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Tetramethylethylene Diamine/Trimethylsilyl Chloride Mediated Addition of Benzyl Copper Reagents to α,β-Unsaturated Esters

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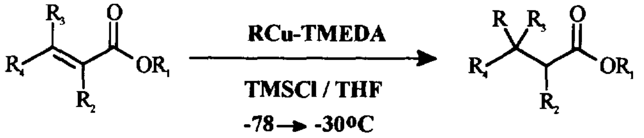
Abstract. Several benzylic copper reagents, benzylcopper, 4-methoxybenzylcopper and 1-phenylethylcopper, facilitate the conjugate addition of the corresponding benzyl ligands to α,β-enoates in the presence of tetramethylethylene diamine and trimethylsilyl chloride in high yields.

Organometallic reagents based on copper have gained wide acceptance for use in organic synthesis.[1] In many respects these are unique reagents for carbon-carbon bond formation, particularly for conjugate addition to α,β-unsaturated compounds, and hence methodology to improve their overall efficiency and specificity is of current interest. One area which has received little attention is the transfer of the highly reactive benzyl ligand to α,β-enoates. Recently, we discussed preliminary results for the facile preparation and transfer of the benzyl ligand to a variety of Michael acceptors.[2] During the course of this work benzyl transfer to the α,β-ethylenic esters, ethylcrotonate **2** and methylcinnamate **3**, were difficult to perform leading to poor yields. Excellent yields (73-86%) were recorded by utilization of the organocopper reagent, benzylcopper (BnCu), in the presence of trimethylsilyl chloride (TMSCl) and the polar additive, tetramethylethylene diamine (TMEDA). Here we report results relevant to the transfer of the benzyl ligand to α,β-unsaturated esters in general and to the compatibility of this system in terms of ligand variation (Scheme 1).



R = Bn, 4-MeOBn and 1-PhEt

Scheme 1

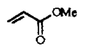
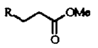
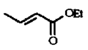
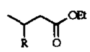
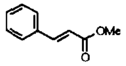
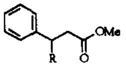
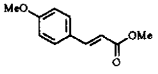
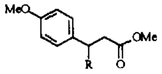
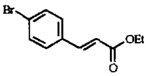
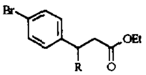
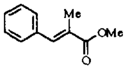
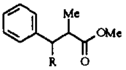
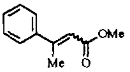
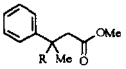
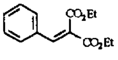
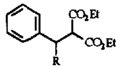
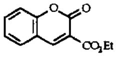
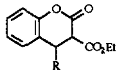
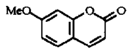
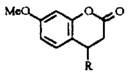
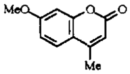
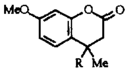
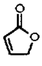
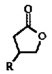
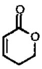
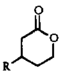
RESULTS AND DISCUSSION

Owing to the thermal instability of benzylic cuprates and the tendency of benzyl anions towards Wurtz-coupling,[3] we opted for the less reactive reagents prepared from organomagnesium compounds. Tetrahydrofuran[4] was found to be a superior medium to diethyl ether for these reactions, probably due to the strong coordination between this solvent and the copper cluster, thereby increasing the stability of the cuprate.[5] Thus, benzyl Grignard reagents, e.g. benzylmagnesium chloride (BnMgCl), 4-methoxybenzylmagnesium chloride (4-MeOBnMgCl) and 1-phenylethylmagnesium chloride (1-PhEtMgCl), were prepared as solutions in THF from respectively benzyl chloride, 4-methoxybenzyl chloride and 1-phenylethyl chloride. The latter two precursors were obtained *via* reduction ($NaBH_4$) and halogenation ($SOCl_2$) of 4-methoxybenzaldehyde and acetophenone, respectively. Subsequent preparation of the CuI-TMEDA complex from CuI and TMEDA, followed by transmetalation in the presence of the Grignard reagents, yielded the corresponding benzylic copper reagents.

