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SILYL NITRONATES, NITRILE OXIDES, AND DERIVED 2-ISOXAZOLINES IN ORGANIC SYNTHESIS. FUNCTIONALIZATION OF BUTADIENE, A NOVEL ROUTE TO FURANS AND 2-ISOXAZOLINES AS AN ALTERNATIVE TO ALDOL-TYPE CONDENSATIONS†

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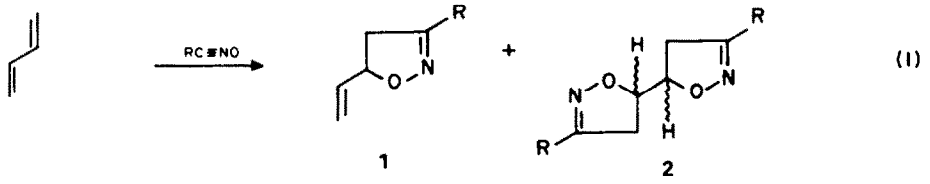
Abstract—Mono- and di-addition of silylnitronates and nitrile oxides is a useful procedure for functionalizing butadiene leading to cyano and acyl derivatives. A novel route to 2,5-disubstituted furans is also established. The potential of the method in carbohydrate synthesis is pointed out. The route *via* 2-isoxazoline is shown to be a useful alternative to aldol-type reactions in organic synthesis. **15a** has been studied by X-ray diffraction and shown to be the *meso* form.

Silyl nitronates, nitrile oxides, and derived 2-isoxazolines have manifested their position as valuable intermediates for a variety of compounds in organic synthesis.[1,2] In the present publication we wish to demonstrate their usefulness in functionalizing butadiene.

The addition of nitrile oxides to butadienes to form 2-isoxazolines has been studied,[3] but little has been done for utilizing the products for further synthetic purposes. Mono-adducts **1** as well as bis-adducts **2** (mixture of stereoisomers) have been obtained (eqn 1). In earlier work[3k] we reacted butadiene with preformed trimethylsilyl ester of *aci*-nitropropane and obtained 3-ethyl-5-vinyl-2-isoxazoline **12b** in 30% yield. The silyl ester of nitromethane is generated *in situ* for the preparation of 3-unsubstituted 2-isoxazolines (Scheme 1). The convenient generation of nitrile oxides from hydroxamic acid hlorides and triethylamine[4] is used in the other cases.



(1)

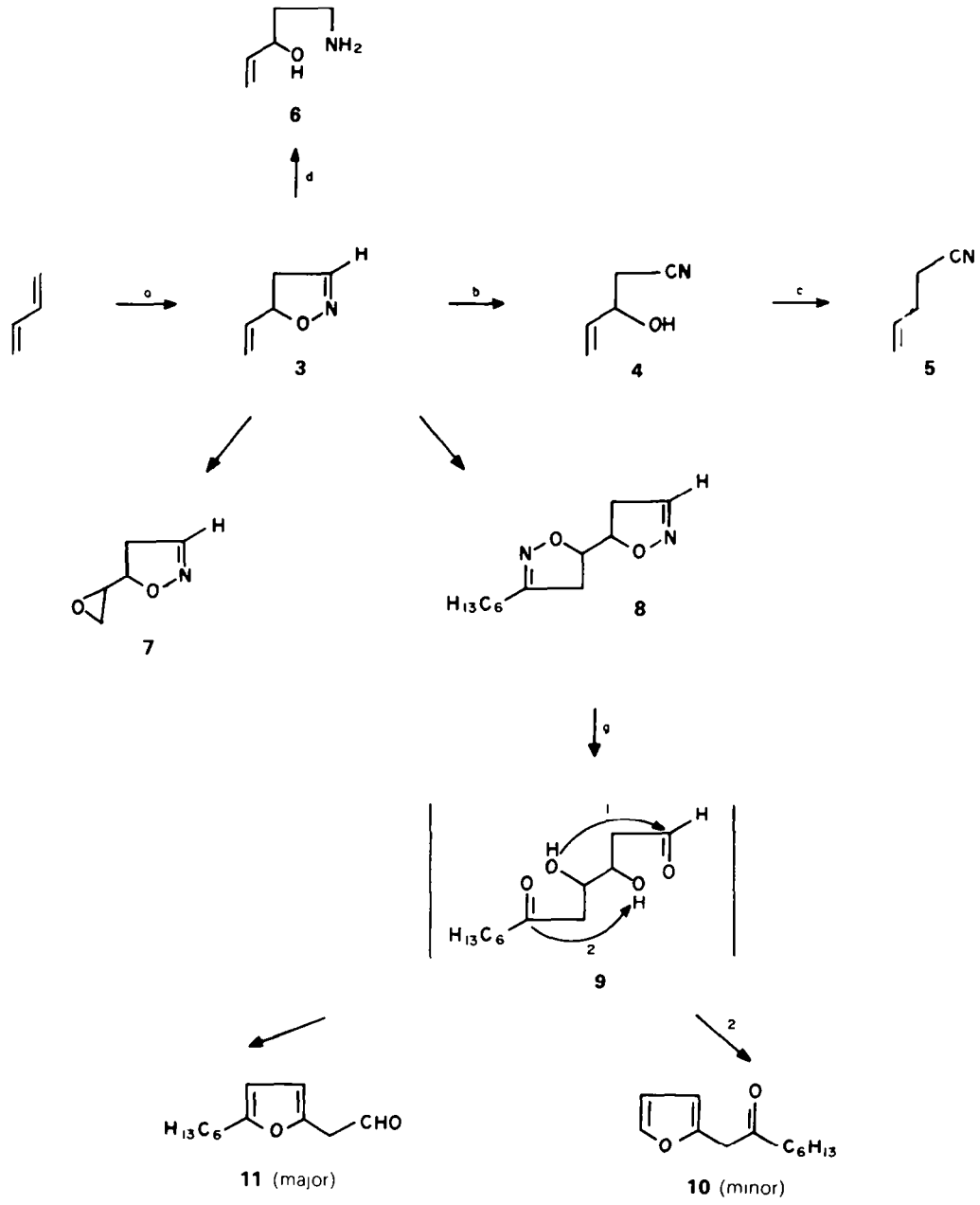
5-Vinyl-2-isoxazoline **3** obtained from the reaction of nitromethane, triethylamine, and chlorotrimethylsilane with butadiene in benzene/acetonitrile solution, is an intermediate with synthetic potential. It can be reduced to the 1,3-aminoalcohol **6** with lithium aluminum hydride. Ring opening with triethylamine gives the 1,2-cyanoalcohol **4**, which by acylation and pyrolysis can be transformed into 1-cyanobutadiene,[5] a reactive compound of interest for preparation of polymers. *m*-Chloroperbenzoic acid epoxidizes selectively the vinyl group to **7** (mixture of isomers, ratio *ca* 2:3), a C_5 compound containing a latent aldehyde function and three oxygenated carbon atoms; actually a 2-deoxypentose derivative. Similarly, epoxidation of **12g** leads to **27** (isomeric mixture). As shown by recent work on amine-alkanols,[6] 1,3-dipolar addition of suitably substituted nitrile oxides or nitrones to oxygenated alkenes can be used in carbohydrate synthesis.

