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Chiral, Densely Functionalized Cycloheptanes from Carbohydrates. I. The Nitrone Route

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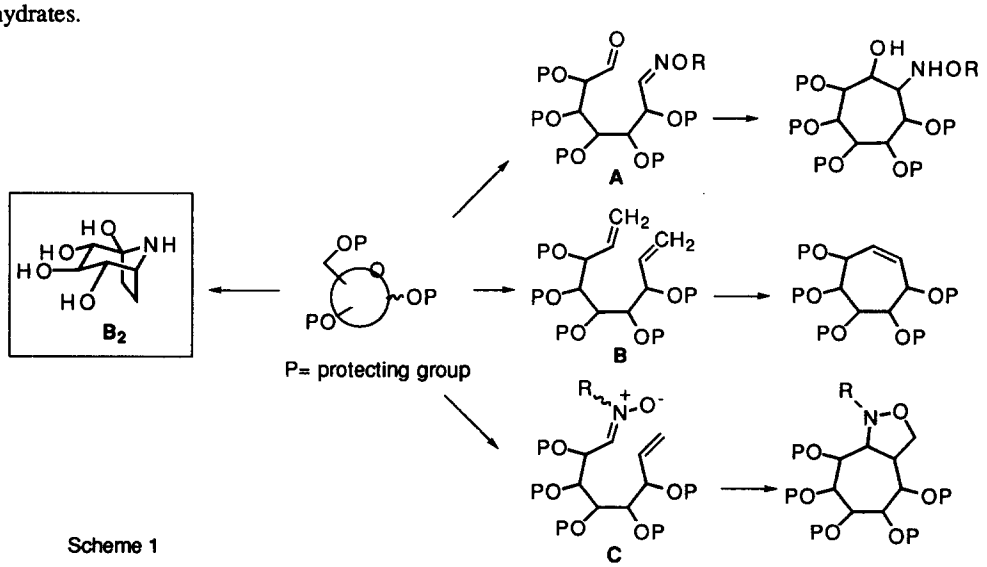
Abstract.- The first intramolecular 1,3-dipolar cycloaddition of an acyclic, chiral, polyfunctionalized 7-alkenyl tethered *N*-benzyl nitrone is reported. This is a new and efficient approach for the synthesis of chiral, densely functionalized cycloheptanes from carbohydrates.

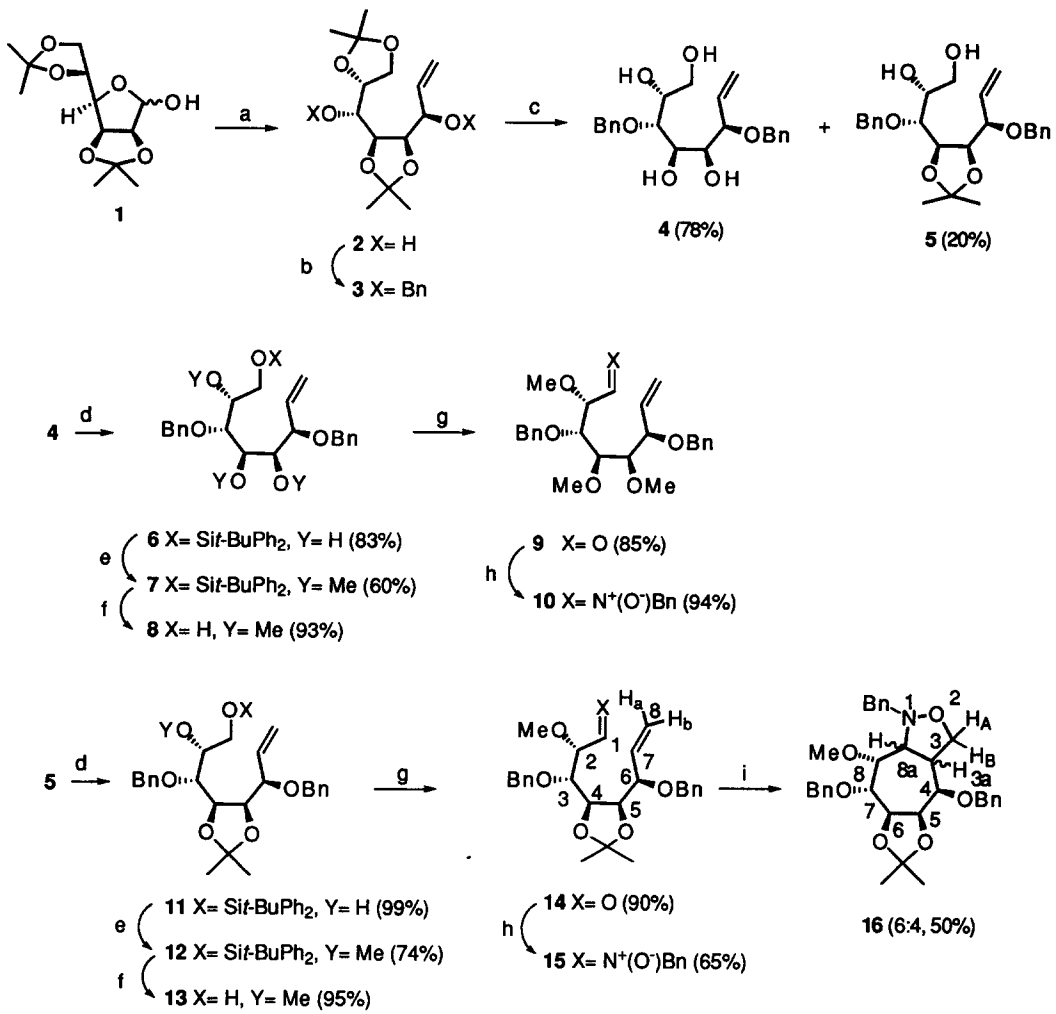
The asymmetric synthesis of cycloheptanes from carbohydrates is limited to some isolated examples: (a) nitro condensation of 1,6-dialdehydo sugar derivatives,[1] (b) ring expansion of enantiomerically pure cyclohexanones[2,3] and (c) the intramolecular 1,3-dipolar cycloaddition (1,3-DC) of nitrile oxides.[4] Our current interest in the synthesis of calystegine $\mathbf{B_2}$ (Scheme 1)[5] and the absence of a general and efficient methodology for the synthesis of chiral cycloheptanes[6] from carbohydrates, prompted us to explore new synthetic possibilities for such a conversion. We have studied a free radical cyclization,[7] a metathesis ring closing[8] and the intramolecular 1,3-DC of 7-alkenyl nitrones,[9,10] *via* intermediates **A**, **B** and **C**, respectively (Scheme 1).

