Total Synthesis of Oleandrose and the Avermecin Disaccharide, Benzyl α-L-Oleandrosyl-α-L-4-acetoxyoleandroside

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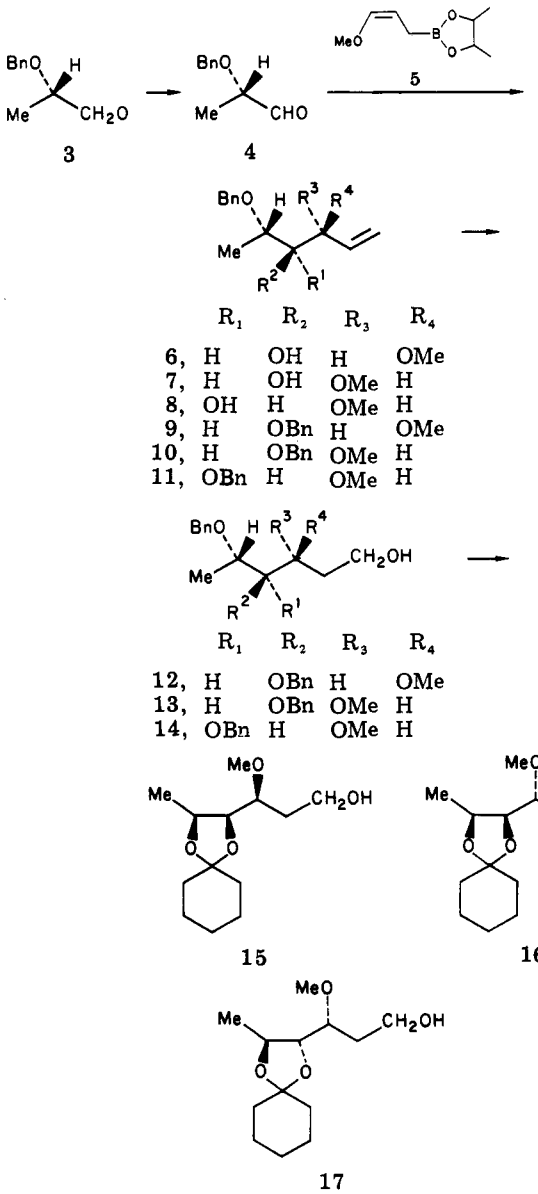
The synthesis of oleandrose, the key carbohydrate of the avermectins, and its elaboration to the avermectin disaccharide are described. The three contiguous asymmetric centers of oleandrose are introduced by the reaction of a γ-methoxyallyl boronate with (*S*)-2-(benzyloxy)propanol to give a 8.7:1.2:1.0 mixture of diastereomers, the major of which has the oleandrose stereochemistry. The disaccharide was prepared by coupling of 1-*S*-(2-pyridyl)-4-*O*-methyl-L-1-thiooleandroside with benzyl α-L-oleandroside in the presence of $Pb(ClO_4)_2$.

The recent isolation and structure determination of the avermectins[1,2] has prompted our interest in their synthesis primarily because of their potent anthelmintic as well as ecto- and endo-antiparasitic activity. Our interest in these compounds has led us to explore the synthesis of the disaccharide fragment which consists of two oleandrose units coupled with a linkage at the C-4 hydroxyl.

We[3] and Hoffmann[4] have recently reported on a method for the stereospecific synthesis of selectively protected 1,2-diol derivatives. We now report on the application of this methodology in the synthesis of oleandrose (1), the key carbohydrate present in the avermectins, and its coupling to form the disaccharide **2**. To secure the carbohydrate in its correct configuration, we chose the L-alcohol **3** ($[\alpha]_D$ +28.48° (neat))[5] as our starting material. Swern[6] oxidation of alcohol **3** gave in 88% yield aldehyde **4** ($[\alpha]_D$ −65.9°), which was treated with boronate **5** to give the triol derivative **6** along with two other minor isomers (**7** and **8**) in an 84% yield and a ratio of 8.7:1.2:1 as determined by GC. This mixture could not be separated on a preparative scale and was thus carried on to the alcohols **12–14** where they were chromatographically separated. The addition reaction is expected to proceed in accord with the Felkin model[7] (Figure 1) where the oxygen substituent is the largest group, and thus the anti form of the diol is produced which has the desired C4–C5 stereochemistry of oleandrose (Scheme I).[8]

The stereochemistry of the remaining two minor isomers was confirmed by conversation of all three isomers to their respective cyclohexanone ketals (**15–17**). This was readily accomplished by protection of the alcohol with benzyl bromide and potassium hydride to give the triethers **9–11**. Hydroboration of the triethers led to alcohols **12–14** which were converted to the cyclohexanone ketals **15–17** after hydrogenolysis of the benzyl groups. Examination of the 360-MHz NMR of the major isomer **15** revealed a 5.86-Hz coupling for H4 and H5 and 7.68 Hz for H3 and H4. The second most abundant isomer had a H4–H5 coupling of 5.86 Hz and an H3–H4 coupling of 8.79 Hz, thus, indicating

Scheme I



stereochemical parity with the major isomer at C4 and C5. This product must then be isomeric at C3 and have the stereochemistry shown in structure **16**. The remaining isomer had coupling constants of 6.00 and 7.60 Hz for H4–H5 and H3–H4, respectively, indicating a different stereochemistry from that of the other two isomers at the C4–C5 bond. This isomer must then be the result of addition of the boronate from the opposite face of the carbonyl (see Figure 1). The C3–C4 stereochemistry of this isomer could not be absolutely confirmed but is presumed

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(2) Springerr, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1981**, *103*, 4221–4224.

(3) Wuts, P. G. M.; Bigelow, S. S. *Synth. Commun.* **1982**, *12*, 779. Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1982**, *47*, 2498.

(4) Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1980**, *21*, 4883; **1981**, *22*, 5263.

(5) Abbott, S. J.; Jones, S. R.; Weinman, S. A.; Bockhoff, W.; McLafferty, F. W.; Knowles, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 4323–4332.

(6) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(7) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.

(8) C. Heathcock makes a similar argument for the selectivity observed in the reactions of enolates with α-alkoxy aldehydes. Hearthcock, C. H. In "Comprehensive Carbanion Chemistry"; Durst, T., Bunsel, E., Eds.; Elsevier: Amsterdam, in press.