Another nitrile oxide can be added to the vinyl function of **3**, giving rise to a stereoisomeric mixture of 5,5'-di(2,2'-isoxazolinyls), **8**. When **8** was reduced with titanous ions, instead of the expected 3,4-dihydroxy-6-ketododecanal **9**, the two furans **10** and **11** were formed in good yields by acid catalyzed cyclization.

Addition of nitrile oxides, generated by the action of triethylamine on hydroxamic acid chlorides to butadiene leads to the vinyl derivatives **12a,c–g**. Reduction of **12a,b,e** gives the corresponding keto-alcohols **13a,b,e**, which by acetylation and thermolysis are transformed into the rather unstable 1-acylated butadienes **14a,b,e** in high yields. The crude dienones are sufficiently pure for further synthetic use. They decompose on distillation *in vacuo*.

Diaddition of nitrile oxides to butadiene always takes place to some extent (eqn 2). **12b** was prepared by the silyl nitronate procedure but no diaddition was observed. The yields of the 5,5'-di(2,2-isoxazolininyls) **15** are increased by using two equivalents or an excess of nitrile oxide. The second step, i.e. the addition of nitrile oxide to the vinyl derivatives **12** is considerably slower, and if the nitrile oxide is generated too rapidly, it undergoes dimerization to the 1-oxa-2,5-diazole-N-oxides (eqn 3), which occasionally were isolated. The unasymmetrical 5,5'-di(2,2'-isoxazolinyls) **8**, **17**, and **18** were prepared by adding a different nitrile oxide to the 5-vinyl-2-isox-

†A crystallographic study has been carried out on **15a** by A. Hazell, B. Jensen and O. Jensen, see Appendix.



Scheme 1. 1. a: CH_3NO_2, Et_3N, $ClSi(CH_3)_3$; b: Et_3N; c: Ac_2O, Δ; d: $LiAlH_4$; e: *m*-Cl-$C_6H_4CO_3H$. f: $|C_6H_{13}C{=}NO|$; g: Ti^{3+}, HOAc, H_2O.

azolines **3** and **12a,e**. Titanous ion reduction of **15a,e** in acetic acid gives a single furan, **16a,e**, respectively, whereas **17** gave two isomers, **19** and **20**, in a ratio of 2:3. This series of reactions constitutes a novel entrance to 2,5-disubstituted furans. Catalytic reduction with RaNi/H_2 in ethanol of **15e** gives 7,12-diketo-9,10-dihydroxyoctadecene which on heating in acetic acid is converted to **16e**.

The structure and ratio of stereoisomers were solved by an X-ray investigation of the symmetric methyl derivative **15a** (Appendix). Practically only one isomer of **15a** was formed; the centrosymmetric *meso* form.[11]

The derivatives **8**, **17**, **18** and **15e** were then related to **15a** by ^{13}C NMR. The shifts of the ^{13}C atoms around the asymmetric centre are slightly different in the two forms and the ratio *meso*: D, L (or *erythro*: *threo*) was calculated from the line intensities, Table 1. The $^{13}\underline{CH_3}$-shift of the *meso*-form **15a** is known from its ^{13}C NMR spectrum and one of the $^{13}\underline{CH_3}$ lines of **17** major (erythro) form coincided with that of **15a**. This gives us the position of the α-methylene carbon atom of C_6H_{13} in **17**, *erythro*-form, and in the same way **8**, **18**, and **15e** are related to **17** and consequently to **15a**. A GLC investigation of the isomeric mixture of **15e** gave a peak ratio that was identical to the ^{13}C NMR peak ratio. It was not possible to enrich the *erythro*-form of **15e** by recrystallization. The stereoselectivity is thus rather poor and it is also poor for epoxidation of **3** and **12g** to **7** and **27**, respectively, ratio, 2:3.

