Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 10, pp. 2535-2546, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00332-0

Enantioselective Synthesis of Succinic Acids and γ-Lactones via Palladium Catalysed Allylic Substitution Reactions

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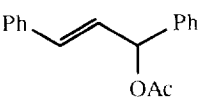
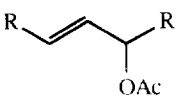
Abstract: The palladium catalysed reaction between non-symmetrical allyl acetates and sodiodimethylmalonate proceeds in high yields and enantioselectivities (up to 99% ee) using a diphenylphosphinoaryl oxazoline ligand. The so-formed substitution products are transformed into enantiomerically enriched succinic acids and also into enantiomerically enriched γ-lactones.

In the last few years, there has been considerable interest in asymmetric variants of the palladium catalysed allylic substitution reaction,[1] and several groups,[2] including ours,[3] have designed ligands capable of effecting highly enantioselective reactions. Very often the test substrate for such reactions is the allyl acetate **1**. In considering possible synthetic applications for this reaction, we felt that the synthesis of related substrates **2**, containing identical termini, would be too cumbersome to be generally useful.

We therefore decided to investigate the use of the alternative substrate **3**, which has been used in palladium catalysed enantioselective allylic substitution reactions by Bosnich[4] and others.[5] The synthesis of the general class of compound **4** is relatively straightforward, as described in this Paper.[6]



1



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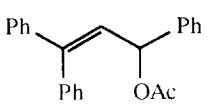
Synthetic accessibility dependent upon R



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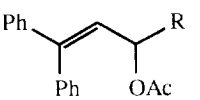


4

Easy to prepare for a wide range of R

The reaction of an organometallic (either an organolithium or a Grignard reagent) with commercially available β-phenylcinnamaldehyde produces a range of allylic alcohols **5a-g** with the yields indicated in Table 1. Acetylation of the alcohols with acetic anhydride, a catalytic amount of DMAP, and triethylamine affords the corresponding acetates **4a-g** in good yields (Table 1).

Dedicated to the memory of Professor Hidemasa Takaya, deceased on 5 October 1995

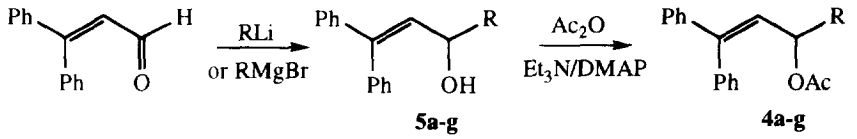


Table 1. Preparation of allyl alcohols and acetates

R=	Alcohol	Yield OH (%)	Acetate	Yield OAc (%)
Me	**5a**	91	**4a**	96
Ph	**5b**	94	**4b**	98
p-ClPh	**5c**	87	**4c**	95
2-Pyr	**5d**	66	**4d**	88
c-Hex	**5e**	91	**4e**	94
Naphth	**5f**	84	**4f**	96
Mesityl	**5g**	86	**4g**	95

With this series of allyl acetates in hand, we turned our attention to the palladium catalysed reactions. Treatment of the regioisomers **4b** and **6**[4] with sodiodimethylmalonate in the presence of 2.5 mol% palladium allyl chloride dimer and 10 mol% of the ligand **7** under the conditions in Table 2 afforded the product **8** with high levels of enantioselectivity and in good yield. Preliminary studies had indicated that the ligand **7** was superior to related oxazoline ligands which have been prepared in this group and others.[2,3]

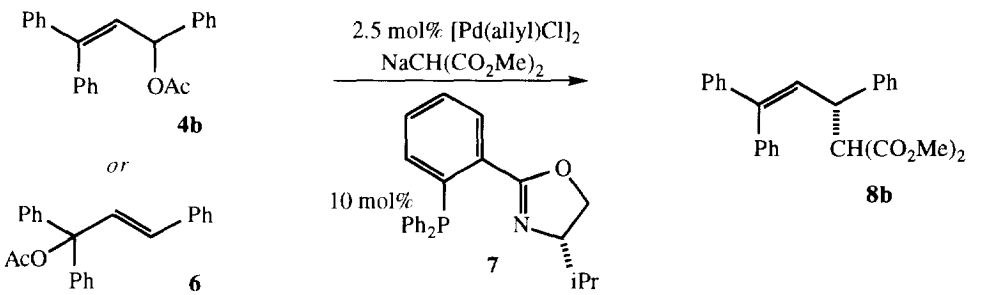


Table 2. Enantioselective allylic substitution of substrates **4b** and **6**

Substrate	Solvent	Temp	Time	yield(%)	e.e.(%)
4b	THF	20°C	36	80	94
4b	THF	reflux	24	93	94
6	THF	20°C	36	91	94
6	THF	reflux	24	95	93
4b	DMF	20°C	36	88	99
4b	DMF	65°C	24	92	99
4b[a]	THF	20°C	96	26	94
4b[a]	THF	reflux	48	82	94
4b[a]	DMF	20°C	96	22	99

[a]These reactions were run using dimethylmalonate with BSA (bistrimethylsilylacetamide) and catalytic KOAc

In no case was the other regioisomer detected and the regiochemistry of the starting material had no effect on the observed product yield and enantioselectivity, indicating a common palladium allyl intermediate in the catalytic cycle, as already demonstrated by Bosnich and co-workers.[4]

The range of acetates prepared previously were utilised in the palladium catalysed allylic substitution procedure. The substitution product was formed in good yield in each case, except for the cyclohexyl substrate **5e**.[7] The yields and enantioselectivities are recorded in Table 3.

