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SYNTHESIS OF SUBSTITUTED TETRAHYDROPYRIDINES AND M-HYDROXYBENZOIC ACIDS

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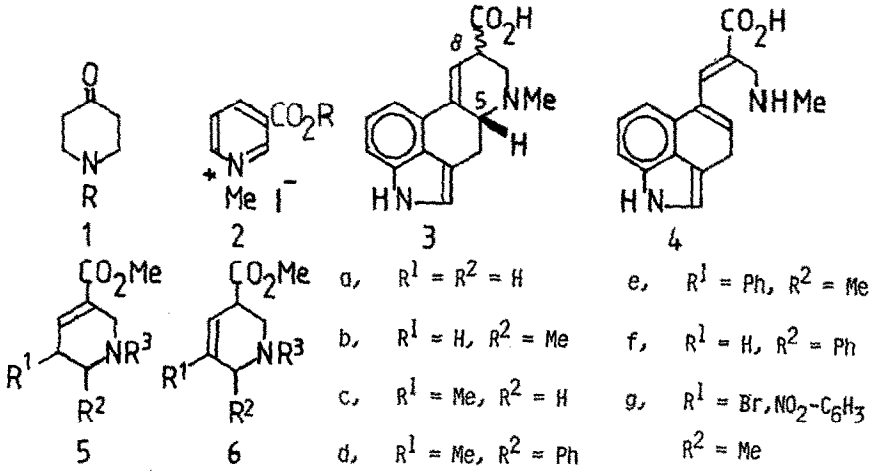
A series of substituted 1,2,3,6- (5) and 1,2,5,6-tetrahydropyridines (6) have been synthesised *via* intramolecular 1,6-Michael addition of methoxycarbonyl-2,4-dienylamines (10). The kinetics of these reactions have been investigated and an explanation of substituent effects is advanced. Also a new route to *m*-hydroxybenzoic acids has been established by cyclisation of substituted hexa-3,4:5,6-dienoic acids.

Although several naturally occurring 1,2,3,6-tetrahydropyridines are known, the most important group is arguably composed of the areca alkaloids[1] isolated from the betel nut, the fruit of *areca catechu*. These have been used as gamma-aminobutyric acid (GABA) uptake inhibitors,[2] and anthelmintics in veterinary medicine.[3] Consequently, the syntheses of the parent ring system has been investigated extensively, even though most approaches have led to common intermediates; for example, the 4-piperidones (1),[4,5,6,7,8] or by the simple approach of reduction of nicotinic methiodide (2) or its relatives.[9,10,11] Other methods have also been exploited, *eg* the rearrangement of cyclobutylamines[12] and application of methodology based on the Diels-Alder reaction.[13]

The observation[14] that optically active lysergic acid and isolysergic acid are racemised in barium hydroxide solution at temperatures greater than ambient indicates that the mechanism of racemisation involves both asymmetric carbons, C-5 and C-8, of (3). This has been rationalised[15] as resulting from stabilisation of the resulting carbanion through an extended, conjugated system when the proton at C-8 is lost, ultimately forming the amine (4). This hypothesis suggested to us that synthesis of intermediate (4) would provide a direct route to lysergic acid, as has indeed proved to be the case.[16]

Encouraged by this fact and observing the increasing importance of the areca alkaloids and analogues as potential GABA-uptake inhibitors[2] we

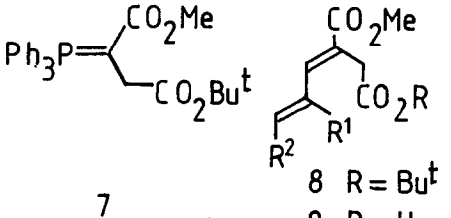
decided to extend this strategy to develop the synthesis of a series of substituted tetrahydropyridines (5) and (6) and further, to investigate the effect of substituents on the rate of cyclisation. *The ultimate objective was to design acyclic pro-drugs of the areca and ergot types.*



Our previous success in constructing dienoic acids[17] utilising the stabilised phosphorane (7)[18] led us to synthesise the required diene system (8) by Wittig reaction of α,β-unsaturated aldehydes with (7). Thus were provided, not only the desired skeletons, but also the essential carboxyl function, needed for transformation into an amino group, and the correct stereochemistry at the double bond α,β to the methoxycarbonyl group required for subsequent cyclisation. The E configuration about this double bond is almost exclusively formed with very stable ylides,[19,20] and this was supported by a study of the product proton n.m.r. spectra, particularly of the chemical shifts of the β-proton of the dienoic esters (8). Estimation of these shifts using the method of additive increments[21] for the various substituents gives δ 7.44 for the proton *cis* to the methoxycarbonyl group and δ 6.87 for a *trans* relation in the intermediates (8). Indeed such intermediates obtained using (7) were found to exhibit a chemical shift between δ 7.3 and 7.5 for the former proton indicating that each has the E configuration in the α,β-unsaturated double bond.

The general experimental procedure for preparation of the series of dienoic esters (8) involved the addition of an excess (2-4 fold) of the α,β-unsaturated aldehyde to a solution of the phosphorane (7) in dichloromethane (CH_2Cl_2) under nitrogen over a period of several days. The solution was kept dilute with respect to aldehyde content in order to

minimise polymerisation and generally the resultant products were triturated with petrol to remove triphenylphosphine oxide before being subjected to purification by rapid chromatography [medium pressure (MPLC) on silica]. It was found that the series (8) were unstable which necessitated storage at low temperature; a pure sample (one spot on TLC) easily decomposed to give four or more spots on TLC all of which were probably related oligomers. However, despite the high sensitivity to polymerisation, it is generally possible to obtain yields between 50 and 95%. In some cases small quantities of methyl t-butyl fumarate were noted during the isolation procedures.



7

8 R = Bu^t

9 R = H

a, $R^1 = R^2 = H$ e, R^1 = Ph, R^2 = Me

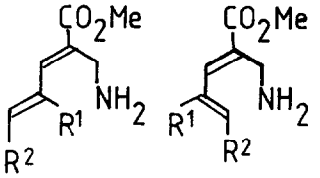
b, R^1 = H, R^2 = Me f, R^1 = H, R^2 = Ph

c, R^1 = Me, R^2 = H g, R^1 = Br,NO_2-C_6H_3

d, R^1 = Me, R^2 = Ph R^2 = Me

Selective hydrolysis of the t-butyl ester group of compounds (8) using aqueous trifluoroacetic acid (H_2O:TFA = 1:2) in a two phase mixture with benzene proved to give the best yields of the corresponding acids (9) but unfortunately there was some concomitant polymerisation. Stirring the t-butyl esters with 90% aqueous TFA gave variable yields which were not improved with time.

The transformation of the carboxylic acid function of (9) into an amino function was accomplished by an adaptation of the successful, modified-Curtius reaction.[17,20] In place of acid chloride or carboxylic mixed anhydride was selected a mixed carboxylic-phosphinic anhydride obtained by reaction of diphenylphosphinic chloride (DppCl) with the carboxylic acid in the presence of N-methylmorpholine. The attraction of these mixed anhydrides is that nucleophilic attack, even in the presence of considerable steric hindrance, occurs exclusively at the carboxylic carbon.[22] A further modification involved the use of the more soluble tetramethylguanidinium azide[23] rather than the more common sodium azide. The acid azides thus obtained were not purified (i.r. spectroscopy showed that they had formed, together with some rearrangement to isocyanate) but were heated in benzene to cause rapid rearrangement to the isocyanates. This reaction always took place in less than two hours although in CH_2Cl_2 rearrangement also occurred, however at a slower rate.



10 11

a, $R^1 = R^2 = H$ e, $R^1 = Ph$, $R^2 = Me$

b, $R^1 = H$, $R^2 = Me$ f, $R^1 = H$, $R^2 = Ph$

c, $R^1 = Me$, $R^2 = H$ g, $R^1 = Br, NO_2\text{-}C_6H_3$

d, $R^1 = Me$, $R^2 = Ph$ $R^2 = Me$

Finally, hydrolysis of isocyanates to amines (10) was achieved in benzene by adding *p*-toluenesulphonic acid monohydrate and stirring until precipitation of the salt of the amine (10) was complete, affording yields in the range 65-85%. The free amino-esters (10) were formed in more than 80% yield in CH_2Cl_2 by shaking the *p*-toluenesulphonates with aqueous sodium hydroxide in a two phase system. Cyclisation occurred *via* a 1,6-Michael (6-*endo*-trig) process to afford the six membered ring in agreement with Baldwin's rules.[24] Preliminary experiments proved encouraging,[20] as a result of which the initial attempts at cyclisation were carried out in methanol (as a protic solvent) with gentle heat which proved to be conditions free from any side reaction, other than a very small amount of polymerisation.

It might be expected that tetrahydropyridines (5, R^3=H) would be the major product formed by heating compounds (10), *ie* the products with the double bond in conjugation with the carbonyl group. Indeed, heating intermediate (10a) in methanol, until disappearance of its characteristic u.v. absorption at 250 nm, afforded a mixture of guvacoline (5a) and 5-methoxycarbonyl-1,2,5,6-tetrahydroxypyridine (6a) in the ratio of approximately 2:1. The base-induced isomerisation (triethylamine in methanol) of this mixture over 43 h afforded the thermodynamic mixture containing *ca* 25% of the β,γ-unsaturated methoxycarbonyltetrahydropyridine (6a). A factor responsible for favouring the β,γ-unsaturated isomer (6) is the nature of the substituent R^1 in (10) which will affect the thermodynamic stability of the trisubstituted β,γ-olefinic bond in the cyclised products. This effect was noted when compound (10c) was heated in methanol under reflux to produce a product mixture containing about 60% 5-methoxycarbonyl-3-methyl-1,2,5,6-tetrahydropyridine (6c) and 40% of 3-methoxycarbonyl-5-methyl-1,2,5,6-tetrahydropyridine (5c).

