

**FURANOTERPENE SYNTHESIS VIA INTRAMOLECULAR NITRILE
OXIDE CYCLOADDITION REACTION:
A TOTAL SYNTHESIS OF (+)-MENTHOFURAN**

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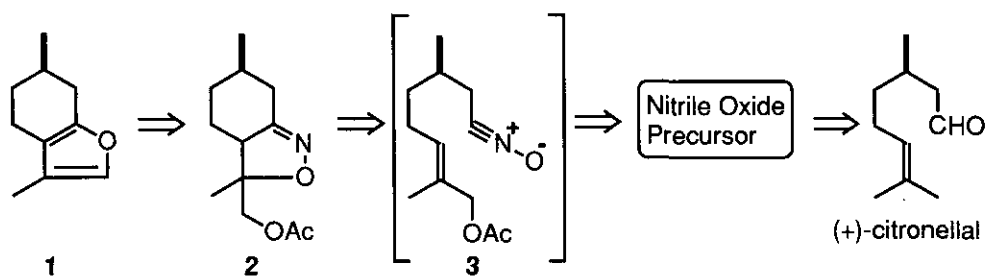
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Abstract - A fused furan assembling strategy based on an intramolecular [3+2] dipolar cycloaddition reaction of nitrile oxide has been applied to a total synthesis of perfumy furanomonoterpene (+)-menthofuran (**1**). The key cycloaddition substrates (**9**) and (**12**) are easily prepared *via* straightforward routes starting from (+)-citronellal and these are treated with sodium hypochlorite and *p*-chlorophenyl isocyanate, respectively. The cycloaddition reactions generate 10 : 1 mixture of diastereoisomeric isoxazolines (**2a**) and (**2b**) in good to excellent yields. The isoxazolines (**2a,b**) thus obtained are converted to (+)-menthofuran (**1**) by sequential reductive hydrolysis and alkaline hydrolysis (or *vice versa*) followed by acid treatment of the resulting β,γ -dihydroxy ketone (**14**).

Menthofuran (**1**), one of the most well-known members of furanoterpenes, was first obtained by Charabot in 1904 from peppermint oil,¹ *Mentha piperita vulgaris* S. Subsequently, Wienhaus² deduced the structure by a series of chemical experiments and the confirmation of it was made by a combination of the synthesis from pulegone and some chemical techniques by Treibs.³ Menthofuran has served not only as an important perfumery, but also as a synthetic intermediate for the other

biologically related natural products, e.g. mintlactone and isomintlactone.⁴ Although the numerous syntheses of this monoterpene have been reported,⁵ the chiral approaches from acyclic substrates are very few. We have recently developed a novel and efficient methodology for assembling a bicyclic fused furans *via* an intramolecular [3+2] dipolar cycloaddition reaction of an acyclic substrate which embodies a nitrile oxide and an allylic acetate as the dipolarophile component, and reported the application to a total synthesis of a marine sesquiterpene (+)-pallesensin A.⁶ In line with our interest in the extension of our methodology to the synthesis of biologically active natural compounds, we describe in this paper a total synthesis of (+)-menthofuran starting from (+)-citronellal.⁷

The plan we envisaged for the synthesis of menthofuran (**1**) is outlined in Scheme 1. The 2,3,4-trisubstituted fused furan structure of **1** would be constructed from the isoxazoline (**2**) by sequential reductive hydrolysis leading to the β -hydroxy- γ -acetoxy ketone, alkaline hydrolysis of the primary acetoxy function and acid treatment of the resulting β,γ -dihydroxy ketone intermediate. The isoxazoline (**2**), a key intermediate of our plan, might be available by an intramolecular cycloaddition reaction of the acyclic nitrile oxide (**3**), which would be generated *in situ* from the suitable nitrile oxide precursors. Considering the *R* configuration of the only stereogenic center presented in the molecule, we chose (+)-citronellal as the starting material. (Scheme 1)



