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Silyl Nitronates in Organic Synthesis. Routes to Heterocycles and Cyclopentanoids. Synthesis of Allethrolone and Calythrone. Acylation and Cyanohydroxylation of Double Bonds. An Exploratory Study

SØREN H. ANDERSEN, NALIN B. DAS, RUTH D. JØRGENSEN, GUNHILD KJELDSEN, JES S. KNUDSEN†, SUBHASH C. SHARMA and KURT B. G. TORSSELL*,**

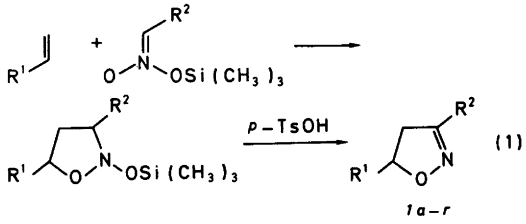
Chemical Institute, Department of Organic Chemistry, University of Aarhus, DK-8000 Aarhus C, Denmark

Silyl nitronates are versatile reagents for the preparation of heterocycles by dipolar addition to double bonds. The intermediate isoxazolidines can be transformed to 2-isoxazolines, isoxazoles, furans, dihydrofuranones, pyrazoles, pyridazines and pyridazones. Reduction of 2-isoxazolines with Ti^{3+} leads to hydroxylated 1,4-diketones, which subsequently can be cyclized to cyclopentenones. Routes to calythrone, rethrolones, prostanoids and a number of naturally occurring dihydrofuranones are devised, as well as synthetic procedures for acylation, preparation of endiones, hydroxyacylation, cyanation and hydroxycyanation of double bonds.

In earlier papers[1,2a] preparations and properties of trimethylsilyl nitronates were described. Of special interest is their use as starting material for preparation of isoxazolidines which can be transformed to a number of heterocycles including 2-isoxazolines, isoxazoles, pyrazoles and pyrrolidones. This work is extended to the preparation of some furans, pyridazines and pyridazones. In this connection we investigated an alternative route to muscimol analogues.

Our isoxazoline synthesis is closely related to Mukaiyama-Hoshino's procedure which generates nitrile oxides by dehydration of primary nitro compounds with phenylisocyanate and catalytic amounts of triethylamine.[2b]

It was envisaged that the 2-isoxazolines obtained from vinyl ketones and silyl nitronates on selective reduction of the N – O bond, hydrolysis, and base catalyzed cyclization should give cyclopentenones, which are important structural units of many natural products of different biogenetic origins. These reactions and a few other modifications of 2-isoxazolines are the subject of the present communication.



1,3-Dipolar addition preparation of starting materials. The three-step sequence: silylation, dipolar addition and silanol elimination that leads to the 2-isoxazolines (1) can with advantage be carried out as a one pot reaction (Table 1). This is, in fact, the only procedure that worked for preparation of *1e* and *1f*. An attempt to prepare the silyl nitronates of nitro-olefins separately gave a product which did not show the presence of olefinic protons, indicating that intramolecular cyclization may have occurred, presumably to a bicyclic product (2). The silylation was therefore performed in the presence of the reactive methyl vinyl ketone, which trapped the intermediate nitronic ester, and *1e,f* were obtained in satisfactory yields. Most of the isoxazolines were prepared in benzene as solvent.

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**To whom inquiries are to be sent.

† Deceased.

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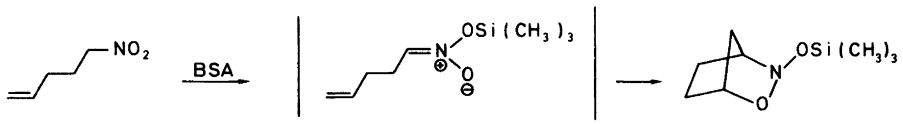
Table 1. Synthesis of 2-isoxazolines.

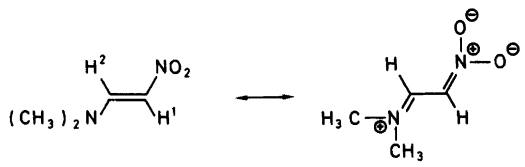
	R^1	R^2	Yield
1a	$COCH_3$	C_2H_5	55
1b	COC_2H_5	C_2H_5	58
1c	$CH=CH_2$	C_2H_5	30
1d	$CH=CHCOOCH_3$	C_2H_5	31
1e	$COCH_3$	$(CH_2)_2CH=CH_2$	55
1f	$COCH_3$	$(CH_2)_3CH=CH_2$	60
1g	$COCH_2OAc$	C_2H_5	47
1h	$COCH_3$	$(CH_2)_2COOCH_3$	52
1i	$COOCH_3$	$CH=CHCOCH_3$	~5
1j	$COOCH_3$	OTs	~10
1k	$COCH_3$	CH_3	76
1l	$COOCH_3$	CH_3	52
1m	$COOCH_3$	C_2H_5	86
1n	$COOCH_3$	C_5H_{11}	81
1o	C_6H_5	CH_3	56
1p	C_6H_5	C_2H_5	79
1q	$OSi(CH_3)_3$, OH	C_5H_{11}	~60
1r	$COCH_3$	$(CH_2)_6COOCH_3$	~100 (crude)



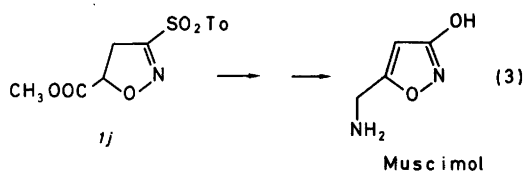
(2)

We later found that the use of acetonitrile or mixtures of acetonitrile and benzene as solvent improved the yield.[2c]

The nitro-olefins required for *1e,f* were prepared from the corresponding bromides. Methyl-3-nitropropanoate was prepared by Michael addition of nitromethane to methyl acrylate and 1-nitropent-2-en-4-one[3] by addition of acetone to 2-dimethylamino-1-nitroethene. This nitroethene derivative shows a small H^1H^2 spin coupling, 10.6 Hz, indicative of a *cis* configuration, but the strongly dipolar nature of the compound could account for this exceptionally small value of the more plausible *trans*-structure. The problem was eventually solved by an X-ray determination proving the *trans* structure.[4]

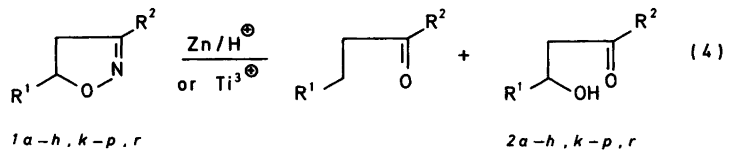


p-Tolyl nitromethyl sulfone was prepared from nitromethane, iodine, and sodium *p*-tolylsulfinate.[5] The nitromethyl sulfone was of interest in context of preparation of muscimol analogues. *1j* could in principle be transformed to muscimols by nucleophilic substitution of the sulfone group[6] by hydroxyl and reduction of the carbomethoxy group to an aminomethyl group (3).[7] The yield of *1j* was disappointingly low, however, so this synthetic route was abandoned. The acetoxymethyl vinyl ketone[8] was prepared according to a slightly modified procedure to avoid polymerization and to free the compound from moisture and acetic acid. Methyl 8-nitrooctanoate was prepared by nitration of cyclooctanone.[9]



1j Muscimol (3)

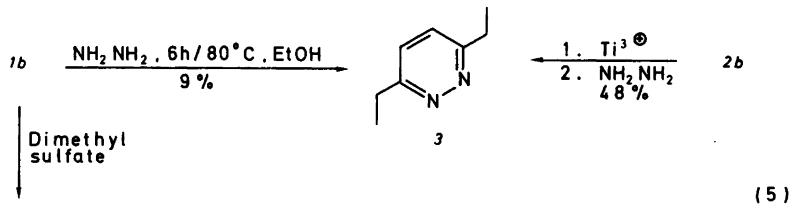
Reduction. The selective reduction presented some problems. Hydrogenation of isoxazolines with Raney-Ni or Pd/C catalysts has been reported to cleave the N–O bond[1,10,11] but is less suitable for the alkene derivatives, *1e* and *f*. 2-Isoxazolines proved to be rather resistant to zinc in acetic acid

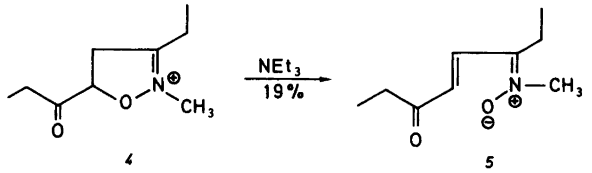


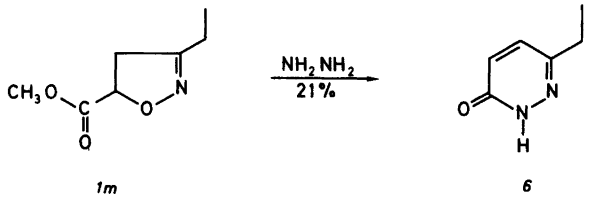
but reduction over a few days or at higher temperatures did cause ring opening at the expense of considerable C–O cleavage (4). The deoxy compound turned out to be the major product. Reduction with titanous ions [12] was slow but selective and the hydroxy derivatives became the major product and were obtained in good yields. The reduction proceeds faster and more satisfactorily at pH 3–4 than under more acidic conditions. The reduction of the acetoxy derivative *1g* turned out to be very sensitive to the reaction conditions. The pH had to be carefully controlled and only the theoretical amount of reducing agent should be used to avoid excessive reductive elimination of the acetoxy group or hydrolysis of the ester. The expected product *2g* was always obtained admixed with *2a* and the corresponding 1-hydroxy derivative.

