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A General Synthetic Approach to 5-Alkyl-2(*5H*)furanones *Via* 1,3-Dipolar Cycloaddition

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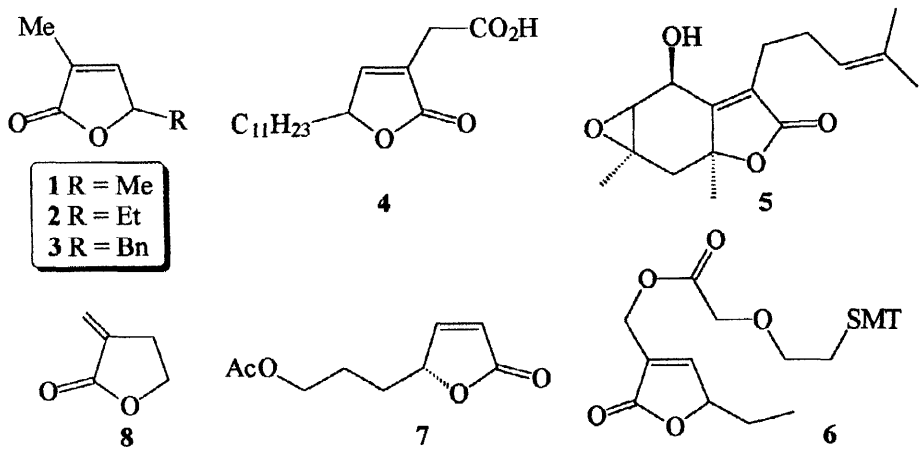
Abstract: [3+2] Cycloaddition methodology provides a general and efficient access to 5-alkyl substituted 2(*5H*)furanones. The synthetic approach has been exploited towards the synthesis of naturally occurring butenolides.

Unsaturated five-membered lactones, butenolides, form an important and various group of naturally occurring oxygen heterocycles, encompassing both fatty acid and terpenoidal biosynthetic origins.[1] Many of such compounds show interesting and different properties; *e.g.* butenolide **1** is a component of mushroom flavor;[2] **2** has fungicidal activity;[3] **3** is a metabolite from *Streptomices griseus*,[4] acarenoic acid **4** is an example of long-chain butenolides present in lichens;[5] paniculides **5** constitute a family of highly oxygenated sesquiterpenes isolated from *Andrographis paniculata*.[6]

Moreover, 2(*5H*)furanones occur as intermediates in the synthesis of many products of biological interest: the lactone **6** and its substituted congeners are useful precursors in the synthesis of ethisolide, isoavenaciolide and avenaciolide which exhibit potent biological activity;[7] **7** is a key fragment in the synthesis of macrolide amphidinolide, cytotoxic against L120 murine leukemia;[8] the α-methylene-γ-butyrrolactone structural unit **8** is present in compounds showing significant antiviral and antitumor activities.[9]



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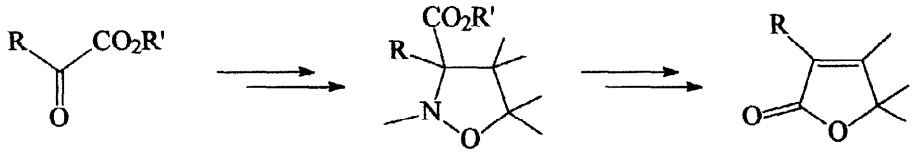
These features have spurred the continued interest in improving known synthetic methods and exploring new ones, which resulted in the development of several interesting and novel synthetic routes.[10,11]

In connection with our work dealing with the exploitation of five-membered *N,O*-heterocycles, easily accessible *via* 1,3-dipolar cycloaddition, as valuable intermediates for organic synthesis,[12,13] we were intrigued by the possibility of effecting the conversion of 3-alkoxycarbonylisoxazolidines **10**, prepared from the corresponding α-ketoesters **9**, into butenolides **11** *via* the ring-opening of the heterocyclic nucleus, followed by intramolecular lactonization, according to the general strategy shown in scheme 1.[14]



9 **10** **11**

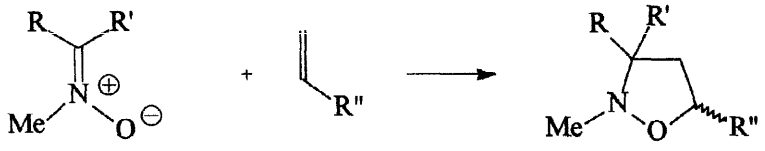
Scheme 1

Preliminary results have been previously described;[15] in this paper we present further experimental details for our synthetic efforts in this area, which have resulted in a general synthetic way towards a series of natural and biologically important butenolides. The method reported herein provides a flexible reaction pathway leading to a variety of α,β-dialkylbutenolides, according to the substitution pattern present on dipole and dipolarophile.

RESULTS AND DISCUSSION

The synthetic approach to 2(*5H*)furanones is outlined in scheme 2. Nitrones **12**, prepared from methyl pyruvate and *N*-methyl hydroxylamine, were reacted with alkenes **13** to give isoxazolidines **14** as epimeric mixtures (55-99% yields), which have not been separated.

As expected, the reaction of *C*-disubstituted nitrones **12** resulted in the observation of a poor stereoselectivity, leading to the formation of a nearly equimolar mixture of the epimeric isoxazolidines.

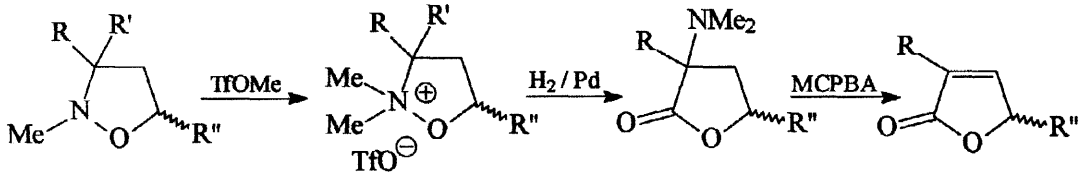


12 **13** **14**

Product	R	R'	R"	Yield %
14a	*n*-Butyl	CO_2Et	Me	68
14b	*s*-Butyl	CO_2Et	Me	68
14c	*n*-Pentyl	CO_2Et	Me	58
14d	*n*-Hexyl	CO_2Et	Me	55
14e	Me	CO_2Me	CH_2OH	99
14f	Me	CO_2Et	CH_2CH_2Ph	75

Scheme 2

Conversion of isoxazolidines **14** into butenolides **17**[16] has been performed by a three-step sequence (Scheme 3): a) treatment with methyl trifluoromethanesulfonate in anhydrous CCl_4 at 0 °C for 3 h afforded, in a nearly quantitative yield, the epimeric isoxazolidinium salts **15** as white sticky oils; b) subsequent hydrogenolysis with 10% palladium on activated carbon in dry methanol at 50 °C for 36 h led to epimeric α-amino-γ-lactones **16** in high yields (90-95%); c) finally, formation of the 3,4-double bond has been accomplished by Cope elimination of the transient *N*-oxides obtained by treatment of **16** with *m*-chloroperbenzoic acid in dry CH_2Cl_2 at 0 °C for 4 h.



14 **15** **16** **17**

Product	R	R'	R"	Overall yield %
17a	*n*-Butyl	CO_2Et	Me	68
17b	*s*-Butyl	CO_2Et	Me	72
17c	*n*-Pentyl	CO_2Et	Me	70
17d	*n*-Hexyl	CO_2Et	Me	69
17e	Me	CO_2Me	CH_2OH	71
17f	Me	CO_2Et	CH_2CH_2Ph	77

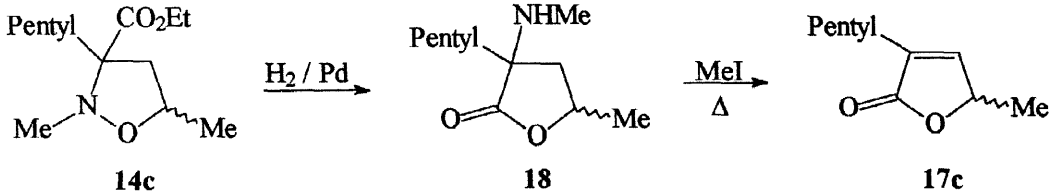
Scheme 3

Unsaturated lactones **17** have been obtained in 48-89% overall yield starting from nitrones **12**.

