suspected that they serve as charge storage areas for O_2 reduction.

Acknowledgment. This work was supported by NIH Grant HL13652 to D.N.H. and NIH Grant GM23386 to C.G.P.

Supplementary Material Available: Tables of atomic positional and thermal parameters for both structures (3 pages). Ordering information is given on any current masthead page.

Stereocontrolled Synthesis of Cis-2,5-Disubstituted Tetrahydrofurans and *cis*- and *trans*-Linalyl Oxides

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Received March 5, 1981

The synthesis of polyether antibiotics is currently receiving considerable attention.[1] A particularly challenging aspect of this work is the stereocontrolled construction of the substituted tetrahydrofuran units found in many of these natural products, particularly those units in which there is a cis relationship between substituents at the 2 and 5 positions. An attractive method for the formation of substituted tetrahydrofurans is electrophilic cyclization of γ,δ-unsaturated alcohols, but the limited information available confirms the expectation that trans isomers are favored.[2] We reasoned that the desired cis-1,3 stereorelationship could be induced via two transient trans-1,2 relationships, by cyclizing olefinic ethers (as depicted in Scheme I). This proposal was supported by the observation of Allred and Winstein that the stereoisomers of 5-methoxy-2-hexyl brosylate solvolyze at different rates ($k_{threo} = 2.4k_{erythro}$) via analogous oxonium ion intermediates.[3] In fact, the cyclization of olefinic benzyl ethers with iodine does provide a general, highly stereoselective method for the synthesis of cis-2,5-disubstituted tetrahydrofurans, as indicated in Table I.[4]

We have gained a qualitative understanding of the factors involved in these cyclizations by studying a variety of derivatives of 5-hexen-2-ol (examples 1–7 in Table I). Loss of the alkyl group R from the oxonium ion intermediates **1** and **2** must be slow in comparison to reversal of their formation so that **2** will be favored thermodynamically and not just kinetically: the benzyl ether for example leads to only a 2:1 preference for cis (example 3). On the other hand, if loss of the alkyl substituent is too slow, side reactions such as cleavage of the other carbon–oxygen bond may ensue, which explains the poor yield which is obtained with the methyl ether (example 2).[3] The alkyl substituent must be bulky enough to exert a significant steric effect, but not so large as to prevent cyclization altogether; the silyl ethers cyclize with moderate selectivity but in poor yield (examples 4 and 5).[5] In the 2,6-dichlorobenzyl group is found the appropriate balance of electronic and steric properties for the 5-hexen-2-yl substrate (example 7). As a class, the substituted benzyl groups have the advantage that they can be tailored to fit the electronic needs of a variety of systems, as demonstrated by the other examples in Table I.

The stereochemistry of the 2-iodomethyl-5-methyltetrahydrofuran isomers was assigned by deiodination ($LiAlH_4$) to give the 2,5-dimethyl derivatives, whose ^1H NMR spectra have been reported.[6] The stereochemical assignments of the other 2,5-disubstituted tetrahydrofurans rest on analogy with this one and

Scheme I

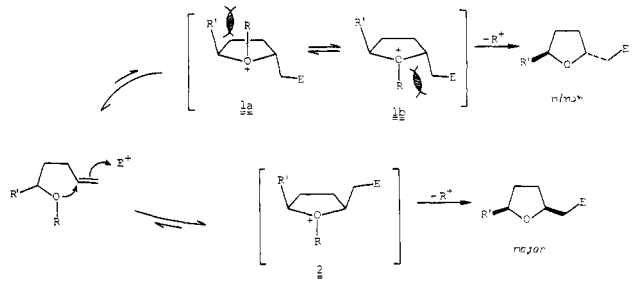
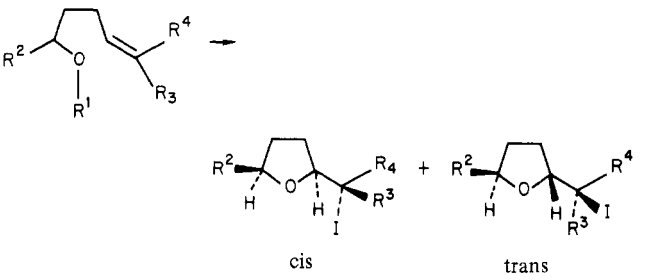


