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Conversion of 7-Methoxy-3,4-dihydro-2*H*-1-benzopyran-2-one into the Corresponding Dimethyl Ortho Ester†

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Abstract: 7-Methoxy-3,4-dihydro-2*H*-1-benzopyran-2-one **2** was converted into 3-(2'-*tert*-butyldimethylsilyloxy-4'-methoxyphenyl)-N-methyl-N-phenylpropanamide **25** and reaction of this with methyl trifluoromethanesulfonate, followed by reaction with sodium methoxide, gave 2,2,7-trimethoxy-2*H*-1-benzopyran **1a** in 55% overall yield from **25**. A similar methylation/methoxide sequence using 3-(2'-benzyloxy-4'-methoxyphenyl)-N-methyl-N-phenylpropanamide **18** gave a mixture which contained trimethyl 3-(2'-benzyloxy-4'-methoxyphenyl)orthopropanoate **20a** and reaction of this mixture with a solution of sodium in *tert*-butanol gave a product in which 2,2,7-trimethoxy-2*H*-1-benzopyran **1a** was detected, but not isolable.

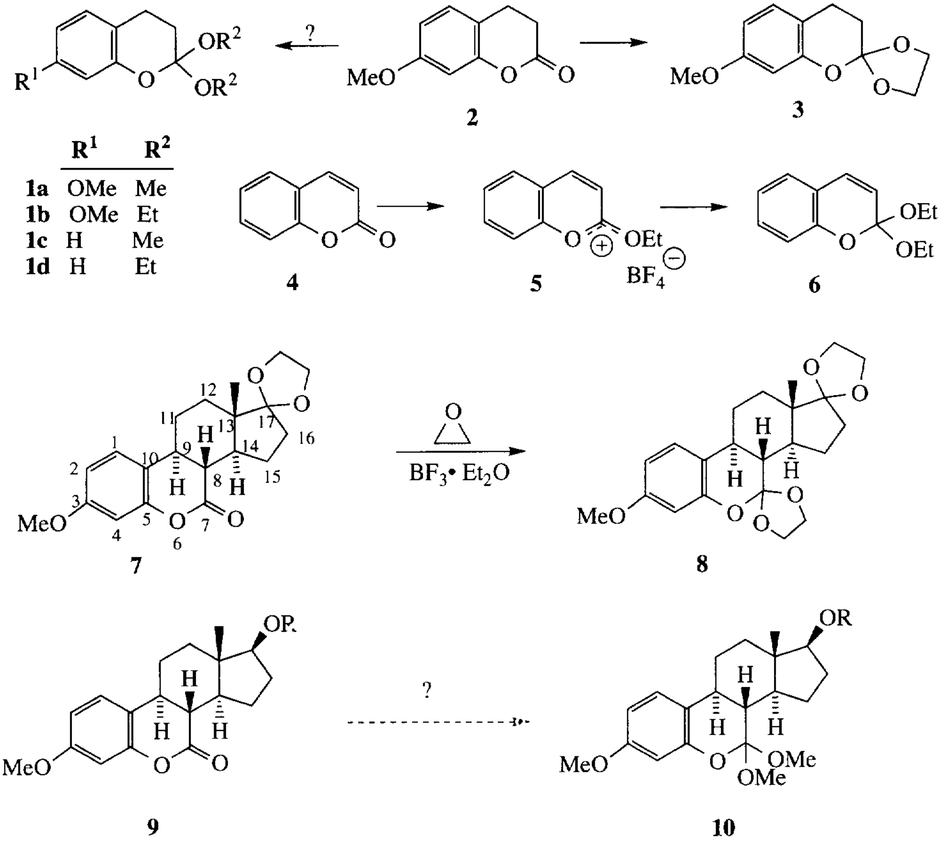
INTRODUCTION

As part of a study of potentially useful reactions of enolic ortho esters[1-3] we synthesised the 6-oxasteroidal spirocyclic ortho ester **8** (**Scheme 1**), but found that its dihydro (Birch-reduced) derivative was relatively resistant to attack at the ortho ester carbon atom by methylmagnesium halides; under forcing conditions, MgX_2-assisted attack of the Grignard reagent also occurred on the C_{17} acetal group, giving a complex mixture.[4] This was in contrast to our finding that an analogous bicyclic coumarin-derived enolic ortho ester underwent addition of methylmagnesium iodide in toluene at 40° and the resulting iodomagnesium enolate was then methylated *in situ*: this was the first reported example of tandem nucleophilic/electrophilic addition to an enolic ortho ester.[1] The low reactivity of the enolic ortho ester derived from **8** is probably due to a combination of steric and stereoelectronic (cf. Deslongchamps[5]) factors, and it was considered that the latter problem could be overcome by having a *gem*-dimethoxy group rather than an ethylenedioxy group at C7. Even though this may entail a small counterproductive increase in steric hindrance, the greater conformational freedom in a dialkyl ortho ester should enable appropriate oxygen lone pair orientation to facilitate C7-O6 cleavage.[5] In addition, it would be advantageous to have C17 at the alcohol oxidation level. Our aim therefore became to generate a 7,7-dimethoxy ortho ester of the type **10** from the corresponding 6-oxasteroidal lactone **9**.

Spirocyclic ortho esters such as **3** and **8** are readily obtained from the corresponding lactones in a single step. For example, the steroidal ortho ester **8** was generated in 42% yield[4] by treatment of the lactone **7** with ethylene oxide in the presence of boron trifluoride etherate (cf.[6,7]). Similarly, the bicyclic lactone **2** gave the ortho ester **3**, but the yield was lower (21%);[8] a much higher yield of **3** (63%) was obtained by reaction of **2**

[†] This paper is dedicated to the memory of Arthur Birch in recognition of his distinguished contributions to science, and with gratitude for stimulating years at the University of Sydney, 1953-1955 (D.J.C.)

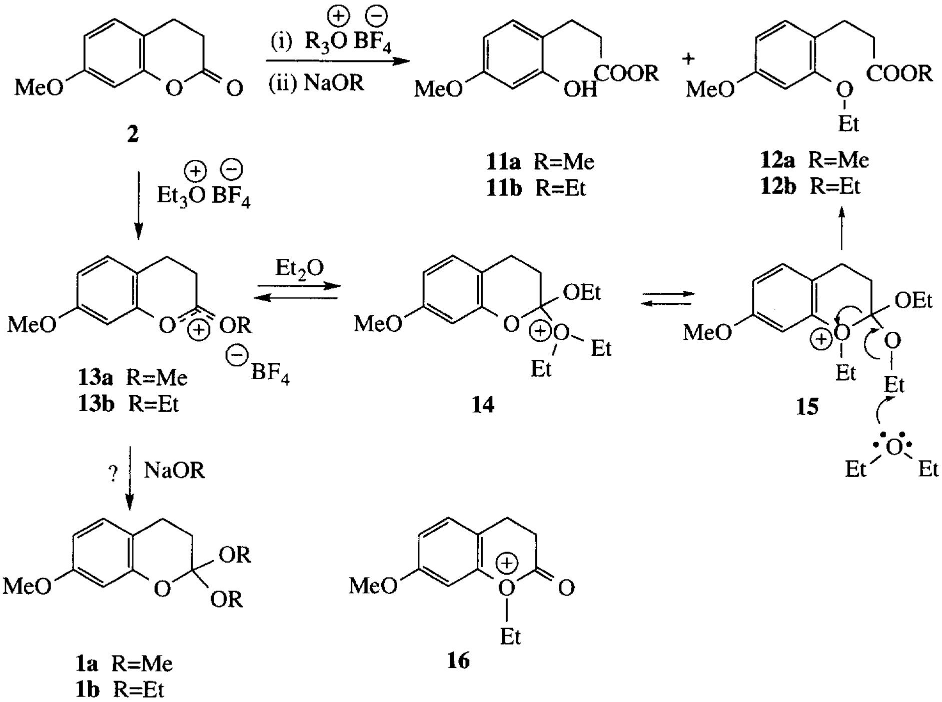
with 1,2-bis-(trimethylsilyloxy)ethane and trimethylsilyl trifluoromethanesulfonate[8] according to the procedure of Yoshimura *et al.*[9] There is no analogous single step procedure for the conversion of lactones into dialkyl ortho esters, and it was necessary to explore pathways to the model compounds **1a** or **1b** before attempting the synthesis of **10** which has the added requirement of suitable protection of the alcohol group at C17. None of the relatively simple compounds **1a-c** have hitherto been reported, but **1d** was obtained in 23% yield from the O-ethyl salt prepared from dihydrocoumarin.[10] Meerwein *et al.*[11]reported quantitative conversion of coumarin **4** into the conjugated, relative stable lactonium salt **5**, and reaction of this with sodium ethoxide gave 89% of the ortho ester **6**.[12] In this paper we describe two different routes for the conversion of 7-methoxy-3,4-dihydro-2*H*-1-benzopyran-2-one **2** into the dimethyl ortho ester **1a**.



