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IODOETHERIFICATION OF 4-PENTEN-1,3-DIOLS: STEREOSELECTIVE SYNTHESIS OF cis 2-IODOMETHYL-3-HYDROXYTETRAHYDROFURANS

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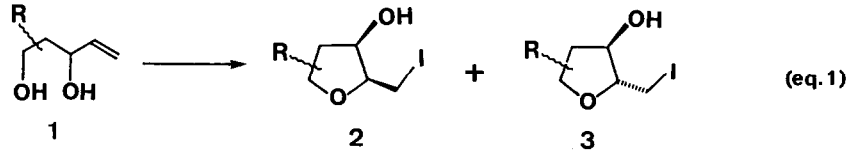
Summary: cis 2-Iodomethyl-3-hydroxytetrahydrofurans have been obtained in high yields and in high selectivities by treatment of 4-penten-1,3-diols with iodine (ether-H_2O, $NaHCO_3$).

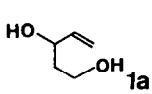
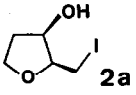
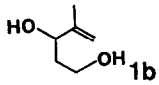
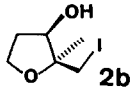
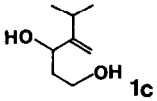
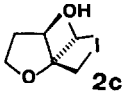
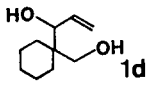
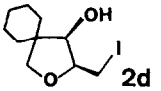
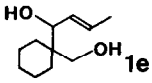
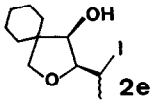
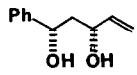
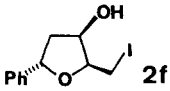
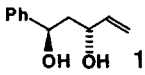
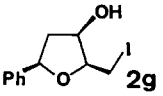
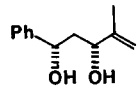
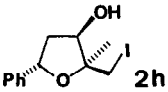
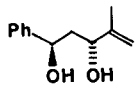
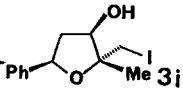
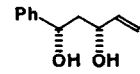
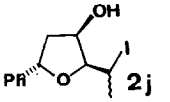
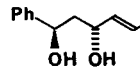
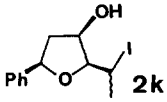
Recently many methodologies have been developed for the stereocontrolled preparation of substituted tetrahydrofurans.[1] Here we describe the very efficient and stereoselective synthesis of cis 2-iodomethyl-3-hydroxytetrahydrofurans by the iodoetherification of 4-penten-1,3-diols (equation 1).[2]



(eq.1)

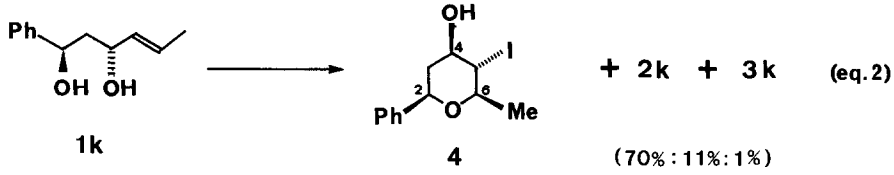
Haloetherificaton was examined under the three different reaction conditions: conditions A; I_2 (1.5 equiv), $NaHCO_3$ (2 equiv) in Et_2O (5 mL)-H_2O (2 mL) to 1 mmol of substrate. Conditions B; N-iodosuccinimide (1.2 equiv) in dichloromethane. Conditions C; Iodonium dicollidine perchlorate[3] (1.5 equiv) in chloroform. In Table I were summarized the reaction temperatures, reaction times, the combined isolated yields of cis and trans 2-iodomethyl-3-hydroxytetrahydrofurans (2 and 3) and their ratios. By examination of the results in Table I, the following general trends become apparent. Although the yields of products are almost the same and equally high irrespective of the reaction conditions A - C, the selectivities of 2 to 3 slightly depend on the conditions. Generally, the conditions A showed the highest cis selectivity (cf. entries 1 and 2, and 5 and 6). Accordingly most of the reactions were performed under the conditions A.

