Tetrahedron: Asymmetry Vol. 2, No. 10, pp. 961-964, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

Carbocycles from Carbohydrates. A Free Radical Route to (1R,2R,3S,4R)-4-Amino-1,2,3-cyclopentanetriol Derivatives

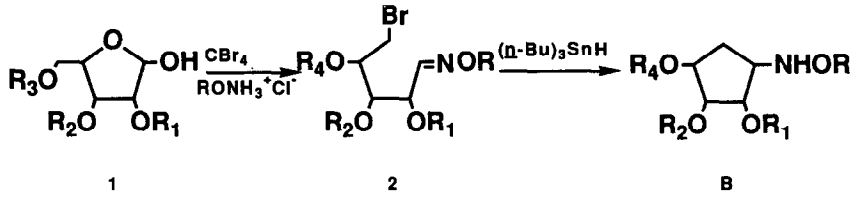
José Marco-Contelles,* Luis Martínez and Angeles Martínez Grau

Instituto de Química Orgánica (CSIC); Juan de la Cierva, 3. 28006-Madrid, Spain

(*Received* 23 *July* 1991)

Abstract: Some derivatives of (1R,2R,3S,4R)-4-amino-1,2,3-cyclopentanetriol have been synthesized in enantiomerically pure form via free radical cyclization of conveniently functionalized carbohydrate intermediates. Moderate yields and good to excellent diastereoselectivities have been obtained in the key intramolecular free radical cyclization step.

4-Amino-1,2,3-cyclopentanetriols are versatile and valuable intermediates in the synthesis of the pharmacologically important carbocyclic nucleosides.[1] Strategies for the synthesis of enantiomerically pure aminocyclopentanetriols are scarce and limited to the resolution of racemates by physical[2] or enzymatic[3] methods and from carbohydrates by the nitromethane reaction;[4] a general and enantiospecific synthetic approach is still lacking. In the last years the synthesis of carbocycles from carbohydrates has attracted considerable interest;[5] the free radical[6] route has proven to be an efficient methodology.[7]

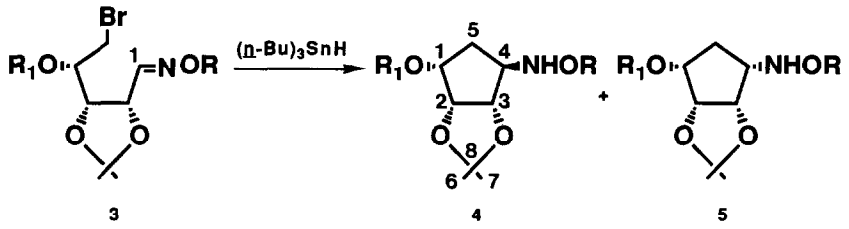


1 2 B

Scheme I

In this communication we report a new and simple route to some derivatives of (1R,2R,3S,4R)-4-amino-1,2,3-cyclopentanetriol via free radical cyclization of acyclic carbohydrate intermediates. The strategy is shown in Scheme 1 ; the protected lactol **1** undergoes bromination and oxime ether

formation giving intermediate **2** ready for free radical cyclization mediated by tributyltin hydride.[8] Because of the differential protection and easy control of the stereochemistry of oxygen functional groups in furanose derivatives **1**, and the mild reaction conditions for carbon-carbon bond formation, this approach would constitute a powerful and general method for the synthesis of chiral polyhydroxy cyclopentylamines.[9]