Scheme 1

RESULTS AND DISCUSSION

The commonly used procedure for conversion of an ester or lactone into the corresponding dialkyl ortho ester is to use a powerful alkylating agent to generate an alkoxonium salt (cf. structure **13**, **Scheme 2**), then to react this with an alkoxide.[13,14] When the lactone **2** was allowed to react with triethyloxonium tetrafluoroborate for periods up to 11 days, and then the crude product was treated with sodium ethoxide, the final product was an approximately 4:1 mixture of the phenolic ester **11b** and the corresponding ethyl ether **12b**. Contrary to expectation, the alkylation step did not produce a deposit of the crystalline oxonium salt **13b**, so the yield of this must have been quite low; the relatively large amount of the phenolic ester **11b** produced, after the addition of sodium ethoxide, was formed directly from the lactone **2**. There are two puzzling aspects to the outcome of these experiments. One is that none of the expected ortho ester **1b** was formed. If **any** of the oxonium salt **13b** had been present at the time sodium ethoxide was added, some of the ortho ester **1b** should have been formed, yet generation of the ethoxy ester **12b** requires the intermediacy of an oxonium species. Meerwein *et al.*[13] observed the formation of ethoxy esters from the reactions of some simple lactones with triethyloxonium tetrafluoroborate and suggested that diethyl ether is involved, but gave no detailed mechanistic explanation. A possible rationalization is shown in **Scheme 2**. Equilibrium formation of the ether adduct **14** could be followed by rearrangement to give the 1-ethyl oxonium salt **15**, and collapse of this, possibly aided by ether as shown, could result in formation of the ethoxy ester **12b**. An alternative possible explanation, which does not involve diethyl ether, is that the ethoxy ester **12b** is formed by attack of ethoxide ion on the 1-ethyl oxonium species **16** but it is unlikely that the equilibrium concentration of **16** would be high, even though there may be some stabilization due to electron enrichment of the benzene ring by the 7-methoxy group. The former explanation seems the more likely. In retrospect, an experiment which could have been done to resolve this question was sequential treatment of the lactone **2** with triethyloxonium tetrafluoroborate and sodium methoxide: the formation of the methyl ester **12a** or the ethyl ester **12b** would be definitive. If the concentration of the species **14** at the point of addition of sodium



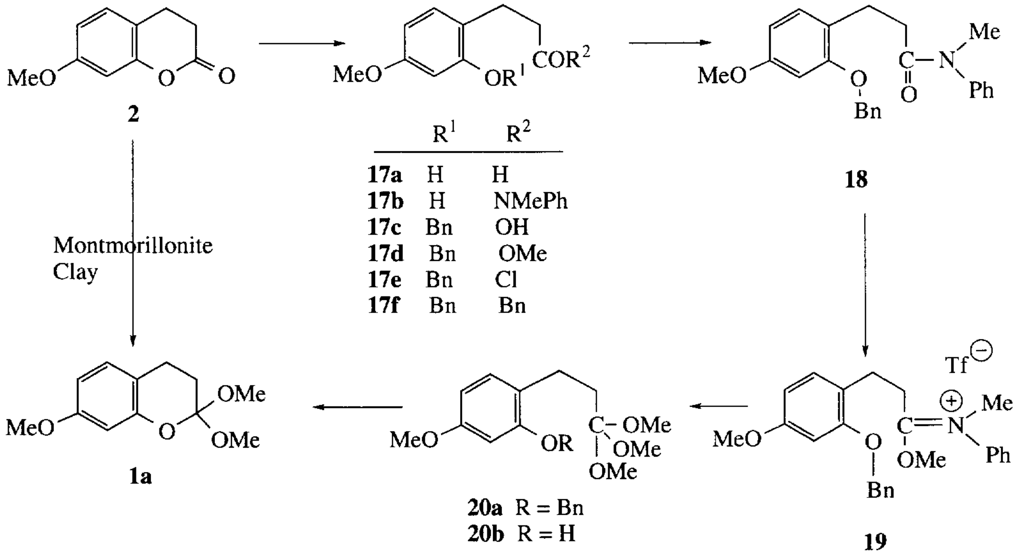
Scheme 2

ethoxide were significant, one would have expected the ortho ester **1b** to have been produced. This was not the case, and the formation of the phenolic ester **11b** as the major product would indicate that the lactone **2** was the most abundant species present at the point of addition of sodium ethoxide. Surprisingly, when the lactone **2** was treated sequentially with trimethyloxonium tetrafluoroborate and sodium methoxide the only product isolated (81%) was the phenolic ester **11a**. There was no precipitate of the methyloxonium salt **13a**, and its concentration at the point of addition of methoxide must have been very small. The ^{1}H nmr spectrum of the crude product showed no signals for the dimethyl ortho ester **1a** which was subsequently synthesised as described below.

A different approach to generation of the ortho ester **1a** involved adaptation of the procedure of McClelland *et al.*[15] who prepared ortho esters from N-methyl-N-phenyl amides via the corresponding amide acetals. In applying this strategy to the conversion of the lactone **2** to the ortho ester **1a** via the phenolic acid **17a**, the phenolic group of the latter must be suitably protected to survive the alkylation step, but the protecting group must be removable under conditions which will not hydrolyse the trialkyl ortho ester intermediate, such as, for example, **20a** (**Scheme 3**).

Reaction of the phenolic acid **17a** with benzyl chloride in the presence of potassium carbonate in dry acetone gave 79% of the benzyloxy benzyl ester **17f**, hydrolysis of which yielded the corresponding benzyloxy acid **17c**. This was more efficient than direct generation of the benzyl ether **17c** by treatment of the lactone **2** with benzyl chloride and aqueous ethanolic potassium hydroxide (general procedure of Capon *et al.*[16]) which gave a 3:2 mixture of the phenolic acid **17a** and its benzyl ether **17c**.

The acid **17c** was converted into the N-methyl-N-phenylamide **18** via the acid chloride **17e**. Reaction of the lactone **2** with N-methylaniline (or with its N-anion) gave a mixture of the phenolic amide **17b** and the phenolic acid **17a**, but the susceptibility of this mixture to revert to the lactone **2** in the presence of mild-base precluded generation of the benzyloxy amide **18** from **17b**.



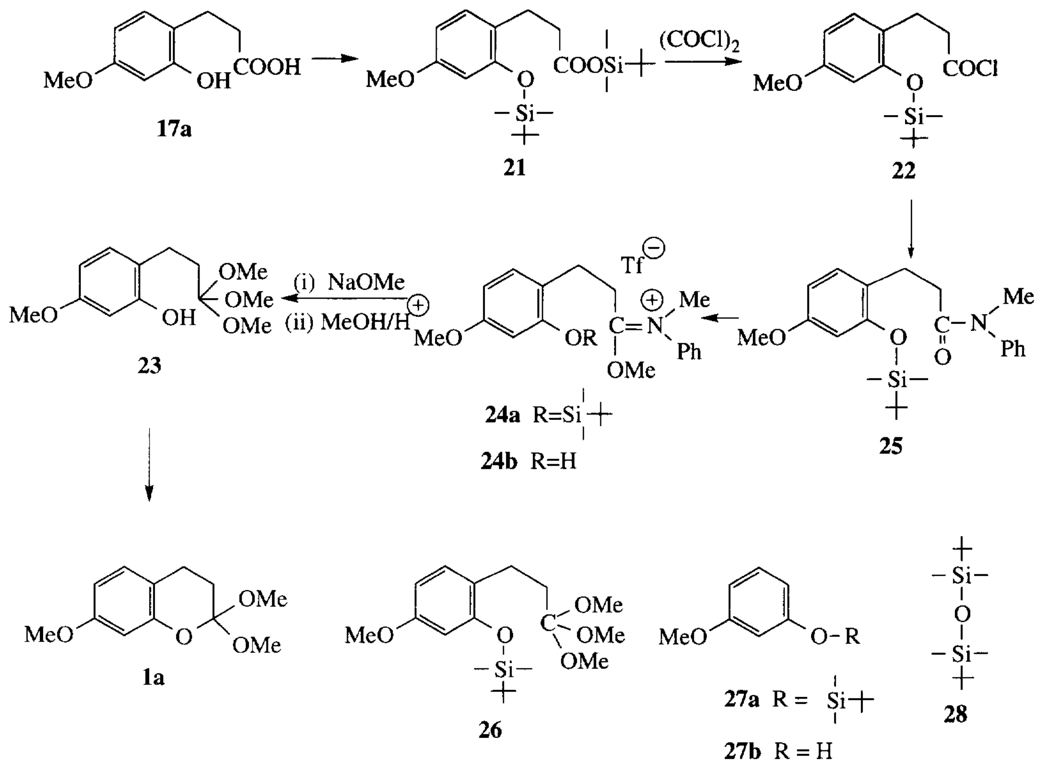
	R^1	R^2
17a	H	H
17b	H	NMePh
17c	Bn	OH
17d	Bn	OMe
17e	Bn	Cl
17f	Bn	Bn

Scheme 3

Reaction of amide **18** with methyl trifluoromethanesulfonate in dichloromethane gave no precipitate of the salt **19** but its formation was shown by the ^{1}H nmr spectrum. The crude salt **19** was treated with methanolic sodium methoxide, and the product was allowed to react with dry methanol containing glacial acetic acid. Chromatography of the oily product gave a small amount (2%) of the methyl ester **17d**, followed by an unresolved mixture of the ester **17d**, starting material **18** and the ortho ester **20a**. The ester **17d** was removed from this mixture by alkaline hydrolysis and separation of the salt of the benzyloxy acid **17c**. The ^{1}H nmr spectrum of the neutral fraction showed it to be an approximately 1:5 mixture of the starting amide **18** and the benzyloxy ortho ester **20a**, corresponding to about 47% yield of the latter.

