Synthesis of (*Z*)-Predominant α,β-Unsaturated Nitriles from Enone Cyanohydrin Diethyl Phosphates: Application to the Synthesis of (±)-Nuciferal, (±)-(*E*)- and -(*Z*)-Nuciferol, and (±)-Manicone

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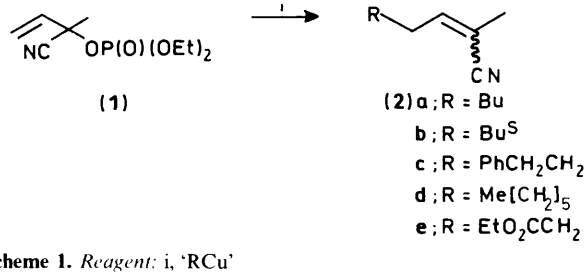
Enone cyanohydrin diethyl phosphates reacted regio- and stereo-selectively with a variety of organocopper reagents to give γ-coupling products, (*Z*)-predominant alk-2-enenitriles. The methodology was applied to the synthesis of (±)-nuciferal, (±)-(*E*)- and -(*Z*)-nuciferol, and (±)-manicone.

Utilization of a variety of cyanohydrin diethyl phosphates (cyano phosphates), which are readily obtained from carbonyl compounds with diethyl phosphorocyanidate [$(EtO)_2P(O)CN$ (DEPC)] and lithium cyanide[1] in tetrahydrofuran (THF), in organic synthesis have been extensively studied.[2] Recently we reported the regiospecific arylations of 1,4-benzoquinone cyano phosphate or but-3-en-2-one cyano phosphate by reaction with aromatic and heteroaromatic compounds in the presence of $BF_3{\cdot}OEt_2$, *via* S_N2' process, to give 3-aryl-4-hydroxybenzonitriles[3] or 4-aryl-2-methylbut-2-ene nitriles.[4] Although the regio- and stereo-specific coupling of secondary allylic phosphate with Grignard reagents in the presence of copper(I) iodide[5] or of enone cyanohydrin acetates with nucleophiles in the presence of a palladium–phosphine complex[6] have been investigated, little is known about the carbon–carbon bond formation of enone cyano phosphates with organometallic reagents. In a continuation of our work upon the synthetic utility of cyano phosphates, we now report a new highly regioselective γ-alkylation of enone (but-3-en-2-one, cyclohex-2-enones, cinnamaldehyde, and crotonaldehyde) cyano phosphates with a variety of organocopper reagents,† which have been widely used for carbon–carbon formation in organic synthesis.[7] Furthermore, its synthetic applications to natural products are also described.

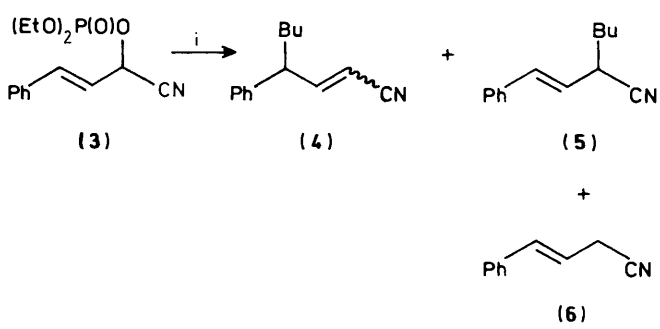
Results and Discussion

In order to examine the coupling reaction, but-3-en-2-one cyano phosphate (**1**) was used as a representative enone cyano phosphate. Results are summarized in Table 1. Treatment of compound (**1**) with butylmagnesium chloride (1.2 mol equiv.) in the presence of 10 mol % of CuI in THF at 0 °C gave the γ-coupling product (**2**)‡ (60%) (Scheme 1) with an *E*:*Z* ratio of 26:74 (entry 1). The structures of (*E*)- and (*Z*)-2-methyloct-2-enenitrile (**2a**) were confirmed by ^1H n.m.r. and mass spectroscopic evidence (see Experimental section). When phosphate (**1**) was coupled with lithium dibutylcuprate (Bu_2CuLi) (1.2 mol equiv.) in diethyl ether at −78 °C, almost the same result was obtained (entry 2). Interestingly, by changing the solvent to THF the stereoselectivity as well as the yield of product (**2**) was improved (83%; *E*:*Z* 18:82) (entry 3). Examination of the crude product of the above reactions by ^1H n.m.r. spectroscopy did not reveal the presence of any α-coupling product. Other cuprate species that might have a useful effect on the *E*/*Z* ratios were investigated, such as Lewis acid-mediated organocoppers[8] (entries 4—6) and particularly the so-called higher-order cuprate[9] (entry 7). However, very little enhancement was achieved in either stereoselectivity or yield. Thus, the coupling reactions of phosphate (**1**) with other lithium dialkylcuprates (entries 8—10) were carried out in THF. It should be noted that only *Z*-predominant γ-coupling products (**2a—d**) were obtained regioselectively, *via* an S_N2' process, in all cases. As is shown in entry 11, the coupling of compound (**1**) with ethoxycarbonylmethylcuprate[10] was also observed in satisfactory stereoselectivity and chemical yield. Thus, but-3-en-2-one cyano phosphate (**1**) would be a useful synthon for the regioselective homologation of the C_5-unit, including an α,β-unsaturated nitrile moiety, by reaction with lithium dialkylcuprates.

Attention was then turned to the coupling reaction of organocopper reagents with γ-substituted enone cyano phosphates, such as cinnamaldehyde cyano phosphate (**3**). The coupling of compound (**3**) with Bu_2CuLi in THF at −78 °C was, however, non-regiospecific, and gave a mixture of *E*- and *Z*-γ-coupling products (**4**) and α-coupling product (**5**) in 61% combined yield, together with a reduced product (**6**) (7%) (Scheme 2). In contrast, regioselectivity was attained when the



Scheme 1. *Reagent:* i, 'RCu'



Scheme 2. *Reagent:* i, 'RCu'

† Similar couplings with Grignard reagents or alkyl-lithium were non-stereospecific and proceeded in low yield (<20%).
‡ This has been reported as an *E*- and *Z*-mixture in ref. 21.

