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Predictive Models for the Overall 5-*endo*-trig Iodocyclisation of Homoallylic Alcohols

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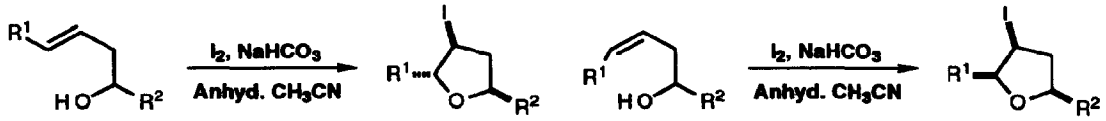
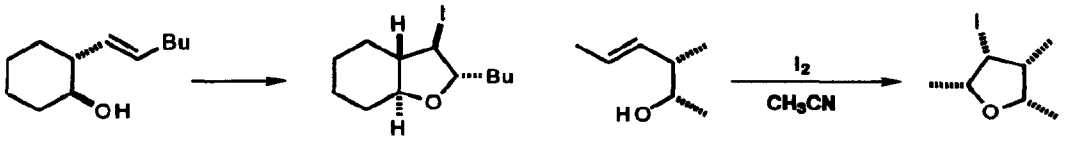
Abstract:- *Iodoetherifications of all isomers of the 3-methylalk-4-en-2-ols [14~17] proceed with excellent levels of stereoselectivity, leading to tetrasubstituted tetrahydrofurans [18~22],* via *overall anti-addition to the alkene function.*

The intramolecular iodoetherification of 4-penten-1-ol functions, an overall 5-*exo*-trig process, constitutes an efficient, generally applicable and often highly stereoselective approach to tetrahydrofurans which is applicable to a wide range of substitution patterns.[1] We have recently reported that related iodoetherifications of the homoallylic alcohols [**1** and **3**; R^1, R^2 = alkyl, silyloxyalkyl], formally *via* a 5-*endo*-trig pathway, can also be very effective in the stereocontrolled elaboration of 2,5-*trans*-(**2**) or 2,5-*cis*-(**4**)-tetrahydrofurans;[2] a crucial feature of these cyclisations is the use of anhydrous acetonitrile as solvent.



1 **2** **3** **4**

There have been only a limited number of reports of this type of cyclisation until recently. The first appears to have been an isolated example reported briefly by Bartlett and Myerson;[3] given a choice, 5-*exo* cyclisations always take preference[4] and even 4-*exo* ring closures can compete successfully.[5] Similar results to ours, but using mainly homoallylic alcohols having heteroaryl substituents at the distal end as substrates, have also been reported by a Korean group.[6] In seeking ways to extend the utility of this type of cyclisation, we have recently shown that such cyclisations can also be applied to the stereoselective elaboration of annulated tetrahydrofurans [*eg.* **6**] by cyclisations of 2-alkenylcycloalkan-1-ols [*eg.* **5**].[7]

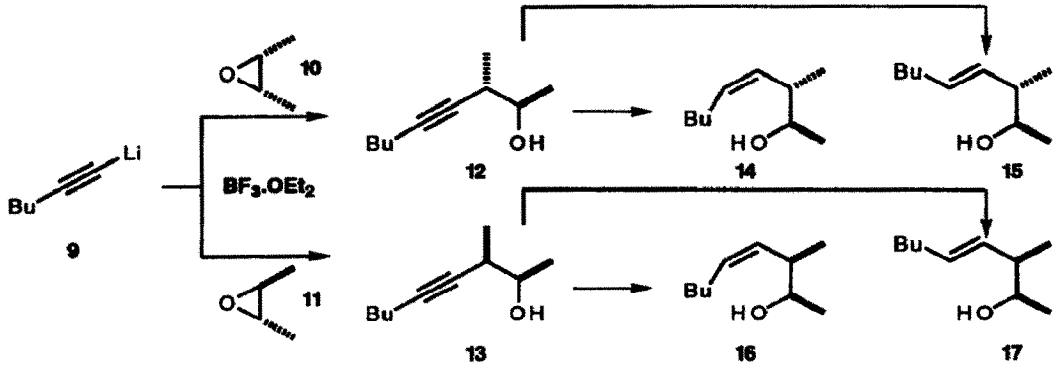


5 **6** **7** **8**

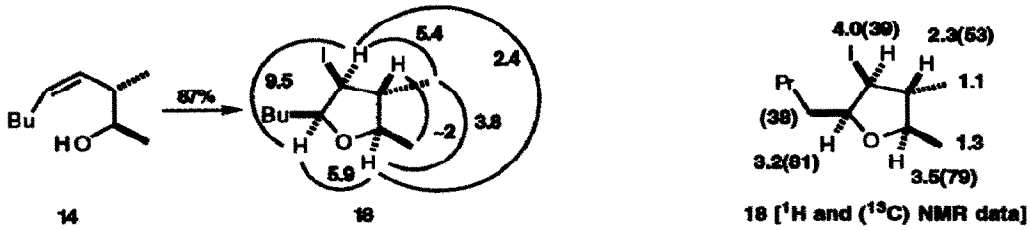
All of these results involve the overall *anti* addition of iodine and the hydroxyl group across the double bond of the homoallylic alcohol. We were therefore attracted by the possibility of using this type of cyclisation to prepare a variety of tetrasubstituted tetrahydrofurans in a highly stereocontrolled manner by starting with more