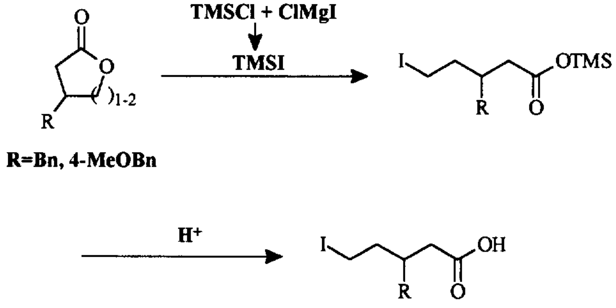
The general applicability of the TMSCl-TMEDA activated cuprate addition of benzyl ligands to α,β-unsaturated esters was assessed by using esters **1-13**. Compounds **1**, **2**, **3** and **12** are commercially available while enoates **4-11** and **13** were prepared as follows: Methyl-4'-methoxycinnamate **4**, ethyl-4'-bromocinnamate **5**, methyl-α-methylcinnamate **6** and methyl-β-methylcinnamate **7** were synthesized *via* Fischer-Speier[6] esterification of 4'-methoxycinnamic acid, Wittig olefination[7] between ethyl chloroacetate and 4-bromobenzaldehyde, Corey-oxidation[8] of α-methylcinnamaldehyde, and Horner-Wadsworth-Emmons olefination[9] between methyl-2-chloropropionate and acetophenone, respectively. Knoevenagel condensation[10] of diethylmalonate with benzaldehyde and salicylaldehyde, afforded ethyl-2-ethylcarboxycinnamate **8** and 3-ethylcarboxycoumarin **9**, respectively, while coumarins **10** and **11** were obtained after dimethylsulphate/K_2CO_3 methylation[11] of 7-hydroxy- and 7-hydroxy-4-methylcoumarin. Lactone **13** was synthesized in two steps *via* α-selenenylation of δ-valerolactone followed by oxidation and *syn*-elimination of the selenoxide.[12]

Table 1 summarizes the TMSCl-TMEDA activated cuprate addition of the benzyl ligands to Michael acceptors **1-13**, and illustrates the efficiency and scope of the present method. Several noteworthy features are apparent from the results: Despite the low reactivity of α,β-unsaturated esters with respect to organocopper additions,[13] consistent high yields were obtained for α- and β-monosubstituted α,β-enoates, the only exceptions being the lactones **12** and **13**. However, as the steric bulk at the reactive site is increased, e.g. α,β- and β,β-disubstituted cinnamic esters, **6** and **7**, this method invariably failed. The inefficiency of the reagent in the latter two cases may probably be attributed to a combination of steric inaccessibility and rotation about the C_{α}-$C_{(C=O)}$ bond, causing an unfavourable orientation of the participating antibonding orbitals, thus preventing effective coordination between the cuprate and substrate. Conjugate addition to the sterically

Table 1 1,4-Michael Addition of Benzyl ligands to Enoates

Substrate	RCu-TMEDA TMSCl	Time (h)	Product		Yield (%)
 (1)	R=Bn R=4-MeOBn	8 8		**(14)** R=Bn **(15)** R=4-MeOBn	90 83
 (2)	R=Bn R=4-MeOBn R=1-PhEt	24 18 8		**(16)** R=Bn **(17)** R=4-MeOBn **(18)** R=1-PhEt	76 81 70
 (3)	R=Bn R=4-MeOBn R=1-PhEt	24 18 10		**(19)** R=Bn **(20)** R=4-MeOBn **(21)** R=1-PhEt	86 85 78
 (4)	R=Bn	36		**(22)** R=Bn	85
 (5)	R=Bn	24		**(23)** R=Bn	84
 (6)	R=Bn R=4-MeOBn	24 24		**(24)** R=Bn **(25)** R=4-MeOBn	0 0
 (7)	R=4-MeOBn	24		**(26)** R=4-MeOBn	0
 (8)	R=Bn R=4-MeOBn	8 8		**(27)** R=Bn **(28)** R=4-MeOBn	87 82
 (9)	R=Bn R=4-MeOBn	8 8		**(29)** R=Bn **(30)** R=4-MeOBn	80 89
 (10)	R=Bn	12		**(31)** R=Bn	83
 (11)	R=Bn	18		**(32)** R=Bn	72
 (12)	R=Bn R=4-MeOBn	12 10		**(33)** R=Bn **(34)** R=4-MeOBn	20 23
 (13)	R=Bn	10		**(35)** R=Bn	30

highly crowded enoates **8**, **9** and **11**, however, proceeded smoothly. It is thus clear that the constraining steric effects in **8** and **9** are compensated for by activation *via* both the carbonyl functionalities, leading to a lowering in the LUMO energy of the substrate and promoting 1,4-addition. This is in agreement with previous findings that highly conjugated substrates are typically more prone to cuprate additions.[14,15] Conjugate addition is presumably enhanced through rotation-restriction (e.g. enoates **9** and **11**), which establishes a more favourable orientation of the antibonding orbitals for nucleophilic addition by copper. Since no starting material was recovered, the low yields observed for the addition to lactones **12** and **13** may be attributed to *in situ* cleavage[16] of the ester functionality during workup (Scheme 2). These results are consistent with literature observations where cuprate additions to lactones occurred in low yields.[17]



Scheme 2

During extention of the above concept to other benzyl ligands it was observed that both primary and secondary benzyl groups can be successfully transfered. In comparison, both the benzyl- and 4-methoxybenzylcuprates exhibited similar reactivity, consistently giving comparable yields and reaction times, while the electron donating methoxy group in 4-MeOBnCu (entries **1-3**, **6-9**, **12**) had little effect on its reactivity. The additions of 1-PhEtCu resulted in slightly lower yields. Apart from steric inaccessability of the bulky cuprate the lower yields can also be attributed to decreased stability and increased reactivity of the reagent, as was evidenced by the reduced reaction times. The facile transfer of the oxygenated (4-MeOBn) and secondary (1-PhEtBn) benzyl groups may be of considerable advantage for further synthetic transformations.