Table 1. Coupling reactions of but-3-en-2-one cyano phosphate (**1**) with organocopper reagents

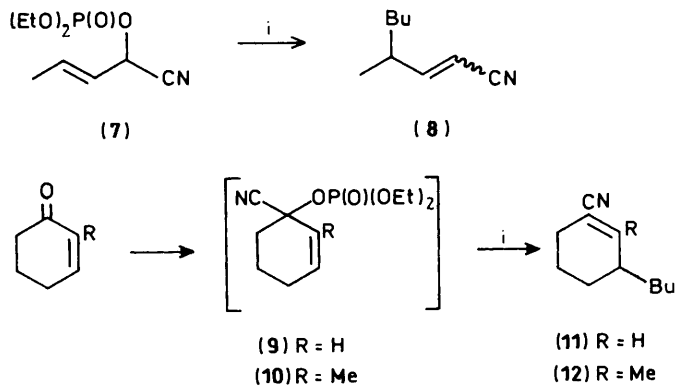
Entry	Reagent ('RCu')	Solvent	Product	Yield (%)	Product ratio (*E*:*Z*)
1[a]	BuMgCl–CuI	THF	(**2a**)	60	26:74
2[b]	Bu_2CuLi	Et_2O	(**2a**)	57	27:73
3[b]	Bu_2CuLi	THF	(**2a**)	83	18:82
4[b]	$BuCu{\cdot}BF_3$	Et_2O	(**2a**)	56	19:81
5[b]	$BuCu{\cdot}BF_3$	THF	(**2a**)	70	20:80
6[b]	$Bu_2CuLi{\cdot}BF_3$	THF	(**2a**)	68	22:78
7[b]	$Bu_2Cu(CN)Li_2$	THF	(**2a**)	70	17:83
8[b]	$Bu^s{}_2CuLi$	THF	(**2b**)	88	14:86
9[b]	$(PhCH_2CH_2)_2CuLi$	THF	(**2c**)	96	15:85
10[b]	Hex_2CuLi	THF	(**2d**)	72	24:76
11[b]	EtO_2CCH_2Cu	THF	(**2e**)	87	12:88

[a] Entry 1: 0 °C, 30 min. [b] Entries 2—11: −78 °C, 15—30 min.

coupling of compound (**3**) was undertaken with $BuCu{\cdot}BF_3$ (1.2 mol equiv.) to give (**4**) in good yield, though the stereoselectivity was unsatisfactory (*E*:*Z* 26:74). The higher-order cuprate was found preferentially to give the reduced product (**6**) (Table 2). Similarly, best results were obtained in the cases of crotonaldehyde cyano phosphate (**7**) and cyclohex-2-enone cyano phosphates (**9**) and (**10**) by coupling with $BuCu{\cdot}BF_3$ to give the γ-coupling products (**8**), (**11**), and (**12**) (Scheme 3), though three equivalents of cuprate were required in the latter.

Table 2. Coupling reaction of cinnamaldehyde cyano phosphate (**3**) with organocopper reagents

	γ- and α-Coupling products Proportions and combined yield (%)			Reduction product Yield (%)
Reagent ('RCu')	(*E*)-(**4**)	(*Z*)-(**4**)	(**5**)	(**6**)
Bu_2CuLi	20	60	20 (61)	7
$BuCu{\cdot}BF_3$	26	74	(84)	
$Bu_2Cu(CN)Li_2$	26	44	30 (36)	52

