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STEREOSELECTIVE C-C BOND FORMATION IN CARBOHYDRATES BY RADICAL CYCLIZATION REACTIONS-II

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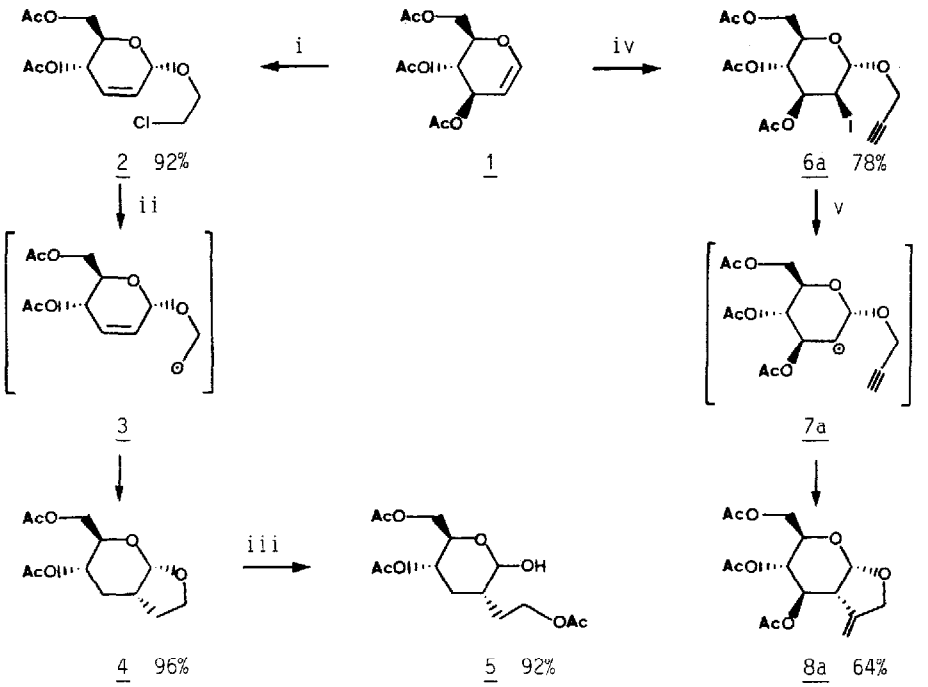
Summary: The synthesis of the bicyclic acetals 8 from the glycal 1 using a radical cyclization reaction is described.

Intensive work has been devoted to the synthesis of C-branched sugars[1-3]. We have recently reported[1] an efficient and stereoselective synthesis of the α-C(2) branched pyranosides 5 by radical cyclization reaction (2 → 4: scheme). The radical acceptor (C=C) is part of the pyranosidic ring and the initial radical 3 is generated on the glycosidic side chain. The crucial final ring scission of the bicyclic acetal 4 is performed with acetyl chloride in the presence of a catalytic amount of $CoCl_2$.



scheme

i = 1.7 eq. HO-CH_2-CH_2-Cl, 0.5 eq. $BF_3.Et_2O$, PhH, RT, 8 min, (2 α/β = 89/11);
ii = 1.5 eq. nBu_3SnH, 0.1 eq. AIBN, PhH (0.01 M), reflux, 20 h, (4 α/β = 86/14);
iii = 0.05 eq. $CoCl_2$, 1.5 eq. MeCOCl, MeCN, 0°C, 5 h, then hydrolysis on silica gel;
iv = 1 eq. HO-CH_2-C≡CH, 1.5 eq. N-iodosuccinimide, MeCN, RT, 24 h; v = 1.5 eq. nBu_3SnH, 0.05 eq. AIBN, PhH (0.01 M), reflux, 24 h.