In contrast to the previous cases, ring closure of (10b) leads only to 5-methoxycarbonyl-2-methyl-1,2,3,6-tetrahydropyridine (5b). The reason for this is probably due to initial formation, as always, of the unconjugated, kinetically controlled product (6b), followed by fast isomerisation to (5b). In this case there is no substituent available to

stabilise the β,γ-olefinic bond in (6b). This hypothesis is reinforced by the observation that (10d), on the other hand, undergoes ring closure affording only 5-methoxcarbonyl-3-methyl-2-phenyl-1,2,5,6-tetrahydropyridine (6d) with no trace of the conjugated ester being observed, even after prolonged heating with an excess of triethylamine.

These observations led us to examine the kinetic properties of the cyclisation reaction as a function of substitution pattern. U.v. spectroscopy seemed the most appropriate investigative tool, requiring only that the counter-ion, *p*-toluenesulphonate, be replaced by the hemi-succinate ion to avoid chromophores absorbing above 230 nm. The hemi-succinate salts are crystalline, stable, easy to prepare and purify and at the same time would provide a natural, innocuous counter-ion for biological testing.

The general methodology adopted was to dissolve the succinate salt (*ca* 4.4 μmol) in ethanol (50 ml) and pre-warm it, with stirring, in a thermostatted water bath to the desired temperature. A solution of triethylamine (66.0 μmol) in ethanol (50 ml), pre-warmed in the bath, was added and timing begun. Periodically a sample was removed and subjected to u.v. monitoring. The disappearance of the peak at *ca* 250-300 nm was used as the basis of a first order kinetic plot to afford the rate constants (k_1) given in Table 1. These rate constants were subsequently used in Arrhenius plots to estimate the enthalpies and entropies of activation shown in Table 2 using the appropriate ancillary equations (1) $k_1 = Ae^{-E/RT}$; (2) $A = kT/h.e^{S/R}$ (at standard temperature 298^{o}K); (3) $\Delta G=\Delta H-T.\Delta S$

Alkyl substituents are well known for enhancing the rate of formation of cyclic compounds and many different explanations have been advanced.[25] As expected, the cyclisation of the 2-methoxycarbonyl-2,4-pentadienylamines (10) did show a rate enhancement with increase in substitution [excepting perhaps the particular case of compound (10f)] but the rate increase is modest. Perusal of Tables 1 and 2 shows that [with the exception of compound (10f)] the entropy change becomes larger with increasing rate of cyclisation. For the purpose of understanding the present, relative, observed rates we have made the following assumptions.

(1) Compounds (10) exist, in solution, in the open chain, S-*trans* conformation which is thermodynamically the more stable.[26] In accord with this assumption, we have noted that the mono-methyl ester (9a) will not undergo the Diels-Alder reaction with maleic anhydride.

(2) There is hydrogen bonding between the carboxylic oxygen and the amino nitrogen atoms in compounds (10). This hydrogen bonding is evinced by comparison of the i.r. frequencies observed for the C=O groups of the diesters (8) [broad bands centred on 1720 cm^{-1}] with those

Table 1. Wavelength Monitored and Calculated Rate Constants (k_1) (sec^{-1} x 10^6)

Salt	λ_{max} (nm)	Temperature (K)				
		323	333	343	351	
10a	249	1.72±0.02	5.00±0.04	14.81±0.09	38.3 ±1.1	
10b	261	3.11±0.04	7.26±0.05	22.8 ±0.5	51.7 ±0.3	
10c	253	4.17±0.08	12.06±0.07	33.2 ±0.5	70.0 ±0.5	
10d	302	15.8 ±0.2	34.5 ±0.3	80.4 ±1.3	170.0 ±3.0	
10f	319*	0.89±0.01	1.96±0.03	6.00±0.11	11.95±0.11	
		273	297	303	308	313
10e	262	7.87±0.05	109±1.0	196±2	306±2	614±10
10g	266	too fast to measure by this method				

Table 2 UV Spectral Details of the Hemi-succinate Salts of the Open Chain Compounds Together with the Enthalpies, Entropies and Free Energies of Cyclisation

Salt	λ_{max} nm	Enthalpy $kJmol^{-1}$	Entropy $Jmol^{-1}$	Free Energy $kJmol^{-1}$
10a	249	104±3	-34±2	114±6
10b	261	96±2	-55±16	112±20
10c	253	95±2	-53±2	111±4
10d	302	80±4	-91±6	106±6
10e	262	76±2	-66±8	96±10
10f	319*	90±5	-84±15	115±20
10g	266	-	-	-

* as the hydrobromide salt, not the hemi-succinate

observed for the amino esters (10) [1710-1705 cm^{-1}]. We assume that, approximately, changes in the degree of hydrogen bonding during the course of the cyclisation are the same between the starting materials and end products in the series.

(3) Any changes in enthalpy and entropy on going from starting materials in which there is no separation of charge to transition states with charge separation are more or less constant across the range of reactions studied because of the similarity of the molecules and reaction conditions.

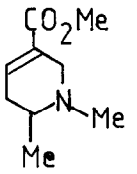
(4) The open chain compounds (10) therefore have a relatively low degree of freedom to rotate about the single C-C bonds which are between the C=C and C=O double bonds.

The observation of high enthalpies supports the contention that there is a barrier to rotation from the preferred S-*trans* conformation of the starting compounds (10) to the S-*cis* reactive form (11). In an effort to probe the stereochemical aspects of the acyclic amines (10) an X-ray structure analysis[27] was made of the two hydrobromides derived from compounds (10f) and (10e), although it must be borne in mind that these are obtained on *solid* samples whereas the proposed arguments refer to solution studies. These X-ray analyses show that both exist in *trans* configurations but compound (10e) demonstrates considerable interference between the proton on the methylene carbon which bears the amino-group and the phenyl ring substituent R^1 causing in turn various distortions relative to (10f) which is essentially planar. The distortions from planarity in (10e) would favour the conformational change to the form (11e) required for cyclisation. This factor, combined with the resonance stabilised styrene moiety in the cyclised product (6e), must account for the remarkable ease of cyclisation of (10e) in the series studied and in the racemisation of lysergic acid (3) already mentioned.

Synthesis of N-Methyltetrahydropyridines. Treatment of the amino ester (10b) with formaldehyde in formic acid was expected to cause mono-methylation of the nitrogen atom followed by swift cyclisation to compound (12) by analogy with that cyclisation observed in the synthesis of a lysergic acid derivative.[16] In fact, the only product obtained was the dimethylated amine (13). Conversion of the cyclic secondary amine (5e, R^3=H) into the cyclised tertiary amine series could be achieved *via* formic acid-formaldehyde, however large excesses of formaldehyde led to both (14) and (15); the latter being formed by reaction of the desired product with formaldehyde. This untoward reaction was avoided by reducing the excess of formaldehyde to 20 molar excess.

In order to prepare the N-methyltetrahydropyridines by more general

methods we chose to temporarily protect the N-atom of the open chain compounds (10) with DppCl in CH_2Cl_2 using triethylamine as base. The phosphinamides thus formed were subjected to N-methylation in 1,2-dimethoxyethane (DME) using sodium hydride and excess methyl iodide, or LDA and excess methyl iodide in tetrahydrofuran (THF). The intermediate anion failed to form in less polar solvents such as benzene, diethyl ether and THF when using sodium hydride. In dimethylformamide (DMF) complex mixtures of products were obtained. Hydrolysis of the N-methylphosphinamides followed by a work-up involving alkaline extraction gave the desired products. Crystallisation of these as hemi-succinates proved difficult but as hydrochlorides there were no problems. It is clear that the tetrahydropyridine systems are interconvertible and the isomerism of (14) to the isomer (16a) on standing represents β,γ to α,β double bond migration with respect to the ester function. Base treatment of the mixture (14, 16a), followed by protonation, affords another isomer (16b) predominantly together with *ca* 5% of (16a). A differentiation between (16a) and (16b) may be made on the basis of the shielding of the secondary C-Me group in (16a), δ 0.64 compared with (16b), δ 1.01 ppm.



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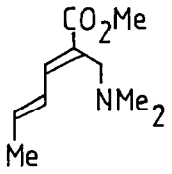

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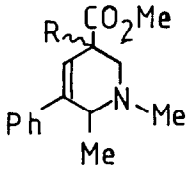
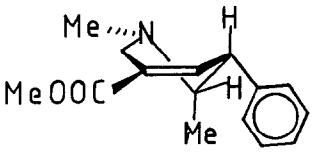


14 R=H
15 R=CH_2OH



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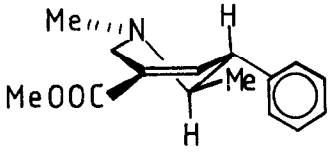
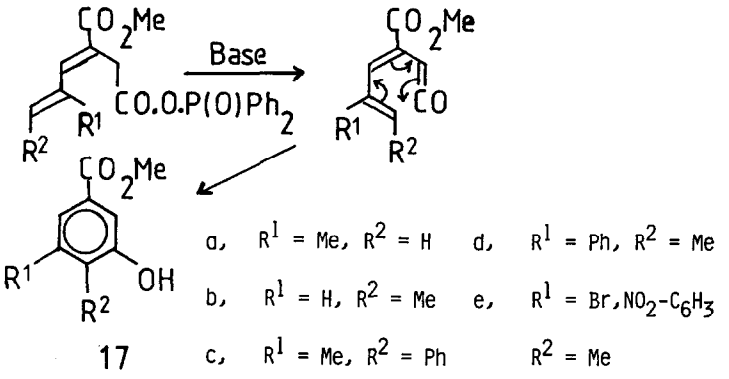


16 b

Conclusion.

