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A New Synthetic Route to Chiral, Multiply Functionalized Cyclopentane Rings+

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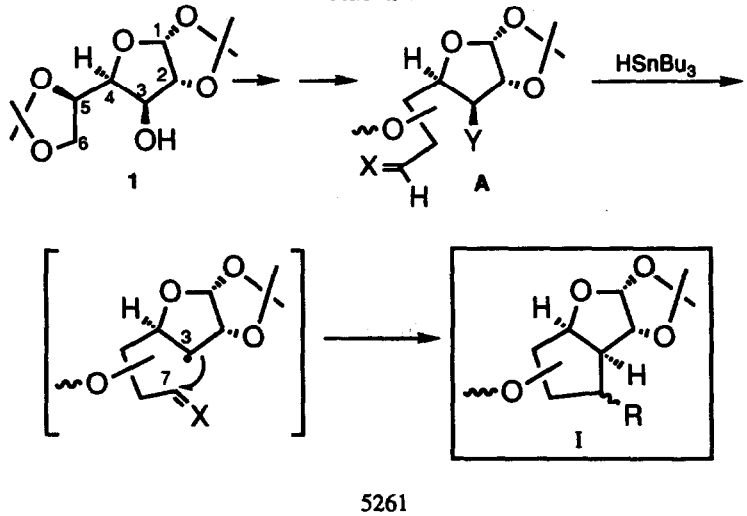
Abstract: The tributyltin hydride mediated free radical cyclization of sugar derivatives **4-6** gives the annulated furanoses **9-11** in good yield and high diastereoselectivity. This protocol is a new synthetic route for the preparation of complex cyclopentanoid molecules.

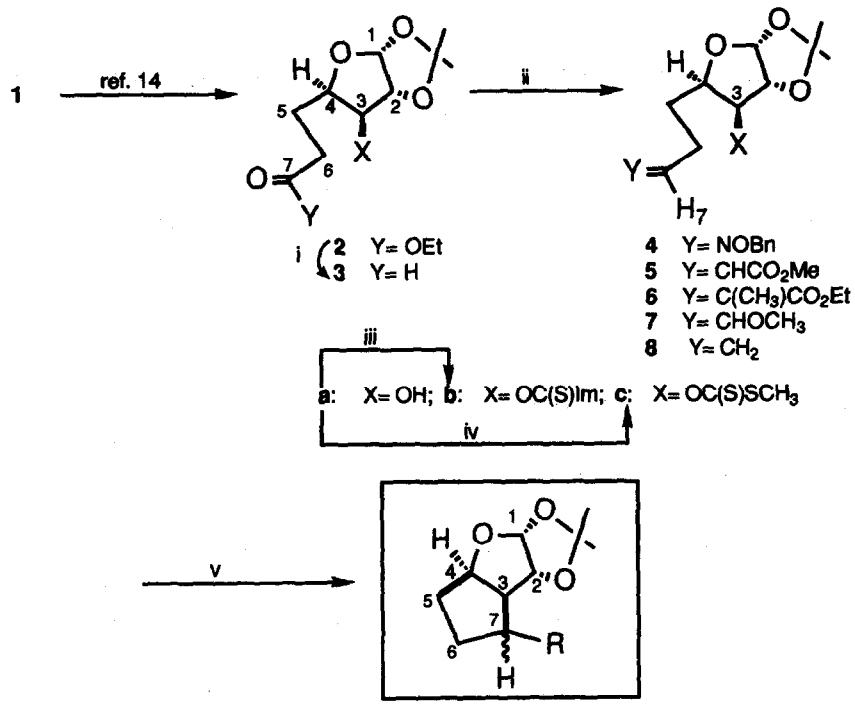
In the last years free radical chemistry has emerged as a powerful method for the synthesis of carbocycles.[1] The seminal studies reported by Wilcox,[2] RajanBabu[3] and Bartlett[4] have established useful strategies for the preparation of chiral polyoxygenated cyclopentanoid molecules *via* 5-hexenyl cyclization of suitable intermediates.

