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STEREOSELECTIVE C-C BOND FORMATION IN CARBOHYDRATES BY RADICAL CYCLIZATION REACTIONS-III. STRATEGY FOR THE PREPARATION OF C(1)-GLYCOSIDES.

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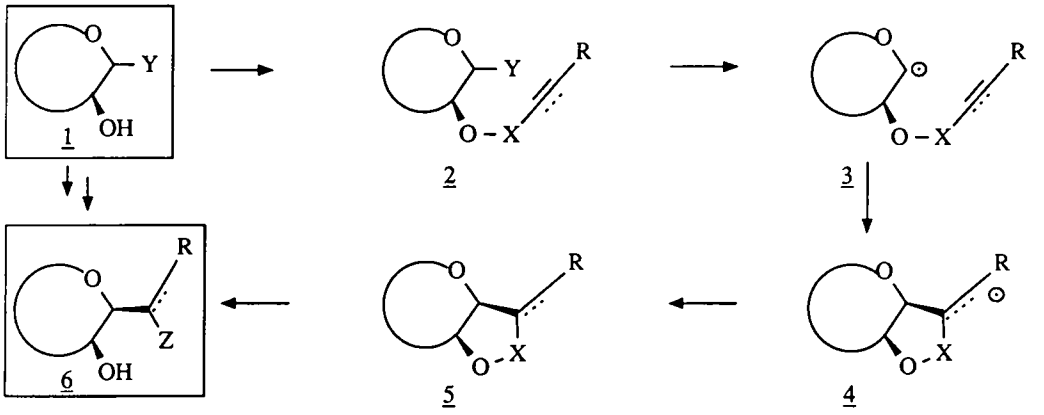
Summary: A new strategy for the stereoselective synthesis of α- and β-C(1)-glycosides based on an intramolecular radical cyclization reaction is described. Intramolecular hydrogen atom transfer was observed depending on the concentration of the reagents, the conformation and the substitution of the cyclized radical.

Intensive work has been devoted to the synthesis of C-branched sugars[1-4]. Among the methods available for the preparation of C(1)-glycosides, the intermolecular addition of glycopyranosidic radicals to olefins has been shown to be very useful[3]. We propose here a new strategy (scheme 1) for the stereoselective C-C bond formation at the anomeric position of carbohydrates based on an intramolecular radical cyclization reaction offering three major advantages in comparison with the intermolecular processes: a) more efficient C-C bond formation, b) higher stereoselectivity due to the exclusive formation of a cis ring junction, c) access to both α- and β-C(1)-glycosides. Generally, the intermolecular addition of anomeric radicals requires an excess of a reactive olefin yielding the α-glycosides[3]. In our approach (scheme 1), the radical acceptor (C=C, C≡C) is connected with the hydroxylic group at C(2) through the function X(1→2) which makes later on the cleavage of the newly formed five-membered ring possible (5→6).

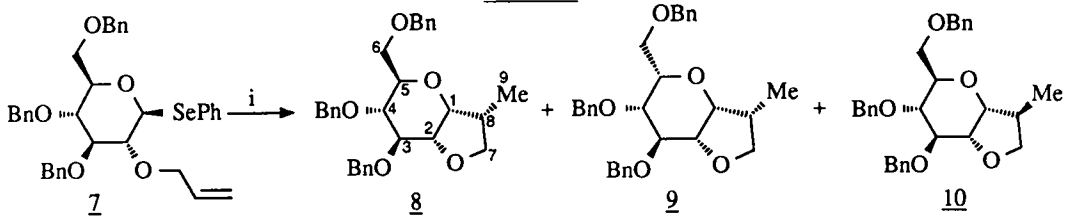
Scheme 1



The main features of these radical cyclizations will be discussed in this communication with X=CH_2. The usefulness of our strategy for the synthesis of C(1)-glycosides will be demonstrated in the accompanying communication[5]. Preliminary experiments were performed on the model compound [6,7]7 (scheme 2). We found that, indeed, an efficient radical cyclization occurred yielding only the cis ring junction[8].

However, a third unexpected component was found under our standard reaction conditions (0.01M[6]), namely the L-idose derivative [9] 9.

