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STEREOSELECTIVE C-C BOND FORMATION IN CARBOHYDRATES BY RADICAL CYCLIZATION REACTIONS-I.

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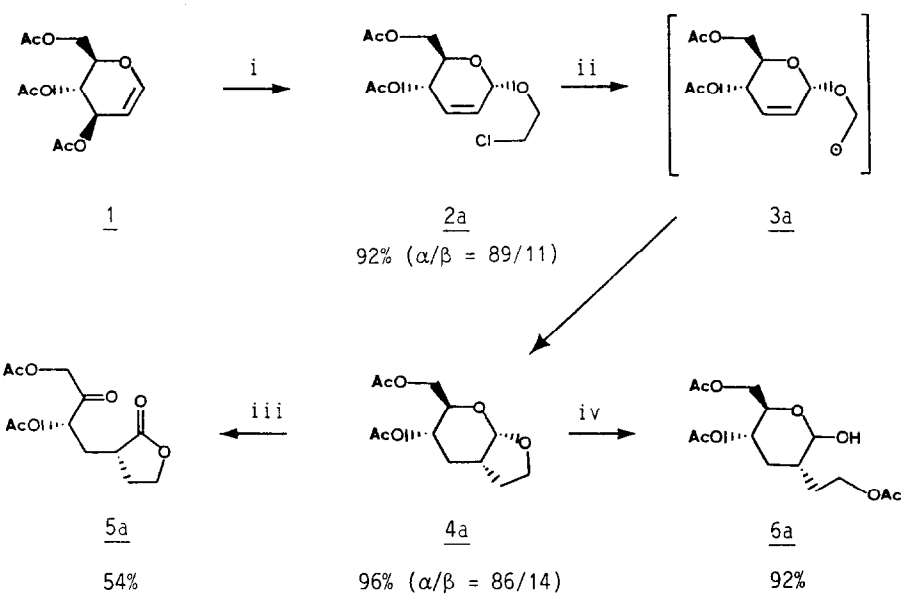
Summary: A three steps synthesis of α-C(2) branched pyranosides from the glycal 1 is described.

Among the several methods used for the synthesis of C-branched sugars[1,2], the intermolecular addition of glycopyranosidic radicals to olefins has been shown to be very useful[3]. Radical reactions should be particularily promising in the field of carbohydrates because they are performed under neutral conditions, they are compatible with most of the protective groups and usually even do not require the protection of functional groups (-OH). Our strategy for the stereoselective C-C bond formation in sugars is based on an intramolecular radical cyclization reaction (scheme) and offers two major advantages in comparison with the intermolecular processes: a) a more efficient C-C bond formation and b) a higher stereoselectivity due to the exclusive formation of a cis ring junction[4]. We report here an example of this strategy. The synthesis of the radical precursors 2 is achieved by the Ferrier reaction[5] starting from the glycal 1.



1 2a 3a

92% (α/β = 89/11)

5a 4a 6a

54% 96% (α/β = 86/14) 92%

scheme

i = 1.7 eq. HO-CH_2-CH_2-Cl, 0.5 eq. $BF_3.Et_2O$, PhH, RT, 8 min; ii = 1.5 eq. nBu_3SnH, 0.1 eq. AIBN, PhH (0.01 M), reflux, 20 h; iii = 3 eq. CrO_3, AcOH, RT, 3 h; iv = 0.05 eq. $CoCl_2$, 1.5 eq. MeCOCl, MeCN, 0°C, 5 h, then hydrolysis on silica gel.

Further examples are listed in the table. The unsaturated sugars 2a-2i are obtained stereoselectively and in high yields if the reaction is quenched with NaH_2PO_4 aq. after few minutes. Longer reaction time leads to decomposition. The reaction conditions are even compatible with an activated chlorine atom as in 2i (table). The cyclization reactions proceed also stereoselectively and very efficiently by stabilized and non stabilized radicals. In general the α and β isomers are separated after cyclization[6]. The reduction products which could arise from the capture of the initial radicals before addition to the unactivated C=C bond were not detected (nBu_3SnH added at once: 0.01-0.05 M). Even at a concentration of 0.1 M of nBu_3SnH in benzene, less than 5% of reduced product is observed starting from 2a. This cyclization can also be carried out successfully, without any interference, in various solvents (acetonitrile, toluene, ethyl acetate, dioxane, dimethylformamide, t-butanol: 80°C). The possibility to perform the ring closure reactions under rather concentrated conditions (0.1 M; nBu_3SnH added at once) and with highly stabilized radicals as in 2i underlines the efficiency of this process.

Furthermore, the analogous bromide of 2a is cyclized at room temperature in the presence of a catalytic amount of nBu_3SnCl[7] (EtOH, 0.1 eq. nBu_3SnCl, 2 eq. $NaBH_4$, hν , RT, 40 min: yield of 4a = 96%).

