# Reactions with α,β-Unsaturated Nitrile Oxides. Synthetic Studies in the Terpene Field. Synthesis of Tagetones, Ocimenones, Deodarone and Atlantone

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The generation and 1,3-dipolar cycloaddition of α,β-unsaturated nitrile oxides are described. Selective reductive cleavage of the isoxazoline ring was achieved. Subsequent elimination of water leads to the 1,4-dien-3-one system. The formation of tetrahydro-γ-pyrones is observed. The reactions were applied to the synthesis of tagetones, ocimenones, deodarone and atlantone.

α,β-Unsaturated aldehyde oximes are seldom used as starting materials in 1,3-dipolar nitrile oxide cycloaddition and there are several reasons for this. The preparation of the oximes is often plagued by the formation of by-products. Halogenation to give the hydroxamic acid chloride could competatively take place at the double bond. Being bifunctional, the nitrile oxides derived could undergo polymerization and finally, selective reductive cleavage of the isoxazoline ring presents problems because the conjugated double bond is easily reduced. Thus, against the odds, we set out to test the applicability of α,β-unsaturated aldehyde oximes in nitrile oxide cycloadditions, because the highly functionalized α,β-unsaturated carbonyl system produced is synthetically interesting and fruitful synthetic application (Scheme 1) would be rewarding.

*α,β-Unsaturated aldehyde oximes.* Oximation of α,β-unsaturated aldehydes can lead to several products depending on the site of attack. The course of the reaction is dependent on the pH of the solution. High yields of the desired α,β-unsaturated aldehyde oximes are obtained as *syn–anti* mixtures by treatment of a suspension of the aldehydes with hydroxylamine hydrochloride in aqueous solution at pH 9
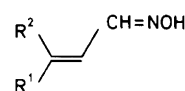


1a R¹ = CH₃; R² = H
 b R¹ = C₆H₅; R² = H
 c R¹ = (CH₃)₂C═CHCH₂CH₂; R² = CH₃
 d R¹ = R² = CH₃

in the presence of excess of sodium hydrogencarbonate. Crotonaldehyde oxime, cinnamaldehyde oxime, β,β-dimethylacrylaldehyde oxime (senecialdehyde oxime) and citraldehyde oxime (1a–d) were prepared according to this procedure.

Senecialdehyde is commercially available but in the present work it was prepared from silylated 2-nitropropane and acrylonitrile[1] (Scheme 2). The N-trimethylsilyloxyisoxazolidine 2 is thermally rearranged and cleaved by fluoride ion to senecialdehyde, which is directly oximated to 1d in a total yield of 40–50 %. The whole sequence of reactions can be performed without isolating the intermediates. The oxime 1d is a building block in the monoterpene synthesis described below.



1. NCS. 2. Et₃N. 3. [H]
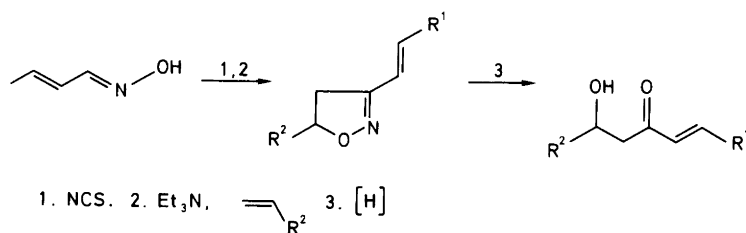
*Scheme 1.*

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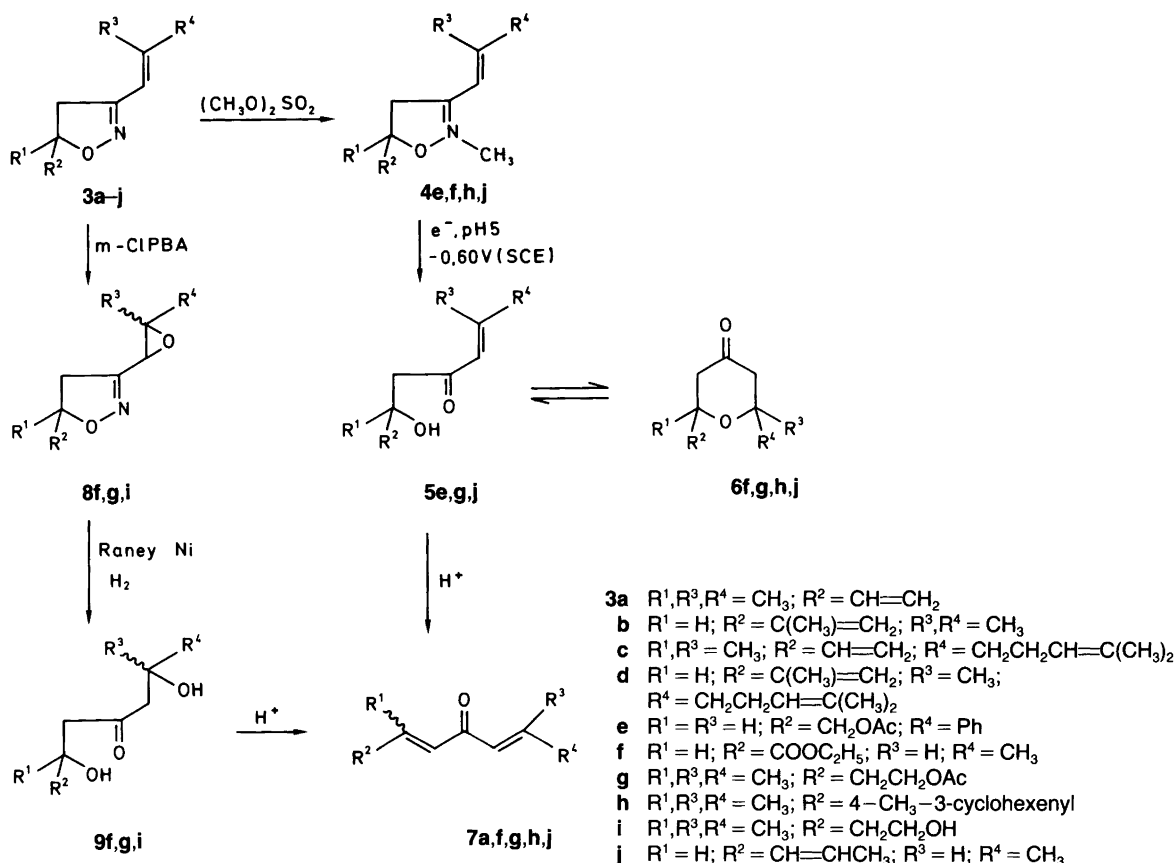
**2**

