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Stereoselective Synthesis of Tetrahydrofurans Using Intramolecular Oxymercurations

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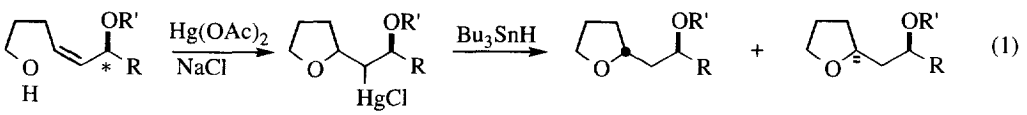
Abstract: The influence of alkene geometry and remote substitution on the stereochemical outcome of intramolecular oxymercurations leading to five-membered rings is described.

Considerable effort has been devoted to the stereoselective synthesis of tetrahydrofuran derivatives.[1] Part of the motivation for this emanates from the interest in biologically-active naturally-occurring compounds which contain one or more 2,5-disubstituted tetrahydrofurans.[2] We were interested in exploring the possibility of constructing such tetrahydrofurans using intramolecular oxymercurations (equation 1) to close the five-membered ring and establish a critical 1,3-stereochemical relationship. Such ring closures have been pioneered by Evans' and Hanessian's groups.[3] In particular we were interested in determining the degree to which the remote stereocentre (e.g. * in **1**) and alkene geometry influence the stereoselectivity of such ring closures in systems of relevance to the subunits of nonactin[4,5] (e.g. nonactic acid[6]) and the pamamycins[7,8].

As we wished to establish the influence of the remote stereocentre without any interference from substituents in the "tether" (i.e. the chain linking the nucleophilic hydroxyl to the alkene) only primary alcohols have been used here. The knowledge gained from such a study could then be applied to more complex substrates.[9] In this Letter we demonstrate that both the alkene geometry and the nature of the remote allylic substituents contribute to the stereoselectivity of these cyclisations.

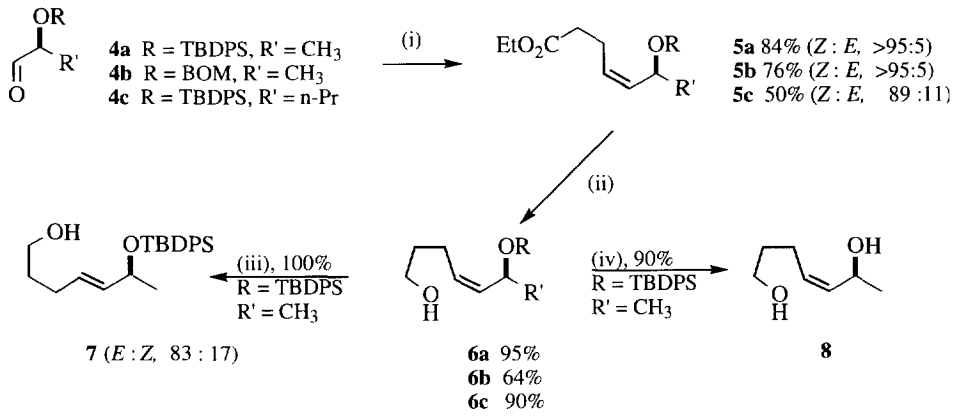


(1)

1 *syn*-**2** *anti*-**2**

We prepared the systems[10] **6a - c**, **7**and **8** (Scheme 1). The choice of R' (Me or n-Pr) was made with a view to their eventual incorporation into our planned synthesis of nonactic acid and the pamamycins. Thus either the *tert*-butyldiphenylsilyl (TBDPS) ether[11] or the benzyloxymethyl (BOM) ether[12] of (*S*)-lactaldehyde, **4a** and **4b**, respectively, was treated with the ylid derived from phosphonium salt **3**[13] providing alkenes **5a** and **5b** with excellent *Z*-selectivity. Carrying out the reaction at -78°C significantly improved the stereoselectivity. Reduction with lithium aluminium hydride gave alcohols **6a** and **6b**. Alkene **6a** was then either photo-isomerised[14] or fluorodesilylated giving **7** and **8** respectively. Aldehyde **4c** was prepared from the known ethyl (*S*)-2-hydroxypentanoate[15] by silylation followed by reduction with diisobutylaluminum hydride. **4c** was then successfully transformed into **6c** in a similar manner to that for aldehydes **4a** and **4b**.

