Synthesis of Branched-Chain Nitro Sugars. A Stereoselective Route to D-Rubranitrose

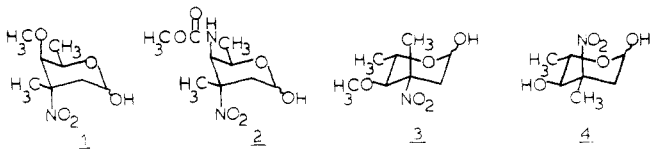
Robert M. Giuliano,* Ted W. Deisenroth, and Walter C. Frank

Department of Chemistry, Villanova University, Villanova, Pennsylvania 19085

Received December 11, 1985

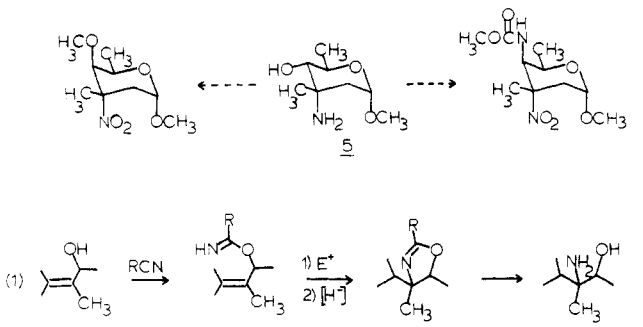
The synthesis of methyl 3-amino-2,3,6-trideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (**5**), a key intermediate in the synthesis of nitro sugars **1** and **2**, is described. Using a new method for the transformation of allylic alcohols to *cis*-1,2-amino alcohols, allylic alcohol **7** was converted to the imidate **12** by reaction with dimethylcyanamide and sodium hydride. Cyclization of **12** in the presence of mercuric trifluoroacetate followed by demercuration gave oxazoline **13** exclusively. Hydrolysis of **13** with barium hydroxide gave the desired amino alcohol **5**. The use of trichloroacetonitrile as a reagent for the conversion of **7** to **5** was also investigated. The amino alcohol **5** was converted to the *N*-acetyl derivative **11**, a known precursor to the nitro sugar D-rubranitrose. Oxidation of **5** with MCPBA gave the corresponding nitro alcohol **14**.

The four naturally occurring nitro sugars, D-rubranitrose[1] (**1**), D-kijanose[2] (**2**), L-evernitrose[3] (**3**), and L-decilonitrose[4] (**4**), exists as components of the antibiotics rubradirin, kijanimicin and tetrocarcins A and B, everninomicin, and arugomycin and decilorubicin, respectively. Owing to their unusual structure and possible role in antibiotic activity,[5] these carbohydrates have been viewed as attractive synthetic targets, and a number of syntheses have been reported.[6-8]



These nitro sugars contain, as a common structural unit, a geminally substituted carbon bearing methyl and nitro groups. It is the construction of this tertiary center, with stereochemical control, that is the most critical part of the synthetic strategy for this class of compounds. With few exceptions, syntheses of branched-chain nitro sugars have relied on the use of spiro-aziridines as intermediates from which the geminal functionality is derived sequentially by reductive ring opening and oxidation of the resulting amine.[6] This approach has also been used in the synthesis of the branched-chain amino sugar vancosamine.[9] Despite its success, the spiro-aziridine route to branched-chain nitro sugars suffers from its considerable length and the production of diastereomers, the latter being most significant in cases where the carbon–nitrogen bond at the C-3 position is axial. These difficulties associated with nitro sugar synthesis indicate the need for more efficient methods.

