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STEREOSELECTIVE C-C BOND FORMATION IN CARBOHYDRATES BY RADICAL CYCLIZATION REACTIONS-IV. APPLICATION FOR THE SYNTHESIS OF α-C(1)-GLUCOSIDES.

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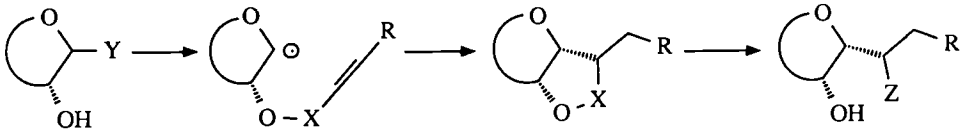
Summary: The synthesis of α-C(1)-glucosides is reported using our new strategy for the C-C bond formation at the anomeric center by radical cyclization reactions.

In the previous communication[1] we proposed a new strategy based on a radical cyclization reaction for the stereoselective C-C bond formation at the anomeric center[2-4]. We have shown that, indeed, the new C-C bond was formed in high yields and selectively either with the α or with the β configuration at C(1). This stereocontrol together with the efficiency of the radical cyclizations even with unactivated double and triple bonds represent certainly an advantage in comparison with the intermolecular processes[3]. However, in order to represent a synthesis of C(1)-glycosides, an auxiliary group X which can be used later on for the cleavage of the newly formed five-membered ring was needed. We report here the successful use of an acetal function (X=CH-OMe) as auxiliary group (scheme 1).

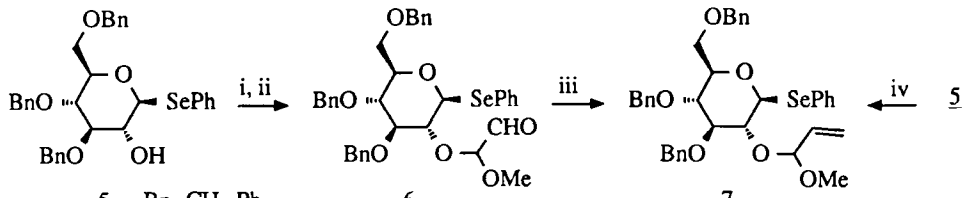
Scheme 1



1 2 3 4

The mixed acetals 7, 11, 15 were prepared by alkylation of the free hydroxylic function at C(2) of 5[5] with MeO-CHBr-CO_2Me[6] followed by reduction with diisobutylaluminium hydride to the corresponding aldehyde 6[7] and Wittig reaction, without interference of the selenophenyl group at the anomeric position which plays the role of radical precursor and protective group (scheme 2). The compound 7 was also obtained in one step by coupling with the dimethylacetal of acrolein under acidic catalysis.

Scheme 2

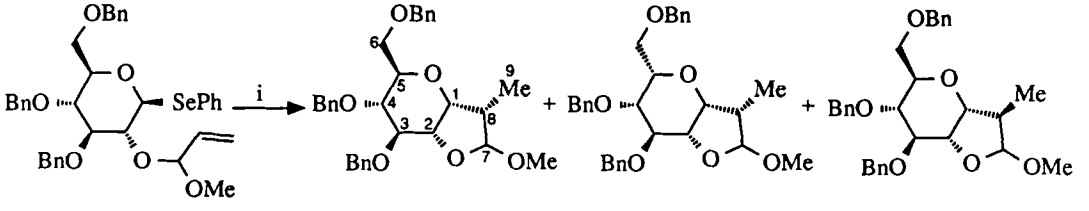


5 Bn=CH_2-Ph 6 7

i= 1.6eq. NaH, 2eq. MeO-CH-Br-CO_2Me, 0.3eq. Bu_4NI, THF, RT, 18 h, 76%; ii= 1eq. iBu_2AlH, -78°C, 4 h, 93%; iii= 1.3eq.PPh_3MeBr, 1.1eq. nBuLi, THF, -78°C→RT, 24 h, 65%; iv= 20eq. CH_2=CH-CH$(OMe)_2$, 0.1eq. TsOH. pyridine, THF, reflux, 1 h, 50%.