**1d** ← NH₂OH
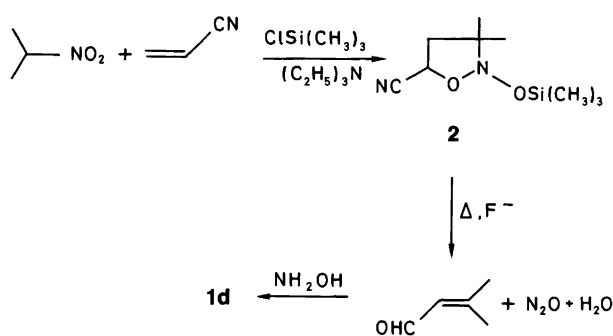
**Scheme 2.**

*Halogenation. α,β-Unsaturated hydroxamic acid chlorides and generation of nitrile oxides.* N-Chlorosuccinimide (NCS) in chloroform has been shown to be the chlorination agent of choice which selectively acts upon the oxime function in the presence of several other reactive functional groups.[2] The present work shows that NCS preferentially reacts with the oxime group of α,β-unsaturated aldehyde oximes. t-Butyl hypochlorite has also been used successfully for this selective chlorination.[3] Triethylamine[4] and sodium hydrogencarbonate in wet ethyl acetate[3,5] are suitable bases for generating the corresponding nitrile oxides. The nitrile oxides react with alkenes to give the expected unsaturated isoxazolines **3**. 3-Alkenylisoxazolines have

been obtained previously by Wittig reaction of 3-alkyl-phospho-substituted isoxazolines with carbonyl compounds.[6]

*The cycloaddition.* The nitrile oxide from senecialdehyde oxime gave with isoprene a mixture of **3a** and **3b** in a ratio of 1:3. A small amount of the diadduct was also isolated. Dimerization or polymerization of the unsaturated nitrile oxide is thus slower than the cycloaddition to the diene. The major product **3b** represents a tail-to-tail coupling of two isoprene units. The NMR spectrum of the product from the cycloaddition of the nitrile oxide from citraldehyde oxime showed formation of **3c** and **3d**, ratio ca. 1:3, and the cyclized product **10**, which is specifically formed from the cis-isomer (neral). This type of intramolecular cyclization has been used in a synthesis of the sesquiterpene (±)-hernandulcin from farnesaldehyde oxime.[7] The cycloaddition of the nitrile oxides from crotonaldehyde oxime with ethyl acrylate, pentadiene and allyl acetate proceeded in satisfactory yields.

*Reduction. The cross conjugated 1,4-dien-3-one system.* The commonly used reductive cleavage over Raney nickel cannot be used because olefinic bonds will also be reduced. Titanous ion selectively reduces the N–O bond in the presence of isolated double bonds but double bond reduction occurs when they are conjugated with carbonyl groups.[8]



**Scheme 3.**

**3a** R¹,R³,R⁴ = CH₃; R² = CH=CH₂
**b** R¹ = H; R² = C(CH₃)=CH₂; R³,R⁴ = CH₃
**c** R¹,R³ = CH₃; R² = CH=CH₂; R⁴ = CH₂CH₂CH=C(CH₃)₂
**d** R¹ = H; R² = C(CH₃)=CH₂; R³ = CH₃;
    R⁴ = CH₂CH₂CH=C(CH₃)₂
**e** R¹ = R³ = H; R² = CH₂OAc; R⁴ = Ph
**f** R¹ = H; R² = COOC₂H₅; R³ = H; R⁴ = CH₃
**g** R¹,R³,R⁴ = CH₃; R² = CH₂CH₂OAc
**h** R¹,R³,R⁴ = CH₃; R² = 4-CH₃-3-cyclohexenyl
**i** R¹,R³,R⁴ = CH₃; R² = CH₂CH₂OH
**j** R¹ = H; R² = CH=CHCH₃; R³ = H; R⁴ = CH₃

Preliminary tests showed that **3a** to a certain extent gave the saturated ketone when reduced with Ti³⁺. Zinc powder in acetic acid gave predominantly the saturated ketone. Selective reductive cleavage was achieved by electrochemical reduction of the isoxazolinium salts[9] **4** under controlled potential, at ca. −0.60 V vs. SCE, which is 0.20–0.25 V above the reduction potential of the conjugated olefinic system (Scheme 3). Reduction of the parent isoxazolines also lead to reduction of the conjugated double bond.

The unsaturated hydroxy ketones **5** undergo ring closure to give tetrahydro-γ-pyrones **6**. Acid-catalyzed elimination of water gives the cross-conjugated dienone system **7**. The same type of compounds were synthesized by protective epoxidation of the double bond with *m*-chloroperbenzoic acid and subsequent reductive cleavage over Raney Ni. The epoxides **8** open regioselectively to give the β-hydroxy ketones **9**, which by acid-catalyzed elimination of water give the α,β-unsaturated ketones **7** (Scheme 3).

