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Cyclopentane Synthesis and Annulation II: Radical Cyclizations of Oxathiolanones

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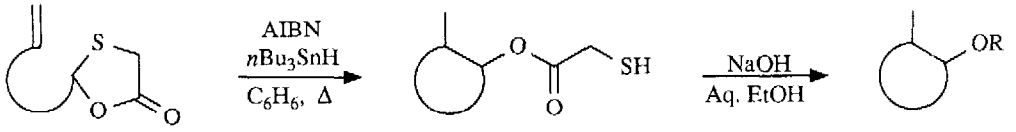
Abstract: A general procedure for the synthesis of diverse cyclopentanols *via* free-radical cyclization of 1,3-oxathiolan-5-ones is described. This permits the rapid assembly, by intramolecular annulation, of various ring systems for use in total synthesis.

Free-radical reactions and their applications continue to evolve at a rapid rate and recent progress is summarized in several reviews.[1-3] In order to supplement classical radical precursors and also incorporate synthetically useful substituents, we recently reported that radical cyclization of thioacetals and ketals, particularly 1,3-oxathiolanes, provided a facile entry to functionalized cyclopentanoids.[4,5] The ether side chain ($-OCH_2CH_2SH$) was cleaved with BCl_3 to generate the alcohol, a process that was sluggish in sterically demanding cases. We wish to report that 5-oxo-1,3-oxathiolanes provide an even more useful route to cyclic systems in which the initial ester is readily cleaved by base hydrolysis to afford the parent alcohol as illustrated below.



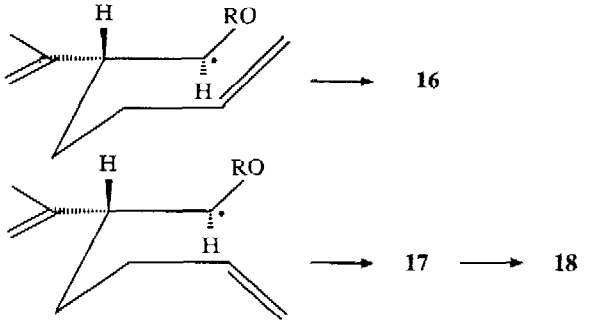
The requisite heterocycles were prepared from the appropriate carbonyl compound in refluxing benzene containing β-mercaptoacetic acid and p-toluenesulfonic acid as catalyst with azeotropic removal of water.[6] In a typical experiment,[7] cyclization of 2-(4-pentenyl)-5-oxo-1,3-oxathiolane (**1**) in refluxing benzene containing n-Bu_3SnH and AIBN (azobis(isobutyronitrile)) afforded, after chromatography and base hydrolysis, a 74% yield of the 2-methylcyclopentanols (**2** and **3**, 3:2). In contrast, the related oxathiolane gave only the *trans* isomer **3**.[4] The difference may reflect the faster cyclization rate in the present case, a consequence of the diminished stability of the intermediate radical due to an acyl rather than an ether substituent.[8] Calculations indicated that the radical stabilization energies of monosubstituted methyl radicals were 2.38 kcal/mole ($\cdot CH_2OCOH$) and 5.30 kcal/mole ($\cdot CH_2OCH_3$), respectively.[8]

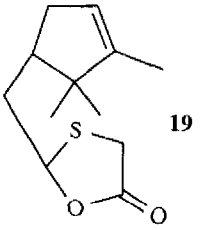
The versatility of this approach is reflected in the following examples. The substituted cyclopentane **4**[9] was converted cleanly to the single diquinane alcohol **5** prepared earlier.[4] In the case of the related cyclopentene **6**, the bicyclo[3.3.0]octan-2-ols **7** and **8** were formed in 95% yield as an 68:32 *endo:exo* mixture.