The organocopper reagents are invariably unreactive towards α,β-unsaturated esters at -78°C. Reactions commence only at higher temperatures (-30°C), with decomposition setting in at -10°C. Thus, to establish successful addition, a good balance between reactivity and stability must be maintained. The highly effective addition reactions may be attributed to activation and stabilization of the benzylcopper reagents by TMEDA, thereby preventing decomposition of the reagent at higher temperatures. This stabilization presumably results from strong coordination between the amine (TMEDA) and the copper atom, as was evidenced by the CuI-TMEDA complex that was previously isolated and analysed.[4] Such ligand (amine) coordination occupying the vacant orbitals on copper, presumably also prevents the Wurtz-like degradation[18,19] that is commonly observed for allylic and benzylic cuprates. This stabilization results in the effective solvation of the copper reagent, whereby the electron density on copper is increased *via* electron donation by the amine nitrogens, giving a more reactive copper reagent.[4] Thus, the reactive copper species remain stable above the required activation temperature to permit the slow transfer of the benzyl ligands. In addition to the dramatic effect of the amine, TMSCl acts as a Lewis acid and decreases the LUMO energy of the enoate during coordination with the carbonyl group, thereby assisting the flow of electrons from the copper nucleophile to the substrate.[20] Alternatively, the TMSCl enhancement may be due to reaction with the enolate intermediate, thus driving the equilibrium towards product formation.[21] A synergistic effect of the TMSCl-TMEDA combination was also postulated where formation of a TMEDA-TMSCl complex increases the electrophilicity of TMSCl, hence accelerating the O-Si bond formation.[22] Since these reactions were unsuccessful in the absence of either TMEDA or TMSCl, the obvious conclusion is that both additives exert a dramatic effect on these otherwise sluggish reactions, and that they are virtually identical in their level of impact.

We have thus developed a novel method for forming relatively thermally stable benzylic cuprates. When combined with a polar additive (TMEDA) and Lewis acid (TMSCl), these reagents possess the proper reactivity profiles to efficiently deliver various benzylic ligands in a 1,4-manner to α,β-unsaturated esters. Application in the syntheses of the rodenticides, brodifacoum and diphenacoum, will be discussed elsewhere.

EXPERIMENTAL

THF was distilled from sodium benzophenone ketyl under an atmosphere of dry N_2 immediately prior to use. CuI was prepared freshly and purified by the method of Whitesides under an argon atmosphere.[23,24] Organometallic reagents were handled under argon and with dried equipment. Enoates **4-11** and **13** were prepared according to literature procedures (see results and discussion), while substrates **8-11** and **13** have been reported previously.[10,25,26] ^{1}H NMR spectra were obtained on a Bruker AM-300 FT-spectrometer at 300 MHz for solutions in $CDCl_3$ with Me_4Si as internal standard. IR spectra were recorded on a Unicam SP 100 spectrophotometer, while mass spectra were obtained on a Kratos MS-80 mass spectrometer. Melting points were obtained on a Reichert hot-stage apparatus and are uncorrected.

(E)-Methyl-4'-methoxycinnamate **4**. mp 88°C; R_f 0.43 (Hexane-Acetone 9:1); ν_{maks} (liquid film)/cm^{-1} 1713 (C=O), 1638, 1464 and 1257; ^{1}H NMR δ 7.65 (1H, d, J 15.5, H-3), 7.47 (2H, d, J 8.5, H-2',6'), 6.9 (2H, d, J 8.5, H-3',5'), 6.31 (1H, d, J 15.5, H-2), 3.83 (3H, s, OMe) and 3.8 (3H, s, OMe); *m/z* 192 (M^+, 74%), 162(11), 161(100), 134(14), 133(30), 118(12), 90(13), 89(16) and 63(13) (found M^+, 192.0787. $C_{11}H_{12}O_3$ requires M^+, 192.0786).

(E)-Ethyl-4'-bromocinnamate **5**. R_f 0.37 (Hexane-Acetone 95:5); ν_{maks} (liquid film)/cm^{-1} 1710 (C=O), 3022, 2404 and 1035; ^{1}H NMR δ 7.59 (1H, d, J 15.5, H-β), 7.49 (2H, d, J 8, H-3,5), 7.35 (2H, d, J 8, H-2,6), 6.4 (1H, d, J 15.5, H-α), 4.24 (2H, q, J 7, O$\underline{CH_2}$CH$_3$) and 1.31 (3H, t, J 7, OCH$_2\underline{CH_3}$); *m/z* 256 and 254 (M$^+$, 40 and 41%), 228(18), 226(19), 211(86), 210(10), 209(88), 184(16), 183(21), 182(22), 181(20), 131(13), 130(13), 103(15), 102(100), 101(21), 76(25), 75(29), 74(14) and 51(25) (found M$^+$, 253.9939 and 255.9920. $C_{11}H_{11}O_2Br$ requires M$^+$, 253.9942 and 255.9923).