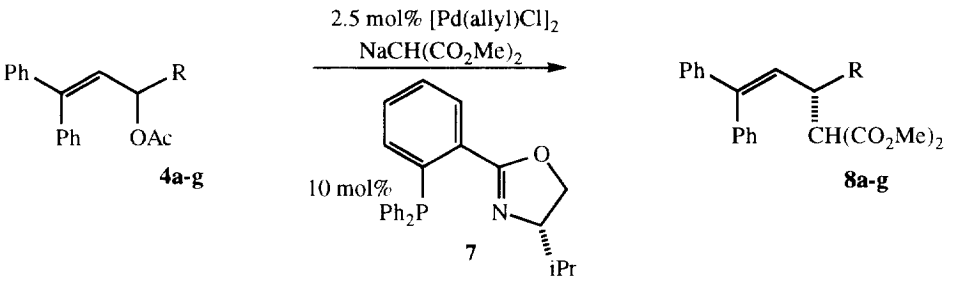


Table 3. Enantioselective allylic substitution of allylic acetates **4a-g**

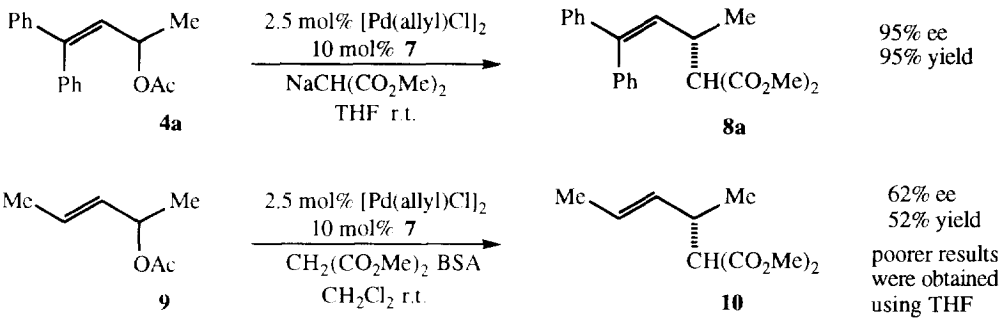
Acetate	R=	Solvent	Temp/°C	Time/Hr	Yield %	e.e. %
4a	Me	THF	67	5	91	80[a]
4a	Me	THF	25	24	95	95[a]
4a	Me	DMF	67	5	86	92[a]
4b	Ph	THF	25	24	97	95[b]
4b	Ph	DMF	25	24	88	99[b]
4c	Cl-Ph	THF	67	5	89	>95[b]
4c	Cl-Ph	THF	25	36	91	>95[b]
4d	Pyr	THF	67	8	92	91[c]
4d	Pyr	THF	25	36	89	92[c]
4e	c-Hex	THF	67	48	0	----
4e	c-Hex	DMF	120	48	0	----
4f	Naphth	THF	67	5	96	>95[a]
4f	Naphth	THF	25	36	94	>95[a]
4g	Mesityl	THF	67	8	91	98[c]
4g	Mesityl	THF	25	36	84	98[c]

[a]Determined from ^{1}H nmr spectrum in the presence of the shift reagent Eu(hfc)$_3$.

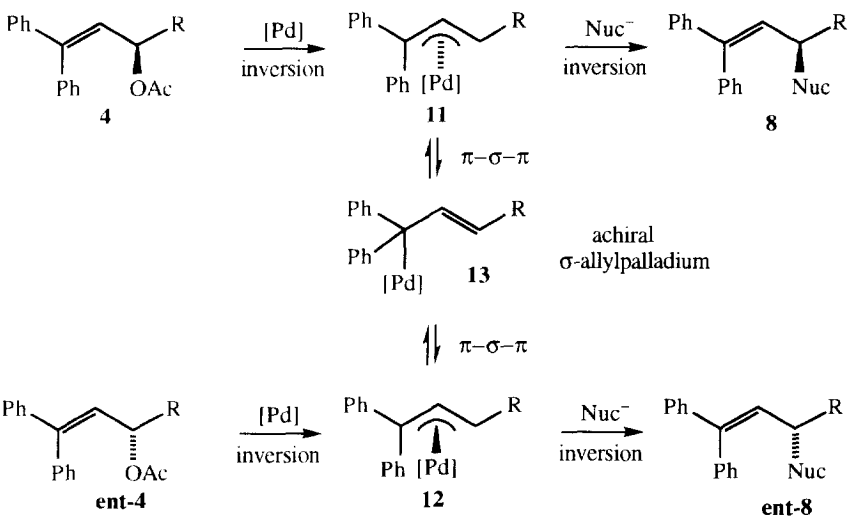
[b]Determined by chiral hplc (Chiracel OJ, hexane : iPrOH (containing 3% Et_3N): 97:3).

[c]Determined by chiral hplc (Chiracel OD, hexane : iPrOH: 99:1).

The results show that a variety of differently substituted racemic allylic acetate precursors may be converted into the substitution products with complete regiocontrol and excellent enantiocontrol. In fact, not only are the substrates **4a-g** easy to prepare, they also appear to give enhanced enantioselectivity in comparison with their counterparts containing identical termini. This is particularly striking in the comparison of the enantioselective palladium catalysed allylic substitution reaction of substrates **4a** and **9** [3d]. The product **8a** is formed with a higher level of enantioselectivity than is **10**. However, there is a price to pay; the less symmetrical substrates **4** are not as reactive than their counterparts **2**. A consequence of this is that we have been unable to employ more sluggish nucleophiles (such as potassium phthalimide and the sodium salt of bis(phenylsulfonyl)methane) in a satisfactory manner, since very little reaction is observed under the conditions that we have examined to date.

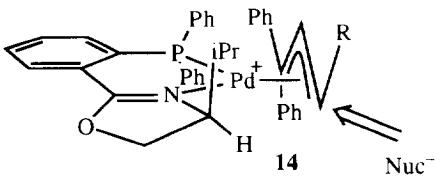


Palladium catalysed allylic substitution reactions are generally considered to proceed *via* overall retention of stereochemistry.[8] Thus for the racemic substrates **4** employed, it would appear (on first inspection) that the only possibility is that racemic product would form (**4** affords **8** and **ent-4** affords **ent-8**). However, as has been established by other researchers,[9] the intermediate allylpalladium complexes are able to undergo interconversion *via* a π–σ–π mechanism.



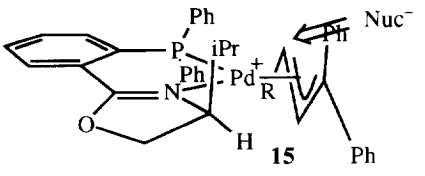
Therefore, the enantioselectivity of the overall process is achieved by the fact that more of complex **12** is converted into **ent-8** than complex **11** being converted into the enantiomeric product **8**. This may either be a consequence of a higher population of complex **12** with respect to complex **11**, or that nucleophilic addition takes place more quickly to complex **12** than to complex **11**.