highly substituted homoallylic alcohols. However, we were somewhat uncertain of the outcome of such cyclisations and the applicability of our predictive models[2] of the likely transition state, in view of some exceptional examples of both seleno- and iodo-etherifications reported by Lipshutz and Barton.[8] For example, these authors reported that iodocyclisation of the (E)-*syn*-homoallylic alcohol **7** led exclusively to the all-*cis*-tetrahydrofuran **8**, apparently as a result of the overall *cis* addition of iodine and the hydroxyl group across the double bond. This type of cyclisation was reported to take place using iodine in acetonitrile with or without added silver trifluoroacetate. Subsequently, a single and non-stereoselective example of a closely related iodoetherification was reported using I_2-AgO_2CCF_3-MeCN, the stereochemical outcome of which cast doubt on the Lipshutz results[8] as the two THF products, obtained as a 60:40 mixture, were apparently formed by a more conventional *anti* addition across the double bond.[9] Herein, we report our studies of this type of cyclisation which we have found can be extremely stereoselective and which proceeds only by *anti* addition to the double bond, a process for which we propose transition state geometries which should be of predictive value.

The substrates for our studies were prepared from *cis*- or *trans*-2,3-epoxybutane [**10** and **11**] by condensation with 1-lithiohexyne **9**-BF_3.OEt_2.[10] The resulting alkynols [**12** and **13**; ~85%][11] were then reduced either under Lindlar conditions to give the *anti*-(Z) **14** and *syn*-(Z) **16** alkenols [~95%][11] or using $LiAlH_4$ (THF-toluene; reflux), leading to the corresponding *anti*-(E) **15** and *syn*-(E) **17** alkenols [90~95%][11].



We were pleased to find that exposure of the *anti*-(Z)-alkenol **14** to three equivalent of iodine in anhydrous acetonitrile containing sodium hydrogencarbonate (3 eq.) at 0°C for 0.75h led to a single iodotetrahydrofuran **18** in 87% yield.[11] The gross structure was deduced mainly from ^1H and ^{13}C NMR spectral data. The CHI function was identified both by its relatively simple coupling pattern (δ_H 4.03; 1H, app. t, J = 8.8 Hz) and by a ^1H-^{13}C correlation spectrum, relying on the unique upfield shift of the methine attached to iodine (δ_C 39.4 ppm).

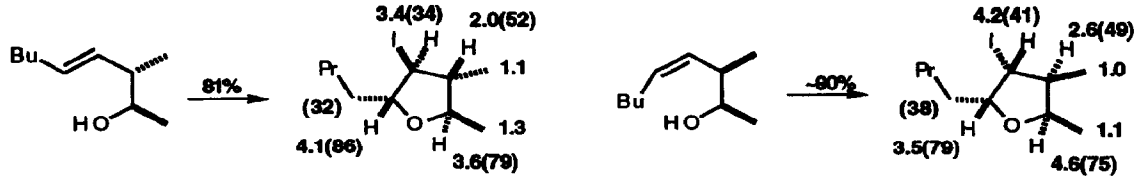


14 **18** **18 [^{1}H and (^{13}C) NMR data]**

A COSY spectrum then allowed all of the remaining resonances to be assigned. The stereochemistry was established primarily on the basis of NOE measurements, the results of which (in %) are shown in the structural diagram. Equally significant were the absent enhancements which also correlated well with this assignment.

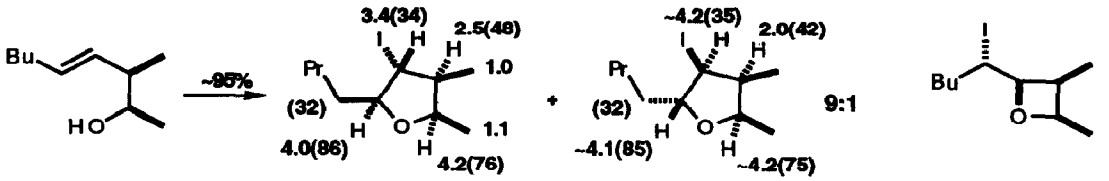
Similar treatment of the *anti*-(E)-isomer **15** also gave, after 3h at 0°C, a single iodotetrahydrofuran **19** in 81% yield,[11,12] the identity of which was established exactly as in the foregoing example.

