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New Chiral Building Blocks and their Application to the Construction of Chiral Aminoalcohols: Enantiomerically Pure *cis*- and *trans*-3-Mesyloxy-4-hydroxy Tetrahydrofurans

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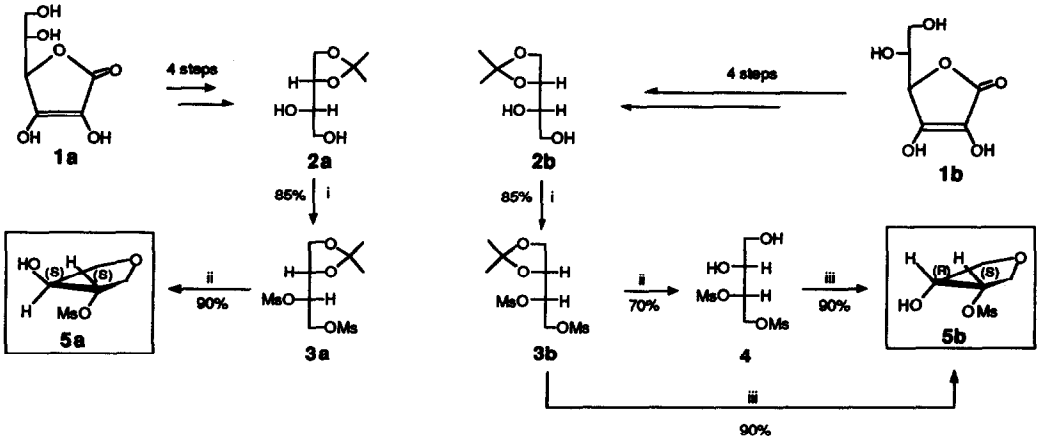
Abstract. The enantioselective synthesis of 3-mesyloxy-4-hydroxy tetrahydrofurans is described, starting from the chiral pool. The usefulness of these building blocks is illustrated by the synthesis of enantiomerically pure 3-amino-4-hydroxy-tetrahydrofurans

Although polyfunctional chiral tetrahydrofurans are widely distributed as base skeletons in monosaccharides, there does not exist a convenient preparation of simple chiral tetrahydrofurans substituted exclusively at C-3 and C-4 position. It appears that furanoses of the carbohydrate series carry too many functional groups to serve as educts for facile conversion to such compounds. Diastereomers of tartaric acid may provide a source for the construction of *trans*-3,4-dihydroxy-tetrahydrofurans, though in case of the *cis*-diol, the chirality is lost due to the plane of symmetry.[1]

As part of a program devoted to the synthesis of chiral aminoalcohols,[2] we have developed a route to enantiomerically pure *cis*- and *trans*-3-mesyloxy-4-hydroxy tetrahydrofurans, applicable to multigram preparations, starting from L-ascorbic acid **1a** and D-isoascorbic acid **1b**. The products may be useful as chiral building blocks. Both precursors may be viewed retrosynthetically as threitol and erythritol derivatives respectively and have been utilized recently in the construction of chiral β-lactams,[3] fatty acids metabolites,[4] long-chain α-hydroxy acids,[5] and prostaglandin intermediates.[6]

The protected tetrol derivatives **2a** and **2b** are prepared from L-ascorbic acid and D-isoascorbic acid respectively, using an established route.[7] Esterification of the free hydroxy groups with methanesulfonyl chloride[8] yields the bis(sulfonates) **3a** and **3b**. In the next step the acetal is hydrolyzed with aqueous HCl and simultaneously the tetrahydrofurans **5a** and **5b** are formed. In the case of the erythritol derivative, isolation of diol **4** may be possible whereas, under the same conditions, the threitol derivative always produces the heterocyle quantitatively.

Obviously, these differences in reactivity depend on the steric relationship between substituents on the incipient ring, which renders the ring closure more difficult in the case of a vicinal *cis*-substitution pattern.

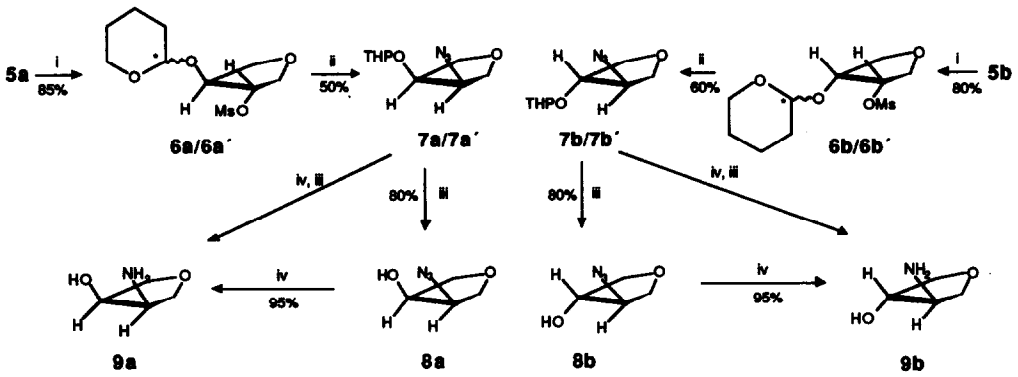


i, MsCl/ py/r.t./12h; ii, HCl/MeOH/H_2O/reflux/1h; iii, HCl/MeOH/H_2O/reflux/8h.

