A Novel Entry to Cyclohexanes and Cyclopentanes from Carbohydrates *via* Inversion of Radical Reactivity in Hex-2-enono-δ-lactones

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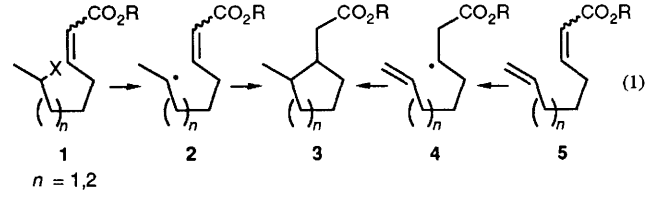
Conjugated addition of benzenethiol, under mild conditions, to carbohydrate derived hex-2-enono-δ-lactones, substituted at C-6 or C-7 with an electron-rich insaturation, affords 3-phenylthio derivatives that, on treatment with tributyltin hydride and AIBN (azoisobutyronitrile), undergo an efficient radical cyclization to give highly functionalized cyclohexanes and cyclopentanes.

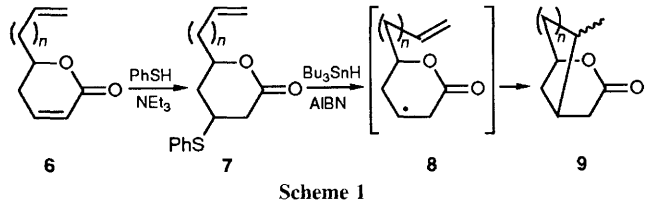
Radical ring-closure reactions[1] are usually carried out by addition of carbon centred radicals to carbon–carbon multiple bonds.[2] Since the rate of addition is accelerated by the presence of electron-withdrawing groups in the alkene,[3] α,β-unsaturated esters have commonly been used as substrates in 5-*exo*-[4] and 6-*exo-trig* cyclizations[5] [*e.g.* **1** → **2** → **3**] [eqn. (1)]. Here, we report a novel route to carbocycles from α,β-unsaturated-δ-lactones derived from carbohydrates that, because the radical is generated β to the carbonyl, as in **4**, operates in the opposite sense [**5** → **4** → **3**] [eqn. (1)].[6]

The method, outlined in Scheme 1 involves: (*a*) conjugated addition of benzenethiol; (*b*) homolytic fission of the resulting carbon–sulfur bond[7] on treatment with tributyltin hydride (TBTH);[8] and (*c*) radical ring closure onto a conveniently located electron-rich alkene. More interestingly, the protocol (Scheme 1) can be carried out in one-pot operations without isolation of the intermediate phenyl sulfides 7.†

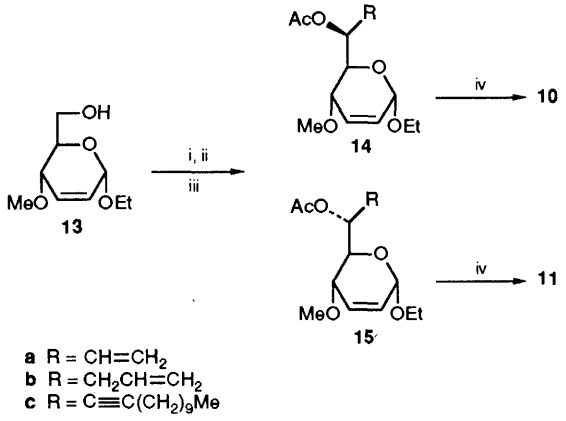
We have applied this protocol to lactones **10**, **11** and **12**.‡ Lactones **10** and **11** were prepared in high yield (Scheme 2) from ethyl 2,3-dideoxy-4-*O*-methyl-α-D-*erythro*-hex-2-enopyranoside **13**§[9] through the sequence: (*a*) one-pot oxidation–addition of the corresponding organometallic compound;[10] (*b*) acetylation of the reaction crude, followed by separation of the isomers; and (*c*) oxidation to the α,β-unsaturated lactone by treatment with *m*-chloroperbenzoic (MCPBA) acid in the presence of boron trifluoride ether.[11]

The results of the cyclization reactions are shown in Table 1. The stereochemical outcome observed in the 5-*exo-trig* cyclizations (entries i, ii and v) seems to be governed by the most favourable conformation for the chain in the transition state,[12] rather than by a preference for a chair-like transition state.[13] Formation of compound **16** (major isomer, entry i) through a boat-like transition state that minimizes the allylic strain is then preferred to ring closure to **17** by a chair-like cyclization transition state (Scheme 3). On the other hand, a chair-like transition state with less strain in the allylic segment is invoked for the formation of **18** (major isomer, entry ii). 6-*Exo-trig* cyclizations leading to cyclohexanes (entries iii and iv, Table 1) appear to take place through chair-like transition states[5] in which 1,3 interactions between the acetoxy substituent and the terminal alkene are minimized, and that will explain the very minor amount of compound **22** observed (entry iii). An electrostatic repulsion between the acetoxy