This new approach to tetrahydropyridines has considerable advantages over previous routes in that the cyclisation reactions are clean and avoid protection and subsequent deprotection of the N-atom. Substitution is possible in every ring position, except C-4, dependent only on the availability of substituted α-β-unsaturated aldehydes. The ease of cyclisation of the series (10a-10g) is dependent upon the nature of the substituents, particularly R^1 which serves to stabilise the β,γ-

unsaturated esters (6). The exception to this generalisation is the case of (12f) where the terminal phenyl substituent strongly stabilises the S-*trans* conformation and offers steric hindrance to the incoming amino nucleophile in the cyclisation of the S-*cis* form (11f).



Scheme 1

m-Hydroxybenzoic Acids. The monomethyl esters of the 3,5-hexadienoic acids (9) were considered to be potential intermediates for the synthesis of substituted *m*-hydroxybenzoic acids. The synthesis of benzenoid compounds from acyclic precursors allows an entry into substitution patterns accessible only with difficulty from benzenoid starting materials.

Thus the previously described phosphinic-carboxylic mixed anhydrides were prepared from the dienoic acids (9) in the presence of N-methylmorpholine or triethylamine and then stirred at ambient temperature for 2-3 h with a further portion of base. An aqueous work-up afforded the methyl ester of the substituted *m*-hydroxybenzenoic acid (17a-e). Formation of the *m*-hydroxybenzoate system by base-catalysed cyclisation of the mixed anhydride can be considered to occur by prior base-induced elimination of diphenylphosphinic acid to give the ketene, which would be expected to cyclise spontaneously[31] (Scheme 1).

Experimental

Melting points were determined on a Kofler hot stage microscope or a Buchi 510 apparatus and are uncorrected. ^{1}H N.m.r. spectra were recorded on Perkin-Elmer R34 (220 MHz), R32 (90 MHz), R12 (60 MHz), Perkin-Elmer-Hitachi R20 (60 MHz), or Bruker WP80 (80 MHz) instruments. The shifts are quoted in ppm downfield from TMS or the sodium salt of 3-(trimethylsilyl)-propanesulphonic acid. ^{31}P and ^{13}C N.m.r. spectra were recorded

on a Bruker WP80 operated at 32.4 and at 24.1 MHz respectively. The ^{31}P spectral shifts are quoted relative to external 85% phosphoric acid assigned as δ 0.0; the ^{13}C spectral shifts are relative to internal $CDCl_3$ centred at δ 77.1. Unless otherwise stated all n.m.r. spectra were obtained in $CDCl_3$. U.v. spectra were recorded in ethanol on Unicam SP800, SP8000, Pye-Unicam SP8-100, or Cary 118X spectrophotometers. I.r. spectra were recorded as liquid films, nujol mulls, or in CH_2Cl_2 solution on Unicam SP200, Perkin-Elmer 125, or 197 instruments. Mass spectra were recorded on AEI MS12 and Kratos MS45 spectrometers. THF was dried over potassium until blue to potassium diphenylketyl. Triethylamine, N-methylmorpholine and tetramethylguanidine were distilled from potassium hydroxide pellets. CH_2Cl_2 was treated consecutively with calcium chloride and grade I alumina. All solvents were distilled prior to use. Gaseous nitrogen was passed through Fieser's solution, lead acetate solution, concentrated sulphuric acid and over potassium hydroxide pellets. Column chromatography was carried out on silica gel 60 (70-230 mesh) or silica gel 60 (230-400 mesh) under medium pressure or on Fluka alumina type 507C. TLC was performed on silica gel G 254 and visualised with u.v. light at 254 nm.

E-2-*Phenylbut-2-enal*. - A mixture of freshly distilled phenylacetaldehyde (93.2 g, 0.78 mol) and acetaldehyde (34.3 g, 0.78 mol) in ethanol (50 ml) was added dropwise to a stirred solution of anhydrous sodium acetate (40.2 g, 0.49 mol) in water (50 ml), under nitrogen, under a total reflux apparatus cooled with dry ice. Upon complete addition, the mixture was stirred for 1 h at ambient and 4 h under reflux then cooled and left stirring at ambient overnight. The two phases were poured into water (500 ml), separated, and the aqueous layer extracted with diethyl ether (3 x 100 ml) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure left a yellow oil which was distilled to afford E-2-phenylbut-2-enal (46.7 g, 41%), b.p. 68-70°C (0.1 mm Hg) [lit.[30] 95-100°C (1.5-2.5 mm Hg)]; ν_{max} (CH_2Cl_2) 2830w, 2700w, 1690s cm^{-1}; λ_{max} (EtOH) 246 nm (ϵ 4150); δ_H 9.6 (1H, s), 7.3 (5H, m), 6.7 (1H, q, 7 Hz), 1.8 (3H, d, 7 Hz); δ_C 192.0d, 150.3d, 143.7d, 131.6, 128.6, 127.1d, 14.5q; m/z 146.0736 (48%, 0.5 M^+), 105.0319 (100%, -2.1, C_7H_5O).

2-Diazo-1-(2-bromo-5-nitrophenyl)ethan-1-one. - N-Methylmorpholine (8.3 g, 82.0 mmol) in ethyl acetate (10 ml) was added to an ice-cold solution of 2-bromo-5-nitrobenzoic acid (20.0 g, 81.3 mmol) in ethyl acetate (300 ml). A solution of ethyl chloroformate (8.8 g, 81.3 mmol) in ethyl acetate (10 ml) was added and stirred at 0°C for 1 h. Precipitated N-methylmorpholine hydrochloride was filtered off and the filtrate treated with ethereal diazomethane (4.8 g, 89.4 mmol) at 0°C for 1 h. The mixture was left overnight at ambient temperature and evaporated to dryness under reduced pressure to leave a bright yellow solid. Recrystallisation from benzene-diethyl ether-petrol afforded *2-diazo-1-(2-bromo-5-nitrophenyl)ethan-1-one* (18.2 g, 83%), m.p. 110-111°C; (Found: C, 35.6; H, 1.3; N, 15.3; Br, 29.4. $C_8H_4BrN_3O_3$ requires C, 35.6; H, 1.5; N, 15.6; Br, 29.6%); ν_{max} (CH_2Cl_2) 2120, 1640, 1540, 1345 cm^{-1}; λ_{max} 276 (ϵ 19000); δ_H 8.33 (1H, d 3 Hz), 8.17 (1H, dd, 3, 9 Hz), 7.85 (1H, d, 9 Hz), 5.75 (1H, s); δ_C ($CDCl_3$/DMSO-d_6 184.1, 145.6, 139.1, 133.9, 130.6, 124.7, 122.4, 56.8; m/z 268.9433 (0.7%, -0.3, M^+).

2-Acetoxy-1-(2-bromo-5-nitrophenyl)ethan-1-one. - 2-Diazo-1-(2-bromo-5-nitrophenyl)ethan-1-one (17.4 g, 64.4 mmol) was added in portions to glacial acetic acid at 70°C and heated under reflux for 1 h. The mixture was evaporated under reduced pressure to leave a yellow solid, m.p. 85-86°C; (Found: C, 39.8; H, 2.5; N, 4.7; Br, 26.2. $C_{10}H_8BrNO_5$ requires C, 39.7; H, 2.7; N, 4.6; Br, 26.5%); ν_{max} (CH_2Cl_2) 1760, 1740, 1610, 1540, 1350 cm^{-1}; λ_{max} 270 (ϵ 8500); δ_H 8.37 (1H, d 3 Hz),

8.24 (1H, dd, 3, 7 Hz), 7.87 (1H, d, 7 Hz), 5.20 (2H, s), 2.17 (3H, s); δ_C (DMSO-d_6) 195.3, 170.0, 146.9, 138.4, 135.6, 127.1, 126.3, 124.1, 67.6, 20.1; m/z 300.9586 (1%, 1.7, M^+).

1-Acetoxy-2-(2-bromo-5-nitrophenyl)but-2-ene. - A solution of n-butyllithium (999 mg, 15.6 mmol) in hexane was added to an ice-cold suspension of ethyltriphenylphosphonium bromide (6.95 g, 18.7 mmol) in ether (20 ml) and stirred for 0.5 h. The bright orange mixture was cooled to -78°C, diluted with THF (150 ml) and treated with a solution of 2-acetoxy-1-(2-bromo-5-nitrophenyl)ethan-1-one (4.7 g, 15.6 mmol) in THF (20 ml). An immediate precipitate was formed. The mixture was stirred at -78°C for 1 h and warmed to ambient temperature. The solvent was removed by evaporation under reduced pressure and the residue purified by flash chromatography using light petrol. Recrystallisation from light petrol afforded *1-acetoxy-2-(2-bromo-5-nitrophenyl)but-2-ene* as a pale yellow solid (a mixture of E and Z-isomers in the ratio of 4:21) (2.3 g, 47%); δ_H 7.94 (3H, m), 6.02 (1H, overlapping q), 5.01 (0.3H, br s), 4.79 (1H, br s), 2.02 (3H, s), 1.85 (0.4H, d 7 Hz), 1.50 (2.6H, d 7 Hz). Further recrystallisation afforded pure Z-isomer, m.p. 67-68°C; (Found: C, 46.1; H, 4.1; N, 4.4; Br, 25.5. $C_{12}H_{12}BrNO_4$ requires C, 45.9; H, 3.9; N, 4.5; Br, 25.4%); ν_{max} (CH_2Cl_2) 3200-2800, 1740, 1610, 1570, 1530, 1350 cm^{-1}; λ_{max} 275 (ϵ 9600); δ_H 7.94 (3H, m), 6.12 (1H, q, 7 Hz), 4.79 (2H, s), 2.02 (3H, s), 1.50 (3H, d, 7 Hz); δ_C 170.5, 147.2, 140.6, 134.3, 133.7d, 131.1, 130.8d, 125.8d, 123.3d, 67.4t, 20.6q; m/z 312.9926 (0.5%, -2.4, M^+).

