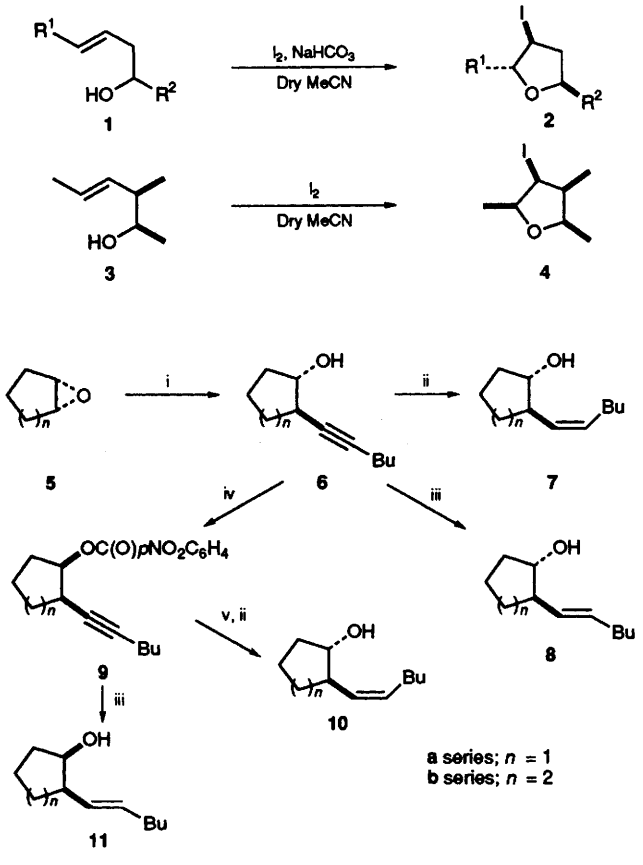
A Stereoselective Approach to Annulated Tetrahydrofurans by Iodocyclisations of 2-Alkenylcycloalkan-1-ols

Jenny M. Barks,[a] David W. Knight*[a] and Gordon G. Weingarten[b]

[a] *Chemistry Department, University Park, Nottingham, UK NG7 2RD*
[b] *Glaxo Group Research Ltd, Greenford Road, Greenford, Middlesex, UK UB6 0HE*

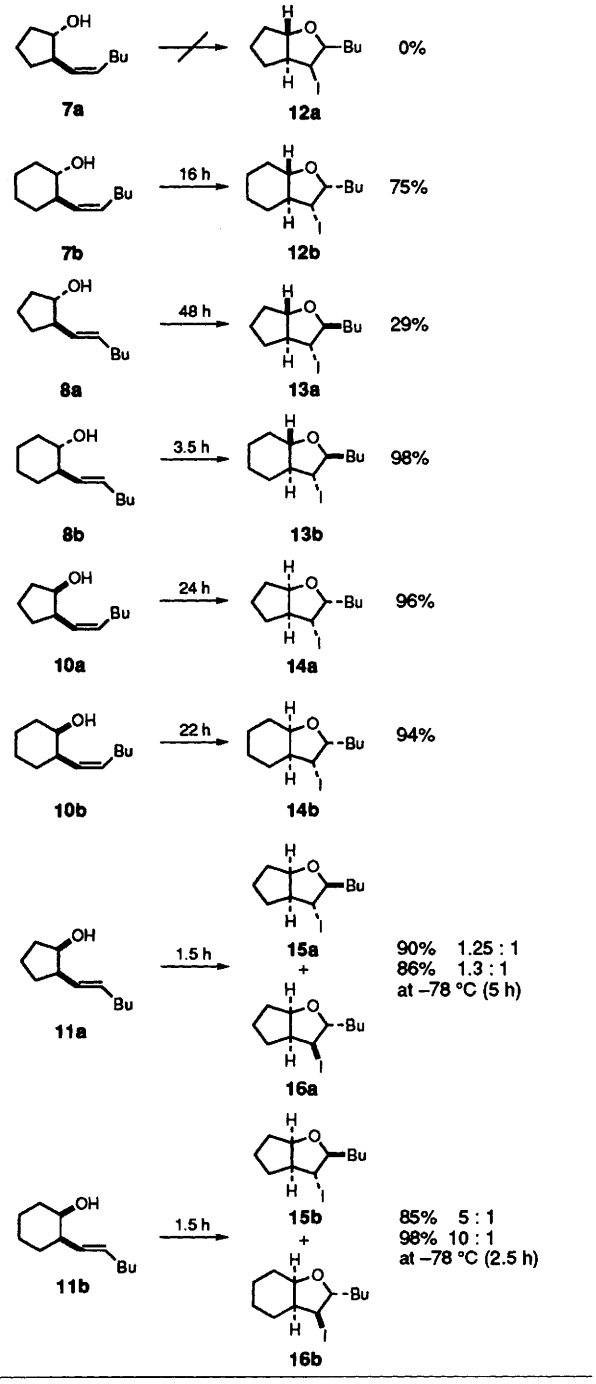
Highly stereoselective iodocyclisations of the 2-alkenylcycloalkan-1-ols **7**, **8**, **10** and **11** under strictly anhydrous conditions give good to excellent yields of the annulated β-iodotetrahydrofurans **12–16**.