0022-3263/83/1948-3489$01.50/0

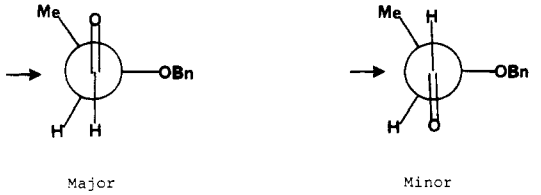
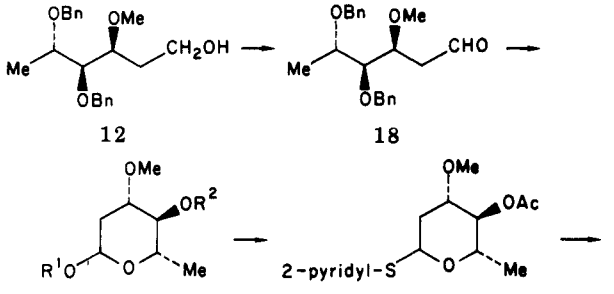
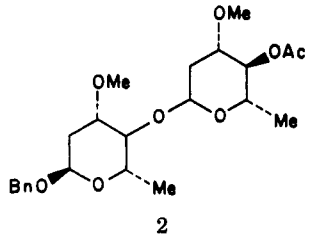


Figure 1. Felkin model for carbonyl addition.

Scheme II



1, H H
19α, Bn H
19β, Bn H
20α, Bn Ac
21β, H Ac
22, Bn MTPA



to be that shown in structure 17, a not unreasonable assumption in light of the usual stereochemical course of the reaction of allylboronates with aldehydes.[3,4]

For completion of the synthesis of oleandrose (Scheme II), the alcohol **12** was oxidized with pyridinium chlorochromate[9] in 77% yield to aldehyde **18** which was deprotected by hydrogenolysis of the benzyl groups to give oleandrose (1) in 85% yield.[12,13] Structural confirmation of our synthetic material was accomplished by conversion to the methyl glycoside which was found to be spectroscopically indistinguishable from the methyl glycoside derived from methanolysis of avermectin B2α.[10,11]

The observed optical rotation for our synthetic oleandrose was found to be +10.3° which is 1.6° lower than that reported for natural oleandrose[12] and must be a result of racemization of the aldehyde **4** either during its preparation or during the condensation with the boron reagent. Racemization was confirmed by synthesis of the MTPA ester of the benzyl glycoside of oleandrose **19a** and examination of the 360-MHz NMR which showed a 20:1 ratio of diastereomers representing a 90% enantiomeric excess (ee) which is in accord with a value of 87% calculated form the optical rotation.[14]

It was felt that racemization probably occurs during the synthesis of aldehyde **4**. For confirmation of this a sample of the aldehyde **4** was reduced with $LiAlH_4$ to give alcohol **3**, $[\alpha]^{21}_D$ +46.0° (*c* 3.95, $CHCl_3$). The optical rotation was found to be 1.4° lower, thus establishing a small degree of racemization in the aldehyde. Furthermore, conversion of the resulting alcohol to the MPTA ester shows a 96.4:3.6 ratio of diastereomers which represents a 89% ee which is within experimental error of the value determined from synthetic oleandrose.

We next turned our attention to the synthesis of the avermectin disaccharide (**2**). The coupling of two oleandrose units requires protection of the C4 hydroxyl and activation of the anomeric center in one unit and a free C4 hydroxyl and protection of the anomeric center of the other unit. These requirements are easily met by first conversion of oleandrose (**1**) to its benzyl glycoside with benzyl alcohol and hydrogen chloride to give a 10:1 mixture of the α and β glycosides **19**α and **19**β in 77% yield. Acetylation of the α isomer gave a 91% yield of acetate **20**α which was deprotected by hydrogenolysis to give in 93% yield acetates **21**α,β. Activation of the anomeric center was accomplished by conversion of pyranosides **21**α,β to the 2-pyridylthioglycosides **23**α and **23**β[15] as a 1:2.4 mixture which could readily be separated, but this proved to be unnecessary for the coupling reaction since the mixture of the pure β isomer gave the same isomeric ratio in the final coupling reaction. The coupling reaction was accomplished by the action of $Pb(ClO_4)_2$ on a mixture of the thioglycosides **23**α and **23**β and benzylglycoside **19**α, giving a 59% yield of a mixture of disaccharides ($\alpha\alpha/\alpha\beta$ ratio of 3:1), with the natural isomer predominating. The α,α stereochemistry of the major isomer could readily be discerned from its NMR spectrum. The anomeric proton for the new glycosidic bond displayed a 3.84-Hz coupling and a 0-Hz coupling for the axial–equatorial and equatorial–equatorial protons whereas the α,β-isomer displayed an axial–axial coupling of 5.28 Hz and an axial–equatorial coupling of 3.84 Hz. The natural material had a 3.0-Hz doublet for the related anomeric hydrogen and thus confirms our isomer assignments. The poor anomeric ratio is presumably due to the fact that oleandrose is a 2-deoxy sugar and thus lacks the electronic and steric directing effects of the C2 substitutent as is commonly observed in glycoside synthesis.[16]

Experimental Section

Preparation of 2(*S*)-(Phenylmethoxy)propanal (4). Under an atmosphere of argon, oxalyl chloride (2.5 mL, 27.5 mmol) in

(9) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(10) We thank the Merck Co. for a generous sample of avermetcin B2α.

(11) Methyl oleandroside was isolated as described in ref 1.

(12) For an early synthesis of oleandrose confirming its absolute configuration see: Blindenbacher, V. F.; Reichstein, T. *Helv. Chim. Acta* **1948**, *31*, 2061–2062. Isolation from oleandrin: Reichstein, T.; Rangaswami, S. *Helv. Chim. Acta* **1949**, *32*, 939–940, $[\alpha]^{20}_D$ = +11.9 + −2.5 (*c* 0.917, H_2O).

(13) For a recent syythesis of 2,6-dideoxy-D-*arabino*-hexose which is enantiomeric with oleandrose and lacks the C-3 *O*-methyl see: Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1982**, *47*, 1371–1737.