2-(2-Bromo-5-nitrophenyl)but-2-enol. - A mixture of anhydrous potassium carbonate (2.64 g, 19.1 mmol) and 1-acetoxy-2-(2-bromo-5-nitrophenyl)-but-2-ene (2.0 g, 6.37 mmol) (as a mixture of E- and Z-isomers) in methanol (30 ml) was stirred for 2 h. The solution was evaporated to low bulk under reduced pressure and the resulting, brown mixture was adsorbed on to silica. Flash chromatography using ethyl acetate-light petrol yielded a yellow oil which was distilled in a Kugelrohr (b.p. 130°C at 0.2 mm Hg), affording an oil which solidified on standing (1.2 g, 70%). There was about 12% E-isomer in the mixture. δ_H 7.90 (3H, m), 5.89 (1H, 2 overlapping q), 4.54 (0.2H, br s), 4.31 (1.8H, br s), 2.29 (1H, br), 1.94 (0.3H, d, 7 Hz), 1.44 (2.7H, d 7 Hz). Recrystallisation from aqueous ethanol afforded *Z-2-(2-bromo-5-nitrophenyl)but-2-enol* with only a trace of the E-isomer, m.p. 83-84°C; (Found: C, 44.3, H, 3.7; N, 5.0; Br, 29.3. $C_{10}H_{10}BrNO_3$ requires C, 44.3; H, 3.7; H, 5.2; Br, 29.5%; ν_{max} (CH_2Cl_2) 3600, 1610, 1570, 1530, 1350 cm^{-1}; λ_{max} 276 (ϵ 10000); δ_H 7.91 (3H, m), 6.01 (1H, q, 7 Hz), 4.32 (2H, s), 1.60 (1H, s, disappears with D_2O shake), 1.46 (3H, d, 7 Hz); δ_C 147.3, 141.2, 139.0, 133.6d, 131.1, 126.8d, 125.8d, 123.3d, 66.5t, 14.1q; m/z 270.9844 (6%, -1.6, M^+).

2-(2-Bromo-5-nitrophenyl)but-2-enal. - Freshly prepared pyridinium dichromate (6.97 g, 18.53 mmol) was added to 2-(2-bromo-5-nitrophenyl)-but-2-enol (3.36 g, 12.4 mmol), as a mixture of isomers) in CH_2Cl_2 (18 ml) and stirred at ambient temperature for 23 h. The mixture was poured into diethyl ether (40 ml), filtered through $MgSO_4$, and evaporated under reduced pressure to leave a brown solid. Flash chromatography using ethyl acetate-light petrol afforded a pale yellow solid. A solution of this in CH_2Cl_2 was washed with 2% hydrochloric acid, dried ($MgSO_4$) and evaporated to dryness under reduced pressure, yielding a yellow solid (2.57 g, 75%) which was approximately 5% E-isomer. Recrystallisation from aqueous acetic acid afforded *Z-2-(2-bromo-5-nitrophenyl)but-2-enal* (2.34 g, 70%), m.p. 73-74°C (Found: C, 44.5; H, 2.8; N, 4.9; Br, 29.7. $C_{10}H_8BrNO_3$ requires C, 44.5; H, 3.0; N, 5.2; Br, 29.6%); ν_{max} (CH_2Cl_2) 1690, 1530, 1350 cm^{-1}; λ_{max} 274 (ϵ 10500); δ_H 9.61 (1H, s), 8.10 (1H, dd, 3,9 Hz), 7.97 (1H, d, 3 Hz), 7.83 (1H, d, 9 Hz), 7.10 (1H, q, 7 Hz), 1.91 (3H, d, 7 Hz); δ_C 191.1, 153.2, 147.0, 143.6, 136.0, 133.8, 131.2, 126.0, 124.1, 15.9; m/z 169 (1%, M^+).

General Preparation of t-Butyl 3-Methoxycarbonylhex-3,5-dienoates (8). This is exemplified by that of the parent compound (**8a**): Acrolein (31.0 g, 0.55 mol) was added over a period of several days in small portions to a stirred solution of 1-methoxycarbonyl-2-t-butyloxycarbonylethyltriphenylphosphorane (7)[16,18] (99.0 g, 0.22 mol) in CH_2Cl_2 (750 ml) under nitrogen at 40°C until TLC (1% MeOH/$CHCl_3$) showed complete disappearance of the phosphorane (R_f 0.30-0.45). Most of the solvent was removed by evaporation under reduced pressure, petrol (300 ml) was added to precipitate triphenylphosphine oxide and the mixture was filtered. The filtrate was further concentrated (200 ml) and cooled to -20°C. A viscous red oil separated out. The supernatant liquid was dried ($MgSO_4$) and evaporated to dryness under reduced pressure, leaving a brown oil (42.7 g) which exhibited two spots on TLC (R_f 0.8 and 0.7). Purification by MPLC (column 2.5 x 150 cm) afforded *t-butyl 3-methoxycarbonylhexa-3,5-dienoate* (**8a**) as a colourless, viscous oil (26.6 g, 53%); (Found: C, 63.7; H, 8.3. $C_{12}H_{18}O_4$ requires C, 63.6; H, 8.0%); ν_{max} (CH_2Cl_2) 2970, 2950, 1725-1710br, 1640, 1590, 1360, 1150 cm^{-1}; λ_{max} 250 (ϵ 11300); δ_H 7.36 (1H), 6.3-6.9 (1H, m), 5.5-5.8 (2H, m), 3.82 (3H, s), 3.43 (2H, s), 1.48 (9H, s).

The use of 2-butenal (crotonaldehyde, 16.8 g, 0.23 mol) and phosphorane (72 g, 0.16 mol) in benzene (800 ml) afforded *t-butyl 3-methoxycarbonylhepta-3,5-dienoate* (**8b**) as a colourless oil (31.3 g, 82%); (Found: C, 64.9; H, 8.5. $C_{13}H_{20}O_4$ requires C, 64.9; H, 8.3%; ν_{max} (CH_2Cl_2 3000-2850, 1730-1710, 1640, 1150 cm^{-1}; λ_{max} 261 (ϵ 20100); δ_H 7.33 (1H), 6.4-6.1 (2H, m), 3.8 (3H, s), 3.39 (2H, s), 1.9 (3H, d), 1.46 (9H, s); m/z 240 (12%, M^+).

The use of 2-methylacrolein (0.62 mol) and phosphorane (70 g, 0.15 mol) in benzene (1200 ml) at 80°C afforded *t-butyl 3-methoxycarbonyl-5-methylhexa-3,5-dienoate* (**8c**) as a colourless oil (25 g, 69%); (Found: C, 64.8; H, 8.6. $C_{13}H_{20}O_4$ requires C, 64.9; H, 8.3%); ν_{max} (CH_2Cl_2) 3000-2850, 1730-1710, 1640, 1150 cm^{-1}; λ_{max} 253 (ϵ 10400); δ_H 7.3 (1H), 5.25 (1H, br), 5.15 (1H, br), 3.82 (3H, s), 3.48 (2H, s), 1.96 (9H, s).

The use of α-methylcinamaldehyde (13 g, 88 mmol) and phosphorane (37.6 g, 83 mmol) in toluene (650 ml) at 110°C afforded *t-butyl 3-methoxycarbonyl-5-methyl-6-phenylhexa-3,5-dienoate* (**8d**) as a colourless oil (22.5 g, 86%); (Found: C, 72.0; H, 7.4. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.6%); ν_{max} (film) 3100-1850, 1730-1710, 1620, 1440, 1370, 1330, 1260, 1150 cm^{-1}; λ_{max} 294 (ϵ 20250); δ_H 7.45 (1H, s), 7.35 (5H, m), 3.82 (3H, s), 3.55 (2H, s), 2.10 (3H, br), 1.47 (9H, s).

The use of cinnamaldehyde (4.4 g, 33.5 mmol) and phosphorane (15.0 g, 33.5 mmol) in CCl_4 under reflux afforded *t-butyl 3-methoxycarbonyl-6-phenylhexa-3,5-dienoate* (**8f**) as a colourless crystalline solid (5.0 g, 50%), m.p. 71-72°C (EtOH); (Found: C, 71.2; H, 7.7. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.4%); ν_{max} (CH_2Cl_2) 1700, 1620 cm^{-1}; λ_{max} 313 (ϵ 38300); δ_H 7.36 (6H, m), 6.98 (2H, m), 3.79 (3H, s), 3.46 (2H, s), 1.42 (9H, s); m/z 302 (39%, M^+).