Specifically, with the use of the phosphorus-containing oxazoline ligand **7**, there are four possible cationic allylpalladium complexes which need to be considered. Since we know the absolute configuration of the substitution products which are formed, we can discount the complexes **16** and **17**, since these would lead to the wrong enantiomer of product. However, there are still two possibilities to consider. Simple modelling experiments clearly indicate that complex **14** experiences considerable steric crowding due to the proximity of four phenyl groups. However, this is a ground state consideration, and we presume that it is the rate of nucleophilic addition to the complexes which will decide between these possibilities and not their relative abundances. It has been established that there is a dramatic difference between phosphorus and nitrogen ligands, and their ability to strongly affect the electrophilicity of the allyl moiety.[10] The *trans* influence directs nucleophilic addition to the allyl terminus *trans* to the better π-acceptor (in this case the phosphorus atom). Therefore, we conclude that the reaction probably proceeds *via* complex **14** rather than complex **15**.



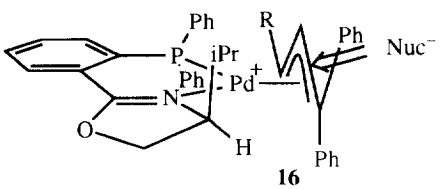
14

Nucleophilic addition to this complex leads to the observed enantiomer of product. Additionally, nucleophilic addition occurs trans to the phosphorus, which is advantageous.



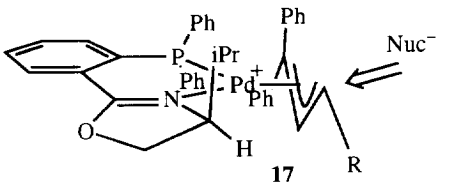
15

Nucleophilic addition to this complex leads to the observed enantiomer of product. However, nucleophilic addition occurs trans to the nitrogen, which makes this much less likely.



16

Nucleophilic addition to this complex leads to the wrong enantiomer of product, and is therefore discounted

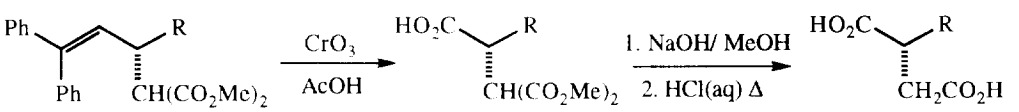


17

Nucleophilic addition to this complex leads to the wrong enantiomer of product, and is therefore discounted

Conversion to Succinic Acids

The palladium catalysed allylic substitution products are readily converted into succinic acids by the following procedure. The 1,1-diphenyl alkenes **8a-c** are readily cleaved using chromic acid in acetic acid[11] to afford the mono-acids **9a-c**. The crude products **9a-c** were then de-esterified using sodium hydroxide in methanol and water. Subsequent acidification with aqueous hydrochloric acid and heating effects decarboxylation to give the substituted succinic acid products **10a-c**. The products were formed without any detectable loss of enantiomeric excess,[12] in good overall yields from the palladium catalysed allylic substitution products **8a-c**.



8a-c **9a-c** **10a-c**

Table 4. Derivatisation of substitution products **8a-c** into succinic acids **10a-c**

R	Product	Yield(%)	e.e.(%)[a]
Me	**10a**	71	90
Ph	**10b**	74	99
Cl-Ph	**10c**	69	>95?[12]

[a] Enantiomeric excess values determined from rotation values in the literature.[12]

Generation of Lactones

Treatment of the products **8** from the palladium catalysed allylic substitution reaction to the Krapcho decarboxylation procedure (dimethyl sulphoxide, sodium chloride and water at high temperature in a pressure vessel)[13] resulted in smooth decarboxylation to the products **11**. The procedure employed is similar to one recently used by Pfaltz and co-workers[2e]. Subsequent treatment of the mono-esters **11** with ozone at -78 °C followed by sodium borohydride results in the cleaving of the olefin to the alcohol, which closes *in situ* to the

corresponding lactone.[14] This procedure was only attempted on two substrates, but afforded the γ-lactones **12** without significant loss of stereochemical purity.

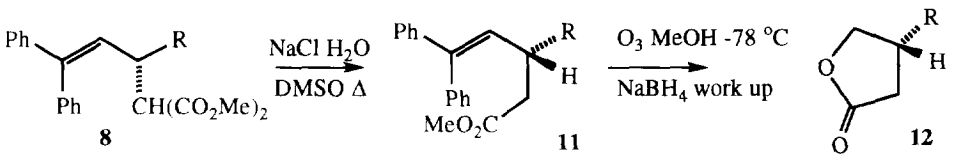


Table 5. Krapcho decarboxylation and (for some substrates) conversion into γ-lactones

Starting material	R	Mono-ester	Yield (%)	Lactone	Yield (%)	ee (%)[a]
8b (95%ee)	Ph	**11b**	79	**12b**	76	94
8c	Cl-Ph	**11c**	76	**12c**	79	96
8g	Mesityl	**11g**	81			
8d	Pyr	**11d**	72			

[a]Enantiomeric excess values determined from specific rotation values in the literature.[15]

In summary, allyl acetates **4** which possess a 1,1-diphenylalkene moiety undergo highly enantioselective palladium catalysed allylic substitution reaction when performed in the presence of the oxazoline ligand **7**. The enantiomerically enriched substitution products **8** have been converted into both enantiomerically enriched succinic acids and also γ-lactones without any apparent loss of stereochemistry.

The use of substrates which do not need to proceed *via* a symmetrical allylpalladium intermediate extends the synthetic potential of this reaction. The research group at Loughborough is investigating further synthetic applications for this process.

EXPERIMENTAL SECTION

General experimental details, including solvent purification and instrumentation have been published elsewhere.[3d]

Synthesis of the allylic acetate **6** and the phosphine oxazoline **7**, have also been reported elsewhere.[16]

General Preparation of alcohols 5a-g

The preparation of alcohols **5a-g** is typified by the preparation of alcohol **5c**.

4-Chlorophenyl magnesium bromide (23ml, 1.0M solution in ether 23mmol) was added gradually to a stirring solution of β–phenylcinnamaldehyde (4g, 19.2mmol) in THF (30 ml) whilst at 0 °C and under a nitrogen atmosphere. After addition was complete the reaction was allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched with saturated ammonium chloride solution (50ml) and extracted with diethylether (2x50ml). The ether extracts were combined and washed twice with water (30ml) dried ($MgSO_4$), filtered and evaporated to give the crude alcohol which was purified by silica column chromatography using petroleum ether / diethylether (3:1) as the eluent.