We have recently found that iodoetherifications of (*E*)-homoallylic alcohols **1** can be carried out to give the iodotetrahydrofurans **2** in usually >95% yields and with >90% stereochemical purity.[1] Although such cyclisations appear to be 5-*endo*-trig processes, their cationic nature together with the likely involvement of an iodonium intermediate suggests that they should not be regarded as exceptions to Baldwin's rules.[2] The key to success in these reactions, which are only slightly less successful when applied to the corresponding (*Z*)-homoallylic alcohols, is the use of dry acetonitrile as solvent.[3,4] The origins of the stereoselection appear to lie in a preference for a chair-like transition state in which the substituent group can be positioned in a pseudoequatorial position. This model suggested that the method should be applicable to the elaboration of ring-fused tetrahydrofurans from 2-alkenyl-cycloalkan-1-ols (Scheme 1) and that high levels of stereoselection should be realized. However, the related and unusual results reported by Lipshutz and Barton threw doubt on the validity of these assumptions and introduced an element of uncertainty regarding the stereochemical outcome of such cyclisations. These authors[5] have found that similar cyclisations of highly substituted homoallylic alcohols (*e.g.* **3**) result in products (*e.g.* **4**) in which, formally,



Scheme 1 *Reagents and conditions:* i, BuCCLi, BF_3·OEt_2, THF, −78 °C; ii, H_2, 5%Pd-C, quinoline, EtOAc, 20 °C; iii, $LiAlH_4$, THF–toluene, reflux; iv, *p*-$NO_2C_6H_4CO_2H$, Ph_3P, EtO_2CN=NCO_2Et, THF, 20 °C; v, NaOH, MeOH, 20 °C

Table 1 Formation of ring fused THFs by iodocyclisation of 2-alkenylcycloalkan-1-ols[a]



[a] Satisfactory spectroscopic and analytical data have been obtained for all compounds. Yields refer to pure, isolated material.

iodine and hydroxy have added in a *syn* fashion to the alkene function; as yet, there is no explanation of this phenomenon. We now report that iodocyclisations of 2-alkenylcycloalkan-1-ols are indeed synthetically viable in many cases and that they appear to fall into a well-defined pattern of transition state conformations involving *anti* additions to the double bond.

The substrates **7**, **8**, **10** and **11** [$n = 1$ ('**a**' series); $n = 2$ ('**b**' series)] were prepared as outlined in Scheme 1, starting from cyclopentene or cyclohexene oxide **5**. Condensation with lithiohex-1-yne in the presence of boron trifluoride–ether[6] led to the *trans*-alkynols **6** (70–75%). Lindlar reduction then gave the *trans*-(*Z*)-isomers **7** (*ca.* 95%) whereas hydride reduction led to the corresponding *trans*-(*E*)-isomers **8** (80–85%). Mitsunobu inversion of the initial *trans*-alkynols **6**, crucially using *p*-nitrobenzoic acid,[7] gave the *cis*-alkynol esters **9** (80–90%). These were then converted into the *cis*-(*Z*)-**10** and *cis*-(*E*)-isomers **11** by the same reductive methods.

The results obtained from iodocyclisations of these substrates are presented in Table 1. In all cases, the conversions were effected by treatment of the alkenol (1 equiv.) and sodium hydrogencarbonate (3 equiv.) in anhydrous acetonitrile (5 ml $mmol^{-1}$ of alkenol) at 0 °C with solid iodine (3 equiv.), for the times specified (TLC monitoring).[1] The stereochemistries of the products (**12–16**) were determined mainly by extensive NOE studies along with comparative coupling constant data.† Most of the cyclisations gave synthetically useful yields of annulated β-iodo-tetrahydrofurans. In the *trans* series (**7**, **8**), a likely transition state arises from the chair-like conformation **17** (= **8b**), which would be expected to lead smoothly to the diastereoisomer **13b** (Fig. 1). The viability of this conformation is indicated by the formation, albeit in only 29% yield,‡ of the strained bicyclic system **13a**. The complete failure of the *trans*-(*Z*)-alkenylcyclopentanol **7a** to give any cyclic products is probably a reflection of this excessive strain associated with *trans*-fused bicyclo[3.3.0]octanes together with a less favourable 'axial' positioning of the pendent butyl side chain.