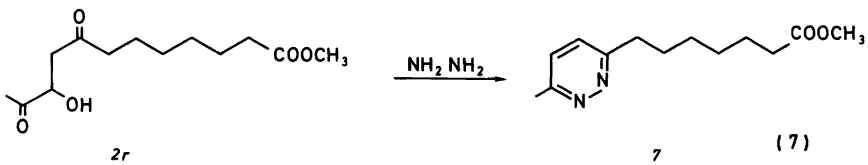
Pyridazines. Treatment of the hydroxydione *2b* obtained by Ti^{3+} reduction of *1b* with hydrazine gave 3,6-diethylpyridazine, *3*.[13] The same compound was formed in lower yield when the isoxazole was treated directly with hydrazine in refluxing ethanol for 6 h. *1b* was transformed to the nitrone *5* by methylation with dimethyl sulfate followed by treatment with triethylamine (5).

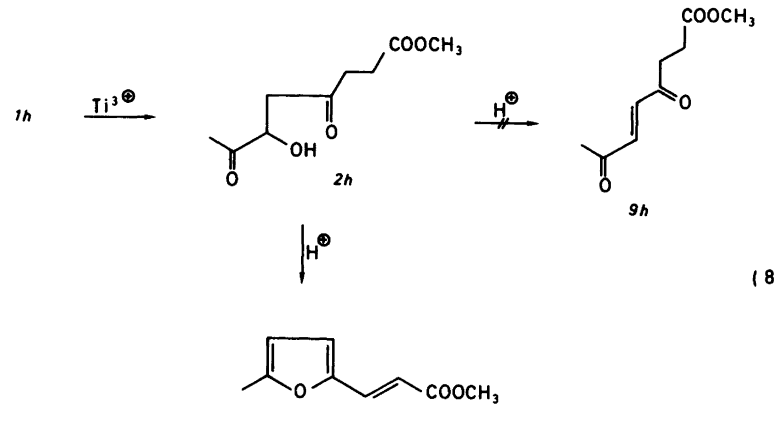
6-Ethyl-3-pyridazone *6* was similarly obtained from 3-ethyl-5-methoxycarbonyl-2-isoxazoline *1m* by refluxing with excess of hydrazine in toluene (6). The long-chain derivative *2r* gave the pyridazine *7* in a yield of 37 % (7).





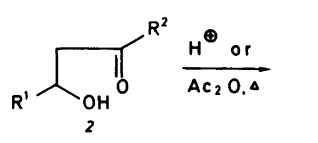






(8)

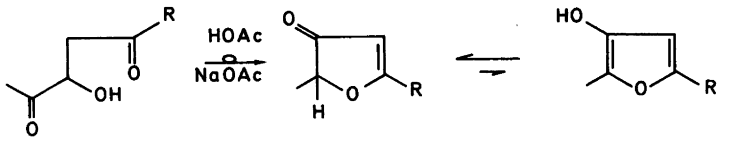
Furans, dihydrofuranones and acylation of olefins. In an attempt to prepare the endione derivative *9h* from *2h* by acid catalyzed elimination of water (*p*-TsOH in refluxing toluene), the furan derivative *8* was unexpectedly formed in a good yield (8). No endione *9h* was observed. This elimination method failed to produce any *9a,b,k—n* from *2a,b,k—n* nor were any furan derivatives obtained. Treatment of *9a,b,k* with hydrochloric acid or perchloric acid under various conditions did not lead to the endione structure. However, elimination of water from the phenyl derivatives, *2o,p* was carried out successfully in high yields by treatment with conc. hydrochloric acid in refluxing methanol. *9p* was obtained admixed with 9 % of the *cis* isomer. The 2-hydroxy esters *21m,n* eventually afforded the corresponding *β*-acylated acrylates by heating with catalytic amounts of conc. perchloric acid in chloroform to which a few drops of methanol had been added. Addition of methanol improved the yield considerably but minor amounts of 2-methoxy esters were obtained as side-products. A search in the literature revealed that elimination of water from 2-hydroxy-1,4-diones can be accomplished by acetylation and subsequent heating.[14] When this method was applied to our hydroxydiones it gave the wanted result (9) albeit in yields somewhat lower than stated earlier. *The procedures described constitute useful preparative methods for β-acylated acrylic esters, vinylketones and styrenes. In a wider context the present method and the complementary 1,3-dipolar addition of nitrile oxides to olefins*[15] *combined with reductive ring opening is a novel and general methods for hydroxyacylation of olefins.* A similar approach to acylation of olefins was recently published by Jäger *et al.*[16]



(9)

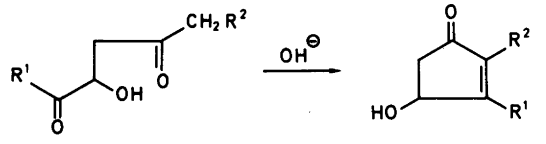
	R^1	R^2
2a, *9a*	CH_3CO	C_2H_5
2d, *9d*	$CH_3OOCCH=CH$	C_2H_5
2h, *9h*	CH_3CO	$(CH_2)_2COOCH_3$
2k, *9k*	CH_3CO	CH_3
2l, *9l*	CH_3OCO	CH_3
2m, *9m*	CH_3OCO	C_2H_5
2n, *9n*	CH_3OCO	C_5H_{11}
2o, *9o*	C_6H_5	CH_3
2p, *9p*	C_6H_5	C_2H_5
2r, *9r*	CH_3CO	$(CH_2)_6COOCH_3$

At this point in the investigation we came to inspect closer the ^1H NMR spectra of the crude hydroxydione *2a* from the Ti^{3+} reduction of 5-acetyl-3-ethyl-2-isoxazoline. They always contained a weak singlet at *ca.* 5.3 ppm which seemed to increase slightly in intensity when the reduction was run for a longer period of time. The peak at δ 5.3 was also visible in several other spectra of crude products from the Ti^{3+} reduction. Purification of *2a* on a preparative TLC plate afforded a small fraction, which gave a ^1H NMR spectrum consistent with *10a*. The lower homologue *10k* is described earlier[17,18] and was therefore synthesized from methyl vinylketone and nitroethane. Small amounts of *10k* were obtained as a side-product (*ca.* 10—15 %), by the Ti^{3+} reduction of *2k*. It turned out that the dihydro-3-furanones *10a,k,r* could be obtained in excellent yields by heating of *2a,k,r* in acetic acid in the presence of sodium



(10)

2a R = C_2H_5 *10a*
2k R = CH_3 *10k*
2r R = $(CH_2)_6COOCH_3$ *10r*



(11)

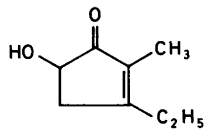
2a $R^1 = R^2 = CH_3$
2b $R^1 = C_2H_5$, $R^2 = CH_3$
2e $R^1 = CH_3$, $R^2 = CH_2CH=CH_2$

11a $R^1 = R^2 = CH_3$
11b $R^1 = C_2H_5$, $R^2 = CH_3$
11e $R^1 = CH_3$ $R^2 = CH_2CH=CH_2$
Allethrolone

acetate as catalyst (10). This novel route to dihydro-3-furanones resembles a procedure involving catalytic reduction of 5-isoxazolylcarbinols and subsequent acid cyclization.[19] According to the ^1H NMR the dihydro-3-furanones occur entirely in their oxo form.

Cyclopentenones, allethrolone, calythrone. 2-Cyclopentanones and pentanones are structural units contained in many important natural products such as rethrolones (insecticides) and prostaglandins (hormones). There are numerous methods for the construction of these structural moieties. One of them is based upon cyclization of 1,4-diketones, which now are available *via* our new route using silyl nitronates. Treatment of *2a,b,e* with dilute aqueous base gave the cyclopentenone derivatives *11a,b,e* (11). The diones can, in principle, cyclize in two directions but for *2a* and *2e* only the condensation involving the methylene group and not the methyl group was observed. Cyclization of *2b*, containing two methylene groups, leads chiefly to *11b* with the hydroxyl group in 4-position, but a small amount of the other isomer, *12*, could be isolated. The hydroxyl group of the major product is thus located in the same position as in natural rethrolones and prostaglandins. The cyclization of *2e* to *11e* completes the synthesis of the rethrolone analogue allethrolone *11e*. The spectral properties of *11e* were identical to those published earlier.[20,21] The hydroxyketone *2e* has been prepared earlier by another route and was cyclized by alkali to *11e*.[14]

11a was oxidized to the cyclopentenedione derivative *13* by treatment with manganese dioxide. *13* was earlier prepared by another route and acylated by isovaleric anhydride to calythrone, *14*.[22] Our route is thus a formal synthesis of this natural product.