(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

(15) Hanessian, S.; Bacquet, C.; Lehong, A. *Carbohydr. Res.* **1980**, *80*, C17. Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Valduchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N. C. *J. Am. Chem. Soc.* **1981**, *103*, 3213 and references therein.

(16) For recent reviews see: Bochkov, A. F.; Zaikov, G. E. "Chemistry of the O-Glycosidic Bond: Formation and Cleavage"; Pergamon Press: Oxford, 1979. Igarashi, K. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 243. Hanessian, S.; Banoub, J. *Adv. Chem. Ser.* **1976**, *No. 39*, 36.

(17) Glycosidation was also attempted by using Konigs–Knorr methodology but proved entirely unsatisfactory. Glycosyl halide formation generally gives both the α and β halides.

63 mL of dry CH_2Cl_2 was placed in a 250-mL three-necked flask equipped with a thermometer, two dropping funnels, and magnetic stirring. The solution was cooled to −60 °C (dry ice, $CHCl_3$), and a solution of Me_2SO (4.25 mL, 55 mmol) in 12 mL of dry CH_2Cl_2 was added with exothermic gas evolution, keeping the temperature below −50 °C. After 20 min, a solution of 2(*R*)-(phenylmethoxy)propanol (1.66 g, 10 mmol) in 25 mL of dry CH_2Cl_2 was added, the addition being completed within 5 min. Stirring was contained for 15 min before triethylamine (17.4 mL, 125 mmol) was added, keeping the temperature below −40 °C. After 5 min the reaction mixutre was warmed to room temperature, and 10 min later the reaction mixture was poured into water, the layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined extracts were washed once with 1% HCl and once with 5% Na_2CO_3, dried over $MgSO_4$, filtered, and concentrated to give 3.61 g (88%) of pure aldehyde after bulb-to-bulb distillation (0.1 mmHg, 100 °C): IR (film) 3070, 3040, 2990, 2870, 2710, 1740, 1500, 1460, 1380, 1130, 1100, 740, 700 cm^{-1}; NMR ($CDCl_3$) 9.66 (d, J = 1.92 Hz, 1 H), 7.32 (m, 5 H), 4.64 (AB q, J = 11.04 Hz, $\Delta\nu$ = 20.17 Hz, 2 H), 3.89 (dq, J_1 = 1.92 Hz, J_2 = 6.72 Hz, 1 H), 1.33 (d, J = 6.7 Hz, 3 H) ppm; $[\alpha]^{20}_D$ −65.85° (neat oil). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.16; H, 7.37.

Preparation of (3*S*,4*S*,5*S*)-5-(Benzyloxy)-4-hydroxy-3-methoxy-1-hexene (6). A solution of 3-methoxypropene (4.3 g, 60 mmol) in dry THF (40 mL) was stirred and cooled to −78 °C under an argon atmosphere. To this was added, via syringe, *sec*-butyllithium (1.1 M in cyclohexane, 54.5 mL, 60 mmol) to produce a cloudy yellow mixture which was stirred 15 min before the addition of 4,5-dimethyl-2-fluoro-1,3-dioxa-2-boracyclopentane (2.4 M in benzene, 25 mL, 60 mmol), discharging the yellow color. Stirring was continued for 30 min at −78 °C whereupon 3.3 g (20.4 mmol) of 2(*S*)-(phenylmethoxy)propanal was added. The solution was allowed to slowly warm to room temperature, and stirring was continued for 7 days. The addition of 20 mL (3.0 M in acetone) of $(EtOH)_3N$ solution produced a fine white precipitate which after an additional hour of stirring was removed by filtering through a Celite pad, washing with dry acetone. The filtrate was concentrated to a thick oil which was washed onto a short column of silica with dry acetone and allowed to stand several hours before elution with 55% ethyl acetate in hexane, gradually increasing the solvent polarity until all the desired triol derivative was collected as determined by TLC analysis of the eluant. This material was concentrated (11.2 g) and purified by MPLC (linear gradient elution, 5–50% ethyl acetate in hexane), affording 4.1 g (84%) of the desired triol derivative along with two minor products in a ratio of 8.7:1.2:1.0 after bulb-to-bulb distillation (0.1 mmHg, 150 °C: IR (film) 3450, 2980, 2940, 1650, 1460, 1090, 745, 705 cm^{-1}; NMR ($CDCl_3$) 7.33 (m, 5 H), 5.71 (ddd, J_1 = 7.71 Hz, J_2 = 11.06 Hz, J_3 = 16.47 Hz, 1 H), 5.28 (m, 2 H), 4.53 (AB q, $\Delta\nu$ = 42.93 Hz, J = 11.72 Hz, 2 H), 3.69 (dd, J_1 = 4.68 Hz, J_2 = 7.70 Hz, 1 H), 3.59 (m, 2 H), 3.29 (s, 3 H), 2.40 (br s, 1 H), 1.24 (d, J = 6.06 Hz, 3 H) ppm; $[\alpha]^{22}_D$ +43.135° (neat oil). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.94; H, 8.38.

Preparation of (3*S*,4*S*,5*S*)-4,5-Bis(benzyloxy)-3-methoxy-1-hexene (9). Potassium hydride (6.40 g, 25% in oil, 40 mmol) was washed twice with hexane and once with dry THF, suspended in 12 mL of dry THF with stirring, and cooled to 0 °C under argon. A solution of 4.06 g (17.2 mmol) of (3*S*,4*S*,5*S*)-5-(benzyloxy)-4-hydroxy-3-methoxy-1-hexene (4.06 g, 17.2 mmol) and benzyl chloride (3.96 mL, 34.4 mmol) in THF (4 mL) was added to the chilled suspension via a dropping funnel in 45 min. The mixture was allowed to warm and stir for 15 min. TLC analysis showed no starting material remaining. The mixture was poured into water, the layers were separated, and the aqueous layer was extracted three times with ether. The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated to an oil. Bulb-to-bulb distillation (180 °C, 0.1 mmHg) gave 5.6 g (100%) of the desired triol derivative, contaminated with a small amount of dibenzyl ether. Column chromatography of 143 mg of distilled oil on 3.7 g of silica, eluting with 10% ethyl acetate in hexane, afforded the analytical sample: IR (film) 3030, 2980, 2930, 2880, 1675, 1505, 1465, 1105, 745, 710 cm^{-1}; NMR ($CDCl_3$) 7.33 (, 10 H), 5.80 (ddd, J_1 = 7.6 Hz, J_2 = 10.30 Hz, J_3 = 17.37 Hz, 1 H), 5.26 (, 2 H), 4.70 (s, 2 H), 4.5 (AB q, $\Delta\nu$ = 41.07 Hz, J = 11.55 Hz, 2 H), 3.79 (m, 2 H), 3.48 (dd, J_1 = 4.35 Hz, J_2 = 5.71 Hz, 1 H), 3.28 (s, 3 H), 1.27 (d, J = 6.26 Hz, 3 H) ppm; $[\alpha]^{29}_D$ +7.75 (neat oil). Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 76.96; H, 7.93.

