Tetrahedron Letters,Vol.29,No.17,pp 2011-2014,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

STEREOSELECTIVE SYNTHESIS OF HYDROXY-SUBSTITUTED TETRAHYDROFURANS

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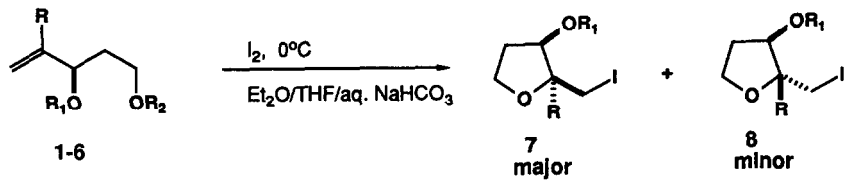
Abstract: *Iodocyclizations of 4-alkene-1,3-diol derivatives proceed with high stereocontrol to provide cis 2-iodomethyl-3-hydroxy(alkoxy)tetrahydrofurans. The effect of alkoxy substituents on the diastereoselectivity has also been assessed.*

The stereoselective preparation of highly substituted oxygen heterocycles, especially structurally complex tetrahydrofurans and tetrahydropyrans, has attracted considerable attention, and provides a challenging synthetic problem.[1,2]

Although electrophilic cyclization of γ,δ- unsaturated alcohols and carboxylic acid derivatives is successfully exploited for the preparation of a wide variety of substituted oxygen heterocycles, the stereocontrol of the cyclization of acyclic substrates has met with mixed results. However, recent studies strongly suggest a unique stereodirecting effect of an allylic oxygen substituent on the adjacent prochiral sp^2 sites in several types of reactions.[3,4] Herein we report a general, stereoselective route to hydroxy(alkoxy)-substituted tetrahydrofurans, where the stereocontrol by an allylic oxygen substituent has been systematically investigated.[5]

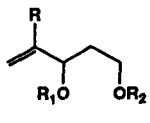
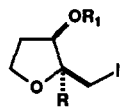
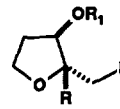
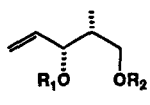
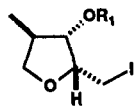
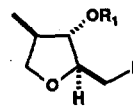
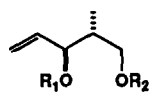
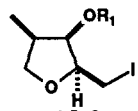
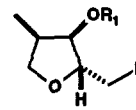
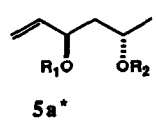
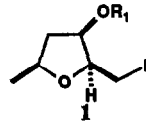
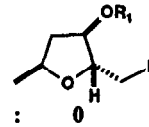
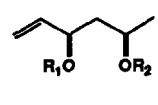
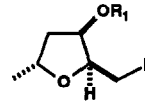
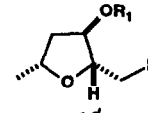


1-6 **7** major **8** minor

The requisite substrates **1,2a-d** were prepared in good yield by the straightforward condensation of t-butyl lithioacetate with acrolein or methacrolein, followed by reduction ($LiAlH_4$, Et_2O) and appropriate protections. Substrates **3** and **4a-c** were conveniently prepared by the procedures of Evans and Fráter, respectively.[6,7] The synthesis of **5,6a-c** was achieved by the clean separation of the diastereomeric mixtures, and their stereochemical assignment was firmly established by an independent synthesis of **5a** starting from 1,4-hexadien-3-ol in two steps [using the Sharpless kinetic epoxidation followed by epoxide opening with Red-Al].[8,9]

The iodoetherification of several 4-penten-1,3-diol derivatives does indeed proceed, with high stereoselectivity, to afford *cis* -2-iodomethyl-3-hydroxy(or alkoxy)tetrahydrofurans, as shown in Table I.[9] The ratios of two diastereomers (*cis* **7** : *trans* **8**) were determined by GC and/or NMR analysis of the crude reaction mixtures, before their separation by chromatography. We have further shown that the separated tetrahydrofurans do not interconvert when resubjected to the identical cyclization conditions. The stereochemical assignments were secured by γ-effects in ^{13}C NMR spectra: owing to steric effects the iodomethyl carbon atom in the *cis* isomer

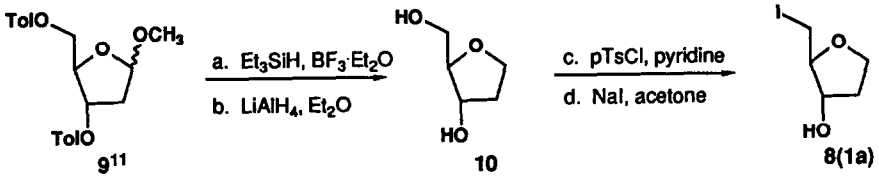
Table I[a]

Substrates[b]	ratios[c] *cis* 7		*trans* 8	chemical shifts δ_7	δ_8	$\Delta\delta_{8-7}$
						