Investigation of the ring forming reaction reveals that the two methansulfonate groups fulfill different tasks. The primary sulfonyl group allows the smooth acid catalyzed cyclization, whilst the secondary sulfonyl group provides the nonsymmetrical substitution pattern in the tetrahydrofuran products **5a** and **5b**. The evident facility and selectivity of the acid catalyzed ring closure is surprising, since the secondary mesyl group is not affected as stated under basic conditions.[9]

Our approach shows two remarkable advantages when compared to the the chemistry of tartaric acid[10]: 1. the specific construction of 3-mesyloxy-4-hydroxy-tetrahydrofurans without formation of the dimesylated byproduct is possible and 2. the dissymmetrization of *meso*-alcohols, represented by their derivatives **2b** and **5b**, has been achieved without the help of enzymes etc.[11]

To demonstrate the utility of the described chiral building blocks, they were converted to chiral aminoalcohols. Protection of the hydroxy group as dihydropyrans gave diastereomers **6a/6a´** and **6b/6b´** respectively, differing only in configuration at the new sterogenic center of the protecting group. Substitution of the mesyl group with azide yielded the azido derivatives with inversion of configuration. These were in turn converted to the corresponding amines by hydrogenation. Of greater interest to us was the preparation of the corresponding hydroxyazides by acidic cleavage of the protecting group, which gave azides **8a** and **8b**. Structures of this type are found in pharmaceutically important 3-azido-furanoses.[12] The azides were hydrogenated to give enantiomerically pure (3R,4S)-3-amino-4-hydroxy-tetrahydrofuran **9a** and its (3R,4R)-isomer **9b**, respectively. The latter has been reported in its racemic form, in the older literature.[13 14]



i, 3.4-dihydro-2H-pyran/PPTS/6h/r.t.; ii, LiN_3/n-Bu_4NI/DMF/24h/r.t.; iii, MeOH/H_2O/CF_3COOH/2h/r.t.; iv, H_2/Pd,C/MeOH/24h/r.t.

Other applications of chiral 3-mesyloxy-3-hydroxy tetrahydrofurans are currently being explored in our respective groups.

Acknowledgments

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8. p-Tosyl chloride was also tried, but all of the tosyl derivatives synthesized were of a sirupy nature, requiring purification by flash chromatography, whereas most mesyl derivatives were crystalline compounds and easily purified by crystallisation from common solvents.
9. Ring closure of 1,4-diols to cyclic ethers has been reported during tosylation in pyridine: Alder, K.; Roth, W., Chem. Ber. 1954, *87*, 161; Birch, S. F.; Hunter, N. J.; McAllan, D. T., J. Org. Chem. 1956, *21*, 970; Zinner, H.; Brandhoff, H.; Schmandke, H.; Kristen, H.; Haun, R., Chem. Ber. 1959, *92*, 3151.
10. For uses of tartaric acid as a chiral building block see, Seebach, D.; Hungerbühler, E. in "Modern Synthetic Methods 1980", Ed. Scheffold, R.; Volume 2, Frankfurt/Main, 1980, p. 91.
11. For an example of the dissymmetrization of 2,3-O-isopropylidene-erythritol see, Pottie, M.; Van der Eycken, J.; Vandewalle, M., Tetrahedron: Asymmetry 1991, *2*, 329; Mori, K.; Kiyota, H., Liebigs Ann. Chem. 1992, 989.
12. 3-Azido-3-deoxy-thymidine plays an important role in the treatment of the aquired immunodeficiency syndrome (AIDS) e.g. Czernecki, S.; Ezzitouni, A., J. Org. Chem. 1992, *57*, 7325 and references cited therein.
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14. All new compounds gave satisfatory microanalytical (C, H, N $\pm$0.4 %) and spectral data. Selected physical data of compounds:

5a: mp 107-108 °C; $[\alpha]^{24} = +16.5$ (*c* 1, acetone)
5b: mp 78 °C; $[\alpha]^{22} = +11.3$ (*c* 1, acetone)
8a: oil; $[\alpha]^{24} = -14.7$ (*c* 0.71, $CHCl_3$)
8b: oil; $[\alpha]^{21} = -59.5$ (*c* 1.12; $CHCl_3$)
9a: oil; $[\alpha]^{25} = +4.8$ (*c* 1.08; CH_3OH).
9b: oil; $[\alpha]^{24} = -16.5$ (*c* 1.08; CH_3OH).

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