Preparation of (3*S*,4*S*,5*S*)-4,5-Bis(benzyloxy)-3-methoxyhexanol (12). To a solution of (3*S*,4*S*,5*S*)-4,5-bis(benzyloxy)-3-methoxy-1-hexene (118 mg, 0.36 mmol) in 5 mL of dry THF was added a solution of 9-BBN in THF (0.5 M) at intervals over 3 days until a total of 2.7 mL (1.35 mmol) had been added. The solution was kept under argon at 50 °C during this time. The reaction was completed by the addition of 2 mL of 30% H_2O_2 and stirring continued for 1 h. The aqueous layer was saturated with sodium chloride and the organic layer separated. The aqueous layer was etracted three times with ether, and the combined organic layers were dried and concentrated to an oil which was chromatographed on silica gel, eluting with 35–50% ethyl acetate in hexane to yield 59 mg (0.18 mmol) of unreacted alkene which could be recycled and 42 mg (0.12 mmol, 34%) of the desired alcohol for a total recovery of 83%: IR (film) 3420, 3060, 3020, 2920, 2870, 1500, 1455, 1380, 1100, 1035, 740, 700 cm^{-1}; NMR ($CDCl_3$) 7.35 (m, 10 H), 4.75 (AB q, $\Delta\nu$ = 50.38 Hz, J = 11.48 Hz, 2 H), 4.56 (AB q, $\Delta\nu$ = 49.10 Hz, J = 11.72 Hz, 2 H), 3.73 (m, 3 H), 3.61 (t, J = 9.24 Hz, 1 H), 3.55 (dd, J_1 = 4.80 Hz, J_2 = 6.72 Hz, 1 H), 3.44 (s, 3 H), 2.17 (m, 1), 1.78 (m, 2 H), 1.33 (d, J = 6.72 Hz, 3 H) ppm. Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.33; H, 8.15.

Preparation of (2*S*,3*S*,1′*S*)-, (2*S*,3*S*,1′*R*)-, and (2*R*,3*S*,1′*R*)-2-(3′-Hydroxy-1′-methoxypropyl)-3-methyl-1,4-dioxaspiro[4.5]decanes (15–17). To a solution containing 33.4 mg (0.2 mmol) of a mixture of (3*S*,4*S*,5*S*)-, (3*R*,4*S*,5*S*)-, and (3*R*,4*R*,5*S*)-1,4,5-trihydroxy-3-methyloxyhexane isomers and cyclohexanone (0.21 mL, 2 mmol) in benzene (12 mL) was added a catalytic amount of *p*-toluenesulfonic acid. The solution was refluxed 3 h with a Dean–Stark trap, K_2CO_3 added, the mixture filtered, and the solvent removed. The crude oil was chromatographed on silica, eluting with 35% ethyl acetate in hexane to afford 8.2 mg (17%) of a 2:1 mixture of minor diastereomers (R_f 0.12 and 0.09) and 36.3 mg (74%) of the major stereoisomer (R_f 0.16): IR (film) 3410, 2930, 2860, 1455, 1370, 1285, 1175, 1130, 1110, 995 cm^{-1}; NMR ($CDCl_3$) 4.22 (dq, J_1 = 6.35 Hz, J_2 = 5.85 Hz, 1 H), 4.06 (dd, J_1 = 5.85 Hz, J_2 = 7.08 Hz, 1 H), 3.79 (m, 2 H), 3.52 (s, 3 H), 3.45 (td, J_1 = 3.90 Hz, J_2 = 7.08 Hz, 1 H), 2.70 (brs, 1 H), 1.85–1.25 (m, 12 H), 1.18 (d, J = 6.35 Hz, 3 H) ppm. Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.70; H, 9.97.

(2*S*,3*S*,1′*R*)- and (2*R*,3*S*,1′*R*)-2-(3′-hydroxy-1′-methoxypropyl)-3-methyl-1,4-dioxaspiro[4.5]decane were inseparable from each other, and the mixture was characterized: IR (film) 3410, 2930, 2860, 1455, 1370, 1285, 1175, 1130, 1110, 995 cm^{-1}. Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.76; H, 10.02.

2*S*,3*S*,1′*R* diastereomer: NMR ($CDCl_3$) 4.39 (dq, J_1 = 6.24 Hz, J_2 = 5.86 Hz, 1 H), 4.02 (dd, J_1 = 5.86 Hz, J_2 = 8.79 Hz, 1 H), 3.83 (m, 2 H), 3.42 (td, J_1 = 5.28 Hz, J_2 = 8.79 Hz, 1 H), 3.35 (s, 3 H), 2.69 (br s, 1 H), 2.08–1.30 (m, 12 H), 1.21 (d, J = 6.24 Hz, 3 H) ppm.

2*R*,3*S*,1′*R* diastereomer: NMR ($CDCl_3$) 4.03 (dq, J_1 = 5.76 Hz, J_2 = 6.00 Hz, 1 H), 3.82 (m, 2 H), 3.59 (dd, J_1 = 6.0 Hz, J_2 = 7.60 Hz, 1 H), 3.43 (s, 3 H), 3.42 (m, 1 H), 1.94–1.20 (m, 12 H), 1.25 (d, J = 5.76 Hz, 3 H) ppm.