Structures of the compounds obtained have been assigned on the basis of analytical and spectroscopic data (see Experimental). In particular, the 3-dimethylaminotetrahydro-2-furanone epimers **16** show the methylene protons at C_4 as doublet of doublets in the range of 1.60-1.72 and 2.50-2.60 ppm respectively; H_5 resonate as multiplets at ≈ 4.50 ppm. For compounds **17** diagnostic are the resonances for vinyl hydrogens at C_4 and H_5 hydrogen, as multiplets, in the range of ≈ 7.05 and of ≈ 5.03 ppm respectively.

Noteworthy, Cope elimination occurred regioselectively to afford exclusively butenolides **17**: regioisomeric γ-methylene lactones were not detected in the crude reaction mixture.

In an alternative route, isoxazolidine **14c**, taken as model compound, was directly cleaved by hydrogenolysis to α-methylaminolactone **18c**; the subsequent treatment with CH_3I and Hofmann elimination afforded compound **17c**. However, in this case, yield is poorer than that previously obtained.

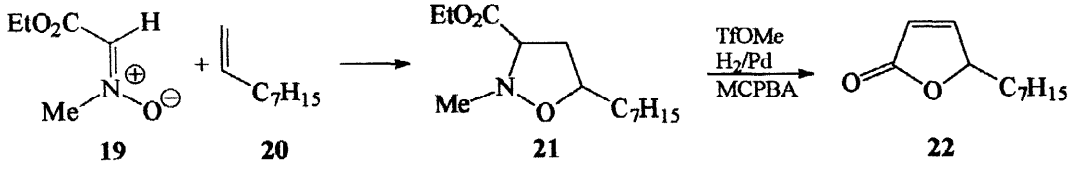


14c **18** **17c**

Scheme 4

The generality and the validity of the outlined scheme has been exploited in the synthesis of some characteristic natural butenolides.

The reaction pathway towards γ-heptylbutenolide **22**, possessing a typical peach flavour,[17] is described in scheme 5.



19 **20** **21** **22**

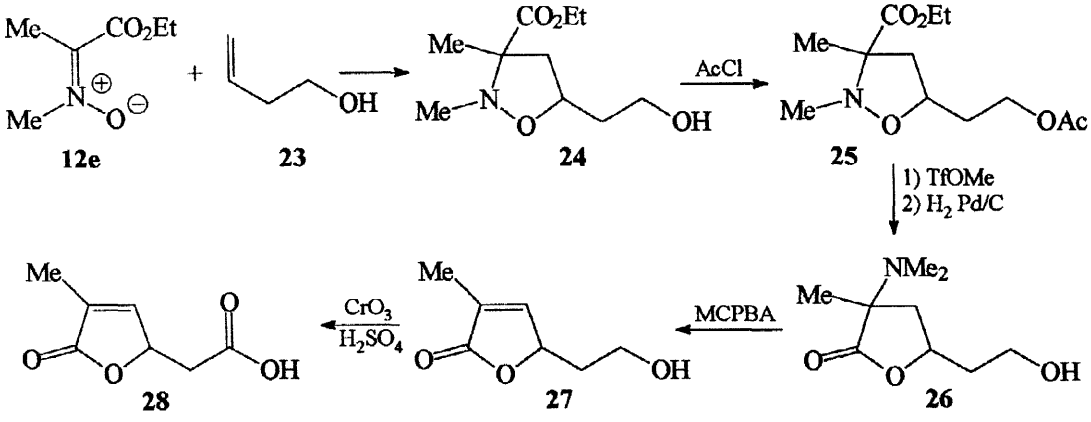
Scheme 5

The 1,3 dipolar cycloaddition of nitrone **19** with 1-nonene **20** (1:2 ratio) in toluene at 80 °C for 12 h afforded the epimeric mixture of 5-substituted isoxazolidines **21** (90% yield) as exclusive adducts. The cycloaddition proceeded with good stereoselectively giving the *trans* isomer as the major product (4:1 ratio). The relative configurational assignment of isoxazolidines **21** was attributed by NOE experiments. In particular, for *trans* epimer, a positive NOE effct observed for the ethyl group on irradiating the H_5 proton is clearly indicative of their *cis* relationship.

The subsequent treatment of the epimeric mixture with methyl triflate, followed by catalytic hydrogenation (H_2/Pd) and Cope elimination afforded the γ-heptylbutenolide **22** in a 70% overall yield starting from nitrone **19**.

The β,γ-dialkylsubstituted butenolides **28** (2-methylmuconolactone)[18] and **34** (mushroom flavour),[5] have been synthesised as reported in scheme 6 and 8 respectively.

Reaction of nitrone **12e** with 3-buten-1-ol **23** (1:1.5 ratio) in toluene at 50 °C for 30 h afforded the epimeric isoxazolidines **24**. The subsequent acetylation followed by treatment with methyl triflate, hydrogenolysis, Cope elimination and CrO_3/H_2SO_4 oxidation furnished muconolactone **28** in a 60% global yield.



12e **23** **24** **25** **26** **27** **28**

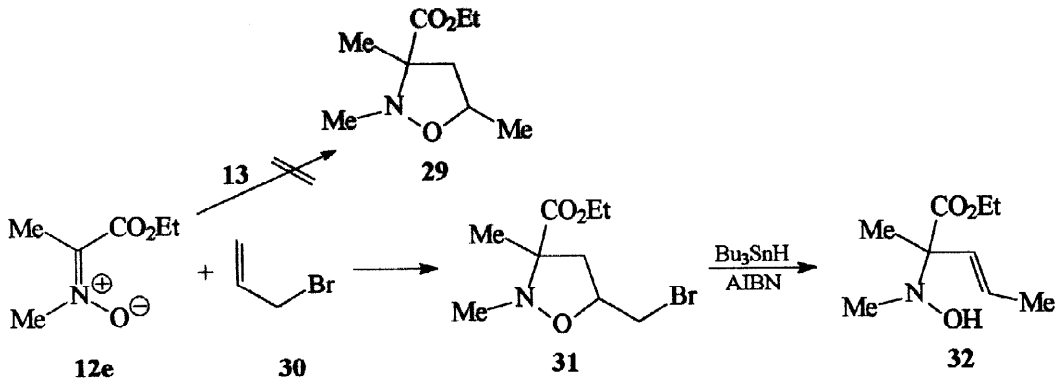
Scheme 6

The approach to 3,5-dimethyl butenolide **34** showed some severe difficulties.

In a first attempt to obtain the key intermediate 3,5-dimethylisoxazolidine **29**, treatment of nitrone **12e** with propene in decaline at various temperatures was performed. However, no useful results have been obtained, linked to the poor relative reactivity of nitrone and alkene: the reaction mixtures afforded only tarry products or starting material was recovered unaltered.

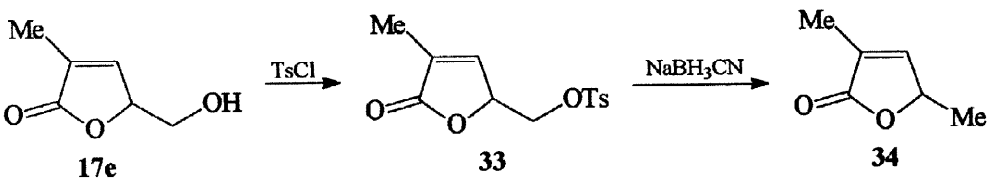
The alternative approach based on the reaction of **12e** with allyl bromide **30** to give isoxazolidine **31**, fol-

lowed by reaction with Bu_3SnH, afforded the hydroxylamine **32**, according to a reaction pathway, where Bu_3SnH promotes the removal of the bromine atom in **31** with subsequent rearrangement of the resulting radical occurring with cleavage of the pentatomic ring (Scheme 7).



