50 mL) was added and the layers were separated. The organic layer was washed with water (1 × 25 mL), saturated aqueous $NaHCO_3$ (1 × 25 mL), and brine (2 × 25 mL), dried over $MgSO_4$ and concentrated. The residue was then purified by flash chromatography (ethyl acetate/hexane, 3:7) to afford alcool **11** (310 mg, 90%) as an oil; $[\alpha]_D^{25}$ +13.7 (*c* 2.1, $CHCl_3$); IR (neat): 3500–3000, 3000–2800, 1373, 1380 cm^{-1}; ^1H NMR ($CDCl_3$): 4.10 (dd, J_1 = 8 Hz, J_2 = 6 Hz, 1H), 4.00 (m, 1H), 3.93 (m, 2H), 3.64 (m, 2H), 3.52 (t, *J* = 7.7 Hz, 1H), 2.48 (br s, 1H), 1.9 (m, 1H), 1.72 (m, 2H), 1.58 (m, 1H), 1.37 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$): 109.49, 108.75, 81.03, 80.28, 77.33, 67.57, 62.46, 30.13, 29.27, 27.14, 26.82, 26.53, 25.12. MS (CI, isobutane) *m/e* (rel. intensity): 261 (MH^+, 10), 203 (90), 145 (100).

7-*O*-Benzyl-5,6-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*lyxo*-heptitol (12)

To a suspension of NaH (36 mg, 1.5 mmol) in dry THF (2 mL) at 0°C and under dry nitrogen atmosphere was added dropwise a solution of **11** (260 mg, 1.00 mmol) in THF (20 mL). The mixture was stirred for 20 min at 0°C and then benzylbromide (256.5 mg, 1.5 mmol) and a catalytic amount (2 mg) of Bu_4NI were added. The mixture was stirred for 30 min at 0°C and then for 24 h at room temperature. The mixture was then filtered through Celite and the filtrate was evaporated. The residue was taken up by EtOAc (40 mL) and this organic phase was washed with water (2 × 15 mL), dried over $MgSO_4$, and evaporated. Flash chromatography on silica gel (EtOAc/hexane, 1:9) gave **12** (311 mg, 89%) as a colorless oil; $[\alpha]_D^{23}$ +13.9 (*c* 2.03, $CHCl_3$); IR (neat): 3000–3100, 2900–3000, 1380, 1370 cm^{-1}; ^1H NMR ($CDCl_3$): 7.33 (m, 5H), 4.52 (s, 2H), 4.11 (dd, J_1 = 7.65 Hz, J_2 = 5.85 Hz, 1H), 4.06 (m, 1H), 3.92 (m, 2H), 3.56 (m, 3H), 1.83 (m, 2H), 1.75 (m, 1H), 1.62 (m, 1H), 1.39 (s, 3H), 1.38 (s, 3H), 1.34 (s, 6H); ^{13}C NMR ($CDCl_3$): 138.73, 128.32, 127.55, 127.46, 109.55, 108.82, 81.33, 80.25, 76.61, 72.95, 70.13, 67.68, 30.29, 27.41, 27.06, 26.73, 26.18, 25.35; MS (CI, isobutane) *m/e* (rel. intensity): 351 (MH^+, 20), 293 (100), 185 (82.5).

Preparation of 4 from 12

A suspension of **12** (200 mg, 0.57 mmol) in water (10 mL) was stirred for 18 h at 60°C in the presence of an acidic Dowex 50 resin (3 g). The mixture was filtered and the filtrate was evaporated. Flash chromatography on silica gel (CH_2Cl_2/methanol, 9:1) provided **4** (148 mg, 96%). Physical and spectral data were identical with those reported above.

Preparation of 6 from 4 (sequence 12 → 4 → 6)

To a solution of **4** (140 mg, 0.52 mmol) and DMAP (3 mg, catalytic amount) in pyridine 3 mL at 0°C was added dropwise 4 mL of acetic anhydride. The solution was stirred for 18 h at room temperature. Ether (20 mL) was added and the resulting organic layer was washed with 3 N HCl (5 mL), water (2 × 10 mL), and brine (3 × 10 mL), and then dried over $MgSO_4$ and evaporated. Flash chromatography on silica gel (petroleum ether/ether, 3:2) afforded **6** (221 mg, 97%) as a colorless oil. Spectral and physical data were identical with those reported above.