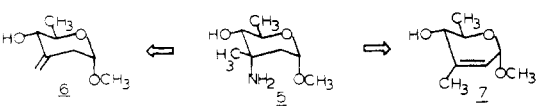
As part of a continuing effort to develop new approaches to the synthesis of branched-chain carbohydrates,[10] we have discovered an efficient synthesis of amino alcohol **5**, a key intermediate for the synthesis of both **1** and **2**. Our approach is based on the electrophilic cyclization of an allylic imidate obtained by the base-catalyzed addition of the corresponding alcohol to a nitrile (eq 1). Cyclization



produces an oxazoline from which the desired amino alcohol is obtained by hydrolysis. The amino functionality is then converted to a nitro group by peracid oxidation. Imidates derived from trichloroacetonitrile and dimethylcyanamide were examined in this approach. The use of the latter has resulted not only in an efficient synthesis of **5** but also in a new method for the conversion of allylic alcohols to cis-1,2-amino alcohols.

Results and Discussion

The successful use of allylic trichloroacetimidates as precursors to cis amino alcohols in the synthesis of nonbranched amino sugars such as daunosamine[11] and ristosamine[12] suggested that these derivatives might provide access to carbohydrates containing geminally functionalized centers if the double bond of the starting allylic alcohol is appropriately substituted. Retrosynthetic analysis of **5** based on this transformation reveals two allylic alcohols, **6** and **7**, as possible precursors.

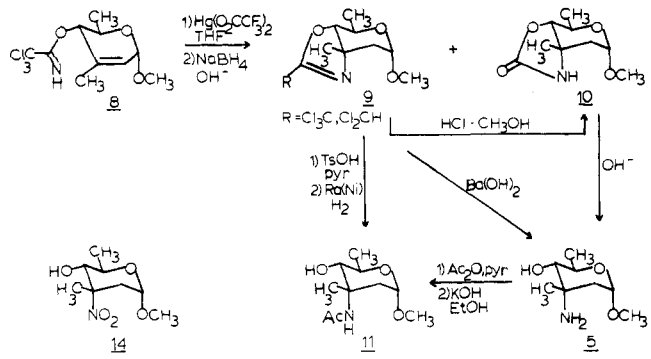


The 3-C-methylene sugar **6** was shown previously[13] to give poor yields of the corresponding imidate when treated

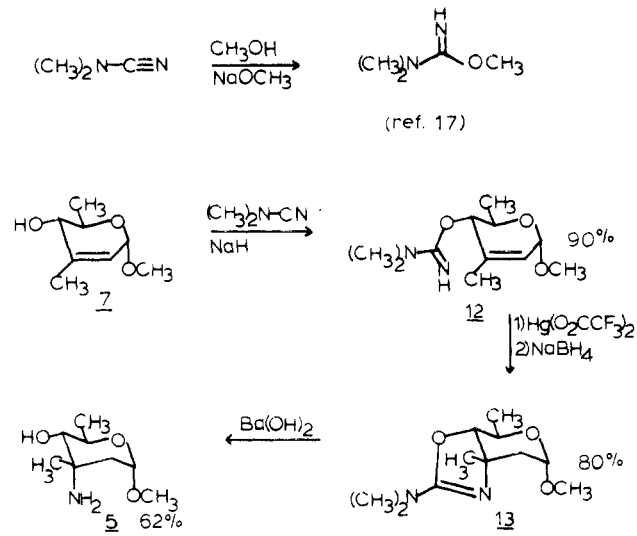
(1) Mizsak, S. A.; Hoeksema, H.; Pschigoda, L. M. *J. Antibiot.* **1979**, *32*, 771–772.
(2) Mallams, A. K.; Puar, M. S.; Rossman, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3938–3940.
(3) Ganguly, A. K.; Sarre, O. Z.; McPhail, A. T.; Onan, K. D. *J. Chem. Soc., Chem. Commun.* **1972**, 313–314.
(4) Kawai, H.; Hayakawa, Y.; Nakagawa, M.; Furihata, K.; Seto, H.; Otake, N. *Tetrahedron Lett.* **1984**, *25*, 1941–1944.
(5) Reusser, F. *J. Antibiot.* **1979**, *32*, 1186–1192.
(6) Yoshimura, J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69–134. Brimacombe, J. S.; Rahman, K. M. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1067–1072, 1073–1079.
(7) Yoshimura, J.; Yasumori, T.; Kondo, T.; Sato, K.-I. *Carbohydr. Res.* **1982**, *106*, C1–C3.
(8) Brimacombe, J. S.; Rahman, K. M. M. *Carbohydr. Res.* **1983**, *114*, C1–C2.
(9) Thang, T. T.; Winternitz, F.; Olesker, A.; Lagrange, A.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1979**, 153–154.
(10) Giuliano, R. M. *Carbohydr. Res.* **1985**, *131*, 341–345.
(11) Fraser-Reid, B.; Pauls, H. W. *J. Chem. Soc., Chem. Commun.* **1982**, 1031–1032.
(12) Bognini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1983**, *39*, 3801–3806.
(13) Frank, W. C. Ph.D. Thesis, University of Virginia, 1982.

