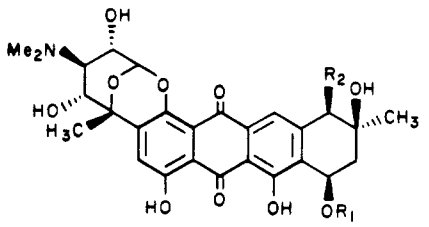
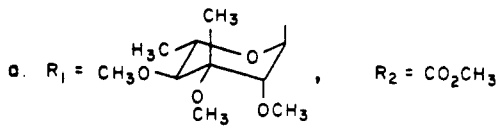
Chiral Syntheses of D-*gluco*- and L-*ido*-2,6-Epoxy-2*H*-1-benzoxocins from a Common Pentose Precursor

Summary: Optically active 2,6-epoxy-2*H*-1-benzoxocins with the D-gluco and L-ido configurations have been prepared from a single aldehydofuranose.

Sir: The anthracycline antibiotic nogalamycin (**1a**)[1,2] has as a structural feature an optically active 2,6-epoxy-2*H*-1-oxocin moiety. Biosynthetically this fragment originates from the dual attachment of a glucose or deoxyaminoglucose moiety to the D ring of the anthracyclinone.[3]



I.



a. $R_1 = CH_3O$, $R_2 = CO_2CH_3$

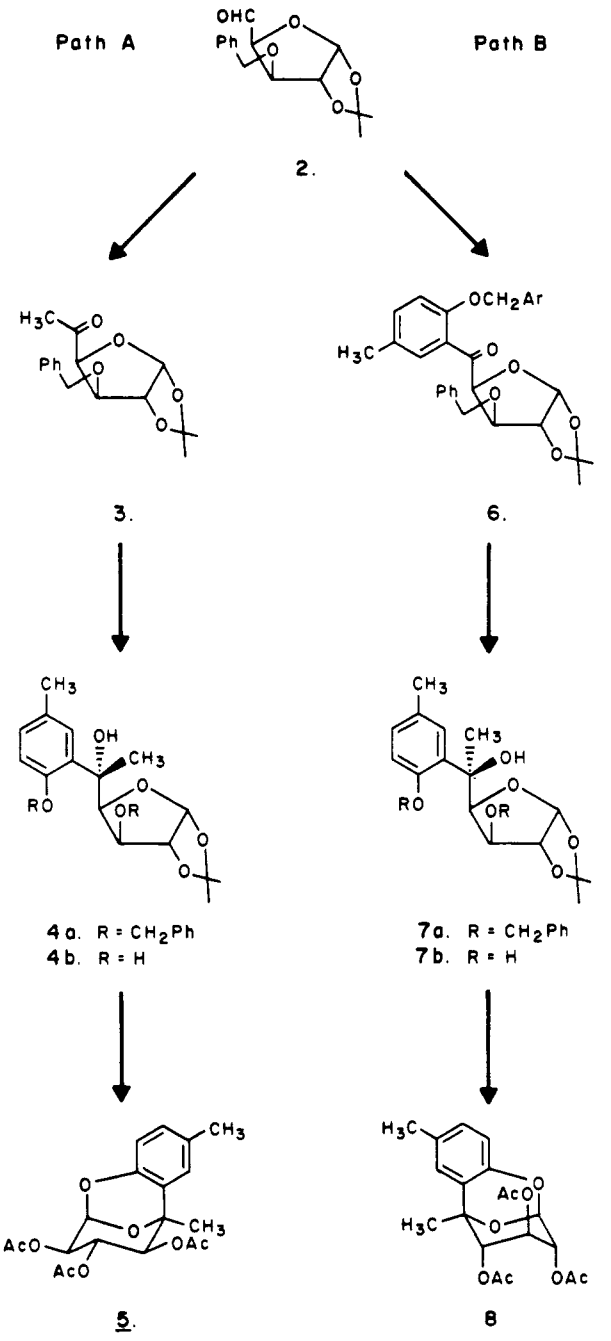
b. $R_1 = CH_3$, $R_2 = H$

The absence of appropriate synthetic methodology to construct highly functionalized epoxyoxocin ring systems[4] coupled with our interest in performing total syntheses of **1a** and the semisynthetic derivative 7-con-O-methylnogarol (**1b**)[5] has led us to explore various procedures to this fragment. Recently, we described an expedient method for preparing racemic oxocin sugar analogues through reconstitution of a furanose intermediate.[6]

We have now developed methods for direct synthesis of optically active 2,6-epoxy-2*H*-1-benzoxocins with the ido and gluco configurations from a single aldehydo sugar. In the course of this work, we have found that unlike the aldehydofuranose **2**, ketofuranoses **3** and **6** react with organometallic reagents in a stereospecific manner.

