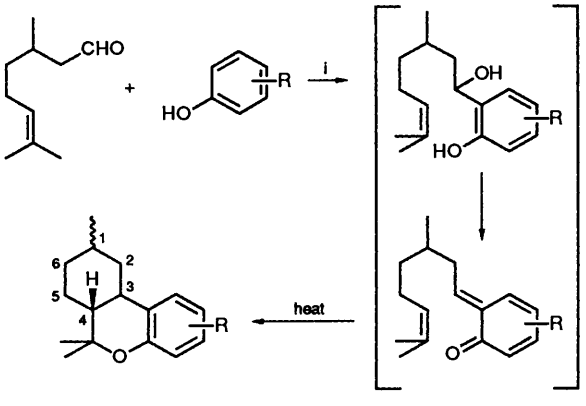
Base-catalysed Reaction of Citronellal with Phenols

William S. Murphy,* Anne Culhane, Brian Duffy and Sudersan Man Tuladhar
Department of Chemistry, University College, Cork, Ireland

Heating phenols with citronellal in organic bases such as quinoline, leads directly to the formation of the corresponding hexahydrocannabinoid.

We recently reported[1] a one-pot synthesis of hexahydrocannabinoids which involves a two step annulation of citronellal (3,7-dimethyloct-6-enal) to phenols in acetic acid, in the presence of phenylboric acid. The methodology is limited however, both by the requirement that the phenol be activated and that the *trans*-fused product normally contains approximately 5% of the less stable axial epimer. In an effort to surmount these limitations, we undertook an investigation employing a basic medium instead. Our confidence in a successful outcome rested both on the knowledge that base-catalysed condensation of aldehydes with phenols is well established[2–4] and that the initially formed *o*-hydroxybenzyl alcohols could be induced to undergo thermal dehydration *in situ* to the corresponding quinonemethide,[5,6] in which case intramolecular cycloaddition with formation of the hexahydrocannabinoid would be anticipated[1] (Scheme 1).



Scheme 1 *Reagent:* i, quinoline, heat

We initiated the study by investigating the reaction of citronellal with resacetophenone (2′,4′-dihydroxyacetophenone). When heated in pyridine at reflux,[7] cannabinoid was indeed formed, albeit in poor yield. This reaction was optimised by varying the molar ratio, duration of reaction, and use of a sealed tube.[8] 2,4,6-Collidine and quinoline were also investigated as alternatives. The most effective was quinoline. The range of phenols which reacted are summarised in Table 1. Particularly low yields were observed in the case of phenol, **4** and *p*-methoxyphenol, **8**.

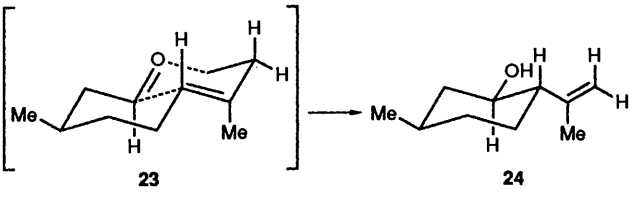
The stereochemistry of all products was unambiguously determined by NMR spectroscopy, as previously described.[1] Products were invariably *trans*-fused, the predominating epimer being that with the methyl group equatorial. Epimeric ratios are summarised in Table 1. The detailed structures of the hexahydrocannabinoids **13–18**, and **20** have been assigned by us previously.[1] The stereochemistry and epimeric ratios of the new products **12** and **21** were similarly determined. The hexahydrocannabinoid **22** has been prepared by others.[9]

The orientation of **12** was unambiguously determined by ^{1}H NMR spectroscopy where *ortho* coupled protons were observed at δ_H 6.3 and 7.46 (J 8.98 Hz). This orientation was that expected on the basis of investigations by Crombie and co-workers.[2] Chelation of the free hydroxy group was confirmed by the IR spectrum, wherein a characteristic OH absorption stretching frequency was absent and a low carbonyl stretching frequency was observed at 1620 cm^{-1}. In the NMR spectrum, this proton was observed at a characteristically low field position, δ_H 13.51.

The orientation of the substituents on the aryl ring of cannabinoid **22** was determined by the chemical shift of 2-H^a, which was observed at δ_H 3.07. The low field position is caused by the in-plane deshielding of the neighbouring hydroxy group. In the absence of any such anisotropic effect, it is normally observed at *ca.* δ_H 1.80.[10,11]

Surprisingly, when resorcinol **5** was treated with two equivalents of citronellal bis-condensation was not observed. The cannabinoid **16** only was isolated in contrast with the corresponding phenylboric acid-catalysed reaction. This result is anomolous since, in general, less reactive phenols such as phenol **4** and *p*-methoxyphenol, **8**, undergo reaction under these basic conditions. Further study will be required to resolve this point.