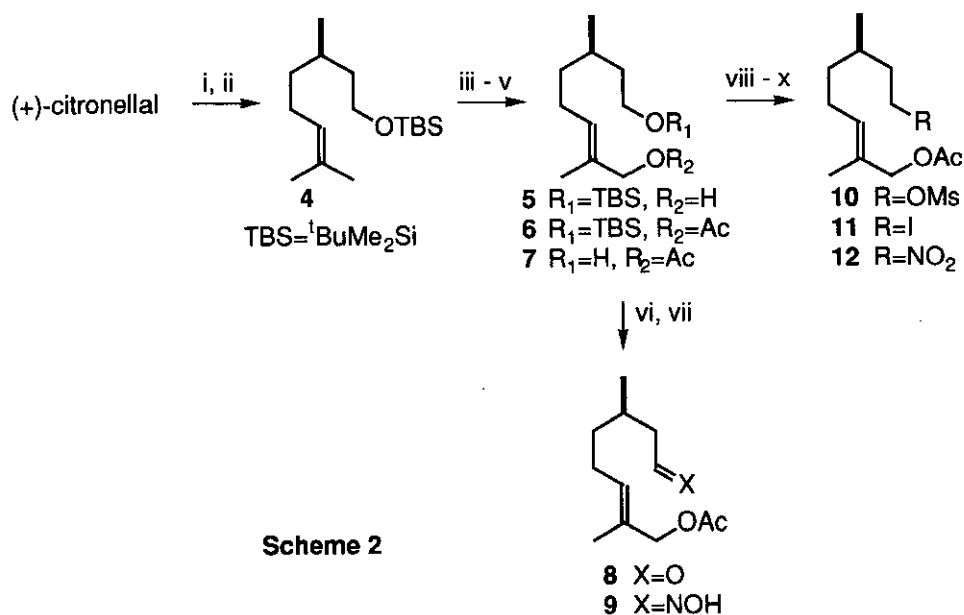
Scheme 1

Our first concern was the evaluation of two different types of nitrile oxide precursors (**9**) and (**12**) for the availability (including the chemical yield) and the reactivity on their cycloaddition reactions. The oxime acetate (**9**) was initially synthesized through a straightforward route. The *tert*-butyldimethylsilyl (TBS) ether (**4**), which was obtained from (+)-citronellal $[\alpha]_D^{+14}$, 28°, lit.,⁸ $[\alpha]_D$

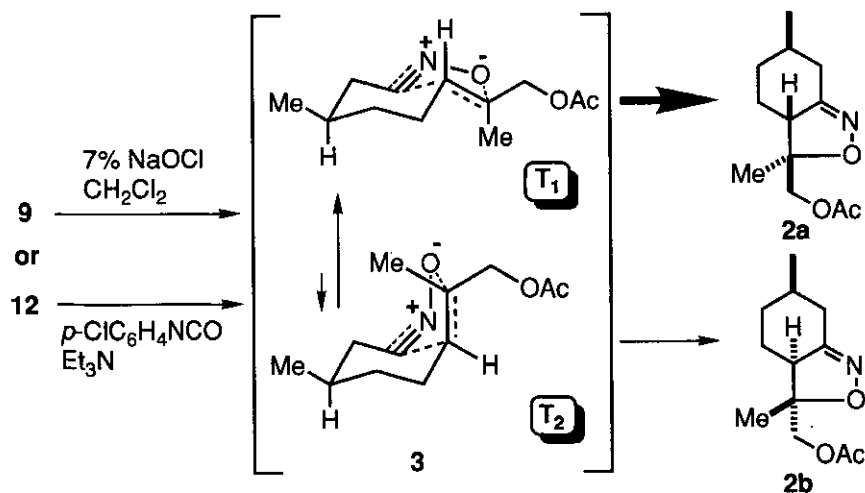
+17, 38°} by sodium borohydride reduction followed by silylation, was treated with a stoichiometric amount of selenium dioxide⁹ in pyridine-ethanol under reflux to afford the allyl alcohol (5) in at best 31 % yield. The allylic hydroxylation was best carried out according to the protocol of Sharpless¹⁰ by using an excess of *tert*-butyl hydroperoxide in methylene chloride in the presence of a catalytic amount of selenium dioxide to provide a much improved yield of 62 %. Acetylation and subsequent desilylation with tetra-*n*-butylammonium fluoride yielded the alcohol (7) which was oxidized by the method of Swern to afford the aldehyde (8). Immediate treatment of the crude 8 with hydroxylamine hydrochloride and sodium acetate produced the required oxime (9) in 87 % overall yield from 5. On the other hand, the nitroalkane (12), the other nitrile oxide precursor, was assembled from the alcohol (7) by standard manipulations. Thus, sequential mesylation, iodination followed by treatment of the resulting iodide (11) with silver nitrite¹¹ gave 12 in 70 % overall yield from 5. (Scheme 2)

Since two substrates (9) and (12) were in hand, their intramolecular [3+2] dipolar cycloaddition reactions¹² were investigated. When the oxime (9) was allowed to react with 7 % aqueous sodium hypochlorite¹³ in methylene chloride at room temperature for 6 h, the cycloadduct isoxazoline was obtained in 76 % yield as an inseparable mixture of two diastereoisomers (2a) and (2b) in a ratio of 10 : 1, that was determined by the ¹H-nmr spectrum in which the methyl hydrogens at the secondary stereogenic center in the major diastereoisomer (2a) absorb at δ 1.04 as a doublet with $J=6.4$ Hz and those for the minor one (2b) appear at δ 0.94 as a doublet with the same coupling constant. Alternatively, the other substrate (12) was treated with *p*-chlorophenyl isocyanate¹⁴ at room temperature for 14 h to provide a mixture of diastereomeric cycloadducts (2a) and (2b) in almost the same ratio as for (9) in 91 % yield. From these results, equality of the efficiency for the preparation of isoxazolines (2) via the two different routes [(7) \rightarrow (9) \rightarrow (2) : 65 %; (7) \rightarrow (12) \rightarrow (2) : 64 %] could be revealed.