The preferential formation of compound 4i documents the possibility of stereocontrol of the new chiral center in C(8).

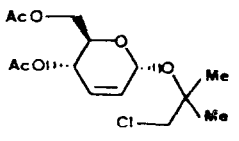
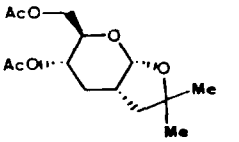
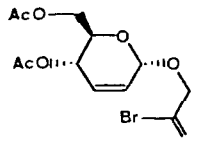
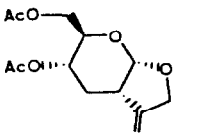
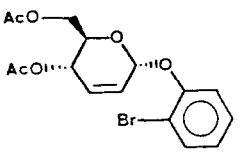
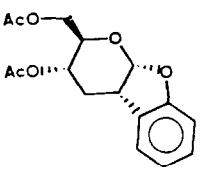
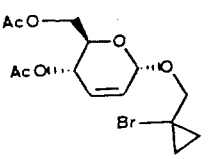
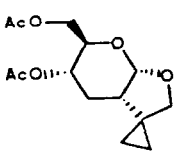
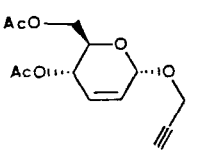
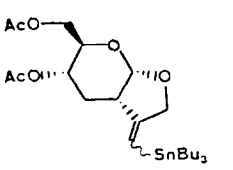
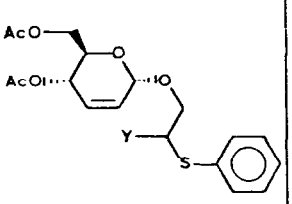
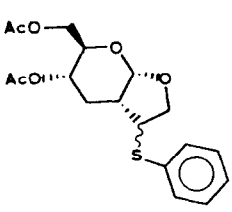
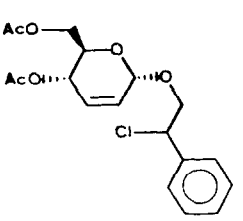
The final step in our sequence for the stereoselective C-C bond formation is the ring scission of the bicyclic systems 4. Interestingly, in the bicyclic acetal 4a the 5- or the 6-membered ring can be cleaved selectively (scheme). With CrO_3 in acetic acid[10] the butyrolactone 5a is obtained. On the other hand acetyl chloride and a catalytic amount of $CoCl_2$[11] yielded 6a; the intermediate anomeric chloride can be isolated but is conveniently hydrolyzed on silica gel.

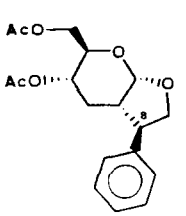
These results allow a short and practical synthesis of some α-C(2) branched sugars. Further developments of this strategy will be reported.

REFERENCES AND NOTES

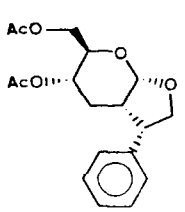
1. a) S. Hanessian in "Total Synthesis of Natural Products: The Chiron Approach", Pergamon Press, (1983); b) J.G. Buchanan, Prog. Chem. Org. Nat. Prod., 44, 243, (1983).
2. For recent contributions see a) S. Hanessian, M. Martin, R.C. Desai, J. Chem. Soc. Chem. Commun., 926, (1986); b) S.A. Babirad, 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. 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 2		(Yield %; α/β)		Cyclized Products 4		(Yield %; α/β)	
2b		80	83/17	4b		96	86/14
2c		96	88/12	4c		89	86/14
2d		46	91/9	4d		91	87/13
2e		83	90/10	4e		88	90/10
2f		98	91/9	4f		67 8	α Z/E 80/20 β Z
2g Y=H 2h Y=Cl[8]		92	82/18	4h		66 from 2g	97/3
2i		88	86/14				



4i[9] 73 %



4j 10 %

4. For stereospecific reductive methylation via a radical cyclization-desilylation process see G. Stork, M.J. Sofia, J. Am. Chem. Soc., 108, 6826, (1986).
5. R.J. Ferrier, N. Prasad, J. Chem. Soc. (c), 570, (1969).
6. For convenience, only the major α isomers are depicted. The minor β isomers 2 cyclize also stereoselectively.