Preparation of (3*S*,4*S*,5*S*)-4,5-Bis(benzyloxy)-3-methoxyhexanal (18). Pyridinium chlorochromate (PCC; 2.3 g, 10.5 mmol), sodium acetate (0.17 g, 2.1 mmol), and Celite were dried in a vacuum desiccator over P_2O_5 for several days and then transferred to a 100-mL round-bottomed flask to which 9 mL of dry CH_2Cl_2 was added, and the mixture was stirred and cooled to 0 °C under an argon atmosphere. A solution of 2.4 g (7.0 mmol) of (3*S*,4*S*,5*S*)-4,5-bis(benzyloxy)-3-methoxyhexanol in 9 mL of dry CH_2Cl_2 was added rapidly to the stirred suspension. The mixture was allowed to warm and stir for 2 h, after which TLC analysis showed remaining starting material, so an additional 1.1 g (5 mmol) of PCC was added and the mixture stirred for an additional hour until the reaction was essentially complete. To the black syrupy mixture was added 10 mL dry ether which caused a black granular precipitate to form. The supernate was decanted and the precipitate washed several times with small portions of dry ether, which were combined and passed through a short column of silica. The eluant was concentrated and purified by

MPLC (linear gradient, 25–50% ethyl acetate in hexane) to afford 1.7 g of the desired alcohol and 79 mg of starting alcohol (77% base on consumed starting alcohol): IR (film) 3040, 2980, 2880, 2740, 1735, 1510, 1465, 1385, 1110, 750, 710 cm^{-1}; NMR ($CDCl_3$) 9.59 (m, 1 H), 7.33 (m, 10 H), 4.67 (AB q, J = 11.40 Hz, $\Delta\nu$ = 60.00 Hz, 2 H), 4.56 (AB q, J = 12.00 Hz, $\Delta\nu$ = 60.00 Hz, 2 H), 3.97 (m, 1 H), 3.82 (m, 1 H), 3.52 (dd, J_1 = 4.80 Hz, J_2 = 5.40 Hz, 1 H), 3.36 (s, 3 H), 2.64 (m, 1 H), 1.38 (d, J = 5.40 Hz, 3 H), 1.25 (m, 1 H) ppm; $[\alpha]^{24}_D$ +16.657° (c 671 mg/mL, $CHCl_3$). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.85; H, 7.48.

Preparation of 2,6-Dideoxy-3-*O*-methyl-L-*arabino*-hexopyranose [L-(+)-oleandrose, 1]. To a solution of 670 mg (1.96 mmol) of (3*S*,4*S*,5*S*)-4,5-bis(benzyloxy)-3-methoxyhexanal in 20 mL of freshly distilled THF was added 70 mg of 20% $Pd(OH)_2$ on carbon. The rapidly stirred mixture was exposed to 1 atm of H_2 for 20 h, at which time TLC showed the starting material to have been consumed. The reaction mixture was filtered through Celite and concentrated. Bulb-to-bulb distillation afforded 294 mg (85%) of an oil, which could not be crystallized: IR ($CDCl_3$) 3420, 2980, 2940, 1460, 1420, 1390, 1115, 1090, 1005 cm^{-1}; NMR ($CDCl_3$) for the α anomer 5.38 (br s, 1 H), 3.94 (dd, J_1 = 6.72 Hz, J_2 = 9.60 Hz, 1 H), 3.59 (m, 1 H), 3.42 (s, 3 H), 3.19 (m, 1 H), 2.73 (m, 1 H), 2.61 (m, 1 H), 2.32 (m, 1 H), 1.51 (m, 1 H), 1.30 (d, J = 6.72 Hz, 3 H) ppm; for the β anomer, 4.84 (m, 1 H), 3.42 (s, 3 H), 3.35 (m, 1 H), 3.17 (m, 1 H), 2.73 (m, 1 H), 2.58 (m, 1 H), 2.44 (m, 1 H), 1.49 (m, 1 H), 1.35 (d, J = 6.24 Hz, 3 H), 1.27 (m, 1 H) ppm; α and β were inseparable; $[\alpha]^{23}_D$ +10.3° (c 1.23, water).

Preparation of Benzyl 2,6-Dideoxy-3-*O*-methyl-L-*arabino*-hexopyranoside (Benzyl L-Oleandroside, 19α and 19β). To a solution of 123 mg of L-(+)-oleandrose in 3 mL of dry benzyl alcohol were added a few drops of benzyl alcohol saturated with HCl. After 15 min, TLC analysis showed complete reaction, and the mixture was distilled under aspirator vacuum to remove most of the benzyl alcohol. When only a small amount of liquid remained in the distillation flask, heating was interrupted, and the remainder was distilled bulb-to-bulb at 0.05 mmHg and 150 °C, affording 137 mg (77%) of the benzyl oleandrosides. GC analysis of the mixture showed an anomeric ratio of α/β of 10:1. The major anomer was readily obtained free of β anomer by column chromatography on silica gel, eluting with 10% ethyl acetate in hexane. Pure β anomer was obtained by HPLC of a 1.4:1 β/α mixture, eluting with 30% ethyl acetate in hexane. The pure β glycoside spontaneously crystallized upon removal of the solvent: mp 84 °C; IR ($CDCl_3$) 3580, 3040, 2980, 2935, 2900, 1460, 1390, 1210 cm^{-1}. For the α isomer: $[\alpha]^{24}_D$ −86.650° (c 397, $CHCl_3$); NMR ($CDCl_3$) 7.34 (m, 5 H), 4.98 (d, J = 2.93 Hz, 1 H), 4.55 (AB q, J = 11.96 Hz, $\Delta\nu$ = 85.20 Hz, 2 H), 3.75 (m, 1 H), 3.56 (m, 1 H), 3.38 (s, 3 H), 3.18 (, 1 H, 2.61 (br s, 1 H), 2.32 (m, 1 H), 1.55 (m, 1 H), 1.32 (d, J = 6.24 Hz, 3 H) ppm. For the β anomer: NMR ($CDCl_3$) 7.36 (m, 5 H), 4.75 (AB q, J = 10.56 Hz, $\Delta\nu$ = 110.45 Hz, 2 H), 4.54 (dd, J_1 = 2.40 Hz, J_2 = 9.12 Hz, 1 H), 3.39 (s, 3 H), 3.33 (m, 1 H), 3.18 (m, 1 H), 2.46 (br s, 1 H) ppm. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.79; H, 7.94.