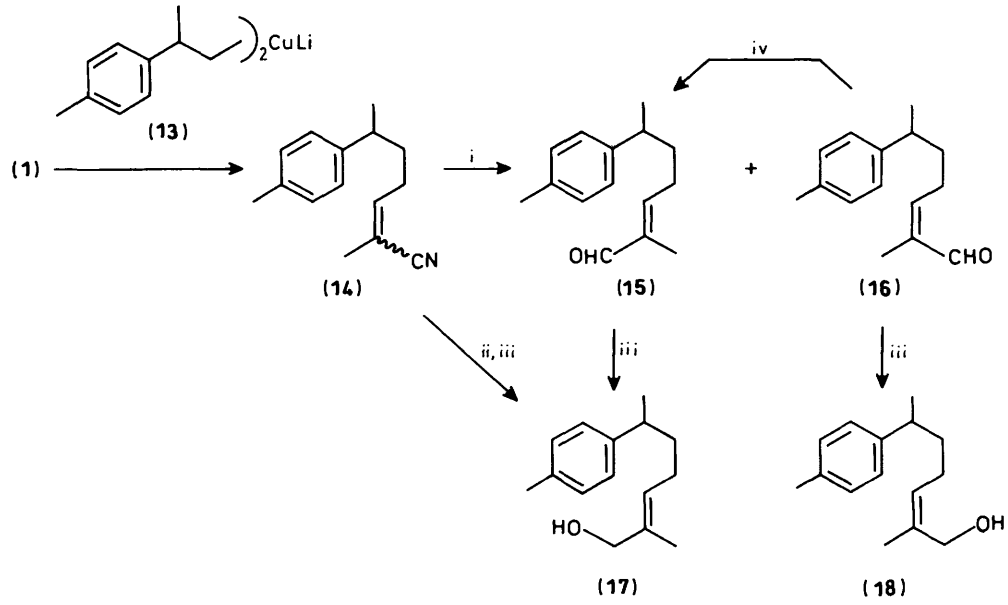


Scheme 3. *Reagent:* i, $BuCu{\cdot}BF_3$

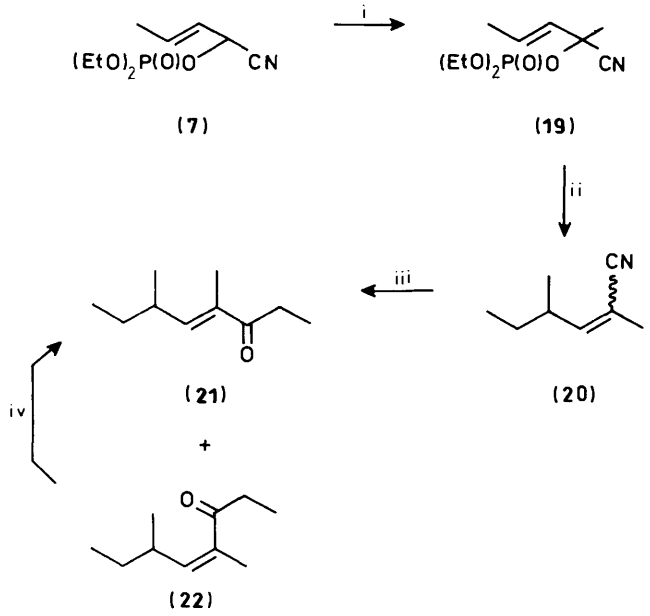
Synthetic Application.—In order to develop the synthetic utility of the present regioselective alkylations of enone cyano phosphates with lithium dialkylcuprates and BF_3-mediated alkyl cuprates, naturally occurring sesquiterpenes (**15**), (**17**), and (**18**) and the pheromone (**21**) were synthesized from readily available cyano phosphates (**1**) and (**7**) (Scheme 4). Nuciferal and nuciferol, isolated from the wood oil of *Torreya nucifera*,[11] were synthesized as follows; the coupling of phosphate (**1**) with lithium bis-[2-(*p*-tolyl)propyl)]cuprate (**13**) (1.2 mol equiv.), prepared from 2-(*p*-tolyl)propyl bromide[12] by the ordinary method, proceeded smoothly to give γ-coupling product (**14**) (*E*:*Z* 11:89) in 88% yield. Pure samples of (*E*)-(**14**) and (*Z*)-(**14**) were separated by column chromatography on silica gel (SiO_2), and the structures were fully characterized on the basis of spectral data (see Experimental section). Di-isobutylaluminium hydride (DIBAH) reduction of nitrite (**14**) in hexane at −78 °C followed by column chromatography on SiO_2 gave a mixture of (±)-nuciferal (**15**)[11] in 19% and the unstable *Z*-isomer (**16**)[13] in 41% yield. When isomer (**16**) was kept in the presence of toluene-*p*-sulphonic acid (TsOH) in benzene, it isomerized to (±)-nuciferal (**15**). Hydrolysis of nitrile (**14**) with potassium hydroxide in refluxing ethylene glycol* followed by lithium aluminium hydride reduction of the resulting carboxylic acid gave (±)-(*E*)-nuciferol (**17**)[14] as a single product in 77% yield, whose ^1H n.m.r. spectrum was in agreement with the sample obtained from nuciferal. (±)-(*Z*)-Nuciferol (**18**)[11] was synthesized from compound (**16**) by reduction with $LiAlH_4$ in quantitative yield.

Furthermore, our procedure was applied to the synthesis of (±)-manicone (**21**), one of the alarm pheromones of two species of ant (*Manica mutica* and *M. bradleyi*).[15] A readily accessible crotonaldehyde cyano phosphate (**7**) was methylated with methyl iodide in the presence of butyl-lithium and tetramethylethylenediamine (TMEDA), the reaction having recently been developed,[16] to give pent-3-en-2-one cyano phosphate (**19**) in 75% yield. This process for the preparation of phosphate (**19**) is superior to the direct cyanophosphorylation of pent-3-en-2-one, because the commercially available pent-3-en-2-one is contaminated with mesityl oxide (30%).[17] The γ-coupling of phosphate (**19**) with $EtCu{\cdot}BF_3$ in THF was performed to give 2,4-dimethylhex-2-enenitrile (**20**) (*E*:*Z* 10:90) in 80% yield. The pure isomers (*E*)-(**20**) and (*Z*)-(**20**) were separated by column chromatography on SiO_2, and the structures were confirmed by ^1H n.m.r. evidence (see Experimental section). Conversion of the CN group into an ethyl carbonyl group by treatment of compound (**20**) with ethyl-lithium followed by water afforded a mixture of (*E*)-4,6-dimethyloct-4-en-3-one [(±)-manicone] (**21**) (10%) and the corresponding *Z*-isomer (**22**) (52%) (Scheme 5). Since *Z*-isomer (**22**) is known to isomerize to manicone (**21**) by treatment with TsOH in benzene,[18] (±)-manicone has thus been successfully synthesized from crotonaldehyde cyano phosphate (**7**) in 37% overall yield. The spectroscopic data of the synthesized sesquiterpenes and pheromone were completely identical with those of the respective natural products.

* Hydrolysis of compound (**14**) (*Z*-isomer) was accompanied by thermal isomerization.



Scheme 4. *Reagents:* i, DIBAH; ii, KOH–ethylene glycol; iii, $LiAlH_4$; iv, TsOH



Scheme 5. *Reagents:* i, BuLi–TMEDA, MeI; ii, EtCu·BF_3; iii, EtLi; iv, TsOH

Experimental

I.r. spectra were recorded on a Shimadzu IR 435 spectrophotometer. ^{1}H N.m.r. spectra were determined with a Varian XL-300 spectrometer (tetramethylsilane as internal standard), and mass spectra with a Hitachi M-80 instrument. Extracts from reaction mixtures were dried over anhydrous magnesium sulphate. For column chromatography, SiO_2 (Merck, Art 9385) was used.

1-Cyano-1-methylallyl diethyl phosphate (**1**),[19] 1-cyano-3-phenylallyl diethyl phosphate (**3**),[19] 1-cyanobut-2-enyl diethyl phosphate (**7**),[19] 1-cyanocyclohex-2-enyl diethyl phosphate (**9**),[20] and 1-cyano-2-methylcyclohex-2-enyl diethyl phosphate (**10**)[20] were prepared by the methods previously described. Butyl-lithium was purchased from Aldrich Chemical Company, Inc., as a solution of hexane, and secondary butyl-lithium and butylmagnesium chloride as solutions in cyclohexane or THF were purchased from Kanto Chemical Co., Ltd. Other alkyl-lithium reagents were prepared and standardized at regular intervals.

Copper(I)-catalysed Reaction of the Phosphate (**1**) *with Butylmagnesium Chloride.*—To a stirred suspension of copper(I) iodide (19 mg, 0.1 mmol) in THF (2 ml) under N_2 at 0 °C was added BuMgCl (1.1M THF solution) (1.08 ml, 1.2 mmol) and the mixture was stirred for 15 min. A solution of the phosphate (**1**) (233 mg, 1 mmol) in THF (2 ml) was then added to the mixture at 0 °C and the mixture was stirred for 10 min, then quenched by the addition of saturated aqueous ammonium chloride (10 ml), and the products were extracted with diethyl ether (2 × 20 ml). The extracts were washed successively with 10% aqueous ammonium hydroxide (10 ml) and water (10 ml) and dried. The solvent was evaporated off and the residue was chromatographed with benzene–hexane (1:1) as eluant to afford (*Z*)-2-methyloct-2-enenitrile (*Z*)-(**2a**)[21] (61 mg) from the first fraction and (*E*)-isomer (*E*)-(**2a**) (22 mg) from the second fraction in 60% combined yield.