0022-3263/86/1951-2304$01.50/0

Scheme I



Scheme II



with trichloroacetonitrile. This is presumably due to the steric effects imposed on the C-4 hydroxyl group by the alkyl substituents on C-3 and C-5 and the axial group at C-1. Endocyclic olefin **7** was chosen on the basis of the assumption that the change in ring conformation from $^4C_1$ in **6** to $^0H_5$ in **7** would result in less steric crowding of the C-4-hydroxyl group. Models suggest that differences would be notable for the anomeric substituent which occupies an axial position in **6** but is extended in a pseudoaxial orientation in **7**.

Allylic alcohol **7** was prepared in seven steps from methyl α-D-mannopyranoside as described by Dyong and Schulte.[14] The conversion of **7** to the desired allylic imidate **8** was carried out in 83% yield with sodium hydride and trichloroacetonitrile in ether (Scheme I), conditions which were unsuccessful in the case of **6**. Treatment of **8** with mercuric trifluoroacetate in tetrahydrofuran followed by sodium borohydride gave oxazoline **9** as a mixture of trichloromethyl and dichloromethyl derivatives. Cyclization occurs from only the α-face of **8** with the imidate nitrogen attacking the more substituted C-3 position exclusively. In an attempt to carry out the cyclization with bis(*sym*-collidine)iodine (I) perchlorate an unsatisfactory yield of oxazoline was obtained. The mercuric trifluoroacetate mediated cyclization has the advantage of not requiring an additional step for removal of the electrophile since demercuration is carried in the same operation. The results of our initial studies of this reaction were difficult to interpret because of the complex nature of the reaction product. In addition to the trichloromethyl and dichloromethyl oxazolines, urethane **10** was present, presumably as a result of the partial hydrolysis of **9** under the basic reaction conditions. The formation of urethanes during the hydrolysis of trichloromethyl oxazolines has not been reported previously.

Since **10** could be further hydrolyzed with base to the desired amino alcohol, we set out to maximize its formation in the cyclization. Prolonged treatment of **9** with base following demercuration did not result in the complete conversion to **10**; however, it was discovered that mild acid hydrolysis of the mixture of products in a subsequent step gave **10** exclusively. Hydrolysis of the urethane with potassium hydroxide gave the crystalline amino alcohol **5** in 25% overall yield from the allylic alcohol **7**. Other methods to open the oxazoline ring of **9** directly were examined. In one of these the mixture of oxazolines was hydrolyzed according to the procedure of Gent and Gigg[15] (TsOH, pyridine–H_2O) to give dichloro- and trichloroacetamide derivatives which were reduced catalytically to the known N-acetyl derivative **11**. Ring opening by this method was accompanied by significant decomposition and low overall yields (10–15%) of **11** were obtained. Better results were obtained when the mixture of oxazolines was refluxed with aqueous barium hydroxide. With this method of ring opening, the three-pot conversion (eq 1) of allylic alcohol **7** to amino alcohol **5** was carried out in 33% yield.