In this communication we present our preliminary results on the last approach, showing the first example of an intramolecular 1,3-DC[11] of an acyclic, 7-alkenyl tethered *N*-benzyl nitrone of type **C** (Scheme 1), that has resulted in a new and efficient asymmetric synthesis of chiral, densely functionalized cycloheptanes from carbohydrates.



Scheme 1

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00769-8



Scheme 2. Reagents: (a) $BrMgCH{=}CH_2$, THF (2:epi-(C-1)-2/ 4:1;75%; separate isomers); (b) BnBr, NaH, THF (85%); (c) $AcOH{:}H_2O$ (4:1), 0.2 M, 55 °C; (d) $ClSi$-t-$BuPh_2$, py; (e) MeI, NaH, THF; (f) Bu_4NF, THF; (g) PCC, NaOAc, molecular sieves; (h) $NaHCO_3$, EtOAc, HONHBn. HCl; (i) Chlorobenzene, 130 °C.

For our studies directed to the synthesis of the required precursors, we selected the readily available 2,3:5,6-bis-*O*-isopropylidene-α-D-mannofuranose (**1**).[12] Vinylmagnesium bromide addition, gave the major isomer **2**[13] that was isolated in good chemical yield (Scheme 2). Benzylation and acid hydrolysis gave a mixture of tetrol **4** and monoacetonide **5**.[14,15] Compound **4** was submitted to standard protocols for the final assembly of the required functionality for nitrone 1,3-cycloaddition (Scheme 2). Silylation followed by methylation under mildly basic conditions[16] and desilylation gave compound **8** in good chemical yield. Product **8** was submitted to oxidation with PCC in the presence of molecular sieves and sodium acetate to give aldehyde **9** that was transformed into the nitrone **10** by the usual methodology. To our great surprise,[4] thermolysis of

compound **10** did not afford any of the expected cycloisoxazolidine adducts; only decomposition to the aldehyde **9** was observed and no cyclized product could be isolated.

In view of these results we turned our attention to the intermediate **5** and submitted it to the same sequence of synthetic transformations that gave compound **10** from **4** in good overall yield. Following these procedures, nitrone **15**[17] was obtained from compound **5**. To our satisfaction, thermolysis of this precursor, in chlorobenzene, afforded product **16** in 50% yield,[17] as a mixture of isomers in 6:4 ratio, that we were unable to separate, and whose relative and absolute stereochemistry at the newly formed stereocenters could not be assigned. From these results it was clear that the 1,3-dioxolane ring at positions C-4 and C-5 in the precursor is a potent and critical structural element that controls the success of the intramolecular reaction leading to the cycloheptane.[18] This structural motif obviously reduces the conformational degrees of freedom in the transition state, and as a result favours the carbocyclization.