Compound (Z)-(**2a**) was an oil; $\nu_{max.}$(neat) 2 200 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.9 (3 H, t, *J* 5 Hz, CH_2*Me*), 1.3—1.5 (6 H, m, 3 × CH_2), 1.93 (3 H, br s, =CMe), 2.33 (2 H, q, *J* 7.2 Hz, =CHCH_2), and 6.14 (1 H, br t, *J* 7.2 Hz, =CH) (Found: M^+, 137.1202. Calc. for $C_9H_{15}N$, *M* 137.1205).

Compound (E)-(**2a**) was an oil; $\nu_{max.}$(neat) 2 200 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.9 (3 H, t, *J* 7 Hz, CH_2*Me*), 1.3– 1.5 (6 H, m, 3 × CH_2), 1.86 (3 H, br s, =CMe), 2.15 (2 H, q, *J* 7.7 Hz, =CHCH_2), and 6.35 (1 H, br t, *J* 7.7 Hz, =CH) (Found: M^+, 137.1202).

Reaction of the Phosphate (**1**) *with Cuprates.*—(A) R_2CuLi. The following procedure represents a general method.

To a stirred suspension of CuI (228 mg, 1.2 mmol) in THF (5 ml) at −30 °C was added BuLi (1.6M hexane solution; 1.5 ml, 2.4 mmol) under N_2 and the mixture was stirred for 10 min. The reaction mixture was then cooled to −78 °C. A solution of the phosphate (**1**) (233 mg, 1 mmol) in THF (2 ml) was then added and the mixture was stirred for 30 min at −78 °C. After the usual work-up as described for the reaction of compound (**1**) with the Grignard reagent, the products were separated by

column chromatography to give (*Z*)-(**2a**) (93 mg) and (*E*)-(**2a**) (21 mg) in 83% combined yield.

Similarly, the reaction of phosphate (**1**) with other R_2CuLi (R = Bu^s, phenethyl and hexyl), which were prepared from RLi and CuI as described for the preparation of lithium dibutylcuprate, were carried out and the results are summarized in Table 1.

(*Z*)-2,5-*Dimethylhept*-2-*enenitrile* (*Z*)-(**2b**) was an oil; $\nu_{max.}$ (neat) 2 200 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.9 (6 H, m, CH*Me* and CH_2*Me*), 1.1—1.6 (3 H, m, MeCH_2C*H*), 1.94 (3 H, br s, =CMe), 2.27 (2 H, m, =CCH_2), and 6.15 (1 H, br t, *J* 7.4 Hz, =CH) (Found: M^+, 137.1203).

(*E*)-2,5-*Dimethylhept*-2-*enenitrile* (*E*)-(**2b**) was an oil; $\nu_{max.}$ (neat) 2 200 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.9 (6 H, m, CH*Me* and CH_2*Me*), 1.1—1.6 (3 H, m, MeCH_2C*H*), 1.86 (3 H, 3′ H, br s, =CMe), 2.09 (2 H, m, =CCH_2), and 6.37 (1 H, br t, *J* 7.5 Hz, =CH) (Found: M^+, 137.1203).

(*Z*)-2-*Methyl*-6-*phenylhex*-2-*enenitrile* (*Z*)-(**2c**) was an oil; $\nu_{max.}$(neat) 2 210 cm^{-1} (CN); $\delta_H(CDCl_3)$ 1.75 (2 H, m, CH_2), 1.91 (3 H, br s, Me), 2.37 (2 H, q, *J* 7.7 Hz, =CHCH_2), 2.64 (2 H, t, *J* 7.5 Hz, CH_2), 6.11 (1 H, br t, *J* 7.7 Hz, =CH), and 7.1–7.3 (5 H, m, ArH) (Found: M^+, 185.1203. $C_{13}H_{15}N$ requires *M*, 185.1205).

(*E*)-2-*Methyl*-6-*phenylhex*-2-*enenitrile* (*E*)-(**2c**) was an oil; $\nu_{max.}$(neat) 2 210 cm^{-1} (CN); $\delta_H(CDCl_3)$ 1.75 (2 H, m, CH_2), 1.81 (3 H, br s, Me), 2.16 (2 H, q, *J* 7.5 Hz, =CHCH_2), 2.62 (2 H, t, *J* 7.8 Hz, CH_2), 6.34 (1 H, br t, *J* 7.5 Hz, =CH), and 7.1—7.3 (5 H, m, ArH) (Found: M^+, 185.1204).

(*Z*)-2-*Methyldec*-2-*enenitrile* (*Z*)-(**2d**) was an oil; $\nu_{max.}$(neat) 2 200 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.88 (3 H, t, *J* 6.5 Hz, *Me*CH_2), 1.2—1.5 (10 H, m, 5 × CH_2), 1.92 (3 H, br s, Me), 2.33 (2 H, q, *J* 7.5 Hz, =CHCH_2), and 6.14 (1 H, br t, *J* 7.5 Hz, =CH) (Found: M^+, 165.1516. $C_{11}H_{19}N$ requires *M*, 165.1518).

(*E*)-2-*Methyldec*-2-*enenitrile* (*E*)-(**2d**) was an oil; $\nu_{max.}$(neat) 2 200 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.89 (3 H, t, *J* 6.9 Hz, *Me*CH_2), 1.2—1.5 (10 H, m, 5 × CH_2), 1.85 (3 H, br s, Me), 2.14 (2 H, q, *J* 7.7 Hz, =CHCH_2), and 6.35 (1 H, br t, *J* 7.7 Hz, =CH) (Found: M^+, 165.1515).

(B) BuCu·BF_3. To BuCu at −78 °C, formed *via* addition of BuLi (0.77 ml, 2.4 mmol) to CuI (228 mg, 1.2 mmol) in THF (2 ml) at −30 °C, was added a solution of BF_3·OEt_2 (169 mg, 1.2 mmol) in THF (2 ml). After the mixture had been stirred for 5 min, a solution of compound (**1**) (233 mg, 1 mmol) in THF (2 ml) was added. The mixture was stirred at −78 °C for 30 min, then quenched and worked up in the usual fashion. Chromatographic separation of the crude products with benzene–hexane (1:1) as eluant gave (*Z*)-(**2a**) (77 mg) and (*E*)-(**2a**) (19 mg) in 70% combined yield.