Preparation of the t-Butyl 3-Methoxycarbonyl-5-arylhepta-3,5-dienoates necessitated a different procedure, exemplified by that of the parent compound (**8e**): 1-Methoxycarbonyl-2-t-butoxycarbonylethyltriphenylphosphorane (7) (100 g, 0.22 mol) was dissolved in hot CCl_4 (400 ml) and E-2-phenylbut-2-enal (29.0 g, 0.20 mol) was added. The mixture was cooled, thoroughly degassed by freeze-pump-thaw cycles and sealed under vacuum. It was heated at 78-80°C for 12 days and evaporated to low bulk under reduced pressure. Light petrol was added and the mixture cooled. Precipitated triphenylphosphine oxide was removed by filtration and the red oil obtained after evaporation was passed through silica gel in 30% diethyl ether-70% light petrol. The resultant mixture (3.2 g, 21.8

mmol), after evaporation of volatiles, appeared to contain triphenylphosphine oxide, methyl tert-butyl fumarate and *ca* 11% unreacted aldehyde. Solid sodium borohydride (228 mg, 6.0 mmol) was added to a solution of the mixture in methanol (70 ml) over 10 min. The solution was poured into water (50 ml) containing 10% hydrochloric acid (2 ml) and extracted with diethyl ether (3 x 50 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave a yellow oil which was purified by flash chromatography using diethyl ether-light petrol. Distillation of the eluate afforded *t-butyl 3-methoxycarbonyl-5-phenylhepta-3,5-dienoate* (8e) (52.5 g, 84%), b.pt. 140-144°C (0.05 mm Hg); (Found: C, 71.8; H, 7.7. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.7%); ν_{max} ($CHCl_3$) 1720-1700, 1620, 1270 cm^{-1}; λ_{max} 262 (ϵ 15400); δ_H 7.49 (1H, s); 7.25 (5H, m), 6.15 (1H, q, 7 Hz), 3.73 (3H, s), 2.92 (2H, s), 1.69 (3H, d, 7 Hz), 1.39 (9H, s); δ_C 169.5, 168.0, 143.1d, 138.7d, 137.6d, 134.8d, 128.6d, 128.2d, 127.0d, 123.4, 79.7, 51.2q, 33.6t, 27.4q, 14.6q; m/z 316 (20%, M^+ only observable by FAB).

The use of 2-(2-bromo-5-nitrophenyl)but-2-enal (2.01 g, 7.45 mmol) and the phosphorane (4.68 g, 10.4 mmol) afforded *t-butyl 5-(2-bromo-5-nitrophenyl)-3-methoxycarbonylhepta-3,5-dienoate* (8g) as a yellow oil) 2.61 g,80%). It was difficult to remove the last traces of solvent and so a full characterisation was not carried out. ν_{max} (CH_2Cl_2) 1715-1710, 1530, 1340 cm^{-1}; λ_{max} 263; δ_H 8.08 (1H, d, 3 Hz), 8.04 (1H, dd, 3, 9 Hz), 7.83 (1H, d, 9 Hz), 7.39 (1H, s), 6.33 (1H, q), 3.74 (3H, s), 2.97 (2H, br s), 1.57 (3H, s), 1.31 (9H, s); m/z 439.0630 (15%, 0.0, M^+), 383.0001 (94%, -0.4, $C_{15}H_{14}BrNO_6$).

The Preparation of the 3-Methoxycarbonylhex-3,5-dienoic Acids (9).

This is exemplified by the following two methods:

(a) The preparation of the parent acid (9a): t-Butyl 3-methoxycarbonylhexa-3,5-dienoate (8a) (12.4 g, 54.8 mmol) was dissolved in dry benzene (130 ml). Trifluoroacetic acid (12.5 g, 110 mmol) and water (0.99 g, 55 mmol) were added and the mixture stirred at 80°C for 3 h. The mixture was evaporated to dryness under reduced pressure, more benzene (or CCl_4) (100 ml) was added and evaporated. The residue was dissolved in $CHCl_3$ and filtered. The filtrate was extracted with 5% aqueous NH_4HCO_3 and this was acidified with 10% hydrochloric acid to pH 4 and extracted with ethyl acetate. This extract was washed with water, dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give a pale yellow oil (7.4 g, 80%). This oil is unstable and must be kept cold in solution. ν_{max} (mull) 3600-2500, 1720-1710br, 1640, 1590, 1430, 1270 cm^{-1}; λ_{max} 250 nm; δ_H 7.4 (1H, d), 6.95-6.35 (1H, m), 5.9-5.5 (2H, m), 3.8 (3H, s), 3.55 (2H).

(b) *The preparation of 3-methoxycarbonyl-5-methylhexa-3,5-dienoic acid* (9c): t-Butyl 3-methoxycarbonyl-5-methylhexa-3,5-dienoate (8c) (15.53 g, 63 mmol) was dissolved in ice-cold, aqueous, 90% trifluoroacetic acid (60 ml) and stirred at room temperature for 4 h. Work up as in (a) afforded an oily residue (10.0 g, 86%); ν_{max} (mull) 3700-2400, 1710br, 1630, 1430, 1290 cm^{-1}; δ_H 7.32 (1H, s), 5.24 (1H, br s), 5.1 (1H, s), 3.8 (3H, s), 3.58 (2H, s), 1.92 (3H, s).

3-Methoxycarbonylhepta-3,5-dienoic Acid (9b) (69%) had m.p. 108-110°C ($CHCl_3$); ν_{max} (mull) 3600-2400, 1715-1710, 1640, 1435 cm^{-1}; λ_{max} 262 nm (ϵ 24750); δ_H 7.35 (1H, d), 6.25 (2H, m), 3.75 (3H, s), 3.46 (2H, s), 1.9 (3H, d).

3-Methoxycarbonyl-5-methyl-6-phenylhexa-3,5-dienoic Acid (9d) (87%) had m.p. 101-102°C (CH_2Cl_2-hexane). (Found: C, 69.3; H, 6.3. $C_{15}H_{16}O_4$ requires C, 69.2; H, 6.1%); ν_{max} (film) 3600-2400, 1725-1710,

1630, 1440, 1280, 1230, 1200 cm^{-1}; λ_{max} 295 nm (ϵ 13950); δ_H 9.95 (1H, br), 7.45 (1H, s), 7.28 (5H, m), 6.65 (1H, br), 3.77 (3H, s), 3.62 (2H, s), 2.05 (3H, s).

3-Methoxycarbonyl-5-phenylhepta-3,5-dienoic Acid (9e) (78%) had m.p. 90-91°C (diethyl ether-light petrol); (Found: C, 69.2; H, 6.2. $C_{15}H_{16}O_4$ requires C, 69.2; H,6.2%); ν_{max} ($CHCl_3$) 3700-2400, 1710, 1620, 1280 cm^{-1}; λ_{max} 262 nm (ϵ 15800); δ_H 11.32 (1H, s), 7.53 (1H, s), 7.23 (5H, m), 6.16 (1H, q, 7 Hz), 3.70 (3H, s), 2.97 (2H, s), 1.68 (3H, d, 7 Hz); δ_C 176.6, 168.2, 144.2d, 138.9, 137.6, 136.0d, 128.7d, 128.4d, 127.4d, 122.2, 51.7q, 32.3t, 14.8q; m/z 260.1047 (62%, -0.1, M^+), 155.0865 (100%, 0.5, $C_{12}H_{12}$).

3-Methoxycarbonyl-6-phenylhexa-3,5-dienoic Acid (9f) (55%) had m.p. 167-168°C (EtOH-water) (lit.[28] 167-168°C); (Found: C, 68.2; H, 5.9. Calc. for $C_{14}H_{14}O_4$; C, 68.3; H, 5.7%); ν_{max} (mull) 2800-2500, 1710, 1695, 1630, 785 cm^{-1}; δ_H (TFA) 7.7-6.8 (8H, m), 3.8 (3H, s), 3.7 (2H, s).

5-(2-Bromo-5-nitrophenyl)-3-methoxycarbonylhepta-3,5-dienoic Acid (9g) (82%) had m.p. 185-186°C (EtOH-water); (Found: C, 47.0; H, 3.8; N, 3.4; Br, 21.2. $C_{15}H_{14}BrNO_6$ requires C, 46.9; H, 3.7; N, 3.7, Br, 20.8%); ν_{max} (KBr) 3700-3300, 3000-2200, 1730-1700, 1525, 1345 cm^{-1}; λ_{max} (CH_3CN) 264 nm (ϵ 22500); δ_H ($CDCl_3$-DMSO-d_6) 8.12 (1H, dd, 3, 9 Hz), 8.05 (1H, d, 3 Hz), 7.89 (1H, d, 9 Hz), 7.50 (1H, s), 6.42 (1H, q, 7 Hz), 3.78 (3H, s), 3.05 (2H, br s), 1.60 (3H, d, 7 Hz); m/z 383,0008 (19.5%, 0.3, M^+).

