Tetrahedron Letters, Vol.32, No.44, pp 6437-6440, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

CARBOCYCLES FROM CARBOHYDRATES: A FREE RADICAL ROUTE TO AMINOCYCLITOL DERIVATIVES

José Marco-Contelles,* Luis Martínez, Angeles Martínez-Grau,
Carmen Pozuelo, and M.L. Jimeno.

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

Abstract: Some derivatives of (1*R*,2*R*,3*R*,4*S*,5*R*) and (1*R*,2*R*,3*R*,4*R*,5*S*)-5-amino-1,2,3,4-cyclohexanetetrol have been synthesized from acyclic carbohydrate intermediates via 6-exo free radical cyclization.

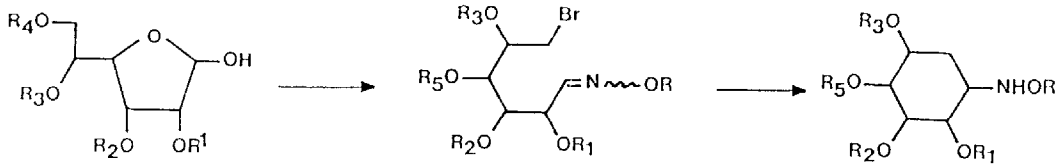
5-Amino-1,2,3,4-cyclohexanetetrols are valuable intermediates in the synthesis of aminocyclitols.[1,2,3] Methods for the synthesis of enantiomerically pure compounds of this type are limited to the transformation of 6-deoxy-5-enopyranosides,[4] the intramolecular nitrone cycloaddition[5] and the nitroalkane cyclization methodology.[6] In the last years the free radical[7] route has proven to be an efficient method for the synthesis of carbocycles from carbohydrates.[8] To our knowledge the 6-exo free radical cyclization of acyclic carbohydrate intermediates has not been explored or has failed to yield cyclized products.[9]

In this communication we report a new and simple route to chiral derivatives of 5-amino-1,2,3,4-cyclohexanetetrols via 6-exo free radical cyclization of acyclic carbohydrate derivatives. The strategy is shown in Scheme I; the protected lactol **1** undergoes bromination and oxime ether formation giving intermediate **2** ready for free radical cyclization mediated by tributyltin hydride.[10]

The radical precursors **3**[11] have been prepared from 6-bromo-6-deoxy-1,2-*O*-isopropylidene α-D-glucofuranose[12] and 3,5-di-*O*-benzyl-6-*O*-trityl-α-D-glucofuranose.[13] The cyclization[14] of these intermediates gave compounds **4** and **5** (Scheme II) in moderate yield and good diastereoselectivity (see Table). The absolute stereochemistry at the new stereocenter in the major isomers **4** has been established by analysis of their ^{1}H-NMR spectra; for major **4a**, for instance, δH_5 3.25 (ddd, $J_{4,5}$ = 10 Hz, $J_{5,6ax}$ = 12.4 Hz, $J_{5,6eq}$ = 4.2 Hz); this is what we can expect for a β substituent at C-5, provided that the cyclohexane ring is in a chair conformation, which is reasonable in this type of compounds.

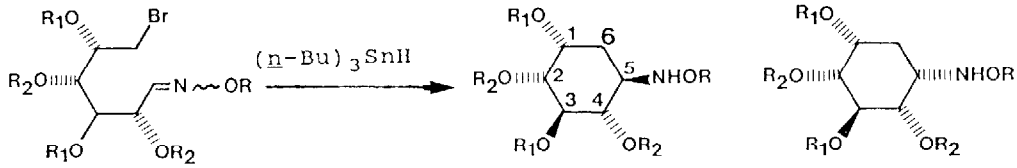
The mannose derivative **6**[11] has been prepared from 2,3-*O*-isopropylidene-α-D-mannofuranose[15] and cyclized giving compounds **7/8** in 50 % yield and excellent diastereoselectivity (**7/8**::97/3); after purification the major isomer was obtained pure. In the ^{1}H-NMR spectrum **7** showed δH_{6eq} 2.16 (dt, $J_{6eq,1} = J_{6eq,5}$ = 5.4 Hz; $J_{6eq,6ax}$ = 13.6 Hz), δH_{6ax} 1.90 (ddd, $J_{5,6ax}$ = 9.8 Hz; $J_{1,6ax}$ = 8.0 Hz; $J_{6eq,6ax}$ = 13.6 Hz); H_5 appears at 3.19 ppm as a multiplet showing a vicinal coupling constant $J_{4ax,5ax}$ = 6.7 Hz, which is consistent with the assigned absolute configuration at C-5, being the carbocycle in a chair-like conformation.