Reduction of **4e** gave the expected unsaturated hydroxy ketone **5e**. Reduction of **4f** gave a product, which according to the ¹H NMR spectrum, contained no olefinic bonds. It was concluded that this compound had either cyclized to the pyrone **6f** or it could conceivably have added water to give the dihydroxy derivative **9f**. Compound **4h** behaved similarly, see below. When **3f** was epoxidized to **8f** and subsequently reduced catalytically over Raney Ni the product obtained had an ¹H NMR spectrum identical with that of the product from the electrochemical reduction. We have assigned the compound the open-chain structure **9f**. Treatment of **9f** with methanesulfonyl chloride and triethylamine gave the cross-conjugated dienone **7j** in 42% yield based on the isoxazoline **3j**. The trienone **7j** was synthesized from **3j** via methylation to **4j**, electrochemical reduction to give **5j** and elimination of water by the methanesulfonyl chloride–triethylamine reagent. Compound **16**, which was obtained as a by-product from the reduction, was formed by addition of ethanol (solvent) to **5j**. These



**10**          **11**
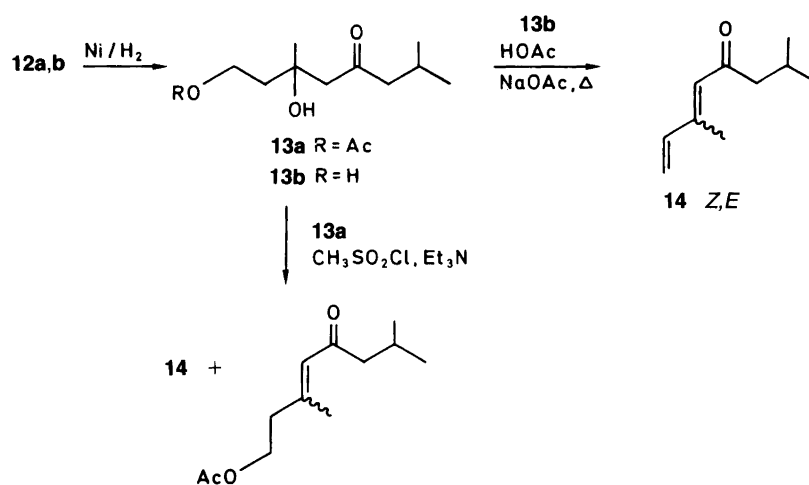


RO
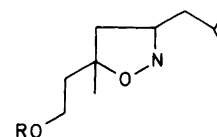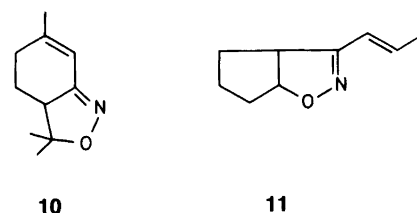
**12a** R = Ac
**12b** R = H
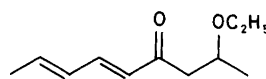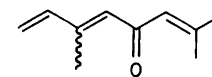


**16**          **7a** Ocimenones

reactions were applied to the syntheses of some simple terpenoids.

The tagetones (**14**) are rather unstable monoterpenes, which have been isolated from various *Tagetes* species as a mixture of *Z*- and *E*-isomers. Several synthesis have been recorded.[10] The current synthesis started from 3-methyl-3-buten-1-ol or its acetate, which by 1,3-dipolar cycloaddition to isovaleronitrile oxide give **12a,b**. Reductive cleavage over Raney Ni gives the corresponding hydroxy ketones **13a,b**. (*Z*)-Tagetone **14** was obtained in a satisfactory yield when crude **13b** was heated in refluxing acetic acid in the presence of sodium acetate for 15 min (Scheme 4). The formation of tagetones from **13a** by acid- or base-catalyzed elimination of water and acetic acid was capricious. At-



**12a,b**  Ni / H₂

RO

OH

**13a** R = Ac
**13b** R = H

**13a**
CH₃SO₂Cl, Et₃N

**13b**
HOAc
NaOAc, Δ

**14** Z,E

**14** +

AcO

*Scheme 4.*          **15**

3h

$(CH_3O)_2SO_4$

$e^-, H_2O, pH \sim 5$
$-0.6V(SCE)$

6h, Deodarone

4h

$H^+$

7h, Atlantone
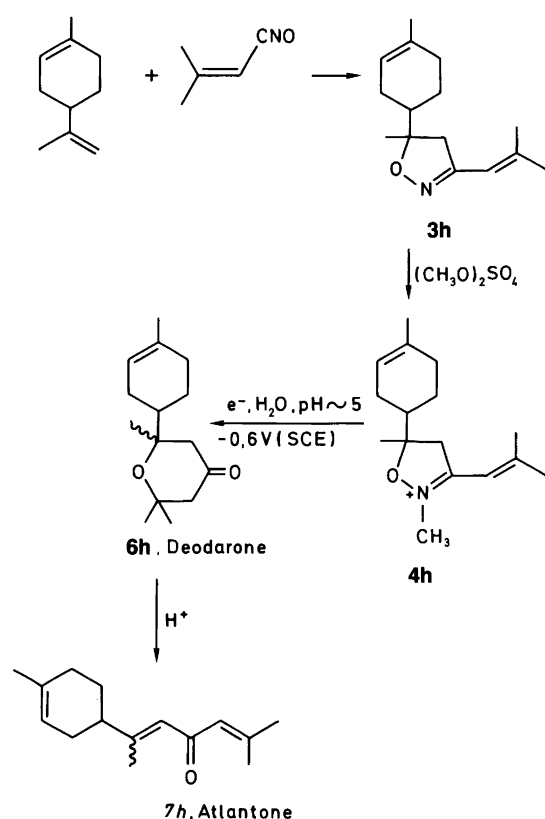
Scheme 5.

tempted water elimination of **13a** with methanesulfonyl chloride and triethylamine led to **14**, $Z,E$ (major) mixture, together with **15**.

