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Radical Cyclisation of some 1,2,6-trideoxy-3,4-di-*O*-benzyl-6-halogeno-L-*arabino*-hex-1-ynitol Derivatives

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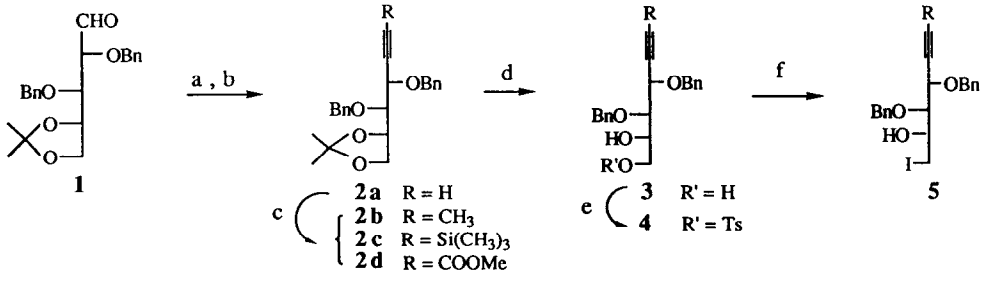
Key Words : Arabinose ; Radical-cyclisation ; Allylic-radical ; Fragmentation.

Abstract : Free radical cyclisation of the title halides **5a**, **5b**, **5c** and **16** led to five-membered carbocycles in good yield. The main products are two isomeric deoxy compounds resulting from the extrusion of benzaldehyde. A three-step process [5-exo-dig-cyclisation, 1,5 hydrogen-atom-transfer, fragmentation] is proposed to explain their formation.

The utility of free radicals in carbon carbon bond formation is now widely recognized.[1] An important feature of the recently developed radical cyclisation methods is their tolerance of a high level of fonctionality. This ability makes such an approach particularly suited for the conversion of carbohydrates to carbocyclic derivatives, an area of continuing interest. Over the past few years, such transformations have been accomplished with several radical acceptors (carbon-carbon double bonds [2], oxime ethers [3] or enol ethers [4]) derived from the initial aldehydic function of the carbohydrate. In spite of the well documented effectiveness of the carbon-carbon triple bond in 5-exo-dig radical ring closure [1], to our knowledge, no cyclisation involving alkynes in which one carbon of the triple bond was the former anomeric center of the sugar, has yet been reported.[5] We recently became interested in the investigation of the synthetic potentialities of such an approach and we wish to report here our preliminary results.

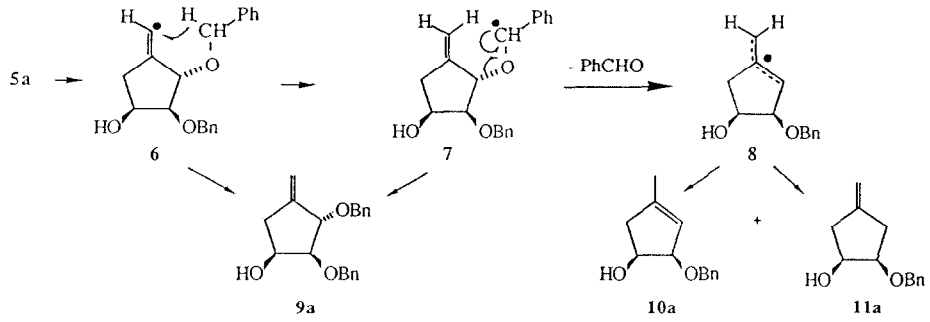
We initiated our study choosing arabinose as the starting material because of its commercial avaibility in both enantiomeric forms. Thus, from L-arabinose, we first prepared, in four steps, the known aldehyde **1**[6] which was then transformed into terminal acetylenic compound **2a** using the method of Toma et al.[7] The synthesis of radical precursor **5a** was then completed by usual transformations