Methyl substituted olefins such as **9** (prepared from citronellal) also reacted, providing menthol **10** and its epimer **11** in a 1:1 ratio via a 6-*exo-trig* ring closure. However, more hindered species (tetrasubstituted double bond) such as the acetal of α-campholenic aldehyde (**19**) failed to cyclize after carbon-sulfur bond cleavage. In principle, the cyclohexene **12** may cyclize via either a 5-*exo-trig* or 6-*exo-trig* pathway to generate the bicyclo[3.2.1]octane and/or bicyclo[2.2.2]octane skeletons. In practice, only the 6-bicyclo[3.2.1]octanols **13** and **14** were formed in a 70:30 *endo-exo* ratio accompanied by 12% of the non-cyclized product, 2-(3-cyclohexenyl)-ethanol. An authentic sample of 2-bicylco[2.2.2]octanol was prepared and shown to be absent.

It was also of interest to examine the diene **15**, which is capable of tandem cyclization of the appropriate *cis* isomer to the bicyclo[2.2.1]heptane and/or the bicyclo[3.2.1]octane nucleus. After cyclization and hydrolysis, four alcohols were isolated. The major component (80%) in which the isopropenyl and alcohol substituents were *trans* was assigned structure **16** on the basis of spectral data[10] and comparison with related compounds including the saturated alcohol obtained by hydrogenation.[10] The minor product (10%) from the initial ring closure was **17**.[10] There was no evidence for a 5-*exo-trig* cyclization to a bicyclo[2.2.1]heptane system. The other products (10%) were methyl epimers from a 6-*endo-trig* ring closure. The major alcohol **18** (8%) contained an axial methyl group, as illustrated, with the hydroxyl function *anti*. A previous study has also observed this preference for *endo* closure to a bicyclo[3.2.1]octane when this choice is available.[11] Thus both **12** and **15** provide a rapid preparation of bicyclo[3.2.1]octanols although the yield in the latter case is rather low.

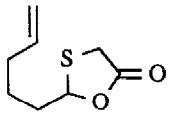
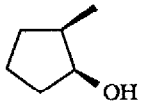
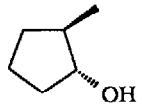
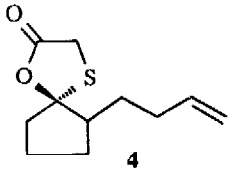
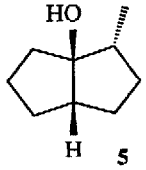
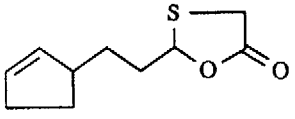
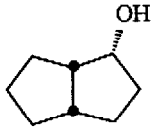
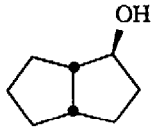
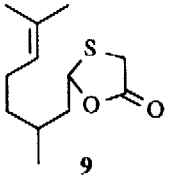
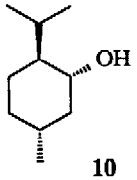
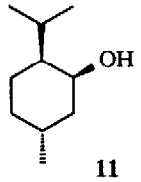
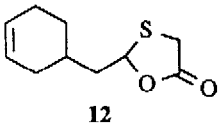
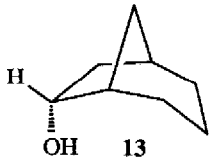
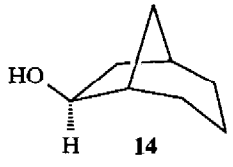
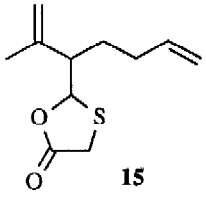
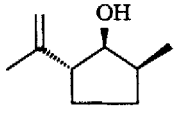
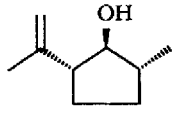
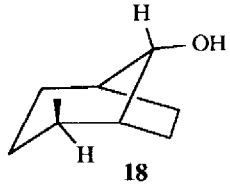
Studies of the stereochemistry of simple substituted 5-hexenyl radical cyclizations have allowed the formulation of guidelines to predict product stereochemistry based on the assumption that the preferred transition state geometry resembles the most favorable cyclohexane chairlike conformation.[12] Recent investigations of highly functionalized carbohydrate derivatives revealed that these additional substitutents may alter the expected 1,5 stereochemistry and a boat conformation is preferred.[13] In the case of **15** the major product arose from a chairlike conformation with the substituents equatorial, while the minor isomer requires a boatlike arrangement to generate the *cis* side chains in **17** approximately half of which cyclized further, as illustrated below.