Scheme 2

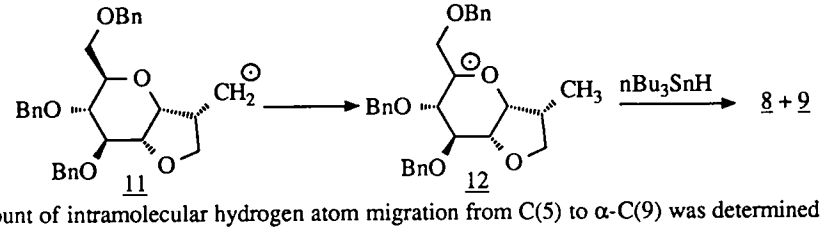


Concentrations(M)	Isomers ratios[9](%)		
0.001	22	23	55
0.01	29	15	56
0.1	43	2	55
0.2	47	not detected	53

i= 1.3eq. nBu_3SnH, 0.1eq. AIBN, PhH, reflux, 24 h: combined isolated yields ≥ 90%.Bn=CH_2Ph

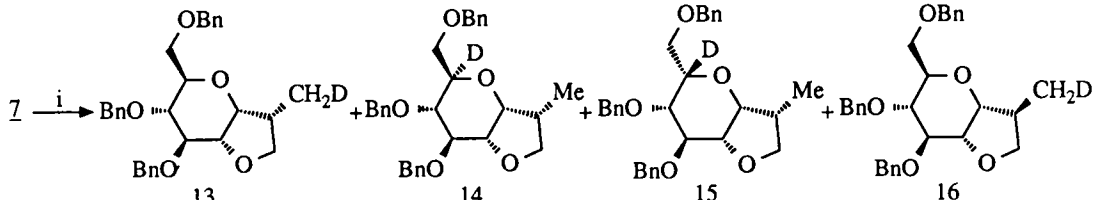
The formation of 9 can be rationalized by an intramolecular hydrogen atom transfer from C(5)-H to the cyclized radical 11 having the α configuration at C(8) followed by the reduction of the C(5) centered radical 12 by nBu_3SnH either from the β face (→9) or from the α face (→8[10]) (scheme 3).

Scheme 3



The total amount of intramolecular hydrogen atom migration from C(5) to α-C(9) was determined by deuteration with nBu_3SnD. These experiments (scheme 4) underline the ease of this process: already at 0.01M a significant amount of deuterium was detected at C(5) in the α-C(9) epimer ((14+15):13). Although intramolecular hydrogen atom transfer was already detected[11] in the presence of nBu_3SnH, it occurred generally from an activated C-H bond (allylic, benzylic) to a destabilized radical (vinylic, arylic, cyclopropylic) and / or under high dilution conditions. In our case, however, a concentration of 0.2M was needed to prevent the formation of 9, fortunately without reduction of the initial anomeric radical [12] (scheme 2).

Scheme 4

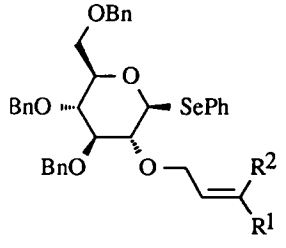
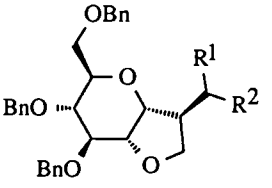
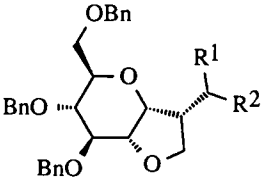
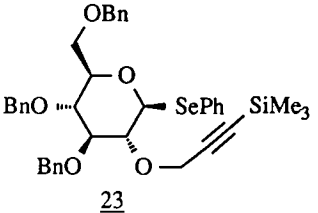
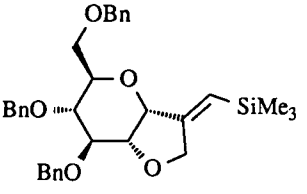
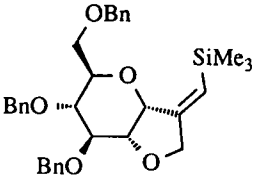
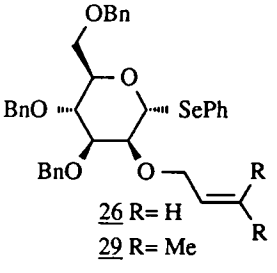
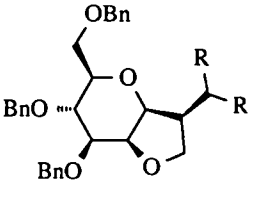
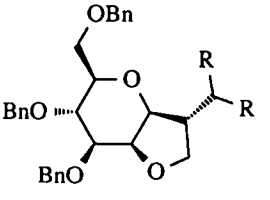