Although the exact stereostructure of the major cycloadduct could not be determined at this stage, it was tentatively assigned as shown in Scheme 3 from the mechanistic point of view.¹⁵ Namely, the transition state T_1 leading to 2a would be sterically more favored over the other possible one T_2 which produces the diastereomer (2b) (Scheme 3). A mixture of diastereoisomers is generated in the cycloaddition reactions, but this is of little consequence in view of the subsequent conversion into menthofuran.

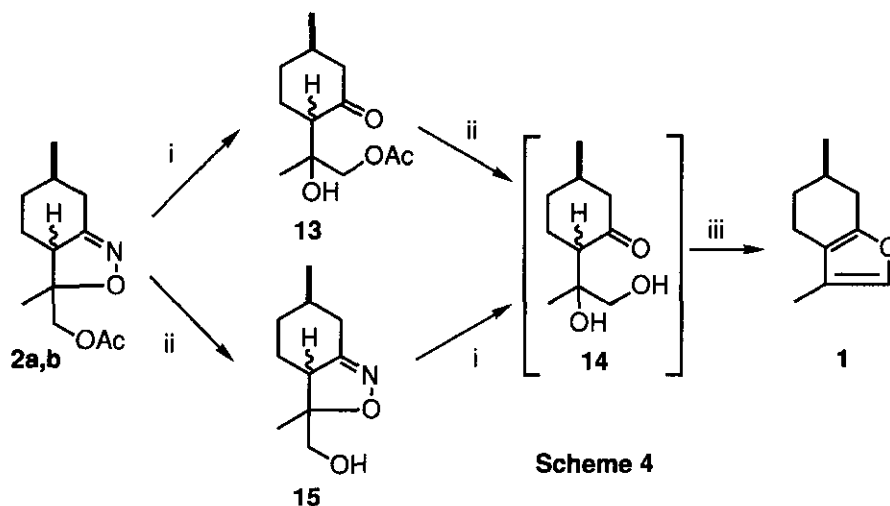


Reagents : i, NaBH₄; ii, ^tBuMe₂SiCl, imidazole, DMF; iii, SeO₂, ^tBuOOH; iv, Ac₂O, pyridine; v, ⁿBu₄NF; vi, (COCl)₂, DMSO, Et₃N; vii, NH₂OH·HCl, AcONa; viii, MsCl, Et₃N; ix, NaI; x, AgNO₂.



With the key isoxazolines (**2a**) and (**2b**) in hand, we examined the conversion of these to menthofuran (**1**) by the same sequence as has been previously described by us.⁶ Reaction of a

mixture of **2a** and **2b** with methyl borate and a catalytic amount of W-2 Raney nickel in aqueous methanol under a hydrogen atmosphere¹⁶ provided 91 % yield of an inseparable diastereomeric mixture of the β -hydroxy- γ -acetoxy ketone (**13**). Then hydrolysis of **13** with lithium hydroxide followed by immediate treatment of the resulting dihydroxy ketone (**14**) with hydrochloric acid at room temperature for 1 h afforded (+)-menthofuran (**1**) in 38 % yield after purification by chromatography on silica gel. The synthetic compound was indistinguishable (¹H-nmr and ir) from authentic material and showed $[\alpha]_D^{25} +75.45^\circ$ ($c=1.10$, EtOH){lit.,¹⁷ $[\alpha]_D^{25} +87.46^\circ$ ($c=1.87$, EtOH)}. Since it was assumed that the lower yield of **1** was presumably due to the lability of **13** and/or **14** under the conditions for the alkaline hydrolysis, we sought to change the order of reaction sequence in the transformation. To this end, a diastereomeric mixture of the isoxazoline acetates (**2a**) and (**2b**) was initially treated with lithium hydroxide to yield the alcohol (**15**), which was then exposed to the conditions of reductive hydrolysis to give a mixture of the dihydroxy ketone (**14**) and a small amount of menthofuran (detected on tic), which was immediately treated with a catalytic amount of *p*-toluenesulfonic acid for 40 min to produce menthofuran (**1**) in 77 % yield. These results demonstrated that the latter sequence was expectedly superior to the former route.



Reagents : i, H₂, Raney Ni, (MeO)₃B, MeOH, H₂O; ii, LiOH·H₂O, THF, H₂O; iii, *p*-TsOH, CH₂Cl₂.

