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Stereochemical features of iodocyclisations of 3-alkene-1,2-diols to β-hydroxytetrahydrofurans

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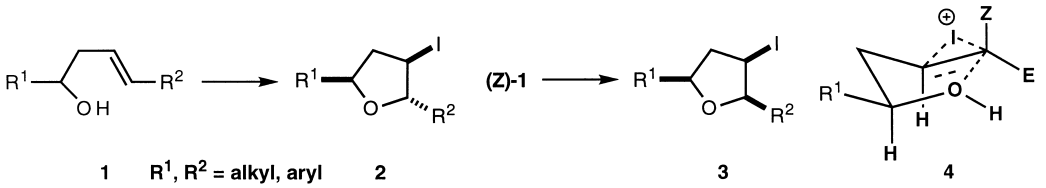
Abstract

5-*endo*-Iodocyclisations of stereoisomers of 3-alkene-1,2-diols **9**, **12**, **15** and **18** are stereoselective and provide an efficient route to β-hydroxytetrahydrofurans.

Keywords: tetrahydrofurans; 5-*endo*; iodocyclisation; stereoselective; 3-alkene-1,2-diols.

Electrophile-driven, overall 5-*endo*-cyclisations of homoallylic alcohols and *N*-tosylamides are now established as viable and highly stereoselective approaches to β-substituted tetrahydrofurans[1–3] and pyrrolidines, respectively.[4] In model studies of the iodocyclisations of homoallylic alcohols (Scheme 1),[2] we found that the (*E*)-isomers **1** were converted exclusively into the trisubstituted tetrahydrofurans **2**, whereas the corresponding (*Z*)-isomers gave the all-*cis*-isomers **3** in poorer yields, accompanied by varying amounts of the related iodohydrins. An explanation lies in the transition state **4**, the chair-like conformation being controlled by the equatorial position of substituent R^1 and is favoured in the (*E*)-isomers **1**, as the second substituent [R^2 in either an (*E*)- or (*Z*)-configuration] is also effectively in an equatorial position. In the (*Z*)-isomers, R^2 is effectively axial, which accounts for the lower efficiency of cyclisations of these isomers.



1 **R^1, R^2 = alkyl, aryl** **2** **3** **4**

Scheme 1.

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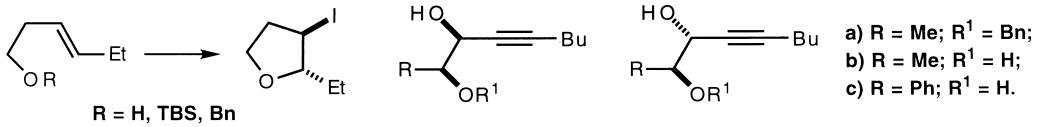
One limitation in our model work[2] is the lack of additional functional groups, both in the side-chains and at the other β-position in the heterocyclic ring. The inherently disfavoured nature of 5-*endo*-cyclisations[5] means that a suitably positioned second hydroxy group will usually compete successfully.[6] Thus, both 4-alkene-1,2-[7] and -1,3-diols[8] undergo exclusively 5-*exo* electrophile-induced cyclisations, often with high levels of stereocontrol, to give β-hydroxytetrahydrofurans, even when the reacting hydroxy group is masked as a benzyl or other ether function.[9] Such favoured 5-*exo* processes, in general, show poor levels of stereocontrol, so it seems that the second hydroxy group participates in these cyclisations, presumably by hydrogen bonding. For these reasons, we were attracted to the idea that 3-alkene-1,2-diols could also undergo 5-*endo*-cyclisations, with useful levels of stereocontrol. Herein, we report the outcome of these studies.

