Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Preparation of Multifunctional Stereodefined Dienes

Fanie R. van Heerden [a], Johan J. Huyser [a] & Cedric W. Holzapfel [a]

[a] Department of Chemistry and Biochemistry, Rand Afrikaans University, P.O. Box 524, Auckland Park, 2006, South Africa

Published online: 23 Sep 2006.

To cite this article: Fanie R. van Heerden, Johan J. Huyser & Cedric W. Holzapfel (1994) Preparation of Multifunctional Stereodefined Dienes, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:20, 2863-2872, DOI: 10.1080/00397919408010606

To link to this article: http://dx.doi.org/10.1080/00397919408010606

SYNTHETIC COMMUNICATIONS, 24(20), 2863-2872 (1994)

PREPARATION OF MULTIFUNCTIONAL STEREODEFINED DIENES

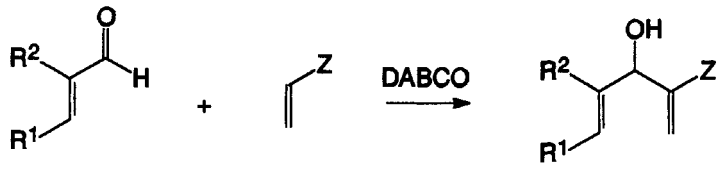
Fanie R. van Heerden,* Johan J. Huyser and Cedric W. Holzapfel

Department of Chemistry and Biochemistry, Rand Afrikaans University,
P.O. Box 524, Auckland Park, 2006, South Africa

Abstract: A number of multifunctional 1,3-dienes with defined stereochemistry were prepared by using the products obtained in DABCO-catalyzed condensation reactions of α,β-unsaturated aldehydes with acrylonitrile or methyl acrylate, as substrates for nucleophilic substitution reactions.

The Baylis-Hillman reaction,[1] *i.e.* the DABCO-catalyzed condensation of acrylate esters with aldehydes, is a versatile carbon-carbon bond forming reaction.[2] However, most applications have been restricted to simple aldehydes, and reactions with α,β-unsaturated aldehydes as substrates received little attention.[2] This is presumably due to the low yields obtained in reactions with these aldehydes as substrates.[3,4] We were interested to investigate the potential of the acetyl derivatives of the Baylis-Hillman condensation products obtained from α,β-unsaturated aldehydes, as substrates for palladium-catalyzed substitution reactions.

*To whom correspondence should be addressed.



1 2 3

Table 1: DABCO-catalyzed condensation of α,β-unsaturated aldehydes with ethyl acrylate or acrylonitrile.

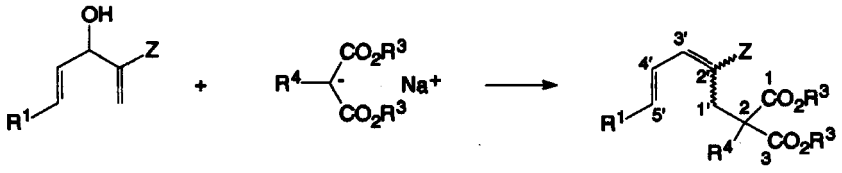
	R^1	R^2	Z	Reaction time (d)	Yield[a] (%)
3a	Ph	H	CO_2Me	6	75
3b	Me	H	CO_2Me	6	18
3c	H	Me	CO_2Me	4	20
3d	Ph	H	CN	3	20
3e	Me	H	CN	3	20
3f[b]	H	Me	CN	4	67

[a]Isolated yield.
[b]Reaction was conducted in the absence of light.