In conclusion, we have described a total synthesis of (+)-menthofuran in at the best 31 % overall yield from (+)-citronellal. This synthesis demonstrates the further utility of the fused furan construction methodology based on an intramolecular nitrile oxide cycloaddition reaction for the synthesis of the furanoterpenes.

EXPERIMENTAL SECTION

Melting points were determined by a Yanagimoto MP-S2 apparatus and are uncorrected. Ir spectra were recorded on a Parkin Elmer 1720FT-IR and a Hitachi 215 spectrophotometers. ¹H-Nmr spectra were recorded at 200 MHz on a JEOL JMS FX-200 spectrometer in deuteriochloroform solutions with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (from TMS). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Ordinary mass spectra and high resolution mass spectra were measured with a JEOL JMS-D300 mass spectrometer. Optical rotations were determined on a Union Giken PM-201 polarimeter. Tlc was carried out with E. Merck Silica gel GOF-254 (0.25 mm thickness) precoated tlc plates. Column chromatography was carried out with silica gel (Kieselgel 60, 70-230 mesh, E. Merck) or with neutral alumina (Aluminium oxide 90, activity I, E. Merck). All reactions were run under an atmosphere of argon. Solvents were freshly distilled prior to use: tetrahydrofuran (THF), toluene and diethyl ether (Et₂O) were distilled from sodium; dichloromethane (CH₂Cl₂) and chloroform (CHCl₃) were distilled from phosphorus pentoxide and kept over 4A molecular sieves; *N,N*-dimethylformamide (DMF) was distilled under reduced pressure after stirring with calcium hydride for 14-15 h. Unless otherwise noted, all reaction mixtures were dried, after workup, over anhydrous magnesium sulfate.

(+)-(6*R*)-8-*tert*-Butyldimethylsilyloxy-2,6-dimethyloct-2-ene (4). Imidazole (1.77 g, 26.0 mmol) and *tert*-butyldimethylchlorosilane (3.14 g, 20.8 mmol) were added to a stirred solution of citronello (2.71 g, 17.3 mmol), prepared from (+)-citronellal, $\{[\alpha]_D^{25} + 14.28^\circ$ ($c=0.49$, CHCl₃), lit.,⁸ $[\alpha]_D^{27} + 17.38^\circ$ ($c=1.06$, CHCl₃)}, by reduction with sodium borohydride (NaBH₄), in DMF (54 ml). After being stirred at room temperature for 1 h, water was added and the mixture was extracted with Et₂O. The extracts were washed with brine and dried. Evaporation of the solvent followed by chromatography

on silica gel (hexane-ethyl acetate, 9 : 1, v/v) gave the TBS ether (**4**) (4.69 g, 100 %) as a colorless oil: $[\alpha]_D^{25} +3.33^\circ$ ($c=2.40$, CHCl_3); $^1\text{H-nmr}$ (200 MHz) δ 0.05 (6H, s, SiMe_2), 0.89 (12 H, m, ^tBu and Me), 1.00 - 1.55 (5H, m, $\text{CH}_2 \times 2$ and CH), 1.60 (3H, br s, olefinic Me), 1.68 (3H, d, $J=1.0$ Hz, olefinic Me), 1.95 (2H, m, $\text{CH}_2\text{CH}=\text{C}$), 3.63 (2H, m, CH_2OTBS) and 5.10 (1H, m, olefinic H); ms m/z 270 (M^+); HRms Calcd for $\text{C}_{16}\text{H}_{34}\text{OSi}$: 270.2379. Found: 270.2350.

(+)-(6R)-(2E)-8-tert-Butyldimethylsilyloxy-2,6-dimethyloct-2-en-1-ol (5). (a) *Stoichiometric selenium dioxide (SeO_2) oxidation:* A solution of a mixture of **4** (3.0 g, 11.1 mmol), freshly sublimed SeO_2 (0.62 g, 5.54 mmol) and pyridine (1.82 g, 22.5 mmol) in dry ethanol (30 ml) was heated under reflux for 4 h. After evaporation of the solvent, water was added to the residue and the mixture was extracted with ethyl acetate. The extracts were washed with brine and dried. Evaporation of the solvent followed by chromatography on silica gel (hexane-ethyl acetate, 8 : 1, v/v) gave the alcohol (**5**) (1.0 g, 31 %) as a light yellow oil: $[\alpha]_D^{25} +2.38^\circ$ ($c=0.84$, CHCl_3); ir (neat) 3350 cm^{-1} (OH); $^1\text{H-nmr}$ (200 MHz) δ 0.05 (6H, s, SiMe_2), 0.89 (9 H, s, ^tBu), 0.89 (3H, d, $J=6.1$ Hz, CH_3CH), 1.11 - 1.63 (6H, m, $\text{CH}_2 \times 2$, CH and OH, D_2O exchangeable), 1.67 (3H, br s, olefinic Me), 2.04 (2H, m, $\text{CH}_2\text{CH}=\text{C}$), 3.63 (2H, m, CH_2OTBS), 4.00 (2H, br s, CH_2OH) and 5.40 (1H, m, olefinic H); ms m/z 229 ($\text{M}^+ - ^t\text{Bu}$). Anal. Calcd for $\text{C}_{16}\text{H}_{34}\text{O}_2\text{Si}$: C, 67.07; H, 11.96. Found: C, 66.59; H, 11.68.