3 **4** **5**

Scheme II

This idea has been reduced to practice transforming 5-bromo-5-deoxy-2,3-O-isopropylidene $-\alpha-$D-ribofuranose[9] into the radical precursors **3**[10] (Scheme II). These compounds have been obtained as mixtures of **syn** and **anti** isomers in a 70:30 ratio, respectively, as we could determine by ^{1}H NMR analysis (**3 syn**: $\delta H_1 \sim 7.30$, d, J=7.3 Hz; **3 anti**:$\delta H_1 \sim 6.80$, d, J=5.5 Hz); we could not separate them and they were processed together.The cyclization of these compounds[11] proceeds in moderate to good yield and excellent diastereoselectivity (see Table, entries 1-3); in these cases only the exo isomer **4** is present in the cyclized products; for compounds **4d** (R_1=Bz, R=Bn) or **4e** (R_1=Bz, R=Me) (see Table, entries 4 and 5)the minor endo isomer **5** could be detected. The absolute configuration at the new stereocenter in the major exo isomer has been established by ^{1}H NMR analysis; for compound **4a**,[12] for instance, ∂H_4 3.42 (dd, $J_{4,5}$ = 3.7 Hz, $J_{4,5'}$ = 4.2 Hz); a $J_{3,4}$ = 0 Hz is a diagnostic value for trans H_4-H_3 in this type of compounds.[13] Compounds **4b** (R_1= t-BuMe_2Si, R=Bn) and **4d** (R_1=Bz, R=Bn) have been transformed by mild acid hydrolysis and sodium methoxide treatment, respectively, into **4a**, confirming the absolute configuration at C-4. Compound **4a** has been hydrogenated giving the aminoalcohol **4f** (R_1=H, OR=H).

As we have been unable to separate the **syn** and **anti** isomers **3**, we could not analyze independently their free radical cyclization : each isomer should yield a different exo-endo ratio.[14] Anyway, the stereochemical results obtained in the cyclization of compounds **3** can be rationalized in terms of the model proposed by Wilcox for the cyclization of analogous α,β –

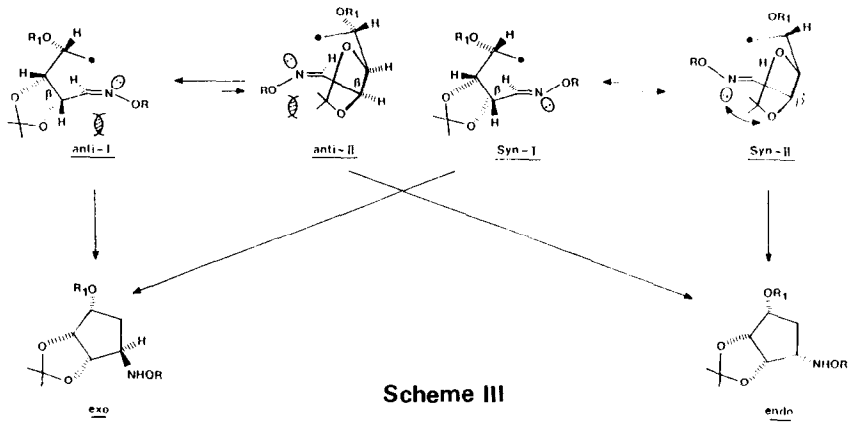
unsaturated esters [9] (Scheme III). In the **anti** isomers the steric interaction between the oxime ether and the ethereal oxygen or the hydrogen on the β-carbon should give the exo isomer predominantly ; in the **syn** isomers the electronic repulsion between the electron pairs at the nitrogen and the oxygen on the β-carbon should also yield major exo isomers. The results obtained in the cyclization of compounds **3d** (R_1=Bz, R=Bn) and **3e** (R_1=Bz, R=Me) point probably to the significance of electronic effects of the aryl ester.

Table. Tin Hydride Mediated Cyclization of Oxime Ethers

entry	substrate (3)		product ratios	
	R_1	R	4/5[a(b)]	yield(%)[c]
1a	H	Bn	only *exo*	75
2b	*t*-BuMe$_2$Si	Bn	only *exo*	53
3c	Ac	Bn	only *exo*	52
4d	Bz	Bn	89/11(91/9)	58
5e	Bz	Me	80/20(88/12)	71

(a) Product ratios computed from NMR analysis of crude mixtures. (b) Product ratios after purification. (c) Total yield of cyclized products

In summary, a stereoselective method for the preparation of derivatives of (1R,2R,3S,4R)-4-amino-1,2,3-cyclopentanetriols has been achieved. The moderate yield in the cyclization is compensated for the good to excellent ratios of the cyclized products and ready availability of the radical precursors. We are currently examining other carbohydrate precursors and will report these studies in due course.