2-Lithiopyridine was prepared by the treatment of 2-bromopyridine(2.2g, 14mmol) in THF at -78 °C with gradual addition of n-BuLi(2M, 7.5ml) and stirring for 1 hour.

1-Lithionaphthalene was prepared by the treatment of 1-bromonaphthalene(5g, 24mmol) in THF at -40 °C and n-BuLi (13.2ml, 26 mmol) was added over 45 minutes then allowed to warm to 0 °C.

4,4-Diphenyl-4-hydroxybut-2-ene (5a) (91%) as a colourless oil.(found M^+, 224.1202 $C_{16}H_{16}O$ requires M^+, 224.1201). ν_{max} / cm^{-1} 3450. δ_H (250 MHz, $CDCl_3$) 1.24(d, 3H, J=6.2Hz, Me), 1.51(s, 1H, OH),

4.30(m, 1H, CHMe), 6.07(d, 1H, J=9.1Hz, CHCHMe), 7.18-7.40(m, 10H, Ar). δ_C (62.5 MHz, $(CD_3)_2SO$) 20.8, 53.8, 127.8, 127.9, 128.5, 128.6, 130.0, 132.6, 139.6, 142.0, 142.9.

1,1,3-Triphenyl-3-hydroxyprop-1-ene (5b) (94%) as a colourless solid. (found M^+, 286.1372 $C_{21}H_{18}O$ requires M^+, 286.1357). ν_{max} / cm^{-1} 3300. δ_H (250 MHz, $CDCl_3$) 2.05(s, 1H, OH), 5.24(d, 1H, J=9.3Hz, CHCHOH), 6.85(d, 1H, J=9.3Hz, CHPh), 7.21-7.44(m, 15H, Ar). δ_C (62.5 MHz, $CDCl_3$) 71.6, 126.1, 127.5, 127.6, 128.1, 128.2, 128.5, 129.7, 130.0, 138.2, 142.1, 143.4.

3-(4-Chlorophenyl)-3-hydroxy-1,1-diphenylprop-1-ene (5c) (87%) as a colourless oil.(found M^+, 320.0968 $C_{21}H_{17}OCl$ requires M^+, 320.0968). ν_{max} / cm^{-1} 3450. δ_H (250 MHz, $CDCl_3$) 2.20(s, 1H, OH), 5.24(d, 1H, J=9.3Hz, CHOH) 6.26(d, 1H, J=9.3Hz, CH=CPh_2), 7.15-7.44(m, 14H, Ar). δ_C (62.5 MHz, $CDCl_3$) 71.1, 116.7, 127.55, 127.6, 127.7, 127.9, 128.2, 128.4, 128.8, 129.4, 129.5, 129.7, 133.3, 138.9, 141.2, 141.8, 144.0.

3-(2-Pyridyl)-3-hydroxy-1,1-diphenylprop-1-ene (5d) (66%) as a colourless oil.(found M^+, 287.1315 $C_{20}H_{17}ON$ requires M^+, 287.1310). ν_{max} / cm^{-1} 3360. δ_H (250 MHz, $CDCl_3$) 4.85(s, 1H, OH), 5.24(d, 1H, J=9.8Hz, CHOH), 6.11(d, 1H, J=9.8Hz, CH=CPh_2), 7.18-7.6(m, 13H, Ar), 8.50(m, 1H, Ar). δ_C (62.5 MHz, $CDCl_3$) 70.0, 121.1, 122.4, 126.1, 126.6, 127.3, 127.5, 127.6, 127.8, 128.0, 128.2, 128.3, 129.2, 129.4, 129.7, 130.1, 136.3, 136.7, 139.7, 148.8.

3-Cyclohexyl,3-hydroxy-1,1-diphenylprop-1-ene (5e) (91%) as a colourless oil.(found M^+, 292.1827 $C_{21}H_{24}O$ requires M^+, 292.1827). ν_{max} / cm^{-1} 3420. δ_H (250 MHz, $CDCl_3$)1.0-2.0(m, 11H, cyc), 3.86(dd, 1H, J=7.3, 9.5, CHOH), 6.09(d, 1H, J=9.5Hz, CH=CPh_2), 7.20-7.41(m, 10H, Ar). δ_C (62.5 MHz, $CDCl_3$) 25.9, 26.1, 26.4, 28.7, 28.9, 44.3, 73.6, 127.2, 128.0, 128.1, 129.6, 130.0, 139.2, 142.3, 144.8.

3-(1-Naphthyl)-3-hydroxy-1,1-diphenylprop-1-ene (5f) (84%) as a colourless oil.(found M^+, 336.1514 $C_{25}H_{20}O$ requires M^+, 336.1525). ν_{max} / cm^{-1} 3332. δ_H (250 MHz, $CDCl_3$) 2.2(d, 1H, OH, J=2.9 Hz), 5.94(dd, 1H, CHOH, J=2.9, 9.3 Hz), 6.46(d, 1H, J=9.3Hz, CH=CPh_2), 7.27-7.53(m, 13H, Ar), 7.73-7.90(m, 4H, Ar). δ_C (62.5 MHz, $CDCl_3$) 69.4, 123.4, 123.8, 125.4, 125.5, 125.9, 127.7, 127.8, 128.1, 128.2, 128.3, 128.6, 129.9, 133.8, 138.4, 138.6, 142.0, 144.1.

3-(2,4,6-Trimethylphenyl)3-hydroxy-1,1-diphenylprop-1-ene (5g) (86%) as a colourless oil.(found M^+, 328.1834 $C_{24}H_{24}O$ requires M^+, 328.1827). ν_{max} / cm^{-1} 3420. δ_H (250 MHz, $CDCl_3$) 1.82(s, 1H, OH), 2.20(s, 6H, Me) 2.28(s, 3H, Me), 5.75(d, 1H, J=8.7Hz, CHOH), 6.70(d, 1H, J=8.7Hz, CH=CPh_2), 6.82(s, 2H, Ar), 7.20-7.46(m, 10H, Ar). δ_C (62.5 MHz, $CDCl_3$) 20.9, 21.2, 69.7, 126.9, 127.3, 127.55, 127.8, 127.9, 127.8, 127.9, 128.7, 129.8, 130.1, 136.7, 136.8, 139.7, 142.1, 144.0.