The next step was to hydrogenolyse the benzyl ether group in **20a** so that the liberated phenolic group in (**20b**) would then effect intramolecular transesterification to give the ortho ester **1a**. In a model experiment, transfer hydrogenolysis of the benzyloxy amide **18** in boiling cyclohexene over 10% palladium/barium sulfate (cf. ref. 17) gave the phenolic amide **17b** in 90% yield, but application of the same procedure to the mixture containing the ortho ester **20a** and the amide **18** gave none of the desired ortho ester **1a**; the only products isolated were the phenolic amide **17b** and the phenolic ester **11a**. The amount of the latter corresponded to the combined amounts of the benzyloxy ester **17d** and benzyloxy ortho ester **20a** present in the starting mixture, showing that the ortho ester group in **20a** was unstable under the reaction conditions. Love and Dawson[18] reported the cleavage of aryl benzyl ethers by treatment with sodium in *tert*-butanol at 70-80°. When the mixture enriched in the benzyloxy ortho ester **20a** was treated with sodium in *tert*-butanol at 60° for 18 hours the neutral material recovered from the ether extract contained only the starting materials, but neutralisation of the residue from the evaporated aqueous phase gave a small amount of material, the ^{1}H nmr spectrum of which revealed the presence of the phenolic amide **17b**, the phenolic ester **11a** and the ortho ester **1a**. The ortho ester **1a** was identified by the signal at 3.38 ppm for the *gem*-dimethoxy group, but estimation of the content of **1a** by integration was not possible. The yield was certainly very low, and the sequence involving masking of the key phenolic group as its benzyl ether was impractical. Attention was then turned to generation of the corresponding silyloxy ortho ester **26** via the corresponding amide **25** (**Scheme 4**). It was expected that **26** could be desilylated under basic conditions, and the resulting phenolate anion would displace methoxide to give **1a**.

Reaction of the phenolic acid **17a** with *tert*-butyldimethylsilyl chloride gave the disilylated compound **21**. Wissner *et al.*[19] reported that reaction of silyl esters with oxalyl chloride in the presence of a catalytic amount of N,N-dimethylformamide gave the corresponding acid chlorides under essentially neutral conditions. Reaction of the disilylated compound **21** with oxalyl chloride generated the acid chloride **22** with the silyl ether group still intact, and treatment of this with N-methylaniline in the presence of pyridine gave the corresponding amide **25**. When the amide **25** was allowed to react with a moderate excess of methyl trifluoromethanesulfonate (~ 1.46 mol) at room temperature for 46 hours, there was no precipitate of a trifluoromethanesulfonate salt, but treatment of the product with methanolic sodium methoxide (~ 2.7 mol) at room temperature for about 2.5 hr, then reaction of the product with dry methanol containing glacial acetic gave 29% of the pure ortho ester **1a**. The other products were the phenolic amide **17b** (43%) and the phenolic ester **11a** (8%). In a similar experiment, but with 3.6 equivalents of methyl triflate for 46 hours at room temperature, and a brief reaction time (30 min) with sodium methoxide at room temperature, the products were 13% of each of the phenolic amide **17b**, and the phenolic ester **11a**, and 54% of the ortho ester **1a**. The ^{1}H nmr spectrum of **1a** showed a six-proton singlet at 3.38 ppm for the *gem*-dimethoxy



Scheme 4

group, and all of the other spectroscopic data were consistent with structure **1a**. To shed some light on the fate of the silyl ether group during the sequence **25** → **24** → **23**, 1-*tert*-butyldimethylsilyloxy-3-methoxybenzene **27a**[20] was treated with 1.1 mol of methyl trifluoromethanesulfonate in dichloromethane at room temperature for 48 h. The ^{1}H nmr spectrum of the resulting mixture showed the presence of starting material **27a**, 3-methoxyphenol **27b** and 1,3-di-*tert*-butyl-1,1,3,3-tetramethyldisiloxane **28** in the mole ratio of 1:2:1. Adventitious moisture, and hence, triflic acid is probably involved here, and some desilylation undoubtedly also occurs during the treatment of the silyloxy amide **25** with methyl triflate to give a mixture containing **24a** and **24b**. The remaining silyl ether present in **24a,b** is rapidly cleaved in the subsequent reaction with sodium methoxide. In a separate experiment, treatment of the silyloxy amide **25** with methanolic sodium methoxide for 10 mins at 0° gave only the phenolic amide **17b**. On the other hand, the silyloxy amide **25** was unaffected by treatment with glacial acetic acid in methanol at room temperature for 10 mins. These observations are consistent with the fact that none of the silyloxy ortho ester **26** was detected in any of the reactions. Some of the ortho ester (**1a**) was produced simply by treatment of (**24a**) with sodium methoxide, but the yield of (**1a**) was increased upon subsequent treatment with methanol/glacial acetic acid.

Montmorillonite clay (K-10), an aluminium silicate, has been used as a catalyst for the conversion of ketones into acetals.[21] When the lactone **2** was treated with trimethyl orthoformate in the presence of Montmorillonite a complex mixture resulted. With the authentic ortho ester **1a** in hand it was possible to detect the presence of a small amount of **1a** in this crude product, but it was not isolable.

The difficulty and inefficiency in the conversion of the lactone **2** into the dimethyl ortho ester **1a** compared with formation of the cyclic ethylene ortho ester **3** highlights the need for a new reagent for the one-pot conversion of a lactone or an ester into the corresponding dialkyl ortho ester. What is required is a reagent capable of the consequential delivery of alkoxide and a carbocation. Indeed, two such reagents are desirable, one with the propensity to deliver an alkoxide first and a carbocation second, and another which is prone to the reverse fragmentation sequence, perhaps with the assistance of an appropriate Lewis acid. For an ordinary lactone or ester the order of the provision of the two reactive species would not matter, but for a phenolic lactone such as **2** it may be necessary to deliver the carbocation first, since initial attack of alkoxide would effect cleavage with formation of the phenolate anion. This is a significant challenge.

EXPERIMENTAL

Melting points and boiling points are uncorrected. Bulb-to-bulb distillations were carried out with a Buchi GKR-50 tube oven, and only oven temperatures are given. Microanalyses were performed by Chemical and Micro Analytical Services Pty Ltd., Melbourne. Infrared spectra were measured with a Perkin-Elmer 1600 FT-IR spectrophotometer. Ultraviolet spectra were recorded with a Hitachi 150-20 spectrophotometer. ^{1}H nmr spectra were recorded at 200 mHz with a Bruker AC-200 spectrometer, or at 300 MHz with a Bruker AM-300 instrument. ^{13}C nmr spectra were recorded at 50.3 MHz or at 75.5 MHz respectively with the above instruments. Chemical shifts (δ) are measured in ppm downfield from $SiMe_4$. Mass spectra and accurate mass measurements were made at 70 eV with V.G. Micromass 7070F spectrometer. Only the molecular ion (if observed) and principal peaks with intensities > 10% are reported. Thin-layer chromatography was performed by using Polygram silica gel/UV_{254} precoated plastic sheets (0.20 mm) with fluorescent indicator UV_{254} (Merck). Flash chromatography was performed using silica gel 60, 230-400 mesh (Merck). Light petroleum refers to the fraction of boiling point 60-70°.

Triethyloxonium Tetrafluoroborate [22]

Epichlorohydrin (11.9 ml, 0.15 mol) was added dropwise to a mixture of freshly distilled boron trifluoride etherate (25.2 ml, 0.20 mol) in ether (50 ml) at a rate sufficient to maintain reflux. The mixture was heated under reflux for a further 1 h then left at room temperature overnight. The ether was evaporated under reduced pressure under an atmosphere of nitrogen to leave a white crystalline mass. This was washed with three portions (50 ml) of ether by decantation, then the solid was stored under ether (50 ml). Triethyloxonium tetrafluoroborate was collected as required by filtering the solid in a glove bag under nitrogen. ^{1}H n.m.r. δ (CD_2Cl_2) 1.61, t, *J* 7.1 Hz, 3H; 4.77, q, *J* 7.1 Hz, 2H.