Table I. Iodocyclization of γ,δ-Unsaturated Ethers and Alcohols[a]



cis trans

example	R^1	R^2	R^3	R^4	cis/trans ratio[c]	yield,[d] %
1	H	CH_3	H	H	0.5	66
2	CH_3	CH_3	H	H	0.5	15
3	CH_2Ph	CH_3	H	H	2	60
4	$SiMe_2$-*t*-Bu	CH_3	H	H	3	43
5	Si-*t*-$BuPh_2$	CH_3	H	H	8	30
6	BB[b]	CH_3	H	H	3.7	74
7	DCB[b]	CH_3	H	H	21	63
8	H	$(CH_3)_2CH$	H	H	0.25	88
9	DCB	$(CH_3)_2CH$	H	H	20	95[e]
10	H	CH_3	CH_3	H	0.5	99
11	DCB	CH_3	CH_3	H	25	75
12	H	CH_3	H	CH_3	0.4	81
13	DCB	CH_3	H	CH_3	12	47
14	CH_2Ph	CH_3	CO_2CH_3	H	6	55
15	DCB	CH_3	CO_2CH_3	H	50	60
16	BB	CH_3	CO_2CH_3	CH_3	10	44

[a] Reaction conditions: I_2, CH_3CN, 0 °C; with the following exceptions: $NaHCO_3$ included for alcohol substrates (examples 1, 8, 10, and 12); cyclizations performed at 21 °C for ester substrates (examples 14–16). [b] BB = 4-bromobenzyl; DCB = 2,6-dichlorobenzyl. [c] Ratio determined by ^{13}C or ^1H NMR spectroscopy. [d] Isolated yield of purified product after chromatography or bulb-to-bulb distillation, unless otherwise indicated. [e] Yield based on ^1H NMR spectroscopy.

† Fellow of the Alfred P. Sloan Foundation, 1979–1981.

(1) Structures: Westley, J. W. *Annu. Rep. Med. Chem.* **1975**, *10*, 246. Westley, J. W. *Adv. Appl. Microbiol.* **1977**, *22*, 172–223. Pressman, B. C. *Annu. Rev. Biochem.* **1976**, *45*, 501–530. For references to initial synthetic work on nonactin, lasalocid A, and monensin, see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2–72. For more recent work on monensin, see: Collum, D. B.; MacDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2117–2121. Walba, D. M.; Edwards, P. D. *Tetrahedron Lett.* **1980**, 3531–3534. Lasalocid A: Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155–1157. Nonactic acid: Bartlett, P. A.; Jernstedt, K. K. *Tetrahedron Lett.* **1980**, 1607–1610. Ireland, R. E.; Vevert, J.-P. *J. Org. Chem.* **1980**, *45*, 4259–4260. Calcimycin (A-23187): Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789–6791. Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537–3539.

(2) Brown, H. C.; Geohegan, P. J., Jr.; Kirek, J. T.; Lynch, G. J. *Organometl. Chem. Synth.* **1970/1971**, *1*, 7–22. Hosokawa, T.; Hirata, M.; Murahashi, S.-I.; Sonoda, A. *Tetrahedron Lett.* **1976**, 1821–1824. Tanaka, O.; Tanaka, N.; Ohsawa, T.; Iitaka, Y.; Shibata, S. *Tetrahedron Lett.* **1968**, 4235–4238.

(3) Allred, E. L.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 3991–3997. The explanation of their results (as well as the ones we report here) may rest on more subtle interactions than those depicted in Scheme I, since the oxonium ion is only slightly pyramidal. A Kos and P. v. R. Schleyer, for example, have shown (using MNDO calculations) that the methyl group of *O*-methyltetrahydrofuran cation lies out of the C_2–O–C_5 plane by only 8.5° and the inversion barrier is of the order of 0.1 kcal/mol (personal communication).