Compound **12e** happened to be one of the first vinyl

Table 1. Ratio of stereoisomers formed by diaddition of nitrile oxides to butadiene[a]

Compound R^1	R^2		meso erythro	D,L threo	Method of determination
CH_3	CH_3	15a	97	3	X-ray, GC, ^{13}C NMR
H	C_6H_{13}	8	69	31	^{13}C NMR
CH_3	C_6H_{13}	17	69	31	^{13}C NMR
C_6H_{13}	$COOC_2H_5$	18	62	38	^{13}C NMR
C_6H_{13}	C_6H_{13}	15e	77	23	^{13}C NMR, GC
C_7H_{15}	C_7H_{15}	15f	79	21	GC

derivatives prepared by us in this series. It had a pleasant, fruity smell reminiscent of pineapple. Therefore, we prepared a number of homologues, **12a–d,f,g**. Heptane nitrile oxide was also condensed with isoprene and 1,3-pentadiene to **21–23** but none of these compounds was as pleasant smelling as **12e**. However, the heteroaromatic 3-hexyl-5-vinyl-isoxazole **24** has a smell similar to **12e**, from which it is prepared by dehydrogenation with dichloro-dicyanoquinone. **25** is prepared from nitromethane and 1,3-pentadiene. The conjugated unsaturated ketone **26** is synthesized from **23** by Ti^{3+} reduction and subsequent elimination of water.

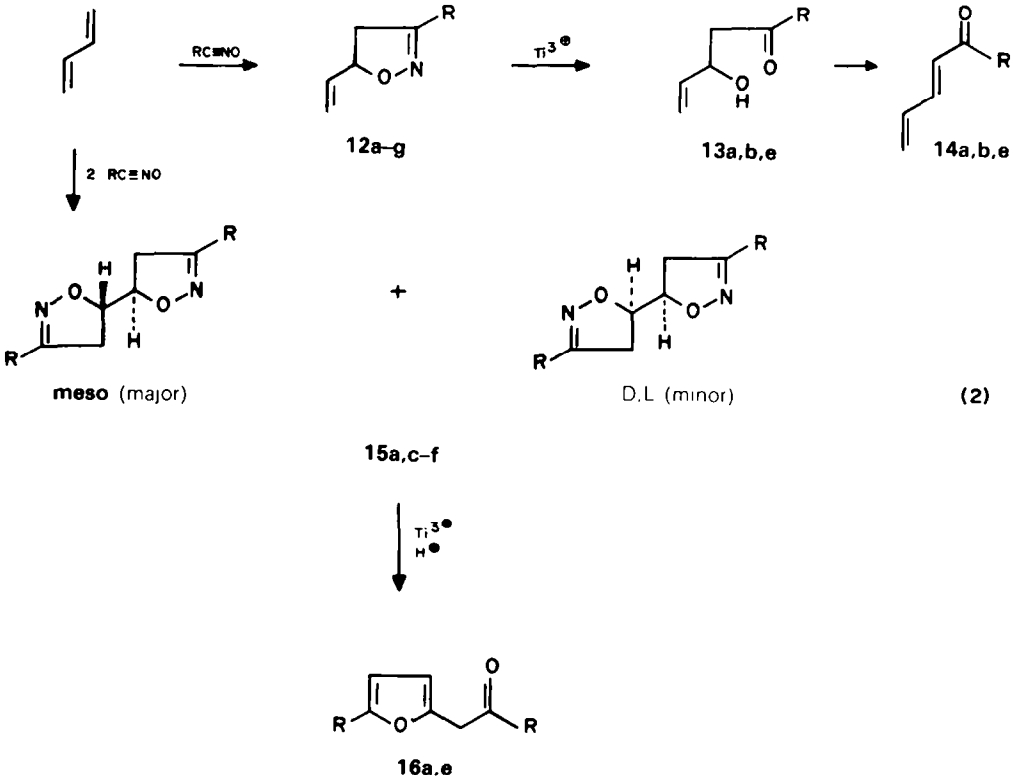
GLC of a petrol ether extract of fresh pineapple was carried out. The components in it did not include one with a peak corresponding to **12e** or to **24**.

Preparation of 2-isoxazolines—an alternative to aldol-type reactions

The well-known aldol-type reactions require two carbonyl functions and involve two carbon atoms, C^1 C^2, in one molecule and one carbon atom, C^3, of the other. Since the starting material is readily available, inexpensive, and the procedures are simple and proceed with satisfactory yields, these condensations constitute one of the most valuable methods for joining carbon atoms, Scheme 2.