The 1,4-dienes **3a-3f** were prepared by the standard procedure[5] (Table 1). The low cost of the starting materials compensated for the low yields that were generally obtained in these condensation reactions. With acrolein as substrate, polymerization was observed, and the reaction with α,β-unsaturated aldehydes with methyl vinyl ketone resulted only in the formation of the self-condensation product 3-methylenehepta-2,6-dione.[6]

Our initial goal was to use the *O*-acetyl derivatives of **3a-3f** as substrates for palladium-catalyzed allylic substitution reactions. With $Pd(PPh_3)_4$ as catalyst, the reaction between **4** (R^3=Et, R^4=allyl) and the acetylated derivative of **3a** resulted in the formation of diene **5a**. However, this approach was hampered by the fact that the acetylated intermediates of **3a** - **3f** were found to be rather unstable. Furthermore, control experiments indicated that the same product could be obtained by reaction between **3a** and **4** (R^3=Et, R^4=allyl) in the absence of the catalyst. It is clear, therefore, that the reaction proceeds *via* a non-catalyzed nucleophilic substitution mechanism, and that activation of the hydroxy group by acetylation is not necessary. Reactions with a variety of substrates and nucleophiles yielded analogous products in good yields (Table 2).

The geometry of the C-2' - C-3' double bonds of **5a-5g** were determined by N.O.E.-experiments. The compounds where an effect could be observed between 1'-H and 4'-H were assigned as the *E*-isomers, whereas an effect between 1'-H and 3'-H characterized the *Z*-isomers. It was found that the geometry of the newly formed double bond depends on the nature of Z in **3**. If Z=CN, the *Z*-isomer is formed, whereas substrates with $Z=CO_2Me$ resulted in the formation of the *E* -isomer. These observations are in agreement with results obtained by Basavaiah and Sarma[7] in the reduction of analogous substrates with lithium aluminium hydride, and seem to be a general phenomenon



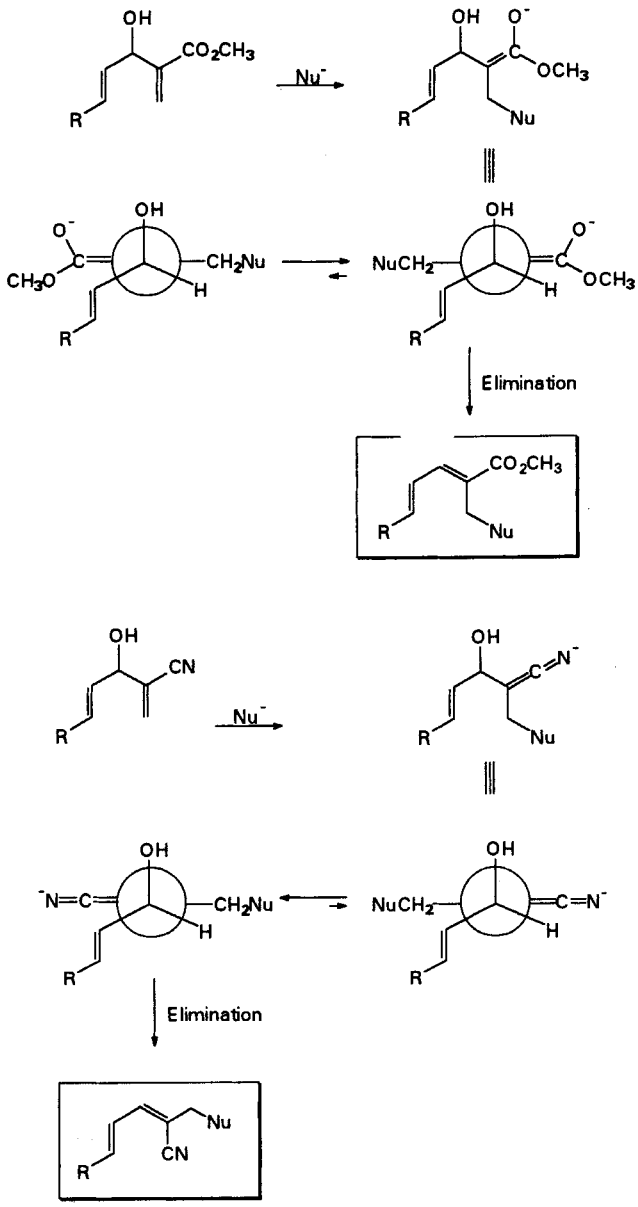
3 4 5

Table 2: Preparation of Stereodefined Dienes.