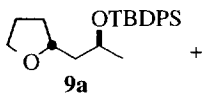
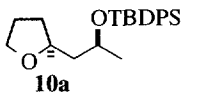
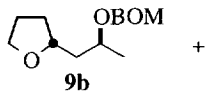
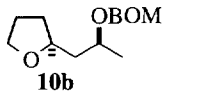
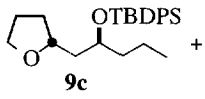
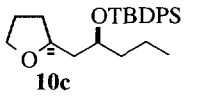
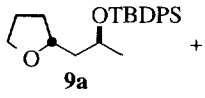
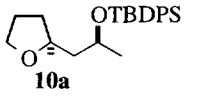
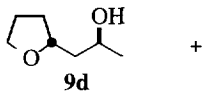
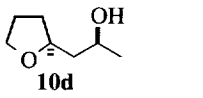
Scheme I. Synthesis of oxymercuration precursors **6a - c**, **7** and **8**.



(i) (a) $NaN(TMS)_2$, THF, 0°C, 30 min. (b) $Br^-Ph_3P^+(CH_2)_3CO_2Et$ (**3**), -78°C, 2h (ii) (a) $LiAlH_4$, Et_2O, reflux, 1h (b) H_2O (iii) Ph_2S_2 (cat.), hv, benzene, r.t., 17h (iv) $Bu_4N^+F^-$ (3 equiv.), THF, r.t.

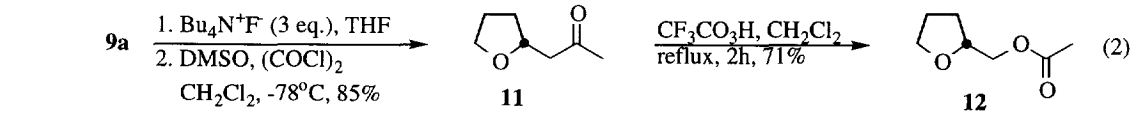
There is much evidence accumulated on the influence of 1,3-allylic strain on the selectivity of electrophilic attack at a double bond.[16] Our expectation was that the combination of a *Z*-alkene and a bulky substituent on the remote oxygen would provide the best results. This was indeed the case. Cyclisations were carried out using mercury(II)acetate in dichloromethane or chloroform followed by reductive demercuration with tributylstannane[17] (Table). As expected, cyclisation of **6a**, **6b** and **6c** provided the best results yielding tetrahydrofurans **9a**, **9b** and **9c**, respectively, (Table, entries 1 to 3) with about ten percent of the other diastereomer in each case. Little selectivity was found in the cyclisations of the *E*-alkene **7** or the allylic alcohol **8**. (Attempts to cyclise **6a** with iodine in acetonitrile[18] were thwarted by competing desilylation. Similar treatment[19] of **6b** was not affected by competing deprotection but showed very poor selectivity (~2:1). Iodocyclisation of **8** gave an approximately 1:1 ratio of **9d** and **10d** as part of a complex mixture of products).

Table Results from Intramolecular Oxymercurations[a] of Hydroxyalkenes **6a - c**, **7** and **8**.