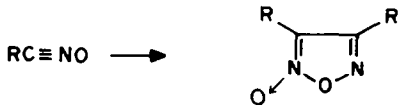
The 2-isoxazolines are formed from one olefin delivering the C^2, C^3 carbon atoms and one aldehyde (precursor of the nitrile oxide) or alternatively one nitro compound delivering C^1 of the chain.

As for the aldol reactions, the starting material is readily available, and the reaction is simple, proceeds in comparable yields, and allows large variation and regioselectivity. The reduction to the aldols proceeds satisfactorily and furthermore, they can be readily isolated. Evidently, the two methods are complementary and the choice between them is a matter of general synthetic strategy. The situation is illustrated with a few examples from this work. **13a** and **13b** are aldols from a conceivable base catalyzed condensation of acrolein with acetone and butanone, respectively. The yields for such reactions are most likely very low, whereas our procedure gives satis-



(2)

a: R = CH_3, b R = C_2H_5, c R = C_4H_9, d R = C_5H_{11}, e R = C_6H_{13}, f R = C_7H_{15}, g R = $COOC_2H_5$



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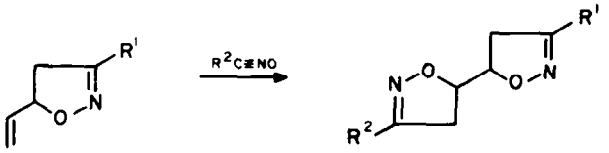
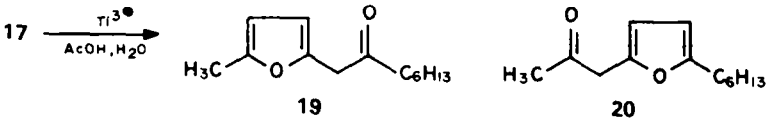


12a,e

17 $R^1 = CH_3$, $R^2 = C_6H_{13}$
18 $R^1 = C_6H_{13}$, $R^2 = COOC_2H_5$

(4)



19 **20** ~ 2 3

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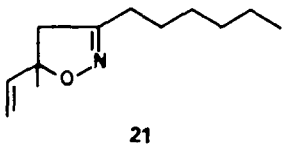

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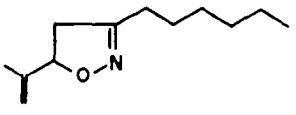

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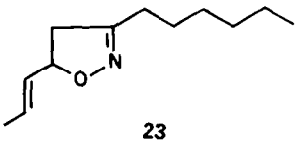

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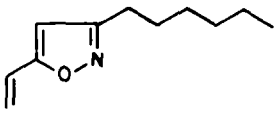

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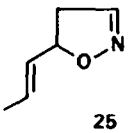

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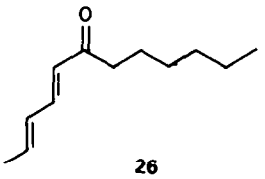

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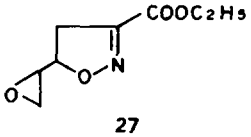

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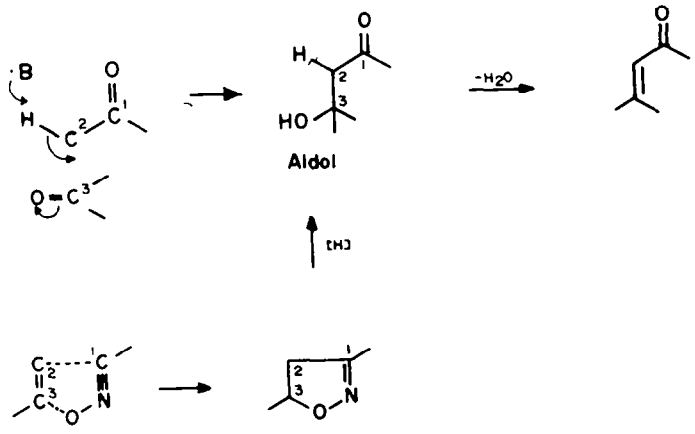

Scheme 2.

factory results both for the aldol and for the dienones **14a,b**.

EXPERIMENTAL

5-Vinyl-2-isoxazoline **3**. To butadiene (5.2 g, 0.096 mole) in benzene–acetonitrile (2:1), 24 ml, nitromethane (4.4 g, 0.072 mole), triethylamine (7.0 g, 0.069 mole) and chlorotrimethylsilane (7.8 g, 0.072 mole) are added at 0°. The mixture was stirred at this temperature for 3 hr and then at room temperature for 3 days. Trifluoracetic acid (0.5 ml) was added and the stirring was continued for 24 hr. The precipitate was filtered and washed with benzene (10 ml). The filtrate is washed with water (30 ml), dried and evaporated yielding **3**, bp_{10} 55–56°, 3.6 g, 52%. ^1H NMR ($CDCl_3$): δ 2.63 (1H, ddd, J 1.6, 8.5, 17.2 Hz), 3.12 (1H, ddd, J 1.6, 10.1, 17.2 Hz), 4.7–6.1 (4H, m), 7.09 (1H, t, J 1.6 Hz). MS: 97 (M^+).