	R^1	R^3	R^4	Z	Conf. C2'-C3'	Yield* (%)
5a	Ph	Et	Allyl	CO_2Me	*E*	80
5b	Me	Et	Allyl	CO_2Me	*E*	60
5c	Me	Et	NHAc	CO_2Me	*E*	44
5d	Ph	Et	Allyl	CN	*Z*	55
5e	Me	Et	Allyl	CN	*Z*	40
5f	Me	Et	Me	CN	*Z*	78
5g	Me	$R^4+R^4=CMe_2$	Me	CN	*Z*	63

*Isolated yield

in the nucleophilic substitution reaction of β-hydroxy(or acetoxy)-α-methylene esters and nitriles, irrespective the size of the nucleophile. Electronic factors would suggest a transition state where the hydroxyl group and the double bond are perpendicular to each other (to accommodate overlapping of the new bond forming orbitals), and steric considerations would favour the more stable rotamer. Since $CO_2Me > CH_2Nu > CN$, the ester compound yielded the *Z*-isomer, whereas the nitrile substrate gave the *E*-isomer (Scheme 1).



SCHEME 1

It is of interest to note that as far as the strereochemical outcome of the reaction is concerned, the same trend was observed in the palladium-catalyzed carbonylation of β-alkoxycarbonyloxy-α-methylenealkanoates and -nitriles.[8] When the ester was used as substrate, the product with *E*-geometry predominated, whereas reaction with the nitrile resulted in the formation of the *Z*-isomer as the major product.

Many compounds of interest contain a conjugated polyene unit.[9] The Baylis-Hillman reaction with α,β-unsaturated aldehydes, followed by nucleophilic substitution of the product, present a useful reaction sequence for the preparation of highly functional dienes with defined stereochemistry.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded with a Varian VXR 200 spectrometer using deuterated chloroform as solvent. All chemical shifts are reported relative to that of $SiMe_4$ at 0.00 ppm. Mass spectra were obtained on a Finnigan-MAT 8200 mass spectrometer at a 70 eV ionizing voltage. Flash chromatography was achieved using Kieselgel 60 (230 - 400 mesh ASTM, Merck). Thin layer chromatography was performed on Merck GF_{254} silica sheets (20 × 20 cm, 250 μm layer).

General procedure for the preparation of (3a) - (3f) - A mixture of the unsaturated aldehyde (10 mmol), either methyl acrylate or acrylonitrile (10 mmol) and DABCO (1.5 mmol) was stirred under nitrogen for several days. CH_2Cl_2 (20 ml) was added and the mixture was extracted with a 1N HCl solution (2 x 20 ml). The organic phase was dried over Na_2SO_4, the solvent was evaporated and the product was isolated by column chromatography (hexane - 20% EtOAc, v/v). The products **3a** - **3f** were isolated as oils. The reaction with methacrylaldehyde was carried out in the absence of light.

Methyl (4*E*)-3-hydroxy-2-methylene-5-phenyl-4-pentenoate (3a)
δ_H 7.39-7.21 (m, 5H, Ph), 6.65 (d, *J* 15.9 Hz, 1H, 5-H), 6.28 (dd, *J* 16.0 and 6.2 Hz, 1H, 4-H), 6.27 (br. s, 1H, $=C\underline{H}_2$), 5.90 (br. s, 1H, $=C\underline{H}_2$), 5.11 (d, *J* 6.1 Hz, 1H, 3-H), 3.77 (s, 3H, $CO_2C\underline{H}_3$); δ_C 166.67 (C-1), 141.80 (C-2), 136.53 (*ipso*-C_{arom}), 129.25 (C-5), 128.79 ($=\underline{C}H_2$), 128.68 (*ortho*-C_{arom}), 127.36 (*meta*-C_{arom}), 126.62 (*para*-C_{arom}), 125.20 (C-4), 70.80 (C-3), 51.50 ($CO_2\underline{C}H_3$); m/z 218 (M^+,90%), 200 (52), 141 (100), 115 (87).