It was observed that in all reactions in pyridine, a side-product derived from citronellal was invariably observed. When heated alone in pyridine at 140 °C, citronellal reacted slowly to give a complex mixture of products. After nine days, there was still some citronellal present from which isopulegol [(1*R*,3*R*,4*S*)-(−)-*p*-menth-8-en-3-ol], **24**, was isolated in 38% yield. The cyclisation is probably a thermal Prins reaction,[12] involving a chair–chair transition state, **23**. The structure of isopulegol was



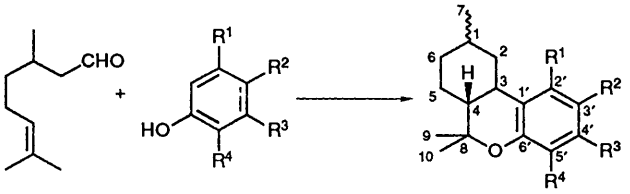
23 **24**

determined by ^{1}H NMR spectroscopy. The doublet of triplets assigned to 1-H, with J 10.8, 10.8 and 4.2 Hz, is consistant only with *trans*-diaxial coupling between 1-H and 2-H. The disposition of the methyl group was determined as equatorial on the basis of the ^{13}C NMR chemical shift observed at δ_C 22.29.[13]

This experimental procedure has the benefit that unactivated phenols undergo annulation. Thus, catechol, *p*-methoxyphenol, phenol, phloroglucinol and resacetophenone all undergo annulation with citronellal, in contrast with phenylboric acid-catalysed reactions.[1] The critical difference between the mechanisms of the acid- and the base-catalysed annulations is that phenoxide—the reactive specie in base—is a much stronger nucleophile than the un-ionised phenol.[4] On the other hand, the citronellal is no longer activated by acid and vigorous conditions remain a prerequisite in base.

With regard to stereoselectivity, disappointingly, annulation

Table 1 Synthesis of hexahydrocannabinoids from citronellal and phenols in boiling quinoline

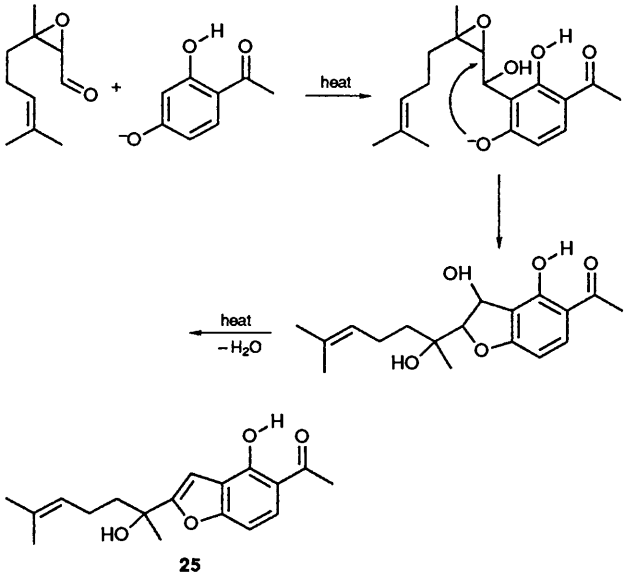


Phenol	Products [yield (%)]	Epimeric ratio equatorial:axial	Reaction time (h)
1 R^1 = OH; R^2 = COMe; R^3 = R^4 = H	**12** (73)	91:9	24
2 R^1, R^2 = C_4H_4; R^3 = R^4 = H	**13** (86)	100:0	21
3 R^1 = R^2 = H; R^3, R^4 = C_4H_4	**14** (88)	95:5	1.5
4 R^1 = R^2 = R^3 = R^4 = H	**15** (19)	—	54
5 R^1 = R^2 = R^4 = H; R^3 = OH	**16** (47)	95:5	32
6 R^1 = R^2 = R^4 = H; R^3 = OMe	**17** (33)	94:6	6
7 R^1 = R^3 = OMe; R^2 = R^4 = H	**18** (69)	81:19	7
8 R^1 = R^3 = R^4 = H; R^2 = OMe	**19** (19)	90:10	91
9 R^1 = R^4 = H; R^2, R^3 = OCH_2O	**20** (60)	100:0	37
10 R^1 = OH; R^2 = R^4 = H; R^3 = OH	**21** (41)	*a*	10
11 R^1 = OH; R^2 = R^4 = H; R^3 = C_5H_{11}	**22** (59)	85:15	24