*Reaction of 7-Methoxy-3,4-dihydro-2*H*-1-benzopyran-2-one (2) with Triethyloxonium Tetrafluoroborate/Sodium Methoxide*

Triethyloxonium tetrafluoroborate (0.32 g, 1.67 mmol) was added to 7-methoxy-3,4-dihydro-2*H*-1-benzopyran-2-one **2** (0.28 g, 1.67 mmol) in dichloromethane (6.0 ml) and the resulting solution was stirred under nitrogen at room temperature for 3 h. The mixture was cooled to -78° and added to a solution of sodium (0.10 g, 4.35 mmol) in ethanol (5.3 ml) at the same temperature. After 1 h the mixture was allowed to warm to room temperature and the ethanol was evaporated in vacuum. Water was added and the product was extracted with ether. The extract was washed with 5% sodium bicarbonate solution, dried (K_2CO_3) and evaporated to give an oil (0.31 g). Flash chromatography (20% ether / light petroleum) followed by bulb-to-bulb distillation (135° / 0.35 mm) afforded pure *ethyl 3-(2'-ethoxy-4'-methoxyphenyl)propanoate* **12b** (0.06 g, 16%) (Found: $M^{+\bullet}$, 252.137±0.002. $C_{14}H_{20}O_4$ requires 252.136). ν_{max} (film) 1734 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 1.23, t, *J* 7.1 Hz, $OCOCH_2$**Me**; 1.41, t, *J* 7.0 Hz, OCH_2**Me**; 2.50-2.63, m, H2,2; 2.80-2.95, m, H3,3; 3.77, s, OMe; 4.00, q, *J* 7.0 Hz, **OCH_2**Me; 4.11, q, *J* 7.2 Hz, OCO**CH_2**Me; 6.35-6.45, m, H3',5'; 7.04, d, *J* 7.9 Hz, H6'. ^{13}C n.m.r. δ ($CDCl_3$) 14.2, $OCOCH_2$**Me**; 14.8, OCH_2**Me**; 25.5, C3; 34.4, C2; 55.3, OMe; 60.1, 63.3, 2 x **OCH_2**Me; 99.1, C3'; 103.6, C5'; 121.4, C1'; 130.1, C6'; 157.6, C2' or C4'; 159.3, C4' or C2'; 173.5, C1. Mass spectrum: *m/z* 252 (M, 15%), 165 (100), 137 (35), 121 (18), 79 (13), 77 (17), 51 (11).

Further elution of the column with 40% ether / light petroleum gave a second colourless oil which upon bulb-to-bulb distillation (175° / 0.45 mm) afforded ethyl 3-(2'-hydroxy-4'-methoxyphenyl)propanoate **11b** (0.21 g, 63%). ν_{max} (film) 3397, 1732, 1705 cm^{-1} (lit.[23] 3450, 1700 cm^{-1}). ^1H n.m.r. δ ($CDCl_3$) 1.23, t, *J* 7.2 Hz, OCH_2**Me**; 2.61-2.73, m, H2,2; 2.77-2.90, m, H3,3; 3.74, s, OMe; 4.14, q, *J* 7.2 Hz, **OCH_2**Me; 6.40-6.49, m, H3',5'; 6.50-6.65, bs, OH (exch.); 6.97, d, *J* 8.1 Hz, H6'. ^{13}C n.m.r. δ ($CDCl_3$) 14.0, OCH_2**Me**; 24.0, C3; 35.4, C2; 55.2, OMe; 61.3, **OCH_2**Me; 102.6, C3'; 106.6, C5'; 119.5, C1'; 130.9, C6'; 155.3, C2'; 159.5, C4'; 175.9, C1. Mass Spectrum: *m/z* 224 (M, 13%), 178 (47), 150 (31), 137 (100), 136 (21), 124 (12), 108 (13), 79 (13), 78 (13), 77 (19), 68 (11), 65 (16), 51 (15), 41 (11). The result was essentially the same when the reaction with triethyloxonium tetrafluoroborate was carried out for extended periods (up to 11 days).

Reaction of 7-Methoxy-3,4-dihydro-2H-1-benzopyran-2-one (2) with Trimethyloxonium Tetrafluoroborate/Sodium Methoxide

A suspension of 7-methoxy-3,4-dihydro-2*H*-1-benzopyran-2-one **2** (100 mg, 0.56 mmol) and trimethyloxonium tetrafluoroborate (90 mg, 0.61 mmol) in dichloromethane (10.0 ml) was stirred under nitrogen at room temperature for 6.5 h. The mixture was cooled to -78° and added to a solution of sodium (40 mg, 1.74 mmol) in methanol (2.0 ml) at the same temperature, then stirring was continued for 1 h. The solution was allowed to warm to room temperature, 5% aqueous sodium bicarbonate was added and the mixture was extracted with dichloromethane. Evaporation of the washed, dried (K_2CO_3) extract gave a white solid which upon recrystallisation from ethanol afforded pure methyl 3-(2'-hydroxy-4'-methoxyphenyl)propanoate **11a** (95 mg, 81%), m.p. 86.5-88° (lit.[24] 88-89°). ν_{max} (Nujol) 3326, 1716 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 2.63-2.75, m, H2,2; 2.79-2.90, m, H3,3; 3.69, s, OCOMe; 3.76, s, 4'-OMe; 6.40-6.50, m, H3',5'; 6.97, d, *J* 8.3 Hz, H6'; 7.40, bs, OH (exch.). ^{13}C n.m.r. δ ($CDCl_3$) 24.2, C3; 35.1, C2; 52.2, OCO**Me**; 55.2, 4'-OMe; 102.6, C3'; 106.6, C5'; 119.5, C1'; 131.0, C6'; 155.2, C2'; 159.5, C4'; 176.2, C1.

3-(2'-Hydroxy-4'-methoxyphenyl)propanoic Acid (17a)

7-Methoxy-3,4-dihydro-2*H*-1-benzopyran-2-one **2** (10.00 g, 0.06 mol) was dissolved in ethanol (200 ml) and a solution of potassium hydroxide (9.50 g, 0.17 mol) in water (100 ml) was added. The mixture was stirred at room temperature for 90 min, the solvents were evaporated, water was added and the mixture was extracted with dichloromethane. Evaporation of the dried (Na_2SO_4) extract gave starting material (0.36 g, 3.6%). The cooled (0°) aqueous phase was acidified with 2 M hydrochloric acid, extracted with ether then dried ($MgSO_4$) and evaporated. Crystallisation of the residue from ether / light petroleum gave 3-(2'-hydroxy-4'-methoxyphenyl)propanoic acid **17a** (10.20 g, 93%), m.p. 136-137.5° (lit.[25] 91-92°) (Found: $M^{+\bullet}$, 196.074±0.002. $C_{10}H_{12}O_4$ requires 196.074). ν_{max} (Nujol) 3377, 1702 cm^{-1}. ^{1}H n.m.r. δ ($CDCl_3$) 1.95, bs, 2 x OH (exch.); 2.70-2.90, m, H2,2,3,3; 3.76, s, OMe; 6.45-6.48, m, H3',5'; 6.99, d, *J* 9.0 Hz, H6'. ^{13}C n.m.r. δ (CD_3OD, ref. MeOH) 26.4, C3; 35.4, C2; 55.5, OMe; 102.3, C3'; 105.5, C5'; 120.7, C1'; 131.4, C6'; 157.2, C2'; 160.7, C4'; 177.6, C1. Mass spectrum: *m/z* 196 (M, 4%), 179 (10), 178 (100), 150 (32), 149 (24), 137 (19), 136 (28), 121 (13), 108 (27), 107 (11), 91 (13), 79 (20), 78 (24), 77 (32), 69 (15), 65 (24), 63 (13), 51 (21). The much lower melting point reported for the phenolic acid **17a** by Kametani *et al.*[23]is probably due to contamination of their sample with some of the corresponding lactone **2**; no n.m.r. data were given for their material, and the microanalytical figures reported are consistent with the presence of a small amount of **2**.