Methyl (4*E*)-3-hydroxy-2-methylene-4-hexenoate (3b)
δ_H 6.20 (s, 1H, $=C\underline{H}_2$), 5.81 (s, 1H, $=C\underline{H}_2$), 5.74 (dq, *J* 15.8 and 6.1 Hz, 1H, 5-H), 5.56 (dd, *J* 15.4 and 6.2 Hz, 1H, 4-H), 4.86 (d, *J* 6.1 Hz, 1H, 3-H), 3.75 (s, 3H, $CO_2C\underline{H}_3$), 2.40 (br. s, 1H, OH), 1.69 (d, *J* 5.9 Hz, 3H, 6-H); δ_C 166.87 (C-1), 141.72 (C-2), 131.05 (C-4), 128.31 (C-5), 125.20 ($=\underline{C}H_2$), 72.06 (C-3), 51.86 ($CO_2\underline{C}H_3$) 17.67 (C-6); m/z 156 (M^+,8%), 141 (14), 124 (40).

Methyl 3-hydroxy-4-methyl-2-methylene-4-pentenoate (3c)
δ_H 6.27 (s, 1H, $=C\underline{H}_2$), 5.83 (s, 1H, $=C\underline{H}_2$), 5.05 (s, 1H, 5-H), 4.94 (s, 1H, 5-H), 4.88 (s, 1H, 3-H), 3.74 (s, 3H, $CO_2C\underline{H}_3$), 1.69 (s, 3H, CH_3); δ_C 166.89 (C-1), 144.55 (C-4), 140.46 (C-2), 126.04 ($C\underline{H}_2$) 112.53 (C-5), 74.47 (C-3), 51.87 ($CO_2\underline{C}H_3$) 18.66 (CH_3); m/z 156 (M^+,7%), 141 (6), 124 (100).

(4*E*)-3-Hydroxy-2-methylene-5-phenyl-4-pentenenitrile (3d)
δ_H 7.20 - 7.50 (m, 5H, Ph), 6.72 (d, *J* 15.9 Hz, 1H, 5-H), 6.18 (dd, *J* 15.9 and 6.9 Hz, 1H, 4-H), 6.08 (s, 1H, $=C\underline{H}_2$), 6.01 (s, 1H, $=C\underline{H}_2$), 4.89 (d, *J* 6.8 Hz, 1H, 3-H); δ_C 136.60 (*ipso*-C_{arom}), 133.78 (C-4), 129.90 (d, C-5), 128.66 (*ortho*-C_{arom}), 128.47 ($=\underline{C}H_2$), 126.81 (*meta*-C_{arom}), 126.62 (*p*ara-C_{arom}), 125.51 (C-2), 116.91 (C-1), 72.87 (C-3); m/z 185 (M^+,64%), 167 (12), 141 (14), 115 (65).

(4*E*)-3-Hydroxy-2-methylene-4-hexenenitrile (3e)
δ_H 5.99 (d, *J* 1,5 Hz, 1H, $=C\underline{H}_2$), 5.94 (d, *J* 1.2 Hz, 1H. CH_2), 5.84 (dqd, *J* 15.3, 6.5 and 1 Hz, 1H, 5-H), 5.48 (ddq, *J* 15.3, 6.2 and 1.7 Hz, 1H, 4-H), 4.64 (br. d, *J* 7.1 Hz, 1H, 3-H), 1.73 (ddd, *J* 6.5, 1.6 and 0.7 Hz, 3H, 6-H); δ_C 131.11 (C-4), 129.39 ($=\underline{C}H_2$ or C-5), 129.14 (C-5 or $=CH_2$), 125.85 (C-2), 117.03 (C-1), 72.87 (C-3), 17.67 (C-6); m/z 123 (M^+,30%), 108 (63), 82 (31).

3-Hydroxy-4-methyl-2-methylene-4-pentenenitrile (3f)
δ_H 6.06 (s, 1H, $=C\underline{H}_2$), 6.02 (s, 1H, $=C\underline{H}_2$), 5.14 (s, 1H, 5-H), 5.04 (s, 1H, 5-H), 4.65 (s, 1H, 3-H), 2.40 (Br.s, OH), +1.69 (s, 3H, CH_3); δ_C 142.47 (C-4), 130.42 ($C\underline{H}_2$), 124.82 (C-2), 116.72 (C-1), 114.84 (C-5), 75.70 (C-3), 17.17 (CH_3); m/z 123 (M^+,9%), 108 (35).