Scheme III

Acknowledgment. We thank Comunidad de Madrid for financial support (Project C195-91A)

References and Notes

1. Márquez, V.E.; Lim, M.J. Med. Res. Rev. ,**1986**, 6, 1.
2. (a) Kelly, R. C.; Schletter, I.; Stein, S. J.; Wierenge, W. J. Am. Chem. Soc., **1979**, 101, 1054. (b) Bedes, J.; Sáji, G.; Tömösközi, I.; Gonber, N.; Gulácsi, E.; Ötvös, L. Tetrahedron Lett., **1988**, 29, 2861.
3. Arita, M.; Adeihi, K.; Ito, Y.; Sawai, H.; Ohno, M. J. Am. Chem. Soc., **1983**,105, 4949.
4. Yoshikawa, M.; Okaichi, Y.; Cha, B. Ch.; Kitagawe, I. Tetrahedron, **1990**, 46, 7549.
5. Fraser-Reid, B. Anderson, A.C. Prog. Chem. Org. Nat. Prod., **1980**, 39, 1.
6. Giese, B. Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds, Pergamon Press; New York, 1986.
7. (a) RajanBabu, T.V. J. Am. Chem. Soc., **1987**, 119, 609. (b) Nugent, W .A.; RajanBabu, T.V. J. Am. Chem. Soc. ,**1988**, 110, 8561. (c) RajanBabu. T.V.; Fukunaga, T.; Reddy, G.S. J. Am. Chem. Soc. ,**1989**, 111, 1759. (d) Wilcox, C.S.; Gaudino, J.J. J. Am. Chem. Soc., **1986**, 108, 3102. (e) RajanBabu, T. V. J. Org. Chem. ,**1988**, 53, 4522.
8. Bartlett, P.A.; McLaren, H.C.; Ting, P.C. J. Am. Chem. Soc., **1988**, 110, 1633.
9. Wilcox, C.S.; Thomasco, L.M. J. Org. Chem., **1985**, 50, 546.
10. All new compounds showed good analytical and spectroscopic data. The synthesis of the radical precursors will be detailed elsewhere.
11. In a typical experiment, compounds **3** dissolved in toluene (0.02 M), were treated with a solution of tributyltin hydride (2.4 equiv.) and AIBN (cat.) in toluene by dropwise addition via syringe pump in 4 h. After 2 h. at reflux, the solvent was removed and the residue diluted with ether plus 15 % aqueous potassium fluoride solution and stirred overnight. The organic phase was separated, dried and evaporated. Flash chromatography using hexane-ethyl acetate mixtures gave the desired products. In these cyclizations small amounts ($\lesssim$10%) of dimerized carbohydrate products incompletely identified, were also present.
12. **4a**: mp 40-42°C ; $[\alpha]_D^{25}$ +4.8 (c 3.6, $CHCl_3$); IR (film) $\bar{\nu}$: 3600 - 3300, 325 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) ∂: 7.40-7.27 (m, 5H, aromatic), 4.64 (s, 2H, NHOC$\underline{H}_2C_6H_5$), 4.39 (dd, $J_{1,2}$=5.2 Hz ,1H, H-2), 4.35 (d, $J_{2,3}$=5.8 Hz, 1H, H-3), 4.19 (ddd, $J_{1,2}$=5.2, $J_{1,5}$=7.6 Hz, $J_{1,5'}$=8.0 Hz, 1H, H-1), 3.42 (dd, $J_{4,5}$=3.7 Hz, $J_{4,5'}$=4.2 Hz, 1H, H-4), 1.81 (m, 2H, H-5) 1.35 ,1.16 (s,s,C^6H_3, C^7H_3);^{13}C NMR (20 MHz, $CDCl_3$)∂: 137.50, 128.61, 128.30, 127.89 (aromatic),111.03 (C-8), 82.27, 78.88, 71.74 (C-1,2,3), 76.72 (NHO$\underline{C}H_2C_6H_5$), 62.95 (C-4), 35.87 (C-5), 25.99,24.13 (C-6, 7).
13. Bélanger, P.; Prasit, P. Tetrahedron Lett. ,**1988**, 29, 5521.
14. We thank the referee for this observation.