Preparation of Benzyl 2,6-Dideoxy-4-*O*-acetyl-3-*O*-methyl-L-*arabino*-hexopyranoside (Benzyl 4-*O*-Acetyl-L-oleandroside, 20α). A solution of 137 mg (0.54 mmol) of benzyl L-oleandrosides in 5 mL of dry THF was cooled with stirring to 0 °C under an argon atmosphere. Triethylamine (0.14 mL, 1.0 mmol), acetic anhydride (0.09 mL, 1.0 mmol), and (dimethylamino)pyridine (DMAP) (24 mg, 0.2 mmol) were added, and stirring was continued, allowing the solution to warm to room temperature. After TLC analysis showed complete reaction (about 2 h), the solvent was evaporated and the oil partitioned in 10% HCl and ether. The aqueous layer was extracted twice with ether, dried over magnesium sulfate and concentrated, affording 0.146 g (91%) of the anomeric glycosides, chromatography of 70 mg of which on 4 g of silica, eluting with 15% ethyl acetate in hexane, followed by bulb-to-bulb distillation, afforded the anlytical sample. The anomers were inseparable by chromatography: IR (film) 3040, 2990, 2950, 2910, 1755, 1470, 1390, 1250, 1055, 750, 710 cm^{-1}. For the α anomer: NMR ($CDCl_3$) 7.35 (m, 5 H), 4.98 (d, J = 2.88 Hz, 1 H), 4.71 (t, J = 9.60 Hz, 1 H), 4.55 (AB q, J = 12.00 Hz, $\Delta\nu$ = 74.71 Hz, 2 H), 3.81 (m, 1 H), 3.68 (m, 1 H), 3.33 (s, 3 H), 2.31 (dd, J_1 = 5.13 Hz, J_2 = 13.18 Hz, 1 H), 2.10 (s, 3 H), 1.66 (m, 1 H), 1.16 (d, J = 6.59 Hz, 3 H) ppm. For the β anomer: NMR ($CDCl_3$) 7.35 (m, 5 H), 4.75 (AB q, J = 11.04 Hz, $\Delta\nu$ = 110.45 Hz, 2 H), 4.54 (dd, J_1 = 0.96 Hz, J_2 = 9.12 Hz, 1 H), 3.35 (m, 2 H), 3.33 (s, 3 H), 2.37 (m, 1 H), 2.10 (s, 3 H), 1.32 (m, 1 H), 1.25 (d, J = 6.24 Hz, 3 H) ppm; $[\alpha]^{23}_D$ −46.546° (c 1.41, $CHCl_3$); 4.3:1 α/β (NMR). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.35; H, 7.61.

Preparation of 2,6-Dideoxy-4-*O*-acetyl-3-*O*-methyl-L-*arabino*-hexopyranoside (4-*O*-Acetyl-L-oleandrose, 21α and 21β). The hydrogenolysis of 438 mg (1.4 mmol) benzyl 4-*O*-acetyl-L-oleandroside in 10 mL freshly distilled THF over 20% $Pd(OH)_2$ at atmospheric pressure, provided 265 mg (93%) of an inseparable mixture of anomers, after filtration and bulb-to-bulb distillation: $[\alpha]^{23}_D$ −33.912° (c 4.09 $CHCl_3$); 2.4:1 α/β (NMR); IR (film) 3410, 2970, 2930, 1745, 1380, 1245, 1100, 1050 cm^{-1}. For the α anomer: NMR ($CDCl_3$) 5.38 (d, J = 2.32 Hz, 1 H), 4.69 (t, J = 9.47 Hz, 1 H), 4.03 (dq, J_1 = 6.72 Hz, J_2 = 9.47 Hz, 1 H), 3.72 (m, 1 H), 3.36 (s, 3 H), 2.7. (br s, 1 H), 2.31 (ddd, J_1 = 2.30 Hz, J_2 = 4.80 Hz, J_3 = 13.92 Hz, 1 H), 2.12 (s, 3 H), 1.65 (m, 1 H), 1.16 (d, J = 6.72 Hz, 3 H) ppm. For the β anomer: NMR ($CDCl_3$) 4.84 (dd, J_1 = 2.40 Hz, J_2 = 9.60 Hz, 1 H), 4.68 (t, J = 9.47 Hz, 1 H), 3.46 (dq, J_1 = 5.76 Hz, J_2 = 10.08 Hz, 1 H), 3.37 (m, 1 H), 3.11 (s, 3 H), 2.79 (br s, 1 H), 2.44 (ddd, J_1 = 1.92 Hz, J_2 = 4.80 Hz, J_3 = 12.48 Hz, 1 H), 2.11 (s, 3 H), 1.54 (m, 1 H), 1.22 (d, J = 5.28 Hz, 3 H) ppm.

Preparation of 2-*S*-(2′-Pyridyl)-2,6-dideoxy-4-*O*-acetyl-3-*O*-methyl-2-thio-L-*arabino*-hexopyranoside [2-*S*-(2′-Pyridyl)-4-*O*-acetyl-L-thiooleandroside, 23α and 23β). A solution of 100 mg of 4-*O*-acetyl-L-oleandrose anomers in 2 mL of dry CH_2Cl_2 was stirred and cooled to 0 °C under an argon atmosphere. 2,2′-Dithiodipyridine (129 mg, 0.59 mmol) was added, followed by (n-Bu)$_3$P (0.15 mL, 0.6 mmol). After 3 h, TLC showed complete reaction. The reaction mixture was concentrated, and flash chromatography afforded the anomeric thiooleandrosides: α, 38.6 mg (26.5%); β, 91.3 mg (62.6%). The β anomer crystallized spontaneously upon evaporation of the solvent and was recrstallized from petroleum ether: mp 94.5–95.5 °C; IR (CCl_4) 3040, 2980, 2920, 2870, 2820, 1745, 1625, 1580, 1530, 1455, 1418, 1375, 1235, 1090 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71; S, 10.78. Found: C, 56.46; H, 6.37; N, 4.59; S, 10.74. For the α anomer: $[\alpha]^{24}_D$ −4.52° ($CHCl_3$); NMR ($CDCl_3$) 8.45 (m, 1 H), 7.55 (m, 1 H), 7.31 (m, 1 H), 7.07 (m, 1 H), 6.38 (d, J = 8.64 Hz, 1 H), 4.73 (t, J = 9.69 Hz, 1 H), 4.12 (m, 1 H), 3.60 (m, 1 H), 3.38 (s, 3 H), 2.52 (m, 1 H), 2.12 (s, 3 H), 1.27 (t, J = 5.76 Hz, 1 H), 1.16 (d, J = 6.24 Hz, 3 H) ppm. For the β anomer: $[\alpha]^{24}_D$ 118° (c 0.076, $CHCl_3$); NMR ($CDCl_3$) 8.48 (m, 1 H) 7.54 (m, 1 H), 7.27 (m, 1 H), 7.06 (m, 1 H), 5.61 (dd, J_1 = 2.40 Hz, J_2 = 10.56 Hz, 1 H), 4.72 (dt, J_1 = 2.88 Hz, J_2 = 9.12 Hz, 1 H), 3.57 (m, 1 H), 3.48 (m, 1 H), 3.37 (s, 3 H), 2.55 (m, 1 H), 2.12 (s, 3 H), 1.88 (m, 1 H), 1.22 (d, J = 5.76 Hz, 3 H) ppm.