(4) Satisfactory spectra and combustion analyses were obtained for all new compounds. Stereoisomers were not separated before characterization.

(5) Addition of iodine itself to the double bond competes with cyclization of these silyl ethers; hence the reaction cannot be driven to completion by the addition of more reagent or by prolonged reaction times.

(6) Gagnaire, D.; Monzeglio, P. *Bull. Soc. Chim. Fr.* **1965**, 474–480.

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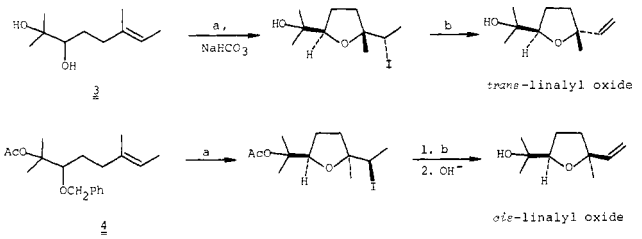
Scheme II[a]



[a] (a) I_2, CH_3CN, 0 °C. (b) KO-*t*-Bu, DMF, 25 °C.

on the internal consistency of obtaining the opposite stereochemical preference on cyclizing alcohols and benzyl ethers. On cyclization of the disubstituted olefins (examples 10–13), we saw no evidence of tetrahydropyran products, although they would be easily distinguishable by ^1H or ^{13}C NMR spectroscopy.[7] The fact that cyclization is successful even when the double bond is deactivated by conjugation with an ester group further establishes the versatility of the approach (examples 14–16).

Our success with the synthesis of cis-2,5-disubstituted tetrahydrofurans prompted us to attempt the stereoselective formation of 2,2,5-*tris*ubstituted analogues, which also appear as subunits of many of the polyether ionophores. As initial targets in this regard, we chose the linalyl oxides, since both isomers are known and well characterized.[8] Previous syntheses have involved nonstereoselective epoxidation and cyclization of linalool or geraniol.[8,9] As illustrated in Scheme II, iodocyclization of the diol **3**[10] and elimination of HI leads to the trans isomer in 70% overall yield. ^1H NMR (250 MHz) spectroscopy showed a trans/cis ratio of 20:1 and gave no indication of tetrahydropyran formation from attack by the tertiary hydroxyl. Most importantly, the cis isomer is produced with a selectivity of 13:1 on cyclization of the benzyl ether acetate **4**,[11] followed by elimination and ester hydrolysis (70% overall yield). In comparison to the formation of disubstituted tetrahydrofurans, in this case the initial cyclization step reverses more rapidly, and even the unsubstituted benzyl group allows sufficient equilibration between the isomeric oxonium ions before it is lost.

Further studies on the generality of this approach and its application to more complex polyethers are currently being pursued.

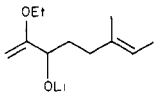
Acknowledgment. Support of this research by the National Institutes of Health (Grant CA-16616) and the National Science Foundation (departmental equipment Grant CHE 79-03763) is gratefully acknowledged. We also thank Dr. Alex Kos and Professor Paul v. R. Schleyer for their help and interest in the structure of the oxonium ion intermediates.

(7) Chemical shift values listed in: Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley: New York, 1972; p 256, give δ 1.8 for the $CH_3C(I)<$ moiety (tetrahydrofuran isomers) and δ 1.2 for the $CH_3C(OR)<$ moiety (tetrahydropyran isomers). The cis and trans products from example 10 (see Table I) show resonances of δ 1.86 and 1.89, respectively, and the cis and trans products from example 12 show resonances at δ 1.85 and 1.87, respectively, for the relevant methyl group.

(8) Felix, D.; Melera, A.; Seibl, J.; Kovâts, E. sz. *Helv. Chim. Acta* **1963**, *46*, 1513–1536.