General procedure for preparation of diene derivatives 5a - 5h. - Sodium hydride (9 mg, 0.25 mmol) was added to a solution of the malonic ester derivative **4** (0.25 mmol) in THF at 0°C. The substrate **3** (0.25 mmol), dissolved in 2 ml THF was added and the reaction mixture was stirred for 2h at room temperature. The solvent was removed under reduced pressure and the product was isolated as a yellow oil by column chromatography (Hexane - 20% EtOAc, v/v).

Diethyl 2-allyl-2-((2*E*,4*E*)-2-methoxycarbonyl-5-phenyl-2,4-pentadienyl) malonate (5a)
δ_H 7.25-7.55 (m, 5H, Ph), 7.37 (d, *J* 11.2 Hz, 1H, 3'-H), 7.11 (dd, *J* 15.3 and 11.3 Hz, 1H, 4'-H), 6.84 (d, *J* 15.4 Hz, 1H, 5'-H), 5.58 (ddt, *J* 17.7, 9.5 and 7.1 Hz, 2''-H), 5.14 - 5.02 (m, 2H, 3''-H), 4.08 (m, 4H, $CO_2C\underline{H}_2CH_3$), 3.37 (s, 3H, $CO_2C\underline{H}_3$), 3.21 (s, 2H, 1'-H), 2.59 (d, *J* 7.2 Hz, 2H, 1''-H), 1.18 (t, *J* 7.2 Hz, 6H, $CO_2CH_2C\underline{H}_3$); δ_C 170.82 ($\underline{C}O_2CH_3$), 168.60 (2 x $\underline{C}O_2CH_2CH_3$), 141.91 (C-3'), 140.31 (C-5'), 136.36 (*ipso*-C_{arom}), 132.90 (C-2''), 128.91 (C-4'), 128.78 (*ortho*-C_{arom}), 127.25 (*meta*-C_{arom}), 126.86 (*para*-C_{arom}), 124.04 (C-2'), 119.00 (C-3''), 61.27 ($CO_2\underline{C}H_2CH_3$), 58.16 (C-2), 51.83 ($CO_2\underline{C}H_3$), 37.67 (C-1''), 29.63 (C-1'), 13.92 ($CO_2CH_2\underline{C}H_3$); m/z 400 (M^+, 5%), 355 (4), 310 (24).

Diethyl 2-allyl-2-((2*E*,4*E*)-2-methoxycarbonyl-2,4-hexadienyl)malonate (5b)
δ_H 7.21 (d, *J* 11.2 Hz, 1H, 3'-H), 6.39 (ddq, *J* 14.9 and 11.3 Hz, 1H, 4'-H), 6.08 (dq, *J* 15.0 and 6.7 Hz, 1H, 5'-H), 5.77 (ddt, *J* 17.6, 9.6 and 7.2 Hz, 2''-H), 5.08 - 5.02 (m, 2H, 3''-H), 4.09 (m, 4H, $CO_2C\underline{H}_2CH_3$), 3.68 (s, 3H, $CO_2C\underline{H}_3$), 3.08 (s, 2H, 1'-H), 2.52 (d, *J* 7.2 Hz, 2H, 1''-H), 1.84 (dd, *J* 6.8 and 1.4 Hz, 3H, 6'-H), 1.21 (t, *J* 7.2 Hz, 6H, $CO_2CH_2C\underline{H}_3$); δ_C 170.81 ($\underline{C}O_2CH_3$), 168.82 (2 x $\underline{C}O_2CH_2CH_3$), 142.29 (C-3'), 139.31 (C-5'), 133.03 (C-2''), 127.53 (C-4'), 124.35 (C-2'), 118.81 (C-3''), 61.14 ($CO_2\underline{C}H_2CH_3$), 58.04 (C-2), 51.69 ($CO_2\underline{C}H_3$), 37.51 (C-1''), 29.29 (C-1'), 18.83 (C-6'), 13.94 ($CO_2CH_2\underline{C}H_3$); m/z 297 (M^+-allyl, 5%), 265 (7), 237 (7).