Cyclisations of the corresponding *syn* diastereoisomers [**16** and **17**] using the I_2-$NaHCO_3$-MeCN method proved to be equally facile and efficient but slightly less stereoselective. Conversion of the *syn*-(Z)-alkenol **16** was complete after ~4h at 0°C and gave the iodo-THF **20**, contaminated with some 5% of the THF **21**, which probably arose by *in situ* isomerization of the (Z)-alkene, in a combined yield of >95%.[11,12] The corresponding *syn*-(E)-alkenol **17** however gave a mixture of two, separable iodoTHFs in a ratio of 9:1 [0°C, 1h], which were assigned the structures shown [**21** and **22**], again from NMR data, as outlined above.[11,12]



15 **19** **16** **20**

The ^1H and ^{13}C NMR data ($CDCl_3$), the latter in parentheses, presented with the structures [**18-22**] shows an encouraging level of internal consistency. For example, a 2,3-*trans* relationship between the butyl chain and the iodine atom [**19**, **21**] results in 2-CH(O) resonances at δ_H ~4.1 and δ_C ~86 ppm, CHI resonances at δ_H ~3.4 and δ_C ~34 ppm and the side-chain CH_2 group at δ_C ~32 ppm, clearly distinguishable from the corresponding resonances for the 2,3-*cis* isomers **18** and **20**. Similar relationships apply to the remainder of the data.

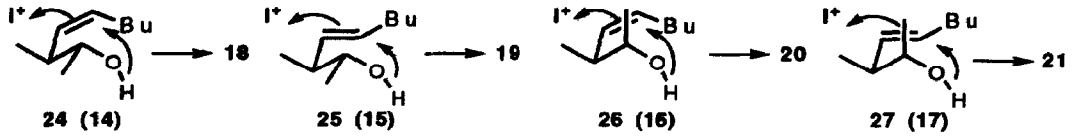


17 **21** **22** **23**

We also briefly examined the use of N-iodosuccinimide [NIS] as an alternative source of iodine for these cyclisations. In general, using dichloromethane as solvent at 20°C, the reactions were much slower (up to 24h for completion) than with I_2-$NaHCO_3$-MeCN; even so, cyclisations of the (Z)- and (E)-*anti*-alkenols [**14** and **15**] gave the same products [**18** and **19** respectively] in similar yields and stereospecificities. Unexpectedly, reaction between NIS and the *syn*-(Z)-alkenol **16** led to a 3:1 mixture of the expected iodoTHF **20** and the iodo-oxetane **23** in a combined yield of 50%. This is the first time that we have observed an oxetane in such cyclisations; the stereochemistry has been tentatively assigned from coupling constant and NOE data. By contrast, reaction between the *syn*-(E)-alkenol **17** and NIS gave the same mixture of iodoTHFs [**21** and **22**] as did iodine, but with reduced selectivity [6:1].

The excellent level of stereoselection in the cyclisations of the *anti*-alkenols **14** and **15** are consistent with the involvement of the transition state geometries **24** and **25** respectively, in which both substituent methyl groups are positioned pseudoequatorially. Cyclisations of the related *syn*-isomers **16** and **17** can be rationalized on the basis of the geometries **26** and **27** wherein there is a distinct preference for the substituent adjacent to the hydroxyl group to be positioned pseudoaxially with the remaining β-Me group in a pseudoequatorial position, resulting in a final positioning of the iodine *trans* to the two substituent methyls. These models should have predictive value in the design of syntheses using this cyclisation method. Finally, we suggest that the results [*eg.* **7** → **8**] reported by Lipshutz and Barton are incorrect,[8,9,13] as all of the foregoing cyclisations appear to

proceed by *anti* addition to the alkene function.



Acknowledgements

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11. Yields refer to isolated products which showed correct spectroscopic and analytical data, with the exception of THF **22**, which was not cleanly separated; hence the approximations in some of the NMR data for **22**.
12. NOE data (%) [numbering system: BuCH(2); ClH(3) etc.]:- **19** H(2)-H(4), 3; H(2)-Me(5), 1.5; H(2)-H(3,5), <1; H(3)-H(5), 2.5; H(3)-Me(4), 5; H(3)-H(4), <1; H(4)-H(5), <1; H(4)-Me(5) 4.5; H(5)-Me(4), 7; **20** H(2)-H(3), 8.5; H(2)-H(4), ~0; H(2)-H(5), <1; H(2)-Me(4), 5.5; H(2)-Me(5), 1; H(3)-H(4), 1; H(3)-H(5), ~0; H(3)-Me(4), 4; H(3)-Me(5), 1.5; H(4)-H(5), 6; H(4)-Me(5), ~0; H(5)-Me(4), ~0; **21** H(2)-H(3), <1; H(2)-H(4), 6; H(2)-H(5), 1; H(2)-Me(4), ~0; H(2)-Me(5), ~0; H(3)-H(4), 1; H(3)-H(5), ~0; H(3)-Me(4), 7.5; H(3)-Me(5), 2.5; H(4)-H(5), 7.5; Me(4)-H(2,5), ~0.
13. Correspondence with Professor Lipshutz has confirmed that he has reached the same conclusions; we are grateful for his helpful comments on our own work.

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