Although our initial goal of synthesizing **5** was realized, there remained difficulties associated with the presence of the trichloromethyl group such as the instability of imidate **8** and the susceptibility of the trichloromethyl group to reduction in the demercuration. These problems prompted us to investigate other reagents for the transformation of allylic alcohol **7** to amino alcohol **5**. Knapp and Patel have demonstrated that thiocarbamidates derived from allylic alcohols and methyl isothiocyanate are suitable precursors to cis-1,2-amino alcohols via a sequence similar to that shown in eq[16] 1; however, allylic alcohol **7** failed to react with MeNCS. The base-catalyzed addition of simple alcohols to dialkylcyanamides has been shown to give imidates.[17] We chose to investigate the reaction of **7** with commercially available dimethylcyanamide (Scheme II). Our initial attempts to prepare imidate **12** by the treatment of **7** with sodium hydride and dimethylcyanamide in ether, conditions used for **8**, were unsuccessful; however, **12** could be obtained in high yield if solvent was omitted from the reaction. Thus, treatment of a solution of **7** in dimethylcyanamide with sodium hydride at room temperature followed by evaporation gave **12** in 90% yield. The cyclization of **12** and the reduction of the intermediate mercurial proceeded smoothly and a single oxazoline **13** was obtained in 80% yield. Hydrolysis of **13** to the amino alcohol was carried out with aqueous barium hydroxide, giving **5** in 41% overall yield from **7**.

The amino alcohol **5** is a well-developed precursor to both D-rubranitrose and D-kijanose. Brimacombe and co-workers have developed an efficient synthesis of rubranitrose from the N-acetyl derivative **11**. To complete a formal synthesis of **1** based on the route described above **5** was treated with acetic anhydride and pyridine to give its diacetyl derivative from which the O-acetyl group was removed selectively to give **11**. The amino and hydroxyl groups of **5** can also be differentiated by selective oxidation. Thus, treatment of **5** with MCPBA in dichloromethane gave nitro alcohol **14**. Studies of the conversion of **14** to kijanose and of further applications of dimethylcyanamide

(14) Dyong, I.; Schulte, G. S. *Chem. Ber.* **1981**, *114*, 1484–1502.
(15) Gent, P. A.; Gigg, R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2748–2750.
(16) Knapp, S.; Patel, D. V. *J. Am. Chem. Soc.* **1983**, *105*, 6985–6986.
(17) Shaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1960**, *26*, 412–418.

to the synthesis of amino alcohols are in progress.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover melting-point apparatus and they are uncorrected. Infrared spectra were recorded on an Analect FX6160 infrared spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian XL-200 spectrometer. Chemical shifts for proton resonances are given relative to tetramethylsilane (δ = 0.0 ppm). Mass spectra were recorded on Hewlett-Packard 5982-A and VG7070 spectrometers. Optical rotations were determined with a Perkin-Elmer Model 241 polarimeter. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. The progress of reactions was monitored by thin-layer chromatography using aluminum-supported plates of silica gel 60 (0.2 mm, F-254, E. Merck). Solvent systems are indicated by volume-to-volume ratios. Components were detected by spraying with concentrated sulfuric acid and heating. Flash chromatography was performed on silica gel 60 (230–400 mesh). Chloroform was dried by passing it through a column of basic alumina (Woelm, activity 1). Tetrahydrofuran was distilled from calcium hydride before use. Methanol was dried by distillation from magnesium. Fast-atom bombardment mass spectra were provided by J. L. Smith of Merck, Sharp, and Dohme, Rahway, NJ.

