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Stereo- and Enantioselective Synthesis of (-)-(1R,3R,5S)-1,3-Dimethyl-2,9-dioxabicyclo [3.3.1] nonane

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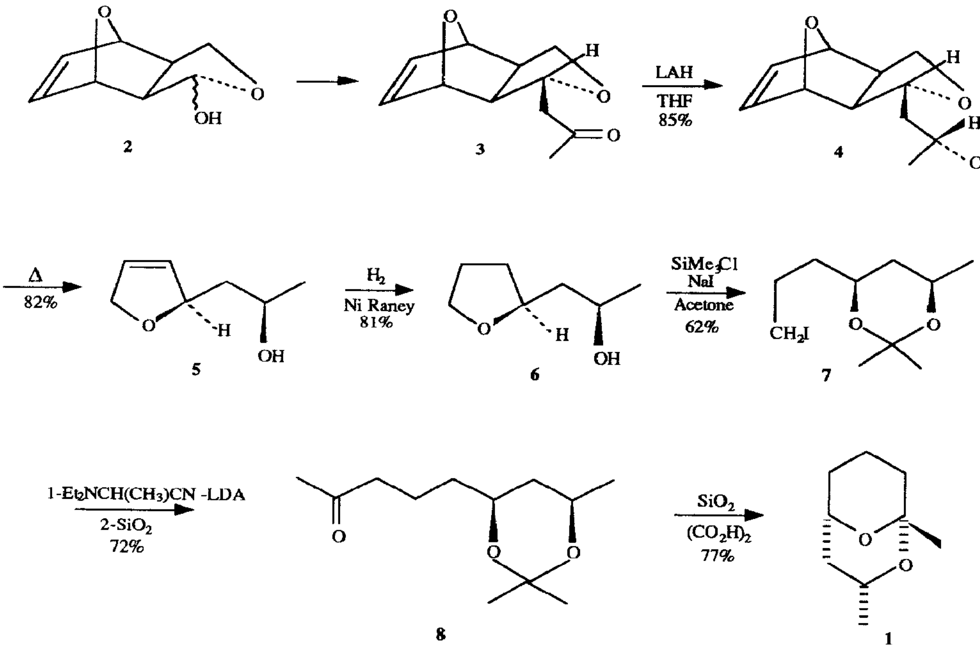
Abstract : The title compound has been synthetised in an enantioselective and diastereoselective manner from an optically pure lactol obtained via an enzymatic hydrolysis.

Endo-1,3-dimethyl-2,9-dioxabicyclo [3.3.1] nonane **1**, isolated for the first time in 1976, has been shown to be a host specific substance for the ambrosia beetle *(Try podendron lineatum oliv.)* that infests the bark of the Norway Spruce [1]. Since the absolute configuration of the natural substance is still not known with certainty, several syntheses of the racemic or of one or the other enantiomer of **1** have been described [2].

We wish to report here a synthesis of (-)-**1** as an application of a new simple preparation of optically active *syn*-1,3-diols. This synthesis, based on the highly regioselective opening of a 2-substituted tetrahydrofuran is illustrated in the scheme. As shown in a previous communication [3], the tricyclic ketone **3** is stereoselectively obtained from the optically pure lactol **2** [4] by a tandem Wittig-Horner/intramolecular Michael reaction. The reduction of the carbonyl group of **3** by a variety of reagents showed that the best diastereoselectivity (9 to 1) was obtained using simply $LiAlH_4$ in THF. The major reduction product **4** ($[\alpha]_D^{25}$ = +1.9 , c = 1.1, CH_3OH) was found by ^1H and ^{13}C NMR to possess a *syn* relationship between the newly created hydroxy group and the β-alkoxy group of the tetrahydrofuran ring. Flash thermolysis of **4** (500°C) gave rise to the dihydrofuran **5** ($[\alpha]_D^{25}$= -95 , c = 1.7, MeOH) which was easily hydrogenated in the presence of Raney-Nickel into the tetrahydrofuran **6** ($[\alpha]_D^{25}$ = -11.6 , c = 1.2, MeOH). Completion of our synthesis now depended on the regioselective opening at the least hindered carbon-atom of the tetrahydrofuran. Towards this end we used the reagent Me_3SiI recently developed for the synthesis of 1,2-diols [5]. Treatment of **6** by Me_3SiCl/NaI in acetone resulted in both the regioselective cleavage of the cyclic ether and the ketalization of the 1,3-diol formed, affording the iodo acetonide **7** in 62% yield (a small amount of the non protected iodo diol was also observed). Alkylation of methyl N-diethylaminoacetonitrile [6] by the iodide **7**, followed by hydrolysis led to the ketone **8** ($[\alpha]_D^{25}$ = -11.7 , c = 1.5, MeOH ; ee ≥ 95% as shown by ^1H NMR in the presence of chiral $Eu(hfc)_3$). Finally the deprotection of the hydroxy groups and the cyclization into (-)-**1** ($[\alpha]_D^{25}$= -35.7 , c = 1, pentane) [7] was realized by an acid catalysis with SiO_2/oxalic acid [8].

Scheme



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(7) The optical rotations reported in the literature[2] for (-)-**1** are somewhat inconsistent, changing between -35.2° and -46.2°.

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