Diethyl 2-acetamido-2-((2*E*,4*E*)-2-methoxycarbonyl-2,4-hexadienyl) malonate (5c) δ_H 7.28 (d, *J* 11.2 Hz, 1H, 3'-H), 6.57 (s, 1H, NH), 6.31 (br. dd, *J* 15.0 and 11.2 Hz, 1H, 4'-H), 6.10 (dq, *J* 15.0 and 6.7 Hz, 1H, 5'-H), 4.19 (m, 4H, $CO_2C\underline{H}_2CH_3$), 3.64 (s, 3H, $CO_2C\underline{H}_3$), 3.41 (s, 2H, 1'-H), 1.85 (s, 3H, NHAc), 1.82 (d, *J* 6.7, 3H, 6'-H), 1.24 (t, *J* 7.2 Hz, 6H, $CO_2CH_2C\underline{H}_3$); δ_C 169.08 ($\underline{C}O_2CH_3$), 168.25 (2 x $\underline{C}O_2CH_2CH_3$), 167.87 ($NH\underline{C}OCH_3$), 144.08 (C-3'), 139.94 (C-5'), 127.32 (C-4'), 122.54 (C-2'), 65.28 (C-2), 62.44 ($CO_2\underline{C}H_2CH_3$), 51.72 ($CO_2\underline{C}H_3$), 29.92 (C-1'), 22.70 ($NH\underline{C}OCH_3$), 18.71 (C-6'), 13.81 ($CO_2CH_2\underline{C}H_3$); m/z 355 (M^+, 14%), 310 (3), 282 (10).

Diethyl 2-allyl-2-((2*Z*,4*E*)-2-cyano-5-phenyl-2,4-pentadienyl)malonate (5d). δ_H 7.25-7.55 (m, 5H, Ph), 7.27 (d, *J* 10.4 Hz, 3'-H), 7.13 (dd, *J* 16.0 and 10.4 Hz, 1H, 4'-H), 6.79 (d, *J* 15.9 Hz, 1H, 5'-H), 6.79 (d, *J* 10.7 Hz, 1H, 5'-H), 5.71 (ddt, *J* 17.0, 10.2 and 6.8 Hz, 2''-H), 5.21 - 5.00 (m, 2H, 3''-H), 4.17 (q, *J* 7.2 Hz, 4H, $CO_2C\underline{H}_2CH_3$), 2.89 (s, 2H, 1'-H), 2.74 (d, *J* 7.3 Hz, 2H, 1''-H), 1.34 (t, *J* 7.2 Hz, 6H, $CO_2CH_2C\underline{H}_3$); δ_C 168.85 (2 x $\underline{C}O_2CH_2CH_3$), 148.71 (C-3'), 140.47 (C-5'), 135.49 (*ipso*-C_{arom}), 131.78 (C-2''), 128.88 (C-4'), 128.83 (*ortho*-C_{arom}), 127.42 (*meta*-C_{arom}), 124.14 (*para*-C_{arom}), 119.98 (C-3''), 117.42 (CN), 106.88 (C-2'), 61.32 ($CO_2\underline{C}H_2CH_3$), 57.58 (C-2), 51.65 (C-1'), 32.77 (C-1''), 14.03 ($CO_2CH_2\underline{C}H_3$); m/z 367 (M^+, 17%), 326 (20), 280 (45).