Preparation of 12 from 4 (from the enzymatic reaction)

Dimethoxypropane (5.8 mmol, 0.71 mL) was added dropwise to a suspension of tetraol **4** (165 mg, 0.58 mmol) in CH_2Cl_2 (3 mL) in the presence of pyridinium *p*-toluenesulfonate (30 mg, 0.12 mmol). The solution was stirred for 3 h at room temperature under dry nitrogen atmosphere. Dichloromethane was added (25 mL) and the resulting organic layer was washed with water (1 × 10 mL), saturated aqueous $NaHCO_3$ (1 × 10 mL), and brine (2 × 10 mL), dried over $MgSO_4$, and evaporated. Flash chromatography (EtOAc/hexane, 1:9) provided **12** (170 mg, 86%). Physical and spectral data were identical to those described above.

7-*O*-Benzyl-5,6-dideoxy-3,4-*O*-isopropylidene-D-*lyxo*-heptitol (13)

To a solution of diacetonide **12** (140 mg, 0.40 mmol) in 90% methanol (10 mL) was added the Dowex 50W-X8 resin

(154 mg). The reaction mixture was stirred for 24 h at room temperature. The resin was removed by filtration and the solution was treated with aqueous saturated $NaHCO_3$ (1 mL), and evaporated. Ethyl acetate was added and the organic phase was washed with brine, dried over $MgSO_4$, and evaporated. Flash chromatography (gradient from EtOAc/hexane 1:9 to 3:7 and then pure EtOAc) provided **13** (75 mg, 60%) along with starting material (24 mg) and fully deprotected compound **4** (10 mg). Compound **13** (colorless oil): $[\alpha]_D^{23}$ +5.52 (*c* 4.5, $CHCl_3$); IR (neat): 3600–3200, 3100–2900, 2900–2800, 1390–1380, 1300–1100 cm^{-1}; ^1H NMR ($CDCl_3$): 7.32 (m, 5H), 4.49 (s, 2H), 4.0 (m, 1H), 3.6–3.8 (m, 4H), 3.52 (m, 2H), 2.65 (br s, 1H), 3.10 (br s, 1H), 1.6–1.9 (m, 4H), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$): 138.12, 128.27, 127.63, 127.52, 108.64, 80.90, 78.95, 72.80, 72.50, 70.07, 63.70, 30.73, 27.21, 26.92, 25.89. MS (CI, isobutane) *m/e* (rel. intensity): 311 (MH^+, 100), 253 (93).

1-*O*-Acetyl-7-*O*-benzyl-5,6-dideoxy-3,4-*O*-isopropylidene-D-*lyxo*-heptitol (14)

To a solution of **13** (44 mg, 0.14 mmol) in dry CH_2Cl_2 (3 mL) cooled at −78°C was added 2,4,6-collidine (12 μL, 2 equiv.). After stirring for 5 min, acetyl chloride (12 μL, 1.2 equiv.) was added dropwise and the solution was stirred for 2 h at −78°C. CH_2Cl_2 (25 mL) was added and the resulting organic phase was washed with water (1 × 10 mL), saturated aqueous $NaHCO_3$ (1 × 10 mL), and brine (2 × 10 mL), and then dried over $MgSO_4$ and evaporated. Flash chromatography on silica gel (hexane/EtOAc, 3:7) gave **14** (45 mg, 90%); $[\alpha]_D^{23}$ +18.76 (*c* 2.1, $CHCl_3$); IR (neat): 3600–3200, 2850–3000, 3050–3150, 1740, 1360 cm^{-1}; ^1H NMR ($CDCl_3$): 7.22 (m, 5H), 4.43 (s, 2H), 4.26 (dd, J_1 = 2.9 Hz, J_2 = 11.7 Hz, 1H), 4.04 (dd, J_1 = 6.7 Hz, J_2 = 11.7 Hz, 1H), 3.97 (m, 1H), 3.74 (m, 1H), 3.55 (t, J = 7 Hz, 1H), 3.45 (m, 2H), 2.54 (d, J = 4.8 Hz, 1H), 2.03 (s, 3H), 1.54–1.79 (m, 4H), 1.43 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$): 171.3, 138.31, 128.23, 127.56, 127.43, 108.87, 80.08, 79.06, 72.75, 71.38, 70.03, 66.18, 30.89, 27.28, 26.92, 25.98, 20.74. MS (CI, isobutane) *m/e* (rel. intensity): 253 (MH^+, 100), 277 (38), 187 (54).