Treatment of 7 by nBu_3SnH in the presence of AIBN as radical initiator furnished in addition to the expected products 8, 10 the L-idose derivative 9[8,9] (scheme 3). As in the case of the model compound (having $X=CH_2$) discussed in the preceding communication[1], the formation of 9 can be rationalized by an intramolecular hydrogen atom transfer[10] from C(5)-H to the cyclized radical having the α configuration at C(8). This epimerization at C(5) seems to be even more favoured in the case of 7 and could be prevented only by working under concentrated conditions (0.3M: 1g of 7 in 5ml of PhH), fortunately without the formation of uncyclized product[11]. The absence of reduced compound even at 0.3M implies a high rate[12] for the cyclization of the anomeric stabilized radical to the unactivated C=C bond by a 5-exo mode.

Scheme 3

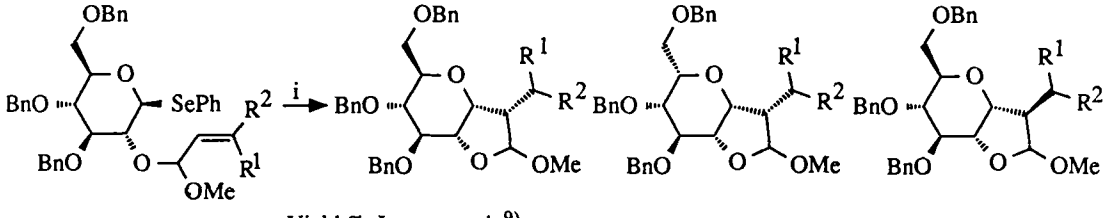


7 Concentrations (M)	8	9 Isomers ratios[9](%)	10
0.01	30	22	48
0.1	45	5	50
0.3	50	not detected	50

i= 1.3eq. nBu_3SnH, 0.1eq. AIBN, PhH, reflux, 24 h: combined isolated yields ≥ 89%.

The intramolecular hydrogen atom transfer from C(5) to α-C(9) occurred even when a secondary radical[13] was obtained after cyclization (scheme 4): 10% of the C(5) epimerized compound 13 were isolated under our standard reactions conditions (0.01M[8]). This hydrogen transfer is favoured by the increase in radical stabilization (secondary at C(9) → tertiary stabilized at C(5)). In addition to the interaction between the SOMO of the single electron with the lone pair of the ring oxygen atom, the vicinal C-O bonds can also contribute[14] to the stabilization of the C(5) centered radical[15].

Scheme 4



Yield %, Isomers ratio[9]

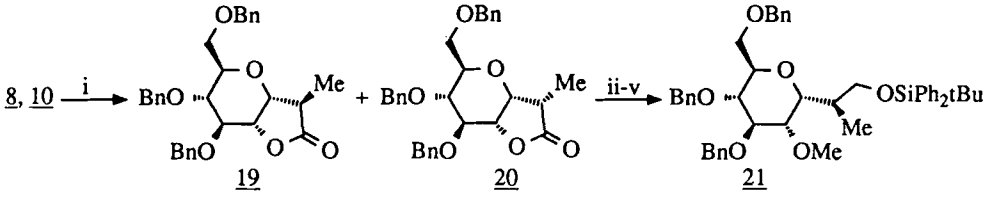
11 R^1= Et, R^2= H	71((12+14):13=90:10)	12	13	14
15 R^1= H, R^2= CO_2Me	90	16	17 (not detected)	18

i= 1.3eq. nBu_3SnH, 0.1eq. AIBN, PhH (0.01M), reflux, 24 h.

Moreover, the lower energy transition state[16] in which the three atoms C(5)-H-C(9) can adopt a colinear arrangement is accessible without strain. No hydrogen migration was detected when a more stabilized radical was formed after cyclization (15, scheme 4).