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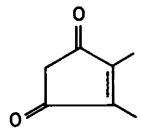

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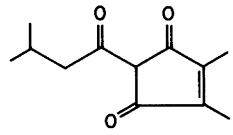
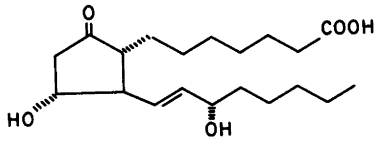


14

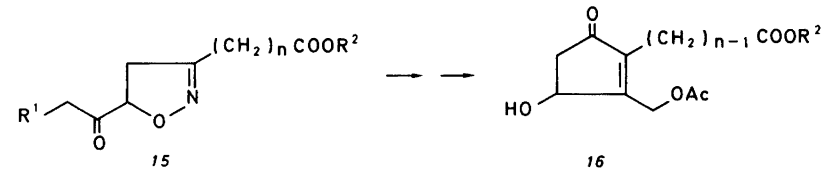
Calythrone

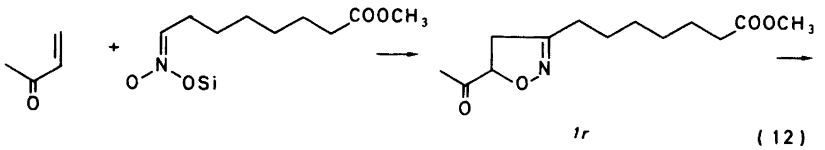
Prostanoids. The cyclopentenones produced by cyclization of the hydroxydiones have structural resemblances to the prostaglandins. If R^2 is a long fatty acid chain, R^1 an allylic alcohol derivative and the endocyclic double bond is reduced, we arrive at PGE_1. The obvious starting materials is therefore an ω-nitrocarboxylic acid for the upper

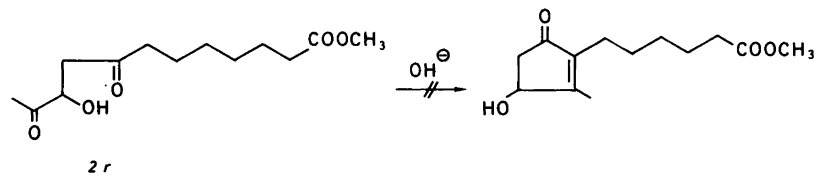


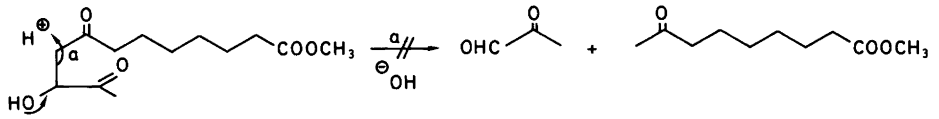
PGE_1

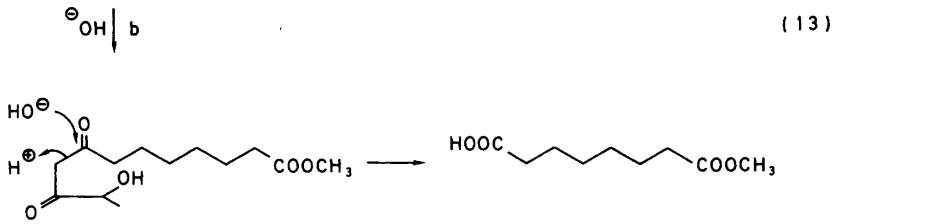
chain, which can be prepared by several methods, *e.g.* nitration of cyclic ketones,[9] and a suitably functionalized vinyl ketone for the lower chain, *e.g.* the easily available acetoxymethyl vinyl ketone.[8] These starting materials should produce the 2-isoxazoline *15*, which on reduction and cyclization could give the prostanoid *16* suited for further elaboration into natural prostaglandins. However, Ti^{3+} reduction of the model compound *1g* showed extensive elimination of the acetoxy function. It was, therefore, decided to start from methyl vinyl ketone and methyl 8-nitrooctanoate in our first attempt. They gave *1r* and subsequently *2r* in excellent yields (12) but the base catalyzed cyclization turned out to be difficult to accomplish despite a considerable variation of the reaction conditions.[14,23-31] The ^1H NMR spectrum of the reaction products showed no sign of the presence of $COCH_3$ or $C{=}C{-}CH_3$ functions, indicating that the starting material had vanished, that cyclization did not occur and that







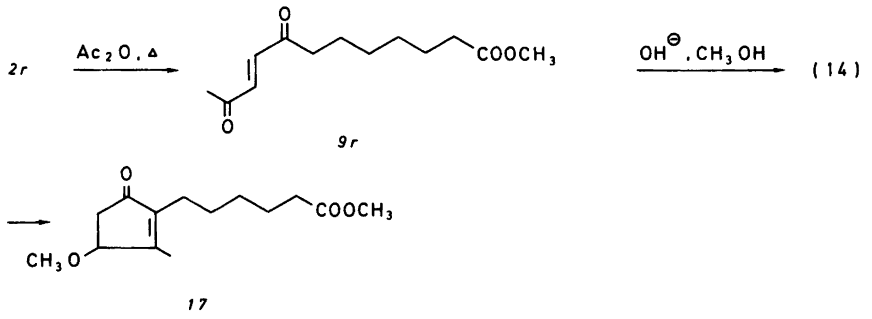




no retroaldol condensation to pyruvic aldehyde and methyl 8-ketononanoate (13a) occurred. A plausible explanation for the failure of the cyclization could be a base catalyzed ketoenol rearrangement followed by a retrocondensation to octadienoate and 3-hydroxy-2-butanone (13b).

It was reported that *trans*-2-en-1,4-diones are cyclized in basic methanol to 3-methoxycyclopentenones.[32,33] *9r* was therefore prepared from *2r* by the acetate procedure and treatment of *9r* with sodium hydroxide in aqueous methanol did indeed give the cyclopentenone *17* in a yield of 67 % (14). The cyclopentenone *18* was similarly prepared from *9a* in a yield of 83 %. The cyclization could be simplified considerably in that it turned out that the intermediate acetate of *2a* could be directly cyclized to *18* in high yield in basic methanol (15). Mechanistically the cyclization is interpreted as base catalyzed elimination of acetate followed by a reversible Michael addition of methanol to the double bond, deprotonation and finally cyclization. The methoxy derivative is evidently not prone to undergo rapid keto-enol rearrangement. Finally we seem to have access to a reliable cyclization method.

Cyano-hydroxylation and cyanation. 2-Isoxazolines with a proton at C^3 are cleaved by bases with formation of cyanohydroxy derivatives[34] (16).



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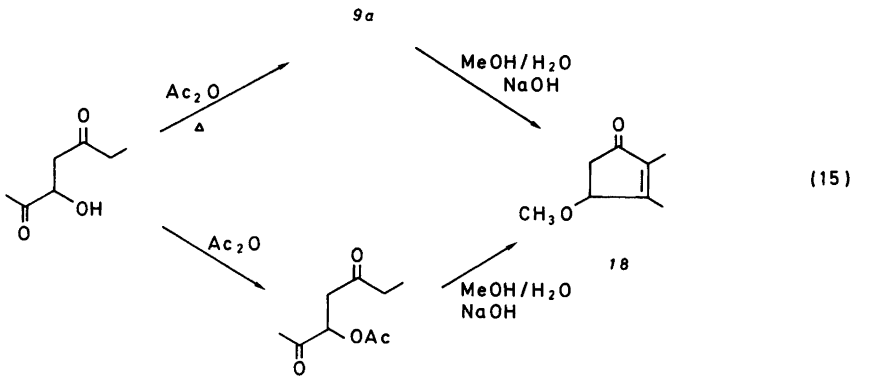

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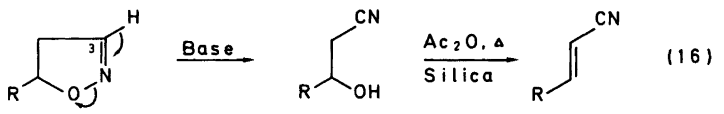
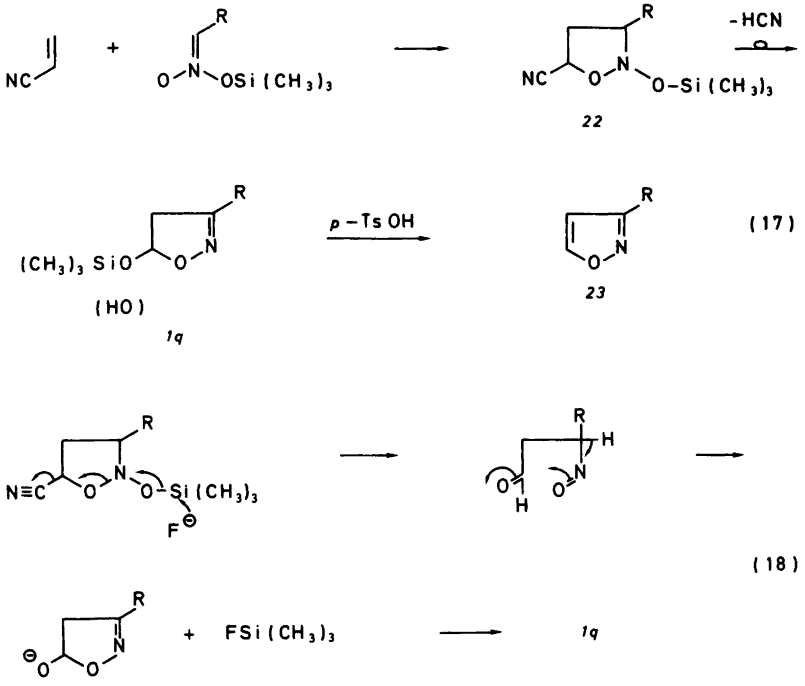


(16)

19a R = C_6H_5 *20a* *21a*

19b R = $COOCH_3$ *20b*



This finding was verified by treatment of 5-phenyl-2-isoxazoline *19a* with sodium methoxide in methanol and by treatment of 5-methoxycarbonyl-2-isoxazoline *19b* with triethylamine at room temperature. The cyano-hydroxylated products *20a,b* were obtained. Acetylation with acetic anhydride followed by thermolysis over basic alumina in refluxing toluene gave cinnamonitrile *21a* (96 %). The corresponding β-cyanoacrylic ester could not be obtained from the acetate of *20b* by this method.