General Preparation of Acetates 4a-g

The preparation of acetates **4a-g** is typified by the preparation of alcohol **4c**.

The chlorophenyl substituted alcohol **5c** (3g, 9.3mmol) was dissolved in dichloromethane (20ml), triethylamine (1.4g, 14mmol), acetic anhydride (1.4 g, 14mmol) and dimethylaminopyridine (DMAP) (10mg). The reaction was stirred at room temperature and monitored by TLC. When all of the alcohol had been converted into acetate (ca. 10 hours) the reaction was quenched with water (50ml) and the dichloromethane layer separated. The dichloromethane layer was then washed with 1M sodium hydroxide solution (2x50ml) followed by water (50ml), dried ($MgSO_4$), filtered and evaporated to give the crude alcohol which was purified by silica column chromatography using petroleum ether / diethylether (4:1) as the eluent.

4,4-Diphenylbut-3-enyl acetate (4a) (96%) as a colourless oil.(found M^+, 266.1308 $C_{18}H_{18}O_2$ requires M^+, 266.1306). ν_{max} / cm^{-1} 1740. δ_H (250 MHz, $CDCl_3$) 1.33(d, 3H, J=6.2Hz, Me), 2.02(s, 3H, OAc), 5.43(m, 1H, C<u>H</u>Me), 6.04(d, 1H, J=8.9Hz, C<u>H</u>=CHMe), 7.2-7.4(m, 10H,Ar). δ_C (62.5 MHz, $CDCl_3$) 20.9, 21.2, 69.4, 127.3, 127.5, 127.6, 127.9, 128.1, 128.2, 129.4, 138.4, 141.2, 144.6, 169.7.

1,3,3-Triphenylprop-2-enyl acetate (4b) (83%) as a colourless solid. M.p. 69-71°C (found MH^+, 328.1454 $C_{23}H_{20}O_2$ requires MH^+ 328.1463). ν_{max} / cm^{-1} 1733. δ_H (250 MHz, $CDCl_3$) 2.08(s, 3H, OAc), 6.30(m, 2H, 2xCH), 7.25-7.50(m, 15H, Ar). δ_C (62.5 MHz, $CDCl_3$) 21.3, 74.1, 126.1, 126.4, 126.6, 126.9, 127.3, 127.4, 127.5, 127.7, 127.8, 127.9, 128.1, 128.3, 128.5, 128.7, 129.5, 140.1, 141.2, 144.5, 169.6.

3,3-Diphenylprop-2-enyl,1-(4-chlorophenyl) acetate (4c) (95%) as a colourless oil.(found M^+, 320.0968 $C_{21}H_{17}OCl$ requires M^+, 320.0968). ν_{max} / cm^{-1} 1737. δ_H (250 MHz, $CDCl_3$) 2.1(s, 3H, OAc), 6.1(m, 2H, CHx2), 7.25-7.60(m, 14H, Ar). δ_C (62.5 MHz, $CDCl_3$) 19.7, 71.9, 121.4, 124.1, 126.0, 126.4, 126.5, 126.7, 126.9, 127.3, 127.9, 128.0, 132.2, 137.1, 137.2, 139.5, 143.5, 168.1.

3,3-Diphenylprop-2-enyl,1-(2-pyridyl) acetate (4d) (88%) as a colourless solid. M.p. 70-72°C (found M^+, 329.1415 $C_{22}H_{19}O_2N$ requires M^+, 329.1416). ν_{max} / cm^{-1} 1738. δ_H (250 MHz, $CDCl_3$) 2.09 (s, 3H, OAc), 6.27 (d, 1H, J=9.3Hz, C<u>H</u>OAc), 6.50 (d, 1H, J=9.3Hz, C<u>H</u>=CPh_2), 7.1-7.6 (m, 13H, Ar), 8.65 (m, 1H, Ar). δ_C (62.5 MHz, $CDCl_3$) 21.1, 74.5, 122.1, 122.7, 124.9, 127.5, 127.7, 127.8, 128.0, 128.1, 128.3, 129.4, 129.6, 136.6, 149.7, 169.8.

3,3-Diphenylprop-2-enyl,1-cyclohexyl acetate (4e) (94%) as a colourless oil.(found M^+, 334.1933 $C_{23}H_{26}O_2$ requires M^+, 334.1933). ν_{max} / cm^{-1} 1735. δ_H (250 MHz, $CDCl_3$) 1.0-1.7(m, 11H, cyc), 2.03(s, 3H, OAc), 5.21 (dd, 1H, J=6.9, 9.4, C<u>H</u>OAc), 6.04(d, 1H, J=9.4, CH=CPh_2), 7.25-7.40(m, 10H, Ar). δ_C (62.5 MHz, $CDCl_3$)21.1, 25.8, 26.0, 26.2, 28.5, 28.6, 42.6, 76.3, 125.8, 127.3, 127.6, 128.0, 129.6, 140.0, 142.4, 145.1, 170.2.

3,3-Diphenylprop-2-enyl,1-(1-naphthyl) acetate (4f) (96%) as a colourless solid M.p. 95-97°C (found M^+, 378.1621 $C_{27}H_{22}O_2$ requires M^+, 378.1619). ν_{max} / cm^{-1} 1746. δ_H (250 MHz, $CDCl_3$) 2.09(s, 3H, OAc), 6.50(d, 1H, J=9.1Hz, C<u>H</u>OAc), 6.99(d, 1H, J=9.1Hz, CH=CPh_2), 7.21-7-88(m, 17H, Ar). δ_C (62.5 MHz, $CDCl_3$) 21.2, 71.9, 123.8, 124.9, 125.2, 125.6, 126.0, 126.1, 127.5, 127.8, 128.1, 128.3, 128.6, 129.6, 133.9, 136.4, 138.7, 141.3, 145.1, 169.4.