The synthesis of carbocycles from carbohydrates has been an area of continous interest in our laboratory.[5] The recent report[6] about the cyclization of a C-3 radical in a pyranoid ring[7] onto convenient acceptors, prompts us to describe here a new synthetic approach to chiral, multiply functionalized cyclopentane rings based on an analogous *first example of intramolecular 5-exo radical cyclization involving the nucleophilic attack of an endocyclic C-3 radical to an electron-deficient exocyclic unsaturated chain in furanose templates* (Scheme 1).[8] Simple chemical manipulations from diacetone glucose **1** should afford intermediates type **A**, conveniently functionalized for free radical cyclization. The resulting annulated furanoses[9,5] **I** are chiral, diversely functionalized and potential useful intermediates for a general approach to cyclopentanoid molecules as prostanoids,[10] iridoids,[11] and polyquinanes.[12]

Scheme 1

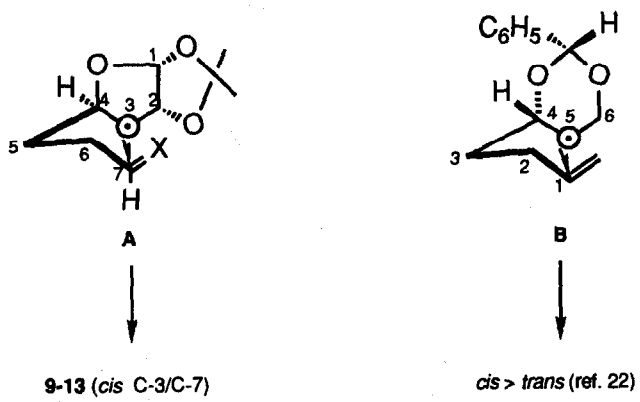


Scheme 2



9 R: NHOBn; **10** R: CH_2CO_2Me; **11** R: $CH(CH_3)CO_2Et$; **12** R: CH_2OCH_3; **13** R: CH_3

Key. i: DIBAH, toluene, -78°C (98%); ii, NH_3OBnCl, pyridine, H_2O, CH_2Cl_2 (**3a**→**4a**, 69%); $Ph_3P{=}CHCO_2Me$, toluene (**3a**→**5a**, 78%); $Ph_3P{=}CHCH_3CO_2Et$, CH_2Cl_2 (**3a**→**6a**, 96%); $Ph_3P{=}CHOCH_3$, THF (**3c**→**7c**, 55%); $Ph_3P{=}CH_2$, THF (**3a**→**8a**, 20%); iii, Dithiocarbonylimidazole, CH_2Cl_2 (~95%); iv, NaH, S_2C, ICH_3, -30°C, THF (83%); v, $HSnBu_3$, toluene.



Figure

In a preliminar study we have selected for simplicity the free radical precursors **4b,c-6b,c**; **7c** and **8b**[13] (Scheme 2). These compounds have been easily synthesized from intermediate **2**.[14] Sequential reduction and carbonyl activation gave compounds **4a-6a** in good yield; at this point we have located the free radical promotor functional group, thiocarbonylimidazole or xanthate, at C-3.[15] We have also explored an alternative route: functionalize first the hydroxyl in C-3 (**2a→2b, c**; ~82%), reduce then the ester group (**2b, c→3b, c**; ~90%) followed by Wittig reaction [**3c→7c**, (50%); **3b, c→5b, c** or **6b, c** (75%)].