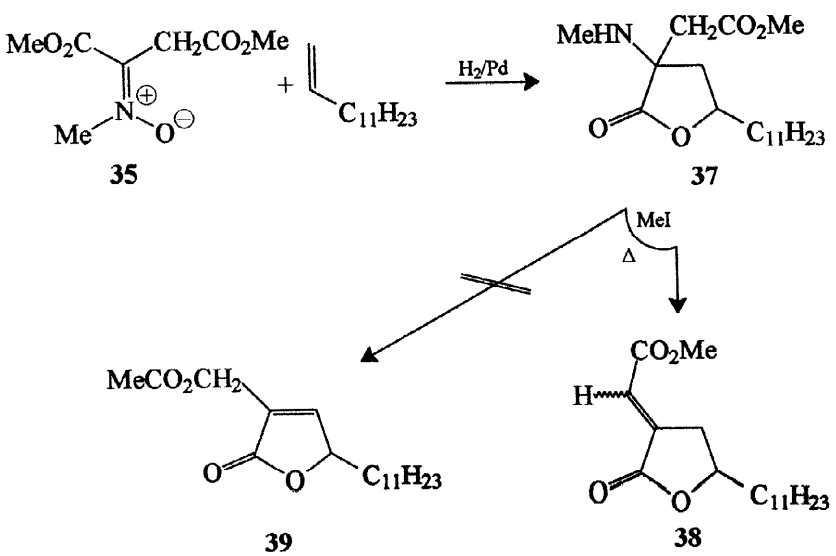
Scheme 7

Finally, good results have been obtained following the reaction route showed in scheme 8: butenolide **17e** was tosylated and then converted, with $NaCNBH_3$, to **34** in 50% yield.



Scheme 8

The synthesis of methyl isoacarenoate **38** is shown in scheme 9. Nitrone **35** was obtained from *N*-methylhydroxylamine and DMAD at room temperature.[19] Iodomethane treatment of lactone **37** led to the thermodynamically more stable compound **38** instead of the methyl acarenoate **39**.[20]



Scheme 9

In conclusion, the [3+2] cycloaddition methodology outlined herein provides a general and efficient access to α,γ-disubstituted 2(*5H*)furanones, with overall high yields and virtually complete regiochemical control. The synthetic approach has been exploited as a useful reaction route towards the synthesis of some naturally occurring butenolides as the peach lactone, the mushroom flavour, the 2-methylmuconolactone and the isoacarenoic acid.

EXPERIMENTAL

Mp were measured on a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer elemental analyzer. Infrared spectra were recorded on a Perkin-Elmer 377 instrument. ^{1}H Nmr spectra were measured on a Bruker WP 80 and 200 SY instrument in $CDCl_3$ as solvent. Chemical shifts are in ppm (δ) from TMS as internal standard. NOE difference spectra were obtained by subtracting alternatively right-off-resonance free induction decays (FIDS) from right-on-resonance-induced FIDS. Merck silica gel 60H was used for preparative short-column chromatography. Nitrones have been prepared in according to literature method.[21] Compounds **15e**, **16e** and **17a-d** have been previously reported by us.[15]

Reaction of nitrones 12a-d with propene.

General procedure. 1.5 mmol of nitrone solution in 30 ml of decalin was stirred under propene atmosphere at 150 °C for 60 h. The reaction mixture was subjected to flash-chromatography on silica gel column with cyclohexane/ethyl acetate 9:1 as eluent.

*Reaction of C-butyl-C-ethoxycarbonyl-N-methylnitrone **12a** with propene*. First elution gave epimeric mixture of 3-butyl-3-ethoxycarbonyl-2,5-dimethylisoxazolidine **14a**, 68% yield. Colorless oil. IR: ν_{max} (neat) 1730 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 0.90 (t, 6H, *J* = 7.2 Hz), 1.18-1.39 (m, 20H), 1.51 (m, 2H), 1.67 (dd, 1H, *J* = 7.7 and 12.4 Hz), 1.82-2.02 (m, 2H), 2.19 (dd, 1H, *J* = 8.7 and 12.4 Hz), 2.56 (dd, 1H, *J* = 5.9 and 12.5 Hz), 2.63 (s, 3H), 2.67 (s, 3H), 2.56 (dd, 1H, *J* = 7.4 and 12.5 Hz), 4.15-4.32 (m, 6H). ^{13}C NMR: δ ($CDCl_3$) 13.82, 14.18, 19.00, 21.44, 23.02, 27.33, 27.47, 33.68, 34.05, 38.86, 39.47, 42.55, 44.13, 60.90, 72.37, 73.17, 74.78, 171.61. Exact mass calculated for $C_{12}H_{23}NO_3$: 229.1678. Found: 229.1675. (Found: C, 62.83; H, 10.10; N, 6.09%. Calc. for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11%).

*Reaction of C-(sec-butyl)-C-ethoxycarbonyl-N-methylnitrone **12b** with propene*. First elution gave epimeric mixture of 3-(*sec*-butyl)-3-ethoxycarbonyl-2,5-dimethylisoxazolidine **14b**, 68% yield. Colorless oil. IR: ν_{max} (neat) 1730 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 0.84-0.96 (m, 12H), 1.25 (d, 3H, *J* = 7.0 Hz), 1.27 (d, 3H, *J* = 7.0 Hz), 1.29 (m, 10H), 1.78-1.94 (m, 2H), 2.17 (dd, 1H, *J* = 8.6 and 12.4 Hz), 2.38 (dd, 1H, *J* = 6.3 and 12.4 Hz), 2.59 (s, 3H), 2.61 (s, 3H), 2.75 (dd, 1H, *J* = 7.7 and 12.3 Hz), 2.83 (dd, 1H, *J* = 7.6 and 12.3 Hz), 4.11-4.30 (m, 6H). ^{13}C NMR: δ ($CDCl_3$) 12.24, 12.64, 14.24, 15.78, 18.71, 21.65, 21.91, 26.81, 36.76, 37.34, 38.38, 38.99, 39.10, 39.32, 39.76, 60.61, 72.36, 72.39, 171.42, 171.75. Exact mass calculated for $C_{12}H_{23}NO_3$: 229.1678. Found: 229.1681. (Found: C, 62.80; H, 10.09; N, 6.10%. Calc. for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11%).

*Reaction of C-ethoxycarbonyl-C-pentyl-N-methylnitrone **12c** with propene*. First elution gave epimeric mixture of 3-ethoxycarbonyl-2,5-dimethyl-3-pentylisoxazolidine **14c**, 58% yield. Colorless oil. IR: ν_{max} (neat) 1730 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 0.88 (t, 6H, *J* = 6.8 Hz), 1.18-1.34 (m, 24H), 1.51 (m, 2H), 1.70 (dd, 1H, *J* = 7.7 and 12.4 Hz), 1.90 (m, 2H), 2.19 (dd, 1H, *J* = 8.7 and 12.4 Hz), 2.55 (dd, 1H, *J* = 5.9 and 12.4 Hz), 2.63 (s, 3H), 2.66 (s, 3H), 2.96 (dd, 1H, *J* = 7.4 and 12.4 Hz), 4.19 (q, 2H, *J* = 7.1 Hz), 4.21 (q, 2H, *J* = 7.1 Hz), 4.26 (m, 2H). ^{13}C NMR: δ ($CDCl_3$) 13.80, 14.13, 18.94, 21.38, 22.23, 24.75, 24.90, 26.77, 30.05, 32.01, 33.85, 34.23, 38.80, 39.42, 42.48, 44.07, 60.83, 72.30, 73.05, 74.75, 171.53, 171.89. Exact mass calculated for

$C_{13}H_{25}NO_3$: 243.1834. Found: 243.1839. (Found: C, 63.98; H, 10.18; N, 5.79%. Calc. for $C_{13}H_{25}NO_3$: C, 64.17; H, 10.35; N, 5.76%).

Reaction of C-ethoxycarbonyl-C-hexyl-N-methylnitrone 12d with propene. First elution gave epimeric mixture of 3-ethoxycarbonyl-3-hexyl-2,5-dimethylisoxazolidine **14d**, 55% yield. Colorless oil. IR: ν_{max} (neat) 1730 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.88 (t, 6H, J = 6.7 Hz), 1.25-1.37 (m, 28H), 1.42-1.50 (m, 2H), 1.70 (dd, 1H, J = 7.7 and 12.3 Hz), 1.81-1.95 (m, 2H), 2.19 (dd, 1H, J = 8.8 and 12.4 Hz), 2.55 (dd, 1H, J = 6.5 and 12.4 Hz), 2.63 (s, 3H), 2.66 (s, 3H), 2.96 (dd, 1H, J = 7.4 and 12.3 Hz), 4.22 (q, 4H, J = 7.1 Hz), 4.25 (m, 2H). ^{13}C NMR: δ ($CDCl_3$) 13.93, 14.15, 18.97, 21.41, 22.42, 25.08, 25.23, 26.80, 29.55, 31.44, 33.92, 34.31, 38.83, 39.46, 42.58, 43.44, 44.10, 80.87, 72.33, 73.10, 74.79, 171.58, 172.35. Exact mass calculated for $C_{14}H_{27}NO_3$: 257.1991. Found: 257.1998. (Found: C, 65.80; H, 10.49; N, 5.52%. Calc. for $C_{14}H_{27}NO_3$: C, 65.34; H, 10.57; N, 5.44%).