3,3-Diphenylprop-2-enyl, 1-(2,4,6-Trimethylphenyl) acetate (4g) (84%) as a colourless oil.(found M^+, 370.1908 $C_{26}H_{26}O_2$ requires M^+, 370.1932). ν_{max} / cm^{-1} 1738. δ_H (250 MHz, $CDCl_3$) 2.02(s, 3H, Me), 2.30(s, 9H, 2xMe+OAc), 6.59(d, 1H, J=8.7Hz, C<u>H</u>OAc), 6.71(d, 1H, J=8.7Hz, C<u>H</u>=CPh_2), 6.79(s, 2H, Ar), 7.18-7.40(m, 10H, Ar). δ_C (62.5 MHz, $CDCl_3$) 20.2, 20.7, 20.9, 71.4, 125.7, 127.0, 127.2, 127.5, 127.6, 127.8, 127.9, 128.0, 129.1, 129.4, 129.7, 130.1, 130.4, 133.3, 136.7, 137.3, 138.8, 141.9, 144.9, 169.5. 3, 3-Diphenylprop-2-enyl, 1-(2,4,6-Trimethylphenyl) Acetate used directly after work up as it was found to be unstable on silica.

General Procedure for Palladium-catalysed Allylic Alkylation

The allylic acetate **4** (200mg, 0.55mmol), $[\{Pd(\eta\text{-}C_3H_5)Cl\}_2]$ (9 mg, 2.5mol%), ligand **7** (20mg, 10mol%), were dissolved in THF (2ml) and stirred at the required temperature for 15 minutes. The resulting yellow solution was treated with dimethyl sodiomalonate (0.32mmol/ml of dry THF). The reaction was monitored by TLC for the disappearance of acetate. When all the acetate had been converted to product (5-48 hr) the reaction

was quenched with water (40ml) and dichloromethane added (3x20ml) and extracted. The dichloromethane layers were combined, dried ($MgSO_4$), filtered and evaporated to give the crude product which was purified by silica column chromatography using petroleum ether / diethylether (4:1) as the eluent.

Methyl 2-carbomethoxy-3-methyl-5,5-diphenylpent-4-enoate (8a) (92%) as a colourless oil.(found M^+, 338.1518 $C_{21}H_{22}O_4$ requires M^+, 338.1518). $[\alpha]_D^{20}$ -173.9 (c=0.46, EtOH). ν_{max} / cm^{-1} 1739. δ_H (250 MHz, $CDCl_3$) 0.86(d, 3H, J=6.5Hz, Me), 3.12(m, 1H, CH), 3.30(d, 1H, C<u>H</u>(CO_2Me)), 3.61(d, 6H, CO_2Me), 6.01(d, 1H, J=10.3Hz, C<u>H</u>=CPh_2), 7.20-7.45(m, 10H, Ar). δ_C (62.5 MHz, $CDCl_3$) 19.2, 34.2, 52.2, 57.5, 127.1, 127.2, 128.0, 128.2, 129.4, 130.0, 139.4, 168.5.

Methyl 2-carbomethoxy-3,5,5-triphenylpent-4-enoate (8b) (95%) as a colourless oil.(found MH^+, 400.1740 $C_{26}H_{25}O_4$ requires MH^+ 400.1740). $[\alpha]_D^{20}$ -186.0 (c=0.44, $CHCl_3$). ν_{max} / cm^{-1} 1735. δ_H (250 MHz, $CDCl_3$) 3.45(s, 3H, CO_2Me), 3.70(s, 3H, CO_2Me), 3.90(d, 1H, J=10.0Hz, C<u>H</u>CO_2Me), 4.22(ap.t, 1H, J=10.0Hz, C<u>H</u>Ph), 6.35(d, 1H, J=10.0Hz, C<u>H</u>=CPh_2), 7.10-7.42(m, 15H, Ar). δ_C (62.5 MHz, $CDCl_3$) 45.1, 52.3, 52.5, 58.4, 126.9, 127.3, 127.4, 127.7, 128.0, 128.1, 128.6, 129.6, 139.0, 141.0, 142.1, 143.6, 168.0.

Methyl 2-carbomethoxy-5,5-diphenyl-3-(4-chlorophenyl),pent-4-enoate (8c) (91%) as a colourless oil.(found $M+NH_4^+$, 452.1629 $C_{26}H_{27}O_4NCl$ requires $M+NH_4^+$, 452.1629). $[\alpha]_D^{20}$ -170.4 (c=0.44, $CHCl_3$). ν_{max} / cm^{-1} 1733. δ_H (250 MHz, $CDCl_3$) 3.68(s, 3H, CO_2<u>Me</u>), 3.70(s, 3H, CO_2Me) 3.82(d, 1H, J=10.1Hz, C<u>H</u>(CO_2Me)$_2$), 4.21(ap t, 1H, J=8.4Hz, C<u>H</u>CH(CO_2Me)$_2$), 6.29(d, 1H, J=10.5Hz, C<u>H</u>=CPh_2), 7.04-7.38(m, 14H, Ar). δ_C (62.5 MHz, $CDCl_3$) 44.4, 52.3, 52.5, 58.2, 126.6, 127.3, 127.5, 128.1, 128.2, 128.7, 129.1, 1299.5, 132.6, 138.8, 139.7, 141.9, 144.2, 167.8, 168.1.

Methyl 2-carbomethoxy-5,5-diphenyl-3(2-pyridyl),pent-4-enoate (8d) (92%) as a colourless oil.(found M^+, 402.1705 $C_{25}H_{23}O_4N$ requires M^+, 402.1705). $[\alpha]_D^{20}$ -260.0 (c=0.5, $CHCl_3$). ν_{max} / cm^{-1} 1732. δ_H (250 MHz, $CDCl_3$) 3.53 (s, 3H, CO_2Me), 3.71 (s, 3H, CO_2Me) 4.44(m, 2H, C<u>H</u>(CO_2Me)$_2$ + C<u>H</u>-CH=Ph_2), 6.34 (d,1H, J=10.1Hz, C<u>H</u>=Ph_2), 7.1-7.6 (m, 13H, Ar), 8.54 (m, 1H, Ar). δ_C (62.5 MHz, $CDCl_3$) 46.4, 52.2, 52.4, 55.6, 121.6, 123.5, 127.0, 127.4, 127.5, 128.0, 128.3, 129.6, 136.5, 139.2, 143.9, 149.1, 160.3, 168.3, 168.6.