Methyl 3-*O*-(Trichloroacetimidoyl)-2,3,6-trideoxy-3-*C*-methyl-α-D-*erythro*-hex-2-enopyranoside (8). Sodium hydride (0.196 g of a 50% dispersion in oil, 7.83 mmol NaH) was washed 3 times with hexane in a round-bottomed flask equipped with a magnetic stirrer and a Firestone valve. The washings were removed by pipet and allylic alcohol **7** (2.45 g, 15.5 mmol) was added as a solution in anhydrous diethyl ether (23 mL). The reaction was stirred for 15 min at room temperature and cooled in an ice bath. Trichloroacetonitrile (2.24 g, 15.5 mmol) was added dropwise and the temperature of the reaction mixture was maintained at 0 °C. Progress of the reaction was monitored by TLC with 2% methanol–dichloromethane. The imidate had R_f 0.73. After 25 min pentane (22.5 mL) containing methanol (0.3 mL) was added with vigorous stirring. The reaction mixture was filtered and the residue was washed with pentane. Evaporation of the solvent gave a brown syrup which was purified by flash chromatography on silica gel with 4:3 petroleum ether–ethyl acetate to give 3.87 g (83%) of **8** as a yellow syrup: $[\alpha]^{20}_D$ +81° (*c* 4.86, $CHCl_3$); IR (film) ν 1665 cm^{-1} (C=N); ^1H NMR (200 MHz, $CDCl_3$ δ 8.51 (br s, 1 H, NH), 5.65 (br s, 1 H, H-2), 5.51 (d, 1 H, H-4, $J_{4,5}$ = 9 Hz), 4.88 (br s, 1 H, H-1), 4.13 (m, 1 H, H-5), 3.45 (s, 3 H, OCH_3), 1.78 (s, 3 H, 3-CH_3), and 1.30 (d, 3 H, H-6, $J_{5,6}$ = 6 Hz); FAB MS, *m/e* 271 (M – OCH_3), 141 (M – OC=NH-(CCl_3)). Satisfactory elemental analysis could not be obtained for **8**. Difficulties in obtaining elemental analyses for trichloroacetimidates have been reported.[18]

(Methyl 2,3,6-trideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranosido)[3,4:4′,5′]oxazolidin-2′-one (10). To a solution of imidate **8** (3.87 g, 12.8 mmol) in tetrahydrofuran (42 mL) was added mercuric trifluoroacetate (5.99 g, 14.1 mmol), and the mixture was stirred 12 h at room temperature. Aqueous 2 N sodium hydroxide solution was added to adjust the pH to 12, followed by 5 mL of a solution of 4 N sodium borohydride in aqueous 2 N sodium hydroxide at 0 °C. The temperature of the reaction mixture was maintained at 0–5 °C during the borohydride addition. The mixture was centrifuged and the supernatant was decanted. Diethyl ether was added and the process was repeated. Water was separated from the combined supernatants which were then dried over sodium sulfate and evaporated to a yellow syrup (2.34 g) which contained, as evidenced by the ^1H NMR and IR spectra (see below), mainly a mixture of oxazolines **9**. Without further purification, the product was dissolved in aqueous 1 N HCl (38.0 mL) and methanol (19.0 mL). The solution was stirred 12 h at room temperature after which water (43 mL) was added. The mixture was extracted with chloroform (3 × 50 mL) and the combined extracts were washed with saturated sodium chloride solution (25 mL), dried over magnesium sulfate, and evaporated to give syrupy urethane **10** (1.0 g, 32%) which crystallized when dried under vacuum: mp 75–76 °C; $[\alpha]^{20}_D$ +179° (*c* 0.4, $CHCl_3$); IR (film) ν 1753 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$) δ 6.73 (br s, 1 H, NH), 4.62 (dd, 1 H, H-4, $J_{4,5}$ = 8 Hz), 3.86 (m, 1 H, H-5), 3.30 (s, 3 H, OCH_3), 2.93 (m, 2 H, H-2a, 2e), 1.32 (s, 3 H, 3-CH_3), and 1.26 (d, 3 H, H-6); mass spectrum (CI, methane), *m/e* (rel intensity) 202 $(M + 1)^+$ (73), 170 (100). Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.42; H, 7.48; N, 6.74.

In a separate experiment, the mixture of oxazolines was purified by column chromatography on silica gel to give a syrup containing both trichloromethyl and dichloromethyl derivatives which displayed the following characteristics: IR (film) 1654 cm^{-1} (C=N); ^1H NMR (200 MHz, $CDCl_3$) δ 6.22 (s, 1 H, $CHCl_2$); mass spectrum (CI, isobutane), *m/e* (rel intensity) 302 (M + 1) (17), 270 (73), 268 (M + 1) (100), 236 (28).