As a prelude to these and also for synthetic expediency, we first determined if *O*-protected homoallylic alcohols would also undergo 5-*endo*-cyclisations. It was far from clear if this would be the case: such disfavoured cyclisations, in contrast to related 5-*exo* processes,[9] might be completely suppressed if an additional barrier, that of breaking an ether C–O or Si–O bond rather than an O–H bond, were to be present. In the event, exposure of the substrates **5** to 3 equivalents each of iodine and sodium hydrogen carbonate in dry acetonitrile[2] in the dark led, in each case, to excellent yields (94, 81 and 80%, respectively) of the β-iodotetrahydrofuran **6**.[2] Cyclisations of the ethers (**5**, R = TBS or Bn) were slightly slower at 0°C (30–45 min versus < 15 min for R = H); in both of the latter cases, formation of the expected iodides (TBSI or $PhCH_2I$) was observed in equal quantities to the tetrahydrofuran **6**. Having thus established that benzyl ethers did undergo such iodocyclisations, we prepared the two alkyne-diols **7a** and **8a** by a non-stereoselective condensation between *O*-benzyl lactaldehyde and 1-lithiohexyne in THF, followed by chromatographic separation.

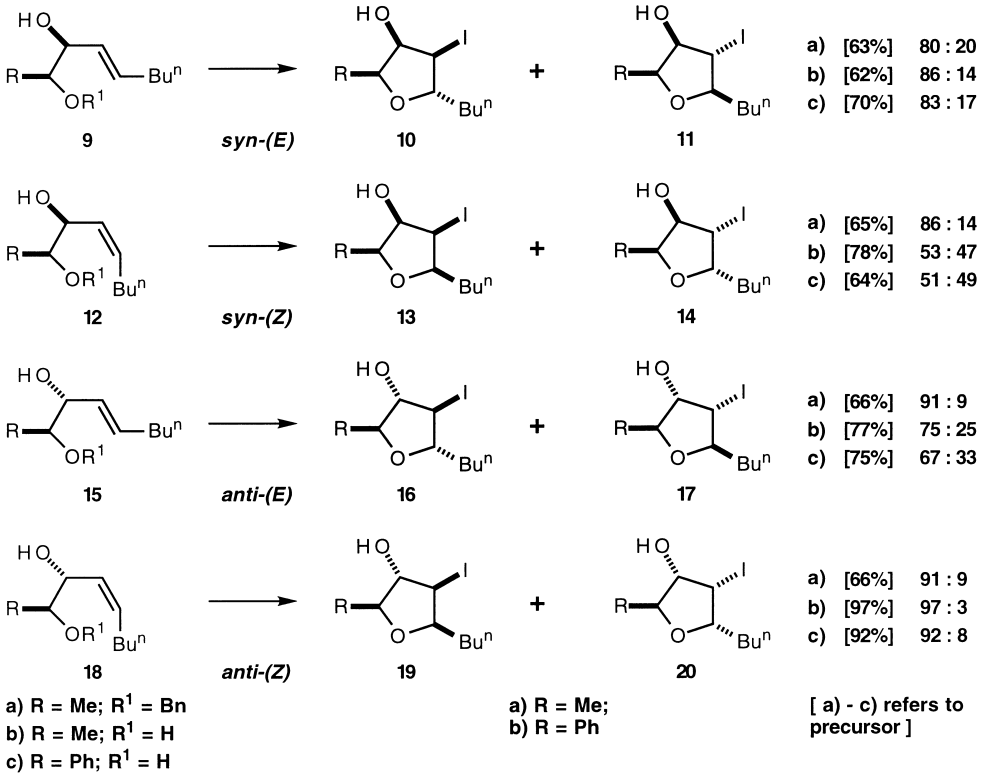


5 **6** **7** **8**

The identity of each was confirmed by comparisons, best made using ^{13}C NMR data, with authentic samples[10] and with the related alkyne-diols **7b**,**c** and **8b**,**c**, prepared by the highly regioselective bis-hydroxylation of the corresponding (*E*)- and (*Z*)-enynes, respectively.[11] Each series was then reduced to the (*E*)-alkene-1,2-diols **9** and **15** (Table 1) using Red-Al® (toluene–ether, 0–20°C) in the cases of the benzyl ethers **7a** and **8a** or $LiAlH_4$ (1:1 ether:THF, reflux, 24 h) for the free diols **7b**,**c** and **8b**,**c**, and to the corresponding (*Z*)-isomers **12** and **18** (Table 1) by Lindlar reduction, all in excellent overall yields.