The ocimenones (**7a**) have been synthesized several times.[10c,d,11] We have applied the method for the tagetones starting with senecialdehyde oxime and 3-methyl-3-buten-1-ol, which gave the isoxazoline **3i**. Epoxidation and catalytic hydrogenation gave **9i**. When crude **9i** was thermolyzed with silica at 200 °C/40 mmHg ocimenone (**7a**) was formed in a poor yield, ca. 10–20 %, predominantly as the Z-isomer. The yield of **7a** was improved when the acetate **3g** was used as the starting material. This was epoxidized to give **8g** and subsequently reduced to **9g**. Minor amounts of the deoxygenation product **13a** were observed in the crude reaction mixture. Dehydration by methanesulfonyl chloride and triethylamine gave predominantly **7g**. Compound **7a** was observed as a minor product even at this stage. Thermolysis of the crude product on silica gave **7a** [$Z,E$ (major) mixture] in ca. 20 % overall yield as calculated from **3g**.

Deodarone (**6h**), and atlantone (**7h**), have a carbon skeleton well suited for construction by our isoxazole methodology. The nitrile oxide generated from senecialdehyde oxime added selectively to the double bond of the isopropenyl group of (+)-limonene to give **3h**, which was methylated to give **4h** and reduced electrolytically. By controlling the potential, the ring double bond as well as the conjugated double bond were left untouched. The product iso-

lated turned out to be deodarone (**6h**), a tetrahydro-γ-pyrone structure. By treatment with acid, **6h** lost water to give atlantone (**7h**). Deodarone was obtained in a 1:1 diastereomeric mixture and atlantone as a cis–trans mixture (Scheme 5).

Deodarone (**6h**) and atlantone (**7h**) have been synthesized earlier by various methods.[10c,11b,12]

## Experimental

*Synthesis of α,β-unsaturated aldehyde oximes.* The unsaturated aldehyde (0.1 mol) was added to an aqueous solution (ca. 100 ml) of hydroxylamine hydrochloride (0.1 mol) and sodium hydrogencarbonate (0.2 mol). The mixture (two-phase system) was stirred at 25 °C overnight, extracted twice with dichloromethane, dried over $MgSO_4$ and evaporated *in vacuo*. The yield was poorer when the oximation was carried out in a one-phase aqueous methanol solution. It is advisable to use the oxime ($Z,E$ mixture) directly after the preparation as it decomposes within a few days at room temperature (crotonaldehyde oxime). It should be stored in the refrigerator. The crude yields were: crotonaldehyde oxime 71 %; citral oxime ($Z,E$), cinnamaldehyde oxime and senecialdehyde oxime were formed in practically quantitative yields.

*Synthesis of senecialdehyde and oxime* **1d**. A mixture of 2-nitropropane (7.0 g), triethylamine (8.1 g), acrylonitrile (4.4 g) and chlorotrimethylsilane (8.9 g) was stirred at 53 °C for 16 h in chloroform (20 ml). The mixture was washed twice with water (20 ml), dried over $MgSO_4$ and evaporated *in vacuo* in a distillation apparatus to give a blue liquid. Finely pulverised potassium fluoride (4.3 g) was added and the mixture was stirred at 25 °C for 30 min. The temperature was slowly raised to 110 °C at 60–70 mmHg. Dinitrogen oxide was evolved and water and senecialdehyde were condensed in the collecting flask (cooled with $CO_2$ and acetone). The crude aldehyde was oximated with hydroxylamine hydrochloride (5 g) according to the procedure described above. The yield of **1b** was 3.2 g. The crude oxime was used in the subsequent reactions ($Z,E$ mixture).

*The cycloaddition of 3,3-dimethylacrylonitrile oxide to isoprene,* **3a,b**. Senecialdehyde oxime (0.99 g) in chloroform (10 ml, with two drops of pyridine added) was chlorinated with N-chlorosuccinimide (NCS) (1.36 g) at 0–5 °C for 15 min. Isoprene (2.1 g) was added and followed by, dropwise, triethylamine (1.05 g) in chloroform (10 ml) over 1.5 h with stirring. The solution was left to stand overnight at 25 °C whereupon it was washed twice with water, dried over $MgSO_4$ and evaporated. The residue was purified by preparative TLC ($SiO_2$, $CHCl_3$, 2 % $CH_3OH$). The major fraction (1.18 g, 72 %) consisted of an oily 1:3 mixture of **3a:3b**. $^1H$ NMR ($CDCl_3$): **3a**, δ 1.47 (3 H, s), 1.89 (3 H, s), 1.95 (3 H, s), ca. 3 (2 H, m), 4.8–5.4 (2 H, m), 5.86 (1 H, br s), 5.98 (1 H, dd, J 16 and 10 Hz). **3b**, 1.74 (3 H, s), 1.89

(3 H, s), 1.95 (3 H, s), 2.7–3.5 (2 H, m), 4.7–5.1 (3 H, m), 5.86 (1 H, br s). The minor fraction (0.18 g, oil) was the product from a biscycloaddition MS: *m/z* 262 (*M*⁺). ¹H NMR (CDCl₃): δ 4.59 (1 H, t, *J* 9 Hz), 5.89 (2 H, br s). In a second experiment the crude product was distilled in a Kugelrohr apparatus at 110 °C/ 0.2 mmHg. **3a,b** were obtained as a light yellow oil. The yield was 78 %.