Methyl 3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (5). A. From Urethane 10. A mixture of urethane **10** (1.00 g, 5 mmol) and 15% aqueous potassium hydroxide (25 mL) was stirred under reflux for 30 min. Water (50 mL) was added and the cooled reaction mixture was extracted with chloroform (3 × 35 mL). The combined chloroform extracts were dried over sodium sulfate and evaporated to give 0.79 g (92%) of crystalline amino alcohol: mp 94–96 °C; $[\alpha]^{20}_D$ +146° (*c* 1.1, $CHCl_3$); ^1H NMR (200 MHz), $CDCl_3$) δ 4.67 (bs, 1 H, H-1), 3.76 (d, 1 H, H-4, $J_{4,5}$ = 8 Hz), 3.44 (m, 1 H, H-5), 3.26 (s, 3 H, OCH_3), 2.83 (d, 1 H, OH), 2.27 (bs, 2 H, NH_2), 1.92–1.52 (m, 2 H, H-2a, H-2e), 1.23 (d, 3 H, H-6, $J_{5,6}$ = 6.5 Hz), 1.03 (s, 3 H, 3-CH_3). Amino alcohol **5** was characterized further as its known N-acetyl derivative **11**.

B. From Oxazoline 13. A mixture of oxazoline **13** (0.85 g, 3.7 mmol) and 2 N barium hydroxide (18.5 mL) was stirred under reflux for 12 h. Water (20 mL) was added and the mixture was filtered through glass wool and extracted with chloroform (3 × 25 mL), and the chloroform extracts were combined, dried over sodium sulfate, and evaported to give white crystals of **5**; yield, 0.40 g (61%).

C. From Oxazoline 9. A mixture of dichloromethyl and trichloromethyl oxazolines (130 mg) was treated with 2 N barium hydroxide (4 mL) as described above to give amino alcohol **5** (45 mg); yield, 40% from **8**.

Methyl 3-Acetamido-2,3,6-trideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (11). A mixture of amino alcohol **5** (70 mg, 0.4 mmol), acetic anhydride (1 mL), and pyridine (2 mL) was stirred under an atmosphere of nitrogen at room temperture for 20 h. Water (2 mL) was added and, after stirring briefly, the reaction mixture was extracted with chloroform (3 × 3 mL). The combined chloroform extracts were dried over sodium sulfate and evaporated to give syrupy diacetate (80 mg) which, without purification, was dissolved in 1:1.5 ethanol–2 N sodium hydroxide (8 mL) and heated under reflux for 10 min. The reaction mixture was diluted with water (4 mL) and extracted with chloroform (3 × 4 mL), and the chloroform extracts were dried over magnesium sulfate and evaporated to give **11** (30 mg, 35%) which crystallized when dried under vacuum: mp 130–131 °C (lit.[6] mp 138–139 °C); $[\alpha]^{20}_D$ +30° (*c* 1.8, $CHCl_3$), lit.[6] +31° (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.17 (bs, 1 H, NH), 4.69 (bs, 1 H, H-1), 3.74 (m, 1 H, H-5), 3.37 (s, 3 H, OCH_3), 3.14 (d, 1 H, H-4, $J_{4,5}$ = 10 Hz), 1.98 (s, 3 H, CH_3CO), 1.90–1.78 (m, 2 H, H-2a, H-2e), 1.59 (s, 3 H, 3-CH_3), 1.29 (d, 3 H, H-6, $J_{5,6}$ = 6 Hz). The ^{13}C NMR spectrum of **11** was identical with that reported.[9]