Isoxazoles. The silyl nitronates from primary nitro compounds react rapidly with acrylonitrile to isoxazolidines, which in a fluoride promoted reaction rearrange to 5-silyloxy-2-isoxazolines[1,2] (17). The mechanism of this rearrangement is formulated in (18). Subsequent treatment with *p*-toluenesulfonic acid in refluxing benzene eliminates trimethylsilanol and 3-substituted isoxazoles are formed. This reaction was applied to 1-nitrohexane. The adduct *22*, R = pentyl, was formed in a yield of 93 % (crude). Treatment with potassium fluoride gave according to the ^{1}H NMR spectrum a mixture of the hydroxy and silyloxy derivatives, *1q*. Both components could be transformed into *23* in an overall yield of 33 % by treatment with *p*-TsOH in refluxing toluene. Preparation of isoxazoles by acid-catalyzed elimination of acetic acid and alcohol, respectively, from 5-acetoxy and 5-alkoxy-2-isoxazolines has been described earlier.[35]

EXPERIMENTAL

Acetoxymethyl vinyl ketone.[8] A mixture of 2-butyne-1,4-diol (1 mol, 86.0 g) and acetic anhydride (1.4 mol, 142 g) was heated carefully to 95–100 °C. The reaction was exothermic and the temperature could easily rise to 120–130 °C. The heating was continued for 2 h. After cooling the product was added dropwise to a mixture of mercuric oxide (4.0 g), conc. sulfuric acid (2.0 g) and acetic acid (40 ml). The reaction was exothermic and the temperature was kept at 50–60 °C by occasional cooling. An additional amount of mercuric oxide (2.0 g) was added and the stirring was continued for 0.5 h. The sulfuric acid was neutralized with sodium acetate (8 g) and the precipitate filtered off. Part of the acetic acid was evaporated *in vacuo* and methylene chloride (100 ml) and water (100 ml) were added. The excess of acetic acid was neutralized to pH 8 with solid sodium bicarbonate and the organic phase was separated. The aqueous phase was extracted once more with methylene chloride (25 ml) and the combined organic phases were

dried over sodium sulfate, evaporated and distilled *in vacuo*. The acetoxymethyl vinyl ketone distilled at 68–74 °C/1 mmHg (lit.[8] 70–71 °C/4 mmHg). It was immediately poured into ice-water, sodium bicarbonate was added until pH 8 and the mixture extracted twice with methylene chloride (75+25 ml). Occasionally the distilled vinyl ketone started to polymerize which could be observed by the formation of a water insoluble film. This film was removed by decanting the aqueous solution. The methylene chloride was dried over sodium sulfate and diluted to a known volume (150 ml). The concentration was determined by evaporation of the solvent from an aliquot. The vinyl ketone can be stored in this form for months in the refrigerator. The yield was *ca.* 70 %. ^{1}H NMR ($CDCl_3$): δ 2.16 (3 H, s), 4.87 (2 H, s), 5.88 (1 H, dd, *J* 4.4, 9 Hz), 6.3–6.4 (2H, m).

The *8-nitrooctanoates* were obtained by the literature methods.[9] Nitration of cyclooctanone with butyl nitrate gave a mixture of *2-nitrocyclooctanone*, bp. 73–74 °C/0.2 mmHg and *butyl 8-nitrooctanoate*, bp. 162 °C/0.6 mmHg. *Methyl 8-nitrooctanoate* was obtained practically quantitatively from the butyl ester (15 g) by treatment with 180 ml methanol containing 5 % dry hydrochloric acid for 20 h. The excess of methanol was evaporated *in vacuo*. The remainder was neutralized with aqueous potassium carbonate and extracted with methylene chloride. Evaporation of the solvent after drying with sodium sulfate gave pure methyl ester (98 %). ^{1}H NMR ($CDCl_3$): δ 1.2–2.4 (12 H, m), 3.64 (3 H, s), 4.32 (2 H, t, *J* 6.7 Hz). *2-Nitrocyclooctanone* (3 g) was also transformed into the methyl ester by treatment with potassium hydroxide (0.5 g) in methanol (50 ml) for 2 h at 65 °C. The excess of methanol was evaporated *in vacuo* and the remainder was neutralized with dilute hydrochloric acid. Extraction with methylene chloride gave 2.7 g *methyl 8-nitrooctanoate*.

The *methyl pentadieneoate* was obtained by esterification of crude pentadienoic acid[36] with dry methanol (5 % hydrogen chloride), bp. 38–40 °C/10 mmHg (lit.[37] 54 °C/24 mmHg). The yield was *ca.* 20 %.

Methyl 3-nitropropanoate was prepared according to the method of Leonard and Felley[38] and *5-nitro-1-pentene* and *6-nitro-1-hexene* were prepared from the corresponding bromides by the silver nitrite method.[39] p-*Tolyl nitromethylsulfone*[5] and *1-nitropent-2-en-4-one*[3] were prepared according to literature. Isopropanol was used as solvent instead of ethanol for the preparation of *2-dimethylamino-1-nitroethane*, mp. 97–101 °C (lit.[3] 104 °C). The yield was 62 %.

3-Ethyl-5-propionyl-2-isoxazoline, 1b, was prepared analogously to *1a*[2] from the trimethylsilyl ester of *aci*-nitropropane and ethyl vinyl ketone, bp. 77–80 °C/0.7 mmHg, 58 %. ^{1}H NMR ($CDCl_3$): δ 1.06 (3 H, t, *J* 7.3 Hz), 1.17 (3 H, t, *J* 7.3 Hz), 2.40 (2 H, qt, *J* 7.3 and 1.0 Hz), 2.69 (2 H, q, *J* 7.3 Hz), 3.20 (2 H, dt, 8.7 and 1.0 Hz), 4.90 (1 H, dd, *J* 8.1 and 9.6 Hz). IR (film): 1700 cm^{-1}. MS: 155 (M^+).

3-Ethyl-5-vinyl-2-isoxazoline, 1c, *and 3-ethyl-5-(2'-methoxycarbonylethenyl)-2-isoxazoline*, 1d, were synthesized from butadiene and methyl pentadienoate, respectively, and the trimethylsilyl ester of *aci*-nitropropane. The reactants were left standing for 2–3 days at room temperature in benzene and then treated with TsOH in the usual way. Distillation gave *1c*, 30 %, bp. 79–83 °C/11 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.14 (3 H, t, *J* 7.5 Hz), 2.38 (2 H, qt, *J* 7.5 and 1 Hz), 2.69 and 3.08 (2 H, $ABXY_2$ system, *J* 16.9, 9.8, 8.7 and 1 Hz), 4.93 (1 H, dd, *J ca.* 9.3 and 6.1 Hz); *1d*, 31 %, bp. 108 °C/0.2 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.15 (3 H, t, *J* 7.4 Hz), 2.38 (2 H, qt, *J* 7.4 and 1 Hz), 2.79 and 3.21 (2 H, $ABXY_2$ system, *J* 16.9, 10.4, 7.9 and 1 Hz), 3.72 (3 H, s), 5.13 (H, m), 6.11 (1 H, dd, *J* 15.8 and 1.3 Hz), 6.86 (1 H, dd, *J* 15.8 and 5.4 Hz).

3-(3'-Butenyl)-5-acetyl-2-isoxazoline, 1e. To 5-nitro-1-pentene (1.15 g, 0.01 mol), methyl vinyl ketone (0.70 g, 0.01 mol) and triethylamine (1.5 g, 0.015 mol) in benzene (25 ml), chlorotrimethylsilane (1.62 g, 0.015 mol) was added and then refluxed for 2 h. The solution was cooled, filtered and TsOH (200 mg) was added. After 1 h stirring the solution was washed with aqueous $NaHCO_3$, dried over anhydrous $CaCl_2$ and evaporated. The crude yield of *1e*, 1.69 g, was pure enough for the further reduction. ^{1}H NMR ($CDCl_3$): δ 2.27 (3 H, s), 2.3–2.5 (4 H, m), 3.14 (2 H, br. d, *J* 9 Hz), 4.82 (1 H, dd, *J* 10.0 and 7.6 Hz), 4.9–5.3 (2 H, m), 5.5–6.1 (1 H, m). IR (film): 1720 cm^{-1}.