Reaction of nitrone 12e with allyl alcohol.

Reaction of C-methoxycarbonyl-C,N-dimethylnitrone 12e with allyl alcohol. A solution of nitrone (17 mmol) in 25 ml of allyl alcohol was heated, at 75 °C for 48 h, in a sealed tube. The reaction mixture was then evaporated under reduced pressure and the residue subjected to flash-chromatography on silica gel column with $CHCl_3$/MeOH 98:2 as eluent. First elution gave epimeric mixture of 5-hydroxymethyl-3-methoxycarbonyl-2,3-dimethylisoxazolidine **14e**, 99% yield. Colorless oil. IR: ν_{max} (neat) 1735 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.39 (s, 3H), 1.41 (s, 3H), 1.99 (dd, 1H, J = 6.6 and 12.5 Hz), 2.22 (dd, 1H, J = 9.0 and 12.0 Hz), 2.61 (s, 3H), 2.64 (s, 3H), 2.73 (dd, 1H, J = 5.9 and 12.9 Hz), 2.85 (dd, 1H, J = 8.3 and 12.5 Hz), 3.67 (m, 2H), 3.68 (m, 2H), 3.76 (s, 3H), 3.77 (s, 3H), 4.28 (m, 1H), 4.31 (m, 1H). ^{13}C NMR: δ ($CDCl_3$) 19.27, 19.47, 38.43, 38.76, 40.60, 41.16, 51.98, 52.34, 63.47, 64.94, 70.00, 70.49, 76.51, 76.53, 172.41, 173.59. Exact mass calculated for $C_8H_{15}NO_4$: 189.1001. Found: 189.0998. (Found: C, 50.85; H, 8.03; N, 7.38%. Calc. for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40%).

Reaction of nitrone 12f with 4-phenyl-1-butene.

Reaction of C-ethoxycarbonyl-C,N-dimethylnitrone 12f with 4-phenyl-1-butene. A solution of nitrone (15 mmol) in 22.5 ml of 4-phenyl-1-butene was heated, at 110 °C for 12 h, in a sealed tube. The reaction mixture was then evaporated under reduced pressure and the residue subjected to flash-chromatography on silica gel column with cyclohexane/ethyl acetate 7:3 as eluent. First elution gave epimeric mixture of 3-ethoxycarbonyl-2,3-dimethyl-5-phenethylisoxazolidine **14f**, 75% yield. Colorless oil. Major isomer: IR: ν_{max} (neat) 1730 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.29 (t, 3H, J = 7.2 Hz), 1.38 (s, 3H), 1.75-2.03 (m, 2H), 2.17 (dd, 1H, J = 8.5 and 12.4 Hz), 2.58 (dd, 1H, J = 6.3 and 12.4 Hz), 2.64 (s, 3H), 2.67 (m, 2H), 4.18 (m, 1H), 4.22 (q, 2H, J = 7.2 Hz), 7.17-7.35 (m, 5H). ^{13}C NMR: δ ($CDCl_3$) 14.20, 19.92, 32.59, 35.79, 38.74, 43.88, 61.16, 70.70, 75.63, 125.78, 128.30, 128.38, 141.64, 173.19. Minor isomer: IR: ν_{max} (neat) 1730 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.28 (t, 3H, J = 7.1 Hz), 1.37 (s, 3H), 1.75 (dd, 1H, J = 7.4 and 12.4 Hz), 1.76-2.01 (m, 2H), 2.66 (s, 3H), 2.71 (m, 2H), 2.92 (dd, 1H, J = 7.8 and 12.4 Hz), 4.13 (m, 1H), 4.20 (q, 2H, J = 7.1 Hz), 7.17-7.31 (m, 5H). ^{13}C NMR: δ ($CDCl_3$) 14.15, 19.53, 32.60, 37.49, 38.99, 45.94, 61.10, 69.96, 75.61, 125.81, 128.33, 141.63, 177.53. Exact mass calculated for $C_{16}H_{23}NO_3$: 277.1678. Found: 277.1686. (Found: C, 68.81; H, 8.33; N, 5.08%. Calc. for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05%).

Reaction of isoxazolidines 14a-d,f with methyl trifluoromethanesulfonate (TfOMe).

General procedure. To a stirred solution of isoxazolidine (2 mmol) in 10 ml of dry CCl_4, at 0 °C, was

added, dropwise, 250 μl (2.2 mmol) of MeTfO. After3 h the solvent was removed under reduced pressure and the residue, a white sticky oil, was used without further purification.

*Reaction of isoxazolidine **14a** with TfOMe.* First elution gave epimeric mixture of 3-butyl-3-ethoxycarbonyl-2,2,5-trimethylisoxazolidinium trifluoromethanesulfonate **15a**, 100% yield. ^{1}H NMR: δ ($CDCl_3$) 0.98 (t, 3H, J = 7.1 Hz), 0.99 (t, 3H, J = 6.9 Hz), 1.15-1.21 (m, 2H), 1.39-1.59 (m, 18H), 1.87-2.17 (m, 2H), 2.25-2.49 (m, 4H), 3.54 (m, 1H), 3.66 (s, 6H), 3.70 (s, 6H), 4.45 (m, 4H), 4.98 (m, 2H). ^{13}C NMR: δ ($CDCl_3$) 13.63, 13.73, 19.09, 19.83, 22.47, 26.71, 27.39, 31.57, 33.30, 37.78, 38.30, 51.55, 51.66, 53.34, 55.21, 64.52, 64.67, 78.16, 79.42, 87.43, 87.94, 163.46, 164.79, 165.39, 165.44.

*Reaction of isoxazolidine **14b** with TfOMe.* First elution gave epimeric mixture of 3-(*sec*-butyl)-3-ethoxycarbonyl-2,2,5-trimethylisoxazolidinium trifluoromethanesulfonate **15b**, 100% yield. ^{1}H NMR: δ ($CDCl_3$) 0.91-1.08 (m, 10H), 1.18-1.24 (m, 4H), 1.35-1.49 (m, 10H), 1.53-1.58 (m, 4H), 2.18-2.48 (m, 2H), 3.08 (m, 2H), 3.51 (m, 2H), 3.60 (s, 3H), 3.62 (s, 3H), 3.68 (s, 3H), 3.70 (s, 3H), 4.41 (m, 4H), 4.84 (m, 1H), 5.06 (m, 1H). ^{13}C NMR: δ ($CDCl_3$) 11.14, 11.61, 13.60, 13.91, 16.84, 17.02, 21.55, 23.87, 25.60, 25.84, 34.16, 34.42, 37.11, 38.21, 38.99, 39.39, 50.47, 51.15, 54.77, 57.60, 64.67, 77.63, 91.42, 91.89, 165.98, 166.25.

*Reaction of isoxazolidine **14c** with TfOMe.* First elution gave epimeric mixture of 3-ethoxycarbonyl-2,2,5-trimethyl-3-pentyl-isoxazolidinium trifluoromethanesulfonate **15c**, 100% yield. ^{1}H NMR: δ ($CDCl_3$) 0.90 (t, 3H, J = 6.6 Hz), 0.91 (t, 3H, J = 6.6 Hz), 1.29-1.53 (m, 24H), 1.91 (m, 2H), 2.26 (m, 2H), 2.42 (dd, 1H, J = 6.1 and 14.2 Hz), 2.97 (d, 1H, J = 8.0 Hz), 3.52 (m, 1H), 4.42 (q, 2H, J = 7.3 Hz), 4.43 (q, 2H, J = 7.3 Hz), 5.01 (m, 2H). ^{13}C NMR: δ ($CDCl_3$) 13.78, 13.85, 19.13, 24.60, 25.33, 28.88, 31.28, 31.82, 33.47, 37.71, 38.09, 51.52, 51.55, 53.23, 55.70, 64.44, 64.690, 78.03, 79.45, 87.35, 87.71, 165.78.

