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A Facile Synthesis of (-)-β-Vetivone

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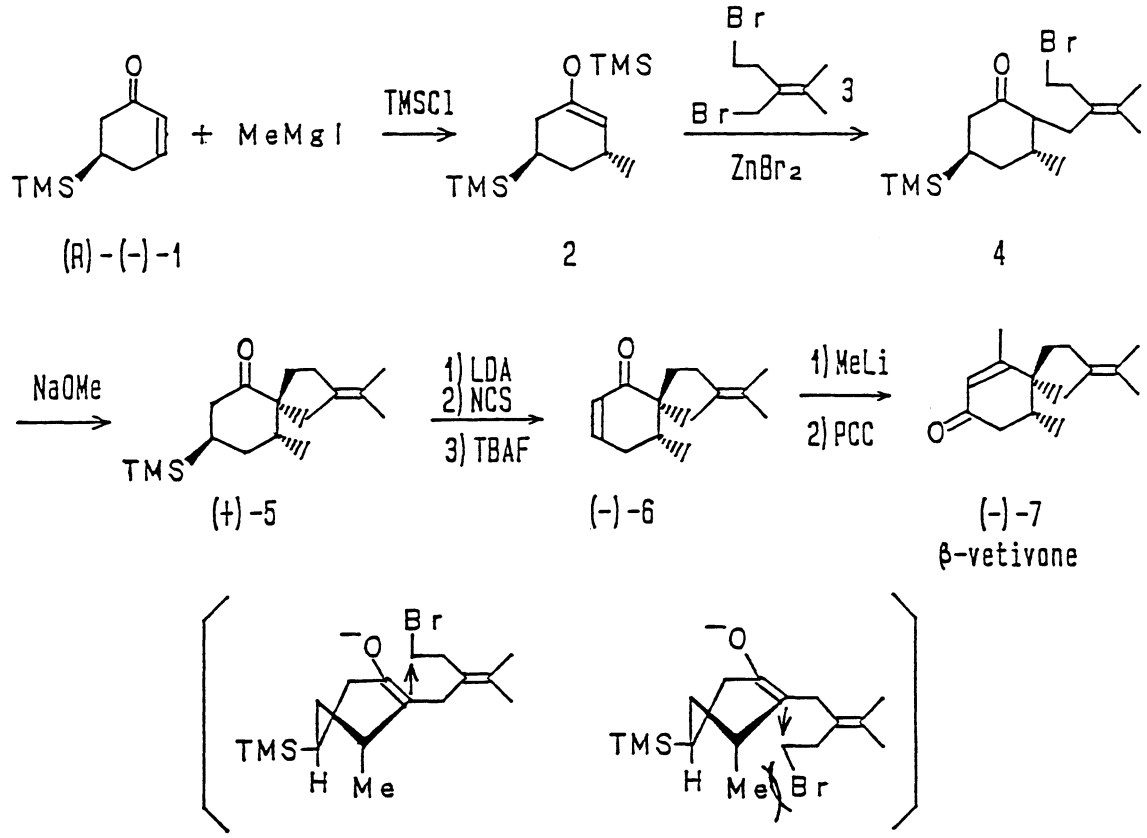
A short step synthesis of the title compound from (R)-(-)-5-trimethylsilyl-2-cyclohexenone via stereoselective intramolecular alkylation is described.

β-Vetivone (**7**) is a constituent of the essential oil of Vetiveria zizanioides and has a unique spiro[5.6]structure.[1] Although many synthetic methods have been reported for racemic **8**,[2] only one report has appeared on the synthesis of chiral one.[3] In this paper we will describe a stereoselective synthesis of (-)-β-vetivone.

Our synthetic sequence (scheme 1) involves two diastereoselective steps, one of which is the stereoselective 1,4-addition of methylmagnesium reagent to (R)-(-)-5-trimethylsilyl-2-cyclohexenone (**1**) and has already been demonstrated.[4] Another one is the stereoselective intramolecular alkylation of 2,3,5-trisubstituted cyclohexanone derivative **4** (**4**⟶**5**). Although such type of stereoselectivity has not been fully elucidated, structure of the possible intermediates illustrated in the scheme 1 suggests the preferential alkylation on the desired side by the steric effect of methyl group which is fixed to pseudo axial orientation by bulky TMS group.

1,4-Addition of methylmagnesium iodide to (R)-(-)-**1** in the presence of CuBr-Me_2S, HMPA, and TMSCl[4] gave the enol silyl ether **2** (bp 83-86 °C/5 mmHg) in 94% yield. Alkylation of **2** with dibromide **3** in the presence of $ZnBr_2$ at rt[5] gave **4** (41%, oil) as a diastereoisomeric mixture, which afforded only one spiro compound [(+)-**5** mp 36-39 °C, $[\alpha]_D^{23}$+11.9°(c 1.67, $CHCl_3$)] in 49% yield upon treatment with NaOMe in THF (at rt for 2 h and then at 50 °C for 40 min). At this stage the stereochemistry of the spiro compound and its diastereomeric homogeneity were unclear, however, the correctness of the assigned structure and the homogeneity were confirmed after the completion of the synthesis. Chlorination of (+)-**5** with LDA and NCS at -78 °C followed by elimination of the TMS and Cl groups by the treatment with tetrabutylammonium fluoride (TBAF) at rt yielded the enone (-)-**6** [52%, oil, $[\alpha]_D^{24}$-155.2°(c 2.19, $CHCl_3$)]. 1,2-Addition of methyllithium (-78 °C-rt, in Et_2O) to (-)-**6** and subsequent oxidation with PCC afforded (-)-β-vetivone [(-)-**7**, mp 43.5-44.0 °C, $[\alpha]_D^{23}$-47.1°(c 1.12, EtOH)][6] in 63% overall yield. ^{1}H-NMR (270 MHz) analysis[7] of the synthesized (-)-β-vetivone revealed the correctness of the assigned structures of (+)-**5**, (-)-**6**, and (-)-**7** and diastereomeric homogeneity.



Scheme 1.

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