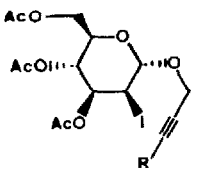
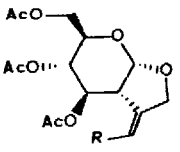
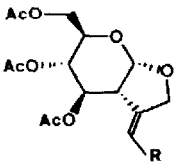
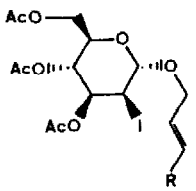
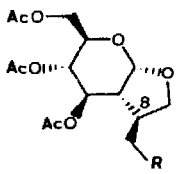
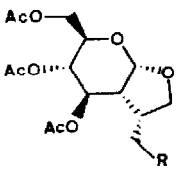
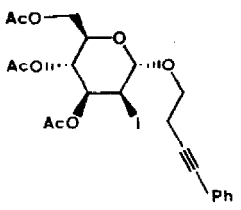
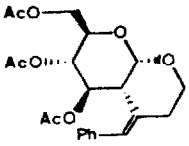
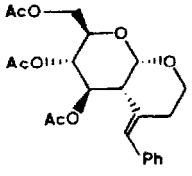
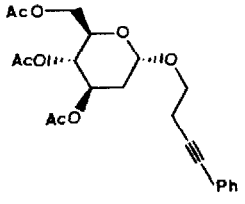
We report here a complementary approach to these systems (1 → 8) in which the initial radical 7a is centered on the pyranosidic ring (C(2)) and the radical acceptor (C=C, C≡C) is located on the glycosidic side chain (scheme). The starting materials 6 are obtained, mainly as α isomers[4], by reaction of the glycal 1 with allylic and propargylic alcohols in the presence of N-iodosuccinimide[5]. In a typical example, 6a[4,6] is treated in refluxing benzene with nBu_3SnH (added at once: 0.01 M) to give 8a (64%). The efficiency and the stereoselectivity of the α glycosidation and of the radical cyclization reactions allow a practical preparation of various bicyclic acetals 8, as shown in the table. Only the cis-fused bicyclic systems 8 are formed by radical cyclization. The reduction products which could result from the capture of the initial radicals 7 by nBu_3SnH before addition to the C=C or C≡C bonds are not detected for the 5-exo mode of cyclization (8a-8f). This was verified for 6b and 6f under more concentrated conditions (nBu_3SnH added at once, 0.05 M). However, in the case of a 6-exo mode of cyclization (6g → 8g), the reduced compound 6h is also formed even at 0.01 M nBu_3SnH.

With the terminal olefin 6e, only the epimers 8e[7] arising, as expected[8], from a 5-exo-mode of cyclization are isolated. Interestingly, some stereocontrol in the formation of the additional new chiral center in C(8) can be achieved in 8f. Smaller steric interactions are present in the transition state leading to the major epimer of 8f[9]. The preferential formation of the Z olefins 8b-c can be rationalized in terms of hydrogen atom transfer from the nBu_3SnH to the vinylic radical intermediate from the less hindered face. However, in the case of 8d, steric interactions between the t-butyl and the C(3) acetyl groups are taking place and therefore the Z/E ratio is inverted. These results, together with our previous report[1] on the crucial ring opening of the bicyclic acetal 4 (scheme) allow a short and practical synthesis of some α-C(2) branched sugars from the commercially available glycal 1. The use of intramolecular radical reactions for the stereoselective formation of C-C bonds at the anomeric position will be reported.

REFERENCES AND NOTES

1. Stereoselective C-C bond formation in carbohydrates by radical cyclization reactions-I; A. De Mesmaeker, P. Hoffmann, B. Ernst, Tetrahedron Lett., submitted.
2. For recent contributions see a) S. Hanessian, M. Martin, R.C. Desai, J. Chem. Soc. Chem. Commun., 926, (1986); b) S.A. Babirad, Y. Wang, Y. Kishi, J. Org. Chem., 52, 1372, (1987); c) K. Luthman, M. Orbe, T. Waglund, A. Claesson, J. Org. Chem., 52, 3777, (1987); d) S.J. Danishefsky, S. DeNinno, P. Lartey, J. Am. Chem. Soc., 109, 2082, (1987).
3. For the C-C bond formation by intermolecular addition of glycopyranosidic radicals to olefins see for example a) B. Giese, T. Witzel, Angew. Chem. Int. Ed. Engl., 25, 450, (1986); b) G.E. Keck, D.F. Kachensky, E.J. Enholm, J. Org. Chem., 50, 4317, (1985); c) B. Giese in "Radicals in Organic Synthesis", Pergamon Press, (1986).

Table

Radical Precursors 6 (yield %)[a]			Cyclized Products 8 (yield %: isomers ratio)[a,b]		
			 		
6b	R = Ph	80	8b	R = Ph	85 (74:26)
6c	R = nBu	83	8c	R = nBu	90 (71:29)
6d	R = tBu	79	8d	R = tBu	91 (36:64)
			 		
6e	R = H	70	8e	R = H	85 (53:47)[7]
6f	R = Ph	78	8f	R = Ph	80 (75:25)
			 		
6g		75	8g		
			8g + 6h		79 (38:31:31)
					
6h					

a) Yields refer to isolated products.

b) The isomers ratios were determined by ^{1}HNMR (300 MHz) on the reaction mixtures.