1-*O*-Acetyl-7-*O*-benzyl-5,6-dideoxy-3,4-*O*-isopropylidene-2-*O*-[2′-(methoxyethoxy)methyl]D-*lyxo*-heptitol (15)

To a solution of **14** (42 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) at 0°C were added DIPEA (62 μL, 0.357 mmol, 3 equiv.) and MEMCl (34 μL, 0.298 mmol, 2.5 equiv.). The solution was stirred for 0.5 h at 0°C, then for 48 h at room temperature under dry atmosphere. CH_2Cl_2 (25 mL) was added and the organic layer was washed with water (1 × 10 mL), with saturated aqueous $NaHCO_3$ (2 × 10 mL), and with brine (2 × 10 mL), dried over $MgSO_4$, and evaporated. Flash chromatography on silica gel (EtOAc/petroleum ether, 3:7) provided **15** (45 mg, 87%) as a colorless oil; $[\alpha]_D^{25}$ +18.4 (*c* 1.1, acetone) (lit. (*7c*) $[\alpha]_D^{25}$ −18.7 (c. 1.87, acetone) for the opposite enantiomer). IR (neat): 2900–3100, 2800–2900, 1740, 1370, 1000–1200 cm^{-1}; ^1H NMR ($CDCl_3$): 7.31 (m, 5H), 4.84 (d, J = 7.1 Hz, 1H), 4.73 (d, J = 7.1 Hz, 1H), 4.48 (s, 2H), 4.1 (dd, J_1 = 6 Hz, J_2 = 12 Hz, 1H), 4.42 (dd, J_1 = 12 Hz, J_2 = 3 Hz, 1H), 4.02 (m, 1H), 3.85 (m, 1H), 3.77 (m, 1H), 3.68 (m, 2H), 3.47–3.59 (m, 4H), 3.51 (s, 3H), 2.05 (s, 3H), 1.59–1.85 (m, 4H), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$): 170.62, 138.48, 128.19, 127.45, 127.36, 108.89, 94.89, 79.54, 78.85, 75.64, 72.70, 71.53, 69.96, 67.33, 63.54, 58.89, 30.73, 27.30, 26.90, 26.20, 20.75. MS (CI, isobutane) *m/e* (rel. intensity): 441 (MH^+, 4), 365 (100), 307 (46), 157 (67).

(2*R*,3*S*,4*R*)-1-*tert*-Butyldimethylsilyloxy-7-benzyloxy-2,3,4-heptanetriol (16)

To a solution of **4** (135 mg, 0.50 mmol) in acetonitrile–pyridine (1:1, 2 mL) in the presence of TMG (12.5 μL, 0.1 mmol) was added TBDMSCl (90 mg, 1.2 equiv.) and the solution was stirred for 3.5 h at room temperature under dry nitrogen atmosphere. CH_2Cl_2 (20 mL) was added and the organic layer was washed with 1 N HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (2 × 10 mL), and dried over $MgSO_4$ and evaporated. Flash chromatography on silica gel (EtOAc/hexane, 3:7) provided **16** (155 mg, 80%); $[\alpha]_D^{23}$ +4.0 (*c* 2.54, $CHCl_3$); IR (neat): 3100–3600, 3030–3090, 2850–3000, 1100–1200 cm^{-1}; ^1H NMR ($CDCl_3$): 7.23 (m, 5H), 4.42 (s, 2H), 3.34–3.76 (m, 7H), 1.60–1.74 (m, 4H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$): 73.91, 72.83, 72.03, 70.33, 70.22, 64.29, 30.78, 26.14, 25.62, 17.99, −5.67. MS (CI, isobutane) *m/e* (rel. intensity): 385 (MH^+, 14), 270 (100).

(2*R*,3*S*,4*R*)-1-*tert*-Butyldimethylsilyloxy-7-benzyloxy-2,3,4-triacetoxyheptane (17)