Concentrations (M)	13	14	15	16
	Isomers ratios[6] (%)			
0.001	10	12	23	55
0.01	20	9	15	56

i= 1.3eq. nBu_3SnD, 0.1eq. AIBN, PhH, reflux, 24 h: combined isolated yields ≥ 90%.

No deuterium was detected at C(2) and C(3) by ^{1}H-NMR difference spectroscopy. Therefore, the ease of the intramolecular hydrogen atom transfer from C(5) to α-C(9) (→14,15) results not only from the increase in radical stabilization (primary in 11 → delocalized, tertiary in 12: scheme 3) but mainly from the favourable conformation in which the three atoms C(5)-H-C(9) can adopt a colinear arrangement[13].This arrangement is not accessible without strain for C(3)-H and for C(2)-H in the α- and β-C(9) radicals respectively. As shown in the following communication[5], the hydrogen atom transfer from C(5) to α-C(9) occurred even in the case of a secondary radical (at C(9)) under our standard reaction conditions (0.01M[6]). However, no hydrogen atom migration was observed when a more stabilized radical was obtained after cyclization (tertiary 21,22; benzylic 18,19; table). A very efficient cyclization took place with the acetylenic derivative 23, without intramolecular hydrogen atom transfer, although a very reactive vinylic radical was formed as intermediate. This process was disfavoured due to the geometrical requirements mentioned above.

Table

Radical Precursors	Cyclized Products[a] (yield%, isomers ratio)		
			
17 R^1= Ph, R^2= H	18	19	89 (71:29)
20 R^1,R^2= Me	21	22	90 (54:46)
			
23	24	25	95 (82:18)
			
26 R= H 29 R= Me	27 30	28 31	92 (10:90) 90 (38:62)

a) Reaction conditions: 1.3eq. nBu_3SnH, 0.1eq.AIBN, PhH (0.01M), reflux.

For the same reason no epimerization arising from an intramolecular hydrogen atom transfer was either observed in the case of the D-mannose derivatives 26 and 29 (table), even under high dilution conditions (0.001M). A colinear arrangement of the three atoms C(4)-H-C(9β) could have been accessible without severe strain but required a disfavoured boat conformation of the six-membered ring[14]. Interestingly the new chiral center C(8) was formed stereoselectively in 28. In conclusion, the proposed strategy is very useful to form C-C bonds at the anomeric position in high yields and stereoselectively. The intramolecular hydrogen atom abstraction can be prevented by working under more concentrated conditions without formation of uncyclized products.

