A Radical Cyclization Route to Collum's Key Intermediate for (+)-Phyllantocin: Annulated Furanoses *via* Radical Cyclizations

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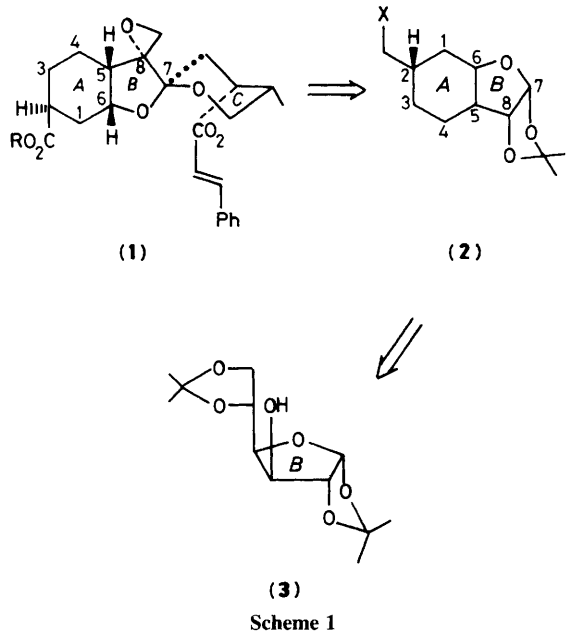
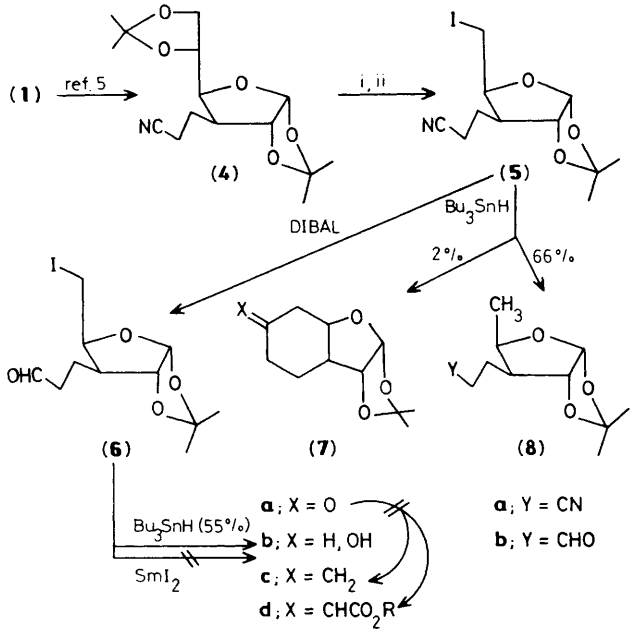
Radical cyclizations of the ω-iodoaldehyde (**6**), ω-iodonitrile (**5**), and ω-iodo-α,β-unsaturated ester (**9**) afford approximately 55, 2, and 80% yields, respectively, of cyclohexanofuranoses; these products are readily formed from the ester cyclizations, providing a key intermediate in Collum's synthesis of phyllanthocin.

We have recently shown that radical aldehyde cyclization can be an efficient procedure for the synthesis of cycloalkanols.[1] Such procedures are particularly promising for transformations involving carbohydrate derivatives because of their mildness,[2] and it was in this context that the reaction was discovered.[1a] We describe some recent studies connected with the synthesis of a key intermediate for phyllanthocin, (**1**), which helps us to evaluate this reaction in the context of some other radical cyclization procedures.

Five syntheses of phyllanthocin and/or its derivatives have been reported so far,[3a—f] and although they all differ in detail, they share the common feature of using a preformed cyclohexane ring as a template for constructing the furanoid moiety. An alternative strategy, summarized retrosynthetically in Scheme 1, is that diacetone glucose (**3**) could be the source of the annulated sugar[4] (**2**), the cyclohexano ring in the latter being formed, hopefully, by radical aldehyde cyclization. A particularly attractive aspect of this plan is that a



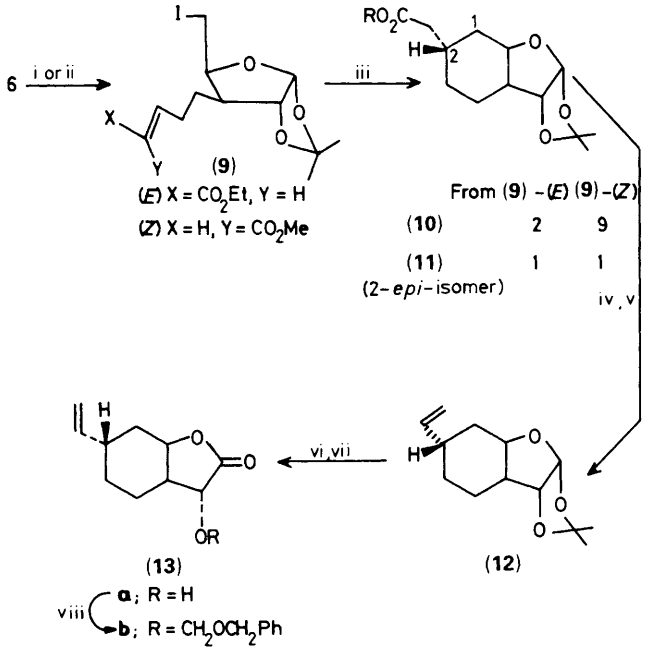
Scheme 1



Scheme 2. *Reagents and conditions*: i, (a) 70% $AcOH/H_2O$, room temp., 30 h; (b) $NaIO_4$, MeOH, H_2O, room temp., 1 h; (c) $NaBH_4$, MeOH, room temp., 1 h [71% from (**2**)]; ii, I_2, Ph_3P, imidazole, toluene, reflux, 3 h (81%).

logical starting material, the propiononitrile (**4**), had already been prepared by an intermolecular radical addition during the seminal studies of Giese and co-workers.[5]

Standard procedures led to the iodonitrile (**5**), and since the cyano group is an excellent radical trap,[6] a ready route to the cyclohexanonone (**7a**) seemed available. However, reaction of (**5**) [Bu_3SnH/azoisobutyronitrile (AIBN)/benzene, reflux] afforded (**7a**) in only 2% yield, the major product being the reduced material, (**8a**) (66%). Alternative methods of radical formation (AIBN/$Bu_3SnSnBu_3$/*hv*/benzene, reflux or Bu_3GeH/AIBN/benzene, reflux) did not lead to formation of (**7a**); compound (**8a**) again was the major product, with substantial recovery of starting material in both cases.