(b) *Catalytic SeO_2 oxidation:* 70 % *tert*-Butyl hydroperoxide (3.99 ml, 31.0 mmol) was added dropwise to a stirred solution of SeO_2 (0.86 g, 7.75 mmol) in dry CH_2Cl_2 (60 ml) and the solution was stirred at room temperature for 0.5 h. To the mixture was added dropwise a solution of **4** (4.2 g, 15.5 mmol) in dry CH_2Cl_2 (20 ml), the resulting mixture was stirred at the same temperature for 2.5 h and then dimethyl sulfide (1.92 g, 31.0 mmol) was added. After being stirred at room temperature for 0.5 h, ethanol (10 ml) was added and the mixture was cooled to 0°C . To the cooled solution was added portionwise NaBH_4 (1.17 g, 30.9 mmol) and the resulting solution was further stirred at 0°C for 0.5 h. After filtration through a pad of Celite, the filtrate was washed with brine and dried. Evaporation of the solvent followed by chromatography on silica gel (hexane-ethyl acetate, 99 : 1, v/v) recovered **4** (0.33 g). From more polar fractions (hexane-ethyl acetate, 9 : 1, v/v), the alcohol (**5**) (2.58 g, 62 %, based on the consumed starting material), was obtained as a colorless oil, which was identical with the sample prepared above.

(+)-(6*R*)-(2*E*)-1-Acetoxy-8-*tert*-butyldimethylsilyloxy-2,6-dimethyloct-2-ene (6). Acetic anhydride (4.33 g, 42.4 mmol) was added to a solution of the alcohol (5) (870 mg, 3.04 mmol) in pyridine (4 ml, 49 mmol) at 0 °C. After being stirred at room temperature for 2 h, the solvent was evaporated and the residue was extracted with CH₂Cl₂. The extracts were successively washed with saturated (sat.) aqueous (aq.) NaHCO₃, water, 5 % aq. HCl and brine and dried. Removal of the solvent followed by chromatography on silica gel (hexane-ethyl acetate, 19 : 1, v/v) provided the acetate (6) (998 mg, 100 %) as a colorless oil: [α]_D²⁵ +3.84° (c=1.04, CHCl₃); ir (neat) 1745 cm⁻¹ (C=O); ¹H-nmr (200 MHz) δ 0.05 (6H, s, SiMe₂), 0.89 (9 H, s, ^tBu), 0.89 (3H, d, J=6.4 Hz, CH₃CH), 1.11 - 1.62 (5H, m, CH₂x2, and CH), 1.65 (3H, br s, olefinic Me), 2.03 (2H, m, CH₂CH=C), 2.07 (3H, s, COCH₃), 3.63 (2H, m, CH₂OTBS), 4.45 (2H, br s, CH₂OAc) and 5.45 (1H, m, olefinic H); ms *m/z* 271 (M⁺ - ^tBu); HRMs Calcd for C₁₄H₂₇O₃Si: 271.1729. Found: 271.1731.

(+)-(6*R*)-(2*E*)-1-Acetoxy-8-hydroxy-2,6-dimethyloct-2-ene (7). Tetra- η -butylammonium fluoride (1.0 M in THF, 2.0 ml, 2.0 mmol) was added dropwise to a stirred solution of 6 (650 mg, 1.98 mmol) in dry THF (13 ml) at 0 °C. The mixture was allowed to warm to room temperature under stirring for 3 h and the mixture was extracted with ethyl acetate after addition of water. The extracts were washed with brine, dried and the solvent was evaporated to give a residue which was chromatographed on silica gel (hexane-ethyl acetate, 4 : 1, v/v) to afford the alcohol (7) (424 mg, 100 %) as a colorless oil: [α]_D²⁵ +4.00° (c=2.00, CHCl₃); ir (neat) 3410 (OH) and 1735 cm⁻¹ (C=O); ¹H-nmr (200 MHz) δ 0.92 (3H, d, J=6.6 Hz, CH₃CH), 1.11 - 1.60 (6H, m, CH₂x2, CH and OH, D₂O exchangeable), 1.66 (3H, s, olefinic Me), 2.05 (2H, m, CH₂CH=C), 2.08 (3H, s, COCH₃), 3.68 (2H, m, CH₂OH), 4.45 (2H, br s; CH₂OAc) and 5.45 (1H, m, olefinic H); ms *m/z* 155 (M⁺ - OAc). Anal. Calcd for C₁₂H₂₂O₃: C, 67.26; H, 10.35. Found: C, 67.72; H, 10.01.