[a] Not observable due to signal overlap.

under these basic conditions suffers the same limitation as the acid-catalysed reactions. Epimeric ratios are even less favourable when basic conditions are employed. The transition state in which the methyl group adopts an axial conformation involves additional strain due to *gauche* interactions.[14] However, the energy differential between this and the more favourable equatorial-*trans* transition state is more readily surmounted at the higher reaction temperatures employed under the basic conditions. The result is a higher percentage of the axial epimer and lower stereoselectivity.

We sought to extend this methodology to the synthesis of Δ^1- and Δ^6-tetrahydrocannabinoids. Our intention was to annulate citral epoxide with appropriate phenols, remove the epoxide functionality[15] to unmask the protected double bond[16] and release the requisite Δ^1-3,4-*trans*-tetrahydrocannabinol, the most physiologically active constituent of cannabis resin.[17] As a model, citral epoxide was heated with resacetophenone in pyridine. The only isolable product, obtained in 20% yield was the 2-substituted benzofuran **25**. There was no evidence for the normal annulation pathway. This unexpected product was probably formed by the mechanism outlined in Scheme 2.



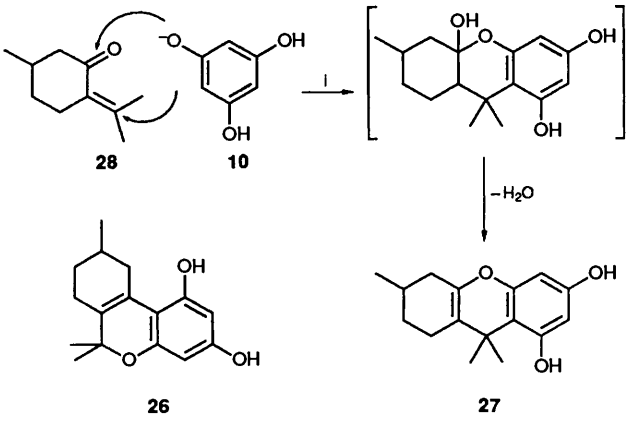
25

Scheme 2

Evidence was also found for the corresponding benzofuran when olivetol (5-pentylresorcinol) was employed. Unfortunately, insufficient pure product was isolable from the complex reaction mixture to allow for an unambiguous structural assignment. No product was isolable from the reaction with phloroglucinol.

A related approach involved employment of 3-hydroxycitronellal (3-hydroxy-3,7-dimethyloct-6-enal), as an alternative to citral epoxide. 3-Hydroxycitronellal was synthesised by reducing citral epoxide with excess lithium aluminium hydride in ether, to the corresponding diol (3,7-dimethyl-3-hydroxyoct-6-en-1-ol) followed by pyridinium fluorochromate[18] oxidation in the presence of sodium acetate buffer.[19] Citral, formed as a side product, was removed most easily as a water soluble bisulfite adduct.[20] 3-Hydroxycitronellal slowly converts into citral on standing and more rapidly on heating. In part for this reason, all attempts at protecting the hydroxy group failed. Attempted annulation of 3-hydroxycitronellal in pyridine at reflux with resacetophenone, olivetol, or phloroglucinol was unsuccessful. The phenols were recovered quantitatively. There was no trace of 3-hydroxycitronellal detected in the product mixture, probably due to retro-aldol condensation under the conditions. The problem was tackled another way. Linaloöl (3,7-dimethylocta-1,6-dien-3-ol) was quantitatively converted into its THP (tetrahydropyranyl) derivative by treatment with dihyropyran in methylene chloride at ambient temperature with pyridinium toluene-*p*-sulfonate (0.1 equivalent), 14 h. Hydroboration followed by oxidation with pyridinium fluorochromate resulted in a complex product mixture. This project was not pursued further.