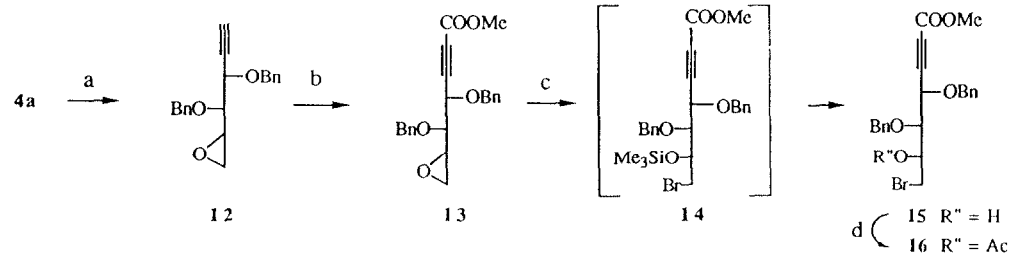
a $Ph_3\overset{+}{P}$-CH_2Cl Cl^-,n-BuLi, TMEDA, THF, 20°C (87%). b n-BuLi 4 eq, THF, - 78°C --> -50°C, H_2O (74%). c **2b** : n-BuLi, TMEDA, CH_3I, - 78°C -> 20°C. (65%) ; **2c** : n-BuLi, -40°C -> 0°C, $ClSiMe_3$. (64%). d MeOH, APTS cat., 20°C. **3a** (87%) ; **3b** (71%) ; **3c** (77%). e p-CH_3-Ph-SO_2Cl 1eq., pyridine, 20°C. **4a** (66%) ; **4b** (67%) ; **4c** (58%). f NaI, acetone, reflux. **5a** (83%) ; **5b** (81%) ; **5c** (80%).

Treatment of a refluxing solution of iodide **5a** (0.5×10^{-3} m) in 20 ml of dry benzene, by slow addition of 2.4 ml (1.2 eq.) of a 0.25 M solution of triphenyltin hydride in benzene containing AIBN (0.01 eq.) over a period of 3h (syringe pump) furnished, mainly unseparable isomeric cyclopentane derivatives **10a** and **11a**, alongside a small amount of compound **9a** and benzaldehyde in good overal yield (Table). No residual carbon-carbon triple bond could be observed in the IR spectrum of the crude product insuring that no uncyclised product was formed. Thus, as expected, the acetylenic linkage confirmed to be an excellent radical acceptor in a 5-exo-dig cyclisation process even with our highly oxygenated starting material.[8]

However, as deoxy compounds **10a** and **11a** were the major products of the reaction, this indicated that the vinylic radical **6** resulting from the initial cyclisation later evolved with extrusion of benzaldehyde. It seems to us that the more likely mechanism is a 1,5 hydrogen-atom-transfer giving **7** followed by fragmentation leading to allylic radical **8**. Several 1,5 (or 1,6) intramolecular hydrogen-atom migrations, particularly those involding benzylic positions, have been reported in the recent literature.[9] In our case, the resulting benzylic radical could be immediately reduced giving rise to a small amount of **9a** or lose benzaldehyde to form the stabilised species **8** and, finally, produce **10a** and **11a** after hydrogen abstraction.[10] Of course **9a** could result, as well, from the direct hydrogen abstraction of **6** (see note (8)).[11]



In order to examine the influence of different functional groups present on the terminal acetylenic carbon on the fragmentation process as well as on the ratio **10** to **11**, we then prepared representative disubstituted alkynes. Compounds **5b** and **5c** were readily obtained from 2a. Because of the formation of O-cyclized products during step e)[12], **5d** could not be similarly prepared. Thus, the preparation of a radical precursor with the required carbomethoxy group and a masked hydroxylic function was then envisaged using the regioselective ring-opening of an epoxide with trimethylsilyl bromide.[13]

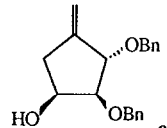
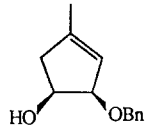
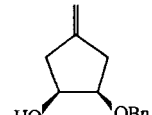
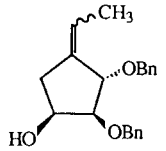
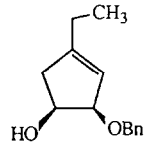
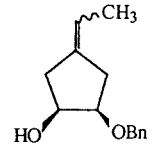
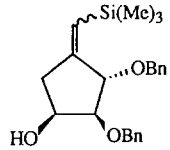
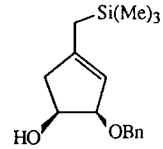
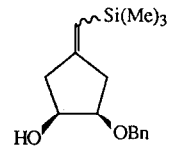
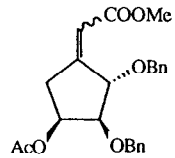
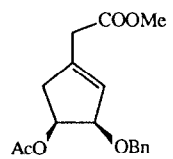
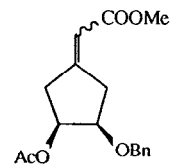


a K_2CO_3, MeOH, 20°C (86%). b n-Buli, TMEDA, ClCOOMe, -78°C --> - 40°C (73%). c $BrSiMe_3$, $CHCl_3$. d AcCl, pyridine. (50% for the steps c and d).

However for unknown reasons, the treatment of the epoxyde **13** with this reactif did not lead to the expected bromoether **14** but to the corresponding alcohol **15**. Since we observed that radical cyclisation of **15** led, once more, to O-cyclised products, the reaction was finally conducted on the acetate **16**.