To a solution of **16** (140 mg, 0.36 mmol) and DMAP (10 mg) in pyridine (1 mL) was added acetic anhydride (0.5 mL) and the solution was stirred for 24 h at room temperature. EtOAc (50 mL) was added and this organic layer was washed with 1 N HCl (3 × 10 mL), with saturated aqueous $NaHCO_3$ (2 × 10 mL), with brine (3 × 10 mL), then dried over $MgSO_4$ and evaporated. Flash chromatography on silica gel (EtOAc/hexane, 1:9) provided **17** (180 mg, 97%) as an oil; $[\alpha]_D^{23}$ +15.7 (*c* 2.8, $CHCl_3$); IR (neat): 3020–3090, 2850–3000, 1740, 1360, 1100–1300 cm^{-1}; ^1H NMR ($CDCl_3$): 7.29 (m, 5H), 5.29 (dd, J_1 = 8.3 Hz, J_2 = 3.3 Hz, 1H), 4.98 (ddd, J_1 = 8.3 Hz, J_2 = 5.1 Hz, J_3 = 3.6 Hz, 1H), 4.45 (s, 2H), 3.71 (dd, J_1 = 11.2 Hz, J_2 = 3.6 Hz, 1H), 3.61 (dd, J_1 = 11.2 Hz, J_2 = 5.1 Hz, 1H), 3.42 (m, 2H), 2.07 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.61 (m, 4H), 0.85 (s, 9H), 0.0 (s, 6H); ^{13}C NMR ($CDCl_3$): 170.39, 169.97, 169.63, 138.49, 128.30, 127.55, 127.46, 72.76, 71.13, 70.96, 70.72, 69.60, 61.50, 25.68, 27.76, 25.44, 20.68, 20.85, 20.91, 5.58. MS (CI, isobutane) *m/e* (rel. intensity): 511 (MH^+, 28), 451 (100), 303 (62), 228 (61).

Acknowledgements

The authors would like to thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support as well as "le Fonds pour les chercheurs et l'aide à la recherche, Québec", for a postgraduate scholarship to M.D.

References

1. B.M. Trost and I. Fleming (*Editors*). Comprehensive organic synthesis. Vol. 2. Pergamon, New York. 1991.
2. C.H. Wong and G.M. Whitesides. *In* Enzymes in synthetic organic chemistry. Pergamon, New York. 1994. Chap. 4.
3. (*a*) E.J. Toone, E.S. Simon, and M.D. Bednarski. Tetrahedron, **45**, 5365 (1989); (*b*) C.H. Wong, R.L. Halcomb, Y. Ichikawa, and T. Kajimoto. Angew. Chem. Int. Ed. Engl. **34**, 412 (1995);

(*c*) W.D. Fessner and G. Sinerius. Angew. Chem. Int. Ed. Engl. **33**, 209 (1994).
4. M. Schultz, H. Waldmann, W. Vogt, and H. Kunz. Tetrahedron Lett. **31**, 867 (1990).
5. M. Shimagaki, H. Muneshima, M. Kubota, and T. Oishi. Chem. Pharm. Bull. **41**, 282 (1993).
6. (*a*) S. Huneck, K. Schreiber, and W. Steglich. Tetrahedron, **29**, 3687 (1973); (*b*) G. Quinkert, N. Heim, J.W. Bats, H. Oschkinat, and H. Kessler. Angew. Chem. Int. Ed. Engl. **24**, 987 (1985).
7. (*a*) D. Enders and O.F. Prokopenko. Justus Liebigs Ann. Chem. 1185 (1995); (*b*) S.C. Sinha and E.J. Keinan. J. Org. Chem. **59**, 949 (1994); (*c*) G. Solladié, I. Fernandez, and C. Maestro. Tetrahedron: Asymmetry, **2**, 801 (1991); (*d*) P.P. Waanders, L. Thijs, and B. Zwanenburg. Tetrahedron Lett. **28**, 2409 (1987); (*e*) G. Quinkert, H. Becker, and G. Dürner. Tetrahedron Lett. **32**, 7397 (1991); (*f*) G. Quinkert, N. Heim, J. Glenneberg, U.M. Billhardt, V. Autze, J.W. Bats, and G. Dürner. Angew. Chem. Int. Ed. Engl. **26**, 362 (1987); (*g*) G. Quinkert, E. Fernholz, P. Eckes, D. Newmann, and G. Dürner. Helv. Chim. Acta, **72**, 1753 (1989).
8. D.A. Evans, K.T. Champman, and E.M. Carriera. J. Am. Chem. Soc. **110**, 3560 (1988).
9. H. Zinner, E. Wittenburg, and G. Rembarz. Chem. Ber. **92**, 1614 (1959).
10. K.H. Park, Y.J. Yoon, and S.G. Lee. Tetrahedron Lett. **35**, 9737 (1994).
11. K. Ishihara, H. Kurihara, and H. Yamamoto. J. Org. Chem. **58**, 3791 (1993).
12. R.L. Pederson, J. Esker, and C.H. Wong. Tetrahedron, **47**, 2643 (1991).
13. I.W. Lawston and T.D. Inch. J. Chem. Soc. Perkin Trans. 1, 2629 (1983).
14. I. Dyong and W. Hohenbrink. Chem. Ber. **110**, 3655 (1977).