1-Cyano-2-hydroxy-3-butene **4**. **3** (1.82 g) was refluxed with triethylamine (3.8 g) for 1 hr in an oil-bath at 100°. Evaporation of triethylamine and distillation of the residue *in vacuo* gives **4**. $bp_{0.8}$ 62–64°. 1.3 g, 70%, contaminated by traces of triethylamine. ^1H NMR ($CDCl_3$): δ 2.60 (2H, d, J 5.6 Hz), 4.0 (1H, br.s), 4.44 (1H, q, J 5.8 Hz), 5.1–6.2 (3H, m).

1-Amino-4-butenol-3 **6**, was obtained by reduction of **3** (0.90 g) with $LiAlH_4$ (0.4 g)[6] in ether (30 ml) under nitrogen with stirring at room temperature for 3 hr and then refluxing for 1 hr. The mixture is hydrolyzed with powdered $Na_2SO_4 \cdot 10\ H_2O$ mixed with Celite moistened with a few drops of water and filtered. Evaporation of ether gave **6** in practically quantitative yield, bp_{10} 90°. ^1H NMR ($CDCl_3$): δ 1.6 (2H, m), 2.8 (3H, s), 2.9 (2H, m), 4.30 (1H, q, J 5.5 Hz), 4.9–5.5 (2H, m), 5.86 (1H, ddd, J 17.3, 9.6, 5.3 Hz).

5-Oxiranyl-2-isoxazoline **7**. **3** (291 mg, 3 mmole) was oxidized with *m*-chloroperbenzoic acid (85%, 1.2 g, *ca* 2 eq) in methylene chloride (10 ml) at room temp for 6 days. The solution was extracted with aqueous potassium carbonate, dried, and evaporated giving crude **7**, which by purification on a TLC plate (silica, CCl_4–$CHCl_3$, 1:1) gave 180 mg, 53%, of a stereoisomeric mixture. ^1H NMR ($CDCl_3$): δ 2.5–3.2 (5H, m), 4.49 (1H, hept, J ~ 4.5 Hz), 7.10 (1H, s). According to the ^{13}C NMR spectrum the isomeric ratio was 2:3.

The preparation of hydroxamic acid chlorides is described in an accompanying paper.[7] Carboethoxy-chloraldoxime was prepared according to Skinner's method.[8]

3-Hexyl-5,5'-di(2,2'-isoxazolinyl) **8**. Hexane hydroxamic acid chloride, prepared by chlorination of heptanal oxime (520 mg, 4 mmole) in chloroform (5 ml), was added dropwise to a mixture of **3** (388 mg, 4 mmole) and triethylamine (404 mg, 4 mmole) in chloroform (5 ml) with stirring at room temp. After 1 hr the solution was washed with water, dried over sodium sulfate, and evaporated to yield **8** as a solid, crystallized from cyclohexane, mp 58–60° (764 mg, 85%) as an isomeric mixture containing 69% of *erythro*-form and 31% of *threo*-form according to ^{13}C NMR. MS. 224 (M^+). ^1H NMR ($CDCl_3$): δ 0.90 (3H, br.t), 1.0–1.9 (8H, m), 2.34 (2H, br.t, J 7 Hz), 2.7–3.2 (4H, m), 4.1–4.7 (2H, m), 7.12 (1H, br.s).

Synthesis of furans **10** *and* **11**. The reduction of **8** (448 mg, 2 mmole) is carried out as described earlier[3k] but with acetic acid as cosolvent instead of methanol. 370 mg of a crude mixture of **10** and **11** is obtained on extraction with chloroform in an extractor. ^1H NMR ($CDCl_3$) **11**: δ 0.88 (3H, br.t), 1.0–1.9 (8H, m), 2.6 (2H, br.t), 3.6 (2H, d, J 2.4), 5.86 (1H, d, J 3.3 Hz), 6.05 (1H, d, J 3.3 Hz), 9.67 (1H, t, J 2.4 Hz). MS: 194 (M^+). Minor peaks at δ 7.1 and at δ 6.0 indicated the presence of **10**. An attempt to separate the isomers on a TLC plate (silica, chloroform–carbontetrachloride, 1:1) led to partial decomposition.

General procedure for preparation of 5-vinyl-2-isoxazolines, **12a–g**. Triethylamine (0.04 mole) in chloroform (10 ml) is added dropwise to a stirred mixture of the hydroxamic acid chloride (0.04 mole) and butadiene (0.06 mole) in chloroform (30 ml) at 0°. The stirring is continued for 1 hr at 25°. The solution is washed with water, dried over sodium sulfate, and evaporated giving **12a–g** as liquids in a yield of *ca* 40–80%. They are often contaminated with the diaddition product, **15**, from which they can be separated by addition of petrol ether, (b.p. 40–60°). The insoluble diaddition product **15** separates often as a crystalline solid. The petrol ether phase is evaporated and **12** is distilled *in vacuo*.

12a, bp_{10} 68–70°, yield 60%, ^1H NMR ($CDCl_3$): δ 1.98 (3H, s), 2.66 (1H, dd, J 17.5, 8.8 Hz), 3.04 (1H, dd, J 17.5, 10.0 Hz), 4.7–5.3 (3H, m), 5.82 (1H, ddd, J 16.0 9.8, 6.2 Hz). MS: 111 (M^+). **15a**, *ca* 10%, separates as a solid by addition of petrol ether and is filtered off, mp 164–165° (from methanol).

12b was prepared according to Ref. 3*k*.