In the planned approach shown in path A of Scheme I, the aldehydofuranose **2** would serve as a chiral synthon for constructing the optically active benzoxocin **5** with the gluco configuration. Grignard addition to **2** followed by oxidation and then a second Grignard reaction would be employed to construct the precursor **4a**.

Scheme I



Since the stereochemistry of the tertiary carbinol fragment in **4** determines the configurational outcome in the benzoxocin product **5**, it was crucial to construct this center with maximum stereochemical control. Hanessian and Wolfrom[7] and Inch,[8] in their pioneering work on the addition of Grignard reagents to aldehydo sugars, found that **2** reacted with methylmagnesium bromide to give a mixture of gluco and ido hexoses with the ido isomer being the major product. The stereochemical course of addition of organometallics to correspondingly structured keto sugars has not been reported. Nevertheless, we expected that the larger steric bulk of an alkyl group in a ketone would lead to greater stereoselectivity.

Addition of methylmagnesium bromide to the aldehydo sugar **2** followed by Collins[9,10] oxidation of the secondary

(1) Wiley, P. F.; Kelly, R. B.; Caron, E. L.; Wiley, V. H.; Johnson, J. H.; MacKellar, F. A.; Misak, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 542.
(2) Wiley, P. F. *J. Nat. Prod. Chem.* **1979**, *42*, 569 and references therein.
(3) Wiley, P. F.; Elrod, D. W.; Marshall, V. P. *J. Org. Chem.* **1978**, *43*, 3457.
(4) (a) The only previously reported route that was employed to prepare an unfunctionalized 2,6-epoxy-2*H*-1-benzoxocin was described by Roffey, P.; Sargent, M. V.; Knight, J. A. *J. Chem. Soc. C* **1967**, 2328. A similar sequence was employed by Townsend et al. in a synthesis of averafin: Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885. (b) While this manuscript was in preparation, Bates and Sammes published a synthesis of an aminoglucose benzoxocin analogue: Bates, M. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1983**, 896.
(5) Stezowski, J. J.; Wiley, P. F. *Tetrahedron Lett.* **1980**, *21*, 507.
(6) Hauser, F. M.; Ellenberger, W. P.; Adams, T. C., Jr. *J. Org. Chem.* **1984**, *49*, 1169.
(7) Wolfram, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800.
(8) Inch, T. D. *J. Carbohydr. Res.* **1967**, *5*, 45.

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alcohol mixture gave the methyl ketone **3**. Reaction of **3** with the Grignard reagent formed from the benzyl ether derivative of 2-bromo-4-methylphenol gave the tertiary carbinol **4a** with the D-gluco configuration as the sole product in 80% yield. Neither the ^1H nor ^{13}C NMR spectra of this product showed the presence of any of the L-ido isomer, indicating that the second Grignard addition proceeded in a stereospecific manner.

The order of Grignard additions to the aldehyde **2** was reversed as shown in path B of Scheme I in order to establish if this observed specificity was general. The inverted process was expected to produce **7a** with the necessary stereochemistry in the tertiary carbinol fragment to furnish the oxocin **8** with the ido configuration. Addition of the Grignard reagent prepared from the benzyl ether derivative of 2-bromo-4-methylphenol to **2** followed by oxidation of the secondary alcohol mixture with Collins reagent[9] (CrO_3·2py, CH_2Cl_2) gave the phenyl keto sugar **6** in 58% overall yield. Reaction of **6** with methyllithium (THF, −78 °C) furnished the tertiary carbinol **7a** as the sole product of the reaction in 82% yield. The ^1H and ^{13}C NMR spectra of the crude and purified product showed only the presence of the L-ido isomer, again indicating that the addition proceeded stereospecifically.

The further conversion of the individually prepared tertiary carbinol epimers **4a** and **7a** to the respective optically active oxocins **5** and **8** was performed. Initial attempts to effect selective cleavage (Pd/C, EtOH) of the benzyl groups in the D-gluco compound **4a** gave approximately 30% of the product resulting from hydrogenolysis of the tertiary alcohol group. Careful monitoring of the reaction resulted in excellent selectivity and the debenzylated product **4b** was isolated in 96% yield.