Benzyl 3-(2'-Benzyloxy-4'-methoxyphenyl)propanoate (17f)

Benzyl chloride (7.5 ml, 0.07 mol), potassium carbonate (14.37 g, 0.10 mol) and potassium iodide (10.79 g, 0.07 mol) were added to a solution of 3-(2'-hydroxy-4'-methoxyphenyl)propanoic acid **17a** (5.10 g, 0.03 mol) in dry acetone (200 ml). The mixture was heated under reflux (nitrogen atmosphere) for 18 h then cooled and, the precipitate was collected. This was washed with acetone (200 ml), then the combined filtrate was stirred with 28% ammonium hydroxide solution (150 ml) for 3 h. The mixture was extracted with ether and the extract was washed with 0.2 M hydrochloric acid, then with water, dried (K_2CO_3) and evaporated to give a yellow oil (7.92 g). Flash chromatography (30% ether / light petroleum) and bulb-to-bulb distillation (250° / 3 mm) of the eluate afforded pure *benzyl 3-(2'-benzyloxy-4'-methoxyphenyl)propanoate* **17f** (7.73 g, 79%) as a colourless oil (Found: C, 76.3; H, 6.3. $C_{24}H_{24}O_4$ requires C, 76.6; H, 6.4%). λ_{max} (EtOH) 277 nm (ε 9720), 225 (15100). ν_{max} (film) 1735 cm^{-1}. ^{1}H n.m.r. δ ($CDCl_3$) 2.63-2.71, m, H2,2; 2.92-3.00, m, H3,3; 3.76, s, OMe; 5.05, s, $\mathbf{OCH_2}$Ph; 5.09, s, $\mathbf{OCH_2}$Ph; 6.40, dd, *J* 8.2, 2.4 Hz, H5'; 6.49, d, *J* 2.4 Hz, H3'; 7.05, d, *J* 8.2 Hz, H6'; 7.28-7.43, m, 10 aromatic H. ^{13}C n.m.r. δ ($CDCl_3$) 25.7, C3; 34.4, C2; 55.2, OMe; 65.9, OCO$\mathbf{CH_2}$Ph; 69.7, $\mathbf{OCH_2}$Ph; 99.7, C3'; 104.1, C5'; 121.3, C1'; 127.0, 127.7, 128.0, 128.1, 128.4, 128.5, 130.3, C6' and 6 aromatic C (benzyl); 136.1, quaternary C (benzyl ester); 137.0, quaternary C (benzyl ether); 157.3, C2'; 159.4, C4'; 173.1, C1. Mass spectrum: *m/z* 376 (M, 6%), 91 (100).

3-(2'-Benzyloxy-4'-methoxyphenyl)propanoic Acid (17c)

A 10% Sodium hydroxide solution (125 ml) was added to a solution of benzyl 3-(2'-benzyloxy-4'-methoxyphenyl)propanoate **17f** (6.95 g, 18.5 mmol) in methanol (125 ml). The mixture was stirred at room temperature for 75 h then the solvents were evaporated in vacuum. Water was added and the mixture was extracted with ether. Evaporation of the dried (K_2CO_3) extract gave starting material (0.12g, 2%). The chilled aqueous layer (0°) was acidified with 2 M hydrochloric acid then extracted with ether. Evaporation of the washed, dried ($MgSO_4$) extract gave a yellow gum (5.18 g) which crystallised from ether / light petroleum to afford *3-(2'-benzyloxy-4'-methoxyphenyl)propanoic acid* **17c** (4.86 g, 92%), m.p. 109-110° (Found: C, 71.3; H, 6.3. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%). ν_{max} (Nujol) 1705 cm^{-1}. ^{1}H n.m.r. δ [$(D_3C)_2SO$] 2.40-2.55, m, H2,2; 2.70-2.82, m, H3,3; 3.71, s, OMe; 5.12, s, $\mathbf{CH_2}$Ph; 6.44, dd, *J* 8.3, 2.3 Hz, H5'; 6.61, d, *J* 2.2 Hz, H3'; 7.06, d, *J* 8.3 Hz, H6'; 7.32-7.48, m, 5 aromatic H; 11.25, s, OH (exch.). ^{13}C n.m.r. δ ($CDCl_3$) 25.3, C3; 34.3, C2; 55.3, OMe; 69.7, $\mathbf{OCH_2}$Ph; 99.7, C3'; 104.2, C5'; 121.2, C1'; 127.0, 127.8, 128.6, 130.3, C6' and 3 aromatic C (benzyl); 137.0, quaternary C (benzyl); 157.3, C2'; 159.4, C4'; 180.0, C1. Mass spectrum: *m/z* 286 (M, 12%), 91 (100).

Preparation of 3-(2'-Benzyloxy-4'-methoxyphenyl)propanoic Acid (17c) from the Lactone (2)

A solution of potassium hydroxide (0.48 g, 8.55 mmol) in water (5 ml) was added to a solution of 7-methoxy-3,4-dihydro-2*H*-1-benzopyran-2-one **2** (0.50 g, 2.81 mmol) in ethanol (10 ml), and the mixture was stirred until it was homogeneous. A solution of benzyl chloride (0.2 ml, 1.74 mmol) in ethanol (1 ml) was then added and stirring was continued for 90 min; additional benzyl chloride (0.2 ml, 1.74 mmol) was then added. After a further 60 min the mixture was extracted with dichloromethane. The aqueous phase was cooled to 0° and acidified with 2 M hydrochloric acid then extracted with ether. Evaporation of the dried ($MgSO_4$) extract gave a white solid (0.55 g). The ^1H n.m.r. spectrum of this showed it to consist of a 3 : 2 mixture of 3-(2'-hydroxy-4'-methoxyphenyl)propanoic acid **17a** and 3-(2'-benzyloxy-4'-methoxyphenyl)propanoic acid **17c**, respectively identical with **17a** and **17c** described above.

*Preparation of 3-(2'-Hydroxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide (17b) from the Lactone (2)*

(i) Using N-methylaniline. *N*-methylaniline (0.13 ml, 1.20 mmol) was added to a solution of 7-methoxy-3,4-dihydro-2*H*-1-benzopyran-2-one **2** (0.20 g, 1.12 mmol) in toluene (10 ml) and the mixture was heated at reflux under nitrogen for 43 h. The mixture was cooled then ether was added and the product was extracted into 5% sodium hydroxide solution. Evaporation of the dried (K_2CO_3) organic phase gave starting material (50 mg, 25%). The basic aqueous extract was cooled to 0°, acidified with concentrated hydrochloric acid, then extracted with dichloromethane. The extract was washed with water, dried (Na_2SO_4) and evaporated to give a yellow solid. Flash chromatography (50% ether / light petroleum) gave pure *3-(2'-hydroxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide* **17b** (190 mg, 59%), m.p. 98.5-101° (Found: $M^{+\bullet}$, 285.137±0.003. $C_{17}H_{19}NO_3$ requires 285.136). ν_{max} (KBr) 3100 (broad, unresolved OH), 1640, 1605 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 2.34-2.55, m, H2,2; 2.69-2.83, m, H3,3; 3.25, s, NMe; 3.75, s, OMe; 6.37, dd, *J* 8.3, 2.6 Hz, H5'; 6.52, d, *J* 2.6 Hz, H3'; 6.79, d, *J* 8.4 Hz, H6'; 7.06-7.11, m, N-phenyl (H3",5"); 7.36-7.42, m, N-phenyl (H2",4",6"); 9.52, bs, OH (exch.). ^{13}C n.m.r. δ ($CDCl_3$) 24.2, C3; 36.7, C2; 37.9, NMe; 55.3, OMe; 102.9, C3'; 106.6, C5'; 120.4, C1'; 127.2, 128.4, 130.1, 131.1, C6' and N-phenyl (C2",3",4",5",6"); 143.2, N-phenyl (C1"); 156.3, C2'; 159.6, C4'; 174.7, C1. Mass Spectrum: *m/z* 285 (M, 7%), 137 (28), 108 (11), 107 (100), 106 (11).

(ii) Using sodium *N*-methylanilide. Sodium hydride (40 mg of an 80% dispersion in oil, 1.33 mmol) was added to a solution of *N*-methylaniline (0.12 ml, 1.11 mmol) in tetrahydrofuran (2 ml) and the mixture was heated under reflux for 1 h under nitrogen. The mixture was cooled to room temperature and a solution of the lactone **2** (0.10 g, 0.56 mmol) in tetrahydrofuran (2 ml) was added. Refluxing was continued for 45 min, then the mixture was cooled to room temperature, and 2 M sulfuric acid and ether were added. The extract was washed with 2 M sulfuric acid, then with water, dried (Na_2SO_4) and evaporated to give an orange oil (150 mg). The ^1H n.m.r. spectrum showed this to be a 3 : 1 mixture of 3-(2'-hydroxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide **17b** and 3-(2'-hydroxy-4'-methoxyphenyl)propanoic acid **17a**, respectively. Crystallisation of this mixture from ethanol or ether / light petroleum gave a white solid enriched in the phenolic acid **17a** (^1H n.m.r. spectrum).