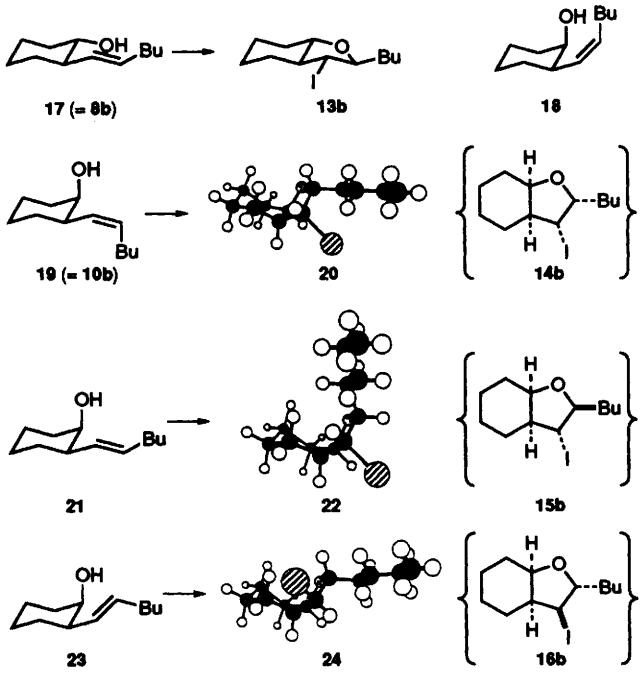


Fig. 1 Possible conformations of products

In the *cis* series, the results of the cyclisations can be understood by a consideration of the likely conformations of the products. Thus, the probable conformation **20** of the sole product **14b** from cyclisation of the *cis*-(*Z*)-cyclohexanol **10b** has the two substituents (I and Bu) positioned away from the ring system. This would arise from an initial conformation **19** rather than the alternative **18** which would lead to a product in which both substituents pointed into the ring system. In the case of the non-stereospecific cyclisations of the *cis*-(*E*)-isomer **11b**, there is competition between the substituents. The favoured initial 'chair-like' conformation **21** leads to the major product **15b** in which the bulkier iodine atom is positioned away from the concave face of the ring system as shown in model **22**. By contrast, the alternative initial 'boat-like' conformation **23** leads to the minor product **16b**, with conformation **24**, in which the iodine atom is pointing into the concave face of the ring system. In all cases, overall *anti* addition to the alkene function has occurred (*cf.* ref. 5). Molecular models (*cf.* conformations **19** and **21**) indicate that the transition states must be rather product-like to allow formation of the ether bond.[8] In the case of the cyclohexanol derivative **11b**, the preference for the 'chair' conformation **21** could be improved by performing the cyclisation at −78 °C rather than at 0 °C,§ resulting in an epimer ratio of 10:1 in favour of isomer **15b**. Little improvement in stereoselection in cyclisations of the corresponding cyclopentanol **11a** was observed when the temperature was lowered, probably as a result of the lower steric bias of the five-membered ring.

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Footnotes

† A number of S_N2 displacements of the iodo function in a selection of the products have also been carried out (*e.g.* by azide, carboxylate and thiophenolate); the independently determined stereochemistries of these products are also consistent with these initial assignments

‡ The remainder of the product was mainly composed of iodohydrins

§ The requisite amount of dry dichloromethane was added to prevent the reaction mixture freezing

References

1 F. Bennett, S. B. Bedford, G. Fenton, D. W. Knight and D. Shaw, *Tetrahedron Lett.*, 1992, **33**, 6507; S. B. Bedford, K. E. Bell, G. Fenton, C. J. Hayes, D. W. Knight and D. Shaw, *Tetrahedron Lett.*, 1992, **33**, 6511, and references therein.

2 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

3 For related examples, see S. H. Kang and S. B. Lee, *Tetrahedron Lett.*, 1993, **34**, 1955 and references therein.

4 For recent reviews of THF synthesis, see T. L. B. Boivin, *Tetrahedron*, 1987, **43**, 3309; J.-C. Harmange and B. Figadere, *Tetrahedron: Asymmetry*, 1993, **4**, 1711.

5 B. H. Lipshutz and J. C. Barton, *J. Am. Chem. Soc.*, 1992, **114**, 1084.

6 M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 1983, **24**, 391.

7 S. F. Martin and J. A. Dodge, *Tetrahedron Lett.*, 1991, **32**, 3017 and references therein.

8 For a discussion of the transition states involved in haloetherifications, see J. Sperka and D. C. Liotta, *Heterocycles*, 1993, **35**, 701.