(C) Bu_2CuLi·BF_3. To Bu_2CuLi at −78 °C, formed *via* addition of BuLi (1.54 ml, 1.2 mmol) to CuI (228 mg, 1.2 mmol) in THF (2 ml) at −30 °C, was added a solution of BF_3·OEt_2 (169 mg, 1.2 mmol) in THF (2 ml). After the mixture had been stirred for 5 min, a solution of phosphate (**1**) (233 mg, 1 mmol) in THF (2 ml) was added. The mixture was stirred at −78 °C for 30 min, then quenched and worked up in the usual fashion. Chromatographic separation of the crude products with benzene–hexane (1:1) as eluant gave (*Z*)-(**2a**) (73 mg) and (*E*)-(**2a**) (21 mg) in 68% combined yield.

(D) $Bu_2Cu(CN)Li_2$. To $Bu_2Cu(CN)Li_2$ at −78 °C, formed *via* addition of BuLi (1.54 ml, 2.4 mmol) to CuCN (108 mg, 1.2 mmol) in THF (2 ml) at 0 °C, was added a solution of phosphate (**1**) (233 mg, 1 mmol). The mixture was stirred at −78 °C for 20 min, then quenched, and worked up in the usual fashion. Chromatographic separation of the crude products with benzene–hexane (1:1) as eluant gave (*Z*)-(**2a**) (80 mg) and (*E*)-(**2a**) (16 mg) in 70% combined yield.

(*Z*)- *and* (*E*)-*Ethyl* 5-*cyanohex*-4-*enoate* (*Z*)-(**2e**) *and* (*E*)-(**2e**). —A solution of lithium di-isopropylamide (3.3 mmol) in THF (2 ml) was added to a solution of ethyl acetate (EtOAc) (264 mg, 3 mmol) and CuI (1.3 g, 6.6 mmol) in THF (3 ml) at −78 °C under N_2. After the mixture had been stirred for 10 min, a solution of the phosphate (**1**) (466 mg, 2 mmol) was added, and the reaction mixture was stirred for 10 min at −78 °C. After the usual work-up, the product was purified by column chromatography with benzene–hexane (1:1) as eluant to give an oil, which showed the presence of two components (*Z*)-(**2e**) and (*E*)-(**2e**) in the ratio 88:12 in its ^{1}H n.m.r. spectrum. Attempts to separate this mixture by column chromatography were unsuccessful. This mixture had the following spectral characteristics: $\nu_{max.}$(neat) 2 200 cm^{-1} (CN); $\delta_H(CDCl_3)$ 1.27 (3 H, t, *J* 7.5 Hz, *Me*CH_2), 1.90 [0.36 H, br s, Me of (*E*)-isomer], 1.94 [2.64 H, br s, Me of (*Z*)-isomer], 2.45 (2 H, m, CH_2CO), 2.65 (2 H, m, =CHCH_2), 4.15 (2 H, q, *J* 7.5 Hz, CH_2Me), 6.18 [0.88 H, br t, *J* 7.8 Hz, =CH of (*Z*)-isomer], and 6.31 [0.12 H, br t, *J* 7.1 Hz, =CH of (*E*)-isomer] (Found: M^+, 167.0946. $C_9H_{13}NO_2$ requires *M*, 167.0946).

Reaction of the Phosphate (**3**) *with Cuprates*.—(A) BuCu·BF_3. The crude product of the reaction of phosphate (**3**) (295 mg, 1 mmol) with BuCu·BF_3 (1.2 mmol), obtained by the procedure as described for the reaction of phosphate (**1**) *via* method (B) above, was purified by column chromatography. Elution with benzene–hexane (1:1) gave (*Z*)-4-phenyloct-2-enenitrile (*Z*)-(**4**) (125 mg) from the first fraction, and the (*E*)-isomer (43 mg) from the second fraction in 88% combined yield.

Compound (*Z*)-(**4**) was an oil; $\nu_{max.}$(neat) 2 210 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.89 (3 H, t, *J* 6.8 Hz, *Me*CH_2), 1.32 (4 H, m, 2 × CH_2), 1.80 (2 H, m, CH_2), 3.87 (1 H, m, ArC*H*), 5.29 (1 H, d, *J* 11 Hz, =CHCN), 6.53 (1 H, t, *J* 11 Hz, =CH), and 7.2–7.4 (5 H, m, ArH) (Found: M^+, 199.1359. $C_{14}H_{17}N$ requires *M*, 199.1362).

Compound (*E*)-(**4**) was an oil; $\nu_{max.}$(neat) 2 210 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.87 (3 H, t, *J* 7.9 Hz, *Me*CH_2), 1.28 (4 H, m, 2 × CH_2), 1.77 (2 H, q, *J* 7.5 Hz, CH_2), 3.39 (1 H, dq, *J* 7.5 and 1.2 Hz, CH), 5.25 (1 H, dd, *J* 16.6 and 1.2 Hz, =CHCN), 6.84 (1 H, dd, *J* 16.6 and 7.5 Hz, =CH), and 7.1—7.3 (5 H, m, ArH) (Found: M^+, 199.1360).

(B) Bu_2CuLi. The crude product of the reaction of phosphate (**3**) (295 mg, 1 mmol) with Bu_2CuLi (1.2 mmol), obtained by the procedure as described for the reaction of phosphate (**1**) *via* method (A), was purified by column chromatography. The first fraction with benzene–hexane (1:1) gave an oil (122 mg, 61%), which showed the presence of three components (*E*)-(**4**), (*Z*)-(**4**), and (**5**) in the proportions 20:60:20 in its ^{1}H n.m.r. spectrum. Attempts to separate the mixture by column chromatography were unsuccessful. The partial ^{1}H n.m.r. spectral data of (**5**) were obtained from the spectrum of a mixture of the three isomers; $\delta_H(CDCl_3)$ 6.04 (1 H, dd, *J* 15.8 and 6.7 Hz, =CH) and 6.72 (1 H, dd, *J* 15.8 and 1.2 Hz, ArC*H*=).

The second fraction with the same solvent afforded 4-phenylbut-3-enenitrile (**6**) (10 mg, 7%), m.p. 55—56 °C (lit.,[22] m.p. 59.5—61 °C); $\delta_H(CDCl_3)$ 3.29 (2 H, dd, *J* 5.4 and 2.1 Hz, CH_2), 6.05 (1 H, dt, *J* 15.9 and 5.4 Hz, CH_2C*H*), 6.74 (1 H, dt, *J* 15.9 and 2.1 Hz, ArC*H*), and 7.32 (5 H, m, ArH).