*3-(2'-Benzyloxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide (18)*

Thionyl chloride (0.70 ml, 9.60 mmol) was added dropwise to a solution of 3-(2'-benzyloxy-4'-methoxyphenyl)propanoic acid **17c** (1.25 g, 4.37 mmol) in tetrahydrofuran (120 ml) and the mixture was heated at reflux for 5 h under nitrogen. The solvent and excess of thionyl chloride were removed under reduced pressure to give the crude acid chloride **17e,** ν_{max} 1800s cm^{-1}. This was dissolved in tetrahydrofuran (120 ml), N-methylaniline (0.70ml, 6.46 mmol) was added and the solution was stirred at room temperature under nitrogen for 17 h. Water was added and the mixture was extracted with ether. The extract was washed sequentially with 1 M hydrochloric acid, water, a 5% sodium hydroxide solution, water, then dried (Na_2SO_4) and evaporated to give a yellow solid. Recrystallisation from ether / light petroleum gave pure *3-(2'-benzyloxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide* **18** (1.24 g, 76%), m.p. 73-76° (Found: C, 77.2; H, 7.1; N, 3.6. $C_{24}H_{25}NO_3$ requires C, 76.8; H, 6.7; N, 3.7%). ν_{max} (Nujol) 1653, 1614 cm^{-1}. ^{1}H n.m.r. δ ($CDCl_3$) 2.33-2.41, m, H2,2; 2.86-2.94, m, H3,3; 3.21, s, NMe; 3.73, s, OMe; 4.87, s, $\mathbf{OCH_2}$Ph; 6.35-6.40, m, H3',5'; 6.93-6.96, m, N-phenyl (H3",5"); 7.02, d, J 8.3 Hz, H6'; 7.22-7.38, m, N-phenyl (H2",4",6") and 5 aromatic H (OCH_2**Ph**). ^{13}C n.m.r. δ ($CDCl_3$) 26.4, C3; 34.2, C2; 37.3, NMe; 55.3, OMe; 69.6, $\mathbf{OCH_2}$Ph; 99.5, C3'; 104.0, C5'; 122.1, C1'; 127.1, 127.3, 127.5, 127.8, 128.5, 129.5, 130.5, C6', N-phenyl (C2",3",4",5",6") and 3 aromatic C (benzyl); 137.1, quatenary C (benzyl); 144.1, quaternary C (N-**Ph**); 157.4, C2'; 159.3, C4'; 172.8, C1. Mass spectrum: m/z 375 (M, 2%), 284 (12), 177 (23), 160 (18), 134 (22), 107 (18), 106 (15), 91 (100), 77 (15).

Acidification of the basic washings, extraction of the mixture with ether and evaporation gave starting material **17c** (0.23g, 18%).

*Preparation of 3-(2'-Hydroxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide (17b) by Hydrogenolysis of Compound (18)*

A mixture containing 3-(2'-benzyloxy-4'-methoxyphenyl)-N-methyl-N-phenylpropanamide **18** (50 mg, 0.13 mmol), dry cyclohexene (1.0 ml, 9.87 mmol) and 10% palladium on barium sulfate (25 mg) in methanol (2.5 ml) was heated at reflux for 5 h under nitrogen. The cooled mixture was filtered through a pad of Celite, which was washed with methanol. Evaporation of the combined filtrate gave a yellow solid which was shown by its ^{1}H n.m.r. spectrum to be 3-(2'-hydroxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide **17b** (45 mg, 90%).

Trimethyl 3-(2'-Benzyloxy-4'-methoxyphenyl)orthopropanoate (20a)

Methyl trifluoromethanesulfonate (1.02 ml, 9.01 mmol) was added dropwise to a solution of 3-(2'-benzyloxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide **18** (2.50 g, 6.66 mmol) in dichloromethane (5.5 ml) and the solution was stirred under nitrogen for 44.5 h. Addition of ether (30 ml) failed to precipitate the trifluoromethanesulfonate salt **19** even though the ^{1}H n.m.r. spectrum showed it was the major product: δ ($CDCl_3$) 2.69-2.76, m, 2H; 2.83-2.89, m, 2H; 3.43, s, COMe; 3.78, s, 4'-OMe; 4.01, s, $^+$NMe; 4.88, s, OCH_2Ph; 6.38, dd, J 8.3, 2.4 Hz, H5'; 6.51, d, J 2.3 Hz, H3'; 6.72, d, J 8.3 Hz, H6'; 7.10-7.45, m, 10 aromatic H. The solvents were removed in vacuum and the residual gum was dissolved in dichloromethane (5.5 ml). This solution was cooled (0°) and added dropwise to an ice-cold solution of sodium (0.41 g, 17.8 mmol) in methanol (11 ml) and the mixture was stirred at 0° for 10 min, then allowed to warm to room temperature and stirred for a further 30 min. The solvents were removed in vacuum and light petroleum (50 ml) was added to precipitate the excess of sodium methoxide and sodium trifluoromethanesulfonate. This was filtered and washed with light petroleum (25 ml) then with dichloromethane (10 ml). Evaporation of the combined filtrate gave a white gum (2.83 g). This was dissolved in methanol (10 ml), glacial acetic acid (0.42 ml, 7.34 mmol) was added, and the mixture was stirred at room temperature for 10 min. Potassium carbonate (2.50 g, 17.8 mmol) was added to destroy the excess of acid, then the methanol was evaporated, water was added, and the product was extracted with ether. Evaporation of the washed, dried (K_2CO_3) extract gave a yellow oil (2.22 g). A portion of this oil (1.00 g) was subjected to chromatography over basic alumina (Activity I) (10% ether / light petroleum) to give *N*-methylaniline followed by methyl 3-(2'-benzyloxy-4'-methoxyphenyl)propanoate (**17d**) (0.02 g, 2%) as a yellow oil (Found: $M^{+\bullet}$, 300.136±0.002. $C_{18}H_{20}O_4$ requires 300.136). ν_{max} (film) 1737 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 2.58-2.70, m, H2,2; 2.90-3.01, m, H3,3; 3.65, s, OCOMe; 3.77, s, 4'-OMe; 5.07, s, **OCH_2Ph**; 6.43, dd, *J* 8.2, 2.4 Hz, H5'; 6.50, d, *J* 2.4 Hz, H3'; 7.08, d, *J* 8.2 Hz, H6'; 7.30-7.50, m, 5 aromatic H. ^{13}C n.m.r. δ ($CDCl_3$) 25.7, C3; 34.4, C2; 51.5, OCO**Me**; 55.4, 4'-OMe; 69.9, **OCH_2**Ph; 99.8, C3'; 104.3, C5'; 121.6, C1'; 127.1, 127.9, 128.6, 130.3, C6' and 3 aromatic C (benzyl); 137.2, quaternary C (benzyl); 157.4, C2'; 159.5, C4'; 173.9, Cl. Mass Spectrum: m/z 300 (M, 23%), 209 (26), 177 (22), 105 (14), 92 (18), 91 (100), 65 (19).

Further elution (20% ether / light petroleum) gave a mixture of the ester **17d**, starting material **18** and trimethyl 3-(2'-benzyloxy-4'-methoxyphenyl)orthopropanoate **20a**. This was dissolved in 2.5% methanolic potassium hydroxide (2.0 ml), water (60 μl) was added and the mixture was heated under reflux for 2 h. This was cooled and the methanol was evaporated, water was added, and the product was extracted with ether. Acidification of the aqueous phase with 2 M hydrochloric acid then re-extraction with ether gave 3-(2'-benzyloxy-4'-methoxyphenyl)propanoic acid **17c** (0.01 g, 1%), identical with the material described above.

The initial ethereal extract was dried (K_2CO_3) and evaporated, then bulb-to-bulb distillation (175°/0.09 mm) of the residue (0.7 g) afforded an oil (0.60 g). The ^1H n.m.r. spectrum of this showed it to consist of the starting material **18** (calculated mass 0.11 g, 10%) and trimethyl 3-(2'-benzyloxy-4'-methoxyphenyl)orthopropanoate **20a** (calculated mass 0.49 g, 47%) from which the spectral data for the ortho ester could be assigned as, ^1H n.m.r. δ ($CDCl_3$) 1.90-2.03, m, H2,2; 2.53-2.65, m, H3,3; 3.15, s, $C(OMe)_3$; 3.78, s, 4'-OMe; 5.02, s, **OCH_2**Ph; 6.43, dd, *J* 8.2, 2.4 Hz, H5'; 6.52, d, *J* 2.4 Hz, H3'; 7.07, d, *J* 8.2 Hz, H6'; 7.28-7.50, m, 5 aromatic H. ^{13}C n.m.r. δ ($CDCl_3$) 24.1, C2 or C3; 30.7, C3 or C2; 49.1, C(**OMe**)$_3$; 55.3, 4'-OMe; 70.0, **OCH_2**Ph; 99.5, C3'; 104.1, C5'; 115.6, C1; 122.6, C1'; 127.8, 128.0, 128.4, 130.2, C6' and 3 aromatic C (benzyl); 136.8, quaternary C (benzyl); 157.5, C2'; 159.2, C4'.