Preparation of the p-toluenesulphonate salts of 2-Methoxycarbonyl-2,4-dienylamines (10)

These are exemplified by that of the parent compound (10a) salt: 3-Methoxycarbonylhexa-3,5-dienoic acid (9a) (3.96 g, 23 mmol) was cooled to -23°C in dry CH_2Cl_2 (130 ml) under nitrogen. N-Methylmorpholine (2.35 g, 23 mmol) and diphenylphosphinic chloride[23] (5.15 g, 23 mmol) were added. After 0.5 h a solution of tetramethylguanidinium azide (11)[23] (3.9 g, 25 mmol) in CH_2Cl_2 (50 ml) was added and stirred for 0.5 h then for 2 h at 0°C. The mixture was poured on to ice-water, separated and extracted with water. The organic layer was evaporated under reduced pressure and the residue taken up in benzene (80 ml) which was heated at 65-70°C for 1.7 h whereupon a vigorous evolution of nitrogen occurred. The mixture was cooled to ambient temperature and *p*-toluenesulphonic acid monohydrate (3.97 g, 20.9 mmol) in diethyl ether (150 ml) was added. The precipitated solid was filtered off and washed with ether to afford *2-methoxycarbonylpenta-2,4-dienylamine* (10a) *p-toluenesulphonate* (5.68 g, 77%), m.p. 144-145°C; ν_{max} (mull) 3300-2600, 1710, 1630, 1515, 1430, 1270 cm^{-1}; λ_{max} 250 nm (ϵ 21500); δ_H (D_2O) 7.75-7.25 (5H, m), 7.0-6.6 (1H, m), 6.0-5.7 (2H, m), 4.0 (2H, s), 3.85 (3H, s), 2.36 (3H, s).

2-Methoxycarbonylhexa-2,4-dienylamine (10b) *p-toluenesulphonate* (71%), m.p. 130-132°C; ν_{max} 3300-2600, 1730, 1715, 1700, 1640 cm^{-1}; λ_{max} 222 (ϵ 11350), 262 nm (25300); δ_H (TFA) 7.8 (2H, d), 7.66 (1H, d), 7.35 (2H, d), 7.05 (3H, m), 6.55 (2H, d), 4.3 (2H, m), 3.95 (3H, s), 2.45 (3H, s), 1.96 (3H, d).

2-Methoxycarbonyl-4-methylpenta-2,4-dienylamine (10c) *p-toluenesulphonate* (64%); m.p. 108-112°C; ν_{max} (mull) 3600-2500, 1710, 1625, 1440, 1260 cm^{-1}; λ_{max} 225, 153 nm; δ_H 8.1-7.0 (9H, m), 5.1 (2H, br s), 4.1-3.7 (2H, q), 3.65 (3H, s), 2.35 (3H, s), 1.8 (3H, s). This salt is quite unstable and was converted to the hemi-succinate for safe storage.

2-Methoxycarbonyl-4-methyl-5-phenylpenta-2,4-dienylamine (10d) *p-toluenesulphonate* (84%); m.p. 193-194°C (EtOH-diethyl ether); (Found:

C, 62.3; H, 6.3; N, 3,3. $C_{21}H_{25}NSO_5$ requires C, 62.5; H, 6.2; N, 3.4%); ν_{max} (mull) 3250-2750, 1710, 1615, 1260, 1030, 1005 cm^{-1}; λ_{max} 222 (ϵ 16700), 299 nm (17900); δ_H (TFA-$CDCl_3$) 7.75-7.65 (3H, m), 7.38 (5H, s), 7.45-7.15 (5H, m), 6.78 (1H, br s), 4.5-4.25 (2H, q), 3.9 (3H, s), 2.4 (3H, s), 2.13 (3H, s).

2-Methoxycarbonyl-4-phenylhexa-2,4-dienylamine (10e) *p-toluenesulphonate* (71%); m.p. 126-127°C (CH_2Cl_2-diethyl ether); (Found: C, 62.8; H, 6.4; N, 3.4; S, 8.0. $C_{21}H_{25}NSO_5$ requires C, 62.5; H, 6.3; N, 3.5; S, 8.0%); ν_{max} ($CHCl_3$) 3300-2400, 2900, 1720-1690, 1620 cm^{-1}; λ_{max} 221 (ϵ 19700), 262 nm (17400); δ_H 7.72 (5H, m), 7.56 (1H, s), 7.25 (7H, m), 6.19 (1H, q, 7 Hz), 3.68 (3H, s), 3.47 (2H, m), 2.36 (3H, s), 1.63 (3H, d, 7 Hz).

2-Methoxycarbonyl-5-phenylpenta-2,4-dienylamine (10f) *p-toluenesulphonate* (55%); m.p. 213-215°C (CH_2Cl_2-diethyl ether) (lit.[28] 140-141°C); (Found: C, 62.2; H, 6.2; N, 3.4; S, 7.8. Calc. for $C_{21}H_{25}NO_5S$, C, 62.5; H, 6.3; N, 3.5; S, 7.9%); ν_{max} ($CHCl_3$) 3100, 1715, 1620, 1600, 1500 cm^{-1}; λ_{max} 322 nm (ϵ 37300); δ_H 8.4 (2H, br s), 7.7-6.7 (14H, m), 4.1 (2H, br t), 3.7 (3H, s), 2.7 (3H, br s), 2.3 (3H, s).

4-(2-Bromo-5-nitrophenyl)-2-methoxycarbonylhexa-2,4-dienylamine (10g) *p-toluenesulphonate* (60%); m.p. 182-183°C (MeOH-diethyl ether); (Found: C, 48.0; H, 4.3; N, 5.3; Br, 15.0. $C_{21}H_{13}BrN_2SO_7$ requires C, 47.8; H, 4.4; N, 5.3; Br, 15.2%); ν_{max} (KBr) 3100-2500, 1730, 1525, 1345 cm^{-1}; λ_{max} 265 nm (ϵ 24500); δ_H 8.08 (1H, d, 3 Hz), 7.92 (1H, dd, 3, 9 Hz), 7.69 (1H, d, 9 Hz), 7.66 (2H, m), 7.35 (1H, s), 7.19 (2H, m), 6.33 (1H, q, 7 Hz), 3.75 (3H, s), 3.69 (2H, s), 1.45 (3H, d, 7 Hz).

Preparation of the 2-Methoxycarbonyl-2,4-penta-2,4-dienylamines (10) is exemplified by that of the parent compound (10a). The *p*-toluenesulphonate salt of the amine (1.25 g, 4 mmol), partially dissolved in CH_2Cl_2 (50 ml) was treated with NaOH (160 mg, 4 mmol) dissolved in aqueous, saturated brine (80 ml). After shaking, the layers were separated, the aqueous layer was further extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$). Evaporation of the volatiles left a yellow oil (515 mg, 90%); ν_{max} 3370, 3300, 1705, 1630, 1590, 1260 cm^{-1}; λ_{max} 250 nm. The free amine was used immediately.

2-Methoxycarbonylhexa-2,4-dienylamine (10b) (87%); ν_{max} 3370, 3300, 300-2840, 1700, 1640, 1435, 1300, 1240 cm^{-1}; λ_{max} 262 nm.

2-Methoxycarbonyl-4-methylpenta-2,4-dienylamine (10c) (93%); ν_{max} 3370, 3300, 1710, 1630, 1430, 1270, 1240 cm^{-1}; λ_{max} 253 nm.

2-Methoxycarbonyl-4-methyl-5-phenylpenta-2,4-dienylamine (10d) (89%); ν_{max} 3400, 3340, 3100-1850, 1710, 1615, 1440, 1260 cm^{-1}.

Preparation of the Hemi-succinate Salts of the Amines (10)

This is exemplified by that of the parent compound. The free amine (10a) (515 mg, 3.6 mmol) was dissolved in a minimum of CH_2Cl_2 and treated with succinic acid (424 mg, 3.6 mmol) dissolved in the minimum of ethanol. The mixture was treated successively with small amounts of n-hexane and evaporation under reduced pressure until a white solid formed. This was recrystallised from CH_2Cl_2-n-hexane to afford *2-methoxycarbonylpenta-2,4-dienylamine* (10a) *hemi-succinate* (775 mg, 82%); m.p. decomp. >315°C; (Found): C, 50.6; H, 6.8; N, 5.2. $C_{11}H_{17}NO_6$ requires C, 50.9; H, 6.6; N, 5.4%); ν_{max} 3500-2300, 1720, 1640, 1260 cm^{-1}; λ_{max} 249 nm (ϵ 19450); δ_H (D_2O) 7.62 (1H, d), 7.1-6.6 (1H, m), 6.1-5.75 (2H, m), 4.0 (2H, s), 3.87 (3H, s), 3.54 (4H, s).

2-Methoxycarbonylhexa-2,4-dienylamine (10b) *hemi-succinate* (81%); m.p. 121-122°C; (Found: C, 52.9; H, 7.3; N, 5.2. $C_{12}H_{19}NO_6$ requires C, 52.7; H, 7.0; N, 5.1%); ν_{max} 3300-2300, 1710, 1630, 1300, 1240 cm^{-1}; λ_{max} 261 nm (ϵ 30150); δ_H (D_2O) 7.56 (1H, m), 6.53 (2H, m), 4.0 (2H, s), 3.82 (3H, s), 2.54 (4H, s), 1.93 (3H, d).

2-Methoxycarbonyl-4-methylpenta-2,4-dienylamine (10c) *hemi-succinate* (72%); m.p. 118.5-119°C; (Found: C, 52.4; H, 7.1; N, 5.1. $C_{12}H_{19}NO_6$ requires C, 52.7; H, 7.0; N, 5.1%); ν_{max} 3500-2400, 1715, 1630, 1600, 1265, 1250 cm^{-1}; λ_{max} 253 nm (ϵ 11200); δ_H 7.55 (1H, s), 5.46 (1H, br s), 5.25 (1H, br s), 4.1 (2H, s), 3.86 (3H, s), 2.53 (4H, s), 2.0 (3H, br s).