**3c,d** *and* **10**. Citral oxime (0.33 g, crude) in chloroform (1 ml) was added slowly to isoprene (0.42 g) and pyridine (0.09 g) and NCS (0.27 g) in chloroform (1 ml) at 0 °C with stirring. The temperature was then kept at 25 °C for 2 h. The solution was washed twice with water, dried over MgSO₄ and evaporated. The residue was purified by preparative TLC (SiO₂, CHCl₃, 1 % CH₃OH). **3c,d** were obtained as an oily mixture (1:3), 0.15 g, 32 %. ¹H NMR (CDCl₃): **3d**, 1.5–2.4 (16 H, m), 2.7–3.5 (2 H, m), 4.7–5.3 (4 H, m), 5.87 (1 H, br s). **3c** shows characteristically one CH₃ signal at δ 1.46. MS: *m/z* 233 (*M*⁺). **10** was obtained as an oil from a band of lower *R*_f value in a yield of ca. 20 %. ¹H NMR (CDCl₃): 1.11 (3 H, s), 1.50 (3 H, s), 1.89 (3 H, s), 1.2–2.4 (4 H, m), 2.84 (1 H, dd, *J* 5 and 12 Hz), 6.17 (1 H, br s). MS: *m/z* 165 (*M*⁺). Compound **10** was obtained in a yield of 27 % when citral oxime was added to NCS and pyridine in chloroform at 25 °C. The product was purified by preparative TLC (SiO₂; petroleum ether–ethyl ether 3:2).

*5-Acetoxymethyl-3-styrylisoxazoline* (**3e**). Cinnamaldehyde oxime (1.47 g) was chlorinated at 0 °C with NCS (1.36 g) in chloroform (10 ml and pyridine 0.1 ml). The solution turned dark brown but it became light yellow after ca. 10 min. After 0.5 h, allyl acetate (1.25 g) was added followed by triethylamine (1.05 g in chloroform, 5 ml), dropwise, with stirring. The solution was kept at 25 °C for 45 min, filtered, washed twice with water, dried over MgSO₄ and evaporated. The residue was recrystallized from methanol to give 0.98 g of **3e**, m.p. 102 °C. From the mother liquor a second crop of crystals (0.15 g) was isolated by preparative TLC (SiO₂; CHCl₃–2 % CH₃OH). The total yield of **3e** was 46 %. ¹H NMR (CDCl₃): δ 2.02 (3 H, s), 2.96 (1 H, dd, *J* 8 and 16 Hz), 3.23 (1 H, dd, *J* 10 and 16 Hz), 4.17 (2 H, d, *J* 4 Hz), 4.83 (1 H, m), 6.72 (1 H, d, *J* 16 Hz), 7.00 (1 H, d, *J* 16 Hz), 7.33 (5 H, br s).

*5-Ethoxycarbonyl-3-propenylisoxazoline* (**3f**). NCS (0.67 g) was added to a mixture of freshly prepared crotonaldehyde oxime (0.43 g), pyridine (0.41 g) and ethyl acrylate (1.0 g) in chloroform (5 ml) at 0 °C. The mixture was stirred for 0.5 h washed with water and dilute hydrochloric acid (pH 2–3). Usual work-up gave **3f** as a yellow oil (0.58 g, 63 %). ¹H NMR (CDCl₃): δ 1.30 (3 H, t, *J* 7 Hz), 1.88 (3 H, d, *J* 5 Hz), 3.30 (2 H, d, *J* 9 Hz), 4.20 (2 H, g, *J* 7 Hz), 4.97 (1 H, t, *J* 9 Hz), 5.96 (1 H, dq, *J* 16 and 6 Hz), 6.29 (1 H, d, *J* 16 Hz).

*5-(2-Acetoxyethyl)-3-(2,2-dimethylvinyl)-5-methylisoxazoline* (**3g**). Senecialdehyde oxime (4.0 g) in chloroform (12 ml and 3 drops of pyridine) was chlorinated with NCS (5.5 g) at 25 °C with stirring. 4-Acetoxy-2-methyl-1-butene (5.6 g) was added followed by triethylamine (4.4 g) over 1 h. The solution was stirred for 20 h, washed with water and with diluted hydrochloric acid (pH 2–3), dried (MgSO₄) and evaporated. The residue was chromatographed through a silica column (petroleum ether–ethyl ether 1:3) to give **3g** as a yellow oil in a yield of 56 % ¹H NMR (CDCl₃): δ 1.38 (3 H, s), 1.86 (3 H, s), 1.86 (3 H, s), 1.92 (3 H, s), 1.99 (2 H, t, *J* 7.8 Hz), 2.02 (3 H, s), 2.85 (1 H, d, *J* 16.5 Hz), 3.03 (1 H, d, *J* 16.5 Hz), 4.18 (2 H, t, *J* 7.8 Hz), 5.86 (1 H, br s).

*3-(2,2-Dimethylvinyl)-5-methyl-5-(4-methyl-3-cyclohexenyl)-isoxazoline* (**3h**). Senecialdehyde oxime (1.98 g) in ethyl acetate (5 ml) was chlorinated with *t*-butyl hypochlorite (2.17 g) in ethyl acetate (3 ml) at 0 °C for 10 min. (+)-Limonene (2.7 g), potassium hydrogencarbonate (3.0 g) and two drops of water were added. The solution was stirred for 20 h after which it was washed twice with water, dried over MgSO₄ and evaporated. Chromatography of the crude product through a silica column (petroleum ether–ethyl ether 4:1) gave **3h** (2.98 g, 64 %) as a yellow oil. ¹H NMR (CDCl₃): δ 1.16 (3 H, s), 1.49 (3 H, s), 1.72 (3 H, s), 1.79 (3 H, 2), 1.55–1.95 (7 H, m), 2.57 (1 H, d, *J* 16.5), 2.61 (1 H, d, *J* 16.5), 2.87 (1 H, d, *J* 16.5), 5.22 (1 H, br s), 5.73 (1 H, br s). **3h** consists of a diastereomeric pair of isomers formed in the ratio 1:1.

*2,2-Dimethylvinyl-5-(2-hydroxyethyl)-5-methylisoxazoline* (**3i**). Senecialdehyde oxime was chlorinated with *t*-butyl hypochlorite at 0 °C for 10 min. Cycloaddition to 3-methyl-3-buten-1-ol and usual work-up gave **3i** as an oil. The crude product was chromatographed on a silica column (ethyl ether–dichloromethane 1:4). The yield was 57%. ¹H NMR (CDCl₃): δ 1.39 (3 H, s), 1.86 (3 H, s), 1.91 (3 H, s), 1.92 (2 H, m), 2.87 (1 H, d, *J* 17.5 Hz), 3.07 (1 H, d, *J* 17.5 Hz), 3.79 (2 H, m), 5.86 (1 H, br s).