The cyclisations were carried out as previously described (3 equivalents each of iodine and $NaHCO_3$ in dry acetonitrile at 0°C and in the absence of light, until TLC analysis indicated completion);[2] the results are presented in the Table 1.[12] Isolated yields are quoted in parentheses, followed by the isomeric ratios, calculated from ^1H NMR integration data. Stereochemistries were determined largely on the basis of NOE measurements (see, for example, **13a** below), along with internal consistency and comparisons of coupling constant data with other tetrasubstituted β-iodotetrahydrofurans;[2] assuming the expected *anti* addition across the alkene [cf. **4**], both the 2,3- and 4,5-relative arrangements were known beforehand. This was borne out by these data. The results show that the cyclisations display many synthetically useful features. The *syn*-(*E*)-isomers

Table 1
Iodocyclisations of 3-alken-1,2-diols and derivatives

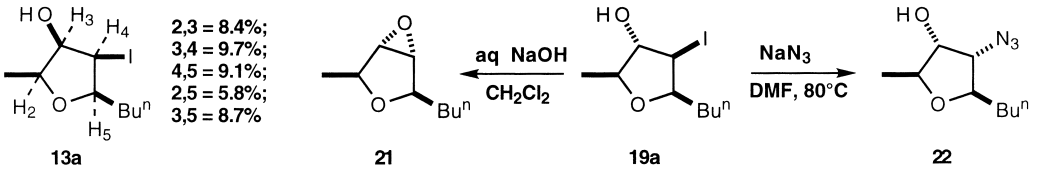


9 all give isomers **10** with ≥4:1 selectivity, consistent with conformation **4** having the 2-hydroxyl positioned axially.

The predominant formation of the all-*cis*-isomer **13a** from the *syn*-(*Z*)-*O*-benzyl ether **12a** can be similarly explained. The almost complete lack of stereoselection in cyclisations of the *syn*-(*Z*)-alkene diols **12b**,**c** may be a result of strong hydrogen bonding between the hydroxyl groups, which is not favoured in the benzyl ether **12a**, and hence attack can occur to an equal extent on the opposite face of the (*Z*)-alkene. In all cases, however, the chemical yields obtained from the (*Z*)-isomers **12** are in direct contrast to those obtained from simpler substrates during our initial model studies.[2] Similarly, cyclisations of the *anti*-(*E*)-*O*-benzyl ether **15a** were highly stereoselective, but less so in the cases of the free alkene diols **15b**,**c**. Again, conformation **4**, with the substituents (R and OH) in equatorial positions accounts for the major products **16**; the minor products **17** might be more favoured when the free diols are cyclised due to hydrogen bonding strong enough to allow the controlling substituents to adopt axial positions. Clearly, with such *anti*-(*E*)-isomers **15**, the results suggest that *O*-benzyl ethers **15a**, rather than free diols, should be used. The real surprise was in both the efficiency and stereoselectivity of all cyclisations of the *anti*-(*Z*) isomers **18**. The major or, in some examples, the sole products **19** could arise via conformation **4** (E = H, Z = Bu) with both sp^3-bound groups (R and OH) equatorial; perhaps the (*Z*)-alkene causes significant eclipsing interactions in the alternative hydrogen-bonded conformations.[13]

However, whatever the explanations, hopefully the results presented in the Table 1 will serve as a useful guide in applications of these cyclisations.

As further evidence of stereochemistry and as an illustration of the utility of these products, we found that exposure of the initial product **19a** to a slight excess of aqueous sodium hydroxide in dichloromethane gave the epoxy-tetrahydrofuran **21** while exposure to sodium azide in hot DMF led exclusively to the hydroxy-azide **22**, both in >95% isolated yields. NOE analysis of the latter confirmed the stereochemical assignment.



Efforts to utilise this chemistry, especially in enantioselective syntheses, are underway.[13]

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12. Full analytical and spectroscopic data have been obtained for all compounds reported, with the exception of some of the minor products **11**, **14**, **17** and **20**.
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