2-Methoxycarbonyl-4-methyl-5-phenylpenta-2,4-dienylamine (10d) *hemi-succinate* (90%); m.p. 108-110°C; (Found: C, 61.5; H, 6.9; N, 3.7. $C_{18}H_{23}NO_6$ requires C 61.8; H, 6.6; N, 4.0%); ν_{max} 3500-2400, 1710, 1610, 1415, 1405, 1270 cm^{-1}; λ_{max} 302 nm (ϵ 20450); δ_H 7.75 (3H, br s), 7.5 (1H, m), 7.31 (5H, s), 6.71 (1H, br s), 4.0 (2H, br s), 3.79 (3H, s), 2.37 (4H, br s), 2.09 (3H, s).

2-Methoxycarbonyl-4-phenylhexa-2,4-dienylamine (10e) *hemi-succinate* (70%); m.p. 93-94°C; (Found: C, 61.9; H, 6.8; N, 3.7. $C_{18}H_{23}NO_6$ requires C, 61.8; H, 6.6; N, 4.0%); ν_{max} 3600-2200, 1700 cm^{-1}; λ_{max} 262 nm (ϵ 16400); δ_H 8.60 (4H), 7.63 (1H, s), 7.35 (5H, m), 6.31 (1H, q, 7 Hz), 3.78 (3H, s), 3.40 (2H, s), 2.42 (4H, s), 1.73 (3H, d, 7 Hz).

General Cyclisation Reactions of 2-Methoxycarbonylpenta-2,4-dienylamines (10).

The free amine [prepared from the *p*-toluenesulphonate salt (6.38 mmol)] was heated at 64-65°C under nitrogen for 95 h in methanol (100 ml). Evaporation of the solvent left an oil which was investigated by i.r. and n.m.r. spectroscopy.

(10a) gave ν_{max} 3350,2950, 2820, 1725-1710, 1640, 1615, 1430, 1260 cm^{-1}; δ_H 6.9 and 5.6, 3.6, 3.3-3.0, 2.6-2.2 representative of 5-methoxycarbonyl-1,2,3,6- and 5-methoxycarbonyl-1,2,5,6-tetrahydropyridine in the approximate ratio of 2:1.

(10b) gave ν_{max} 3320, 2950-2800, 1710, 1650, 1430, 1250 cm^{-1}; δ_H 7.05-6.8 (1H, m), 3.7 (3H, s), 3.7-3.5 (1H, m), 3.45-3.2 (1H, m), 2.3-1.7 (3H, m) representative of *5-methoxycarbonyl-2-methyl-1,2,3,6-tetrahydropyridine* (5b) which as the hydrochloride had m.p. 194-196°C and as the picrolonic acid salt had m.p. 240-244°C; (Found: C, 51.8, H, 5.2; N, 16.6. $C_{18}H_{21}N_5O_7$ requires C, 51.5; H, 5.0; N, 16.7%).

(10c) gave ν_{max} 3000-2700,1725, 1430, 1200 cm^{-1}; δ_H 6.27 and 5.7-5.5 (m), 3.75 and 3.7, 3.25-2.75, 1.8 and 1.7 representative of a mixture of 5-methoxycarbonyl-3-methyl-1,2,5,6-tetrahydropyridine (6c) and 5-methoxycarbonyl-3-methyl-1,2,3,6-tetrahydropyridine (5c)in the approximate ratio of 3:2.

(10d) gave ν_{max} 3350, 3100-2800, 1730, 1430, 1190, 1160 cm^{-1}; δ_H 7.15 (5H, m), 5.7 (1H, m), 4.1 (1H, m), 3.6 (3H, s), 3.05 (3H, br s), 2.0 (1H, m, exchanges with D_2O), 1.47 (3H, br s) representative of *5-methoxycarbonyl-3-methyl-2-phenyl-1,2,5,6-tetrahydropyridine* (6d) which afforded the fumarate, m.p. 129-131°C (CH_2Cl_2-n-hexane); (Found: C, 62.5; H, 6.3; N, 3.7. $C_{18}H_{21}NO_6$ requires C, 62.2; H, 6.0; N, 4.0%).

(10e) gave ν_{max} 3350, 1740 cm^{-1}; δ_H 7.28 (5H, s), 6.0 (1H, br s), 3.96 (1H, q), 3.72 (1.7H, s), 3.64 (1.3H, s), 3.38-2.99 (3H, m), 2.44 (1H, br si, exchanges with D_2O), 1.09 (3H). Recrystallisation of the oxalate

salt of the product mixture of pyridines gave pure *5-methoxycarbonyl-2-methyl-3-phenyl-1,2,5,6-tetrahydropyridinium oxalate*; m.p. 149-150°C (EtOH); (Found: C, 59.6; H, 6.2; N, 4.1. $C_{16}H_{19}NO_6$ requires C, 59.8; H, 6.0; N, 4.4%); ν_{max} 3450, 3200-2200, 1740 cm^{-1}; λ_{max} 237 nm (ϵ 11300); δ_H ($CDCl_3$-DMSO-d_6) 7.37 (5H, s), 6.7-5.8 (1H, br s, collapses on D_2O shake), 4.53 (1H, m), 3.98-3.02 (4H, m), 2.78 and 2.70 (3H), 1.29 (3H).

(10f) gave ν_{max} 1705, 1655, 1270 cm^{-1}; δ_H 7.26, 7.02, 3.8-3.0, 3.64,2.3, 1.9 representative of a mixture of 5-methoxycarbonyl-2-phenyl-1,2,5,6 and 5-methoxycarbonyl-2-phenyl-1,2,3,6-tetrahydropyridine. Column chromatography on grade III alumina using benzene-light petrol as eluant yielded *5-methoxycarbonyl-2-phenyl-1,2,3,6-tetrahydropyridine* (5f) (72%); m.p. 62-64°C (n-pentane); (Found: C, 72.7; H, 7.4; N, 6.1. $C_{13}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 4.1%).

(10g) was prepared as above and immediately treated with succinic acid. The only product was a mixture of 5-methoxycarbonyl-2-methyl-3-(2-bromo-5-nitrophenyl)-1,2,5,6- and 5-methoxycarbonyl-2-methyl-3-(2-bromo-5-nitrophenyl)-1,2,3,6-tetrahydropyridinium hemi-succinates. ν_{max} 3500-2100, 1719, 1530, 1380 cm^{-1}; δ_H 7.92, 6.87, 6.11-5.42, 5.85, 3.9-2.6, 3.74, 1.8, 3.67, 2.53, 2.41, 0.92, 0.77. Heating the amine (10g) in methanol for 10 min then treating with oxalic acid allowed the formation of *5-methoxy-carbonyl-2-methyl-3-(2-bromo-5-nitrophenyl)-1,2,5,6-tetrahydropyridinium hemi-oxalate*; m.p. 181-182°C; (Found: C, 43.0; H, 3.8; N, 6.2; Br, 18.0. $C_{16}H_{17}BrNO_8$ requires C, 43.1; H, 3.9; N, 6.3; Br, 17.8%); ν_{max} 3450, 3100-2200, 1740, 1530, 1350 cm^{-1}; λ_{max} 275 nm (ϵ 7000); δ_H (D_2O) 8.13 (3H, m), 6.20 (1H, s), 4.09-3.54 (6H, m), 3.90 (s), 3.94 (s), 1.36 (3H, d), plus one proton obscured by HOD peak at 4.7.

1,2-Dimethyl-5-methoxycarbonyl-1,2,3,6-tetrahydropyridine (12). - Triethylamine (202 mg, 2 mmol) was added to a solution of 2-methoxycarbonyl-2,4-hexadienylamine (310 mg, 2 mmol) in CH_2Cl_2 (20 ml) and cooled to 0°C. A cooled solution of diphenylphosphinic chloride (482 mg, 2 mmol) in CH_2Cl_2 (15 ml) was added and the whole stirred for 18 h at ambient temperature. The solution was washed with water (2 x 20 ml), 5% $NaHCO_3$ (3 x 20 ml), water (2 x 20 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford a quantitative yield of N-(2-methoxycarbonylhexa-2,4-dienyl)diphenylphosphinamide; ν_{max} 3370, 3170, 2950, 1705, 1640, 1445, 1310 cm^{-1}; λ_{max} 225, 265 nm; δ_H 8.2-7.1 (1H, m), 6.2-5.9 (2H, m), 4.1-3.6 (3H, m), 3.78 (3H, s), 1.75 (3H, d). A portion of this (395 mg, 1.1 mmol) in DME (10 ml) was added to a suspension of sodium hydride (19 mg, 1.2 mmol) in DME (5 ml). It was stirred for 1 h at 70-80°C during which time a solid was formed. It was cooled to ambient temperature, methyl iodide (1.85 g, 13 mmol) was added and the whole was stirred for 17 h and then 1 h at 80°C. The mixture was filtered through celite and the filtrate diluted with CH_2Cl_2 and washed thrice with water and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford N-(2-methoxycarbonylhexa-2,4-dienyl)-N-methyldiphenylphosphinamide (74%); ν_{max} 3400, 3200, 2950, 1705, 1640, 1440 cm^{-1}; λ_{max} 225, 265 nm; δ_H 8.2-7.2 (11H, m), 6.9-5.8 (2H, m), 4.0 (2H, d), 3.7 (3H, s), 2.5 (3H, d), 1.85 (3H, d). A portion of this (250 mg, 0.67 mmol) in benzene (5 ml) was added to a solution of *p*-toluenesulphonic acid monohydrate (132 mg, 0.69 mmol) in diethyl ether (20 ml) and stirred at room temperature for 48 h during which time diphenylphosphinic acid (125 mg) precipitated and was removed by filtration. The filtrate was evaporated under reduced pressure to afford an oil. This was dissolved in CH_2Cl_2 (20 ml) and treated with NaOH (39 mg, 0.98 mmol) dissolved in saturated brine (40 ml). The layers were separated; the aqueous layer was washed with CH_2Cl_2 (2 x 10 ml) and the combined organic layers were washed with water (2 x 10 ml) and dried ($MgSO_4$). The solvent was removed by evaporation under reduced pressure and the residue was taken up in

$CHCl_3$-methanol (20 ml) and stirred at 60-70°C for 73 h. The solvent was removed by evaporation, the residue was taken up in $CHCl_3$, washed with 5% $NaHCO_3$, water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue, in $CHCl_3$, was treated with picrolonic acid in ethanol. The solvent was removed under reduced pressure and the solid formed upon trituration with ether was recrystallised from MeOH to afford *1,2-dimethyl-5-methoxycarbonyl-1,2,3,6-tetrahydropyridium picrolonate* (30%), m.p. 190-193°C; (Found: C, 52.6; H, 5.3; N, 16.2. $C_{19}H_{23}N_5O_4$ requires C, 52.7; H, 5.4; N, 16.2%); ν_{max} 3000-2200, 1719, 1640, 1590, 1510-1490, 1325 cm^{-1}; δ_H 7.85 (4H, s), 6.7 (1H, m), 3,37 (3H, s), 2.48 (3H, br s), 2.02 (3H, s), 1.0 (4H, m).