12c, $bp_{0.8}$ 60–68°, crude yield *ca* 25%, purified by TLC (silica, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.91 (3H, br.t), 1.0–2.0 (4H, m), 2.33 (2H, t, J 7 Hz), 2.70 (1H, dd, J 16.5, 8.5 Hz), 3.02 (1H, dd, J 16.5, 10.0 Hz), 4.7–6.1 (4H, m). No di-addition product **15c** was precipitated on addition of petrol ether to the crude product.

12d was obtained in a poor yield (*ca* 25%) with a wide boiling range, $bp_{0.1}$ 40–50°. It was further purified by TLC (silica, $CHCl_3$). ^1H NMR ($CHCl_3$): δ 0.89 (3H, br.t), 1.0–2.0 (6H, m), 2.38 (2H, t, J 7.5 Hz), 2.72 (1H, dd, J 16.6, 8.6 Hz), 3.05 (1H, dd, J 16.6, 10.0 Hz), 4.7–6.2 (4H, m). When petrol ether was added to the crude product, no **15d** precipitated. The reaction was not optimized.

12e, $bp_{0.1}$ 72–74°, yield 72%. ^1H NMR ($CDCl_3$): δ 0.88 (3H, br.t), 1.0–1.8 (8H, m), 2.32 (2H, br.t), 2.66 (1H, dd, J 16.8, 8.9 Hz), 3.03 (1H, dd, J 16.8, 9.9 Hz), 4.65–5.35 (3H, m), 5.76 (1H, ddd, J 16.2, 9.4, 6.0 Hz). MS: 181 (M^+). **15e** is formed as a side product which is precipitated by addition of petrol ether to the crude product, yield *ca* 15%, mp 90–92° (methanol).

12f, $bp_{0.08}$ 78–81°, yield *ca* 40%. ^1H NMR ($CDCl_3$): δ 0.88 (3H, br.t), 1.0–1.8 (10H, m), 2.32 (2H, br.t), 2.66 (1H, dd, J 16.7, 8.6 Hz), 3.02 (1H, dd, J 16.7, 9.8 Hz), 4.65–5.35 (3H, m), 5.77 (1H, ddd, J 16.2,

9.5, 6.1 Hz). **15f** is obtained as a side product, *ca* 18%, mp 98–100°. It separates as a solid by addition of petrol ether to the crude product.

12g[3k]. Ethylchloro-oximinoacetate was added dropwise to the mixture of 1,3-butadiene and triethylamine in chloroform at 0°. $Bp_{0.06}$ 68–74°, yield 80%. ^1H NMR ($CDCl_3$): δ 1.36 (3H, t, J 7.1 Hz), 2.95 (1H, dd, J 17.2, 8.8 Hz), 3.34 (1H, dd, J 17.2, 10.5 Hz), 4.30 (2H, q, J 7.1 Hz), 4.9–6.1 (4H, m). MS: 169 (M^+).

12a,b,e (0.01 mole) were reduced to **13a,b,e** with Ji^{3+}[12] (0.025 mole, aqueous solution, neutralized with sodium bicarbonate to pH 3–4) in acetic acid–water (1:1, 200 ml) for 2 days at 25° under nitrogen. Usual workup using a chloroform extractor gave **13a,b,e** as oils in a yield of 50–70%, purified by preparative TLC (silica, $CHCl_3$).

13a. ^1H NMR ($CDCl_3$): δ 2.19 (3H, s), 2.63 (2H, d, J 6.2 Hz), 4.2 (1H, br.s), 4.55 (1H, q, J 5.9 Hz), 4.9–5.3 (2H, m), 5.81 (1H, ddd, J 5.4, 9.6, 16.9 Hz). MS: 114 (M^+).

13b. ^1H NMR ($CDCl_3$): δ 1.03 (3H, t, J 7.2 Hz), 2.46 (2H, q, J 7.2 Hz), 2.61 (2H, d, J 6.2 Hz), 3.8 (1H, br.s), 4.53 (1H, q, J 5.9 Hz), 4.9–5.3 (2H, m), 5.82 (1H, ddd, J 5.4, 9.7, 17.0 Hz). MS: 128 (M^+).

13e. ^1H NMR ($CDCl_3$): δ 0.87 (3H, br.t), 1.0–1.9 (8H, m), 2.42 (2H, t, J 7.4), 2.60 (2H, d, J 6.0 Hz), 3.3 (1H, br.s), 4.53 (1H, q, J 5.8 Hz), 4.9–5.3 (2H, m), 5.82 (1H, ddd, J 5.4, 9.6, 17.2 Hz). MS: 184 (M^+).

Synthesis of 1-*acylbutadienes* **14a,b,e**. **13** (1 mmole), acetic anhydride (2 mmole) and sodium acetate (50 mg) were mixed and kept over night at 25° and then heated in an oil bath at 100° for 10 min and cooled.[9] Chloroform and aqueous sodium bicarbonate were added; the organic phase separated, dried over sodium sulfate and evaporated. The 1-acylbutadienes **14** obtained were formed in yields of 70–80% contaminated by some acetic anhydride. Purification of **14a,b** on a TLC plate led to partial decomposition but **14e** was obtained pure in a yield of 72% (silica, $CHCl_3$). **14a**. ^1H NMR ($CDCl_3$): δ 2.27 (3H, s), 5.3–7.3 (5H, m). **14b**. ^1H NMR ($CDCl_3$): δ 1.10 (3H, t, J 7.2 Hz), 2.58 (2H, q, J 7.2 Hz), 5.3–7.2 (5H, m). **14e**. ^1H NMR ($CDCl_3$): δ 0.88 (3H, br.t), 1.0–1.9 (8H, m), 2.56 (2H, t, J 8 Hz), 5,3–7.3 (5H, m). MS: 166 (M^+).