The residue from the bulb-to-bulb distillation was shown by its ^1H n.m.r. spectrum to be starting material **18** (0.10 g, 10%).

Debenzylation of Trimethyl 3-(2'-Benzyloxy-4'-methoxyphenyl)orthopropanoate (20a)

(i) By transfer hydrogenation A mixture containing trimethyl 3-(2'-benzyloxy-4'-methoxyphenyl)orthopropanoate **20a** (27 mg, 0.08 mmol), 3-(2'-benzyloxy-4'-methoxyphenyl)-N-methyl-N-phenylpropanamide **18** (11.5 mg, 0.03 mmol), methyl 3-(2'-benzyloxy-4'-methoxyphenyl)propanoate **17d** (1.5 mg, 0.01 mmol) and N-methylaniline (10 mg, 0.09 mmol) was dissolved in methanol (2.5 ml). Dry cyclohexene (1.0 ml, 9.87 mmol) and 10% palladium on barium sulfate (25 mg) were added and the mixture was heated at reflux for 5 h under nitrogen. The mixture was cooled and filtered through a pad of Celite which was washed with methanol. Evaporation of the combined filtrate gave a yellow solid (25 mg) which was shown by its ^1H n.m.r. spectrum to contain only a 1:3 mixture of 3-(2'-hydroxy-4'-methoxyphenyl)-*N*-

methyl-*N*-phenylpropanamide **17b** and methyl 3-(2'-hydroxy-4'-methoxyphenyl)propanoate **11a** respectively. A similar reaction carried out at room temperature for 26 h gave only starting materials.

(ii) By radical reduction The same mixture containing the ortho ester **20a** (54 mg, 0.16 mmol), the amide **18** (23 mg, 0.06 mmol), the ester **17d** (3 mg, 0.02 mmol) and N-methylaniline (20 mg, 0.09 mmol) was dissolved in dry *tert*-butanol (0.5 ml) then the mixture was heated under nitrogen to 60°. Sodium (5.6 mg, 0.24 mmol) was added and the mixture was stirred for 30 min at 60° then for a further 120 min at room temperature. More sodium (7.5 mg, 0.33 mmol) was added and the mixture was stirred again at 60° for 18 h. The solution was cooled, water (1 ml) was added then the mixture was extracted with ether. Evaporation of the dried (K_2CO_3) extract gave an orange oil (60 mg), the ^1H n.m.r. spectrum of which showed only starting materials. The aqueous phase was evaporated to give an orange solid (50 mg). This was dissolved in methanol (2.0 ml) and glacial acetic acid (15 μl, 0.26 mmol) was added. The mixture was stirred at room temperature for 30 min then potassium carbonate (70 mg, 0.51 mmol) was added. The solvent was evaporated in vacuum, water was added, and the mixture was extracted with ether. Evaporation of the dried (K_2CO_3) extract gave a yellow oil (7 mg), the ^1H n.m.r. spectrum of which showed the presence of 3-(2'-hydroxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide **17b**, methyl 3-(2'-hydroxy-4'-methoxyphenyl)propanoate **11a** and 2,2,7-trimethoxy-2*H*-1-benzopyran **1a**, identical with the material described below.

t-Butyldimethylsilyl 3-(2'-t-Butyldimethylsilyloxy-4'-methoxyphenyl)propanoate **(21)**

3-(2'-Hydroxy-4'-methoxyphenyl)propanoic acid **17a** (4.10 g, 0.02 mol) was dissolved in dry N,N-dimethylformamide (17.5 ml), then imidazole (5.70 g, 0.08 mol) and t-butyldimethylsilyl chloride (8.20 g, 0.05 mol) were added and the mixture was stirred under nitrogen at 60° for 71 h. Additional t-butyldimethylsilyl chloride (1.00 g, 0.07 mol) was added and stirring was continued for a further 45 h. The mixture was cooled, water was added, and the product was extracted with ether. The extract was washed with a saturated sodium bicarbonate solution and water, then dried ($MgSO_4$) and evaporated. Bulb-to-bulb distillation of the residue (165° / 0.4 mm) afforded pure *t-butyldimethylsilyl 3-(2'-t-butyldimethylsilyloxy-4'-methoxyphenyl)propanoate* **21** (8.60 g, 97%) as a colourless oil (Found: C, 62.3; H, 9.9. $C_{22}H_{40}O_4Si_2$ requires C, 62.2; H, 9.5%). ν_{max} (Nujol) 1726 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$, $CHCl_3$ ref 7.26) 0.24, apparent s, 2 x $SiMe_2$; 0.91, s, CMe_3 (of silyl ether); 1.00, s, CMe_3 (of silyl ester); 2.52-2.63, m, H2,2; 2.78-2.90, m, H3,3; 3.75, s, OMe; 6.36, d, *J* 2.5 Hz, H3'; 6.43, dd, *J* 8.3, 2.5 Hz, H5'; 7.03, d, *J* 8.3 Hz, H6'. ^{13}C n.m.r. δ ($CDCl_3$, $CHCl_3$ ref 77.1) -4.8, -4.1, 2 x $SiMe_2$; 17.6, 18.2, 2 x CMe_3; 25.6, 25.8, 2 x $C\mathbf{Me_3}$; 26.0, C3; 36.4, C2; 55.2, OMe; 105.4, C3' or C5'; 105.6, C5' or C3'; 123.6, C1'; 130.2, C6'; 154.4, C2'; 159.0, C4'; 173.8, C1. Mass spectrum: m/z 424 (M, < 1%), 368 (12), 367 (42), 352 (27), 252 (12), 251 (51), 195 (16), 193 (13), 147 (22), 134 (26), 121 (11), 75 (37), 74 (18), 73 (100), 59 (17), 57 (13).

3-(2'-t-Butyldimethylsilyloxy-4'-methoxyphenyl)-N-methyl-N-phenylpropanamide **(25)**

t-Butyldimethylsilyl 3-(2'-*t*-butyldimethylsilyloxy-4'-methoxyphenyl)propanoate **21** (5.00 g, 11.7 mmol) was dissolved in dichloromethane (2 ml), *N,N*-dimethylformamide (3 drops) was added and the solution was cooled to 0°. Oxalyl chloride (1.6 ml, 18 mmol) was added dropwise under nitrogen and the mixture was stirred at 0° for 1.5 h, then at room temperature for 3 h. The solvents were evaporated at room temperature under reduced pressure to give crude *3-(2'-t-butyldimethylsilyloxy-4'-methoxyphenyl)propanoyl* *chloride* **22**. ν_{max} (film) 1803 cm^{-1}. ^{1}H n.m.r. (CDCl$_3$) 0.26, s, SiMe; 0.27, s, SiMe; 1.01, s, CMe$_3$; 2.83-2.95, m, H2,2; 3.10-3.20, m, H3,3; 3.76, s, OMe; 6.39, d, *J* 2.4 Hz, H3'; 6.45, dd, *J* 8.3, 2.5 Hz, H5'; 7.04, d, *J* 8.3 Hz, H6'.

The acid chloride **22** was dissolved in ether (6.5 ml), pyridine (3.0 ml, 37 mmol) and *N*-methylaniline (3.0 ml, 28 mmol) were added and the solution was stirred at room temperature for 17 h. The ether was evaporated, water was added and the product was extracted with dichloromethane. The extract was washed sequentially with 1 M hydrochloric acid, 5% aqueous sodium hydroxide, and water, then dried (MgSO$_4$) and evaporated to yield a yellow oil. Bulb-to-bulb distillation (160° / 10 mm) afforded pure *3-(2'-t-butyldimethylsilyloxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide* **25** (4.14 g, 95%) as a colourless oil (Found: C, 68.7; H, 8.7; N, 3.8. $C_{23}H_{33}NO_3Si$ requires C, 69.1; H, 8.3; N, 3.5%). ν_{max} (film) 1660 cm^{-1}. ^{1}H n.m.r. δ (300 MHz, CDCl$_3$, CHCl$_3$ ref 7.26) 0.15, s, SiMe$_2$; 0.91, s, CMe$_3$; 2.22-2.39, m, H2,2; 2.72-2.88, m, H3,3; 3.23, s, NMe; 3.73, s, OMe; 6.29, d, *J* 2.4 Hz, H3'; 6.40, dd, *J* 8.3, 2.5 Hz, H5'; 6.97, m, H6' and N-phenyl (H3",5"); 7.27-7.38, m, N-phenyl (H2",4",6"). ^{13}C n.m.r. δ (CDCl$_3$, CHCl$_3$ ref 77.1) -4.2, SiMe$_2$; 18.1, CMe$_3$; 25.7, **CMe$_3$**; 26.3, C3; 34.3, C2; 37.2, NMe; 55.2, OMe; 105.2, C3' or C5'; 105.3, C5' or C3'; 124.1, C1'; 127.2, 127.5, 129.6, 130.6, C6' and N-phenyl (C2",3",4",5",6"); 144.0, N-phenyl (C1"); 154.3, C2'; 158.8, C4'; 172.6, C1. Mass spectrum: m/z 399 (M, 11%), 343 (26), 342 (100), 73 (17).