(C) $Bu_2Cu(CN)Li_2$. The crude product of the reaction of compound (**3**) (295 mg, 1 mmol) with $Bu_2Cu(CN)Li_2$ (1.2 mmol), obtained by the procedure as described for the reaction of phosphate (**1**) *via* method (D), was purified by column chromatography with benzene–hexane (1:1) to give an oily mixture (73 mg, 36%) of (*Z*)-(**4**), (*E*)-(**4**), (**5**), and (**6**) (74 mg, 52%).

Reaction of 1-*Cyanobut*-2-*enyl Diethyl Phosphate* (**7**) *with* BuCu·BF_3.—The crude product of the reaction of compound (**7**) (233 mg, 1 mmol) with BuCu·BF_3 (1.2 mmol), obtained by the usual procedure, was purified by column chromatography. Elution with benzene–hexane (1:1) gave (*Z*)-4-methyloct-2-ene-

nitrile (*Z*)-(**8**) (60 mg) from the first fraction and (*E*)-isomer (*E*)-(**8**) (26 mg) from the second fraction in 64% combined yield.

Compound (Z)-(**8**) was an oil; $\nu_{max.}$(neat) 2 210 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.9 (3 H, t, *J* 7.5 Hz, *Me*CH_2), 1.3 (6 H, m, 2 × CH_2), 1.06 (3 H, d, *J* 6.6 Hz, *Me*CH), 2.75 (1 H, m, CH), 5.26 (1 H, dd, *J* 10.5 and 1.3 Hz, =CH), and 6.26 (1 H, t, *J* 10.5 Hz, =CHCN) (Found: M^+, 137.1203. $C_9H_{15}N$ requires *M*, 137.1205).

Compound (E)-(**8**) was an oil; $\nu_{max.}$(neat) 2 210 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.89 (3 H, t, *J* 6.8 Hz, *Me*CH_2), 1.04 (3 H, d, *J* 7.9 Hz, *Me*CH), 1.3 (6 H, m, 2 × CH_2), 2.3 (1 H, m, MeC*H*), 5.28 (1 H, dd, *J* 16.5 and 1.4 Hz, =CHCN), and 6.63 (1 H, dd, *J* 16.5 and 7.9 Hz, =CH) (Found: M^+, 137.1203).

3-*Butylcyclohex*-1-*enecarbonitrile* (**11**) *and* 3-*Butyl*-2-*methylcyclohex*-1-*enecarbonitrile* (**12**).—*General procedure.* A mixture of enone (Scheme 3) (1 mmol), DEPC (326 mg, 2 mmol), and LiCN (66 mg, 2 mmol) in THF (10 ml) was stirred at room temperature for 10 min. The solvent was removed under reduced pressure and the residue was dissolved in a mixture of water (10 ml) and EtOAc (30 ml). The organic layer was separated, washed with brine, dried, and evaporated to give cyano phosphate (**9**) or (**11**). The cyano phosphate was treated with freshly prepared $BuCu{\cdot}BF_3$ (3 mmol) as described for the reaction of phosphate (**1**) *via* method (B). After usual work-up, the product was purified by column chromatography with benzene–hexane (1:1). The following products were obtained.

Nitrile (**11**) (73%) was an oil; $\nu_{max.}$(neat) 2 210 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.9 (3 H, t, *J* 7.0 Hz, *Me*CH_2), 1.22—1.88 (10 H, m, 5 × CH_2), 2.18 (3 H, m, CH_2C=CCH), and 6.52 (1 H, s, =CH) (Found: M^+, 163.1360. $C_{11}H_{17}N$ requires *M*, 163.1362).

Nitrile (**12**) (78%) was an oil; $\nu_{max.}$(neat) 2 200 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.91 (3 H, t, *J* 6.9 Hz, *Me*CH_2), 1.28 (6 H, m, 3 × CH_2), 1.59 (4 H, m, 2 × CH_2), 2.01 (3 H, br s, =CMe), 2.07 (1 H, br, CH), and 2.20 (2 H, m, CH_2C=) (Found: M^+, 177.1515. $C_{12}H_{19}N$ requires *M*, 177.1516).

(Z)- *and* (E)-2-*Methyl*-6-(p-*tolyl*)*hept*-2-*enenitriles* (Z)-(**14**) *and* (E)-(**14**).—To lithium bis-[2-(*p*-tolyl)propyl]cuprate (**13**), prepared *via* addition of 2-(*p*-tolyl)propyl-lithium (12 mmol) to CuI (1.14 g, 6 mmol) in THF (10 ml) at between −78 and 0 °C, was added a solution of the phosphate (**1**) (1.17 mg, 5 mmol) in THF (5 ml) at −78 °C and the mixture was stirred for 10 min. After the usual work-up, the product was purified by column chromatography with benzene–hexane (1:1) to give the title nitrile (*Z*)-(**14**) (834 mg) from the first fraction and its isomer (*E*)-(**14**) (101 mg) from the second fraction in 88% combined yield.

Compound (Z)-(**14**) was an oil; $\nu_{max.}$(neat) 2 200 cm^{-1} (CN); $\delta_H(CDCl_3)$ 1.24 (3 H, d, *J* 6.9 Hz, *Me*CH_2), 1.67 (2 H, m, CHCH_2), 1.86 (3 H, br s, MeC=), 2.24 (2 H, m, CH_2CH=), 2.31 (3 H, s, Ar*Me*), 2.66 (1 H, m, ArC*H*), 6.04 (1 H, br t, *J* 7.5 Hz, =CH), and 7.0—7.1 (4 H, m, ArH) (Found: M^+, 213.1515. $C_{15}H_{19}N$ requires *M*, 213.1518).

Compound (E)-(**14**) was an oil; $\nu_{max.}$(neat) 2 200 cm^{-1} (CN); $\delta_H(CDCl_3)$ 1.23 (3 H, d, *J* 6.9 Hz, *Me*CH_2), 1.68 (2 H, m, CH_2CH), 1.72 (3 H, br s, MeC=), 2.03 (2 H, m, CH_2CH=), 2.32 (3 H, s, Ar*Me*), 2.64 (1 H, m, ArC*H*), 6.28 (1 H, br t, *J* 7.6 Hz, =CH), and 7.0—7.1 (4 H, m, ArH) (Found: M^+, 213.1520).