Methyl 2-carbomethoxy-5,5-diphenyl-3-(1-naphthyl),pent-4-enoate (8f) (96%) as a colourless oil.(found 450.1838 $C_{30}H_{26}O_4$ requires M^+ 450.1831). $[\alpha]_D^{20}$ +86.3 (c=1.1, $CHCl_3$). ν_{max} / cm^{-1} 1750. δ_H (250 MHz, $CDCl_3$) 3.32(s, 3H, CO_2Me), 3.70(s, 3H, CO_2Me), 4.05(d, 1H, J=9.3Hz, C<u>H</u>CO_2Me), 5.14(dd, 1H, J=9.3Hz, 10.2Hz, C<u>H</u>CHCO_2Me), 6.14(d, 1H, J=10.2Hz, CH=CPh_2), 6.97-7.71(m, 17H, Ar). δ_C (62.5 MHz, $CDCl_3$) 39.7, 52.2, 52.5, 56.5, 123.6, 125.4, 125.5, 125.8, 127.4, 127.66, 127.7, 128.1, 128.2, 128.7, 129.9, 130.6, 134.1, 137.6, 139.6, 142.3, 143.8, 167.8, 168.3.

Methyl 2-carbomethoxy-5,5-diphenyl-3-mesityl,pent-4-enoate (8g) (91%) as a colourless oil. (found M^+, 442.2150 $C_{29}H_{30}O_4$ requires M^+, 442.2144). $[\alpha]_D^{20}$ -68.8 (c=1.96, EtOH). ν_{max} / cm^{-1} 1758. δ_H (250 MHz, $CDCl_3$) 1.48(s, 3H, Me), 2.19(s, 3H, Me), 2.54(s, 3H, Me), 3.27(s, 3H, CO_2Me), 3.79(s, 3H, CO_2Me), 4.18(d, 1H, J=10.9Hz, C<u>H</u>CO_2Me), 4.79(dd, 1H, J=8.9, 10.9, C<u>H</u>CH=CPh_2), 6.47(d, 1H, J=8.9Hz, CH=CPh_2), 6.57(s, 1H, Ar), 6.74(s, 1H, Ar), (s, 1H, Ar), 7.08-7.32(m, 10H, Ar).

Preparation of Succinic Acids

The alkylation product (1.0mmol) was dissolved in acetic acid (3ml) and was stirred as a chromic acid solution (CrO_3 0.3g, 3mmol dissolved in H_2O (0.5ml) and acetic acid (5ml) was added. The resulting solution was stirred for 3 hours when TLC showed no remaining starting material and then poured into water (10ml) and

ether (20ml). The aqueous layer was washed three times with ether (20ml) and the ether extracts were combined and washed with water (10ml), dried with $MgSO_4$ and evaporated to give the acid and benzophenone as an oil. This oil was dissolved in methanol (5ml) and to this was added a solution of sodium hydroxide (0.5g, 12.5mmol in water (5ml). The mixture was refluxed for 1 hour then cooled and partially neutralised with aqueous hydrochloric acid (10M, 4ml and water 4ml) and then the solution was evaporated to a small volume. The residue was diluted with water (10ml) and acidified to pH 2 with aqueous hydrochloric acid. The aqueous layer was washed with dichloromethane (4x20ml). The solution was then refluxed for 5 hours. The cooled solution was extracted with (4x50ml) and the combined extracts were dried (Na_2SO_4) and evaporated to give a white solid .

Methylsuccinic acid (10a) (71%) as a colourless solid M.p. 116-119 °C (found M^+ 132.0422, $C_5H_8O_4$ requires M^+, 132.0422). $[\alpha]_D^{20}$ +13.9 (c=1.0, EtOH). ν_{max} / cm^{-1} 1702. δ_H (250 MHz, $(CD_3)_2SO$) 1.02(d, 3H, J=7.2Hz, Me), 2.18(dd, 1H, J=5.6Hz,16.5Hz, CH), 2.42(dd, 1H, J=8.3Hz, 16.5Hz,CH), 2.58(m, 1H, CHMe), 6.51(s, 2H, CO_2H). δ_C (62.5 MHz, $(CD_3)_2SO$) 21.8, 40.2, 42.2, 178.1, 181.4.

Phenylsuccinic acid (10b) (74%) as a colourless solid M.p.164-169 °C (found M^+194.0579, $C_{10}H_{10}O_4$ requires M^+ 194.0579). $[\alpha]_D^{20}$ +148 (c=0.9, EtOH). ν_{max} / cm^{-1} 1700. δ_H (250 MHz, CDCl3) 2.52(dd, 1H, J=5.1Hz, 16.8Hz, CH), 2.97(dd, 1H, J=10.2Hz, 16.8Hz, CH), 3.89(dd, 1H, J=5.1Hz,10.2Hz, CHPh), 6.14(s, 2H, CO_2H), 7.21-7.36(m, 5H, Ar). δ_C (62.5 MHz, CDCl3) 42.4, 51.9, 132.3, 132.9, 133.5, 143.8, 177.8, 179.2.

(4-Chlorophenyl)succinic acid (10c) (69%) as a colourless solid M.p.184-190 °C (found M^+, 228.0191 $C_{10}H_9O_4Cl$ requires M^+, 228.0189). $[\alpha]_D^{20}$ +122.2 (c=0.46, EtOH). ν_{max} / cm^{-1} 1718. δ_H (250 MHz, $(CD_3)_2SO$) 2.46(dd, 1H, J=5.3Hz, 16.7Hz, CH), 2.94(dd, 1H, J=9.9Hz, 16.7Hz, CH), 3.99(dd, 1H, J=5.3Hz, 9.9Hz, CHPh), 5.94(s, 2H, CO_2H), 7.28-7.40(m, 4H, Ar). δ_C (62.5 MHz, $(CD_3)_2SO$) 42.3, 51.3, 133.6, 134.8, 136.9, 142.8, 177.6, 178.8.

General procedure for decarboxylation of substitution products 8

A de-gassed solution of the starting material **8** (1mmol) in DMSO (5ml) containing NaCl (2.6mmol) and H_2O (2.8mmol) was heated in a sealed tube for 14 hours at 180 °C. After cooling to room temperature the mixture was diluted with dichloromethane (30ml) and brine (100ml) added and then extracted followed by two further extractions with dichloromethane(30ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Column chromatography petroleum ether : ether 3:1 afforded the title product as detailed.