When reacted in the same manner as previously described for **5a**, halides **5b**, **5c**, and **16** gave similar results (Table).[14] Deoxy compounds **10** and **11** remained the major products of the reaction contaminated, or not, by a small amount of **9**.This unfragmented compound **9** was not observed with **16.** Thus, the carbomethoxy group favored the fragmentation leading, in this case, to a particularly stabilized radical. In this context the recently reported radical stabilizing effect of the trialkylsilylgroup [15] could explain the minor formation of **9** with **5c** (compared to **5a** or **5b**). In other respects, as one could predict, the regioselectivity of the hydrogen abstraction by the allylic intermediate **8** is, to a large extent, influenced by the terminal alkyne function (compare **5c** and **16**) but, nevertheless, a mixture of the two regioisomers was obtained in the four cases examined.

Table

Starting halide	Reaction products	Ratio 10/11
5a	 **9a (8 %)** a) +  **10a** +  **11a (80%)**	b) 78/22
5b	 **9b (16%)** +  **10b** +  **11b (80%)**	b) 62/38
5c	 **9c (3%)** +  **10c** +  **11c (74%)**	b) 86/14
16	 **9d (0%)**  **10d (19%)**  **11d (44%)**	30/70

a) Yields are reported for isolated products (silica-gel chromatographic purifications).

b) Determined from the signals of the vinylic protons in the ^{1}H NMR (300 MHz) spectrum of the isomeric mixture.(see note (14)).

In conclusion, our results show the effectiveness of a 5-exo-dig radical cyclisation process for the conversion of L-arabinose into highly functionalized five-membered carbocycles. Studies from L-arabinose derivatives protected with groups other than benzyl are in progress. The preparation of bicyclic compounds after trapping of intermediate **8** by a convenient extra radical acceptor would be also envisaged since several cyclisations of allylic radical have been recently reported.[16]

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8. We observed that a slow addition of triphenyltin hydride was not required in our case for the cyclisation : when the stannane reduction of **5a** was carried out by adding all the triphenyltin hydride in one portion, we obtained about the same result with the exception of a larger amount of unfragmented compound **9a** (17 %).
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10. For a similar extrusion leading to benzophenone and α-keto-radical see : Feldman, K.S.; Vong A.K.K. *Tetrahedron Lett.*, **1990**, *31*, 823-826.
11. We observed that compound **9a** did not lead to deoxy compounds **10a** and **11a** when treated with triphenyltin hydride and a catatylic amount of AIBN in refluxing benzene and was recovered unchanged.
12. Fontanel, M-L ; Malanda, J-C ; Doutheau, A. : unpublished results.
13. Kricheldorf, H.R. ; Morber, G. ; Regel, W. *Synthesis* , **1981**, 383-384.
14. Full spectroscopic data were obtained for all new compounds with the reservation that unseparable compounds **10** and **11** (except **10d** and **11d**) were analysed as an isomeric mixture. Selected NMR data ($CHCl_3$, δ ppm, internal reference : TMS) ^1H (300 MHz) **9a** : 7.3 (m, 10H), 5.25 (pseudo quartet, J = 2 Hz, 1H), 5.05 (pseudo quartet, 1H), 4.65 (broad s, 2H), 4.63 (AB, 2H), 4.4 (dm, J = 3.2 Hz, 1H), 4.2 (m, 1H), 3.83 (dd, J = 6.1, J = 4.5 Hz, 1H), 2.64 (ABX, 1H), 2.45 (ABX, 1H).
Compounds **10** and **11** (vinylic protons). **10a** : 5.35 (m). **11a** : 4.80 (m). **10b** : 5.45 (m). **11b** : 5.34 (m). **10c** : 5.20 (m). **11c** : 5.35 (m). **10d** : 5.70 (m). **11d** (Z + E) : 5.77 (m), 5.75 (m).
^{13}C (75.47 MHz, multiplicity : DEPT). **9a** : 145.5 (s), 138.4 (s, arom.), 137.6 (s, arom.), 128.7, 128.6, 128.4, 128.1 (d, arom.), 111.9 (t), 85.6 (d), 82.5 (d), 72.2 (t, OBn), 71.8 (t, OBn), 68.5 (d), 36.7 (t).
Compounds **10** and **11**(C = C). **10a** : 144.7 (s), 123.2 (d). **11a** : 108.6 (t), 146.0 (s). **10b** : 149.(s), 119.7 (d). **11b** (Z + E) : 137.2 (s), 137.0 (s) ; 117.0 (d), 116.9 (d). **10c** : 147.1 (s), 120.0 (d). **11c** : 122.6 (d), 155.0 (s). **10d** 138.7 (s), 127.6 (d). **11d** (Z + E) : 114.5 (d), 144.4 (d) ; 159.7 (s), 159.6 (s).
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