Table I. cis Selective Iodoetherification of 4-Penten-1,3-diols

entry	4-penten-1,3-diol	reaction conditions[a]	main product[b] (cis:trans, isolated yield)
1	 1a	A (0°C, 3 h)	 2a (95:5, 87%)
2		B (-78°C, 2 h)	(92:8, 89%)
3	 1b	A (0°C, 3 h)	 2b (91:9, 94%)
4	 1c	A (0°C, 6 h)	 2c (100:0, 73%)
5	 1d	A (0°C, 2 h)	 2d (98:2, 98%)
6		C (0°C, 1 h)	(85:15, 99%)
7	 1e	B (-78°C, 2 h)	 2e (93:7, 93%)
8	 1f	A (0°C, 12 h)	 2f (100:0, 98%)[c]
9	 1g	A (20°C, 24 h)	 2g (94:6, 81%)[d]
10	 1h	A (0°C, 0.5 h)	 2h (98:2, 93%)[c]
11	 1i	A (20°C, 3 h)	 3j (39:61, 94%)
12	 1j	A (0°C, 10 h)	 2j (93:7, 79%)[c]
13	 1k	A (20°C, 3 h)	 2k (95:5, 12%)[e]

(a) Conditions A: I_2 (1.5 equiv), $NaHCO_3$ (2 equiv), ether (5 mL)-H_2O (2 mL) to 1 mmol of 1. Conditions B: NIS (1.2 equiv) in dichloromethane. Conditions C: $I(collidine)_2ClO_4$ in chloroform. (b) Product ratio was determined by H-1, C-13 NMR spectra and/or HPLC. (c) Diastereomeric mixture of diols (1f:1g = 55:45, 1h:1i = 55:45, 1j:1k = 57:43) was used and the yield was calculated from the content of the syn-diol. (d) Yield was based on 80% conversion. (e) In addition to these, 4 was isolated in 70% yield (equation 2).

Each of the three pairs of diastereomers 1f and 1g, 1h and 1i, and 1j and 1k showed a large differences in reactivity and regio- and stereoselectivities. When a 55:45 mixture of 1f and 1g was reacted with 1.5 equiv of I_2[4] at 0°C, only the 1,3-syn diol isomer 1f reacted and the 1,3-anti diol 1g remained unreacted and was recovered quantitatively. And hence, the yield in entry 8 is based on the content of the diastereomer 1f in the mixture. The product obtained here consisted of only a single isomer, cis,trans 2-iodomethyl-3-hydroxy-5-phenyl-tetrahydrofuran 2f and no other products, such as 3f and 2g, were detected. In the other two pairs of diastereomers, the similar large differences in reactivity were also observed. The 1,3-syn diols 1h and 1j were much more reactive than the 1,3-anti diols 1i and 1k, respectively. The starting diastereomeric mixtures of diols could not be separated by means of column chromatography, however, according to the above kinetic separation, the 1,3-anti diols could be obtained in a stereochemically homogeneous state.[5]



(eq.2)

The reactivity of the 1,3-anti diols toward iodine were such that they were subjected to the reactions at 20°C. In addition to the low reactivity, the 1,3-anti diol isomers showed rather different stereo and regioselectivities. On exposure of 1g to I_2 at 20°C, the 2,3-cis isomer 2g was obtained in high selectivity, while the reaction of 1i with iodine provided the 2,3-trans isomer 3i in a slight preference over its cis isomer 2i. This is the only one example, ever examined, which does not show the cis selectivity. The main product of the reaction with 1k was not the tetrahydrofuran derivatives (2k, 3k), but the tetrahydropyran derivative 4 (equation 2). Interestingly, however, the high cis selectivity was retained in the formation of tetrahydrofurans (2k:3k = 95:5). The tetrahydropyran structure of 4 with all the substituents at equatorial positions was determined on the basis of the characteristic coupling patterns of the ring protons in the ^1H NMR spectrum (H_2: d.d., J = 2.2 and 11.2 Hz; H_5: t, J = 10.3 Hz; H_6: d.q, J = 10.3 and 7.2 Hz) and also the unusual low field resonance of the carbon (C_5) bearing iodine (46.8 ppm, cf., 23.5 ppm for the CHI of 2k) in the ^{13}C NMR spectrum.[6]