1,2-Dimethyl-5-methoxycarbonyl-3-phenyl-1,2,5,6-tetrahydropyridine (14).

2-Methoxycarbonyl-4-phenylhexa-2,4-dienylamine *p*-toluenesulphonate (2.5 g, 6.19 mmol) was treated with NaOH (248 mg, 6.1 mmol) to form amine (**12e**) as described above. This was heated in refluxing methanol (45 ml) to effect cyclisation and the solvent removed by evaporation under reduced pressure. The resultant pale yellow oil was dissolved in a mixture of 90% formic acid (37 ml, 0.72 mol) and 40% formaldehyde (9,3 ml, 0.124 mol) and heated under reflux for 30 min under nitrogen. The solvent was evaporated under reduced pressure to leave a solid which was dissolved in 10% NaOH (30 ml) and extracted with CH_2Cl_2 (3 x 25 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford a mixture of α,β- and β,γ-isomers of (14) (80%) as an oil. (Found: C, 73.3; H, 7.9; N, 5.4. $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7%); ν_{max} 3100-2750, 1730 cm^{-1}; λ_{max} 237 nm (ϵ 10700); δ_H 7.26-7.23 (5H, m), 5.98 (1H, br s), 3.7 (1.57H), 3.66 (1.43H), 3.81-2.52 (4H, m), 2.49 (3H, s), 1.03 (3H, m); m/z 245 (37%, M^+).

The oxalate salt was prepared by adding a solution of anhydrous oxalic acid (460 mg, 5.1 mmol) in ethanol (2 ml) to a solution of the above amine in ethanol (2 ml), cooling and filtering the salt of (**14**) which was recrystallised from ethanol to give (1.13 g, 71%), m.p. 154-156°C. (Found: C, 61.0; H, 6.5; N, 4.0. $C_{17}H_{21}NO_6$ requires C, 60.9; H, 6.3; N, 4.2%); λ_{max} 237 (ϵ 11000).

1,2-Dimethyl-5-methoxycarbonyl-3-phenyl-1,2,3,6-tetrahydropyridine (16a).

The β,γ-unsaturated ester (14) was converted into the conjugated isomer (**16a**) on prolonged standing or by MPLC on SiO_2 eluting with ethyl acetate-petrol (60-80). The product was isolated as an oil. (Found: C, 73.4; H, 8.0; N, 5.7. $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7%); ν_{max} 3050-2750, 1710 cm^{-1}; λ_{max} 224 (ϵ 11,000); δ_H 7.22 (5H, m), 7.08 (1H, m), 3.73 (3H, s), 3.90-2.65 (4H, m), 2.38 (3H, s), 0.64 (3H, d), [this spectrum also indicates the presence of *ca* 5% of the isomer (**16b**)]; m/z 245.1405 (30%, -1.1, M^+). The oxalate salt was prepared as in the previous experiment, m.p. 123-124°C. (Found: C, 60.6; H, 6.1; N, 3.9. $C_{17}H_{21}NO_6$ requires C, 60.9; H, 6.3; N, 4.2%); λ_{max} 224 (ϵ 11,000).

Equilibration of (16a) to (16b).

To a freshly prepared 1% solution of KOMe in dry methanol (50 ml) was added a mixture of (14) and (**16a**) (1.45 g, 10 mmol) in dry methanol (10 ml) and the solution stirred at ambient temperature for 10 h. the solvent was removed and after the usual work up the product was purified by MPLC on SiO_2 using ethyl acetate-petrol (60-80) to afford (**16b**) as an oil contaminated with *ca* 5% of (16a). ν_{max} 3100-1750, 1710 cm^{-1}; λ_{max} 226 (ϵ 11,900); δ_H 7.23 (5H, m), 6.90 (1H, m), 3.73 (3H, s), 3.81-2.32 (4H, m), 2.39 (3H, s), 1.01 (3H, d); m/z 245.1418 (23%, 1.5, M^+).

Methyl 3-hydroxy-5-methylbenzoate (17a).

A solution of N-methylmorpholine (348 mg, 3.4 mmol) and then diphenylphosphinic chloride (810 mg, 3.4 mmol) in CH_2Cl_2 were added to a solution of 3-methoxycarbonyl-5-methylhexa-3,5-dienoic acid (9c) (627 mg, 3.4 mmol) in CH_2Cl_2 (25 ml) at -23°C under nitrogen and left stirring for 28 min. Triethylamine (347 mg, 3.4 mmol) in CH_2Cl_2 was added and stirred for 10 min at -23°C, 10 min at 0°C and 1.5 h at ambient temperatures. The solution was washed with water and dried ($MgSO_4$). Solvent was removed under reduced pressure and the residue chromatographed on silica gel (15 g) to afford a white solid which was recrystallised from CH_2Cl_2-n-hexane to afford methyl 3-hydroxy-5-methylbenzoate (17a) (50%), m.p. 92.5-93.5°C. (Found: C, 64.7; H, 6.0. $C_9H_{10}O_3$ requires C, 65.0; H, 6.0%); ν_{max} 3580, 2950, 1720, 1620, 1600, 1330, 1230 cm^{-1}; λ_{max} 242 (ϵ 6850), 301 (2650); λ_{max} (+NaOH) 255 (5600), 334 nm (3000); δ_H 7.43-7.21 (2H, m), 6.85 (1H, m), 4.84-4.0 (1H, br, exchanges with D_2O), 3.92 (3H, s), 2.34 (3H, q).

In the same way (9b) afforded *methyl 3-hydroxy-4-methylbenzoate* (17b) (59%), m.p. 116-117°C. (Found: C, 65.0; H, 6.1. $C_9H_{10}O_3$ requires C, 65.0; H, 6.0%); ν_{max} 3670, 3580, 3100-2800, 1715, 1590, 1290 cm^{-1}; λ_{max} 246 (ϵ 11250), 298 (4000); λ_{max} (+NaOH) 244 (8650), 298 nm (2950); δ_H 7.57-7.39 (3H, m), 4.84-4.21 (1H, br), 3.87 (3H, s), 2.28 (3H, s).

(9d) afforded *methyl 3-hydroxy-5-methyl-4-phenylbenzoate* (17c) (47%), m.p. 125.5-126°C. (Found: C, 74.6; H, 5.8. $C_{15}H_{14}O_3$ requires C, 74.3; H, 5.8%); ν_{max} 3540, 3100-2800, 1715, 1600, 1570, 1225 cm^{-1}; λ_{max} 255 (ϵ 12600), 306 (4150); λ_{max} (+NaOH) 237 (25250), 346 nm (4250); δ_H 7.59-7.18 (7H, m), 4.81 (1H, s, exchanges with D_2O), 3.9 (3H, s), 2.09 (3H, s).

(9e) afforded *methyl 3-hydroxy-4-methyl-5-phenylbenzoate* (17d) (62%), m.p. 134-135°C. (Found: C, 74.0; H, 6.1. $C_{15}H_{14}O_3$ requires C, 74.3; H, 5.8%); ν_{max} 3580, 1720, 1580, 1240 cm^{-1}; λ_{max} 266 (ϵ 28000), 303 nm (3700); δ_H 7.48 (7H, m), 6.18 (1H, br s, exchanges with D_2O), 3.94 (3H, s), 2.23 (3H, s); m/z 242.0940 (100%, -0.3, M^+).

(9g) afforded *methyl 3-(2-bromo-5-nitrophenyl)-5-hydroxy-4-methylbenzoate* (17e) (56%), m.p. 207-208°C. (Found: C, 49.0; H, 3.1; N, 3.5; Br, 21.5. $C_{15}H_{12}BrNO_5$ requires C, 49.2; H, 3.3; N, 3.8; Br, 21.8%; ν_{max} 3570, 1720, 1530, 1345 cm^{-1}; λ_{max} 245 (ϵ 11300), 279 nm (9900); δ_H 9.41 (1H, br s, exchanges with D_2O), 8.10 (1H, dd, 2, 8 Hz), 8.08 (1H, s), 7.81 (1H, d, 8 Hz), 7.61 (1H, d, 2 Hz), 7.30 (1H, d, 2 Hz), 3.85 (3H, s), 1.97 (3H, s); m/z 365 (99%, M^+).

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