(E)-2-*Methyl*-6-(p-*tolyl*)*hept*-2-*enal* (**15**) [(±)-*Nuciferal*] *and* (Z)-2-*Methyl*-6-(p-*tolyl*)*hept*-2-*enal* (**16**).—To a solution of the nitrile (*Z*)-(**14**) (214 mg, 1 mmol) in hexane (4 ml) at −78 °C was added dropwise DIBAH (1.5M solution in toluene; 2 ml, 3 mmol), and the mixture was stirred for 15 min. Methanol (2 ml) and then saturated aqueous ammonium chloride (5 ml) were added to the reaction mixture, which was then stirred at room temperature for 15 min and extracted with diethyl ether (2 × 30 ml). The extracts were washed with brine (10 ml), dried, and evaporated and the residue was chromatographed with benzene–hexane (1:1) as eluant to afford the *Z*-aldehyde (**16**) (88 mg) from the first fraction and nuciferal (**15**) (42 mg) from the second fraction in 60% combined yield.

Compound (**15**). The spectroscopic data (^{1}H n.m.r.) of compound (**15**) were consistent with those of the natural product reported in the literature;[11] $\nu_{max.}$(neat) 1 690 cm^{-1} (CO); $\delta_H(CCl_4)$ 1.24 (3 H, d, *J* 6.9 Hz, *Me*CH), 1.59 (3 H, s, 2-Me), 1.74 (2 H, q, *J* 7.9 Hz, CHCH_2), 2.20 (1 H, m, ArC*H*), 2.31 (3 H, s, Ar*Me*), 2.66 (2 H, m, =CHCH_2), 6.28 (1 H, br t, *J* 6.0 Hz, =CH), 6.9—7.1 (4 H, m, ArH), and 9.26 (1 H, s, CHO) (Found: M^+, 216.1516. Calc. for $C_{15}H_{20}O$: *M*, 216.1513).

Compound (**16**) was an oil; $\nu_{max.}$(neat) 1 690 cm^{-1} (CO); $\delta_H(CCl_4)$ 1.23 (3 H, d, *J* 6.9 Hz, *Me*CH), 1.68 (3 H, s, 2-Me), 1.7—1.8 (2 H, m, CHCH_2), 2.3—2.7 (3 H, m, =CHCH_2 and ArC*H*), 2.30 (3 H, s, Ar*Me*), 6.31 (1 H, br t, *J* 8.2 Hz, =CH), 6.9—7.1 (4 H, m, ArH), and 9.83 (1 H, s, CHO) (Found: M^+, 216.1507).

When (*Z*)-isomer (**16**) was kept at room temperature in the presence of TsOH in benzene for 2 h, it was found (t.l.c.) to have isomerised to the natural (*E*)-(±)-nuciferal (**15**).

(E)-*Nuciferol* (**17**).—*Method A.* A solutuion of (*Z*)-(**14**) (584 mg, 3.07 mmol) and potassium hydroxide (560 mg, 10 mmol) in ethylene glycol (10 ml) was refluxed for 5 h, and the stirred reaction mixture was diluted by the addition of diethyl ether (10 ml) and water (30 ml). The aqueous layer was separated, acidified by the addition of 10% hydrochloric acid, and extractd with diethyl ether (2 × 30 ml). The extracts were dried and evaporated to give an oil, which was stirred with $LiAlH_4$ (228 mg, 6 mmol) in diethyl ether (5 ml) at room temperature for 1 h. The reaction mixture was cooled to 0 °C, quenched by the addition of water (1 ml) followed by 10% HCl (2 ml), and extracted with diethyl ether (2 × 20 ml). The extracts were washed with brine (10 ml), dried, and evaporated. The residue was purified by column chromatography with benzene–EtOAc (15:1) to give pure (*E*)-nuciferol (**17**) (502 mg, 77%). The spectroscopic data (^{1}H n.m.r.) of compound (**17**) were consistent with those of the natural product reported in the literature;[11] $\nu_{max.}$(neat) 3 310 cm^{-1} (OH); $\delta_H(CCl_4)$ 1.20 (3 H, d, *J* 7.0 Hz, *Me*CH), 1.51 (3 H, br s, MeC=), 1.60 (2 H, m, CHCH_2), 1.88 (2 H, m, =CHCH_2), 2.30 (3 H, s, Ar*Me*), 2.61 (1 H, m, C*H*Me), 3.82 (2 H, br s, CH_2OH), 5.26 (1 H, br t, *J* 7.0 Hz, =CH), and 6.98 (4 H, s, ArH); *m/z* 218 (M^+).

Method B. A mixture of nuciferal (**15**) (22 mg, 0.1 mmol) and $LiAlH_4$ (10 mg, 0.25 mmol) in diethyl ether (2 ml) was stirred at 0 °C for 2 h. After being quenched by the addition of 5% HCl (1 ml), the mixture was extracted with diethyl ether (20 ml). The extract was washed with brine (5 ml), dried, and evaporated. The residue was purified by column chromatography with benzene–EtOAc (5:1) to give pure compound (**17**) (20 mg, 96%), which was identical with the authentic sample on comparison of their ^{1}H n.m.r. spectra.

(Z)-*Nuciferol* (**18**).—A mixture of compound (**16**) (46 mg, 0.21 mmol) and $LiAlH_4$ (19 mg, 0.5 mmol) in diethyl ether (2 ml) was treated as described for the reduction of compound (**15**) (Method B) to give compound (**18**) (45 mg, 98%) as an oil. The spectroscopic data (^{1}H n.m.r.) of compound (**18**) were consistent with those of the natural product reported in the literature;[11] $\nu_{max.}$(neat) 3 380 cm^{-1} (OH); $\delta_H(CCl_4)$ 1.18 (3 H, d, *J* 7.0 Hz, *Me*CH), 1.56 (2 H, m, CH_2CH), 1.70 (3 H, br s, MeC=), 1.88 (2 H, m, =CHCH_2), 2.29 (3 H, s, Ar*Me*), 2.60 (1 H, m, C*H*Me), 3.85 (2 H, br s, CH_2OH), 5.14 (1 H, br t, *J* 7.0 Hz, =CH), and 6.96 (4 H, s, ArH); *m/z* 218 (M^+).