The usefulness of our strategy for the construction of C(1)-glycosides is demonstrated by the following example (scheme 5). The 1:1 mixture of isomers 8 and 10 was oxydized[17] to the lactones 19 and 20 which were separated by chromatography on silica gel. After ring opening with $LiAlH_4$ and selective protection of the two hydroxylic functions, the compound 21 was ready for further elaboration into naturally occurring C-branched sugars. The same sequence was realized on 12 and 14.

Scheme 5



i= 1.1eq.mCPBA, 0.5eq. $BF_3.Et_2O$, CH_2Cl_2, RT, 17 h, 82%; ii= separation of 20; iii= 0.6eq. $LiAlH_4$, THF, -20°C→RT, 1 h, 77%; iv= 1.1eq. $tBuPh_2SiCl$, 2eq. imidazole, DMF, RT, 16 h, 84%; v = 1.4eq. NaH, 2eq. MeI, THF, RT, 3 h, 86%.

The described strategy is currently applied to the synthesis of complex C-branched sugars.

Acknowledgments: The authors thank Dr. G. Szekely for the separation of the isomers of 8-10.

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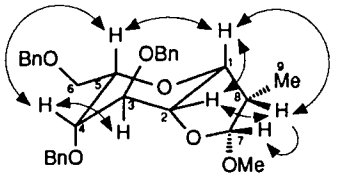
1. Stereoselective C-C Bond Formation in Carbohydrates by Radical Cyclization Reactions-III: A. De Mesmaeker, P. Hoffmann, B. Ernst, P. Hug, T. Winkler, Tetrahedron Lett., preceding paper.
2. For radical cyclization reactions in carbohydrates see references cited in 1.
3. For C-C bond formation by intermolecular addition of glycopyranosidic radicals to olefins see references cited in 1.
4. For some other methods to form C-glycosides see for example a) A. O. Stewart, R. M. Williams, J. Am. Chem. Soc., 107, 4289, (1985); b) A. Giannis, K. Sandhoff, Tetrahedron Lett., 26, 1479, (1985); c) M. D. Lewis, J. K. Cha, Y. Kishi, J. Am. Chem. Soc., 104, 4976, (1982); d) A. H. Davidson, L. R. Hughes, S. S. Qureshi, B. Wright, Tetrahedron Lett., 29, 693, (1988); e) D. Rouzaud, P. Sinay, J. Chem. Soc., Chem. Commun., 1353, (1983); f) J. E. Baldwin, R. M. Adlington, N. G. Robinson, Tetrahedron Lett., 29, 375, (1988); g) S. J. Danishefsky, S. De Ninno, P. Lartey, J. Am. Chem. Soc., 109, 2082, (1987); h) T. Kametani, K. Kawamura, T. Honda, J. Am. Chem. Soc., 109, 3010, (1987), and reference cited there.
5. The derivative 5 was prepared on a multigram scale and in high yield by substitution of the anomeric chloride by PhSeH (MeCN, NEt_3, RT) having an OAc group at C(2) which was then cleaved by MeONa (MeOH, RT).
6. The reaction mixture contained mainly the substitution product and the starting material 5 which was readily recovered after acetylation (Ac_2O, pyridine, RT).
7. The aldehyde 6 was filtered through silica gel and dried under high vacuum. Addition of molecular sieves 4A to the solution of 6 in THF prior to the Wittig reaction is recommended for the complete removal of water from 6 (hydrate formation).
8. In all the radical cyclizations described here, the reagents were mixed at once.
9. The isomers ratios were determined by ^{1}H-NMR (300MHz) on the reaction mixtures. The stereoisomers were separated by chromatography on silica gel and their structures elucidated on the basis of completely analyzed ^{1}H-NMR spectra and ^{1}H-NOE experiments. The configuration at C(8)