3-(4'-Pentenyl)-5-acetyl-2-isoxazoline, 1f, was prepared analogously from 6-nitro-1-hexane, bp. 104–106 °C/0.9 mmHg in a yield of 60 %. ^{1}H NMR ($CDCl_3$): δ 1.4–2.2 (4 H, m), 2.26 (3 H, s), 2.37 (2 H, t, *J* 7.5), 3.14 (2 H, br. d, *J* 9 Hz), 4.82 (1 H, dd, *J* 10.0 and 7.6 Hz), 4.8–5.2 (2 H, m), 5.5–6.1 (1 H, m). IR (film): 1723 cm^{-1}.

3-Ethyl-5-acetoxyacetyl-2-isoxazoline, 1g. The mixture of the silyl ester of *aci*-nitropropane (30 g, 0.19 mol), acetoxymethyl vinyl ketone (23 g, 0.18 mol) and 0.2 ml triethylamine in methylene chloride (50 ml) was kept for 2 days at room temperature. TsOH (1 g) was added and the solution stirred for *ca.* 1 h. After usual work-up and distillation of the product *in vacuo*, 23 g of *1g*, 47 %, bp. 110–112 °C/0.2 mmHg, was obtained. The compound crystallized slowly in the flask, m.p. 40 °C. Found: C 54.27, H 6.68; calc. for $C_9H_{13}NO_4$: C 54.26, H 6.58. ^{1}H NMR ($CDCl_3$): δ 1.19 (3 H, t, *J* 7.3 Hz), 2.15 (3 H, s), 2.42 (2 H, q, *J* 7.3 Hz), 3.26 (2 H, d, *J* 9 Hz), 4.99 (2 H, s), 5.03 (1 H, dd, *J* 9.7 and 7.8 Hz).

3-(2'-Methoxycarbonylethyl)-5-acetyl-2-isoxazol-

ine, 1h, was prepared from the trimethylsilyl ester of methyl 3-*aci*-nitropropanoate[2] by condensation with methyl vinyl ketone (1.1 eqv.) in benzene at room temperature overnight and then refluxing the solution for 30 min. Trimethylsilanol was eliminated by addition of TsOH and the solution was washed with aqueous $NaHCO_3$, dried and evaporated. *1h* was obtained pure on distillation *in vacuo*, b.p. 120–122 °C/0.7 mmHg, 52 %. ^{1}H NMR ($CDCl_3$): δ 2.26 (3 H, s), 2.66 (4 H, s), 3.20 (2 H, d, *J* 9 Hz), 3.69 (3 H, s), 4.88 (1 H, dd, *J* 9.8 and 8.2 Hz).

1i. 1-Nitropent-2-en-4-one[3] (1.53 g, 0.012 mol), methyl acrylate (1.4 g, 0.016 mol) triethylamine (1.5 g, 0.015 mol) and trimethylchlorsilane were refluxed in benzene (10 ml) for 2 h and filtered. TsOH (0.5 g) was added and the reflux was continued for 0.5 h. Washing with water, drying over sodium sulfate and evaporation gave a crude material which according to the ^{1}H NMR spectrum contained a small amount of *1i*. Separation on a preparative TLC plate (SiO_2, $CHCl_3$) gave 5% of pure *1i* as an oil. ^{1}H NMR ($CDCl_3$): δ 2.35 (3 H, s), 3.39 (2 H, d, *J* 9 Hz), 3.80 (3 H, s), 5.16 (1 H, dd, *J* 10 and 9 Hz), 6.29 (1 H, d, *J* 16 Hz), 7.32 (1 H, d, *J* 16 Hz).

1j. When the preceding procedure was applied for *p*-tolyl nitromethyl sulfone *ca.* 10 % of pure oily *1j* was obtained from the preparative TLC plate (SiO_2/$CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.21 (3 H, s), 3.59 (2 H, d, *J* 9 Hz), 3.77 (3 H, s), 5.18 (1 H, dd, *J* 10 and 9 Hz), 7.36 (2 H, d, *J* 8 Hz), 7.82 (2 H, d, *J* 8 Hz). Two other products were also isolated in about 10 % yield, the structures of which according to the ^{1}H NMR spectra, proved to be the Michael addition product, *methyl 3-p-toluenesulfonyl-3-nitropropanoate* and p-*tolyl* p-*toluenethiosulfonate*.

1k was prepared in the same way as *1a*.[2] The yield was 76 %, b.p. 50–60 °C/0.1–0.2 mmHg. ^{1}H NMR ($CDCl_3$): δ 2.00 (3 H, s), 2.27 (3 H, s), 3.16 (2 H, d, *J* 9.2 Hz), 4.82 (1 H, dd, *J* 9.8 and 8.0 Hz).

1l,m,o,p were prepared according to literature.[1]

1n. *3-Pentyl-4-carbomethoxy-2-isoxazoline.* 1-Nitrohexane (0.50 g), triethylamine (0.58 g), trimethylchlorosilane (0.62 g) and methyl acrylate (0.46 g) were refluxed for 30 min in acetonitrile–benzene, 1:1 (8 ml). After cooling and filtration *p*-toluenesulfonic acid (100 mg) was added and the refluxing was continued for 1 h. The reaction mixture was washed with water (10 ml) and aqueous sodium bicarbonate (10 ml), dried and evaporated. Nearly pure *1n*, 0.62 g, 81 %, oil, was obtained. ^{1}H NMR ($CDCl_3$): δ 0.90 (3 H, t, *J* 7 Hz), 1.1–1.7 (6 H, m), 2.36 (2 H, t, *J* 7 Hz), 3.20 (2 H, d, *J* 6.8 Hz), 3.77 (3 H, s), 4.98 (1 H, t, *J* 6.8 Hz).

1q. *3-Pentyl-5-trimethylsilyloxy-2-isoxazoline and 3-pentylisoxazole*, 23. A mixture of 1-nitrohexane (5.0 g, 0.038 mol), triethylamine (5.8 g, 0.057 mol), trimethylchlorosilane (6.2 g, 0.057 mol) and acrylonitrile (2.8 g, 0.053 mol) in benzene–acetonitrile (1:1, 60 ml) was refluxed for 30 min. The solution was cooled, filtered, washed with ice-water, dried over sodium sulfate and evaporated. Potassium fluoride (1 g) was added to the crude product, *2-trimethylsilyloxy-3-pentyl-5-cyanoisoxazolidine*, (9.1 g, 93 %). The mixture was cooled in a water bath at 25 °C and stirred for 24 h. The flask is placed in a well-ventilated hood because hydrocyanic acid evolves during the reaction. Filtration gave 4.5 g of crude *1q*, which according to the ^{1}H NMR spectrum is admixed with the corresponding 5-hydroxy derivative. ^{1}H NMR ($CDCl_3$): δ 0.17 (9 H, s), 0.91 (3 H, t, *J* ~6 Hz), 1.1–1.8 (6 H, m), 2.42 (2 H, br. t, *J* ~7 Hz), 2.7–3.1 (2 H, m), 4.92 (1 H, br. s), 5.81 (1 H, dd, *J* 5.5 and 2.0 Hz). The mixture is dissolved in toluene (10 ml) and refluxed for 2 h with *p*-TsOH (1 g). The solution is filtered and washed with conc. aqueous sodium bicarbonate. The aqueous phase is extracted with chloroform and the combined organic phases are dried over sodium sulfate. Evaporation of the solvent and distillation *in vacuo* gave 1.8 g (33 %) of *23*, bp. 48–51 °C/0.12 mmHg. ^{1}H NMR ($CDCl_3$): δ 0.90 (3 H, t, *J* 5.5 Hz), 1.16–1.52 (4 H, m), 1.67 (2 H, br. t, *J* ~8 Hz), 2.70 (2 H, t, *J* 7.0 Hz), 6.18 (1 H, d, *J* 1.7 Hz), 8.29 (1 H, d, *J* 1.7 Hz).

3-(6'-Methoxycarbonyl)hexyl-5-acetyl-2-isoxazoline, 1r. A mixture of methyl 8-nitrooctanoate (8.12 g, 0.04 mol), triethylamine (9.0 g, 0.09 mol), trimethylchlorosilane (9.2 g, 0.084 mol) and methyl vinyl ketone (8.4 g, 0.12 mol) in acetonitrile–benzene (30+60 ml) was refluxed for 30 min then cooled and filtered. *p*-TsOH (2 g) was added to the filtrate that was refluxed for another hour. Methylene chloride (50 ml) was added and the solution extracted with a saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and evaporated. 10.7 g (*ca.* 100 % calc. on the nitroester) of crude liquid *1r* were obtained, sufficiently pure for further reactions. ^{1}H NMR ($CDCl_3$): δ 1.1–1.8 (8 H, m), 2.0–2.5 (4 H, m), 2.30 (3 H, s), 3.12 (2 H, d, *J* ~9 Hz), 3.65 (3 H, s), 4.81 (1 H, dd, *J* 10.0 and 7.2 Hz).