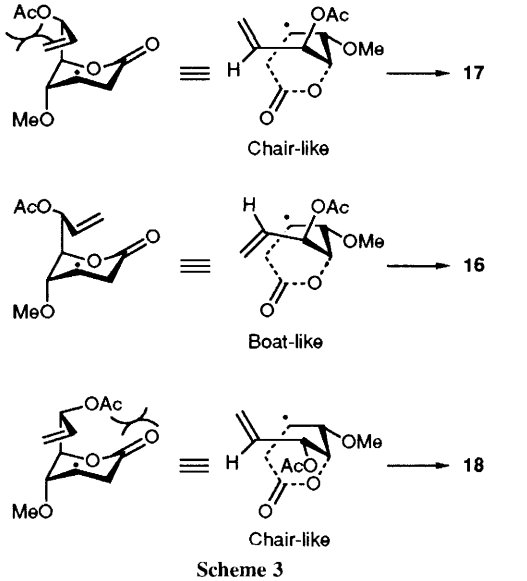




Scheme 1



Scheme 2 *Reagents and conditions*: i, Oxalyl chloride, dimethyl sulfoxide, NEt_3, tetrahydrofuran (THF), then **a** $BrMgCH{=}CH_2$; **b** $BrMgCH_2CH{=}CH_2$; **c** $LiC{\equiv}C(CH_2)_9Me$, −78 °C; ii, Ac_2O, NEt_3, 4-dimethylaminopyridine, CH_2Cl_2; iii, flash chromatography (hexane : ethyl acetate 19 : 1); iv, MCPBA, $BF_3{\cdot}OEt_2$, 0 °C



Scheme 3

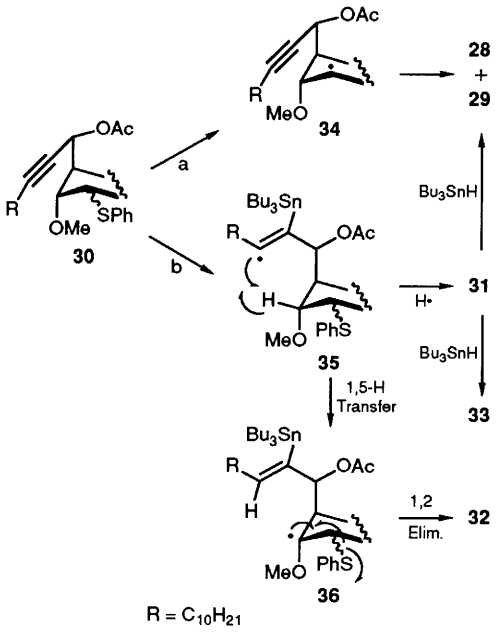
† *Typical procedure*: A solution of the lactone **6**, benzenethiol (1.1 equiv.), and NEt_3 (2 equiv.), was refluxed in THF. After disappearance of the starting lactone, monitored by TLC (usually 1–3 h), the solution was evaporated twice with toluene; benzene was added and the resulting solution thoroughly degassed. Syringe pump addition (over 10 h) of TBTH (2 equiv.) and AIBN (0.05 equiv.) followed by chromatography afforded **9**.

‡ All new compounds gave satisfactory spectroscopic and analytical data.

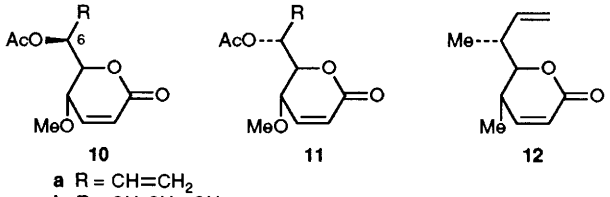
§ Lactone **12** was stereoselectively obtained by a different route, developed in this laboratory, and details for its preparation will be disclosed elsewhere.

group in the chain and the lactone carbonyl group (as in Scheme 3) seems to be responsible for the formation of **20** and **25** (entries ii and iv). According to that, no anomalous 6-*endo-trig* cyclization product is observed with lactone **12** (entry v).