(E)-Methyl-α-methylcinnamate **6**. mp 33°C; Rf 0.75 (Hexane-Benzene-Acetone 6:3:1); ν_{maks} (liquid film)/cm^{-1} 1722 (C=O), 3016, 2404 and 1317; ^{1}H NMR δ 7.7 (1H, q, J 1.5, H-3), 7.4-7.3 (5H, m, Ph), 3.82 (3H, s, OMe) and 2.12 (3H, d, J 1.5, 2-Me); *m/z* 176 (M$^+$, 58%), 175(20), 145(38), 121(21), 117(90), 116(100), 115(88), 91(40), 85(20), 83(28), 77(18), 65(19), 63(20), 51(22), 44(17) and 39(22) (found M$^+$, 176.0836. $C_{11}H_{11}O_2$ requires M$^+$, 176.0837).

(E/Z)-Methyl-β-methylcinnamate 7. R_f 0.51 (Hexane-Acetone 95:5); ν_{maks} (liquid film)/cm^{-1} 1716 (C=O), 3022, 2404 and 1044; ^{1}H NMR δ 7.48-7.17 (5H, m, Ph), 6.12 [1H, q, J 1.5, H-2(E)], 5.9 [1H, q, J 1.5, H-2 (Z)], 3.75 [3H, s, OMe(E)], 3.54 [3H, s, OMe(Z)], 2.57 [3H, d, J 1.5, 3-Me(E)] and 2.17 [3H, d, J 1.5, 3-Me (Z)]; *m/z* 176 (M$^+$, 72%), 175(29), 146(11), 145(100), 144(32), 135(11), 117(45), 116(28), 115(70), 102(13), 91(33), 77(13), 63(14) and 51(22) (found M$^+$, 176.0843. $C_{11}H_{12}O_2$ requires M$^+$, 176.0837).

Preparation of benzyl Grignard reagents. The benzyl halide (0.16 mol), e.g. BnCl, 4-MeOBnCl and 1-PhEt, in dry THF (40 ml) was slowly (*ca.* 1 hour) added to magnesium turnings (0.64 mol, 4 eq) and iodine (catalytic) in dry THF (60 ml) at room temperature under an argon atmosphere. After stirring for another hour, the metal alkylate solution was transfered to a flask fitted with a rubber septum and standardized.[22,27]

General procedure for the organocopper 1,4-addition of benzyl ligands to enoates. To a dry round bottom flask was added Cu(I) iodide (310 mg, 1.62 mmol, 2eq) and dry THF (8 ml). The flask was then sealed with a rubber septum, flushed with argon and dry TMEDA (0.28 ml, 1.78 mmol, 2.2 eq) was added. After the contents were stirred at room temperature for 10 minutes the flask was cooled to -78°C and the benzyl Grignard reagent (1.62 mmol, 2 eq) was added followed by stirring at -78°C for 15 minutes. TMSCl (0.52 ml, 4.06 mmol, 5 eq) and the enoate (0.812 mmol), as a solution in dry THF (4 ml), was then injected and stirring continued while the temperature was allowed to rise to -30°C. After the indicated time the cold reaction mixture was poured into a separatory funnel containing a saturated NH_4Cl-NH_4OH solution (3:2, 40 ml) and extracted with diethyl ether (2x50 ml). The combined ether extracts were then washed with H_2O (50 ml) and dried over Na_2SO_4. Concentration of the resulting ether extract and prep. TLC separation gave the pure products.

Methyl-4-phenylbutanoate **14**. R_f 0.75 (Hexane-Benzene-Acetone 6:3:1); ν_{max}(liquid film)/cm^{-1} 1725 (C=O), 2950, 1443, and 1230; ^{1}H NMR δ 7.32-7.26 (2H, m, Ph), 7.21-7.17 (3H, m, Ph), 3.65 (3H, s, OMe), 2.34 (2H, t, J 7, 2-CH$_2$), 2.65 (2H, t, J 7, 4-CH$_2$) and 2.0-1.9 (2H, m, 3-CH$_2$).

Methyl-4-(4'-methoxyphenyl)-butanoate **15**. R_f 0.62 (Hexane-Benzene-Acetone 6:3:1); ν_{maks} (liquid film)/cm^{-1} 1746 (C=O), 2944, 1443 and 1266; ^1H NMR δ 7.1 (2H, d, J 8.5, H-2',6'), 6.83 (2H, d, J 8.5, H-3',5'), 3.8 (3H, s, OMe), 3.62 (3H, s, OMe), 2.59 (2H, t, J 7, 4-CH_2), 1.97-1.87 (2H, m, 3-CH_2), 2.32 (2H, t, J 7.5, 2-CH_2); *m/z* 208 (M^+, 27%), 177(13), 135(10), 134(86), 121(100), 91(11) and 78(14) (found M^+, 208.1097. $C_{12}H_{16}O_3$ requires M^+, 208.1100).