Finally, the base-catalysed reaction of pulegone [(*R*)-(+)-*p*-menth-4(8)-en-3-one] **28** with phenols was investigated. It was anticipated that if reaction did occur, then the unusual $\Delta^{3,4}$-tetrahydrocannabinoid **26** would be expected by analogy with the reactions of citronellal described above. The acid-catalysed reaction with olivetol has been studied and shown[21] to result in a mixture of the analogues of both cannabinoid **26** and of the xanthane **27**. The three phenols resacetophenone **1**, phloroglucinol **10**, and olivetol **11** were each heated with pulegone in pyridine at 140 °C for prolonged periods. A reaction product with phloroglucinol only was detected. It was isolated in 35% yield after 46 h. The product was assigned the structure **27** on the basis of the ^1H and ^{13}C NMR spectra. The most probable mechanism for the course of this reaction is outlined in Scheme 3.



Scheme 3 *Reagent:* i, pyridine, heat

Experimental

General.—For general experimental details see ref. 1.

General Procedure for the Reaction and Work-up of Annulations of Citronellal with Phenols in Base.—To the appropriate base (3 mmol) was added the phenol (3 mmol) and citronellal (3,7-dimethyloct-6-enal) (3 mmol). The solution was heated to reflux for the specified period and monitored regularly by TLC. When completed, the flask was cooled to ambient temperature and the contents diluted with ether. The ether solution was washed successively with hydrochloric acid (3 × 30 cm^3, 10%) and saturated brine solution (3 × 30 cm^3). The solution was dried ($MgSO_4$) and evaporated. Purification was achieved using chromatographic means, as described previously.[1]

Reaction with resacetophenone (2',4'-*dihydroxyacetophenone*) **1**. A colourless viscous oil **12** (73%) (Found: C, 75.4; H, 8.3. $C_{18}H_{24}O_3$ requires C, 75.0; H, 8.4%); ν_{max}/cm^{-1} 2970, 2940, 2920, 2860, 1620 and 1485; δ_H 0.65 (1 H, q, $J_{2a.2e} = J_{2a.1a} = J_{2a.3a}$ = 12.45, 2-H$^{\beta}$), 0.93 (3 H, d, *J* 6.60, 1-Me), 1.06 (3 H, s, 8-Me$^{\alpha}$), 1.38 (3 H, s, 8-Me$^{\beta}$), 1.06–1.81 (6 H, m), 2.50 (1 H, br dt, 3-H), 2.51 (3 H, s, COMe), 3.20 (1 H, br d, *J* 13.00, 2-H$^{\alpha}$), 6.30 (1 H, d, *J* 8.98, ArH) and 7.46 (1 H, d, *J* 8.98, ArH); δ_C 19.23 (q), 22.55 (q), 26.05 (t), 27.48 (q), 27.97 (q), 32.75 (t), 35.15 (d), 35.48 (d), 38.20 (t), 48.79 (d), 78.75 (s), 104.61 (d), 112.99 (s), 129.95 (d), 149.63 (s), 161.14 (s), 164.25 and 202.65 (s).

Reaction with p-*methoxyphenol* **6**. A colourless *oil* **17** (19%) (Found: C, 78.6; H, 9.6. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.3%); ν_{max}/cm^{-1} 3030, 2960, 2920, 2860, 1725, 1610, 1580 and 1490; δ_H 0.96 (1 H, q, $J_{2e.2a} = J_{2a.3a} = J_{2a.1a}$ = 12.1, 2H$^{\beta}$), 1.05 (3 H, d, *J* 6.6, 1-Me), 1.16 (3, s, 8-Me$^{\alpha}$), 1.43 (3 H, s, 8-Me$^{\beta}$), 0.94–1.67 (6 H, m), 2.45 (1 H, dt, 3-H), 1.88 (1 H, br d, *J* 12.1, 2-H$^{\alpha}$), 3.80 (3 H, s, O-Me) and 6.74–6.84 (3 H, m, 2'-, 4'- and 5'-H); δ_C 19.95 (q), 22.61 (d), 27.60 (q), 28.00 (q), 32.55 (d), 34.83 (t), 36.00 (t), 39.63 (t), 46.91 (q), 55.68 (d), 76.80 (s), 111.30 (d), 111.92 (d), 117.97 (d), 126.11 (s), 146.29 (d) and 153.01 (s).