*2,2,7-Trimethoxy-2*H*-1-benzopyran (1a)*

Methyl trifluoromethanesulfonate (1.0 ml, 9.12 mmol) was added dropwise to a solution of 3-(2'-*t*-butyldimethylsilyloxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide **25** (2.50 g, 6.26 mmol) in dichloromethane (6.0 ml) and the solution was stirred under nitrogen for 45 h. Addition of ether (30 ml) failed to afford any precipitate, so the solvents were removed in vacuum and the residual gum was dissolved in dichloromethane (6.0 ml). This solution was added dropwise to a cooled (0°) solution of sodium (0.39 g, 16.7 mmol) in methanol (11.5 ml) and the mixture was stirred for 10 min, then allowed to warm to room temperature and stirred for a further 2.25 h. The solvents were removed under vacuum and light petroleum (50 ml) was added to precipitate the excess of sodium methoxide and sodium trifluoromethanesulfonate. This was filtered and washed with light petroleum then with dichloromethane, and evaporation of the combined filtrate gave a white gum (2.59 g). This was dissolved in methanol (20 ml), glacial acetic acid (0.45 ml, 7.86 mmol) was added and the mixture was stirred at room temperature for 10 min. Potassium carbonate (3.50 g, 25.3 mmol) was added to destroy the excess of acid, the methanol was evaporated then water was added and the mixture was extracted with ether. The extract was washed with 5% sodium hydroxide solution then with water, dried (K$_2$CO$_3$) and evaporated to give a yellow oil (1.59 g). Bulb-to-bulb distillation of this (145° / 0.125 mm) gave a forerun of *N*-methylaniline followed by pure *2,2,7-trimethoxy-2*H*-1-benzopyran* **1a** (0.40 g, 29%) (Found: C, 64.6; H, 7.6. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.2%). ν_{max} (film) 2948s, 2838m, 1625s, 1587s, 1507s, 1465m, 1444s, 1359m, 1338w, 1318m, 1302m, 1271s, 1247m, 1225s, 1202s, 1160s, 1126s, 1113s, 1093s, 1074s, 1035s, 992m, 960m, 916m, 890w, 876m, 834w, 801w, 741w cm^{-1}. ^{1}H n.m.r. δ (CDCl$_3$) 2.07, t, *J* 6.9 Hz, H3,3; 2.78, t, *J* 6.8 Hz, H4,4; 3.38, s, 2-(OMe)$_2$; 3.76, s, 7-OMe; 6.47, d, *J* 2.9 Hz, H8; 6.50, dd, *J* 8.1, 2.9 Hz, H6; 6.97, d, *J* 8.1 Hz, H5. ^{13}C n.m.r. δ (CDCl$_3$) 22.5, C3 or C4; 26.8, C4 or C3; 49.4, 2-(OMe)$_2$; 55.3, 7-OMe; 101.8, C8; 107.9, C6; 112.7, C2 or C4a; 114.0, C4a or C2; 129.3, C5; 153.2, C8a; 159.1, C7. Mass spectrum: m/z 224 (M, 58%), 208 (14), 194 (14), 193 (100), 191

(16), 178 (21), 177 (37), 166 (16), 161 (14), 151 (17), 150 (17), 121 (20), 108 (11), 88 (25), 76 (12), 58 (11).

Acidification of the basic washings with 2 M hydrochloric acid then extraction with ether gave a mixture, the ^1H n.m.r. spectrum of which showed it to consist of 3-(2'-hydroxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide **17b** (calculated mass 0.76 g, 43%) and methyl 3-(2'-hydroxy-4'-methoxyphenyl)propanoate **11a** (calculated mass 0.11 g, 8%).

A similar reaction using 3.6 equivalents of methyl trifluoromethanesulfonate and reaction with sodium methoxide for 30 min at room temperature gave the optimum yield of the ortho ester **1a** (55%). Also isolated in this case were the phenolic amide **17b** (13%) and the phenolic ester **11a** (13%).

1-t-Butyldimethylsilyloxy-3-methoxybenzene (27a)

3-Methoxyphenol **27b** (0.30 g, 2.42 mmol) was dissolved in dry *N,N*-dimethylformamide (1.0 ml) and the solution was cooled to 0°. Imidazole (0.41 g, 6.02 mmol) and *t*-butyldimethylsilyl chloride (0.44 g, 2.92 mmol) were added then the mixture was stirred under nitrogen at room temperature for 48 h. The usual work up gave a colourless liquid, and bulb-to-bulb distillation (150° / 20 mm, lit.[20] 134-136° / 15 mm) afforded pure 1-*t*-butyldimethylsilyloxy-3-methoxybenzene **27a** (0.27 g, 47%). ^1H n.m.r. δ ($CDCl_3$) 0.20, s, $SiMe_2$; 0.98, s, CMe_3; 3.78, s, OMe; 6.38-6.56, m, H2,4,6; 7.12, t, *J* 8.1 Hz, H5. ^{13}C n.m.r. δ ($CDCl_3$) -4.3, $SiMe_2$; 18.3, CMe_3; 25.8, $C\mathbf{Me}_3$; 55.3, OMe; 106.4, C2 or C4; 106.9, C4 or C2; 112.7, C6; 129.8, C5; 156.9, C1; 160.8, C3. The ^1H n.m.r. spectrum corresponded with the data reported by Sinhababu *et al.*[18]

Reaction of 1-t-Butyldimethylsilyloxy-3-methoxybenzene (27a) with Methyl Trifluoromethanesulfonate

Methyl trifluoromethanesulfonate (10 µl, 91 µmol) was added to a solution of 1-*t*-butyldimethylsilyloxy-3-methoxybenzene **27a** (20 mg, 84 µmol) in deuterated dichloromethane (1.0 ml) and the mixture was allowed to stand in a sealed tube at room temperature for 48 h. After this time the ^1H and ^{13}C n.m.r. spectra showed the presence of starting material **27a**, 3-methoxyphenol **27b** and 1,3-di-*t*-butyl-1,1,3,3-tetramethyldisiloxane **28** in the ratio of 1 : 1.7 : 1. The disiloxane **28** was detected by the following signals; ^1H n.m.r. δ (CD_2Cl_2) 0.04, s, $SiMe_2$; 0.89, s, CMe_3. ^{13}C n.m.r. δ (CD_2Cl_2) -2.8, $SiMe_2$; 18.2, CMe_3; 25.9, $C\mathbf{Me}_3$. (cf.[26,27]).

Reaction of 3-(2'-t-Butyldimethylsilyloxy-4'-methoxyphenyl)-N-methyl-N-phenylpropanamide (25) with Sodium Methoxide

A solution of 3-(2'-*t*-butyldimethylsilyloxy-4'-methoxyphenyl)-*N*-methyl-*N*-phenylpropanamide **25** (50 mg, 0.13 mmol) in dichloromethane (0.2 ml) was added to a cooled (0°) solution of sodium (7.7 mg, 0.33 mmol) in methanol (0.25 ml) and the mixture was stirred at 0° for 10 min then allowed to warm to room temperature and stirred for an additional 30 min. The solvents were evaporated and the residue was extracted with dichloromethane. The extract was washed with 2 M hydrochloric acid then dried ($MgSO_4$) and evaporated to give a white solid which was shown by its ^1H n.m.r. spectrum to be the phenolic amide **17b** (34 mg, 93%).

*Reaction of 7-Methoxy-3,4-dihydro-2*H*-1-benzopyran-2-one (2) with Trimethyl Orthoformate and Montmorillonite Clay*

A slurry of K-10 montmorillonite clay (2.00 g) and trimethyl orthoformate (3.0 ml, 27.4 mmol) was filtered, but not drained, so that the clay remained moist. A portion of this impregnated clay (0.50 g) was added to a solution of 7-methoxy-3,4-dihydro-2*H*-1-benzopyran-2-one **2** (0.15 g, 0.85 mmol) in dry carbon tetrachloride (2.0 ml) and the suspension was stirred under nitrogen at room temperature for 6 h. More of the impregnated clay with trimethyl orthoformate (0.02 g), was added, and the suspension was stirred overnight. The mixture was filtered and the clay pad was washed with dichloromethane. The combined filtrate was washed with 5% sodium bicarbonate solution, water, then dried (K_2CO_3) and evaporated to give a colourless gum (0.16 g). The ^{1}H n.m.r. spectrum showed the presence of methyl 3-(2'-hydroxy-4'-methoxyphenyl)propanoate **11a** and 2,2,7-trimethoxy-2*H*-1-benzopyran **1a** in the ratio of 2 : 1, together with triethyl orthoformate, methanol, and several unidentified compounds.

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