Ethyl-3-methyl-4-phenylbutanoate **16**.[28] R_f 0.59 (Hexane-Acetone 95:5); ν_{max}(liquid film)/cm^{-1} 1728 (C=O), 2968, 1377 and 1155; ^1H NMR δ 7.31-7.25 (2H, m, Ph), 7.21-7.14 (3H, m, Ph), 4.11 (2H, q, J 7, $O\underline{CH_2}CH_3$), 2.63 (1H, dd, J 13 and 6.5) and 2.49 (1H, dd, J 13 and 7)(4-CH_2), 2.35-2.22 (2H, m, 2xCH), 2.18-2.08 (1H, m, CH), 1.25 (3H, t, J 7, $OCH_2\underline{CH_3}$) and 0.94 (3H, d, J 6.5, 3-CH_3); *m/z* 206 (M^+, 15%), 164(25), 161(25), 160(11), 119(14), 118(100), 117(18), 115(5), 91(90), 88(40), 65(13), 61(13) and 60(14).

Ethyl-4-(4'-methoxyphenyl)-3-methylbutanoate **17**. R_f 0.45 (Hexane-Acetone 9:1); ν_{maks} (liquid film)/cm^{-1} 1731 (C=O), 1506, 1323 and 1113; ^1H NMR δ 7.08 (2H,d, J 8.5, H-2',6'), 6.82 (2H, d, J 8.5, H-3',5'), 4.11 (2H, q, J 7, $O\underline{CH_2}CH_3$), 3.8 (3H, s, OMe), 2.56 (1H, dd, J 13.5 and 6.5) and 2.44 (1H, dd, J 13.5 and 7)(4-CH_2), 2.31 (1H, dd, J 13.5 and 5.5) and 2.1 (1H, dd, J 13.5 and 7)(2-CH_2), 2.29-2.19 (1H, m, H-3), 1.25 (3H, t, J 7, $OCH_2\underline{CH_3}$), 0.93 (3H, d, J 6.5, 3-CH_2); *m/z* 236 (M^+, 12%), 191(10), 148(39), 121(100) and 78(10) (found M^+, 236.1407. $C_{14}H_{20}O_3$ requires M^+, 236.1413).

Ethyl-3-methyl-4-phenylpentanoate **18** (mixture of *syn* and *anti* isomers).[29] R_f 0.62 (Hexane-Acetone 9:1); ν_{maks} (liquid film)/cm^{-1} 1731 (C=O), 1455, 1380 and 1284; ^1H NMR δ 7.32-7.24 (2H, m, Ph), 7.21-7.15 (2H, m, Ph), 4.12 [2H, q, J 7, $O\underline{CH_2}CH_3$(a)], 4.07 [2H, q, J 7, $O\underline{CH_2}CH_3$(b)], 2.7-2.6 [2H, m, H-4(a)], 2.64-2.54 [2H, m, H-4(b)], 2.44 [1H, dd, J 14.5 and 4.5, 2-CH(a)], 2.29-2.15 [3H, m, 2-CH(b) and H-3 (a+b)], 2.05 [1H, dd, J 14.5 and 9, 2-CH(a)], 1.95 [1H, dd, J 14 and 9, 2-CH(b)], 1.27 [3H, d, J 7, 5-CH_3 (a)], 1.25 [3H, d, J 7.5, 5-CH_3(b)], 1.25 [3H, t, J 7, $OCH_2\underline{CH_3}$(a)], 1.22 [3H, t, J 7, $OCH_2\underline{CH_3}$(b)], 0.97 [3H, d, J 7, 3-CH_3(b)] and 0.82 [3H, d, J 7, 3-CH_3(a)].

Methyl-3,4-diphenylbutanoate **19**. R_f 0.48 (Hexane-Acetone 9:1); ν_{max}(liquid film)/cm^{-1} 1734 (C=O), 2956, 1455 and 1146; ^1H NMR δ 7.28-7.03 (8H, m, Ph), 7.09-6.99 (2H, m, Ph), 3.52 (3H, s, OMe), 3.46-3.36 (1H, m, H-3), 2.93 (1H, dd, J 13 and 7) and 2.88 (1H, dd, J 13 and 7.5)(4-CH_2), 2.67 (1H, dd, J 15 and 6.5) and (1H, dd, J 15 and 8)(2-CH_2); *m/z* 254 (M^+, 14%), 223(6), 181(14), 180(51), 163(10), 121(100), 104(16), 103(10), 91(27) and 74(10).