Scheme 3. *Reagents and conditions*: i, $Ph_3{=}CHCO_2Et$, toluene, room temp., 12 h (95%); ii, $(CF_3CH_2O)_2POCH_2CO_2Me$, $(Me_3Si)_2NK$ (KHMDS), 18-crown-6, tetrahydrofuran (THF), −78 °C, 30 min (75%); iii, $HSnBu_3$ (1.2 equiv.), AIBN (cat.), (**6**)-*E* or (**7**)-*Z* 0.03 M in toluene, 100 °C (bath temperature), slow addition, syringe pump, 2 h [from (**9Z**): 84%; from (**9E**): 74%], separate isomers; iv, $LiAlH_4$, THF, room temp., 12 h (86%); v, (a) *N*-(phenylseleno)phthalimide, Bu_3P, THF, 80% (taking into account the recovered starting material); (b) O_3, CH_2Cl_2, −78 °C, 90 min; then Et_2NH, CCl_4, reflux, 75 min (76%); vi, 0.5% H_2SO_4, 1,2-dioxane, 70 °C, 10 h (83%); vii, Ag_2CO_3/Celite, toluene, reflux, 75 min (74%); viii, NaH, $ClCH_2OCH_2Ph$, tetrabutylammonium iodide (cat.), THF, room temp., 90 min (73%). (**13b**): M.p. 44—46 °C, $[\alpha]_D^{25}$ +99.5° (*c* 2.95, $CHCl_3$); lit.[3a] m.p. 47—48 °C, $[\alpha]_D^{15}$ + 106.2° (*c* 2.11, $CHCl_3$).

In spite of these poor results for (**5**), we decided to examine the iodoaldehyde (**6**), obtained from (**5**) with reduction with di-isobutylaluminium hydride (DIBAL). Reaction with Bu_3SnH and AIBN in refluxing benzene gave a mixture of the epimeric alcohols (**7b**) in 55% yield, along with a lesser amount of the deiodinated aldehyde (**8b**). As an alternative, compound (**6**) was subjected to samarium(III) iodide under the conditions described by Molander.[7] However, (**7b**) was not formed at all in this experiment, the major product being a high molecular weight material (probably a dimer). Thus, the radical cyclization of the iodoaldehyde had provided the best method for ring formation, even though the yield of (**7b**) was only moderately good.

Our initial plan had been to develop the C-2 carboxy group of (**1**) *via* the exocyclic methylene derivative, (**7c**). Accordingly, the alcohol (**7b**) was oxidized to ketone (**7a**); but use of methylenetriphenylphosphorane gave only a 5% yield of the alkene (**7c**). Attempts at the Peterson alkenation protocol[8] failed at the first stage with addition of trimethylsilylmethylmagnesium bromide. Attempts to prepare the carboxymethylene analogue (**7d**) by using Wittig or Horner–Emmons reagents failed similarly. The problems in alkenation of (**7a**) are probably due to β-elimination of the ring oxygen, being the first step of extensive decomposition.†

† Dr. J. Cobb of Glaxo Laboratories (North Carolina) has informed us that in their synthesis[3c] problems were encountered in alkenation of an analogous ketone.

The attempts described above to obtain (**7d**) had been geared towards the C-2 vinyl derivative (**13b**), which was a key intermediate in Collum's pioneering synthesis of phyllanthocin.[3a] An alternative synthon would be the C-2 acetate (**10**), which would be obtained by radical cyclization of the α,β-unsaturated ester (**9**). In connection with this, Hanessian and co-workers[9] have shown that the desired C-2 configuration in (**10**) should be controllable by the geometry of the double bond in (**9**), and to this end, both geometric isomers were examined. These were obtained as major products by using standard Wittig methodology for (**9*E***), and the variation developed by Still and Genari[10] for (**9*Z***). These geometric isomers cyclized in 74 and 85% yields, respectively, the ratios of the C-2 isomers (**10**) and (**11**) being 2:1 and 9:1, respectively, as indicated in Scheme 3. The major isomer, which was the same from both precursors, was expected to be (**10**) based on chair-like transition states, and the observed ratios are consistent with the associated non-bonded interactions, as postulated by Hanessian and co-workers.[9] The accuracy of these assignments was borne out in the subsequent transformations to authentic materials (*vide infra*).

With (**10**) in hand, the C-2 acetate side chain was converted into a vinyl group in the furanose (**12**) and the furano ring was then converted into the γ-lactone (**13a**). Benzyloxymethylation thereafter afforded (**13b**), whose physical constants were identical to those of Collum's intermediate[3a] (see Scheme 3).

The results from (**5**), (**6**), and (**9**) provide interesting information with respect to the formation of cyclohexyl systems. Success with α,β-unsaturated esters is well precedented,[9] but the contrasting yields from (**5**) and (**6**) were unexpected. Further study to clarify the role of the radical acceptor in formation of cycloalkanes of different ring sizes is underway in our laboratory.

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