*Reaction of isoxazolidine **14d** with TfOMe.* First elution gave epimeric mixture of 3-ethoxycarbonyl-3-hexyl-2,2,5-trimethylisoxazolidinium trifluoromethanesulfonate **15d**, 100% yield. ^{1}H NMR: δ ($CDCl_3$) 0.90 (t, 3H, J = 6.6 Hz), 0.91 (t, 3H, J = 6.7 Hz), 1.30-1.55 (m, 28H), 1.93 (m, 2H), 2.27 (m, 2H), 2.41 (dd, 1H, J = 6.0 and 14.3 Hz), 2.97 (d, 1H, J = 8.0 Hz), 3.52 (m, 1H), 4.42 (q, 2H, J = 7.1 Hz), 4.43 (q, 2H, J = 7.1 Hz), 5.01 (m, 2H). ^{13}C NMR: δ ($CDCl_3$) 13.75, 13.89, 19.08, 22.34, 24.64, 25.31, 28.92, 31.22, 31.81, 33.55, 37.75, 38.01, 51.52, 51.54, 53.27, 55.68, 64.46, 64.60, 78.13, 79.49, 87.43, 87.84, 165.69.

*Reaction of isoxazolidine **14f** with TfOMe.* First elution gave epimeric mixture of 3-ethoxycarbonyl-2,2,3-trimethyl-5-phenethylisoxazolidinium trifluoromethanesulfonate **15f**, 100% yield. ^{1}H NMR: δ ($CDCl_3$) 1.35 (t, 3H, J = 7.2 Hz), 1.37 (t, 3H, J = 7.1 Hz), 1.85 (s, 3H), 1.87 (s, 3H), 2.10-2.21 (m, 2H), 2.34 (dd, 1H, J = 6.0 and 14.1 Hz), 2.60-2.74 (m, 3H), 2.81 (dd, 1H, J = 7.4 and 14.1 Hz), 3.05 (dd, 1H, J = 9.2 and 14.1 Hz), 3.58 (s, 6H), 3.62 (s, 6H), 4.38 (q, 4H, J = 7.2 Hz), 4.79 (m, 2H), 7.16-7.34 (m, 10H). ^{13}C NMR: δ ($CDCl_3$) 13.50, 20.11, 22.18, 31.49, 35.83, 36.09, 39.81, 40.06, 51.51, 51.79, 52.63, 55.08, 64.49, 80.69, 82.55, 83.14, 83.57, 126.35, 128.29, 128.59, 139.73, 139.87, 165.98, 166.27.

Ring opening of isoxazolidinium salts 15a-d,f.

General procedure. The solution of isoxazolidine, or isoxazolidinium salt, (1 mmol) in 20 ml of methanol was stirred under hydrogen atmosphere with 10% Pd on activated carbon for 48 h at 70 °C. After removal of catalyst by celite filtration, the filtrate was evaporated at reduced pressure and the residue subjected to silica gel flash chromatography using a mixture of cyclohexane/ethyl acetate 1:1 as eluent ($CHCl_3$/MeOH 98:2 for **16c**).

*Hydrogenolysis of isoxazolidinium salt **15a**.* First elution gave epimeric mixture of 3-butyl-3-dimethylamino-5-methyltetrahydro-2-furanone **16a**, 80% yield. Colorless oil. IR: ν_{max} (neat) 1770, 1180 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 0.89 (t, 3H, J = 7.1 Hz), 0.90 (t, 3H, J = 7.0 Hz), 1.34 (m, 8H), 1.38 (d, 3H, J = 6.3 Hz), 1.40 (d, 3H, J = 6.1 Hz), 1.74 (m, 4H), 2.00 (m, 2H), 2.26 (s, 6H), 2.31 (s, 6H), 2.38 (m, 2H), 4.51 (m, 2H),. ^{13}C

NMR: δ ($CDCl_3$) 13.88, 21.58, 22.12, 22.77, 22.95, 23.01, 25.18, 26.26, 68.09, 69.17, 73.11, 74.11, 176.80, 177.26. Exact mass calculated for $C_{11}H_{21}NO_2$: 199.1572. Found: 199.1578. (Found: C, 66.51; H, 10.58; N, 6.99%. Calc. for $C_{11}H_{21}NO_2$: C, 66.30; H, 10.62; N, 7.03%).

Hydrogenolysis of isoxazolidinium salt ***15b***. First elution gave epimeric mixture of 3-(*sec*-butyl)-3-dimethylamino-5-methyltetrahydro-2-furanone **16b**, 82% yield. Colorless oil. IR: ν_{max} (neat) 1765, 1190 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.84-1.01 (m, 12H), 1.11-1.40 (m, 8H), 1.58-1.96 (m, 6H), 2.11-2.22 (m, 2H), 2.28 (s, 6H), 4.18 (m, 1H), 4.48 (m, 1H). ^{13}C NMR: δ ($CDCl_3$) 12.18, 12.36, 12.60, 12.83, 21.86, 22.22, 22.48, 22.97, 26.06, 33.43, 36.65, 39.39, 39.91, 71.81, 72.65, 73.54, 73.70, 74.23, 176.93, 177.18. Exact mass calculated for $C_{11}H_{21}NO_2$: 199.1572. Found: 199.1574. (Found: C, 66.43; H, 10.60; N, 7.01%. Calc. for $C_{11}H_{21}NO_2$: C, 66.30; H, 10.62; N, 7.03%).

Hydrogenolysis of isoxazolidinium salt ***15c***. First elution gave epimeric mixture of 3-dimethylamino-5-methyl-3-pentyltetrahydro-2-furanone **16c**, 83% yield. Colorless oil. IR: ν_{max} (neat) 1770, 1180 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.80 (t, 6H, J = 6.6 Hz), 1.14-1.43 (m, 18H), 1.54-1.83 (m, 6H), 1.88 (dd, 1H, J = 7.5 and 12.3 Hz), 2.17 (dd, 1H, J = 6.2 and 12.3 Hz), 2.26 (s, 6H), 2.29 (s, 6H), 4.24 (m, 4H), 4.56 (m, 2H). ^{13}C NMR: δ($CDCl_3$) 13.77, 21.30, 21.50, 22.26, 22.57, 22.76, 23.13, 29.71, 29.85, 31.78, 35.17, 36.44, 38.02, 39.10, 39.37, 40.14, 65.04, 72.85, 73.70, 177.86, 178.76. Exact mass calculated for $C_{12}H_{23}NO_2$: 213.1729. Found: 213.1731. (Found: C, 66.99; H, 10.86; N, 6.55%. Calc. for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57%).

Hydrogenolysis of isoxazolidinium salt ***15d***. First elution gave epimeric mixture of 3-dimethylamino-3-hexyl-5-methyltetrahydro-2-furanone **16d**, 81% yield. Colorless oil. IR: ν_{max} (neat) 1770, 1170 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.88 (t, 6H, J = 6.1 Hz), 1.22-1.31 (m, 20H), 1.39 (d, 3H, J = 6.2 Hz), 1.42 (d, 3H, J = 6.1 Hz), 1.73 (m, 2H), 2.00 (m, 2H), 2.28 (s, 6H), 2.32 (s, 6H), 4.53 (m, 2H). ^{13}C NMR: δ($CDCl_3$) 14.03, 21.64, 22.19, 22.58, 23.04, 24.12, 29.58, 31.59, 33.77, 34.41, 36.00, 37.76, 39.32, 39.60, 68.16, 69.22, 73.15, 74.15, 177.08, 177.35. Exact mass calculated for $C_{13}H_{25}NO_2$: 227.1885. Found: 227.1884. (Found: C, 68.59; H, 11.10; N, 6.15%. Calc. for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16%).