(9) Klein, E.; Farnow, H.; Rojahn, W. *Liebigs Ann. Chem.* **1964**, *675*, 73–82. Ohloff, G.; Schulte-Elte, K.-H.; Willhalm, B. *Helv. Chim. Acta* **1968**, *47*, 602–626. Kametani, T.; Nemoto, H.; Fukumoto, K. *Bioorg. Chem.* **1978**, *7*, 215–220.

(10) Prepared from 3-methyl-3-buten-2-ol by vinyl ether exchange and Claisen rearrangement, ethoxyvinyllithium addition to give intermediate i, hydrolysis, and reaction with methyllithium.[4]



i

(11) Prepared from i by benzylation, hydrolysis, methyllithium addition, and acetylation.[4]

A Widely Useful Chiral Stationary Phase for the High-Performance Liquid Chromatography Separation of Enantiomers

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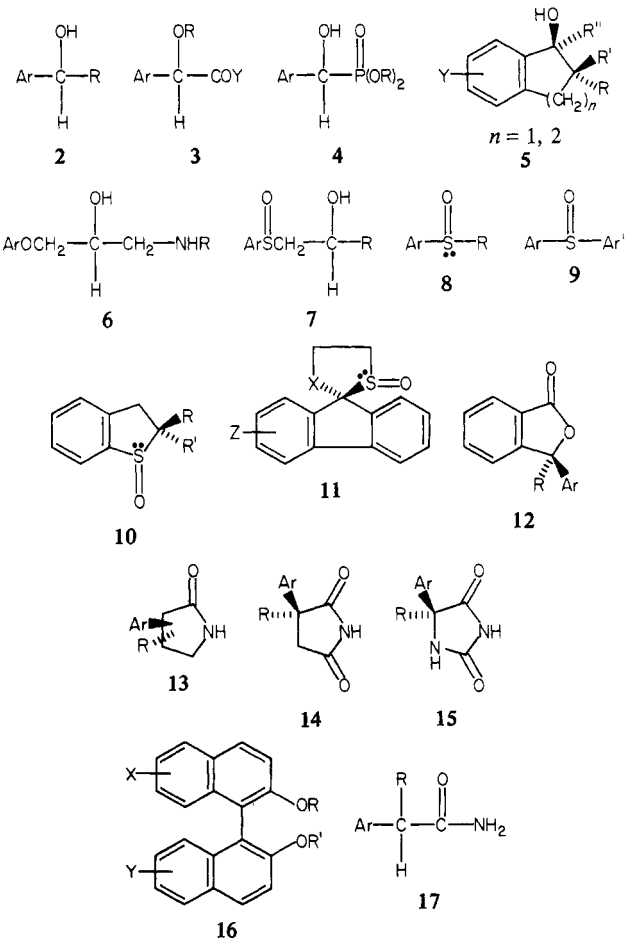
Received November 17, 1980

With the heightened interest in stereochemistry that today pervades most branches of chemistry, biochemistry, and pharmacology, the need for better methods of ascertaining enantiomeric purities and absolute configurations is obvious to many. An almost ideal solution to such problems would be the direct HPLC separation of the enantiomers of interest upon a column packed with a suitable chiral stationary phase (CSP). While no CSP will ever separate all enantiomers, considerable progress has been made in our laboratories in devising relatively "broad spectrum" CSP's for HPLC applications.[1,2] Although our initial fluoroalcohol CSP's are not yet widely available, we can now describe an ionically bonded CSP that shows even greater generality than does the fluoroalcohol CSP's and is extremely simple to prepare. Owing to its availability, its scope, and its myriad potential applications, this CSP should find wide and immediate acceptance. This preliminary paper is intended solely to document the widespread utility of this ionically bonded CSP. Later papers will describe the effects of structural variations within each solute category, relationships between absolute configuration and elution order, and relevant chiral recognition rationales.



(1) Pirkle, W. H.; House, D. W. *J. Org. Chem.* **1979**, *44*, 1957.

(2) Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatogr.* **1980**, 192, 143.

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