(-)-(6*R*)-(2*E*)-1-Acetoxy-7-hydroxyimino-2,6-dimethylhept-2-ene (9). Dimethyl sulfoxide (88 mg, 1.12 mmol) was added to a stirred solution of oxalyl chloride (71 mg, 0.56 mmol) in dry CH₂Cl₂ (3 ml) at -78 °C, and a solution of the alcohol (7) (100 mg, 0.47 mmol) in dry CH₂Cl₂ (2 ml) was then added to the chilled solution. After the solution had been stirred at the same temperature for 5 min,

triethylamine (236 mg, 2.33 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature for 1 h. After addition of water, the mixture was extracted with CH_2Cl_2 and the extracts were washed with brine and dried. Evaporation of the solvent gave the crude aldehyde (**8**) (97 mg, 98%), a colorless oil, which was used to the next reaction without further purification. A solution of the crude aldehyde (**8**) (97 mg, 0.46 mmol) in dry benzene (1.5 ml) was added to a stirred solution of hydroxylamine hydrochloride (67 mg, 0.93 mmol) and sodium acetate (96 mg, 1.17 mmol) in dry benzene (1.5 ml) at room temperature. After being stirred at the same temperature for 2 h, the organic phase was washed with brine, and dried and the solvent was evaporated to leave a residue which was chromatographed on silica gel (hexane-ethyl acetate, 4 : 1, v/v) to give the oxime (**9**) (92 mg, 87%), a colorless oil, as an inseparable mixture of two diastereoisomers: $[\alpha]_D^{25} -0.96^\circ$ ($c=1.04$, CHCl_3); ir (neat) 3365 (OH) and 1740 cm^{-1} (C=O); $^1\text{H-nmr}$ (200 MHz) δ 0.95 (3/2H, d, $J=6.7$ Hz, CH_3CH), 0.97 (3/2H, d, $J=6.7$ Hz, CH_3CH), 1.34 (3H, m, CH_2 and CH), 1.66 (3H, s, olefinic Me), 2.00 - 2.46 (4H, m, $\text{CH}_2\text{CH}=\text{C}$ and $\text{CH}_2\text{CH}=\text{N}$), 2.08 (3H, s, COCH_3), 4.45 (2H, br s, CH_2OAc), 5.44 (1H, m, olefinic H), 6.75 (1/2H, t, $J=4.6$ Hz, $\text{CH}=\text{N}$), 7.43 (1/2H, t, $J=5.1$ Hz, $\text{CH}=\text{N}$) and 8.13 (1H, br s, OH, D_2O exchangeable); ms m/z 227 (M^+). Anal. Calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.30; H, 9.68; N, 5.90.

(-)-(6R)-(2E)-1-Acetoxy-8-iodo-2,6-dimethyloct-2-ene (11). Diisopropylethylamine (364 mg, 2.82 mmol) and methanesulfonyl chloride (281 mg, 2.45 mmol) were added to a stirred solution of the alcohol (**7**) (465 mg, 2.17 mmol) in dry CH_2Cl_2 (9 ml) at 0 °C. After being stirred at room temperature for 1 h, the mixture was quenched by the addition of water and extracted with CH_2Cl_2 . The extracts were washed successively with 5% aq. HCl, sat. aq. NaHCO_3 and brine and dried. Evaporation of the solvent left the crude mesylate (**10**) (645 mg, 100%), yellow oil, which was taken up into dry acetone (10 ml). To the solution was added sodium iodide (650 mg, 4.34 mmol) and the mixture was heated under reflux for 4 h. After filtration of the resulting inorganic material, the filtrate was removed to give a residue which was extracted with ethyl acetate. The extracts were washed with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ and brine, and dried. Concentration of the solvent followed by chromatography on silica gel (hexane-ethyl acetate, 4 : 1, v/v) afforded the iodide (**11**) (682 mg, 97%) as a colorless oil: $[\alpha]_D^{26} -2.91^\circ$ ($c=1.03$, CHCl_3); ir (neat) 1735 cm^{-1} (C=O); $^1\text{H-nmr}$ (200 MHz) δ 0.

90 (3H, d, $J=6.4$ Hz, CH_3CH), 1.11-1.61 (5H, m, $\text{CH}_2 \times 2$ and CH), 1.66 (3H, br s, olefinic Me), 2.05 (2H, m, $\text{CH}_2\text{CH}=\text{C}$), 2.08 (3H, s, COCH_3), 3.19 (2H, m, CH_2I), 4.45 (2H, br s, CH_2OAc) and 5.44 (1H, m, olefinic H); ms m/z 324 (M^+). Anal. Calcd for $\text{C}_{12}\text{H}_{21}\text{O}_2\text{I}$: C, 44.46; H, 6.53. Found: C, 44.35; H, 6.76.