In order to extend the versatility of these procedures, the use of allyl stannanes was investigated.[14] Allyl transfer worked well with both allyltri-n-butylstannane and methallyltri-n-butylstannane, but in each case the intermediate radical was trapped directly upon carbon-sulfur bond cleavage prior to cyclization. Thus, for this strategy to succeed, either a more rapid cyclization step and/or a slower trapping sequence will be required.

TABLE

Entry	Reactant	Product(s)
1.	 **1**	 **2**  **3**
2.	 **4**	 **5**
3.	 **6**	 **7**  **8**
4.	 **9**	 **10**  **11**
5.	 **12**	 **13**  **14**
6.	 **15**	 **16**  **17**  **18**

In conclusion, 1,3-oxathiolan-5-ones are useful precursors of radical intermediates for ring closure. This provides a facile route to both *tertiary* and *secondary* cyclic alcohols. The products retain synthetically useful functionality for subsequent manipulation unlike conventional alkenyl halide precursors in which a net loss of two functional groups results. These features should facilitate the extended use of these methods in synthesis.

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7. *n*-Bu_3SnH (1.5 mmol) and AIBN (4 mol% with respect to *n*-Bu_3SnH) in dry benzene (9 mL) were added to a refluxing benzene solution (16 mL) containing the 5-oxo-1,3-oxathiolane (1.0 mmol) at a rate of 0.49 mL/h using a syringe pump. Reflux was continued for 4 h after addition was complete. Solvent removal, flash chromatography on silica gel, and hydrolysis with 5% aqueous ethanolic NaOH afforded the cyclic alcohol.
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9. The material employed was a 70:30 (glc) mixture of diastereoisomers.
10. **16** ^{1}Hnmr δ 4.70 (bs, 2H, CH_2=C), 3.84 (t, 1H, J=6.4Hz, HCOH), 2.35 (m, 1H, HC allylic), 1.67 (s, 3H, MeC=C), 0.92 (d, 3H, J=7Hz, MeCH); ^{13}Cnmr δ 146.7, 110.0, 77.8, 54.1, 37.2, 30.7, 27.4, 20.6, 14.1; **16** hydrogenation product ^{1}Hnmr δ 3.80 (dd, 1H, J=6, 3.4Hz, HCOH), 0.98 (d, 3H, J=7Hz, MeCH), 0.95 (d, 3H, J=6.5Hz, iPr), 0.86 (d, 3H, J=6.5Hz, iPr); ^{13}Cnmr δ 78.5, 55.6, 39.2, 31.6, 31.4, 27.6, 21.5, 20.4, 13.6.
17 ^{1}Hnmr δ 5.02 (bs, 1H, HC=C), 4.86 (bs, 1H, HC=C), 3.75 (bs, 1H, HCOH), 2.08 (m, 1H, HC allylic), 1.82 (s, 3H, MeC=C), 1.01 (d, 3H, J=6.8Hz, MeCH); ^{13}Cnmr δ 144.6, 112.9, 79.4, 51.4, 41.7, 31.8, 27.0, 24.0, 20.8. **18** ^{1}Hnmr δ 3.74 (s, 1H, HCOH), 0.83 (d, 3H, J=6.7Hz, MeCH); ^{13}Cnmr of acetate δ 170.8, 85.3, 80.3, 45.8, 38.8, 34.8, 30.3, 26.3, 25.8, 21.7, 19.5.
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