TOTAL SYNTHESIS OF (+)-MENTHOFURAN#

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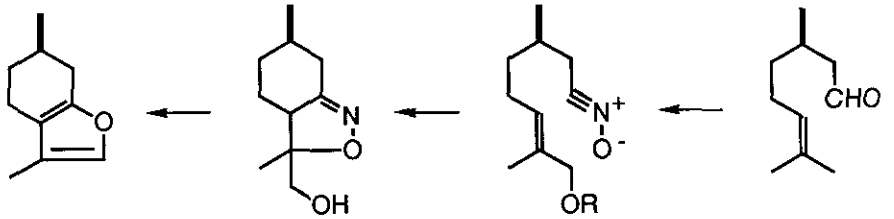
Abstract - Total synthesis of optically active menthofuran, a perfumy monoterpene, has been accomplished employing the intramolecular [3+2] cycloaddition-based methodology for the construction of fused furans.

We have recently devised a new and facile construction of disubstituted fused furans based on the intramolecular [3+2] cycloaddition of nitrile oxide and reported its application to the synthesis of furanosesquiterpene (+)-pallescensin A.[1] Our main objective in this area centers not only on the extension of this methodology to more complex systems but also on the application to the synthesis of biologically active natural products.

In this communication, we wish to report a total synthesis of monoterpene (+)-menthofuran (**1**),[2] one of the important perfumeries isolated from peppermint oil (*Mentha piperita*),[3] starting from (+)-citronellal (**2**) employing the extended strategy for the construction of *trisubstituted fused furans* (Scheme 1).



1 **3** **2**

Scheme 1

Reduction of (+)-citronellal (**2**) { $[\alpha]_D$+14.28°; lit.,[4] $[\alpha]_D$+17.38° } with sodium borohydride followed by protection of the primary alcohol provided the t-butyldimethylsilyl ether (**4**). The allylic hydroxylation of **4** was best carried out in 62 % yield using an exess of t-butyl hydroperoxide in the presence of a catalytic amount of selenium dioxide.[5] The allyl alcohol thus obtained was

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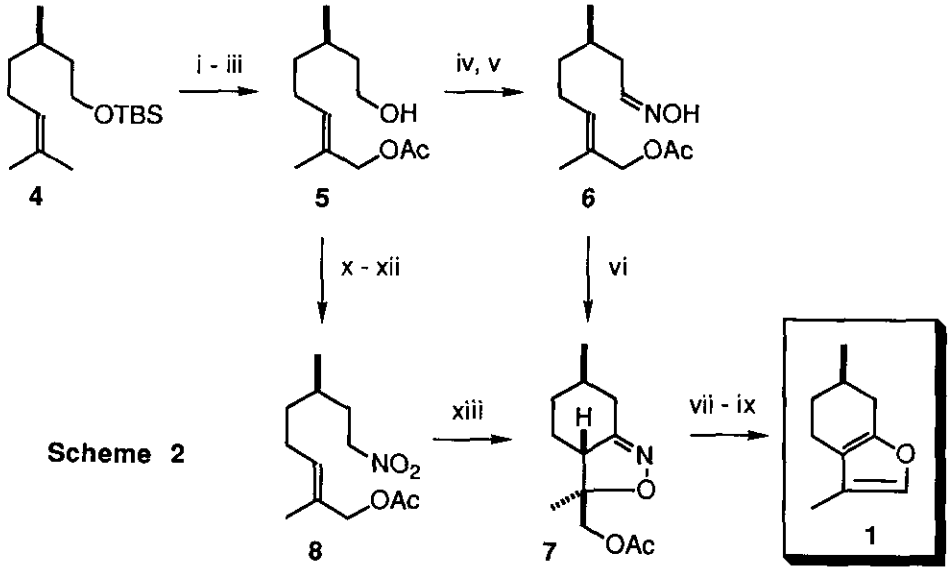
 # Dedicated to Dr. Masatomo Hamana on the occasion of his 75th birthday

acetylated and desilylated successively to give the alcohol (**5**), which was then transformed into the oxime (**6**) by sequential Swern oxidation and oxime formation in 84 % overall yield from **4**. Treatment of **6** with 7% aqueous sodium hypochlorite[6] in methylene chloride at room temperature provided the isoxazoline (**7**) as an inseparable mixture of diastereoisomers (*ca.* 8:1 from ^{1}H nmr) in 76 % yield. Although the exact configuration of the newly developed stereogenic centers of the cycloadduct was not determined by the ^{1}H nmr, the stereostructure of the major diastereoisomer was tentatively assigned as depicted in **7** from the mechanistic point of view.[7] Alternatively, the isoxazoline (**7**) was also assembled by treatment of the nitroalkane (**8**), prepared from the alcohol (**5**) via the standard transformations, with *p*-chlorophenyl isocyanate[8] in 91 % yield. Conversion of **7** into the target molecule was achieved in three-step sequence in 75 % overall yield. Thus, treatment of **7** with lithium hydroxide provided the alcohol (**3**) which was exposed to the conditions of reductive hydrolysis followed by immediate treatment of the crude product[9] with *p*-toluenesulfonic acid to give (+)-menthofuran (**1**)[11] { $[\alpha]_D$+75.45°; lit.,[10] $[\alpha]_D$+87.46° }, identical with an authentic sample by ^{1}H nmr and ir spectrometric comparisons (Scheme 2).



Scheme 2

Reagents : i, SeO_2, ^{t}BuOOH ; ii, Ac_2O, pyridine ; iii, ^{n}Bu$_4$NF ; iv, $(COCl)_2$, DMSO, Et_3N ; v, NH_2OH•HCl, AcONa ; vi, 7% aq. NaOCl ; vii, LiOH•H_2O ; viii, Raney Ni, H_2, $(MeO)_3B$; ix, PTSA ; x, MsCl, Et_3N ; xi, NaI ; xii, $AgNO_2$; xiii, *p*-ClC_6H_4NCO, Et_3N.

The synthesis described above represents an application of the trisubstituted fused furan construction to the synthesis of (+)-menthofuran. Further work is in progress to extend this methodology to the synthesis of other types of biologically active furanoids.

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9. The tlc of crude product showed two spots. The faster spot is menthofuran and the slower one may be the β,γ-dihydroxy ketone which converged on the former after treatment of the mixture with PTSA.
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11. Colorless oil; bp_{25} 85 °C (Kugelrohr)(lit.,[2b] $bp_{2.8}$ 48 °C); ^{1}H nmr (200 MHz, $CDCl_3$) δ: 1.07 (3H, d, J=6.3 Hz), 1.92 (3H, d, J=1.0 Hz), 2.65 (1H, dd, J=15.5 and 5.3 Hz), 7.03 (1H, br s).

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