1a R = H	15.2	:	1	1.57	6.91	5.34
1b	8.5	:	1	2.34	7.48	5.14
1c	5.8	:	1	"	"	"
1d	1	:	0	1.57	6.91	5.34
2a R = CH_3	8.8	:	1	11.05	14.85	3.80
2b	12.9	:	1	12.45	16.00	3.55
2c	1	:	1.1	"	"	"
2d	1	:	2.4	11.05	14.85	3.80
						
3a*	1	:	0	1.95	*e*	*e*
3b*	37.8	:	1	2.55	7.83	5.28
3c*	65.7	:	1	"	"	"
						
4a	15.9	:	1	2.26	7.20	4.94
4b	2.0	:	1	2.96	7.92	4.96
4c	1	:	1	"	"	"
						
5a*	1	:	0	1.41	*e*	*e*
5b	20	:	1[d]	2.35	8.56	6.21
5c	1	:	0[d]	"	"	"
						
6a	10.0	:	1[d]	2.30	7.50	5.20
6b	9.7	:	1	2.81	8.13	5.32
6c	1.8	:	1	"	"	"

a: R_1, R_2 = H; b: R_1 = Bzl, R_2 = H; c: R_1, R_2 = Bzl; d: R_1 = H, R_2 = Bzl.

(*a*) Iodoetherification condition: I_2(1.5 equiv) in THF, ether/saturated aqueous bicarbonate, 0°C. (*b*) All substrates are racemic, except those indicated(*). (*c*) Determined by glass capillary (a VOCOL 60m x 0.75mm i.d., 1.50μm d_f column) GC analysis.[15] (*d*) As GC did not allow separation of these diastereomers, their ratios were determined by ^1H and ^{13}C NMR spectra. (*e*) Not measured.

is shielded by *ca.* 5 ppm relative to the *trans* isomer.[10] The stereochemistry was unambiguously confirmed by an independent synthesis of **8(1a)**, as illustrated below, as well as of **7(3a)** and **7(3b)**.



Tol = p-methylbenzoyl

Most importantly, from the results summarized in Table I emerges the generality of an efficient acyclic stereocontrol by an allylic oxygen substituent to mainly produce the *cis* isomers **7**. Other chiral centers present in substrates, or protecting groups of the alcohols, were found to have little overall effect on the diastereomeric ratios, except for **2c,d**, **4b,c** and **6c**. It is noted, however, that the stereoselectivity was consistently enhanced by the use of free hydroxy groups.[12] As noted earlier by Yoshida et al.,[5] substrates **5** and **6** exhibited a considerable difference in reactivity. Thus, when an equal mixture of **5b** and **6b** was subjected to the standard cyclization conditions, alcohol **6b** underwent complete cyclization whereas *ca.* 50% of **5b** remained unreacted. Interestingly, attenuated selectivity was found for substrates **6a-c** than the corresponding **5a-c**.

The poor stereoselectivity observed in the cyclization of benzyl ether **6c** might be ascribed to the less favorable transient *cis*-1,2 relationship of the largely pyramidal oxonium ion intermediate, leading to **7(6c)**. The importance of the electrofugal properties of benzyl ether groups in such intermediates has been addressed by Bartlett in his elegant preparation of *cis*-2,5-disubstituted tetrahydrofurans under "thermodynamic" conditions (I_2 in CH_3CN in the absence of base).[2a] In addition, the use of the benzyl ethers in the disubstituted olefins resulted in a poor, but reversed diastereoselectivity (**2c** and **2d**). This striking irregularity exhibited by the benzyl protection of the nucleophilic alcohol moiety in these cases (including **4c**) may suggest the intervention of equilibration between the benzyl oxonium ion intermediates, where debenzylation becomes the rate-determining step of the iodocyclization reaction.[13] In any event, both functional groups present in tetrahydrofuran **7** can be easily manipulated for further structural elaborations.

Although the origin of the observed stereochemical outcome remains unclear, an attractive hypothesis concerning related electrophilic cyclizations was recently proposed by Chamberlin, Hehre and their coworkers, based on an early (reactant-like) transition state, i.e., a π-complex, rather than an "iodonium" ion.[14]

Further studies on acyclic stereoselection by an allylic oxygen substituent and its application to natural product synthesis are currently in progress.

Acknowledgment is made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health (GM 35956) for support of this research.

References and Footnotes

1. For general reviews, see (a) Boivin, T. L. B. *Tetrahedron*, **1987**, *43*, 3309. (b) Bartlett, P. A. In *Asymmetric Synthesis*, Morrison, J. D. Ed., Academic Press, New York, 1984, Vol. 3, Chapter 6. (c) Semple, J. E.; Joullié, M. M. *Heterocycles*, **1980**, *14*, 1825.

2. For recent examples of stereoselective tetrahydrofuran syntheses, see *inter alia*, (a) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.*, **1978**, *100*, 3950; Rychnovsky, S. D.; Bartlett, P. A. *ibid.*, **1981**, *103*, 3963. (b) Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'sa, A. *ibid.*, **1984**, *106*, 2641. (c) Dolle, R. E.; Nicolaou,