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Stereocontrolled Synthesis of 2,5-Disubstituted Di- and Tetrahydrofurans

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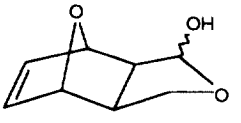
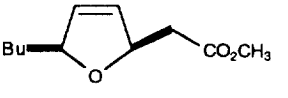
Abstract : Starting from lactol **1**, a highly stereoselective synthesis of either *cis* or *trans* 2,5-disubstituted dihydrofurans is described, which can be applied to the obtention of enantiopure compounds.

Due to the widespread occurence of *cis* as well as *trans* 2,5-disubstituted di- and tetrahydrofurans units in a number of natural products, versatile and stereoselective synthesis of such structural features has received considerable attention in recent years.[1] If electrophilic cyclizations of γ,δ-unsaturated alcohols have been well developed, reports on cyclizations of such alcohols via a simple intramolecular Michael reaction are relatively scarce.[2] We have recently shown that enantiopure 2-substituted di- and tetrahydrofurans could be easily obtained from lactol **1** through stereocontrolled tandem Wittig-Horner/Michael reactions followed by thermal cycloreversion and hydrogenation.[3] We report in this paper an extension of this method to the highly stereoselective formation of either *cis* or *trans* 2,5-disubstituted dihydrofurans. This method is illustrated herein by the synthesis of **2** and **3** from the same starting material, the lactol **1**.



1



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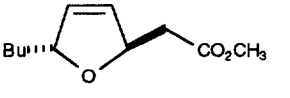
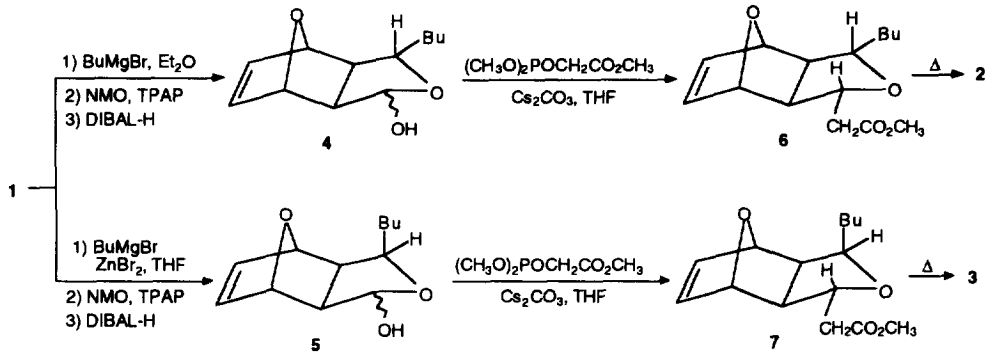


3

Addition of butylmagnesium bromide to lactol **1** either in diethyl ether, or in tetrahydrofuran in the presence of $ZnBr_2$ (1 eq.), gave rise respectively to the *like* (86% yield, de = 78%) or the *unlike* (73% yield, de = 86%) primary, secondary diols[4] which were transformed into lactols **4** and **5** by oxidation at room temperature with 4-methylmorpholine N-oxide (NMO, 2.5 eq.) and tetrapropylammonium perruthenate (TPAP) [5] to the corresponding lactones,[6] followed by DIBAL-H reduction. This transformation could also be achieved with fair yields (45% to 55%), in a single step, by controlled oxidation[7] of the diols at 0°C with NMO (1.1 eq.)/TPAP. Tandem Wittig-Horner/intramolecular Michael reactions afforded the tricyclic ethers **6** from lactol **4** and **7** from lactol **5** in 58% and 74% isolated yields respectively.



The Michael ring closure reactions proved to be highly stereoselective since **6** is the unique stereomer formed in the first reaction and **7** is the major component (81%) of the mixture obtained in the second reaction (the minor compound is the stereomer of **7** in which the two substituents are in a *cis, endo* position). The stereochemistry of these three compounds have been assigned by careful examination of ^{1}H NMR data.[3] From these results, it can be concluded that, whatever was the configuration of the carbon bearing the butyl group, the carbomethoxymethyl substituent adopt preferentially an *exo* position in order to minimize 1,2 and 1,3 interactions. The formation of *cis*-disubstituted compound **6** was not in full agreement with a report dealing with the major formation of *trans*-disubstituted compounds in similar systems.[2d] However in our case, the preferred formation of **6** is supported by simple molecular mechanics calculations (MMX program, PC M5 version) : **6** was found thermodynamically more stable than the corresponding *trans* stereomer by 10.4 kJ/mol. Heating of compounds **6** and **7** in flash thermolysis conditions (450°C, 1 ms contact time) gave rise with excellent yields (92-95%) respectively to *cis* and *trans* dihydrofurans **2** and **3** [8] which could be hydrogenated in the presence of Pt/C or Raney Nickel to afford the corresponding tetrahydrofurans.

In summary we described here an efficient methodology which can be applied to the synthesis of enantiopure *cis* or *trans* 2,5-disubstituted di- or tetrahydrofurans, starting from easily available [9] pure enantiomers of lactol **1**.

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8. **2** : ^{1}H NMR ($CDCl_3$) δ 0.92 (bt, 3H), 1.21-1.62 (m, 6H), 2.49-2.64 (m, 2H), 3.71 (s, 3H), 4.8 (m, 1H), 5.15 (m, 1H), 5.84 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 14.0, 22.7, 27.4, 36.5, 42.1, 51.6, 81.8, 86.4, 128.8, 131.1, 171.3.
   3 : ^{1}H NMR ($CDCl_3$) δ 0.91 (bt, 3H), 1.18-1.64 (m, 6H), 2.43-2.68 (m, 2H), 3.69 (s, 3H), 4.85 (m, 1H), 5.2 (m, 1H), 5.85 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 14.0, 22.8, 27.2, 35.6, 41.1, 51.7, 81.8, 85.9, 128.8, 131.2, 171.5.
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