Application of the method to lactone **11c** (entry vi) was planned to shed some light on the scope of this protocol, because its corresponding phenylthio derivative, **30**, possesses two sites susceptible to reaction with TBTH. Compounds **28** and **29** (20%) (Table 1, entry vi) were isolated along with tin-containing products, **31** (16%),[14] **32** (29%) and **33** (11%). The formation of bicyclic compounds **28** and **29** could be rationalized by attack of TBTH to either of the two reactive sites in **30** (see below). Homolytic desulfurization to **32** (pathway a, Scheme 4) followed by 5-*exo-dig* cyclization could give rise to **28** and **29**; on the other hand, TBTH addition to the triple bond (pathway b) would produce an intermediate vinyl radical, **35**, that could either be reduced to **31** or experience a 1,5-hydrogen shift from H-4 to the vinyl radical,[15] followed by a 1,2-radical elimination process[16] to give **32**. Further treatment of **31** with TBTH would also lead to

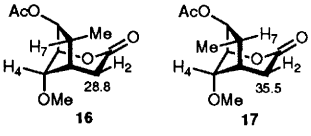
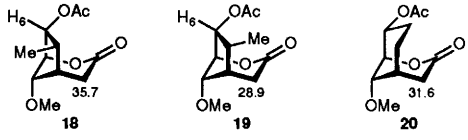
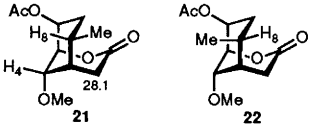
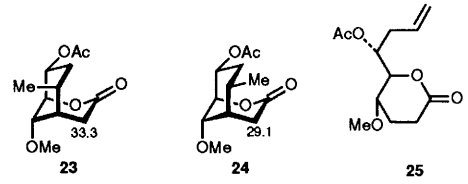
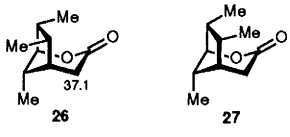
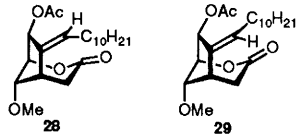


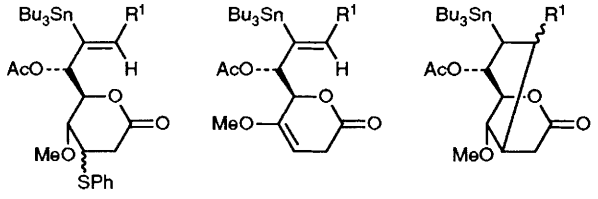
Scheme 4



a R = $CH{=}CH_2$
b R = $CH_2CH{=}CH_2$
c R = $C{\equiv}C(CH_2)_9Me$

Table 1

Entry	Substrate	Products	Isomeric ratio [yield (%)]
i	**10a**	 **16** **17**	4 : 1 (92)
ii	**11a**	 **18** **19** **20**	2.5 : 1.2 : 1 (78)
iii	**10b**	 **21** **22**	12.5 : 1 (83)
iv	**11b**	 **23** **24** **25**	11 : 3 : 1 (76)
v	**12**	 **26** **27**	6 : 1 (72)
vi	**11c**	 **28** **29**	1 : 1 (20)



31 32 33

28 and **29**[17] and/or **33**.¶ In the light of these results radical addition to the triple bond appeared to be, at least, slightly faster than radical desulfurization.

The configuration at C-6 in all the stereostructures derived from **11** was rigorously assigned on the basis of diagnostic nuclear Overhauser effects (NOE) obtained between H-4 and H-6 in the corresponding bicyclic products. The *endo* or *exo* orientation of the methyl group at C-7 or C-8 in all the bicyclic products was deduced from their NOE with either H-2 or H-4, respectively, and further confirmed by the quite different chemical shift for C-2 in their ^{13}C NMR spectra (see Table 1) for each of the isomers.

The protocol disclosed here allows a ready and efficient entry into cycloalkanes from carbohydrates,[4,12,18] in which some degree of stereocontrol can be attained. The α,β-unsaturated lactone functionality in the carbohydrate precursor allows selective activation at C-3, and the C-1 carbonyl group facilitates the conformational change [18a,c,19] required for the radical cyclization to take place. Finally, secondary phenyl sulfides‖[20] have been shown to be synthetically useful precursors for carbon-centred radicals in ring-closure reactions on treatment with TBTH.**

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¶ In a separate experiment, compound **31** was subjected to the reaction conditions to yield a mixture of cyclized products **28** and **29** (by a radical addition–elimination process)[17] along with **33**.

‖ Under the same reaction conditions a primary phenyl sulfide was recently reported by us[7] not to undergo 6-*exo-trig* cyclization but simply desulfurization.

** The efficiency of the use of phenyl sulfides in conjunction with TBTH, here disclosed, does not seem to be related with the presence of a β-oxygen substituent[21] to the radical. This is probed by the formation of **26** and **27** from lactone **12** (entry v), where the substituent at C-4 is a methyl group.

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