With these compounds in hands we have performed the key tributyltin hydride + AIBN mediated cyclization.[16] From compound **4b** [obtained as a mixture of *syn* + *anti* isomers (65:35) that we could not separate; *syn*: δ H-7, 7.46, t, *J*= 5.6 Hz; *anti*: δ H-7, 6.72, t, *J*= 5.6 Hz] we have prepared the *O*-benzyl hydroxylamine **9** [55% yield; diastereomeric excess (d.e.) in the crude mixture 80%]; after extensive chromatography only pure major **9**(C-7 *S*)[17] was isolated. The same protocol for precursor **5b** or **5c** (obtained as unseparable, *E/Z:* 12/1, mixtures; *E:* δ H-7, 6.92, dt, *J*= 15.6 Hz, *J*= 7.1 Hz) gave the ester **10** (80% yield; d.e. in crude 76%); after chromatography we only could isolate major **10** (C-7 *S*) in an improved ratio (d.e. 80%). From compound **6b** or **6c** [*E* isomer only[18]; δ H-7: 6.70, tq, *J*= 17.5 Hz, *J*= 1.4 Hz] we have obtained the desired compound **11** (76% yield) as an unseparable mixture of the four possible isomers (^{1}H NMR analysis showed H-1 at 5.85, 5.83, 5.75 and 5.70 in a 2/1/11.3/2.3 ratio, respectively). The absolute configuration at the new stereocenter (C-7 *S*) in the major isomer of compound **9** has been proved by careful analysis of the ^{1}H-^{1}H coupling constants and by n.O.e. difference experiments (both mono and bidimensional); this analysis was assisted by comparison with calculated atomic distances, dihedral angles and coupling constants obtained using molecular mechanics in conjunction with Altona's equation[19] as implemented by PCMODEL;[20] according to this we have observed vicinal coupling constants as [**9** (*S*) $J_{3,7}$= 9.1 Hz, $J_{3,4}$=5.0 Hz; and n.O.e. between H-3/H-7 (8.7%)]. For major **10** (C-7 *S*) we have also analyzed in ^{1}H NMR δ H-3: 2.77 (dd, $J_{3,4}$= 5.2 Hz, $J_{3,7}$= 9.7 Hz); in compound **11** we have detected H-3 at 2.86 ppm ($J_{3,4}$= 5.9 Hz, $J_{3,7}$= 9.6 Hz); then, by comparison with compound **9**, these values have also established that the absolute configuration at C-7 in these products is *S*. In compound **11** we could not separate isomers and we have been unable to establish the absolute configuration in the side chain [**11** R: $CHCH_3CO_2Et$]. In the transformation of precursors **7c** and **8b**, using relatively poor free radical acceptors, we have obtained low yields,[6] and consistent d.e., s of the cyclized compounds [**12**: 30%; d.e. 82 %; **13**: 40%; d.e. 83%]. As in the other cases we have tentatively assigned as *S* the absolute stereochemistry at C-7; according to this in the ^{1}H-NMR spectrum we have observed for compound **12** (δ H-3: 2.71, dd, $J_{3,7}$= 9.9 Hz, $J_{3,4}$= 5.0 Hz) and **13** (δ H-3: 2.62, dd, $J_{3,4}$= 5.1 Hz, $J_{3,7}$= 10.5 Hz). The stereochemical outcome of these processes can be rationalized assuming a chair like transition state for the 5-hexenyl cyclization[21] (radical **A**; see Figure). A similar result has been described during the free radical cyclization of the analogous cyclic radical **B** (sugar numbering; Figure) derived from D-glucose.[22]

In summary, a new synthetic route for the chiral preparation for complex cyclopentanoid molecules has been developed. Work is now in progress in order to extend this methodology to other substrates and will be reported in due course.

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References and Notes

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17. **9** (C-7 *S*): Oil; $[\alpha]_D^{25}$ +13 (*c* 2.1, $CHCl_3$); ^{1}H NMR (300 MHz $CDCl_3$) δ 7.35 (m, 5 H, $C_6\underline{H}_5$), 5.73 (d, $J_{1,2}$=3.6 Hz, 1 H, H-1), 5.42 (br s, 1 H, N$\underline{H}$OBn), 4.92 (d, $J_{1,2}$=3.6 Hz, 1 H, H-2), 4.81 (m, $J_{4,3}$=5 Hz, $J_{4,5}$=$J_{4,5'}$=3.9 Hz, 1 H, H-4), 4.72 (d, J=11.6 Hz, 1 H, O$C\underline{H}_2C_6H_5$), 4.69 (d, J=11.6 Hz, 1 H, O$C\underline{H}_2C_6H_5$), 3.57 (m, $J_{7,6}$=$J_{7,6'}$=7.6 Hz, $J_{7,3}$=9.1 Hz, 1 H, H-7), 2.70 (dd, $J_{3,7}$=9.1 Hz, $J_{3,4}$=5.0 Hz, 1 H, H-3), 1.90-1.58 (m, 4 H, 2 H-5, 2 H-6), 1.50, 1.32 (s, s; 3 H, 3 H).
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