*3,5-Diprop-1-enylisoxazoline* (**3j**). Crotonaldehyde oxime (2.66 g, freshly prepared) was chlorinated in dichloromethane (5 ml) by slow addition of *t*-butyl hypochlorite (3.46 g in 5 ml of CH₂Cl₂) at 10–15 °C. (*E*)-1,3-pentadiene (1.77 g), potassium hydrogencarbonate (4 g) and water (0.1 ml) were added and the mixture was stirred for 20 h. The usual work-up gave a crude product, which, when purified by column chromatography (SiO₂; ethyl ether–petroleum ether 1:4), gave **3j** (2.26 g, 58 %). ¹H NMR (CDCl₃): δ 1.72 (3 H, d, *J* 6 Hz), 1.89 (3 H, d, *J* 6 Hz), 2.79 (1 H, dd, *J* 16 and 8 Hz), 3.10 (1 H, dd, *J* 16 and 9 Hz), 4.92 (1 H, m), 5.5–6.6 (4 H, m).

N-*Methylation of isoxazolines. Preparation of* **4e,f,h,j**: *General procedure*. The isoxazoline (1 mol), dimethyl sulfate (DMS, 2 mol) and sodium hydrogencarbonate (0.15

mol, finely ground) were stirred for 20 h at 45–50 °C. If the isoxazoline did not dissolve in DMS a few milliliters of chloroform were added. The crude monomethyl sulfate salts formed highly viscous oils, which could be used directly for the electrochemical reduction. Usually they were purified by being partitioned between diethyl ether and water. Diethyl ether dissolved impurities and the excess of DMS and the salt went into the aqueous phase, from which it was precipitated by addition of sodium perchlorate (1.5 mol). The ether phase was washed once with water and the water phases were combined. The perchlorates were often solids, and were filtered off after cooling of the aqueous solution in the refrigerater. Oily perchlorates were isolated by extraction with chloroform. The yields were in the range 70–90 %. In the $^1$H NMR spectrum the N–CH$_3$ group is located at δ ca. 3.8. Compound **4e** is a slightly yellow solid, m.p. 180–190 °C, decomp. (from water–methanol 1:3). **4h**, m.p. 118–123 °C (from ethyl acetate; as perchlorate). $^1$H NMR (CD$_3$CN): δ 2.03 (3 H, s), 3.86 (3 H, s), 3.8–4.2 (2 H, m). 4.35 (2 H, d, $J$ 5 Hz), 5.33 (1 H, m), 7.18 (1 H, d, $J$ 16 Hz), 7.3–7.9 (5 H, m), 7.81 (1 H, d, $J$ 16 Hz). IR(KBr): 1735 cm$^{-1}$ (s). **4f,j** formed viscous oils. $^1$H NMR (CDCl$_3$): **4f**, δ 1.31 (3 H, t, $J$ 7 Hz), 2.17 (3 H, d, $J$ 6 Hz), 3.7–4.2 (2 H, m), 3.89 (3 H, s), 4.27 (2 H, q, $J$ 7 Hz), 5.50 (1 H, dd, $J$ 10 and 8 Hz), 6.64 (1 H, d, $J$ 15 Hz), 7.16 (1 H, dq, $J$ 15 and 6 Hz). **4h**, 1.46 and 1.48 (3 H, two diastereomers 1:1), 1.58 (3 H, br s), 1.6–2.1 (7 H, m), 2.12 (3 H, s), 2.14 (3 H, s), 3.62 (2 H, br s), 3.75 (3 H, s), 5.30 (1 H, br s), 6.26 (1 H, s). **4j**, 1.79 (3 H, d, $J$ 6 Hz), 2.14 (3 H, d, $J$ 6 Hz), 3.4–3.8 (2 H, m), 3.81 (3 H, br s), 5.3–5.9 (2 H, m), 6.61 (1 H, d, $J$ 17 Hz), 7.12 (1 H, dq, $J$ 17 and 6 Hz).

*The electrochemical reduction of the 3-alkenylisoxazolium salts* **4**. This was carried out in aqueous ethanol (40 % ethanol, pH ca. 5, acetate buffer) at ca. −0.60 V (vs. SCE).[9] The polarogram showed two waves separated by 0.20–0.25 V. The conjugated olefinic function was reduced at the more negative potential. The ethanol was removed *in vacuo* and the remaining aqueous emulsion was extracted with chloroform. The organic phase was dried over Na$_2$SO$_4$ and evaporated to give the crude β-hydroxy ketone.

*1-Acetoxy-2-hydroxy-6-phenyl-5-hexen-4-one* (**5e**). This was obtained as a colourless oil from the reduction of **4e**. The crude product was purified by preparative TLC (SiO$_2$; dichloromethane–diethyl ether 4:1). The yield was 39 %. $^1$H NMR (CDCl$_3$): δ 2.03 (3 H, s), 2.88 (2 H, d, $J$ 6 Hz), 4.13 (2 H, d, $J$ 5 Hz), 4.36 (1 H, m), 5.0 (1 H, br s), 6.72 (1 H, d, $J$ 16 Hz), 7.0–7.5 (5 H, m), 7.54 (1 H, d, $J$ 16 Hz).