In another experiment butyl 8-nitrooctanoate was used instead of the methyl ester and the excess of triethylamine, trimethylchlorosilane and methyl vinyl ketone was kept at *ca.* 50 %. The crude yield of *1r* (butyl ester) was 80–85 %. ^{1}H NMR ($CDCl_3$): δ 0.96 (3 H, t, *J* ~6 Hz), 1.1–1.8 (12 H, m), 2.1–2.5 (4 H, m), 2.18 (3 H, s), 3.10 (2 H, d, *J* ~9 Hz), 4.3 (2 H, t, *J* 6.3), 4.80 (1 H, dd, *J* 9.8 and 7.8 Hz)

General procedure for reduction of 2-isoxazolines. The acid Ti^{3+} solution (Merck, 1 M) was treated with some powdered zink in order to ensure that it kept its full reducing power. It was neutralized with solid sodium bicarbonate to pH 3–4 and rapidly filtered or centrifued. The Ti^{3+} solution (2.3 mol) was added to a methanolic solution of the 2-

isoxazoline (1 mol) and the mixture was left standing under nitrogen for 3–4 days at room temperature with occasional stirring. Water was added and the product was extracted with methylene chloride in a continuous extractor to avoid emulsions. Drying and evaporation of solvent gave a crude hydroxyketone sufficiently pure for further reactions. The yield was *ca.* 80 % or better. If the reduction is carried out at *ca.* 0 °C, the reaction time has to be increased to about a week.

Reduction of 3-ethyl-5-acetyl-2-isoxazoline, 1a, *with* Ti^{3+} *and cyclization to* 11a. *1a* (1.40 g, 0.01 mol) in methanol (40 ml) was reduced with Ti^{3+} (1 M $TiCl_3$ solution, Merck, neutralized with solid $NaHCO_3$ to pH 3.5–4, 40 ml, 0.04 mol) under N_2 for 8 days at 5 °C. Water was added and the solution extracted with chloroform. Drying over anhydrous Na_2SO_4 and evaporation gave 1.1 g (80 %) of nearly pure 3-hydroxy-2,5-heptandione, *2a*, that was directly cyclized to *11a* with aqueous sodium hydroxide (1 M, 15 ml) for 24 h at 25 °C. The solution was saturated with sodium chloride and extracted with methylene chloride. Evaporation of the organic solvent gave *11a* (0.83 g, crude), bp. 106–108 °C/0.3 mmHg (0.25 g, 27 %, lit.[40] 108–110 °C/0.29 mmHg).

11a was obtained in a yield of 63 % when *2a* (200 mg) in methanol (1 ml) was cyclized with potassium carbonate (6 ml, 20 %, aqueous solution) for 20 h at 25 °C. Neutralization with hydrochloric acid and extraction with chloroform gave *11a* (110 mg, purified on TLC). ^{1}H NMR ($CDCl_3$) *2a:* δ 1.07 (3 H, t, *J* 7.2 Hz), 2.27 (3 H, s), 2.52 (2 H, q, *J* 7.2 Hz), 2.90 (2 H, m), 4.38 (1 H, dd, *J* 6.0 and 4.4 Hz). *11a:* δ 1.68 (3 H, s), 2.08 (3 H, s), 2.25 and 2.70 (2 H, ABX spectrum, *J* 18.4, 5.8 and 2.1 Hz), 4.1 (1 H, br. s), 4.71 (1 H, br. d, *J* 5.8 Hz).

The reduction time was reduced to 2.5 days by running the reaction at room temperature. 30 ml of Ti^{3+} solution was used for 1.4 g of *1a*. The yield was 82 %. The product contained *ca.* 10 % of *10a*.

Reduction of *1a* with acid Ti^{3+} solution at room temperature for 6 days under N_2 led to a mixture of *2a* (major) and *2,5-heptandione*. They could be separated by TLC. ^{1}H NMR of *2,5-heptandione* ($CDCl_3$): δ 1.07 (3 H, t, *J* 7.4 Hz), 2.19 (3 H, s), 2.50 (2 H, q, *J* 7.4 Hz), 2.70 (4 H, s). When the reduction was carried out in acid Ti^{3+} solution in the presence of Zn powder, *2,5-heptandione* became the major product.

2b. *4-Hydroxy-3,6-octandione.* ^{1}H NMR ($CDCl_3$): δ 1.05 (3 H, t, *J* 7.2 Hz), 1.10 (3 H, t, *J* 7.2 Hz), 2.52 (2 H, q, *J* 7.2 Hz), 2.64 (2 H, q, *J* 7.2 Hz), 2.9 (2 H, m), 4.43 (1 H, dd, *J* 6.2 and 4.8 Hz). IR (film): 1715 cm^{-1}. MS: 157 ($M^+ - 1$).

2c. *3-Hydroxy-1-hepten-5-one.* ^{1}H NMR ($CDCl_3$): δ 1.08 (3 H, t, *J* 7.3 Hz), 2.49 (2 H, q, *J* 7.3 Hz), 2.66 (2 H, d, *J* 6.1 Hz), *ca.* 3.0 (1 H, br. s), 4.60 (1 H, br. q, *J* 6 Hz), 5.0–5.5 (2 H, m), 5.9 (1 H, ddd, *J* 17.3 9.8 and 5.0 Hz).

2d. *Methyl 4-hydroxy-6-oxo-2-octenoate.* ^{1}H NMR ($CDCl_3$): δ 1.08 (3 H, t, *J* 7.2 Hz), 2.47 (2 H, q, *J* 7.2 Hz), 2.67 (2 H, d, *J* 6.5 Hz), 3.74 (3 H, s), 4.74 (1 H, m), 6.11 (1 H, dd, *J* 16.9 and 2 Hz), 6.86 (1 H, dd, 16.9 and 4.1 Hz).

2e. *7-Hydroxy-1-nonen-5,8-dione.* ^{1}H NMR ($CDCl_3$): δ 2.25 (3 H, s), 2.3–2.8 (4 H, m), 2.9 (2 H, br. d, *ca.* 5 Hz), 4.35 (1 H, br. t, *J ca.* 5 Hz), 4.7–5.3 (2 H, m), 5.4–6.1 (1 H, m).

2f. *8-Hydroxy-1-decen-6,9-dione.* ^{1}H NMR ($CDCl_3$): δ 1.4–2.3 (4 H, m), 2.25 (3 H, s), 2.49 (2 H, t, *J* 6.9 Hz), 2.9 (2 H, br. d, *J ca.* 5 Hz), 4.35 (1 H, dd, *J* 5.8 and 4.7 Hz), 4.75–5.25 (2 H, m), 5.4–6.1 (1 H, m).

Reduction of 1g. *1g* (0.5 g, 2.5 mmol) was reduced at 25 °C with 2.5 eqv. of Ti^{3+} in aqueous methanolic solution at pH 3.3 for 24 h. Extraction with methylene chloride gave 0.42 g an inseparable mixture of *2a*, *2g* and *1,3-dihydroxyheptan-2,5-dione*. When the reaction was carried out at 0 °C the relative amount of *2g* was slightly raised. *2g*, ^{1}H NMR ($CDCl_3$): δ 1.04 (3 H, t, *J* ~7 Hz), 2.13 (3 H, s), 2.49 (2 H, q, *J* ~7 Hz), 2.92 (2 H, d, *J* ~5.5 Hz), 3.87 (1 H, br. s), 4.51 (1 H, t, *J* ~5.5 Hz), 5.01 (2 H, s).

2h. *Methyl 6-hydroxy-4,7-dioxooctanoate.* ^{1}H NMR ($CDCl_3$): δ 2.26 (3 H, s), 2.50–2.75 (4 H, m), 2.91 (1 H, d, *J* 6 Hz), 2.92 (1 H, d, *J* 5.0), 3.65 (1 H, br. s), 3.68 (3 H, s), 4.36 (1 H, dd, *J* 6.0 and 5.0 Hz). The crude product was chromatographed on a silica column ($CHCl_3$, 2 % CH_3OH). The yield was 68 %.

2k. *3-Hydroxyhexan-2,5-dione.* ^{1}H NMR ($CDCl_3$): δ 2.21 (3 H, s), 2.24 (3 H, s), 2.90 (2 H, m), 3.8 (1 H, br. s), 4.32 (1 H, br. t, *J* 5 Hz). The yield was 82 %. The crude product contained *10k*, 16 %, which could be separated from *2k* by TLC.

2l. *Methyl 2-hydroxy-4-oxopentanoate.* The crude yield was 92 %. ^{1}H NMR ($CDCl_3$): δ 2.19 (3 H, s), 2.94 (2 H, d, *J* 5 Hz), 3.75 (3 H, s), 4.19 (1 H, br. s), 4.52 (1 H, t, *J* 5 Hz).

2m. *Methyl 2-hydroxy-4-oxohexanoate. 1m* (0.79 g, 0.005 mol) was dissolved in methanol (10 ml) and an aqueous solution of $TiCl_3$ (10 ml, 1 M, pH adjusted to 3.6) was added. The mixture was stirred for 3 days under N_2 at 25 °C. pH had changed to 1.6 after that time. The aqueous solution was extracted in a continuous extractor with chloroform. The organic solution gave after drying with Na_2SO_4 and evaporation practically pure *2m* (760 mg, 95 %). ^{1}H NMR ($CDCl_3$): δ 1.04 (3 H, t, *J* 7 Hz), 2.50 (2 H, q, *J* 7 Hz), 2.94 (2 H, d, *J* 5 Hz), 3.77 (3 H, s), 4.55 (1 H, t, 5 Hz), 4.74 (1 H, OH, br. s).