Scheme I



1 2 A

Scheme II



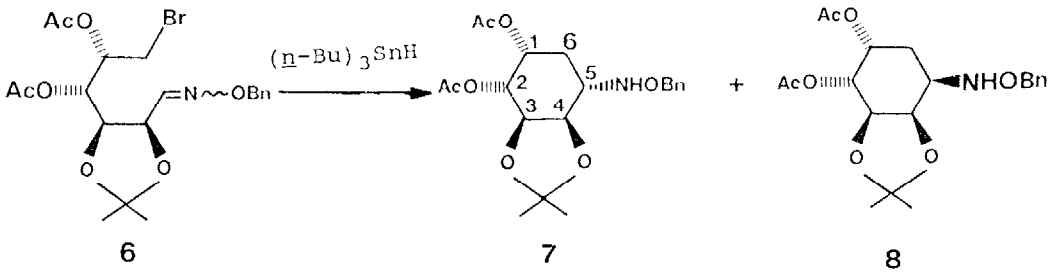
3 4 5

Table. Tin Hydride Mediated Cyclization of Oxime Ethers

	substrate (3)			product ratios	
entry	R_1	R_2	R	4/5[a(b)]	yield(%)[c]
1	a Ac	Ac	Bn	83/17 (only β)	52
2	b Bz	Bz	Bn	75/25 (80:20)	55
3	c Bz	Bz	Me	73/27 (only β)	50
4	d Bn	H	Bn	80/20 (94:6)	40
5	e Bn	Ac	Bn	78/22 (89:11)	42

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

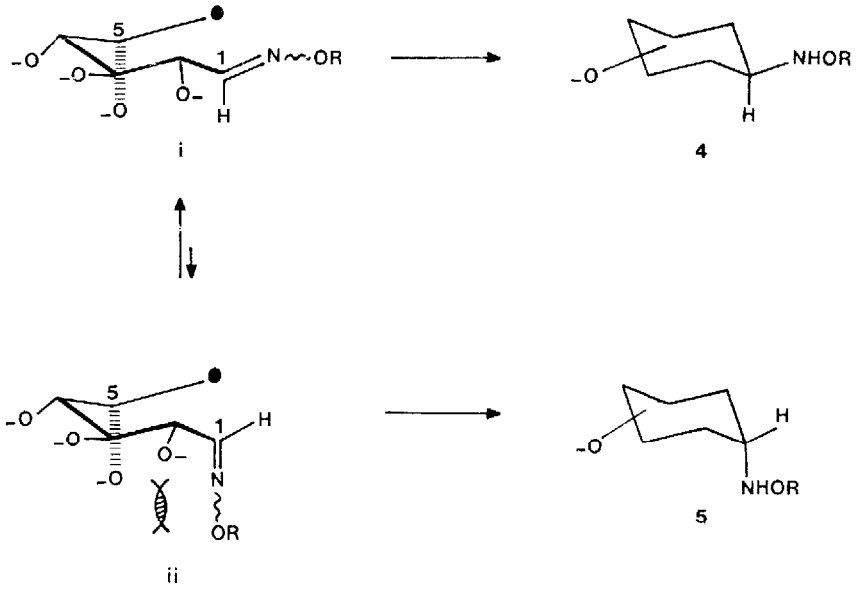
Scheme III



6 7 8

In Scheme IV we show a possible model for the stereochemical results obtained in the cyclization of substrates **3**. Assuming a chair-like conformation for these carbon centered radicals,[16] the steric interaction between the substituent at C-5 and the oxime ether at C-1 (sugar numbering) drives the equilibrium to conformer i leading to compounds **4** predominantly; in this picture we cannot exclude the influence of stereoelectronic effects of the aryl esters or ethers functional groups.[8b]

Scheme IV



In summary, a stereoselective method for the preparation of enantiomerically pure 5-amino-1,2,3,4-cyclohexanetetrols derivatives has been achieved. These are useful chiral building blocks for further development. The moderate yields in the cyclization is overcomed by the good to excellent ratios of the cyclized products and the easy availability of the radical precursors. We are currently examining other carbohydrate precursors and will report these studies in due course.

References and Notes

1. Umezawa, S. *Adv. Carbohydr. Chem. Biochem.*, **1974**, *30*, 111.
2. Balci, M.; Stbeyaz, Y.; Secen, H. *Tetrahedron*, **1990**, *46*, 3715.
3. Mallams, A.K. In *Carbohydrate Chemistry*, Kennedy, J.F. Ed., Clarendon Press, Oxford, 1988; pp 73-133.
4. (a) Ferrier, R.J. *J. Chem. Soc., Perkin Trans 1*, **1979**, 1455. (b) Semeria, D.; Philippe, M.; Delaumeny,

J.M.; Sepulchre, A.M.; Gero, S.D. *Synthesis*, **1983**, 710.