Methyl 3,5,5-triphenylpent-4-enoate (11b) (79%) M.p, 86-87 °C (Found: M^+, 342.1619, $C_{24}H_{22}O_2$ requires M^+, 342.1619); $[\alpha]_D^{20}$ -125.0 (c=0.72, CHCl3). ν_{max} / cm^{-1} 1736; δH(250MHz; $CDCl_3$) 2.75(d, 2H, J=7.5Hz, CH_2), 3.59(s, 3H, CO_2Me), 3.98(m, 1H, CH), 6.26(d, 1H, J=10.4Hz, CH), 7.14-7.41(m, 15H, Ar). δC(63MHz, $CDCl_3$) 41.8, 41.9, 51.5, 126.5, 127.1, 127.2, 127.3, 128.0, 128.1, 129.6, 130.2, 139.5, 142.2, 143.4, 171.8.

Methyl 5,5-diphenyl-3-(4-chlorophenyl)pent-4-enoate (11c) (76%) M.p. 67-69 °C (Found: M^+,376.1572 , $C_{24}H_{21}O_2Cl$ requires M^+, 376.1572); $[\alpha]_D^{20}$ -125.0 (c=0.32, CHCl3). ν_{max} / cm^{-1} 1736; δH(250MHz; $CDCl_3$) 2.72(d, 2H, J=7.5Hz, CH_2), 3.59(s, 3H, CO_2Me), 3.95(m, 1H, CH), 6.20(d, 1H, J=10.3Hz, CH), 7.10-7.43(m, 14H, Ar). δC(63MHz, $CDCl_3$) 41.2, 41.7, 51.5, 127.3, 127.4, 128.1, 128.2, 128.4, 128.7, 129.5, 129.6, 138.4, 142.0, 142.6, 172.1.

Methyl 5,5-diphenyl-3-(2-pyridyl)pent-4-enoate (11d) (72%) as a viscous oil (Found: M^+, 343.1572 , $C_{22}H_{21}O_2N$ requires M^+, 343.1572). $[\alpha]_D^{20}$ -3.3 (c=3.0, $CHCl_3$). ν_{max} / cm^{-1} 1735. δH(250MHz; $CDCl_3$) 2.79(dd, 1H, J=7.0, 15.5Hz, CH_2), 3.06(dd,1H, J=7.5, 15.5, CH_2), 3.53(s, 3H, CO_2Me), 4.15(m, 1H, CHPyr), 6.38(d, 1H, J=10.3, CH), 7.05-7.59(m, 17H, Ar), 8.59(m, 1H, Ar). δC(63MHz, $CDCl_3$) 39.4, 43.4, 51.5, 121.5, 123.0, 127.2, 128.0, 128.3, 128.5, 129.4, 129.5, 136.7, 141.6, 142.8, 149.0, 172.2.

Methyl 5,5-diphenyl-3-(2,4,6-trimethylphenyl)pent-4-enoate (11g) (81%) as a colourless oil (Found: M^+, 384.2088, $C_{27}H_{28}O_2$ requires M^+, 384.2089). $[\alpha]_D^{20}$ +153.5 (c=2.8, $CHCl_3$). ν_{max} / cm^{-1} 1738. δH(250MHz; $CDCl_3$) 2.26(s, 9H, 3xMe), 2.59(dd, 1H, J=5.3, 14.7Hz, CH), 2.93(dd, 1H, J=10.2, 14.7, CH), 3.68(s, 3H, CO_2Me), 4.38(m, 1H, CH), 6.60(d, 1H, J=8.7Hz, CH), 6.77(s, 1H, Ar), 7.01(m, 1H, Ar), 7.26-7.34(m, 10H, Ar). δC(63MHz, $CDCl_3$)20.6, 37.4, 39.3, 51.5, 126.9, 126.9, 127.0, 128.1, 128.2, 129.5, 129.8, 130.6, 135.4, 137.6, 139.7, 142.0, 142.7, 172.4.

General procedure for reductive ozonolysis of alkenes to give lactones

The starting monoester **11** (1.0mmol) was dissolved in methanol (20ml) and was cooled to -78 °C with oxygen bubbled through for 5 minutes. Ozone was then generated and bubbled through the reaction mixture until the reaction solution turned blue (indicating an ozone saturated solution) or TLC analysis revealed no more starting material was present. Oxygen was bubbled through the mixture again for 5 minutes and then sodium borohydride (2.0mmol) was added carefully and the mixture was allowed to warm to room temperature overnight. The reaction was diluted with dichloromethane and then washed with saturated aqueous ammonium chloride(50ml), saturated brine(2x50ml) and water (50ml). The combined extracts were dried ($MgSO_4$) filtered and evaporated under reduced pressure. Column chromatography (petroleum ether : ether (2:1)) of the residue afforded the lactones as colourless solids.

3-Phenylbutyrolactone (12b) (76%) M.p. 60-62 °C , (Found: M^+, 162.0680, $C_{10}H_{10}O_2$ requires M^+, 162.0681). $[\alpha]_D^{20}$ 49.0 (c=3.1, $CHCl_3$). ν_{max} / cm^{-1} 1776. δH(250MHz; $CDCl_3$) 2.60(dd, 1H, J=17.5, 9.0Hz, CH), 2.85(dd, 1H, J=8.5, 17.5Hz, CH), 3.70(q, 1H, J=8.4Hz, CH), 4.19(dd, J=8.0, 9.0Hz, CH), 4.59(dd, 1H, J=7.8, 9.0Hz, CH) 7.20-7.41(m, 5H, Ar). δC(63MHz, $CDCl_3$) 35.6, 41.0, 73.9, 126.6, 127.6, 129.0, 176.6.

3-(4-Chlorophenyl)butyrolactone (12c) (79%) M.p. 71 °C (Found: M^+, 196.0291, $C_{10}H_9ClO_2$ requires M^+, 196.0291). $[\alpha]_D^{20}$ 44.5 (c=0.42, $CHCl_3$). ν_{max} / cm^{-1} 1778. δH(250MHz; $CDCl_3$) 2.62(dd, 1H, J=17.5, 8.9Hz, CH), 2.94(dd, 1H, J=17.5, 8.7, CH), 3.80(q, 1H, J=8Hz, CH), 4.13(dd, 1H, J=9.1 and 7.9Hz, CH), 4.62(dd, 1H, J=9.1, 7.8Hz, CH), 7.20-7.43(m, 4H, Ar). δC(63MHz, $CDCl_3$) 35.6, 40.5, 73.3, 128.0, 129.3, 137.9, 175.0.

Acknowledgement

We are grateful to Glaxo Wellcome Research and Development Limited for funding a studentship (to GJD)

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(*Received in UK* 22 *July* 1995)