2a β 4a β

7. E.J. Corey, J.W. Suggs, J. Org. Chem., 40, 2554, (1975).
8. The precursor for the radical cyclization 2h is obtained by chlorination of 2g with SO_2Cl_2 in the presence of lutidine and used without further purification.
9. The stereochemistry of 4i is established by ^{1}H-NMR NOE experiments.
10. S.J. Angyal, K. James, Aust. J. Chem., 23, 1209, (1970).
11. S. Ahmad, J. Iqbal, Chem. Lett., 953, (1987).
12. Selected ^{1}H-NMR data of the major α isomers (300 MHz, δ(ppm), J(Hz)); 4a; 1.50 (H_{3ax},ddd, $J_{3ax-3eq}$=13.0, J_{3ax-2}=J_{3ax-4}=10.0); 1.77 (H_8,m); 2.05 (oAc,s); 2.08 (oAc,s); 2.05-2.20 (H_8,+H_2,m); 2.34 (H_{3eq},m); 3.92 (H_7,ddd, $J_{7-7'}$=11.5); 3.97 (H_5,m); 4.10-4.17 (H_6+$H_{7'}$,m); 4.30 ($H_{6'}$,dd, $J_{6-6'}$=12.0, $J_{6'-5}$=5.1); 4.79 (H_4, ddd, J_{4-5}= 10.0, J_{4-3eq}=5.0); 5.33 (H_1,d, J_{1-2}=4.3); 4c; 1.69 (H_{3ax}, ddd, $J_{3ax-3eq}$=13.5, J_{3ax-2}=J_{3ax-4}=9.5); 2.03 (oAc,s); 2.09 (oAc,s); 2.22 (H_{3eq},ddd, J_{3eq-4}=4.8, J_{3eq-2}=7.0); 2.80 (H_2,m); 4.03 (H_5,m); 4.15 (H_6,dd, $J_{6-6'}$=12.0, J_{6-5}=2.5); 4.29 ($H_{6'}$, dd, $J_{6'-5}$=5.0); 4.35 (H_7,dm, $J_{7-7'}$=13.5); 4.66 ($H_{7'}$,dm); 4.80 (H_4,ddd, J_{4-5}=9.5); 4.95 (H_9,m); 5.02 ($H_{9'}$,m); 5.38 (H_1,d,J_{1-2}=4.5); 4d; 1.78 (oAc,s); 2.08 (H_3,ddd, $J_{3-3'}$=14.7, J_{3-2}=J_{3-4} =4.6); 2.10 (oAc,s); 2.33 ($H_{3'}$, ddd, $J_{3'-2}$=$J_{3'-4}$=5.6); 3.55 (H_2,m); 3.87 (H_5,m); 4.18-4.20 (H_6,m); 4.92 (H_4, m), 6.10 (H_1,d, J_{1-2}=7.5); 6.83-6.92 ($2H_{Ar}$,m); 7.08-7.18 ($2H_{Ar}$,m); 4i; 1.71 (H_3, ddd, $J_{3-3'}$=14.5, J_{3-2}=J_{3-4}=5.8); 2.10 (oAc,s); 2.13 (oAc,s); 2.19 ($H_{3'}$,ddd, $J_{3'-2}$=$J_{3'-4}$=5.8); 2.41 (H_2,tdd); 3.46 (H_8, dt, J_{8-2}=7.5); 3.92 (H_7,dd, $J_{7-7'}$= 9.0, J_{7-8}=7.2); 4.10 (H_5,ddd, J_{4-5}=7.7); 4.21 (H_6,dd, $J_{6-6'}$=12.0, J_{6-5}=3.2); 4.28 ($H_{6'}$,dd, $J_{6'-5}$=5.8); 4.49 ($H_{7'}$,dd, $J_{7'-8}$=7.5); 4.90 (H_4, td); 5.56 (H_1, d, J_{1-2}=5.5); 7.10-7.40 ($5H_{Ar}$,m).
13. Selected 'H-NMR data of the minor β isomers (300 MHz, δ(ppm), J(Hz); 4a; 3.64 (H_7, ddd, $J_{7-7'}$=8.7, J_{7-8}=$J_{7-8'}$=4.2); 4.21 (H_6,dd, $J_{6-6'}$=8.5, J_{5-6}=3.5); 4.88 (H_4, ddd, J_{3ax-4}=J_{4-5}=9.7, J_{3eq-4}=5.0); 5.14 (H_1,d, J_{1-2}=3.8); 4d; 2.04 (oAc,s); 2.09 (oAc,s); 2.16-2.34 (H_3+$H_{3'}$,m); 3.61 (H_2,m); 3.83 (H_5,m); 4.14 (H_6,dd, $J_{6-6'}$=12.0, J_{6-5}=6.0); 4.21 ($H_{6'}$,dd, $J_{6'-5}$=3.8); 4.81 (H_4,ddd, J_{4-3}=4.2, J_{4-5} =$J_{4-3'}$=7.0); 5.86 (H_1,d,J_{1-2}=5.9); 6.82-7.00 ($2H_{Ar}$,m); 7.10-7.22 ($2H_{Ar}$,m).

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