Entry	Hydroxyalkene	Product tetrahydrofurans	Yield[b] (%)	Ratio (**9** : **10**)
1	**6a**	 **9a** +  **10a**	93 (92)[c]	7 : 1 (8.2 : 1)[c]
2	**6b**	 **9b** +  **10b**	92 (74)[c]	4.5 : 1 (7.4 : 1)[c]
3	**6c**	 **9c** +  **10c**	76 (92)[c]	7 : 1 (10 : 1)[c]
4	**7**	 **9a** +  **10a**	75	1 : 1.6
5	**8**	 **9d** +  **10d**	85	2.5 : 1

(a) $Hg(OAc)_2$, CH_2Cl_2 , r.t., 18h; Aq. NaCl (ii) Bu_3SnH, THF, r.t. (b) Total isolated yield (c) $CHCl_3$ used instead of CH_2Cl_2 .

The relative stereochemistry of **9a** was established by conversion to the known acetate (-)-**12** (equation (2)).[20] The Baeyer-Villiger oxidation[7a] proved to be surprisingly sluggish at room temperature. However, heating the reaction mixture at reflux for two hours resulted in good overall conversion. The optical rotation of compound **12** ($[\alpha]^{20}_D$ -25.2° *c* 0.0082 gml^{-1}, $CHCl_3$) produced in this work was comparable to that of an authentic sample of (-)-**12** ($[\alpha]^{20}_D$ -23.6° *c* 0.0087 gml^{-1}, $CHCl_3$) prepared by acetylation of the corresponding alcohol.[20]

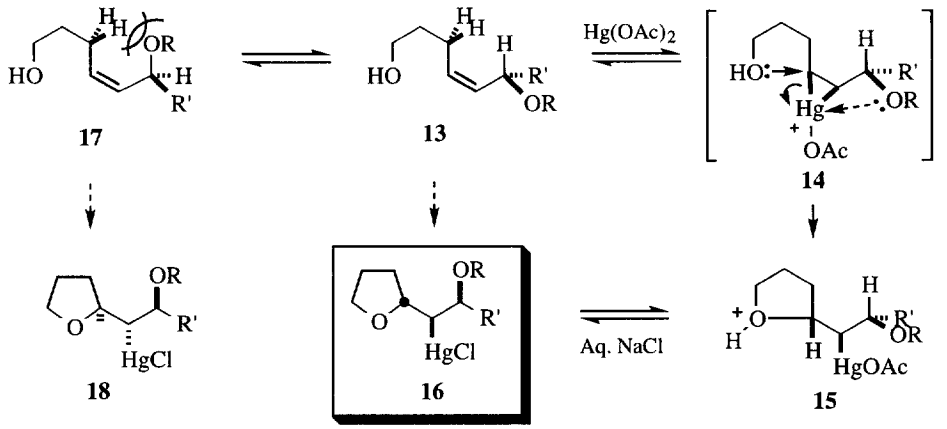


(2)

In line with Evans' suggestions[3b] we propose that each of the cyclisation substrates containing a *Z*-alkene adopts a similar "hydrogen-eclipsed" conformation (structure **13**, Scheme II), especially where the two non-hydrogen allylic substituents are sterically demanding, as in **6a**, **6b** and **6c**. Coordination-controlled mercuronium ion formation then occurs (**13** → **14**) followed by intramolecular nucleophilic attack by the tethered primary alcohol (**14** → **15**). Such coordination control has not been proposed before for a silyl ether but is supported by the very similar results obtained here with the BOM ether **6b**, where coordination is more likely (entry 2). The poorer selectivity associated with the cyclisation of **8** (entry 4) is most likely due to reaction of two conformers, **13** and **17** (R = H), of similar energy. Finally, the poor selectivity associated

with the cyclisation of *E*-alkene **7** (entry 5) results from the reduced conformational bias as there is probably no significant allylic strain.[21] We are currently applying this process to the synthesis of the nactic acids as well as the pamamycins.[22] The results of these studies will be published in due course.

Scheme II. Proposed mechanism for the stereoselective intramolecular oxymercurations.



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9. The influence of additional substituents on the stereoselection of these intramolecular oxymercurations has been examined and will be reported shortly, Garavelas, A.; Mavropoulos, I.; Perlmutter, P.; Westman, G. manuscript in preparation.
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