Reaction with phloroglucinol **10**. A colourless crystalline *solid* **21** (41%); m.p. 79–81 °C (ethanol); (Found: C, 73.0; H, 8.4%; M^+, 262. $C_{16}H_{22}O_3$ requires C, 73.3; H, 8.5%; *M*, 262); ν_{max}/cm^{-1} 2960, 1620 and 1590; δ_H 0.63 (1 H, m, 2-H$^{\beta}$), 0.91 (3 H, d, *J* 6.6, 1-Me), 1.03 (3 H, s, 8-Me$^{\alpha}$), 1.33 (3 H, s, 8-Me$^{\beta}$), 1.07–1.74 (6 H, m), 2.4 (1 H, m, 3-H), 2.97 (1 H, br d, *J* 12.0, 2-H$^{\alpha}$), 5.89 (1 H, d, *J* 1.8, 5'-H) and 5.98 (1 H, d *J* 1.8, 3'-H); δ_C 18.97, 22.55, 27.61, 27.94, 32.68, 35.15, 35.48, 39.05, 49.18, 77.71, 96.16, 96.87, 106.17, 154.70, 155.55 and 156.13.

Reaction of citral epoxide with resacetophenone **1**. The solution was heated at reflux for 44 h; the product was a colourless viscous *oil* **24** (20.1%) (Found: C, 71.9; H, 7.4%; M^+, 302. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%; *M*, 302); ν_{max}/cm^{-1} 3450, 2980, 2915 and 1625; δ_H 1.54 (3 H, s), 1.63 (6 H, br s, CH=C*Me*$_2$), 1.97–2.01 (4 H, m, 2 × CH_2), 2.58 (3 H, s, COMe), 3.08 (1 H, br s, tertiary OH), 5.03 (1 H, br t, CH=C*Me*$_2$), 6.80 (1 H, s, 3-H), 6.91 (H, d, *J* 9, 7-H), 7.51 (1 H, d, *J* 9, 6-H) and 13.12 (1 H, s, chelated OH); δ_C 17.67 (q), 22.66 (q), 26.77 (q), 41.26 (t), 71.86 (s), 99.80 (d), 103.57 (d), 114.29 (s), 118.18 (s), 123.71 (d), 126.76 (d), 132.22 (s), 158.41 (s), 159.91 (s), 162.37 (s) and 204.21 (s).

Reaction of pulegone [(R)-(+)-p-*menth*-4(8)-*en*-3-*one*] **10**. The solution was heated at reflux for 46 h; the product was a crystalline *solid* **27** (35%); m.p. 80–82 °C (hydrate, from aq. acetone) (dehydro- m.p. 150–151 °C) (Found: C, 69.2; H, 8.3. $C_{16}H_{20}O_3H_2O$ requires C, 69.0; H, 8.0%); ν_{max}/cm^{-1} 3360, 2870, 1630 and 1595; δ_H (CD_3COCD_3) 1.01 (3 H, d, *J* 6, CH*Me*), 1.47 and 1.50 (3 H each, s, C*Me*$_2$), 1.63–2.18 (7 H, m), 3.46 (2 H, br s, H_2O), 5.91 (1 H, d, *J* 2.4, 2- or 4-H), 6.15 (1 H, d, *J* 2.4, 4- or 2-H) and 8.41 (2 H, br s, OH); δ_C 21.70, 22.22, 26.57, 26.90, 29.60, 32.10, 33.46, 35.61, 94.99, 99.15, 108.25, 112.86, 140.21, 152.36, 156.78 and 157.56. When heated *in vacuo* 5 h, **27** melted at 150–151 °C (Found: M^+, 260. $C_{16}H_{20}O_3$ requires *M*, 260).

Methylation of **27** (0.15 g, 0.58 mmol) was effected with methyl iodide (1.37 g, 9.63 mmol) in the presence of anhydrous potassium carbonate (2.25 g, 16.28 mmol) in acetone under reflux to yield the white crystalline *dimethyl derivative* (78%); m.p. 106–108 °C (Found: C, 74.5; H, 8.1. $C_{18}H_{24}O_3$ requires C, 75.0; H, 8.4%); ν_{max}/cm^{-1} 2960, 2920, 2850, 1625 and 1585; δ_H 1.05 (3 H, d, *J* 6.0, CH*Me*), 1.42 and 1.44 (3 H each, s, C*Me*$_2$), 1.28–231 (7 H, m), 3.69 and 3.74 (3 H each, s, 2 × OMe), 6.07 (1 H, d, *J* 2.4, 2- or 4-H) and 6.21 (1 H, d, *J* 2.4, 4- or 2-H).