Methyl 2,3,6-Trideoxy-3-*C*-methyl-4-*O*-(dimethylamidino)-α-D-*erythro*-hex-2-enopyranoside (12). To a mixture of **7** (0.5 g, 3.16 mmol) in dimethylcyanamide (1.2 mL) was added sodium hydride (78 mg, of a 50% dispersion oil, 1.6 mmol NaH) and the mixture was stirred at room temperature under nitrogen. The reaction was quenched after 24 h by adding 4 mL of pentane containing 0.2 mL of methanol. Water (2 mL) was added and the mixture was extracted with chloroform (3 × 7 mL). The chloroform extracts were combined, dried over magnesium sulfate, and concentrated (30 °C) to give **12** (0.65 g, 90%) as a light brown syrup: $[\alpha]^{20}_D$ +86.7° (*c* 1.35, chloroform); ^1H NMR (200 MHz, $CDCl_3$) δ 5.52 (bs, 1 H, H-2), 4.83 (m, 2 H, H-4 and H-1), 3.98 (m, 1 H, H-5), 3.42 (s, 3 H, OCH_3), 2.86 (s, 6 H, $N(CH_3)_2$), 1.71 (s, 3 H, 3-CH_3), and 1.25 (d, 3 H, *J* = 8 Hz, 5-CH_3); FAB MS, *m/e* 289 (M + H), 197 (M – OCH_3), 141 (M – $O(CH_3)_2N$=NH).

Methyl 2,3,6-Trideoxy-3-*C*-methyl-4,3-(2-(dimethylamino)-1-oxa-3-azaprop-2-eno)-α-D-*ribo*-hexopyranoside (13).

(18) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901–2910.

Into a round-bottomed flask was placed **12** (1.79 g, 7.90 mmol) along with mercuric trifluroacetate 3.7 g (8.65 mmol) and 30 mL of dry THF. The mixture was stirred at room temperature for 12 h, after which the reaction was made basic (pH 10–14) with aqueous 2 N sodium hydroxide (1.6 mL added) and cooled to 0 °C. A solution of 4 N sodium borohydride in 2 N sodium hydroxide (3 mL, 3 mmol) $NaBH_4$) was added slowly. During the addition the temperature was maintained around 5 °C. Deposited mercury was removed by centrifugation and the supernatant was decanted and extracted twice with 20 mL of diethyl ether. Ether layers were combined and dried with sodium sulfate, and solvent was removed to give **13**: $[\alpha]_D$ +113° (*c* 0.513, $CHCl_3$); IR (thin film) ν 1662 cm^{-1} (C=N): ^1H NMR (200 MHz, $CDCl_3$) δ 4.68 (m, 1 H, H-1), 3.85 (m, 1 H, H-5), 3.70 (d, 1 H, H-4, $J_{4,5}$ = 9 Hz), 3.38 (s, 3 H, OCH_3), 2.86 (s, 6 H, $N(CH_3)_2$) 2.15 (dd, 1 H, H-2 eq, $J_{2a,2e}$ = 15 Hz, $J_{1,2}$ = 6 Hz), 1.73 (dd, 1 H, $J_{1,2a}$ = 9 Hz), and 1.24 (m, 6 H, 3-CH_3 and CH_3 at C-5); FAB MS, *m/e* 229 (M + H), 197 (M – OCH_3).

Methyl 3-Nitro-2,3,6-trideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (14). A solution of MCPBA (2.16 g, 12.5 mmol) in dry dichloromethane was heated to reflux under an atmosphere of nitrogen. Amino alcohol **5** (300 mg, 1.72 mmol) in dichloromethane (7.5 mL) was added over a 20-min period with stirring. Progress of the reaction was monitored by TLC using 3:4 ethyl acetate–petroleum ether (*R* of **14** = 0.54). After a total of 40 min, the reaction mixture was cooled and successively washed with 10% aqueous sodium sulfite solution, 10% aqueous sodium carbonate solution, and water, dried (sodium sulfate), and evaporated. Purification by flash chromatography (3:4 ethyl acetate–petroleum ether) gave 150 mg (42%) of crystalline nitro alcohol: mp 97–99 °C (lit.[19] (enantiomer) mp 101.5–103 °C); $[\alpha]_D$ +183° (*c* 3.68, $CHCl_3$) lit.[19] (enantiomer) –172 (*c* 0.25, $CHCl_3$). The ^1H NMR spectrum of **14** at 200 MHz was identical with that reported[19] for its enantiomer at 360 MHz.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. Support from Villanova University is also acknowledged.