5,5'-*Di*-(3,3-*dimethyl*-2,2'-*isoxazolinyl*) **15a** is obtained as a by-product (*ca* 10%) by the synthesis of **12a**. It was anticipated that the yield of **15a** should increase by using 2 moles of the methane hydroxamic acid chloride and 2 mole of triethylamine per mole of butadiene. However, the yield increased only to 15–20%. *Ca* 20% **12a** was also obtained. ^1H NMR ($CDCl_3$): δ 2.0 (6H, s), 2.8–3.2 (4H, m), 4.2–4.6 (2H, m). ^{13}C NMR ($CDCl_3$): δ 13.03 (CH_3), 41.67 (CH_2), 79.97 (CH), 155.51 (C=N), (TMS). MS: 168 (M^+), mp 164–165°. **15a** was obtained in 45% yield when methanehydroxamic acid chloride and triethylamine was reacted with **12a**.

15e, mp 90–92°, is obtained in 81% yield from butadiene and 2 eq of hexanehydroxamic acid chloride and triethylamine. According to the ^{13}C NMR spectrum it is composed of two stereoisomers, *meso*: D,L = 77:23. ^1H NMR ($CDCl_3$, stereoisomeric mixture): δ 0.90 (6H, br.t), 1.0–1.8 (16H, m), 2.35 (4H, br.t), 3.0 (4H, br.t), 4.1–4.7 (2H, m). MS: 308 (M^+). A small quantity of **12e** separated from the crude product by washing with cold petrol ether.

15f, mp 98–100° (methanol) separates as a by-product from crude **12f** by addition of petrol ether, yield *ca* 15%. ^1H NMR ($CDCl_3$): δ 0.89 (6H, br.t), 1.0–1.8 (20H, m), 2.36 (4H, br.t), 3.0 (4H, br.t), 4.1–4.7 (2H, m).

16a. When **15a** was reduced with titanous ions in aqueous acetic acid according to the usual procedure and workup (see **11**), the furan derivative **16a** was obtained, oil, 69%. ^1H NMR ($CDCl_3$): δ 2.11 (3H, s), 2.22 (3H, s), 3.59 (2H, s), 5.85 (1H, d, J 2.8 Hz), 5.99 (1H, d, J 2.8 Hz). MS: 138 (M^+).

16e, from **15e**, oil, 83%. ^1H NMR ($CDCl_3$): δ 0.87 (6H, br.t), 1.0–1.8 (16H, m), 2.3–2.7 (4H, m), 3.59 (2H, s), 5.86 (1H, d, J 3 Hz), 5.99 (1H, d, J 3 Hz). MS: 278 (M^+). **15e** absorbed rapidly 2 mole of H_2 by catalytic reduction with Raney nickel at 1 atm and 25° in ethanol. The product is the corresponding 7,12-diketo-9,10-dihydroxy-octadecane, which by heating in acetic acid for 1 hr at 90° cyclizes quantitatively to **16e**.

17 is prepared from **12a** and hexane hydroxamic acid chloride, mp 64–66°, 79%, *meso*: D,L = 69:31 (^{13}C NMR). ^1H NMR ($CDCl_3$): δ 0.89 (3H, br.t), 1.0–1.8 (8H, m), 1.98 (3H, s), 2.0–3.2 (6H, m), 4.1–4.6 (2H, m). MS: 238 (M^+).

18 is prepared from **12e** and ethyl chloro-oximinoacetate. It is a viscous oil, 54%, purified by TLC (silica, $CHCl_3$), *meso*: D,L = 62:38 (^{13}C NMR). ^1H NMR ($CDCl_3$): δ 0.90 (3H, br.t). 1.0–1.8 (8H, m), 1.36 (3H, t, J 7.1 Hz), 2.35 (2H, br.t), 2.6–3.5 (4H, m), 4.32 (2H, q, J 7.1 Hz), 4.2–4.9 (2H, m). MS: 296 (M^+). A band located near the front of the TLC consisted of 3,5-diethoxycarbonyl-1-oxa-2,5-diazol-2-N-oxide. ^1H NMR ($CDCl_3$): δ 1.39 (3H, t, J 7.2 Hz), 1.42 (3H, t, J 7.2 Hz), 4.42 (2H, q, J 7.2 Hz), 4.48 (2H, q, J 7.2 Hz).

