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SYNTHETIC UTILITY OF CHIRAL TETRAHYDROFURANS: PREPARATION OF (1R,3R,5S)-1,3-DIMETHYL-2,9-DIOXABICYCLO[3.3.1]NONANE

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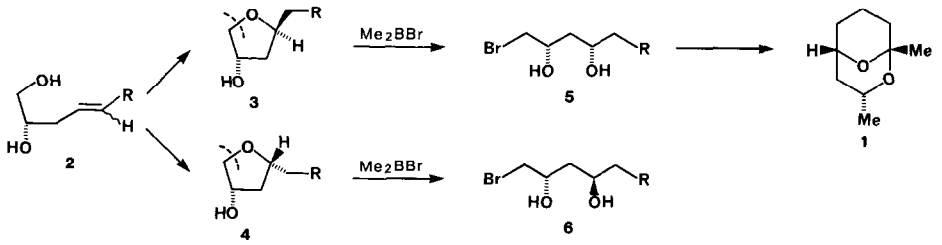
Abstract: The use of the iodoetherification reaction for the selective preparation of optically active trans-2,4-disubstituted tetrahydrofurans and the use of the latter compounds as precursors of syn-1,3-diols is exemplified in the synthesis of (1R,3R,5S)-Endo-1,3-Dimethyl-2,9-Dioxabicyclo [3.3.1]nonane(1).

Optically active 1,3-diols are important and useful synthons in the synthesis of natural products.[2] The present paper describes an approach to the stereoselective synthesis of a 1,3-diol equivalent and its application in the synthesis of optically active (1R,3R,5S)-Endo-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane 1, a biologically interesting host-specific substance.[3]

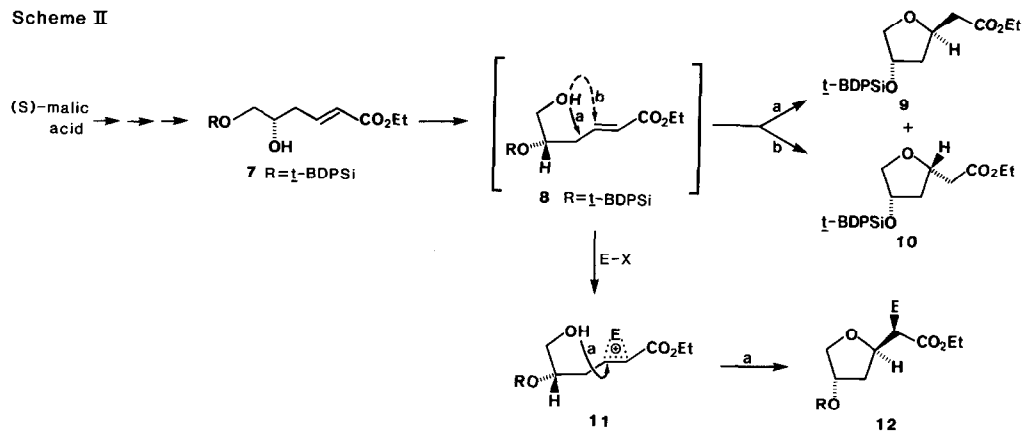
Scheme I

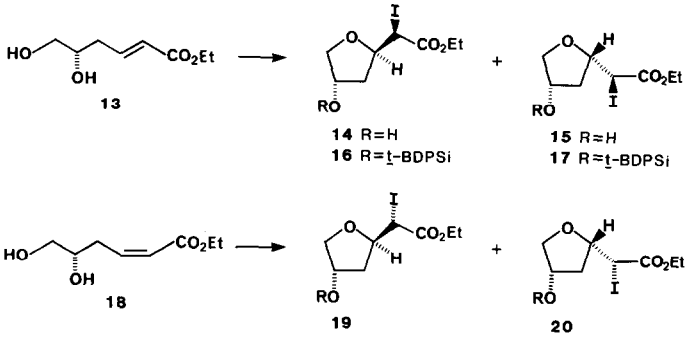


Our approach to the synthesis of 1,3-diols (Scheme I) is based on the following: a) transformation of a simple chiral precursor bearing one asymmetric hydroxyl group into a stereochemically well defined trans-(or cis-)2,4-disubstituted tetrahydrofuran; b) subsequent ring opening at the least hindered carbon-atom in the tetrahydrofuran would then result in the formation of the desired syn-(or anti-)1,3-diol. It should be noted that this process results in the stereocontrolled formation of a new chiral center. In order to optimize the viability of this approach, an efficient method for the synthesis of 2,4-disubstituted tetrahydrofurans was sought.[4] As described previously, exposure of 7 to base (cat. NaOEt, EtOH, reflux) afforded a mixture of isomeric cyclic ethers 9 and 10 (87%) in a ratio of 2:1.[5] Under milder conditions (0°C, 2.5h) the cis-isomer 10 predominated (9 to 10, 1:1.7). Although 10 can be recycled to 9,[6] a more stereoselective preparation of the trans-isomer 9 was desired. As

shown in Scheme II, the kinetically favored cis-isomer 10 results from nucleophilic attack on the si-face of 8 (path b), addition to the re-face (path a) affords the thermodynamically more stable trans-isomer 9. This suggested that if the same kinetic face (si-face) of the Michael acceptor were to be the site of attack by an electrophile (E-X) in a bimolecular reaction process, it could be possible to control the stereochemistry of the cyclization reaction. Subsequent intramolecular nucleophilic attack of the hydroxyl group in 11 on the re-face would then result in the formation of the trans-ester 12.