Hydrogenolysis of isoxazolidinium salt ***15f***. First elution gave epimeric mixture of 3-dimethylamino-3-methyl-5-phenethyltetrahydro-2-furanone **16f**, 90% yield. Colorless oil. IR: ν_{max} (neat) 3060, 3040, 1770, 1170 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.32 (s, 3H), 1.41 (s, 3H), 1.64 (dd, 1H, J = 8.0 and 14.0 Hz), 1.91-2.04 (m, 5H), 2.30 (m, 1H), 2.33 (s, 6H), 2.53 (dd, 1H, J = 6.8 and 13.8 Hz), 2.66-2.88 (m, 2H), 4.48 (m, 1H), 4.53 (m, 1H), 7.18-7.30 (m, 10H). Exact mass calculated for $C_{15}H_{21}NO_2$: 247.1572. Found: 247.1575. (Found: C, 72.89; H, 8.56; N, 5.67%. Calc. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66%).

Reaction of furanones 16e and 16f with *m*-chloroperbenzoic acid (MCPBA).

General procedure. To an ice-cooled solution containing 0.2 mmol of furanone in 2 mL of CH_2Cl_2 was added a solution containing 0.29 mmol of MCPBA in 5 mL of CH_2Cl_2. After the addition was complete, the mixture was stirred for 3 h at 25 °C, then extracted with 10% Na_2CO_3 solution, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to leave behind a light yellow oil which was subjected to silica gel chromatography (CH_2Cl_2/MeOH 95:5 for **17e** and cyclohexane/ethyl acetate 1:1 for **17f**).

Cope elimination of furanone ***16e***.[15] First elution gave 5-hydroxymethyl-3-methyl-2,5-dihydro-2-furanone **17e**, 83% yield. Colorless thick syrup. IR: ν_{max} (neat) 3450, 1750, 1170 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.95 (dd, 3H, J = 0.4 and 1.8 Hz), 3.73 (dd, 1H, J = 4.9 and 12.4 Hz), 3.98 (dd, 1H, J = 3.7 and 12.4 Hz), 5.03 (dddq, 1H, J = 0.4, 1.6, 3.7 and 4.9 Hz), 7.06 (dq, 1H, J = 1.6 and 1.8 Hz). ^{13}C NMR: δ ($CDCl_3$) 10.74, 67.85, 77.51, 131.50, 143.70, 172.90. Exact mass calculated for $C_6H_8O_3$: 128.0473. Found: 128.0471. (Found: C, 56.20; H, 6.28%. Calc. for $C_6H_8O_3$: C, 56.25; H, 6.29%).

Cope elimination of furanone 16f. First elution gave 3-methyl-5-phenethyl-2,5-dihydro-2-furanone **17f**, 85% yield. Colorless oil. IR: ν_{max} (neat) 1750, 1160 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.90 (m, 3H), 1.97 (m, 2H), 2.78 (m, 2H), 4.87 (m, 1H), 6.98 (m, 1H), 7.17-7.29 (m, 5H). ^{13}C NMR: δ ($CDCl_3$) 10.56, 31.30, 35.12, 80.07, 126.19, 128.42, 128.48, 129.87, 140.44, 148.58, 174.18. Exact mass calculated for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0995. (Found: C, 77.25; H, 6.99%. Calc. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98%).

Alternative synthesis of 17c.

Hydrogenolysis of isoxazolidine 14c. First elution gave epimeric mixture of 3-methylamino-5-methyl-3-pentyltetrahydro-2-furanone **18**, 68% yield. Colorless oil. IR: ν_{max} (neat) 3150, 1770, 1180 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.80 (t, 6H, J = 6.6 Hz), 1.15-1.41 (m, 18H), 1.55-1.82 (m, 6H), 1.89 (dd, 1H, J = 7.5 and 12.4 Hz), 2.17 (dd, 1H, J = 6.2 and 12.4 Hz), 2.28 (s, 3H), 2.32 (s, 3H), 3.27 (bs, 2H), 4.22 (m, 4H), 4.55 (m, 2H). ^{13}C NMR: δ ($CDCl_3$) 13.99, 14.00 21.52, 21.57, 22.02, 22.58, 22.63, 22.67, 29.75, 29.81, 31.69, 31.73, 34.80, 34.83, 43.88, 43.91, 64.23, 64.24, 72.97, 73.03, 172.50, 172.51. Exact mass calculated for $C_{11}H_{21}NO_2$: 199.1572. Found: 199.1574. (Found: C, 66.35; H, 10.59; N, 7.04%. Calc. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03%).

Treatment of furanone 18 with iodomethane. A solution of furanone (2 mmol) in 5 ml of iodomethane was heated, at 50 °C for 12 h, in a sealed tube. The reaction mixture was then evaporated under reduced pressure and the residue subjected to flash-chromatography on silica gel column with cyclohexane/ethyl acetate 85:15 as eluent. First elution gave 5-methyl-3-pentyl-2,5-dihydro-2-furanone **17c**, 53% yield.[15]

Synthesis of 5-heptyl-2,5-dihydro-2-furanone 22.

Reaction of C-ethoxycarbonyl-N-methylnitrone 19 with 1-nonene 20. A solution of nitrone (5 mmol) and 1-nonene (10 mmol) in 20 ml of dry toluene was heated, at 80 °C for 12 h, in a sealed tube. The reaction mixture was then evaporated under reduced pressure and the residue, an epimeric mixture (*trans/cis* 4:1), was subjected to flash-chromatography on silica gel column with cyclohexane/ethyl acetate 7:3 as eluent. First elution gave the major isomer 3-ethoxycarbonyl-5-heptyl-2-methylisoxazolidine **21**, 72% yield. Colorless oil. IR: ν_{max} (neat) 1735 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.80 (t, 3H, J = 6.6 Hz), 1.15-1.17 (m, 15H), 2.13 (ddd, 1H, J = 7.8, 8.9 and 12.5 Hz), 2.58 (ddd, 1H, J = 6.3, 6.9 and 12.5 Hz), 2.82 (s, 3H), 3.29 (dd, 1H, J = 6.3 and 8.9 Hz), 4.10 (m, 1H), 4.25 (q, 2H, J = 7.2 Hz). Exact mass calculated for $C_{14}H_{27}NO_3$: 257.1991. Found: 257.1997. (Found: C, 65.61; H, 10.59; N, 5.43%. Calc. for $C_{14}H_{27}NO_3$: C, 65.34; H, 10.57; N, 5.44%).

Reaction of isoxazolidine 21 with TfOMe. First elution gave 3-ethoxycarbonyl-5-heptyl-2,2-dimethylisoxazolidinium trifluoromethanesulfonate, 100% yield. ^1H NMR: δ ($CDCl_3$) 0.90 (t, 3H, J = 6.6 Hz), 1.29 (m, 12H), 1.41 (t, 3H, J = 7.5 Hz), 2.92 (m, 1H), 3.15 (m, 1H), 3.71 (s, 3H), 4.01 (s, 3H), 4.41 (q, 2H, J = 7.5 Hz), 4.88 (m, 1H), 6.04 (dd, 1H, J = 9.0 and 9.3 Hz).

Hydrogenolysis of 3-ethoxycarbonyl-5-heptyl-2,2-dimethylisoxazolidinium trifluoromethanesulfonate. First elution gave 3-dimethylamino-5-heptyltetrahydro-2-furanone, 87% yield. Colorless oil. IR: ν_{max} (neat) 1770, 1170 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.85 (t, 6H, J = 6.2 Hz), 1.22-1.43 (m, 10H), 1.47-1.63 (m, 2H), 1.75 (m, 1H), 2.29 (m, 1H), 2.37 (s, 6H), 3.61 (dd, 1H, J = 9.0 and 12.0 Hz), 4.27 (m, 1H). ^{13}C NMR: δ($CDCl_3$) 13.97, 22.51, 24.93, 29.00, 29.18, 29.93, 31.61, 35.37, 41.48, 41.60, 64.31, 77.08, 171.88. Exact mass calculated for $C_{13}H_{25}NO_2$: 227.1885. Found: 227.1887. (Found: C, 68.76; H, 11.11; N, 6.14%. Calc. for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16%).

Cope elimination of 3-dimethylamino-5-heptyltetrahydro-2-furanone. First elution gave 5-heptyl-2,5-dihydro-2-furanone **22**,[22] 89% yield. Colorless oil. IR: ν_{max} (neat) 1750, 1150 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.88 (t,

3H, J = 6.8 Hz), 1.27 (m, 10H), 1.69 (m, 2H), 5.03 (dddd, 1H, J = 1.6, 1.8, 5.4 and 7.0 Hz), 6.11 (dd, 1H, J = 1.8 and 5.8 Hz), 7.46 (dd, 1H, J = 1.6 and 5.8 Hz). ^{13}C NMR: δ ($CDCl_3$) 14.02, 22.56, 29.00, 29.22, 29.67, 31.64, 33.14, 83.47, 121.48, 156.33, 173.26. Exact mass calculated for $C_{11}H_{18}O_2$: 182.1307. Found: 182.1308. (Found: C, 72.51; H, 9.95%. Calc. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95%).