19 and **20** were obtained as a mixture (2:3) by Ti^{3+} reduction of **17** in aqueous acidic acid for 2 days at 25° under nitrogen. They could be separated by TLC (silica, CCl_4–$CHCl_3$, 1:1). The plate was eluted several times with the solvent mixture. **19**: ^1H NMR ($CDCl_3$): δ 0.89 (3H, br.t), 1.0–1.8 (8H, m), 2.24 (3H, s), 2.44 (2H, br.t), 3.60 (2H, s), 5.85 (1H, d, J 3 Hz), 5.99 (1H, d, J 3 Hz). **20**: ^1H NMR ($CDCl_3$): δ 0.89 (3H, br.t), 1.0–1.8 (8H, m), 2.13 (3H, s), 2.57 (2H, t, J 7 Hz), 3.60 (2H, s), 5.87 (1H, d, J 3 Hz), 5.99 (1H, d, J 3 Hz).

3-*Hexyl*-5-*methyl*-5-*vinyl*-2-*isoxazoline*, **21**, *and* 3-*hexyl*-5-*isopropenyl*-2-*isoxazoline*, **22**, were obtained as a mixture (~1:2, 31%, liquid) by reacting isoprene with hexanehydroxamic acid chloride in the usual way, $bp_{0.1}$ 76–86°. ^1H NMR ($CDCl_3$): **21**: δ 1.43 (5-CH_3, s); **22**: δ 1.71 (5-CH_3CH = , s).

3-*Hexyl*-5-*propenyl*-2-*isoxazoline*, **23**, was obtained in 54% yield from 1,3-pentadiene and hexanehydroxamic acid chloride, bp_{12} 103–104°. ^1H NMR ($CDCl_3$): δ 0.90 (3H, br.d), 1.1–1.9 (8H, m), 1.70 (3H, d, J 5.4 Hz), 2.36 (2H, br.t), 2.67 (1H, dd, J 17.9, 9.4), 2.99 (1H, dd, J 17.9, 9.3 Hz), 4.7–5.9 (3H, m).

3-*Hexyl*-5-*vinyl*-*isoxazole* **24**. **12e** (362 mg, 2 mmole) was refluxed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[10] (DDQ, 681 mg, 3 mmole) in benzene (5 ml) for 18 hr. Petrol ether (40–60°, 30 ml) is added and the solution was filtered and evaporated. Purification of the remainder on TLC (SiO_2, $CHCl_3$) gave **24**, 250 mg, 70% as a colourless liquid. ^1H NMR ($CDCl_3$): δ 0.89 (3H, br.t), 1.0–1.9 (8H, m), 2.64 (2H, t, J 7.0 Hz), 5.46 (1H, dd, J 10.5, 1.6 Hz), 5.90 (1H, dd, J 10.5, 1.6 Hz), 6.00 (1H, s), 6.51 (1H, dd, 17.6, 10.5 Hz). MS: 179 (M^+).

5-*Propenyl*-2-*isoxazoline*, **25** was obtained from 1,3-pentadiene and nitromethane according to the procedure described for **3** above, bp_{10} 78–80°, yield 40%. ^1H NMR ($CDCl_3$): δ 1.70 (3H, d, J 5.8 Hz), 2.6–3.4 (2H, m), 4.0–6.0 (3H, m), 7.09 (1H, br.s).

6-*Keto*-2,4-*dodecadiene* **26**. **23** is reduced with Ti^{3+} in aqueous acidic acid as described. The crude 4-hydroxy-6-keto-2-dodecaene (containing minor amounts of **26**) is dehydrated[3k] to **26**, oil, obtained as a *cis-trans*-mixture, yield *ca* 90%. ^1H NMR ($CDCl_3$): δ 0.88 (3H, br.t), 1.0–2.0 (11H, m), 2.58 (2H, t, J 7 Hz), 5.7–6.3 (3H, m), 6.8–7.3 (1H, m). MS: 180 (M^+).

3-*Carbethoxy*-5-*oxiranyl*-2-*isoxazoline*, **27** was obtained by epoxidation of **12g** as described for **7**. oil, yield 59%, purified by TLC (silica, $CHCl_3$–CCl_4, 3:1), stereoisomer ratio, 2:3 (^{13}C NMR). ^1H NMR ($CDCl_3$): δ 1.35 (3H, t, J 7.0 Hz), 2.6–3.4 (4H, m), 4.29 (2H, q, J 7.0 Hz), 4.5–5.0 (1H, m).

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APPENDIX

CRYSTALLOGRAPHIC STUDY OF **15a**

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15a crystallized as a mixture of rectangular plates and rhombic plates, which could be a mixture of the *meso* and D,L forms. Oscillation, Weissenberg, and precession photographs taken with Cu Kα radiation showed the two types to be identical, and to be monoclinic, space-group $P2_1/c$ (No. 14). The cell dimensions, measured from the setting angles of 20 reflections are $a = 5.649(2)$ Å, $b = 7.316(4)$ Å, $c = 10.550(6)$ Å, and $\beta = 102.23(4)$. The volume corresponds[1] to $V/18 \approx 24$ non-hydrogen atoms i.e. there are 2 molecules in the cell and the molecule must possess a centre of symmetry. Hence **15a** occurs as the *meso* form.

From the cell dimensions, space-group, and the fact that the molecule is on a symmetry centre, the expected[2,3] morphology is that {011} is the most prominent face, then {100} followed by {001}. The rectangular crystals have {001} as the prominent face and with poorly developed {011} as the prominent face and with poorly developed {011} and {100} faces. The rhombic shaped crystals have {100} as the prominent face and are bounded by {011} and sometimes {011}.

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