Scheme II



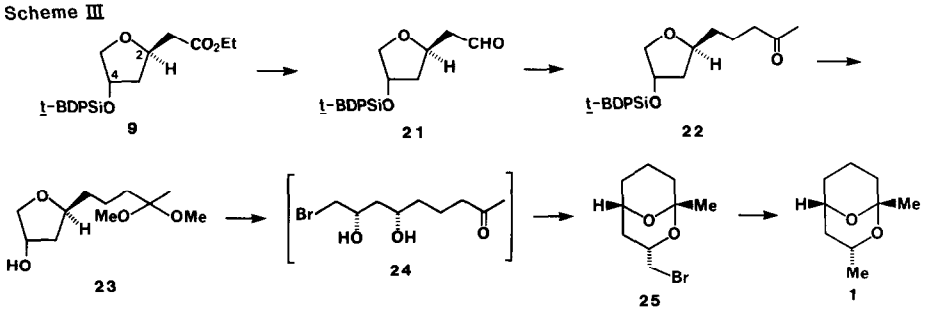


Treatment of 13 with iodine (5.0 equiv.) in the presence of solid $NaHCO_3$ (3.0 equiv., THF, 0°C., 6h) gave a 4.8:1 mixture of the α-iodo esters 14 and 15 in excellent yield (87%). Even more impressive was the ratio of 14 and 15 (8.5 to 1, respectively) when the reaction (0°C, 24h) was performed in ether (73%). These mixtures were silylated (tBDPSi-Cl, iPr_2NEt, DMAP, CH_2Cl_2) and the products then separated by flash chromatography.[7] Gratifyingly, treatment of 16 with nBu_3SnH (AIBN, hexane, reflux) resulted in clean reduction of the iodine to produce 9 in excellent yield (93%).[8]

Although iodoetherification has been used previously for the synthesis of substituted tetrahydrofurans,[9] to our knowledge the present work is the first example in which an iodoetherification reaction has been used to establish a 2,4-disubstituted tetrahydrofuran with

high trans stereoselectivity. It should be noted that due to the presence of the Michael acceptor this reaction proceeded in a completely regioselective fashion, and none of the corresponding tetrahydropyran was obtained.[9b,c] Interestingly, the geometry of the olefin did not effect the stereochemical preference for the trans-tetrahydrofuran.[9c] Thus, treatment of the less readily available cis-alcohol 18[10] with iodine in ether (0°C, 24h) followed by silylation of the crude reaction mixture gave the α-iodo esters 19 and 20 (R=tBDPSi) in a ratio of greater than 7 to 1, respectively. Furthermore, compounds 16, 17, 19 and 20 were stereochemically homogeneous with respect to the newly formed carbon-iodine bond.[11,12]

Scheme III



Having established a useful method for the selective preparation of trans-2,4-disubstituted tetrahydrofurans we proceeded to transform 9 into the bicyclic ketal 1,[13] (Scheme III).

Reduction of 9 (DIBAl-H, toluene, -78°C) afforded the aldehyde 21 (72%) along with a small amount of the corresponding alcohol. Wittig reaction ($Ph_3PCHCOCH_3$, CH_2Cl_2, room temperature, 18h) and subsequent hydrogenation (H_2, 10% Pd/C, EtOH) then gave the ketone 22 (85%), $[\alpha]_D$ +20.0° (c 1.1, $CHCl_3$). Protection of the ketone as its dimethyl acetal[14] (dry HCl, MeOH, $(MeO)_3CH$) and desilylation (nBu_4NF) cleanly afforded the ketal alcohol 23.[15]

Completion of our synthetic strategy now depended on the crucial ring opening of the tetrahydrofuran moiety. Towards this end, we have developed a powerful new reagent, dimethylboron bromide, with predictable SN_2 reactivity for the regiocontrolled cleavage of a variety of carbon-oxygen bonds.[16] Treatment of 23 with dimethylboron bromide (4.0 equiv, CH_2Cl_2, 0°C to room temperature) in the presence of diisopropylethylamine (1.1 equiv.) effected cleavage of both the dimethyl ketal and the cyclic ether to directly afford after work-up (aqueous $NaHCO_3$-Et_2O) the volatile bromo-bicyclic ketal 25 (53%). Presumably the reaction intermediate corresponding to 24 underwent ketalization during work-up. Reduction (nBu_3SnH, AIBN, hexane reflux) then gave the bicyclic ketal 1 (76%),$[\alpha]_D$ -35.2°.(c 0.3, pentane), lit.[13a] $[\alpha]_D$ -37.3°.