Preparation of Benzyl 4-*O*-(4-*O*-Acetyl-L-oleandrosyl)-L-oleandroside (2). A solution of 1-*S*-(2′-pyridyl)-4-*O*-acetyl-L-thiooleandroside anomers (176 mg, 0.529 mmol) and benzyl α-L-oleandroside (45 mg, 0.178 mmol) in 2 mL of dry THF was kept over 4A molecular sieves under an argon atmosphere for 12 h. A separate solution of $Pb(ClO_4)_2$ (0.27 M in THF) was prepared from dry $Pb(ClO_4)_2$ (vacuum desiccator, P_2O_5) and kept dry in a similar manner over 4A sieves, until 3.7 mL (1.0 mmol) of this was added to the solution of glycosides. After 4 h, 1 mL (0.3 mmol) of additional $Pb(ClO_4)_2$ solution was added, and 4 h later this was repeated. The reaction was followed by TLC during this time, and no further change was noted after 8 h. The reaction mixture was concentrated and chromatographed on a silica column, eluting with 25–50% ethyl acetate in hexane, affording 46 mg (59%) of a mixture of disaccharides (3:1 $\alpha\alpha/\alpha\beta$ by GC). A similar experiment in which only β-L-thiooleandrosie was used afforded essentially the same anomeric mixture: IR (CCl_4) 2970, 2940, 2860, 1755, 1465, 1130, 1245 cm^{-1}; $[\alpha]^{24}_D$ −141.739° (c 0.23, $CHCl_3$). Anal. Calcd for $C_{23}H_{34}O_8$: C, 63.00; H, 7.82. Found: C, 63.11; H, 7.83. For the $\alpha\alpha$ anomer: NMR ($CDCl_3$) 7.36 (m, 5 H), 5.40 (d, J = 3.84 Hz, 1 H), 4.95 (d, J = 3.84 Hz, 1 H), 4.67 (t, J = 10.08 Hz, 1 H), 4.56 (AB q, J = 11.04 Hz, $\Delta\nu$ = 78.25 Hz, 2 H), 3.85 (dq, J_1 = 6.72 Hz, J_2 = 3.84 Hz, 1 H), 3.74 (dq, J_1 = 5.76 Hz, J_2 = 3.84 Hz, 1 H), 3.62 (m, 2 H), 3.35 (s, 6 H), 3.26 (t, J = 8.64 Hz, 1 H), 2.30 (m, 2 H), 2.11 (s, 3 H), 1.65 (m, 1 H), 1.55 (m, 1 H), 1.30 (d, J = 6.24 Hz, 3 H), 1.15 (d, J = 6.24 Hz, 3 H) ppm. For the $\alpha\beta$ anomer: NMR ($CDCl_3$) 7.36 (m, 5 H), 5.66 (dd, J_1 = 3.84 Hz, J_2 = 5.28 Hz, 1 H), 4.94 (m, 1 H), 4.67 (t, J = 10.08 Hz, 1 H), 4.55

(AB q, J = 12.00 Hz, $\Delta\nu$ = 68.16 Hz, 2 H), 3.98-3.62 (m, 4 H), 3.37 (s, 6 H), 3.26 (m, 1 H), 2.30 (m, 2 H), 2.05 (s, 3 H), 1.60 (m, 2 H), 1.32 (d, J = 6.24 Hz, 3 H), 1.26 (d, J = 6.24 Hz, 3 H) ppm.

Preparation of Benzyl 2-*O*-[α-Ethxoy-α-(trifluoromethyl)phenylacetyl]-β-L-oleandroside (22). Benzyl β-L-oleandroside (5 mg, 0.02 mmol) was dissolved in 2 mL of dry CCl_4, and 5 drops of dry pyridine were added, followed by distilled (-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.09 g, 0.3 mmol). The solution was stirred 12 h at ambient temperature before being passed through a column of silica gel, eluting with 25% ethyl acetate in hexane, to yield 10 mg (100%) of the desired ester. GC and 360-MHz ^{1}H NMR analyses showed a 20:1 ratio of the desired diastereomeric esters. A 90-MHz ^{13}C NMR broad-band decoupled spectrum failed to show any diasteromeric material: IR (CCl_4) 3060, 3030, 2940, 1765, 1500, 1460, 1250, 1200, 1130, 1030, 925, 865 cm^{-1}; NMR ($CDCl_3$) 7.63 (m, 2 H), 7.39 (m, 8 H), 4.94 (t, J = 9.60 Hz, 1 H), 4.75 (AB q, J = 11.52 Hz, $\Delta\nu$ = 113.33 Hz, 2 H), 4.54 (dd, J_1 = 1.44 Hz, J_2 = 10.08 Hz, 1 H), 3.59 (d, J = 0.48 Hz, 3 H), 3.42 (m, 2 H), 3.33 (s, 3 H), 2.45 (ddd, J_1 = 1.44 Hz, J_2 = 4.80 Hz, J_3 = 12.48 Hz, 1 H), 1.69 (m, 1 H), 1.22 (d, J = 5.76 Hz, 3 H) ppm; $[\alpha]^{22}_D$ +39.25° (c 0.823). Anal. Calcd for $C_{24}H_{27}O_6F_3$: C, 61.53; H, 5.81; F, 12.17. Found: C, 61.32; H, 5.77; F, 12.30.