Synthesis of 2-methylmuconolactone 28.

Reaction of C-ethoxycarbonyl-C,N-dimethylnitrone 12e with 3-buten-1-ol 23. A solution of nitrone (17 mmol) in 30 ml of 3-buten-1-ol was heated, at 75 °C for 48 h, in a sealed tube. The reaction mixture was then evaporated under reduced pressure and the residue subjected to flash-chromatography on silica gel column with $CHCl_3$/MeOH 98:2 as eluent. First elution gave epimeric mixture of 3-ethoxycarbonyl-5-(2-hydroxyethyl)-2,3-dimethylisoxazolidine **24**, 97% yield. Colorless oil. IR: ν_{max} (neat) 3450-3350, 1735 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 1.30 (t, 3H, J = 7.1 Hz), 1.31 (t, 3H, J = 7.1 Hz), 1.38 (s, 3H), 1.39 (s, 3H), 1.83-1.91 (m, 4H), 2.24 (dd, 1H, J = 8.2 and 12.9 Hz), 2.63 (s, 3H), 2.64 (s, 3H), 2.65-2.77 (m, 2H), 2.96 (dd, 1H, J = 6.8 and 12.9 Hz), 3.74 (t, 3H, J = 6.7 Hz), 3.77 (t, 3H, J = 6.7 Hz), 4.20 (q, 2H, J = 7.1 Hz), 4.21 (q, 2H, J = 7.1 Hz), 4.33 (m, 2H). ^{13}C NMR: δ ($CDCl_3$) 17.35, 25.42, 26.18, 41.78, 42.23, 42.99, 62.31, 63.15, 76.67, 177.13. Exact mass calculated for $C_{10}H_{19}NO_4$: 217.1314. Found: 217.1311. (Found: C, 55.36; H, 8.83; N, 6.44%. Calc. for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45%).

Reaction of isoxazolidine 24 with acetyl chloride. To a solution of acetyl chloride (22 mmol) and dry pyridine (22 mmol) in 20 mL anhydrous carbon tetrachloride was added a carbon tetrachloride solution of isoxazolidine **24** (20 mmol). The reaction mixture was stirred for 4 h; the precipitate was filtered off, the solvent was evaporated under reduced pressure and residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 85:15). First elution gave epimeric mixture of 5-[2-(acetyloxy)ethyl]-3-ethoxycarbonyl-2,3-dimethylisoxazolidine **25**, 87% yield. Colorless oil. IR: ν_{max} (neat) 1740, 1735 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 1.28 (t, 3H, J = 7.2 Hz), 1.30 (t, 3H, J = 7.2 Hz), 1.34 (s, 3H), 1.35 (s, 3H), 1.80-1.95 (m, 4H), 2.01 (s, 3H), 2.02 (s, 3H), 2.21 (dd, 1H, J = 8.6 and 12.3 Hz), 2.54-2.72 (m, 2H), 2.59 (s, 3H), 2.60 (s, 3H), 2.93 (dd, 1H, J = 7.9 and 12.3 Hz), 4.17 (m, 10H). ^{13}C NMR: δ ($CDCl_3$) 14.79, 14.90, 21.50, 21.63, 33.28, 35.38, 36.70, 39.33, 39.43, 39.56, 46.71, 61.76, 61.78, 61.83, 62.39, 70.56, 73.70, 73.99, 171.59, 173.65. Exact mass calculated for $C_{12}H_{21}NO_5$: 259.1419. Found: 259.1420. (Found: C, 55.66; H, 8.13; N, 5.42%. Calc. for $C_{12}H_{21}NO_5$: C, 55.59; H, 8.16; N, 5.40%).

Reaction of isoxazolidine 25 with TfOMe. First elution gave epimeric mixture of 5-[2-(acetyloxy)ethyl]-3-ethoxycarbonyl-2,2,3-trimethylisoxazolidinium trifluoromethanesulfonate, 100% yield. Colorless oil. ^{1}H NMR: δ ($CDCl_3$) 1.39 (t, 3H, J = 7.1 Hz), 1.41 (t, 3H, J = 7.1 Hz), 1.91 (s, 3H), 1.97 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.13 (m, 4H), 3.21 (m, 2H), 3.51 (m, 2H), 3.68 (s, 6H), 3.69 (s, 6H), 4.03-4.21 (m, 4H), 4.42 (m, 4H), 4.93-5.05 (m, 2H).

Cope elimination of furanone 26. First elution gave 5-(2-hydroxyethyl)-3-methyl-2,5-dihydro-2-furanone **27**, 83% yield. Colorless oil. IR: ν_{max} (neat) 3450-3350, 1755, 1150 cm^{-1}. ^{1}H NMR: δ ($CDCl_3$) 1.68-1.79 (m, 1H), 1.94 (s, 3H), 2.01-2.18 (m, 1H), 3.75-3.82 (m, 2H), 3.89-3.93 (m, 1H), 5.03 (m, 1H), 7.07 (m, 1H),. ^{13}C NMR: δ ($CDCl_3$) 15.07, 33.98, 61.73, 78.02, 131.45, 149.15, 172.00. Exact mass calculated for $C_7H_{10}O_3$: 142.0630. Found: 142.0629. (Found: C, 59.10; H, 7.08%. Calc. for $C_7H_{10}O_3$: C, 59.15; H, 7.09%).

Oxidation of butenolide 27. A solution of butenolide **27** (3.72 mmol) in 10 ml of acetone was placed in a 50-ml round-bottom flask under nitrogen and cooled to 0 °C. To the magnetically stirred solution was added, dropwise, a solution consisting of 2 mL of 8 *N* Jones reagent in 18 mL of acetone. The Jones solution was added over a period of 30 m until an orange tint persisted in the reaction mixture. Isopropyl alcohol was then added

dropwise to destroy excess Jones reagent, as indicated by the reappearance of a deep green color. The reaction mixture was then extracted twice with ether, and the combined ether extracts were washed (water and brine), dried over anhydrous magnesium sulfate. The solvent was then evaporated under reduced pressure and the residue subjected to silica gel flash-chromatography with chloroform/methanol 7:3 as eluent. First elution gave 2-methylmuconolactone **28**, 77% yield.[18]

Synthesis of hydroxylamine derivative 32.

Reaction of C-ethoxycarbonyl-C,N-dimethylnitrone 12e with allyl bromide 30. A solution of nitrone (15 mmol) in 20 ml of allyl bromide was heated, at 70 °C for 24 h, in a sealed tube. The reaction mixture was then evaporated under reduced pressure and the residue subjected to flash-chromatography on silica gel column with chloroform as eluent. First elution gave epimeric mixture of 5-bromomethyl-3-ethoxycarbonyl-2,3-dimethylisoxazolidine **31**, 33% yield. Light yellow oil. IR: ν_{max} (neat) 1735 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.30 (t, 3H, J = 7.0 Hz), 1.31 (t, 3H, J = 7.0 Hz), 1.39 (s, 6H), 1.94 (dd, 1H, J = 6.7 and 12.7 Hz), 2.32 (dd, 1H, J = 8.7 and 13.0 Hz), 2.64 (s, 3H), 2.65 (s, 3H), 2.73 (dd, 1H, J = 5.3 and 13.0 Hz), 3.00 (dd, 3H, J = 7.9 and 12.7 Hz), 3.35 (dd, 3H, J = 7.4 and 9.9 Hz), 3.52 (m, 2H), 3.54 (dd, 3H, J = 5.7 and 9.9 Hz), 4.22 (q, 2H, J = 7.0 Hz), 4.23 (q, 2H, J = 7.0 Hz), 4.33 (dddd, 1H, J = 5.7, 6.7, 7.4 and 7.9 Hz), 4.34 (m, 2H). ^{13}C NMR: δ ($CDCl_3$) 14.18, 19.56, 33.08, 34.83, 38.70, 38.91, 43.66, 44.95, 46.57, 61.07, 61.34, 70.32, 71.13, 75.77, 76.03, 171.63, 172.38. Exact mass calculated for $C_9H_{16}BrNO_3$: 265.0313. Found: 265.0317. (Found: C, 41.13; H, 6.04; N, 5.28%. Calc. for $C_9H_{16}BrNO_3$: C, 40.62; H, 6.06; N, 5.26%).