The stereostructures of tetrahydrofurans rely on the higher field resonances of the iodomethyl carbons of the cis isomers relative to those of the corresponding trans isomers (by

ca. 5 ppm) in their ^{13}C NMR spectra[6] and also the larger down field shifts of the resonances of iodomethyl protons in the cis isomers compared with those of the corresponding trans isomers, as observed in the doping experiments with $Eu(fod)_3$ in their ^1H NMR spectra.[6] The authentic trans isomers were prepared either by the inversion of cis isomers according to Mitsunobu method[7] or by the oxidation-reduction sequence (CrO_3-(pyridine)$_2$ in dichloromethane-$NaBH_4$ in THF/methanol, 2c:3c = 1:2.5).

The utility of the present reaction may be augmented by (1) the ease with which the reaction can be performed, (2) the ready availability of the starting materials with a wide structural variety,[2] (3) the large difference of reactivities of the starting diastereomeric diols with which each of them can be cyclized stepwise, (4) the general and high cis selectivity,[8] and (5) the unique structure of the products assembled with functionalities desirable for the further transformations.

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(2) 4-Penten-1,3-diols were prepared readily and in almost quantitative yields by the sequential aldol condensation and reduction with $LiAlH_4$ in ether at room temperature.

(3) Lemieux, R. V.; Morgan, A. R.; Can. J. Chem. 1965, 43, 2190.

(4) Iodine (1.5 mmol) to 1 mmol of the diastereomeric mixture of diols was used.

(5) The unambiguous structure characterization of these diols relies on the structures of their acetonide derivatives, prepared by treatment of a mixture of diols with a large excess of 2,2-dimethoxypropane in the presence of a catalytic amount of toluenesulfonic acid (room temperature, 2 days). The acetonide of 1h: ^1H NMR ($CDCl_3$) 1.54 (s, 3 H), 1.58 (s, 3 H), 1.58 (m, 2 H), 1.74 (s, 3 H), 4.40 (d.d, J = 10.3 and 3.4 Hz, 1 H), 4.80-5.08 (m, 3 H), 7.33 (m, 5 H). ^{13}C NMR ($CDCl_3$) 18.2 (Me), 19.6 (Me), 30.2 (Me), 37.9 (CH_2), 71.4, 72.3, 98.9 (Me_2C), 110.8, 125.7, 127.4, 128.2, 142.2, 144.9. The acetonide from 1i: ^1H NMR ($CDCl_3$) 1.48 (s, 6 H), 1.79 (s, 3 H), 1.97-2.19 (m, 2 H), 4.30 (t, J = 7.8 Hz, 1 H), 4.80-5.07 (m, 3 H). ^{13}C NMR ($CDCl_3$) 18.4 (Me), 24.7 (2 Me), 38.4 (CH_2), 68.5, 69.6, 100.7 (Me_2C), 110.2, 125.8, 127.2, 128.3, 142.5, 145.0.

(6) (a) Gaudemer, A. In "Stereochemistry", Kagan, H. B., Ed., Georg Thieme Verlag, 1977. (b) Levy, G. C.; Lichter, R. L.; Nelson, G. L. "Carbon-13 NMR Spectroscopy", 2nd Ed., Wiley, 1980.

(7) Mitsunobu, O. Synthesis, 1981, 1.

(8) For the leading references for the diastereoselection in the reactions with electrophiles toward allylic alcohols, see (a) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. J. Am. Chem. Soc. 1983, 105, 5819. (b) Semmelhack, M. F.; Bodurow, C.; Baum, M. Tetrahderon Lett. 1984, 25, 3171. (c) Midland, M. M.; Halterman, R. L. J. Org. Chem. 1981, 46, 1229. (d) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. J. Am. Chem. Soc. 1984, 106, 1079. (e) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. Tetrahedron Lett. 1984, 25, 1063.

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