In summary, the iodoetherification reaction has been used for the stereoselective synthesis of a trans-2,4-disubstituted tetrahydrofuran. The utility of the latter compound as a masked chiral 1,3-diol was exemplified in the efficient synthesis of optically active (1R,3R,5S)-Endo-(1).

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1. Undergraduate Research Participant Université de Sherbrooke, Sherbrooke, Quebec, Canada.
2. T. Nakata, S. Takao, M. Fukui, T. Tanaka and T. Oishi, Tetrahedron Lett., 24, 3873 (1983) and references cited therein.
3. Compound 1 was first isolated from Norway spruce infested by the ambrosia beetle (Trypodendrum lineatum Oliv., see (a) V. Heemans and W. Francke, Naturwiss, 63, 344 (1976); (b) J.P. Vite and W.Francke, ibid., 63, 550 (1976).
4. Previously we have shown that chiral tetrahydrofurans are important precursors to a variety of chiral acyclic molecules; see (a) Y. Guindon, R. Zamboni, C.-K. Lau and J. Rokach, Tetrahedron Lett., 23 739 (1982); (b) J. Rokach, C.-K. Lau, R. Zamboni and Y. Guindon, Tetrahedron Lett., 22, 2763 (1981).
5. Y. Guindon, C. Yoakim, M. A. Bernstein and H. E. Morton, Tetrahedron Lett., 26, 1185 (1985).
6. Equilibration of either pure 9 or 10 with base (NaOEt, EtOH, reflux 5h) afforded a 2:1 mixture of 9 and 10, respectively. Longer reaction times failed to increase the ratio of the trans-product 9.
7. The cis/trans stereochemical assignments were unambiguously determined using ^{1}H nOe. M.A. Bernstein, H.E. Morton and Y. Guindon, manuscript submitted (1985).
8. Treatment of 13 with $Hg(OAc)_2$ in CH_2Cl_2 followed by demercuration ($NaBH_4$, EtOH; see F. H. Gouzoules and R. A. Whitney, Tetrahedron Lett., 26, 3441 (1985)) and silylation gave 9 and 10 in a ratio of 4:1, respectively. The use of PhSeCl was much less effective for the cyclization reaction.
9. Recently, several reports have appeared on the use of the haloetherification reaction for the steroselective preparation of 1,5-cis-[a] and 2,3-cis-[b] substituted tetrahydrofurans. The high selectivity observed in these reactions presumably results from 1,2-steric interactions in the developing transition state of the ring closure[a,c] or by 1,2-hydroxyl direction in the cyclization of allylic diols[b,d]. (a)S. D. Rychnovsky and P. A. Bartlett, J. Amer. Chem. Soc., 103, 3963, (1981).(b)Y. Tamaru, S.-i. Kawamura and Z.-i.Yoshida, Tetrahedron Lett., 26, 2885, (1985);(c)F. Freeman and K. D. Robarge, Tetrahedron Lett., 26, 1943 (1985);(d)D. R. Williams and F. H. White, ibid., 26, 2529 (1985).
10. This compound was obtained as a minor component during the preparation of 7.
11. Based on the mechanistic considerations of the iodoetherification reaction the stereochemistries at the acyclic carbon atoms of 16, 17, 19 and 20 were assigned as shown.
12. The factors responsible for the high trans-stereoselectivity are currently under investigation in our laboratories.
13. The absolute stereochemistry of 1 is as yet unknown. For previous syntheses of the (1R,3R,5S)- isomer see (a) H. Redlich, B.Schneider, R. W. Hoffmann, and K. J. Geueke, Liebigs Ann Chem, 393 (1983); (b) T. Nakata, S. Nagao, S. Takao, T. Tanaka and T. Oishi, Tetrahedron Lett., 26, 73 (1985) and references cited therein.
14. Reaction of the unprotected ketone 22 with Me_2BBr afforded rearrangement products. The dimethylketal was chosen as the protecting group on the basis that it would undergo cleavage with Me_2BBr to give the corresponding α-bromo ether which upon work-up, would afford the ketone; see ref. 16b and c.
15. The reactivity of Me_2BBr is very sensitive to steric factors. Therefore the bulky silyl protecting group was removed to improve the regiochemistry of the opening.
16. (a) Y. Guindon, C. Yoakim and H. E. Morton, Tetrahedrom Lett., 24 2969 (1983); (b) Y. Guindon H. E. Morton and C. Yoakim, ibid., 24 3969 (1983); (c) Y. Guindon, C. Yoakim and H. E. Morton, J. Org. Chem., 49 3912 (1984).

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