Reduction of isoxazolidine 31 with tri-n-butyltin hydride. A solution of isoxazolidine **31** (10 mmol), tri-*n*-butyltin hydride (12 mmol) and azoisobutyronitrile (AIBN; 0.2 mmol) in 5 mL of dry benzene are heated to 80 °C, under nitrogen, for 2 h. The reaction mixture was then evaporated under reduced pressure and the residue subjected to flash-chromatography on silica gel column with chloroform as eluent. First elution gave *E/Z* mixture of ethyl 2-[hydroxy(methyl)amino]-2-methyl-3-pentenoate **32**, 51% yield. Light yiellow oil. IR: ν_{max} (neat) 3450-3350, 1735, 1610 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.92 (t, 3H, J = 7.2 Hz), 1.31 (dd, 3H, J = 1.8 and 6.7 Hz), 2.48 (bs, 1H), 2.68 (s, 3H), 4.22 (q, 2H, J = 7.2 Hz), 5.09 (dq, 1H, J = 1.8 and 13.5 Hz), 5.74 (dq, 1H, J = 6.7 and 13.5 Hz) . Exact mass calculated for $C_9H_{17}NO_3$: 187.1208. Found: 187.1210. (Found: C, 56.99; H, 9.18; N, 7.49%. Calc. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48%).

Synthesis of 3,5-dimethyl-2,5-dihydro-2-furanone 34 (mushroom flavour).

Reaction of isoxazolidine 17e with tosyl chloride. Tosyl chloride (6.0 mmol) was added in 30 m to a cooled (0 °C) and stirred mixture of isoxazolidine **17e** (5.6 mmol) and triethylamine (8.4 mmol) in dichloromethane (50 mL). Stirring was continued for 6 h. The reaction mixture was washed repeatedly with ice-water and dried over sodium sulfate. The solvent was then evaporated under reduced pressure and the residue subjected to flash-chromatography on silica gel column with chloroform as eluent. First elution gave (4-methyl-5-oxo-2,5-dihydro-2-furanyl)methyl-4-methyl-1-benzenesulfonate **33**, 99% yield. White solid, mp 78-79 °C. IR: ν_{max} (neat) 1770 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.91 (d, 1H, J = 1.2 Hz), 2.46 (s, 3H), 4.18 (m, 2H), 5.03 (m, 1H), 6.99 (dq, 1H, J = 1.2 and 1.2 Hz), 7.37 (d, 2H, J = 8.0 Hz), 7.77 (d, 2H, J = 8.0 Hz). ^{13}C NMR: δ ($CDCl_3$) 10.73, 21.63, 67.86, 77.52, 127.89, 130.00, 132.05, 132.54, 133.67, 143.72, 145.43, 172.90. Exact mass calculated for $C_{13}H_{14}SO_5$: 282.0562. Found: 282.0558. (Found: C, 55.19; H, 5.01; S, 11.33%. Calc. for $C_{13}H_{14}SO_5$: C, 55.31; H, 5.00; S, 11.36%).

Reduction of furanone 33 with sodium cyanoborohydride. A solution of furanone **33** (2 mmol) and sodium cyanoborohydride (5 mmol) in hexamethylphosphoramide (HMPA; 5 mL) was heated, at 110 °C for 12 h, in a

sealed tube. At the end of this time the mixture was poured in ice-water and extracted with dichloromethane. The solvent was then evaporated under reduced pressure and the residue subjected to flash-chromatography on silica gel column with cyclohexane/ethyl acetate 7:3 as eluent. First elution gave 3,5-dimethyl-2,5-dihydro-2-furanone **34**, 49% yield.[23]

Synthesis of methyl (*E*)-2-(2-oxo-5-undecyltetrahydro-3-furanyliden)acetate 38 (methyl isoacarenoate).

Reaction of C-methoxycarbonyl-C-(2-methoxy-2-oxoethyl)-N-methylnitrone[19] ***35*** *with 1-tridecene.* A solution of nitrone (5 mmol) and 1-tridecene (10 mmol) in 20 ml of dry toluene was heated, at 80 °C for 12 h, in a sealed tube. The reaction mixture was then evaporated under reduced pressure and the residue subjected to flash-chromatography on silica gel column with cyclohexane/ethyl acetate 7:3 as eluent. First elution gave 3-(2-methoxy-2-oxoethyl)-3-ethoxycarbonyl-2-methyl-5-undecylisoxazolidine **36**, 84% yield. Colorless oil. IR: ν_{max} (neat) 1730 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.88 (t, 3H, J = 6.5 Hz), 1.11-1.42 (m, 20H), 1.82 (m, 1H), 2.35 (m, 1H), 2.59 (s, 3H), 4.01 (m, 1H), 4.18 (m, 1H). ^{13}C NMR: δ ($CDCl_3$) 14.13, 22.68, 26.23, 29.34, 29.55, 31.90, 33.45, 35.64, 38.91, 39.64, 44.13, 44.60, 51.86, 52.34, 71.16, 76.83, 171.20, 171.32. Exact mass calculated for $C_{20}H_{37}NO_5$: 371.2672. Found: 371.2676. (Found: C, 65.15; H, 10.08; N, 3.75%. Calc. for $C_{20}H_{37}NO_5$: C, 64.66; H, 10.04; N, 3.77%).

Hydrogenolysis of isoxazolidine 36. First elution gave methyl 2-[3-(methylamino)-2-oxo-5-undecyltetrahydro-3-furanyl]acetate **37**, 71% yield. Colorless oil. IR: ν_{max} (neat) 3250, 1770, 1170 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.92 (t, 3H, J = 6.7 Hz), 1.30 (m, 18H), 1.44-1.85 (m, 2H), 2.03 (bs, 1H), 2.05 (dd, 1H, J = 8.8 and 13.7 Hz), 2.39 (s, 3H), 2.52 (dd, 1H, J = 6.8 and 13.7 Hz), 2.73 (s, 2H), 3.74 (s, 3H), 4.46 (m, 1H). ^{13}C NMR: δ($CDCl_3$) 14.06, 22.63, 25.19, 29.28, 29.45, 29.56, 29.82, 31.86, 35.88, 36.02, 40.17, 52.01, 62.92, 170.16, 177.37. Exact mass calculated for $C_{19}H_{35}NO_4$: 341.2566. Found: 341.2567. (Found: C, 66.86; H, 10.34; N, 4.09%. Calc. for $C_{19}H_{35}NO_4$: C, 66.83; H, 10.33; N, 4.10%).

Treatment of furanone 37 with iodomethane. A solution of furanone (2 mmol) in 5 ml of iodomethane was heated, at 50 °C for 12 h, in a sealed tube. The reaction mixture was then evaporated under reduced pressure and the residue subjected to flash-chromatography on silica gel column with cyclohexane/ethyl acetate 85:15 as eluent. First elution gave methyl (*E*)-2-(2-oxo-5-undecyltetrahydro-3-furanyliden)acetate **38**, 50% yield. Colorless oil. IR: ν_{max} (neat) 1740, 1725, 1130 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 0.88 (t, 3H, J = 6.7 Hz), 1.26 (m, 18H), 1.69 (m, 2H), 2.93 (ddd, 1H, J = 3.3, 5.5 and 20.2 Hz), 3.50 (ddd, 1H, J = 2.9, 7.5 and 20.2 Hz), 3.81 (s, 3H), 4.62 (m, 1H), 6.76 (dd, 1H, J = 2.9 and 3.3 Hz). ^{13}C NMR: δ ($CDCl_3$) 14.09, 22.65, 24.70, 29.23, 29.30, 29.41, 29.57, 31.87, 33.93, 36.38, 52.09, 78.98, 123.77, 142.82, 165.88, 169.69. Exact mass calculated for $C_{18}H_{30}O_4$: 310.2144. Found: 310.2142. (Found: C, 68.91; H, 9.71%. Calc. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74%).

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