2n. *Methyl 2-hydroxy-4-oxononanoate.* Yield 49 %. ^{1}H NMR ($CDCl_3$): δ 0.89 (3 H, t, *J* 7 Hz), 1.1–1.8 (6 H, m), 2.43 (2 H, t, *J* 7 Hz), 2.90 (2 H, d, *J* 5 Hz),

3.74 (3 H, s), 4.0 (1 H, OH, br. s), 4.49 (1 H, t, *J* 5 Hz).

2o and *2p* were obtained in practically quantitative yields by reduction of *1o* and *1p* with aqueous methanolic Ti^{3+} solution (2.2 mol) for 2.5 days under nitrogen at 25 °C. The pH was adjusted to 3.8 with sodium bicarbonate at the start of the reduction. It decreased to 1.8 after 2 days. *2o* and *2p* were extracted with a continuous chloroform extractor to avoid emulsification. *2o*, ^{1}H NMR ($CDCl_3$): δ 2.10 (3 H, s), 2.75 (1 H, d, *J* 5.5 Hz), 2.77 (1 H, d, *J* 7.0 Hz), 3.6 (1 H, OH, br. s), 5.05 (1 H, dd, *J* 7.0 and 5.5 Hz), 7.0 – 7.4 (5 H, m). *2p*. ^{1}H NMR ($CDCl_3$): δ 1.02 (3 H, t, *J* 7.5 Hz), 2.41 (2 H, q, *J* 7.5 Hz), 2.76 (1 H, d, *J* 5.5 Hz), 2.78 (1 H, d, *J* 7.5 Hz), 3.4 (1 H, OH, br. s), 5.11 (1 H, dd, *J* 7.5 and 5.5 Hz), 7.3 (5 H, m). *2o* contained small amounts of *9o*. When the reduction is carried out at lower pH and for longer times the amount of *9o* increases. Some *4-phenylbutan-2-one* is formed. This compound arises by Ti^{3+} reduction of *9o*.

2r. *Methyl 10-hydroxy-8,11-dioxododecanoate* was prepared from *1r* (2.58 g, 0.01 mol) by reduction with Ti^{3+} solution (1 M, pH 3.6, 25 ml, 2.5 eqv.) in methanol (125 ml) and water (100 ml) under nitrogen at 25 °C for 3 days. Extraction with chloroform gave *2r* (2.34 g crude, 90 %) containing small amounts of *10r*. ^{1}H NMR ($CDCl_3$): δ 1.1 – 1.9 (8 H, m), 2.1 – 2.4 (4 H, m), 2.24 (3 H, s), 2.90 (2 H, d, *J* ~5 Hz), 3.63 (3 H, s), 4.34 (1 H, t, *J* ~5 Hz). The butyl ester was reduced with approximately the same yield but gave a mixture of butyl and methyl esters by transesterification.

Manganese dioxide oxidation of 11a *to 4,5-dimethyl-4-cyclopenten-1,3-dione*, 13. *11a* (120 mg) was dissolved in methylene chloride (10 ml) and stirred with manganese dioxide (commercial active, Merck, 400 mg) for 10 min at room temperature. Filtration and evaporation of the solvent gave *13* (oil, 50 mg), the spectral data of which agreed with those in the literature.[22] In another experiment with a less active MnO_2 the oxidation was run for 4 days. *13* was obtained in a yield of 87 %. ^{1}H NMR ($CDCl_3$): δ 2.00 (6 H, s), 2.83 (2 H, s).

Synthesis of allethrolone, 11e. Crude *2e* (1.2 g) from above was cyclized with sodium hydroxide (1 M, 20 ml aqueous methanol) at 5 °C for 18 h. The product, obtained on extraction with chloroform was purified by TLC (silica $CHCl_3$, 1 % MeOH). It gave *alletrolone 11e* (0.4 g). Its spectral properties agreed with data found in literature.[20,21] A minor band with a higher R_f value consisted of *deoxyallethrolone* arising from cyclization of *1-nonen-5,8-dione*, formed in minor quantities by the Ti^{3+} reduction. MS: 136 (M^+).

Base catalyzed cyclization of 2b (1.0 g) in methanol – water (1:4, 50 ml, 1 % NaOH) for 20 h at room temperature gave after work-up a crude product which was separated by preparative TLC into three components: *11b* (175 mg, oil, 20 %), *12* (25 mg, oil, 3 %) and a crystalline orange compound (20 mg) which was not investigated further. *11b*, ^{1}H NMR ($CDCl_3$): δ 1.15 (3 H, t, *J* 7.7 Hz), 1.69 (3 H, s), 2.51 (2 H, q, *J* 7.7 Hz), 2.25, 2.72 (2 H, ABX-spectrum, *J* 19.7, 6.0 and 2.1 Hz), 4.83 (1 H, br. d, *J ca.* 5 Hz). *12*, ^{1}H NMR ($CDCl_3$): δ 1.15 (3 H, t, *J* 7.7 Hz), 1.71 (3 H, s), 2.46 (2 H, q, *J* 7.7 Hz), *ca.* 2.5 (2 H, m), 4.43 (1 H, br. d, *J ca.* 5 Hz). MS: 140 (M^+).

3,6-Diethylpyridazine, 3. *2b* (200 mg, 0.0013 mol), hydrazine (150 mg, 0.0047 mol) and TsOH (50 mg), were refluxed in methanol (3 ml) for 3 h. Chloroform was added and the solution was washed with aqueous sodium bicarbonate (5 %) dried and evaporated. Preparative TLC (SiO_2, $CHCl_3$, 2 % CH_3OH) gave pure *3* (85 mg, 48 %). ^{1}H NMR ($CDCl_3$): δ 1.36 (6 H, t, *J* 7.5), 2.95 (4 H, q, *J* 7.5 Hz), 7.15 (2 H, s). MS: 137 ($M^+ + 1$). *3* was obtained in a yield of 9 % when *1b* (400 mg), hydrazine (200 mg) and TsOH (80 mg) were refluxed for 6 h in ethanol (6 ml). The work-up was carried out as above. The hydrazone and the hydrazine of *1b* were also detected in the reaction mixture.

6-Methylimino-4-octen-3-one N-*oxide*, 5. *1b* (300 mg, 0.0019 mol) was reacted with dimethyl sulfate (260 mg, 0.0021 mol) for one week at 25 °C. Triethylamine (200 mg, 0.002 mol) and chloroform were added and the mixture was refluxed for 2 h. The mixture was washed with water, evaporated and chromatographed on a TLC-plate (SiO_2, $CHCl_3$, 4 % CH_3OH). 60 mg of *5* (19 %) were obtained. ^{1}H NMR ($CDCl_3$): δ 1.10 (3 H, t, *J* 7.1 Hz), 1.15 (3 H, t, *J* 7.1 Hz), 2.66 (2 H, q, *J* 7.1 Hz), 2.70 (2 H, q, *J* 7.1 Hz), 3.98 (3 H, s), 6.42, 7.53 (AB-spectrum, 2 H, *J* 15 Hz). IR (film): 1690, 1670, 1590, 1300. MS: 169 (M^+).

6-Ethyl-3-pyridazone, 6. 5-Methoxycarbonyl-3-ethyl-2-isoxazoline (400 mg, 0.0025 mol) and hydrazine (200 mg, 0.0063 mol) were refluxed in toluene (6 ml) for 24 h. The toluene was evaporated and from the residue *6* (65 mg, oil, 21 %) was isolated. ^{1}H NMR ($(CD_3)_2CO$): δ 1.19 (3 H, t, *J* 7.5 Hz), 2.61 (2 H, q, *J* 7.5 Hz), 6.79, 7.25 (AB-spectrum, 2 H, *J* 10 Hz). IR (film): 1675 cm^{-1}. MS: 124 (M^+).

3-Methyl-6-(6'-methoxycarbonylhexyl)pyridazine, 7 was prepared by refluxing *2r* (150 mg, crude) with hydrazine (80 mg, 98 %) in methanol (1.5 ml) for 3 h. Evaporation of the solvent *in vacuo* and purification of the remainder on TLC (SiO_2, $CHCl_3$: $CH_3COOC_2H_5$; 4:1) gave *7* (50 mg, 36 %) as a light yellow liquid. ^{1}H NMR ($CDCl_3$): δ 1.0 – 2.0 (8 H, m), 2.30 (2 H, t, *J* 7.6 Hz), 2.66 (3 H, s), 2.93 (2 H, t, *J* 7.2 Hz), 3.64 (3 H, s), 7.18 (2 H, s).