(+)-(6*F*)-(2*E*)-1-Acetoxy-8-nitro-2,6-dimethyloct-2-ene (12). A solution of the iodide (11) (1.30 g, 4.01 mmol) in dry Et_2O (10 ml) was added dropwise to a stirred solution of silver nitrite (1.23 g, 7.99 mmol) in dry Et_2O (10 ml) at 0°C . After being stirred at 0°C for 24 h and at room temperature for 48 h, the mixture was filtered and the filtrate was evaporated off to leave a residue which was chromatographed on silica gel (hexane-ethyl acetate, 19 : 1, v/v) to provide 12 (698 mg, 72 %) as a colorless oil: $[\alpha]_D^{25} +3.96^\circ$ ($c=1.01$, CHCl_3); ir (neat) 1735 ($\text{C}=\text{O}$) and 1555 cm^{-1} (NO_2); $^1\text{H-nmr}$ (200 MHz) δ 0.96 (3H, d, $J=6.3$ Hz, CH_3CH), 1.11-1.91 (5H, m, $\text{CH}_2 \times 2$ and CH), 1.66 (3H, br s, olefinic Me), 2.07 (2H, m, $\text{CH}_2\text{CH}=\text{C}$), 2.08 (3H, s, COCH_3), 4.41 (4H, m, CH_2NO_2 and CH_2OAc) and 5.42 (1H, m, olefinic H); ms m/z 243 (M^+). Anal. Calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.89; H, 9.09; N, 5.44.

The Isoxazoline Acetate (2). (a) From the oxime (9): 7 % Aq. NaOCl (5.0 ml, 4.67 mmol) was added to a solution of the oxime (9) (708 mg, 3.12 mmol) in CH_2Cl_2 (14 ml) at room temperature. After being stirred at the same temperature for 5.5 h, the mixture was extracted with CH_2Cl_2 , and the extracts were washed with brine and dried. Evaporation of the solvent followed by chromatography on silica gel (hexane-ethyl acetate, 93 : 7, v/v) gave 2 (535 mg, 76 %), colorless prisms, mp $52 - 53^\circ\text{C}$ (from hexane), a 10 : 1 inseparable mixture of two diastereoisomers: $[\alpha]_D^{25} -74.75^\circ$ ($c=1.03$, CHCl_3); ir (neat) 1740 cm^{-1} ($\text{C}=\text{O}$); $^1\text{H-nmr}$ (200 MHz) δ 0.94 (3/11H, d, $J=6.4$ Hz, CH_3CH), 1.04 (30/11H, d, $J=6.4$ Hz, CH_3CH), 1.09-1.89 (6H, m, $\text{CH}_2 \times 2$, CH and $\text{CHHC}=\text{N}$), 1.27 (3H, s, Me), 2.09 (3H, s, COCH_3), 2.76 (2H, m, $\text{CHC}=\text{N}$ and $\text{CHHC}=\text{N}$) and 4.06 (2H, m, CH_2OAc); ms m/z 225 (M^+). Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.63; H, 8.82; N, 6.00.

(b) From the nitroalkane (12): *p*-Chlorophenyl isocyanate (204 mg, 1.33 mmol) and Et_3N (145 mg, 1.43 mmol) were added successively to a stirred solution of 12 (150 mg, 0.62 mmol) in dry benzene (3

ml) at room temperature. After being stirred at the same temperature for 14 h, the mixture was taken up into CHCl_3 , and the solution was again filtered. Concentration of the filtrate followed by chromatography on silica gel afforded **2** (127 mg, 91 %) a mixture of two diastereoisomers, which was identical in all respects with the sample prepared above.

Reductive Hydrolysis of 2. Trimethyl borate (740 mg, 7.22 mmol) was added to a suspension of a mixture of the isoxazoline (**2**) (163 mg, 0.72 mmol) and a catalytic amount of Raney nickel (W-2) in methanol (7 ml)-water (0.6 ml), and the resulting mixture was stirred under a hydrogen pressure of 2.0 Kg/cm^2 at room temperature for 11 h. After filtration through a pad of Celite, the filtrate was concentrated to leave a residue which was extracted with CHCl_3 . The extracts were washed with brine, dried, and evaporated to give an oily residue which was chromatographed on silica gel (hexane-ethyl acetate, 4 : 1, v/v) to provide **13** (150 mg, 91 %), a colorless oil, as an inseparable mixture of diastereoisomers: $[\alpha]_D^{25} +5.83^\circ$ (c=1.20, CHCl_3); ir (neat) 3485 (OH), 1740 (C=O) and 1690 cm^{-1} (C=O); $^1\text{H-nmr}$ (200 MHz) δ 0.96 (3/22H, d, J=6.1 Hz, CH_3CH), 1.04 (6/22H, d, J=6.1 Hz, CH_3CH), 1.21 (3H, s, Me), 1.27-1.98 (6H, m, $\text{CH}_2 \times 2$, CH and OH, D_2O exchangeable), 2.09 (1H, m, CHHC=O), 2.10 (3H, s, COCH_3), 2.35 - 2.63 (2H, m, CHC=O and CHHC=O) and 4.04 (2H, s, CH_2OAc); ms m/z 169 ($\text{M}^+ - \text{OAc}$). Anal. Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_4$: C, 63.14; H, 8.83. Found: C, 62.82; H, 8.40.