Reaction of citronellal with pyridine. A solution of citronellal (0.55 cm^3, 3 mmol) in pyridine (0.25 cm^3, 3 mmol) under nitrogen, was heated to 140 °C with constant stirring. The reaction was monitored by TLC (chloroform) and after nine days citronellal was still present together with a large number of minor products. The mixture was cooled, diluted with ether (50 cm^3) and the ethereal solution washed with 10% HCl (3 × 20 cm^3), water, and brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a dark brown oil. The major product (0.18 g, 1.1 mmol, 38%) was isolated by flash chromatography (CH_2Cl_2). It proved to be isopulegol [(1*R*,3*R*,4*S*)-(−)-*p*-menth-8-en-3-ol], a colourless liquid (Found: C, 77.6; H, 11.9. Calc. for $C_{10}H_{18}O$: C, 77.9; H, 11.8%) ν_{max}/cm^{-1} 3400, 2920, 2860 and 1640; δ_H 0.95 (3 H, d, *J* 4.8, 5-Me), 1.73 (3 H, s, CH_2=CH_3), 1.15–2.25 (8 H, m), 3.45 (1 H, dt, *J* 10.8 and 4.2, C*H*OH) and 4.90 (2 H, br s, CH_2=C); δ_C 19.23 (q), 22.29 (q), 29.76 (t), 31.51 (d), 34.37 (t), 42.82 (t), 54.12 (d), 70.45 (d), 112.73 (t) and 146.71 (s).

References

1 W. S. Murphy, S. M. Tuladhar and B. Duffy, *J. Chem. Soc., Perkin Trans. 1*, 1992, 605.
2 D. G. Clarke, L. Crombie and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1007 and refs. therein.
3 (*a*) M. J. Begley, L. Crombie, R. W. King and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2393; (*b*) J. O. Asgill, L. Crombie and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1978, 59; (*c*) D. A. Whiting, in *Comprehensive Organic Chemistry*, ed. J. F. Stoddart, Pergamon Press, Oxford, 1979, vol. 1, p. 707; (*d*) S. E. N. Mohamed, P. Thomas and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1983, 738; (*e*) L. Crombie, S. D. Redshaw, D. A. Slack and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1411; (*f*) L. Crombie, *Nat. Prod. Rep.*, 1984, **1**, 3.
4 W. S. Murphy and S. Wattanasin, *Chem. Soc. Rev.*, 1983, 213.
5 J. J. Talley, *J. Org. Chem.*, 1985, **50**, 1695.
6 See for example: (*a*) M. A. Tius and X. Q. Gu, *J. Chem. Soc., Chem. Commun.*, 1989, 1171; (*b*) L.-F. Tietze, S. Brand, T. Brumby and J. Fennen, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 665.
7 W. M. Bandaranayake, L. Crombie and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1969, 58.
8 P. Tuntiwachwuttikul, O. Pancharoen, V. Reutrakul and L. T. Byrne, *Aust. J. Chem.*, 1984, **37**, 449.

9 G. Casiraghi, M. Cornia, G. Casnati, G. G. Fava and M. F. Belicchi, *J. Chem. Soc., Chem. Commun.*, 1986, 271.
10. B. Berger, G. von Kiedrowski and L.-F. Tietze, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 221.
11 J. P. Marino and S. L. Dax, *J. Org. Chem.*, 1984, **49**, 3671.
12 R. T. Arnold and P. Veeravagu, *J. Am. Chem. Soc.*, 1960, **82**, 5411.
13 J. B. Stothers *^{13}C-NMR Spectroscopy*, Academic Press, London, 1972, 66.
14 Ref. 1 and refs. cited therein.
15 A. Ohlsson and I. Emanuelson, *Acta Pharm. Succ.*, 1979, **16**, 396; C. E. Turner, M. L. Mole, L. Hanus and H. N. Elsohly, *J. Nat. Prod.*, 1981, **44**, 27.
16 H. Suzuki, T. Fuchita, A. Iwasa and T. Mischina, *Synthesis*, 1978, 905.
17 R. Mechoulam, A. Shani, H. Edery and Y. Grunfeld, *Science*, 1970, **169**, 611.
18 M. N. Bhattacharjee, M. K. Chaudhuri, H. S. Dasgupta and N. Roy, *Synthesis*, 1982, 588.
19 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647.
20 A. Russel and R. L. Kenyon, *Org. Synth.*, 1955, Coll. Vol. 3, p. 747.
21 U. Claussen, P. Mummenhoff and F. Korte, *Tetrahedron*, 1968, **24**, 2897.

Paper 2/04466H
Received 18*th August* 1992
Accepted 9*th September* 1992