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Registry No. α-1, 87037-59-0; β-1, 87037-60-3; **2** (isomer 1), 86971-99-5; **2** (isomer 2), 86972-00-1; **3**, 33106-64-8; **4**, 81445-44-5; **5**, 86972-01-2; **6**, 86972-02-3; **7**, 87037-61-4; **8**, 87037-62-5; **9**, 86972-03-4; **10**, 87037-63-6; **11**, 87037-64-7; **12**, 86972-04-5; **13**, 87037-65-8; **14**, 87037-66-9; **15**, 86972-05-6; **16**, 87037-67-0; **17**, 87037-68-1; **18**, 86972-06-7; **19**α, 86972-07-8; **19**β, 86972-08-9; **20**α, 86972-09-0; **20**β, 86972-10-3; **21**α, 86972-11-4; **21**β, 86972-12-5; **22**, 86972-13-6; **23**α, 86972-14-7; **23**β, 86972-15-8; oxalyl chloride, 79-37-8; 2(*R*)-(phenylmethoxy)propanol, 87037-69-2; 3-methoxypropene, 627-40-7; 4,5-dimethyl-2-fluoro-1,3-dioxa-2-boracyclopentane, 86972-16-9; (-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 39637-99-5.

Chemical and Enzymatic Syntheses of 6-Deoxyhexoses. Conversion to 2,5-Dimethyl-4-hydroxy-2,3-dihydrofuran-3-one (Furaneol) and Analogues[1]

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6-Deoxy-D-fructose 1-phosphate (6-deoxyF-1-P) forms when a solution containing D-fructose 1,6-diphosphate (FDP) and D-lactaldehyde is treated with the enzymes aldolase and triosephosphate isomerase (Scheme I). This transformation involves three reactions: aldolase-catalyzed cleavage of FDP to a mixture of dihydroxyacetone phosphate and D-glyceraldehyde phosphate, triosephosphate isomerase catalyzed equilibration of dihydroxyacetone phosphate and D-glyceraldehyde phosphate, and aldolase-catalyzed condensation of dihydroxyacetone phosphate and D-lactaldehyde to 6-deoxyF-1-P. An analogous process converts a mixture of FDP and L-lactaldehyde to 6-deoxysorbose 1-phosphate (6-deoxyS-1-P). Aldolase-catalyzed reaction of dihydroxyacetone phosphate, prepared separately, with D-lactaldehyde yields 6-deoxyF-1-P directly; similar reaction of dihydroxyacetone phosphate with α-hydroxybutyraldehyde yields a mixture of 6-methyl-6-deoxyhexose 1-phosphates. Acid-catalyzed hydrolysis of the sugar phosphates releases the corresponding free sugars. A mixture containing 6-deoxyhexoses is formed directly by base-catalyzed aldol condensation of dihydroxyacetone and D,L-lactaldehyde. Treatment of any of the 6-deoxyhexoses with acids generates 2,5-dimethyl-4-hydroxy-2,3-dihydrofuran-3-one (Furaneol, a flavor principle). Furaneol can also be prepared in moderate yields by hydrogenolysis of FDP and other hexose phosphates in alkaline media.

Introduction

This paper describes procedures using enzyme-catalyzed and conventional chemical steps for the preparation of unusual sugars. We have described previously the use of aldol condensations catalyzed by aldolase (EC 4.1.2.13, from rabbit muscle) as a route to isotopically labeled glucose 6-phosphate and fructose 6-phosphate.[3] The work reported here uses aldolase in analogous preparations of 6-deoxyhexoses and 6,7-dideoxyheptoses and compares enzymatic and conventional chemical routes to these substances. These deoxyhexoses are precursors to 2,5-dimethyl-4-hydroxy-2,3-dihydrofuran-3-one[4-6] (Furaneol, a caramel flavor component[2]). Because 6-deoxy sugars are relatively unusual in nature, we were interested in developing practical synthetic routes to them.

Rabbit muscle aldolase is commercially available and stable in the immobilized form. It requires dihydroxyacetone phosphate (DHAP)[7] as one reactant in the aldol

(1) Supported by the National Institutes of Health, Grants GM-26543 and GM 30367, and by Firmenich, SA. Inquiries should be addressed to G.M.W. at the Department of Chemistry, Harvard University, Cambridge, MA 02138.

(2) Firmenich, SA, Geneva, Switzerland. Furaneol is a registered trademark of Firmenich, Inc.

(3) Wong, C-H.; Whitesides, G. M. *J. Am. Chem. Soc.* **1983**, *105*, 5012. Attempted oxidation of D,L-glycerol phosphate (easily prepared from glycerol by reaction with $POCl_3$ in acetone in 50% yield) with bromine or hypochlorite resulted in low yields of product (~10% of the starting material was oxidized on treatment with these oxidants for 24 h at room temperature). The product contained both DHAP and D,L-glyceraldehyde 3-phosphate.

(4) Matsui, M.; Ogawa, T.; Tagaki, K. (T. Hagegawa, Co. Ltd.), Jpn. Kokai Tokkyo Koho 79, 19962, 15 feb 1979. In addition to 6-deoxyglucose, 6-deoxy-L-mannose has been converted to Furaneol. We have also found that both 6-deoxy-D-galactose (D-fucose) and 6-deoxy-L-galactose (L-fucose) are good starting materials for the preparation of Furaneol. Of the reaction conditions tested, piperidine acetate in absolute ethanol is the best acid-base catalyst system for the conversion and Furaneol has been prepared consistently in ~80% yield at ~80 °C from 6-deoxyhexoses with use of this catalyst.

(5) Hadyi, J. E. U.S. Patent 2 936 308.

(6) Prepared chemically from: 3-hexyne-2,5-diol (Re, L.; Maurer, B.; Ohloff, G. *Helv. Chim. Acta* **1973**, *56*, 1882-94); 2,5-dimethylfuran, and pyruvaldehyde (Büchi, G.; Demole, E. *J. Org. Chem.* **1973**, *38*, 123-5).

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