Methyl-4-(4'-methoxyphenyl)-3-phenylbutanoate **20**. R_f 0.35 (Hexane-Acetone 9:1); ν_{maks} (liquid film)/cm^{-1} 1740 (C=O), 1614, 1458 and 1299; ^1H NMR δ 7.27-7.13 (5H, m, Ph), 6.95 (2H, d, J 8.5, H-2',6'), 6.75 (2H, d, J 8.5, H-3',5'), 3.75 (3H, s, OMe), 3.52 (3H, s, OMe), 3.42-3.32 (1H, m, H-3), 2.88 (1H, dd, J 13.5 and 7) and 2.82 (1H, dd, J 13.5 and 7.5)(4-CH_2), 2.67 (1H, dd, J 15.5 and 6.5) and 2.59 (1H, dd, J 15.5 and 8.5)(2-CH_2); *m/z* 284 (M^+, 7%), 122(10), 121(100), 78(9) and 77(8) (found M^+, 284.1411. $C_{18}H_{20}O_3$ requires M^+, 284.1413).

Methyl-3,4-diphenylpentanoate **21** (mixture of *syn* and *anti* isomers). R_f 0.57 (Hexane-Ethyl acetate 95:5); ν_{maks} (liquid film)/cm^{-1} 1734 (C=O), 1455, 1440 and 1158; ^{1}H NMR δ 7.36-7.08 (7H, m, Ph), 6.98-6.94 (3H, m, Ph), 3.5 (3H, s, OMe), 3.44-3.36 [1H, m, H-3(a)], 3.37 (3H, s, OMe), 3.28-3.20 [1H, m, H-3(b)], 3.1-3.0 [1H, m, H-4(a)], 2.92-2.82 [1H, m, H-4(b)], 2.78 (1H, dd, J 15 and 5.5) and 2.65 (1H, dd, J 15 and 9.5)[2-CH$_2$(a)], 2.47 (1H, dd, J 15.5 and 8.5) and 2.40 (1H, dd, J 15.5 and 5.5)[2-CH$_2$(b)], 1.29 [3H, d, J 6.5, 5-CH$_3$(a)] and 1.01 [3H, d, J 6.5, 5-CH$_3$(b)], *m/z* 268 (M$^+$, 1.3%), 121(34), 106(9), 105(100), 104(34), 103(12), 91(11), 77(15) and 51(8) (found M$^+$, 268.1475. $C_{18}H_{20}O_2$ requires M$^+$, 268.1463).

Methyl-3-(4'-methoxyphenyl)-4-phenylbutanoate **22**. R_f 0.43 (Hexane-Acetone 9:1); ν_{max}(liquid film)/cm^{-1} 1734 (C=O), 3034, 1482 and 1047; ^{1}H NMR δ 7.24-7.14 (3H, m, Ph), 7.04 (2H, d, J 8.5, H-2',6'), 7.05-7.01 (2H, m, Ph), 6.78 (2H, d, J 8.5, H-3',5'), 3.78 (3H, s, OMe), 3.53 (3H, s, OMe), 3.4-3.3 (1H, m, H-3), 2.86 (2H, d, J 7, 4-CH$_2$), 2.64 (1H, dd, J 15 and 5.5) and 2.55 (1H, dd, J 15 and 8.5)(2-CH$_2$); *m/z* 284 (M$^+$, 8%), 193(63), 152(15), 151(100), 134(20) and 91(18) (found: M$^+$, 284.1412. $C_{18}H_{20}O_3$ requires M$^+$, 284.1412).

Ethyl-3-(4'-bromophenyl)-4-phenylbutanoate **23**. R_f 0.31 (Hexane-Acetone 95:5); ν_{max}(liquid film)/cm^{-1} 1734 (C=O), 1491, 1266 and 1011; ^{1}H NMR δ 7.37 (2H, d, J 8.5, H-3',5'), 7.26-7.16 (3H, m, Ph), 7.04-7.00 (2H, m, Ph), 7.01 (2H, d, J 8.5, H-2',6'), 3.99 (2H, q, J 7, O$\underline{CH_2}$OCH$_3$), 3.43-3.33 (1H, m, H-3), 2.9 (1H, dd, J 13.5 and 7) and 2.85 (1H, dd, J 13.5 and 7.5)(4-CH$_2$), 2.66 (1H, dd, J 15.5 and 6.5) and 2.57 (1H, dd, J 15.5 and 8)(2-CH$_2$), and 1.13 (3H, t, J 7, OCH$_2\underline{CH_3}$); *m/z* 348 (M$^+$, 10%), 261(22), 260(79), 259(23), 258(84), 257(28), 255(28), 215(96), 213(100), 185(27), 184(24), 183(21), 182(23), 180(20), 179(24), 178(26), 132(28), 104(32), 103(35), 102(24), 91(99), 77(34), 65(29) and 51(22) (found M$^+$, 346.0570 and 348.0543. $C_{18}H_{19}O_2Br$ requires M$^+$, 346.0569 and 348.0549).