Methyl 3-[2'-(5'-methylfuryl)] acrylate, 8. *2h* (250 mg, crude) and TsOH (30 mg) were refluxed in toluene (5 ml) for 3 h. The solution was washed with aqueous sodium bicarbonate and the solvent evaporated. Preparative TLC (SiO_2, $CHCl_3$, 2 % CH_3OH)

gave 7 (140 mg, oil, 62 %). ^{1}H NMR ($CDCl_3$): δ 2.36 (3 H, s), 3.78 (3 H, s), 6.10 (1 H, d, J 3.5 Hz), 6.25 (1 H, d, J 16 Hz), 6.53 (1 H, d, J 3.5 Hz), 7.39 (1 H, d, J 16 Hz).

2,5-Dioxo-trans-*heptene*, 9a, was obtained in a yield of *ca.* 50 % from *2a* together with 30–40 % of the acetate of *2a* by Schechter's method.[14]

Methyl 6-oxo-2,4-octadienoate, 9d, was obtained in practically quantitative yield (crude) by refluxing *2d* in benzene for 4 h with a catalytic amount of TsOH. Purified by preparative TLC it melted at 93–94 °C. ^{1}H NMR ($CDCl_3$): δ 1.13 (3 H, t, J 7.3 Hz), 2.64 (2 H, q, J 7.3 Hz), 3.79 (3 H, s), 6.0–6.6 (2 H, m), 7.1–7.5 (2 H, m). MS: 168 (M^+).

The *β-acylated methyl acrylates* 9l,m,n, were obtained in a yield of 70–90 % by refluxing *2l,m,n* (0.01 mol) in chloroform (24 ml), methanol (1.2 ml) and conc. perchloric acid (1.6 ml, 70 %) for 3 h. Ice-water (10 ml) is added and the organic phase is separated and evaporated. The crude *9l,m,n* obtained are contaminated by small amounts of the corresponding 2-methoxy derivatives formed by addition of methanol across the double bond. The ^{1}H NMR data of *9l,m,n* agree with the data given in the literature.[41] *9l* was obtained pure in a yield of 66 % by using the acetate procedure.[14]

trans-*1-Phenyl-1-buten-3-one*, 9o, *and* trans-*1-phenyl-1-penten-3-one*, 9p, were obtained in 90–95 % yields by keeping *2o,p* (0.01 mol) in methanol (30 ml) and conc. hydrochloric acid (5 ml) at 25 °C for 24 h. Most of the methanol is evaporated *in vacuo*, methylene chloride is added and the solution is washed with water and sodium bicarbonate. Evaporation of the solvent gives practically pure *9o,p*. ^{1}H NMR ($CDCl_3$) *9o*: δ 2.30 (3 H, s), 6.59 (1 H, d, J 16 Hz), 7.39 (1 H, d, J 16 Hz), 7.0–7.4 (5 H, m). *9p*: δ 1.14 (3 H, t, J 7.0 Hz), 2.66 (2 H, q, J 7.0 Hz), 6.69 (1 H, d, J 16 Hz), 7.2–7.6 (5 H, m), 7.51 (1 H, d, J 16 Hz). According to the NMR spectrum *9p* contained 9 % of the *cis*-isomer (J 13 Hz) which was separated by prep. TLC.

Methyl 8,11-dioxo-9-trans-*dodecanoate*, 9r. *2r* (1.2 g, 0.0046 mol) was acetylated with acetic anhydride (2.4 g) and sodium acetate (0.3 g) at 25 °C for 24 h and heated on an oil bath at 100 °C for 10 min. Chloroform (10 ml) was added and the solution extracted with aqueous sodium bicarbonate, dried and evaporated. *9r* (1.0 g) was obtained as a semi-solid which was recrystallized from methanol yielding 0.68 g, 68 %, of white crystals, m.p. 46–47 °C. ^{1}H NMR ($CDCl_3$): δ 1.1–1.9 (8 H, m), 2.3 (2 H, t, J ~6 Hz), 2.35 (3 H, s), 2.63 (2 H, t, J ~6 Hz), 3.65 (3 H, s), 6.77 (2 H, s). MS: 240 ($M^{\ominus}$).

General procedure for preparation of dihydro-3-furanones. The 2-hydroxy-1,4-dione, (*2a,k,r*, 3 mmol) is refluxed with sodium acetate (1.0 g) in acetic acid (10 ml) for 3 h. Chloroform (15 ml) is added and the solution extracted once with ice-water (15 ml) and once with conc. aqueous sodium bicarbonate. Evaporation of the solvent gives nearly pure dihydro-3-furanone in 80–90 % yield. The product can be further purified by Kugelrohr distillation or TLC (SiO_2, $CHCl_3$, 2 % CH_3OH). *10a*, b.p. 66–68 °C/15 mmHg, 49 %. ^{1}H NMR ($CDCl_3$): δ 1.44 (3 H, d, J 7.0 Hz), 2.44 (3 H, d, J 0.8 Hz), 4.50 (1 H, q, J 7.0 Hz), 5.43 (1 H, s). *10k*, b.p. 88 °C/15 mmHg, 51 %. ^{1}H NMR ($CDCl_3$): δ 1.16 (3 H, t, J 7.0 Hz), 1.42 (3 H, d, J 7.0 Hz), 2.51 (2 H, q, J 7.0 Hz), 4.45 (1 H, q, J 7.0 Hz), 5.36 (1 H, s). *10r*, 61 %, TLC, liquid. ^{1}H NMR ($CDCl_3$): δ 1.1–1.9 (8 H, m), 1.41 (3 H, d, J 7 Hz), 2.1–2.7 (4 H, m), 3.62 (3 H, s), 4.46 (1 H, q, J 7 Hz), 5.37 (1 H, s). MS: 240 (M^+).

2-(5'-Methoxycarbonylpentyl)-3-methyl-4-methoxy-2-cyclopentenone, 17. *9r* (120 mg, 0.50 mmol) was left standing for 48 h at 25 °C in methanol (15 ml) and aqueous sodium hydroxide (1 %, 2 ml). Ice-water was added and the solution acidified with dilute hydrochloric acid, and extracted with methylene chloride. Evaporation of the solvent and purification of the product on TLC (SiO_2, $CHCl_3$, 5 % ethyl acetate) gave *17*, liquid, 67 %. ^{1}H NMR ($CDCl_3$): δ 1.1–1.8 (6 H, m), 2.06 (3 H, s), 1.9–2.8 (6 H, m), 3.38 (3 H, s), 3.65 (3 H, s), 4.31 (1 H, m). MS: 254 (M^+).

4-Methoxy-2,3-dimethyl-2-cyclopentenone, 18, was prepared from *9a* as described for *17*. The yield was 83 %, liquid, TLC, (SiO_2, $CHCl_3$, 2 % CH_3OH). ^{1}H NMR ($CDCl_3$): δ 1.70 (3 H, s), 2.03 (3 H, s), 2.28 (1 H, dd, J 18.0 and 2.5 Hz), 2.61 (1 H, dd, J 18.0 and 5.5 Hz). 3.38 (3 H, s), 4.30 (1 H, m).

18 was also prepared directly from the acetate of *2a*. *2a* (400 mg, 2.8 mmol) was treated with acetic anhydride (800 mg) and sodium acetate (100 mg) for 24 h at 25 °C. Chloroform (5 ml) was added and the solution was washed with conc. aqueous sodium bicarbonate and evaporated. TLC (SiO_2, ethyl acetate–CH_2Cl_2, 2:1) gave 380 mg of the acetate (74 %) which was treated with a mixture of methanol (60 ml) and aqueous sodium hydroxide (8 ml, 1 %) for 2 days at 25 °C. The solution is neutralized with dilute hydrochloric acid and most of the methanol evaporated *in vacuo*. Extraction with methylene chloride gave *18* (250 mg, 87 %; TLC, SiO_2, $CHCl_3$, 2 % CH_3OH).

2-Phenyl-2-hydroxypropiononitrile, 20a. *19a*[1,2] (295 mg) was treated for 3 h at 25 °C in methanol (8 ml) with sodium methylate (100 mg). Methylene chloride and ice-water were added. The organic phase gave *20a* in practically quantitative yield. The spectroscopic data of *20a* agreed with the literature data.[34]

Methyl 2-hydroxy-3-cyanopropanoate, 20b, was obtained quantitatively from *19b*[1,2] by the method of Huisgen and Christl.[34]

The *acetates* of *20a* and *20b* were prepared by the method described for the acetate of *2a* above.

20a-Acetate, m.p. 97–99 °C, 97 %. ^{1}H NMR ($CDCl_3$): δ 2.10 (3 H, s), 2.81 (2 H, d, *J* 6.0 Hz), 5.90 (1 H, t, *J* 6.0 Hz), 7.30 (5 H, s). *20b*-Acetate, liquid, 86 %. ^{1}H NMR ($CDCl_3$): δ 2.17 (3 H, s), 2.93 (2 H, d, *J* 6.0 Hz), 3.77 (3 H, s), 5.27 (1 H, t, *J* 6.0 Hz).

Cinnamonitrile, 21a. *20a*-Acetate (320 mg, 1.7 mmol) was refluxed with Al_2O_3 (basic, Merck, 90 active I) in toluene (20 ml) for 3 h with stirring. Filtration and evaporation gave *21a* (210 mg, 96 %). ^{1}H NMR ($CDCl_3$): δ 5.82 (1 H, d, *J* 18 Hz), 7.32 (1 H, d, *J* 18 Hz), 7.37 (5 H, br. s).

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