(19) Brimacombe, J. S.; Rahman, K. M. M. *Carbohydr. Res.* **1985**, *140*, 163–166.

Rapid and Convenient Syntheses of Polyoxin Peptides Containing *N*-Methylated Peptide Bonds

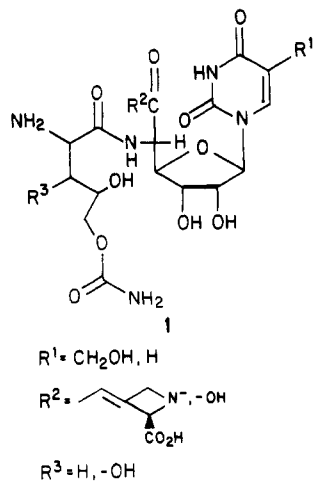
Jeffrey C. Boehm* and William D. Kingsbury

Smith Kline & French Laboratories, Department of Medicinal Chemistry, Swedeland, Pennsylvania 19479

Received November 26, 1985

The N-methylated di- and tripeptide polyoxins **3** and **4** were rapidly prepared by the Ugi four component condensation (4CC) reaction and subsequent deblocking. Alternatively, entry into the dipeptide system was achieved by a short synthesis based upon the Strecker reaction. Methods for chromatographic separation of the diastereomeric intermediates were developed. The polyoxin amides **21a** and **21b** and the polyoxin nitrile **22** were also prepared.

The polyoxins **1** are pyrimdine nucleoside peptide antibiotics produced by *Streptomyces cacaoi*.[1] They have marked activity against phytophathogenic fungi but are not toxic to bacteria, plants, or animals.[2] Their biological effects apparently are due to their ability to inhibit the enzyme chitin synthase which catalyzes the final step in the biosynthesis of chitin, an essential component of the fungal cell wall structure.[3]



1

Although the chitin synthase from *Candida albicans*, a medically important human pathogen, is highly sensitive to the polyoxins in cell free systems[4] ($K_i \sim 10^{-6}$ M), the growth of intact cells can be inhibited only through selective manipulation of the growth medium.[5] This discrepancy between a high level of activity against the isolated enzyme and inactivity against whole cells could result either from failure of the polyoxin to penetrate the cell and reach the site of the chitin synthase[6] or from intracellular cleavage of the polyoxin dipeptide to the amino acid polyoxin C (**2a**) which is relatively inactive against fungal chitin synthase ($K_i \sim 10^{-3}$ M).[7]

In an attempt to prepare polyoxin analogues with activity against *C. albicans*, we focused our research on the preparation of polyoxins possessing a peptide bond that is stable to the enzymatic environment inside the fungal cell. The *N*-methylpolyoxins **3** and **4** were selected as

(1) Isomo, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490.
(2) (a) Isono, K.; Negatsu, J.; Kawashima, Y.; Suzuki, S. *Agric. Biol. Chem.* **1965**, *29*, 848. (b) Isomo, K.; Nagatsu, J.; Kobinata, K.; Sasaki, K.; Suzuki, S. *Agric. Biol. Chem.* **1967**, *31*, 190.
(3) Gooday, G. W., *Abh. Dtsch. Akad. Wiss.* DDR, *Abt. Math. Naturwiss., Tech.*, Issue 2N, **1979**, p 159.
(4) Becker, J. M.; Covert, N. L.; Shenbagamurthi, P. S.; Steinfeld, A.; Naider, F. *Antimicrob. Agents Chemother.* **1983**, *23*, 926.
(5) Mehta, R. J.; Kingsbury, W. D.; Valenta, J.; Actor, P. *Antimicrob. Agents Chemother.* **1984**, *25*, 373.
(6) Bowers, B.; Levin, G.; Cabib, E. *J. Bacteriol.* **1974**, *199*, 564.
(7) Shenbaganurthi, P.; Smith, H. A.; Becker, J. M.; Steinfeld, A.; Naider, F. *J. Med. Chem.* **1983**, *26*, 1518.

0022-3263/86/1951-2307$01.50/0