Attempted hydrolysis of **4b** and rearrangement to the oxocin **5** with dilute mineral acids produced a complex mixture. The use of an acidic ion exchange resin (Amberlite IR-120) gave a much cleaner reaction, but again several products were evident by TLC. The initially received material was acetylated (Ac_2O, pyridine; room temperature) and then chromatographed in order to facilitate isolation of the products. A modest yield (16%) of the D-gluco isomer **5** along with a nearly equal amount (17%) of the L-ido compound **8** was obtained. Examination by TLC during the course of the hydrolysis showed the presence of material with an R_f corresponding to the acetonide of the L-ido compound **7b**, indicating that the loss of stereochemical integrity at the tertiary carbinol center was occurring prior to hydrolysis of the acetonide.

In contrast to the conversion of the D-gluco intermediate **4a** to the corresponding oxocin **5**, the transformation of intermediate **7a** to the oxocin **8** with L-ido configuration proceeded smoothly and with high stereoselectivity. Hydrogenolysis of **7a** (Pd/C, EtOH) was uneventful and gave the debenzylated product **7b** in 95% yield. Hydrolysis of **7b** (EtOH, H_2O, Amberlite IR-120, 12 h) followed by acetylation (Ac_2O, pyridine) and then chromatographic purification (silica) furnished a 57% yield of the L-ido compound **8** and a 4% yield of the D-gluco compound. The ^1H NMR spectrum of the L-ido oxocin triacetate **8** was striking. The methyl group of the axially oriented C-3 acetoxy functionality lies in the shielding cone of the aromatic moiety and was shifted upfield to 1.60 ppm.

Our observation that keto sugars **3** and **6** undergo stereospecific reaction with organometallic reagents in accordance with Cram's rule[11] indicates that the configurational and transition-state geometries are significantly more rigid than in a aldehyde sugar,[2] which undergoes only stereoselective addition. These findings have significant implications for the use of 5-ketofuranoses as precursors to other sugar configurations and also their utilization as chiral synthons to other classes of natural products.

While the origins of the enhanced reactivity of the gluco furanose intermediate **4** to acid are uncertain, the data indicate that the ido isomer **7** is thermodynamically more stable. Examination of models does not provide a straightforward explanation and further studies will be necessary to rationalize this observation. In conclusion, our studies show that optically active oxocins can be prepared by using sugars as synthons. The use of protective groups that can be cleaved under nonacidic conditions will likely enhance the feasibility of using this approach to prepare oxocins with the gluco configuration.

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Supplementary Material Available: The entire experimental procedures for the accomplished study (7 pages). Ordering information is given on any current masthead page.

(9) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.
(10) Kiely, D. E.; Walls, H., Jr.; Black, R. L. *Carbohydr. Res.* **1973**, *31*, 387.
(11) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245 and previous papers in this series.

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Silver Ion Assisted Acetolysis of the Tropenium Ion Analogue of *exo*-2-Bromobenzonorbornene, "*exo*-2-Bromotropenonorbornene" Hexafluoroantimonate

Summary: The preparation, characterization, and solvolysis (HOAc, CH_3CN, 3:1, v/v) of *exo*-5-bromobicyclo-[2.2.1]heptenotropenium (*exo*-2-bromotropenonorbornene) hexafluoroantimonate is described.

Sir: The pronounced solvolytic reactivity of exo-2-substituted benzonorbornenes is well-known.[1] Their solvolyses proceed with high exo/endo rate ratios and with complete exo product formation.[2] Mechanistic concensus implicates aryl π-participation in their solvolysis.[3] Also well-known is that tropenium ion (tropylium ion) is an "aromatic" analogue of benzene.[4] We have prepared the tropenium ion analogue of *exo*-2-bromobenzonorbornene (1-Br), dubbed "*exo*-2-bromotropenonorbornene",[5] as its

(1) Lancelot, C. J.; Cram, D. J.; Schleyer, P. v. R. in "Carbonium Ions"; ed. Olah, G. A., Schleyer, P. v. R., Ed.; Wiley-Interscience: New York, 1972; Vol. III, Chapter 27, pp 1420–1435.
(2) In 80% ethanol at 25 °C, the exo/endo ratio for the bromo derivatives is 2500. The exo bromide forms ~100% exo alcohol in aqueous dioxane. Cf. Wilt, J. W.; Chenier, P. J. *J. Org. Chem.* **1970**, *35*, 1571.
(3) Endemic to the area of *exo*-2-norbornyl and related solvolyses is the seemingly endless argument about the extent of this participation. Cf. Brown, H. C. "The Nonclassical Ion Problem"; Plenum Press: New York, 1977.
(4) Pietra, F. *Chem. Rev.* **1973**, *73*, 293.

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