Hydrolysis of 2. Lithium hydroxide monohydrate (100 mg, 2.37 mmol) was added to a stirred solution of **2** (485 mg, 2.15 mmol), a mixture of two diastereoisomers, in THF (12 ml)-water (7 ml) at room temperature. After being stirred at the same temperature for 2 h, the solvent was evaporated off to leave a residue which was extracted with CHCl_3 . The extracts were washed with brine, dried and evaporated to give a residue which was chromatographed on silica gel (hexane-ethyl acetate, 6 : 1, v/v) to afford the alcohol (**15**) (363 mg, 92 %), an inseparable mixture of two diastereoisomers, as a colorless oil: $[\alpha]_D^{26} -85.18^\circ$ (c=1.08, CHCl_3); ir (CHCl_3) 3410 cm^{-1} (OH); $^1\text{H-nmr}$ (200 MHz) δ 0.93 (1/3H, d, J=6.4 Hz, CH_3CH), 1.04 (8/3H, d, J=6.4 Hz, CH_3CH), 1.20 (3H, s, Me), 1.34 - 1.92 (6H, m, $\text{CH}_2 \times 2$, CH and CHHC=N), 2.23 (1H, br s, OH, D_2O exchangeable), 2.63 - 3.03 (2H, m, CHC=N

and $\text{CHHC}=\text{N}$) and 3.37 - 3.68 (2H, m, CH_2OH); ms m/z 183 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{17}\text{NO}_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.53; H, 9.79; N, 7.16.

(+)-Menthofuran (1). (a) *From 13*: Lithium hydroxide monohydrate (74 mg, 1.8 mmol) was added to a stirred solution of **13** (134 mg, 0.59 mmol) in THF (3 ml)-water (1 ml) at room temperature. After being stirred at the same temperature for 1 h, conc. HCl was added to acidify and the resulting mixture was further stirred for 1 h. The mixture was extracted with ethyl acetate, and the extracts were washed with brine, dried and evaporated to give a residue which was chromatographed on silica gel (hexane-ethyl acetate, 19 : 1, v/v) to afford (+)-menthofuran (**1**) (33 mg, 38 %) as a colorless oil: $[\alpha]_{\text{D}}^{25} +75$. 45° (c=1.10, EtOH) {lit.,¹⁷ $[\alpha]_{\text{D}}^{25} +87$. 46° (c=1.87, EtOH)}; $^1\text{H-nmr}$ (200 MHz) δ 1.07 (3H, d, $J=6.6$ Hz, CH_3CH), 1.33 (1H, m, CH_3CH), 1.84 (2H, m, CH_2), 1.91 (3H, d, $J=1.2$ Hz, $\text{CH}_3\text{-C}=\text{CH}$), 2.13 (1H, m, CHH), 2.34 (2H, m, CH_2), 2.65 (1H, dd, $J=15.1$ and 5.0 Hz, $\text{CH}_3\text{-CH-CHH-C}=\text{}$), and 7.03 (1H, br s, $\text{C}=\text{CH-O}$); ms m/z 150 (M^+); HRms Calcd for $\text{C}_{10}\text{H}_{14}\text{O}$: 150.1045. Found: 150.1055.

(b) *From 15*: Trimethyl borate (6.13 g, 59.0 mmol) was added to a suspension of **15** (1.08 g, 5.90 mmol) and a trace amount of Raney nickel (W-2) in methanol (40 ml)-water (4 ml), and the resulting mixture was stirred under a hydrogen pressure of 2.0 Kg/cm^2 at room temperature for 9 h. After filtration through a pad of Celite, the filtrate was concentrated to give a residue which was extracted with CHCl_3 . The extracts were washed with brine, dried, and evaporated to leave a residue which was taken up into CH_2Cl_2 (20 ml). A catalytic amount of *p*-toluenesulfonic acid was added to the solution and the mixture was stirred at room temperature for 40 min. Water was added to the mixture, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 . The combined extracts were washed with brine, dried, and chromatographed on alumina (hexane) to afford (+)-menthofuran (**1**) (740 mg, 84 %) as a colorless oil. (+)-Menthofuran thus obtained was further purified by Kugelrohr distillation, bp₂₅ 85°C (lit.,^{5h} bp_{2.8} 48°C).

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