Reactions with $\alpha,\beta$-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 $\alpha,\beta$-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-$\gamma$-pyrones is observed. The reactions were applied to the synthesis of tagetones, ocimenones, deodarone and atlantone.

$\alpha,\beta$-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 competitively 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 $\alpha,\beta$-unsaturated aldehyde oximes in nitrile oxide cycloadditions, because the highly functionalized $\alpha,\beta$-unsaturated carbonyl system produced is synthetically interesting and fruitful synthetic application (Scheme 1) would be rewarding.

$\alpha,\beta$-Unsaturated aldehyde oximes. Oximation of $\alpha,\beta$-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 $\alpha,\beta$-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 in the presence of excess of sodium hydorgen carbonate. Crotonaldehyde oxime, cinnamaldehyde oxime, $\beta,\beta$-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 (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.

$1 \rightarrow 2 \rightarrow 3$

Scheme 1.

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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. 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. Triethylamine and sodium hydrogencarbonate in wet ethyl acetate are suitable bases for generating the corresponding nitrile oxides. The nitrile oxides react with alkenes to give the expected unsaturated isoxazolines. 3-Alkenylisoxazolines have been obtained previously by Wittig reaction of 3-alkylphospho-substituted isoxazolines with carbonyl compounds.  

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 diaduct 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 3e 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. 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.
Preliminary tests showed that 3a to a certain extent gave the saturated ketone when reduced with Ti²⁺. Zinc powder in acetic acid gave predominantly the saturated ketone. Selective reductive cleavage was achieved by electrochemical reduction of the isoxazolium salts 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 led to reduction of the conjugated double bond.

The unsaturated hydroxy ketones 5 undergo ring closure to give tetrahydro-γ-pyrroles 6. Acid-catalyzed elimination of water gives the cross-conjugated diene 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 diene ⁷j in 42% yield based on the isoxazoline ⁷j. The triene 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 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 syntheses have been recorded. 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 ³³a, b. (Z)-Tagetone 14 was obtained in a satisfactory yield when crude ³³b was heated in refluxing acetic acid in the presence of sodium acetate for 15 min (Scheme 4). The formation of tagetones from ³³a by acid- or base-catalyzed elimination of water and acetic acid was capricious. At-
\[ \text{Scheme 5.} \]

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

The oicirones (7a) have been synthesized several times.\textsuperscript{10a,a11} We have applied the method for the tagetones starting with senealdehyde 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 oicirone (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 deoxyenation 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.

Deodorone (6b), and atlantone (7b), have a carbon skeleton well suited for construction by our isoxazole methodology. The nitrile oxide generated from senealdehyde 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-
(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 bis-cycloaddition 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 yellow oil. The yield was 78 %.

3c, d and 10. Citral oxime (0.33 g, crude) in chloroform (1 mL) was added slowly to isopropene (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 Rf, 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–ethylether 3:2).

5-Acetoxyethyl-3-styrylisoxazoline (3c). 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 3c, 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 3c 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-Ethoxy carbonyl-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 1:4) 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-Dimethylinyl-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 electroreduction chemical. 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 refrigerator. Oil perchlorates were isolated by extraction with chloroform. The yields were in the range 70–90 %. In the 1H NMR spectrum the N–CH₃ 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). 1H NMR (CD₂CN): 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. 1H NMR (CDCl₃): 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, dd, 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, d, 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). 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 Na₂SO₄ 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 (SiO₂; dichloromethane–diethyl ether 4:1). The yield was 39 %. 1H NMR (CDCl₃): 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 MgSO₄ 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 MgSO₄, 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 MgSO₄ and evaporated. Purification of the residue by preparative TLC (SiO₂; CH₃Cl₂) gave 0.28 g of 7f. The overall yield from 3f was 42 %. 1H NMR (CDCl₃): 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 1H NMR spectrum of the crude product was identical with that of the product from catalytic reduction of 8f.

**Deodarone (6h).** The isoxazoline 3b was methylated and reduced electrochemically as described above. The crude product was purified by preparative TLC (SiO₂; CHCl₃–diethyl ether 95:5) to give directly the tetrahydro-γ-pyrone, deodarone (6h) in a yield of 50 %. The 1H 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.³⁶

**Atlantione (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 MgSO₄ and evaporated to give 7h in a yield of 55 %. The 1H NMR and MS spectral data of 7h were in agreement with published data.³⁵

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 1H 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 MgSO₄ and evaporated in vacuo. Purification of the residue by preparative TLC (SiO₂; CH₃Cl₂) gave 7j, 33 % and 16 19 %, as colourless liquids. 1H NMR (CDCl₃): 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 1i (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 over 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. 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)- and (E)-ocimenones 7aa contaminated with a small amount of tagetones 14a. 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, d, 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-buten (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 (2H, 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 i-buty1 hypochlorite (6.8 g, dropwise addition) at 0°C. 3-Methyl-3-buten-1-ol (4.4 g) and potassium hydrogen carbonate (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): 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 4.8 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 hydrogen carbonate, 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 (CDCl₃): 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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References


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