REFERENCES AND NOTES

1. We reported the synthesis of α-C(2)-branched sugars by radical cyclization reactions; A. De Mesmaeker, P. Hoffmann, B. Ernst, Tetrahedron Lett., 29, 6585, (1988) and 30, 57, (1989).
2. For radical cyclization reactions in carbohydrates see; C. S. Wilcox, J. J. Gaudino, J. Am. Chem. Soc., 108, 3102, (1986); C. Audin, J. M. Lancelin, J. M. Beau, Tetrahedron Lett., 29, 3691, (1988); Y. Chapleur, N. Moufid, J. Chem. Soc., Chem. Commun., 39, (1989); Y. Araki, T. Endo, Y. Arai, M. Tanji, Y. Ishido, Tetrahedron Lett., 30, 2829, (1989); J. C. Lopez, B. Fraser-Reid, J. Am. Chem. Soc., 111, 3450, (1989); G. D. Vite, R. Alonso, B. Fraser-Reid, J. Org. Chem., 54, 2268, (1989); T. V. Rajanbabu, T. Fukunaga, G. S. Reddy, J. Am. Chem. Soc., 111, 1759, (1989); K. S. Gröninger, K. F. Jäger, B. Giese, Liebigs Ann. Chem., 731, (1987); and references cited there.
3. For C-C bond formation by intermolecular addition of glycopyranosidic radicals to olefins see B. Giese, T. Witzel, Angew. Chem. Int. Ed. Engl. 25, 450, (1986); G. E. Keck, D. F. Kachensky, E. J. Enholm, J. Org. Chem., 50, 4317, (1985); Y. Araki, T. Endo, M. Tanji, J. Nagasawa, Y. Ishido, Tetrahedron Lett., 28, 5853, (1987); For reviews see B. Giese, "Radicals in Organic Synthesis", Pergamon Press, (1986); G. Descotes, J. Carbohydr. Chem., 7, 1, (1988).
4. For some leading references concerning C-branched sugars see S. Hanessian, " Total Synthesis of Natural Products: The Chiron Approach ", Pergamon Press, (1983); J. G. Buchanan, Prog. Chem. Org. Nat. Prod., 44, 243, (1983).
5. Stereoselective C-C Bond Formation in Carbohydrates by Radical Cyclization Reactions -IV: A. De Mesmaeker, P. Hoffmann, B. Ernst, P. Hug, T. Winkler, Tetrahedron Lett., following paper.
6. In all the radical cyclizations described here, the reagents were mixed at once.
7. The derivatives 7, 17, 20, 23, 26, 29 were obtained in high yields by alkylation of the hydroxylic function at C(2) (NaH, RBr, Bu_4NI, THF, RT). The PhSe group was introduced previously by substitution of the anomeric chloride (PhSeH, NEt_3, MeCN, RT).
8. For recent reviews on radical cyclization reactions see D. P. Curran, Synthesis, 417, (1988) and 489, (1988); W. P. Neumann, Synthesis, 665, (1987); M. Ramaiah, Tetrahedron, 43, 3541, (1987).
9. The isomers ratios were determined by ^{1}H-NMR (300MHz) on the reaction mixtures. The stereoisomers were separated by chromatography on silicagel and their structures elucidated on the basis of completely analyzed ^{1}H-NMR spectra and ^{1}H-NOE experiments. The configuration at C(8) was corroborated in most cases by ^{13}C-NMR. See also reference 5.
10. For the isomerization of D-glucuronic acid to L-iduronic acid derivatives see T. Chiba, P. Sinay, Carbohydr. Res., 151, 379, (1986).
11. A. L. J. Beckwith, D. M. O'Shea, S. Gerba, S. W. Westwood, J. Chem. Soc., Chem. Commun., 666, (1987); J. K. Choi, D. J. Hart, Tetrahedron, 41, 3959, (1985); S. M. Bennet, D. L. J. Clive, J. Chem. Soc., Chem. Commun., 878, (1986); B. Chenera, C. P. Chuang, D. J. Hart, L. Y. Hsu, J. Org. Chem., 50, 5409, (1985); D. P. Curran, D. Kim, H. T. Liu, W. Shen, J. Am. Chem. Soc., 110, 5900, (1988); D. C. Lathbury, P. J. Parsons, I. Pinto, J. Chem. Soc., Chem. Commun., 81, (1988); R. C. Petter, D. G. Powers, Tetrahedron Lett., 30, 659, (1989).
12. In all the cases described here , no uncyclized product could be detected by ^{1}H-NMR (300MHz) of the crude reaction mixtures.
13. Colinearity is considered to be favoured in intramolecular hydrogen atom abstractions by alkoxy radicals; A. L. J. Beckwith, Tetrahedron, 37, 3073, (1981); see also A. E. Dorigo, K. N. Houk, J. Am. Chem. Soc., 109, 2195, (1987).
14. Although no epimerization was observed in 27, 28 even at 0.001M,an intramolecular hydrogen transfer from C(4)-H to C(9β) cannot be rigorously excluded until these experiments are performed with nBu_3SnD. These are under current investigation.

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