5. (a) Bernet, B.; Vasella, A. *Helv. Chim. Acta*, **1979**, *62*, 1990 (b) Shing, K.M.T., Elsly, D.A.; Gillhouley, J.G. *J. Chem. Soc., Chem. Commun.*, **1989**, 1280.
6. (a) Grosheintz, J.M.; Fischer, H.O.L. *J. Am. Chem. Soc.*, **1948**, *70*, 1476. (b) Bauer, H.H.; Siemsen, L. Astles, O.J. *Carbohydr. Res.*, **1986**, *156*, 247.
7. (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon Press; New York, 1986. (b) Curran, D.P. *Synthesis* **1989**, Part 1, p.417; Part 2, p. 489.
8. (a) RajanBabu, T.V. *J. Am. Chem. Soc.*, **1987**, *119*, 609. (b) Wilcox, C.S.; Thomasco, L.M. *J. Org. Chem.*, **1985**, *50*, 546. (c) Nugent, W.A.; RajanBabu, T.V. *J. Am. Chem. Soc.*, **1988**, *110*, 8561. (d) RajanBabu, T.V.; Fukunaga, T.; Reddy, G.S. *J. Am. Chem. Soc.*, **1989**, *111*, 1759. (e) Wilcox, C.S.; Gaudino, J.J. *J. Am. Chem. Soc.*, **1986**, *108*, 3102. (f) RajanBabu, T.V. *J. Org. Chem.*, **1988**, *53*, 4522.
9. Yeung, B.-W.A.; Alonso, R.; Vite, G.; Fraser-Reid, B. *J. Carbohydrate Chem.*, **1989**, *8*, 413.
10. Bartlett, P.A.; McLaren, K.L.; Ting, P.C. *J. Am. Chem. Soc.*, **1988**, *110*, 1633.
11. All new compounds showed good analytical and spectroscopic data. The synthesis of the radical precursors will be detailed elsewhere.
12. Whistler, R.L.; Anisuzzaman, A.K.M. *Methods Carbohydr. Chem.*, **1980**, *8*, 227.
13. Dax, K.; Wolflehner, W.; Weidmann, H. *Carbohydr. Res.*, **1978**, *65*, 132.
14. In a typical experiment, compounds **3** (2.5-3.5 mmol; obtained as mixtures of **syn** + **anti** isomers that we could not separate) dissolved in benzene (0.01 M), were treated with tributyltin hydride (2.4 equiv) and AIBN (cat.) at reflux, under argon for 3 h. The solvent was removed and the residue diluted with ether plus 10% 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 the cyclization of compound **3** and **6** small amounts (< 10%) of dimerized carbohydrate products incompletely identified were also present in the reaction. *Selected spectroscopic data.* **4a**: mp 116-118°C; $[\alpha]^{25}_D$ -72° (c 4.5, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34-7.26 (m, 5H, aromatic), 5.44 (q, J = 3.1 Hz, 1H, H-1), 5.35 (t, J = 10 Hz, 1H, H-3), 5.21 (t, J = 10 Hz, 1H, H-4), 4.92 (dd, J = 10 and 3.1 Hz, 1H, H-2), 4.61 (s, 2H, $OCH_2C_6H_5$), 3.25 (ddd, J = 10, 12.4 and 4.2 Hz, 1H, H-5), 2.10, 2.09, 2.01, 1.98 (s,s,s,s, $OCOCH_3$, H-6eq), 1.88 (ddd, J = 3.1, 12.4 and 14.5 Hz, H-6ax). ^{13}C-NMR (20 MHz, $CDCl_3$) δ: 170.23, 170.05, 169.97, 169.91 ($OCOCH_3$), 139.14, 128.67, 128.55, 128.14 (aromatic), 76.99 ($OCH_2C_6H_5$), 71.87, 71.72, 71.20, 67.82 (C-1, 2, 3, 4), 56.87 (C-5), 29.78 (C-6), 21.01, 20.84, 20.75, 20.06 ($OCOCH_3$). MS (70 eV) m/z: 438 (M+1, 8), 378 (1), 287 (2), 91 (100), 77 (3), 43 (14). **7**: oil; $[\alpha]^{25}_D$ +2.7° (c 2.2, $CHCl_3$) ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.40-7.27 (m, 5H, aromatic), 5.30-5.20 (m, 2H, H-1, H-2), 4.70 (s, 2H, $OCH_2C_6H_5$), 4.22 (m, 2H, H-3, H-4), 3.19 (m, 1H, H-5), 2.16 (dt, $J_{6eq,1} = J_{6eq,5} = 5.4$ Hz, $J_{6eq,6ax} = 13.6$ Hz, 1H, H-6eq), 1.90 (ddd, $J_{5,6ax} = 9.8$ Hz, $J_{1,6eq} = 8$ Hz, $J_{6eq,6ax} = 13.6$ Hz, 1H, H-6ax). MS (70 eV) m/z: 378 (M^+-15, 1), 269 (17), 267 (13), 91 (100), 43 (30).
15. Freudenberg, K.; Wolf, A. *Chem. Ber.*, **1927**, *60*, 1232.
16. Hannesian, S.; Dhanoa, D.S.; Beaulieu, P. *Can. J. Chem.*, **1987**, *65*, 1859.

(Received in UK 29 August 1991)