*Ethyl 2,5-dihydroxy-4-oxoheptanoate* (**9f**) *and ethyl 4-oxo-2,5-heptadienoate* (**7f**). *Method 1.* Compound **3f** (2.95 g) was epoxidized with *m*-chloroperbenzoic acid (3.2 g) in dichloromethane (20 ml) at 25 °C for 20 h. The

solution was filtered, washed with aqueous sodium hydroxide (pH 10–11), dried over MgSO$_4$ and evaporated to give crude **8j** (3.4 g) which was catalytically reduced over Raney Ni in methanol. The catalyst was filtered off through Celite® and the filtrate evaporated to a small volume *in vacuo*. The residue was dissolved in dichloromethane, dried over MgSO$_4$, filtered and the solvent evaporated to give crude **9f** (3.08 g). Methanesulfonyl chloride (1.4 g, 3 equiv.), was added dropwise with stirring to **9f** (0.77 g) and triethylamine (3.7 g, 9 equiv.) in chloroform (15 ml) at 0 °C. The solution was refluxed for 15 min, cooled, washed twice with water, dried over MgSO$_4$ and evaporated. Purification of the residue by preparative TLC (SiO$_2$; CH$_2$Cl$_2$) gave 0.28 g of **7f**. The overall yield from **3f** was 42 %. $^1$H NMR (CDCl$_3$): **7f**, δ 1.24 (3 H, t, $J$ 7.5 Hz), 1.90 (3 H, d, $J$ 7 Hz), 4.19 (2 H, q, $J$ 7.5 Hz), 6.30 (1 H, d, $J$ 16.5 Hz), 6.65 (1 H, d, $J$ 16.5 Hz), 6.97 (1 H, dq, $J$ 16.5 and 7 Hz), 7.30 (1 H, d, $J$ 16.5 Hz). **8f**, 1.25 (3 H, t, $J$ 7.5 Hz), 2.9–3.2 (3 H, m), 3.53 (1 H, br s), 4.19 (2 H, q, $J$ 7.5 Hz), 4.97 (1 H, m). **9f**, 1.17 (3 H, d, $J$ 6 Hz), 1.26 (3 H, t, $J$ 7.5 Hz), 2.62 (2 H, d, $J$ 6 Hz), 2.93 (2 H, m), 4.0–4.6 (4 H, m).

*Method 2.* Electrochemical reduction of **4f** according to the general procedure described above gave **9f**. The $^1$H NMR spectrum of the crude product was identical with that of the product from catalytic reduction of **8f**.

*Deodarone* (**6h**). The isoxazoline **3h** was methylated and reduced electrochemically as described above. The crude product was purified by preparative TLC (SiO$_2$; CHCl$_3$–diethyl ether 95:5) to give directly the tetrahydro-γ-pyrone, deodarone (**6h**) in a yield of 50 %. The $^1$H NMR spectrum showed two diastereomeric **6h** in the ratio 1:1. The spectral data (NMR, IR, MS) were in agreement with data from the literature.[10c]

*Atlantone* (**7h**). This was obtained by treating deodarone (**6h**) with *p*-toluenesulfonic acid (1:1) in dichloromethane at 30 °C for 20 h. The solution was washed with water, pH 8–9, dried over MgSO$_4$ and evaporated to give **7h** in a yield of 55 %. The $^1$H NMR and MS spectral data of **7h** were in agreement with published data.[13]

*2,4,7-Nonatrien-6-one* (**7j**) *and 8-ethoxy-2,4-nonadien-6-one* (**16**). These were obtained by electrochemical reduction of **4j** in aqueous ethanol. The $^1$H NMR spectrum of the impure crude product indicated the presence of **5j** and **6j**. It was directly dehydrated in chloroform with methanesulfonyl chloride (3 mol) and triethylamine (9 mol) at 0 °C for 15 min and then at 30 °C for 2 h. The chloroform solution was washed with water and dilute hydrochloric acid, dried over MgSO$_4$ and evaporated *in vacuo*. Purification of the residue by preparative TLC (SiO$_2$; CH$_2$Cl$_2$) gave **7j**, 33 % and **16** 19 %, as colourless liquids. $^1$H NMR (CDCl$_3$): **7j**, δ 1.75–1.95 (6 H, m), 6.1–6.4 (4 H, m), 6.85 (1 H, dq, $J$ 16.5 and 7.5 Hz), 7.20 (1 H, m). MS: *m/z* 136 ($M^+$). **16**, 1.05–1.20 (6 H, m), 1.84 (3 H, d, $J$ 5.5 Hz), 2.50 (1 H, dd,

*J* 16 and 6 Hz), 2.83 (1 H, dd, *J* 16 and 6.5 Hz), 3.3–3.6 (2 H, m), 3.90 (1 H, m), 6.05 (1 H, d, *J* 16.5 Hz), 6.16 (2 H, m), 7.11 (1 H, m). MS: *m/z* 182 (*M⁺*).

*Compound 8i.* Isoxazoline **3i** (0.18 g) was epoxidized with *m*-chloroperbenzoic acid (0.20 g) in dichloromethane at 4°C for 20 h. The precipitate was filtered off and the solution washed with basified water, pH ca. 10, dried over MgSO₄ and evaporated. Crude **8i** (0.19 g) was obtained, which was used directly for catalytic reduction. ¹H NMR (CDCl₃): δ 1.35 (3 H, s), 1.39 (6 H, s), 1.94 (2 H, t, *J* 6.6 Hz), 2.74 (1 H, dd, *J* 17.8 and 6.7 Hz), 2.96 (1 H, dd, *J* 17.8 and 6.7 Hz), 3.49 (1 H, br s), 3.79 (2 H, m).

*Synthesis of ocimenones* (**7a**). *Method 1.* The epoxide **8i** (0.19 g), was reduced catalytically over Raney Ni in methanol (4 ml) in the presence of boric acid (0.3 g). The solution was filtered through Celite, which was washed with a few milliliters of methanol. The solvent was evaporated *in vacuo,* dichloromethane (10 ml) and MgSO₄ (drying agent) were added and the suspension was filtered. Silica (3 g) was added and solvent removed *in vacuo.* The silica was heated in a Kugelrohr apparatus at 200°C/40 mmHg, and the condensate, which consisted mainly of (*Z*)-ocimenone (**7a**) was purified by preparative TLC (SiO₂; petroleum ether–ethyl ether 7:1). The yield was 10–20%. The NMR spectrum was in agreement with published data.¹¹ᵉ A small amount of a faster-running compound was tagetone (**14**).