4. In general, after chromatography, the pure α anomers are used for the radical cyclization reactions. For 6a, the separation of the α and β isomers is easier after cyclization 8a.
5. For the glycosidation mediated by N-iodosuccinimide see a) J. Thiem, H. Karl, J. Schwentner, Synthesis, 696, (1978); b) J. Thiem, P. Ossowski, J. Carbohydrate Chem., 3, 287, (1984).
6. The corresponding β anomer of 6a having the substituents in C(1) and C(2) in a trans diequatorial arrangement is also formed (α/β = 9/1; ^{1}H-NMR ($CDCl_3$, 300 MHz): 6a α δH_1 = 5.37 ppm, d, $^3J_{1-2}$ = 1 Hz; 6a β δH_1 = 4.88 ppm, d, $^3J_{1-2}$ = 9Hz).
7. In this case the identity of the 2 epimers in C(8) was not determined.
8. Generally, the 5-exo mode of cyclization is preferred to the 6-endo mode. However, the formation of a 6-membered ring by radical cyclization on a terminal olefin is known. For recent reviews of this subject see a) D.P. Curran, Synthesis, 417, (1988); b) W.P. Neumann, Synthesis, 665, (1987); c) M. Ramaiah, Tetrahedron, 43, 3541, (1987).
9. For recent examples of stereoselective radical cyclization reactions in carbohydrates see a) C.S. Wilcox, L.M. Thomasco, J. Org. Chem., 50, 546, (1985); b) C.S. Wilcox, J.J. Gaudino, J. Am. Chem. Soc., 108, 3102, (1986); c) T.V. Rajanbabu, J. Am. Chem. Soc., 109, 609, (1987); d) T.V. Rajanbabu, J. Org. Chem., 53, 4522, (1988).
10. After the submission of this article the synthesis of 8a and 8e was described using similar conditions; C. Audin, J. M. Lancelin, J.M. Beau, Tetrahedron Lett., 3691, (1988).
11. Selected ^{1}H-NMR data (300MHz, $CDCl_3$, δ (ppm), J(Hz,); 8a; 2.04 (oAc,s); 2.08 (oAc,s); 2.12 (oAc,s); 2.78 (H_2, dd, J_{2-3}=8.4, J_{2-1}=4.5); 4.11 (H_6, dd, $J_{6-6'}$=12.0, J_{6-5}=2.3); 4.18 (H_5, ddd, J_{4-5}=9.3, $J_{6'-5}$=4.5); 4.39 ($H_{6'}$,dd); 4.36 (H_7, dm, $J_{7-7'}$=14.0); 4.68 ($H_{7'}$, dm); 4.98 (H_9,m); 5.02 (H_4,dd); 5.10 ($H_{9'}$,m); 5.17 (H_3, dd, $J_{2-3} = J_{3-4}$ = 8.4); 5.44 (H_1, d); 8f (major); 1.87 (oAc,s); 1.99 (oAc,s); 2.06 (oAc, s); 2.13 (H_2, ddd, J_{1-2}=5.0, J_{2-3}=8.0, J_{2-8}=1.5); 2.47-2.89 (H_8+H_9, m); 3.70 (H_6,dd, $J_{6-6'}$=12.0, J_{6-5}=3.5); 4.01-4.05 (H_5, m); 4.07 ($H_{6'}$, dd, $J_{6'-5}$=2.3); 4.28-4.45 (H_7, m); 4.92 ($H_{3(4)}$, dd, J=9.0); 4.99 ($H_{4(3)}$, dd, J=8.0); 5.53 (H_1,d); 7.08-7.33 ($5H_{Ar}$,m); 8f (minor); 1.88 (oAc,s); 2.03 (oAc,s); 2.08 (oAc,s); 2.54 (H_2, ddd, J_{1-2}=5.0, J_{2-3}=9.5, J_{2-8}=5.5); 2.47-2.89 (H_8+ H_9,m); 3.80-3.90 (H_6+$H_{6'}$,m); 4.11-4.16 (H_5, m); 4.28-4.45 (H_7,m); 5.03 (H_4,dd, J_{4-3}= J_{4-5} = 9.5); 5.30 (H_3, dd); 5.50 (H_1,d); 7.08-7.33 ($5H_{Ar}$, m); 6g; 2.00 (oAc,s); 2.09 (oAc,s); 2.10 (oAc,s); 2.74 (H_8, dd, J_{8-7}=$J_{8-7'}$=6.7); 3.72 (H_7,m, $J_{7-7'}$=9.5); 3.86 ($H_{7'}$, m); 4.14-4.20 (H_6,m); 4.22 (H_5,m); 4.58 (H_2, dd, J_{2-3}=4.3, J_{1-2}= 1.4); 4.69 (H_3,dd, J_{3-4}=9.5); 5.28(H_1,d); 5.38 (H_4,dd, J_{3-4}=J_{4-5}=9.5); 7.26-7.32 ($3H_{Ar}$, m); 7.36-7.45 ($2H_{Ar}$,m).

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