1-*Cyano*-1-*methylbut*-2-*enyl Diethyl Phosphate* (**19**).—A solution of the phosphate (**7**) (466 mg, 2 mmol) in THF (5 ml) was

added to a solution of BuLi (15% hexane solution; 1.5 ml, 2.4 mmol) and TMEDA (278 mg, 2.4 mmol) in THF (10 ml) at −78 °C under N_2. After being stirred for 30 min, the mixture was treated with a solution of methyl iodide (568 mg, 4 mmol) in THF (10 ml) added dropwise (at −78 °C). The reaction flask was then removed from the cooling bath and the mixture was stirred for 1.5 h, then concentrated under reduced pressure, and the residue was dissolved in a mixture of water (5 ml) and EtOAc (30 ml). The organic layer was separated, washed with brine (20 ml), dried, and evaporated. The residual oil was purified by column chromatography with benzene–EtOAc (4:1) as eluant to give the *title compound* (**19**) (370 mg, 75%) as an oil; $\nu_{max.}$(neat) 1 270 and 1 100—900 cm^{-1} [OP(O)O]; $\delta_H(CDCl_3)$ 1.35 (6 H, m, 2 × $MeCH_2$), 1.81 (3 H, dd, *J* 6.6 and 1.6 Hz, =CH*Me*), 1.88 (3 H, d, *J* 1.3 Hz, NC–CMe), 4.16 (4 H, m, 2 × CH_2Me), 5.70 (1 H, br d, *J* 15.5 Hz, =CH), and 6.21 (1 H, dq, *J* 15.5 and 6.6 Hz, MeC*H*=) (Found: M^+, 247.0970. $C_{10}H_{18}NO_4P$ requires *M*, 247.0971).

(Z)-2,4-*Dimethylhex*-2-*enenitrile* (Z)-(**20**) *and* (E)-2,4-*Dimethylhex*-2-*enenitrile* (E)-(**20**).—A solution of ethyl-lithium (1.2M diethyl ether solution; 4 ml, 4.8 mmol) was added to a suspension of CuI (912 mg, 4.8 mmol) in THF (10 ml) at −30 °C and the mixture was stirred for 5 min, then cooled to −78 °C. A solution of BF_3·OEt_2 (682 mg, 4.8 mmol) in THF (5 ml) was added. After being stirred for 5 min, the mixture was treated with a solution of the phosphate (**19**) (410 mg, 1.6 mmol) in THF (10 ml) added dropwise (at −78 °C). The reaction mixture was stirred for 10 min, then quenched and worked up in the usual fashion. The products were purified by column chromatography with benzene–hexane (1:1) as eluant to give (*Z*)-(**20**) (144 mg) from the first fraction and (*E*)-(**20**) (16 mg) from the second fraction in 80% combined yield.

Compound (Z)-(**20**) was an oil; $\nu_{max.}$(neat) 2 200 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.89 (3 H, t, *J* 7.7 Hz, $MeCH_2$), 1.02 (3 H, d, *J* 6.5 Hz, *Me*CH), 1.2—1.4 (2 H, m, $MeCH_2$), 1.93 (3 H, d, *J* 1.1 Hz, =CMe), 2.59 (1 H, m, C*H*Me), and 5.09 (1 H, br d, *J* 10.2 Hz, =CH) (Found: M^+, 123.1045. $C_8H_{13}N$ requires *M*, 123.1047).

Compound (E)-(**20**) was an oil; $\nu_{max.}$(neat) 2 200 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.86 (3 H, t, *J* 7.7 Hz, $MeCH_2$), 0.99 (3 H, d, *J* 6.6 Hz, *Me*CH), 1.2—1.5 (2 H, m, $MeCH_2$), 1.86 (3 H, d, *J* 1.7 Hz, =CMe), 2.39 (1 H, m, C*H*Me), and 6.11 (1 H, br d, *J* 10.3 Hz, =CH) (Found: M^+, 123.1048).

(E)-4,6-*Dimethyloct*-4-*en*-3-*one* [(±)-*Manicone*] (**21**) *and* (Z)-4,6-*Dimethyloct*-4-*en*-3-*one* (**22**).—To a solution of the nitrile (*Z*)-(**20**) (122 mg, 1 mmol) in diethyl ether (6 ml) at −78 °C was added dropwise EtLi (1.2M diethyl ether solution; 3.2 ml, 4 mmol), and the mixture was stirred at room temperature for 18 h. The reaction mixture was recooled, quenched by the addition of water (2 ml), and extracted with pentane (2 × 30 ml). The extracts were dried and evaporated, and the residue was chromatographed with benzene–hexane (1:1) to give the *Z*-enone (**22**) (80 mg) from the first fraction and (±)-manicone (**21**) (16 mg, 10%) from the second fraction in 62% combined yield.

Compound (**21**) was an oil, the spectroscopic data (^1H n.m.r.) of which were consistent with those of the natural product reported in the literature;[18] $\nu_{max.}$(neat) 1 665 (CO) and 1 640 cm^{-1} (C=C); $\delta_H(CCl_4)$ 0.88 (3 H, t, *J* 7.2 Hz, 7-Me), 1.02 (3 H, d, *J* 7.2 Hz, *Me*CH), 1.05 (3 H, t, *J* 7.2 Hz, $MeCH_2CO$), 1.2—1.5 (2 H, m, 7-Hz), 1.74 (3 H, d, *J* 1.1 Hz, =CMe), 2.44 (1 H, m, CH), 2.60 (2 H, q, *J* 7.2 Hz, $MeCH_2$), and 6.22 (1 H, br d, *J* 10 Hz, =CH); *m/z* 154 (M^+).

Compound (**22**) was an oil, the spectroscopic data (^1H n.m.r.) of which were consistent with those reported in the literature;[18] $\nu_{max.}$(neat) 1 660 (CO) and 1 640 cm^{-1} (C=C); $\delta_H(CCl_4)$ 0.83 (3 H, t, *J* 7.1 Hz, 7-Me), 0.93 (3 H, d, *J* 7.2 Hz, *Me*CH), 1.04 (3 H, t, *J* 7.2 Hz, $MeCH_2CO$), 1.1—1.4 (2 H, m, 7-H_2), 1.89 (3 H, d, *J* 1.7 Hz, =CMe), 2.44 (2 H, q, *J* 7.2 Hz, $MeCH_2$), 2.57 (1 H, m, CH), and 5.25 (1 H, br d, *J* 10 Hz, =CH); *m/z* 154 (M^+).

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