*Method 2.* The isoxazoline **3g** was epoxidized as described for **8i**. The crude product was reduced over Raney Ni as described above and subsequently dehydrated with methanesulfonyl chloride/triethylamine (3.5 mol/9 mol). Usual work-up gave a product, which without purification was thermolyzed on silica (crude acetate, **7g**, SiO₂, flash gel, 230–400 mesh, 2 g) in a Kugelrohr apparatus at 180°C/ 60 mmHg for 30 min. The distillate was a mixture of (*Z*)-(major) and (*E*)-ocimenones **7a** contaminated with a small amount of tagetones **14**. The overall yield was ca. 20% as calculated from **3g**.

*Compound 11.* The yellow oil was prepared from crotonaldehyde oxime and cyclopentene according to the usual procedure. The yield was 23%. ¹H NMR (CDCl₃): δ 1.0–2.2 (6 H, m), 2.15 (3 H, d, *J* 7.5 Hz), 3.65 (1 H, m), 5.00 (1 H, m), 6.00 (1 H, dq, *J* 16 and 5 Hz), 6.19 (1 H, d, *J* 16 Hz).

*5-(2-Acetoxyethyl)-3-isobutyl-5-methylisoxazoline* (**12a**). Isovaleraldehyde oxime (17 g) was chlorinated at 20°C with NCS (26 g, added in portions) in chloroform (80 ml and 0.2 ml pyridine). The solution turned blue during the chlorination but the color faded towards the end of the reaction. After 1 h, 4-acetoxy-2-methyl-1-butene (22 g) was added followed by triethylamine (20 g) over 3 h. The solution was stirred for a further 20 h, washed with water and with dilute hydrochloric acid (pH 2), dried over

MgSO₄ and evaporated *in vacuo.* The residue was purified by column chromatography (SiO₂; CDCl₃–2% CH₃OH) to give **12a** in a yield of 47%. ¹H NMR (CDCl₃): δ 0.93 (6 H, d, *J* 7.5 Hz), 1.34 (3 H, s), 1.83 (1 H, m), 1.96 (2 H, t, *J* 7.5 Hz), 2.01 (3 H, s), 2.16 (2 H, d, *J* 7.5 Hz), 2.60 (1 H, d, *J* 17.5 Hz), 2.80 (1 H, d, *J* 17.5 Hz), 4.16 (2 H, t, *J* 7.5 Hz).

*5-(2-Hydroxyethyl)-3-isobutyl-5-methylisoxazoline* (**12b**). Isovaleraldehyde oxime (6.3 g) in ethyl acetate (30 ml) was chlorinated with *t*-butyl hypochlorite (6.8 g, dropwise addition) at 0°C. 3-Methyl-3-buten-1-ol (4.4 g) and potassium hydrogencarbonate (15 g) and water (0.1 ml) were added. The mixture was stirred at 25°C for 20 h. Usual work-up gave 5.2 g of **12b** (yellow oil, 69%) by chromatographic purification on a silica column (dichloromethane–ethyl ether 6:1). The product was slightly impure. The presence of the furoxan derivative was observed. ¹H NMR (CDCl₃): δ 0.95 (6 H, d, *J* 6 Hz), 1.33 (3 H, s), 1.6–2.4 (5 H, m), 2.78 (2 H, d, *J* 6.5 Hz), 3.72 (2 H, t, *J* 7 Hz).

Compounds **13a,b** were obtained by catalytic reduction of **12a,b** over Raney Ni in methanol–water (10:1) in the presence of boric acid (ca. 2 equiv. relative to the substrate). The solution was filtered through Celite, evaporated and extracted with ethyl ether. The ether solution was dried over MgSO₄ and evaporated to give crude **13a,b** which was used directly for further synthesis. The crude yields are practically quantitative. ¹H NMR (CDCl₃): **13a**, δ 0.89 (6 H, d, *J* 6 Hz), 1.20 (3 H, s), 1.82 (2 H, dt, *J* 1.2 and 7.5 Hz), 2.00 (3 H, s), 2.24 (2 H, d, *J* 8 Hz), 2.54 (1 H, d, *J* 17.5 Hz), 2.58 (1 H, d, *J* 17.5 Hz), 4.17 (2 H, t, *J* 7.5 Hz).

*Synthesis of tagetones* (**14**). **13b** (0.39 g, crude) and sodium acetate (1.0 g) were heated to reflux in acetic acid (2.5 ml) for 15 min. Part of the acetic acid was evaporated at 35°C/ 20 mmHg and dichloromethane was added. The mixture was washed with aqueous sodium hydrogencarbonate, dried over MgSO₄, evaporated (20°C/ 20 mmHg) and purified on a TLC plate (SiO₂; petroleum ether–ethyl ether 10:1) to give 0.22 g (67%) of **14**. It consisted of nearly pure *Z*-isomer. ¹H NMR (CDCl₃): δ 0.88 (6 H, d, *J* 7 Hz) 1.92 (3 H, s), 2.12 (1 H, m), 2.27 (2 H, d, *J* 7 Hz), 5.40 (1 H, d, *J* 11 Hz), 5.57 (1 H, d, *J* 17 Hz), 6.02 (1 H, br s), 7.69 (1 H, dd, *J* 11 and 17 Hz). MS: *m/z* 152 (*M⁺* 45%), 113 (68%), 95 (100%), 85 (42%). The *Z*-isomer rearranges slowly to the *E*-isomer. ¹H NMR (CDCl₅): δ 5.40 (1 H, d, *J* 11 Hz), 5.61 (1 H, d, *J* 17 Hz), 6.09 (1 H, br s), 6.32 (1 H, dd, *J* 11 and 17 Hz).

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