The analytical [correct elemental analysis for $C_{33}H_{39}NO_6$; MS: *e/m* (70 eV): 545 (M^+, 21), 530 (M^+-15), 91 (C_7H_7,$^+$ 100)] and spectroscopic data (full set of NMR experiments: ^1H, ^{13}C, DEPT, COSY HMQC) of compound **16** clearly supported the regiospecific formation of the bicyclo[5.3.0] type of isoxazolidine, instead of the alternative bicyclo[5.2.1] type of isoxazolidine[19] (the absence of signals at ~26.0 ppm, typical for a methylene in the bridge position[19] was significant and moved us to discard this hypothesis). Particularly diagnostic was the analysis of the ^{13}C NMR spectrum of the mixture; in this spectrum we could observe coherent[20] and significant signals for compound **16** [in the major isomer: (δ) 42.4 (C3a), 67.0 (C-3), 67.6 (C-8a), 62.3 (N-$CH_2C_6H_5$), 58.1 (OCH_3); in the minor isomer: (δ) 44.4 (C3a), 68.3 (C-3), 67.5 (C-8a), 64.6 (N-$CH_2C_6H_5$), 61.1 (OCH_3)]. In agreement with this assumption, in the ^1H NMR spectrum of compounds **16**, we could analyze H-3A (3.53, dd, *J*= 10.8, 6.6 Hz), H-3a (2.75, dt, *J*= 10.8, 8.1 Hz), H-8a (2.90, m) for the major isomer, and H-3A (3.68, dd, *J*= 10.9, 7.6 Hz), H-3a (3.00, m), H-8a (3.19, m) for the minor isomer.

In summary, we have described the first successful intramolecular 1,3-DC of an acyclic, chiral, polyfunctionalized 7-alkenyl tethered *N*-nitrone. We have found that the presence of an annulated ring in the precursor (i. e., an acetonide in positions O-C4 and O-C5 in compound **15**) was critical for the success of the process. These results pave the way for a new, simple and efficient synthesis of chiral, densely functionalized cycloheptanes from carbohydrates. Work is in progress to check the scope and limits of this methodology.

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References and Notes

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14. All new compounds showed excellent analytical and spectroscopic data.
15. After some experimentation, conditions were found (AcOH:H_2O/4:1, 0.2 M, 55 °C) to improve the yields of compounds **4** and **5** for the synthesis of the advanced intermediates **10** and **15**, in order to compare their respective reactivity in the 1,3-DC reaction.
16. The 60% yield in the synthesis of compound **7** from **6** was not optimized. In this reaction other more polar (probably mono and/or disubstituted methylated derivatives) were detected, but not isolated.
17. To a solution of aldehyde **14** (50 mg, 0.11 mmol) and *N*-benzylhydroxylamine hydrochloride (54 mg, 0.34 mmol) in dry methylene chloride (1 mL) pyridine (0.031 mL, 0.39 mmol) was added and the mixture was refluxed for 12 h. The solution was cooled, diluted with methylene chloride, washed with brine and dried. After evaporation, the residue was submitted to flash chromatography (hexane: ethyl acetate, 1:1) to give pure nitrone **15** (38 mg, 65%) [oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.26 (m, 15 H, aromatic), 6.90 (d, $J_{1,2}$= 7.3 Hz, H-1), 5.80 (ddd, $J_{7,8\ cis}$= 9.8 Hz, $J_{7,8\ trans}$= 17.3 Hz, $J_{7,6}$= 8.5 Hz, 1 H, H-7), 5.41 (dd, $J_{6,8\ cis}$= 1.6 Hz, 1 H, H-8a), 5.27 (dd, $J_{6,8\ trans}$= 1.3 Hz, 1 H, H-8b), 4.85 (m, 1 H, H-2; s, 2 H, $NCH_2C_6H_5$), 4.80 and 4.62 (d, d, AB system, J= 12.6 Hz, 2 H, $OCH_2C_6H_5$), 4.53 and 4.12 (d, d, AB system, J= 11.3 Hz, 2 H, $OCH_2C_6H_5$), 4.22 (dd, $J_{5,6}$= 8.5, $J_{5,4}$= 5.4 Hz, 1 H, H-5), 4.11 (dd, $J_{3,4}$= 7.0 Hz, 1 H, H-4), 3.98 (dd, $J_{2,3}$= 1.7 Hz, 1 H, H-3), 3.83 (t, 1 H, H-6), 3.2 (s, 3 H, OCH_3), 1.40 and 1.26 (s, s, 3 H, 3 H, $OC(CH_3)_2O$]. This product was dissolved in chlorobenzene (3 mL) and refluxed (bath at 130 °C) for 20 h. The solvent was removed and the residue was submitted to chromatography (hexane: ethyl acetate, 1:3) to give adduct **16** (16 mg, 50%) as an oil.
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