Ethyl-2-ethylcarboxy-3,4-diphenylbutanoate **27**. R_f 0.69 (Hexane-Benzene-Acetone 6:3:1); ν_{max} (liquid film)/cm^{-1} 1758(C=O), 1374, 1290 and 1098; ^{1}H NMR δ 7.20-7.05 (8H, m, Ph), 6.94-6.90 (2H, m, Ph), 4.25 (2H, q, J 7, O$\underline{CH_2}$CH$_3$), 3.88 (2H, q, J 7, O$\underline{CH_2}$CH$_3$), 3.79 (1H, d, J 10, H-2), 3.66 (1H, ddd, J 10.5, 10.5 and 4, H-3), 3.09 (1H, dd, J 13 and 4) and 2.83 (1H, dd, J 13 and 9.5)(4-CH$_2$), 1.31 (3H, t, J 7, OCH$_2\underline{CH_3}$) and 0.92 (3H, t, J 7, OCH$_2\underline{CH_3}$); *m/z* 340 (M$^+$, 0%), 181(22), 180(100), 179(10), 135(12), 131(25), 103(14) and 91(16).

Ethyl-2-ethylcarboxy-4-(4'-methoxyphenyl)-3-phenylbutanoate **28**. R_f 0.52 (Hexane-Benzene-Acetone 6:3:1); ν_{maks} (liquid film)/cm^{-1} 1746 (C=O), 1467, 1287 and 1098; ^{1}H NMR δ 7.23-7.13 (3H, m, Ph), 7.06-7.02 (2H, m, Ph), 6.82 (2H, d, J 8.5, H-2',6'), 6.67 (2H, d, J 8.5, H-3',5'), 4.25 (2H, q, J 7, O$\underline{CH_2}$CH$_3$), 3.87 (2H, q, J 7, O$\underline{CH_2}$CH$_3$), 3.77 (1H, q, J 10.5, H-2), 3.72 (3H, s, OMe), 3.61 (1H, ddd, J 10.5, 10 and 4, H-3), 3.03 (1H, dd, J 13 and 4) and 2.77 (1H, dd, J 13 and 10)(4-CH$_2$), 1.31 (3H, t, J 7, OCH$_2\underline{CH_3}$) and 0.92 (3H, t, J 7, OCH$_2\underline{CH_3}$); *m/z* 370 (M$^+$, 0%), 211(12), 210(55), 131(9), 122(9), 121(100) and 77(9).

4-Benzyl-3-ethylcarboxy-2-chromanone **29**. mp 63°C; R_f 0.58 (Hexane-Benzene-Acetone 6:3:1); ν_{maks} (liquid film)/cm^{-1} 1776(C=O), 1491, 1260 and 1164; ^{1}H NMR δ 7.34-7.24 (4H, m, Ph), 7.11-6.97 (5H, m, Ph), 4.07-3.95 (2H, m, $O\underline{CH_2}CH_3$), 3.75 (1H, d, J 2, H-3), 3.62 (1H, ddd, J 9, 7, and 2, H-4), 2.93 (1H, dd, J 13.5 and 7) and 2.77 (1H, dd, J 13.5 and 9)(4-$\underline{CH_2}$Ph), 1.0 (3H, t, J 7, $OCH_2\underline{CH_3}$); *m/z* 310 (M^+, 4%), 237(39), 196(40), 173,(14), 148(10), 147(100), 118(18), 91(76), 90(10), 89(13), 65(16) and 63(11) (found M^+, 310.1190. $C_{19}H_{18}O_4$ requires M^+, 310.1205).

3-Ethylcarboxy-4-(4'-methoxybenzyl)-2-chromanone **30**. mp 95°C; R_f 0.55 (Hexane-Benzene-Acetone 6:3:1); ν_{maks} (liquid film)/cm^{-1} 1782 (C=O), 1749, 1464 and 1149; ^{1}H NMR δ 7.31-7.25 (1H, m, Ph), 7.11-6.99 (2H, m, Ph), 7.02 (2H, d, J 8.5, H-2',6'), 6.84 (2H, d, J 8.5, H-3',5'), 4.08-3.94 (2H, m, $O\underline{CH_2}CH_3$), 3.8 (3H, s, OMe), 3.75 (1H, d, J 2, H-3), 3.57 (1H, ddd, J 8.5, 6.5 and 2, H-4), 2.88 (1H, dd, J 13 and 7) and 2.7 (1H, dd, J 13 and 8.5)(4-$\underline{CH_2}$*p*MeOPh), and 1.0 (3H, t, J 7, $OCH_2\underline{CH_3}$); *m/z* 340 (M^+, 3%), 122(10), 121(100), 78(7) and 77(5) (found M^+, 340.1310. $C_{20}H_{20}O_5$ requires M^+, 340.1311).