Diethyl 2-allyl-2-((2*Z*,4*E*)-2-cyano-2,4-hexadienyl)malonate (5e) δ_H 6.58 (d, *J* 10.7 Hz, 1H, 3'-H), 6.46 (br. dd, *J* 14.1 and 11.1 Hz, 1H, 4'-H), 6.05 (dq, *J* 14.1 and 7.1 Hz, 1H, 5'-H), 5.62 (ddt, *J* 16.9, 9.6 and 7.4 Hz, 2''-H), 5.17 - 5.05 (m, 2H, 3''-H), 4.18 (q, *J* 7.1 Hz, 4H, $CO_2C\underline{H}_2CH_3$), 2.80 (s, 2H, 1'-H), 2.69 (d, *J* 7.3 Hz, 2H, 1''-H), 1.84 (d, *J* 6.7 Hz, 3H, 6'-H), 1.23 (t, *J* 7.2 Hz, 6H, $CO_2CH_2C\underline{H}_3$); δ_C 168.82 (2 x $\underline{C}O_2CH_2CH_3$), 149.02 (C-3'), 139.59 (C-5'), 131.82 (C-2''), 128.17 (C-4'), 119.90 (C-3''), 117.58 (CN), 104.59 (C-2'), 61.67 ($CO_2\underline{C}H_2CH_3$), 57.52 (C-2), 36.21 (C-1' or C-1''), 36.53 (C-1' or 1''), 18.54 (C-6'), 13.98 ($CO_2CH_2\underline{C}H_3$); m/z 264 (M^+, 18%), 219 (8), 191 (9).

Diethyl 2-((2*Z*,4*E*)-2-cyano-2,4-hexadienyl)-2-methylmalonate (5f) δ_H 6.59 (d, *J* 11.0 Hz, 1H, 3'-H), 6.45 (br. dd, *J* 14.5 and 10.8 Hz, 1H, 4'-H), 6.06 (dq, *J* 14.2 and 7.1 Hz, 1H, 5'-H), 4.17 (q, *J* 7.1 Hz, 4H, $CO_2C\underline{H}_2CH_3$), 2.78 (s, 2H, 1'-H), 1.84 (d, *J* 6.7 Hz, 3H, 6'-H), 1.44 (s, 2-CH_3) 1.23 (t, *J* 7.1 Hz, 6H, $CO_2CH_2C\underline{H}_3$); δ_C 170.92 (2 x $\underline{C}O_2CH_2CH_3$), 148.99 (C-3'), 139.58 (C-5'), 128.18 (C-4'), 117.76 (CN), 104.82 (C-2'), 61.66 ($CO_2\underline{C}H_2CH_3$), 53.88 (C-2), 46.17 (C-1'), 39.34 (2-$\underline{C}H_3$), 18.53 (C-6'), 13.92 ($CO_2CH_2\underline{C}H_3$); m/z 279 (M^+, 100%), 234 (39), 205 (20).

ACKNOWLEDGEMENT

We gratefully acknowledge the financial support of the Foundation for Research Development and Sasol Technology Limited.

REFERENCES

1. Baylis, A.B. and Hillman, M.E.D., German Patent, 1972, 2155113 (Chem. Abstr., 1972, 77, 34174q).

2. For a review, see: Drewes, S.E. and Roos, G.H.P., Tetrahedron, 1988, 44, 4653.

3. Janecki, T., Synth. Commun., 1993, 23, 641.

4. Drewes, S.E., Emslie, N.D., Khan, A.A. and Roos, G.H.P., Synth. Commun., 1989, 19, 959.

5. Hoffmann, H.M.R. and Rabe, J., Angew. Chemie, Int. Ed Engl., 1983, 22, 795.

6. Amri, H. and Villieras, J., Tetrahedron Lett. 1986, 27, 4307, Basavaiah, D., Gowriswari, V.V.L. and Bharathi, T.K., Tetrahedron Lett., 1987, 28, 4591.

7. Basavaiah, D. and Sarma, P.K.S., J. Chem. Soc., Chem. Comm., 1992, 955.

8. Yamamoto, K., Deguchi, R. and Tsuji, J., Bull. Chem. Soc. Jpn., 1985, 58, 3397. Wang, S.Z., Yamamoto, K., Yamada, H. and Takahashi, T., Tetrahedron, 1992, 48, 2333.

9. Xu, Y.-C., Roughton, A.L., Plante, R., Goldstein, S. and Deslongchamps, P., Can. J. Chem., 1993, 71, 1152.

(Received in the UK 28 March 1994)