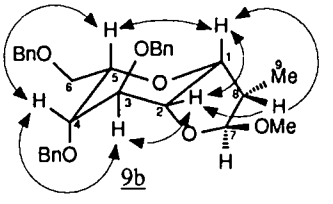
was corroborated in most cases by ^{13}C-NMR. Selected ^{1}H-NMR data (400MHz, $CDCl_3$, δ(ppm), J(Hz)); 9a; 1.11 (H_9, d, J_{8-9}=6.6); 2.26 (H_8, m); 3.24 (OMe, s); 3.51 (H_4, ddd, J_{3-4}=3.5, J_{4-5}=2.6, J_{2-4}=1.0); 3.69 (H_6, dd, $J_{6-6'}$=10.0, J_{6-5}=6.3); 3.73 ($H_{6'}$, dd, $J_{6'-5}$=5.8); 3.84 (H_5, ddd); 3.87 (H_2, ddd, J_{2-3}=3.2, J_{1-2}=3.5); 3.92 (H_3, dd); 3.98 (H_1, dd, J_{1-8}=4.9); 4.43 and 4.60 (-O-CH_2-Ph, AB, J=12.0); 4.50 and 4.58 (-O-CH_2-Ph, AB, J=12.0); 4.58 and 4.63 (-O-CH_2-Ph, AB, J=12.1); 4.83 (H_7, d, J_{7-8}=5.9); 7.20-7.38 (H_{Ar}, m).



^{1}H-NOEs observed

9a

9b. 1.18 (H_9, d, J_{8-9}=6.7); 2.20 (H_8, m); 3.43 (H_4, ddd, J_{3-4}=2.4, J_{4-5}=1.6, J_{2-4}=1.2); 3.47 (OMe, s); 3.59 (H_6, dd, $J_{6-6'}$=10.1, J_{6-5}=5.6); 3.67 ($H_{6'}$, dd, $J_{6'-5}$=6.4); 3.86 (H_5, ddd); 3.92 (H_3, dd, J_{2-3}=2.4); 4.04 (H_1, dd, J_{1-2}=2.3, J_{1-8}=4.3); 4.11 (H_2, ddd); 4.41 and 4.62 (-O-CH_2-Ph, AB, J=12.2); 4.51 and 4.56 (-O-CH_2-Ph, AB, J=12.0); 4.52 and 4.59 (-O-CH_2-Ph, AB, J=12.0); 4.87 (H_7, d, J_{7-8}=6.2); 7.26-7.40 (H_{Ar}, m).



^{1}H-NOEs observed

9b

10. For intramolecular hydrogen atom transfer in the presence of nBu_3SnH see references cited in 1.
11. No uncyclized product could ever be detected by ^{1}H-NMR (300MHz) of the crude reaction mixtures.
12. For some rate constants for 5-exo radical cyclizations see A. L. J. Beckwith, Tetrahedron, 37, 3100, (1981).
13. Due to the very fast reduction of radicals by nBu_3SnH, generally intramolecular hydrogen atom transfer can only compete when occurring from an activated C-H bond (allylic, benzylic) to a destabilized radical (vinylic, arylic, cyclopropylic) and / or under high dilution conditions[10].
14. a) D.H.R. Barton, W. Hartwig, W.B. Motherwell, J. Chem. Soc., Chem. Commun., 447, (1982); b) J. Dupuis, B. Giese, D. Rüegge, H. Fischer, H.G. Korth, R. Sustmann, Angew. Chem. Int. Ed. Engl., 23, 896, (1984).
15. The influence of the β C-O bonds on the ease of this intramolecular hydrogen atom transfer is under current investigation.
16. Colinearity is considered to be favoured in intramolecular hydrogen atom abstractions by alkoxy radicals; see reference 12 and A. E. Dorigo, K. N. Houk, J. Am. Chem. Soc., 109, 2195, (1987).
17. P. A. Grieco, T. Oguri, Y. Yokoyama, Tetrahedron Lett., 419, (1978).

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