4-Benzyl-7-methoxy-2-chromanone **31**. mp 66°C; R_f 0.39 (Hexane-Benzene-Acetone 6:3:1); ν_{maks} (liquid film)/ cm^{-1} 1779(C=O), 1632, 1458 and 1131; ^{1}H NMR δ 7.31-7.21 (3H, m, Ph), 7.10-7.06 (2H, m, Ph), 6.89 (1H, d, J 8.5, H-5), 6.63-6.59 (2H, m, H-6,8), 3.8 (3H, s, OMe), 3.23-3.13 (1H, m, H-4), 2.93 (1H, dd, J 13.5 and 6.5) and 2.71 (1H, dd, J 13.5 and 8.5)(4-$\underline{CH_2}$Ph) and 2.72 (2H, d, J 4.5, 3-CH_2); *m/z* 268 (M^+, 5%), 178(12), 177(100), 121(17) and 91(18) (found M^+, 268.1100. $C_{17}H_{16}O_3$ requires M^+, 268.1100).

4-Benzyl-7-methoxy-4-methyl-2-chromanone **32**. mp 75°C; R_f 0.5 (Hexane-Benzene-Acetone 6:3:1); ν_{maks}(liquid film)/cm^{-1} 1767 (C=O), 1587, 1446 and 1125; ^{1}H NMR δ 7.25-7.21 (3H, m, Ph), 6.97 (1H, d, J 8.5, H-5), 6.90-6.86 (2H, m, Ph), 6.66 (1H, dd, J 8.5 and 2.5, H-6), 6.62 (1H, d, J 2.5, H-8), 3.8 (3H, s, OMe), 2.8 (1H, d, J 13) and 2.73 (1H, d, J 13)(4-CH_2Ph), 2.73 (1H, d, J 15.5) and 2.53 (1H, d, J 15.5)(3-CH_2) and 1.32 (3H, s, 4-CH_3); *m/z* 282 (M^+, 0.5%), 192(13), 91(21) and 65(8) (found M^+, 282.1250. $C_{18}H_{18}O_3$ requires M^+, 282.1256).

β-Benzyl-γ-butyrolactone **33**. R_f 0.17 (Hexane:Acetone 9:1); ν_{maks} (liquid film)/cm^{-1} 1782 (C=O), 3022, 1524 and 1047; ^{1}H NMR δ 7.37-7.23 (3H, m, Ph), 7.17-7.13 (2H, m, Ph), 4.33 (1H, dd, J 9 and 6.5) and 4.04 (1H, dd, J 9 and 6)(5-CH_2), 2.91-2.81 (1H, m, H-4), 2.80-2.74 (2H, m, 4-$\underline{CH_2}$Ph), 2.6 (1H, dd, J 17 and 7.5) and 2.29 (1H, dd, J 17 and 6.5)(3-CH_2); *m/z* 176 (M^+, 20%), 117(15), 92(53), 91(100), 65(130 and 39(12) (found M^+, 176.0837. $C_{11}H_{12}O_2$ requires M^+, 176.0837).

β-(4'-Methoxybenzyl)-γ-butyrolactone **34**. R_f 0.2 (Hexane-Benzene-Acetone 6:3:1); ν_{maks} (liquid film)/cm^{-1} 1776 (C=O), 1512, 1443 and 1281; ^{1}H NMR δ 7.05 (2H, d, J 8.5, H-2',6'), 6.83 (2H, d, J 8.5, H-3',5'), 4.31 (1H, dd, J 9 and 6.5) and 4.0 (1H, dd, J 9 and 6)(5-CH_2), 3.72 (3H, s, OMe), 2.85-2.75 (1H, m, H-4), 2.73-2.67 (2H, m, 4-$\underline{CH_2}$*p*MeOPh), 2.57 (1H, dd, J 17 and 7.5) and 2.26 (1H, dd, J 17 and 6.5)(3-CH_2); *m/z* 206 (M^+, 14%), 122 (100), 78(8) and 77(7) (found M^+, 206.0945. $C_{12}H_{14}O_3$ requires M^+, 206.0943).

β-Benzyl-δ-valerolactone **35**. R_f 0.3 (Hexane-Benzene-Acetone 6:3:1); ν_{maks} (liquid film)/cm^{-1} 1734 (C=O), 3010, 1221 and 678; ^{1}H NMR δ 7.34-7.20 (3H, m, Ph), 7.17-7.13 (2H, m, Ph), 4.42 (1H, ddd, J 11.5, 5 and 3.5) and 4.22 (1H, ddd, J11.5, 10.5 and 4)(6-CH_2), 2.71-2.61 (3H, m, 3-CH, 4-$\underline{CH_2}$Ph), 2.33-2.17 (2H, m, 3-CH, H-4), 1.94-1.88 (1H, m) and 1.65-1.50 (1H, m)(5-CH_2); *m/z* 190 (M^+, 10%), 117(13), 92(13), 91(100) and 65(10) (found M^+, 190.0995. $C_{12}H_{14}O_2$ requires M^+, 190.0994).

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