Accelerating effect of *meta* substituents in the ester-mediated nucleophilic aromatic substitution reaction

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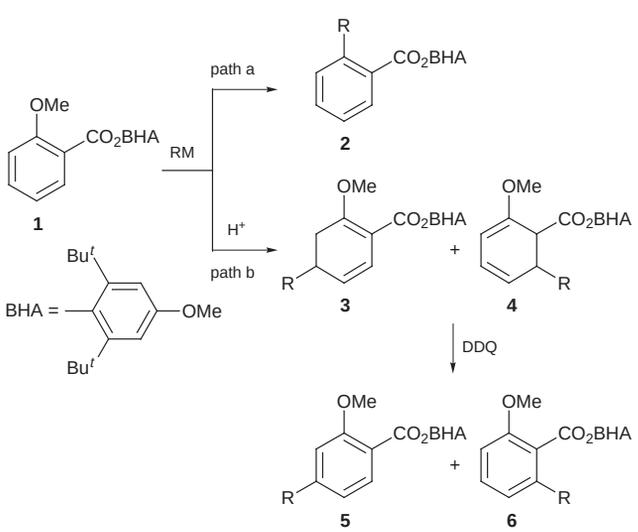
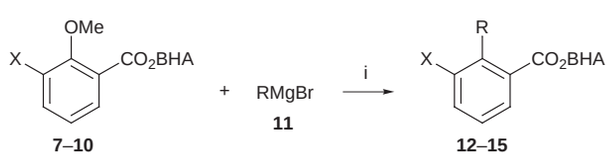
The ester-mediated nucleophilic aromatic substitution (S_NAr) reaction of 2-methoxybenzoic ester **1** with Grignard reagents **11** is greatly accelerated by introduction of a methoxy or halo substituent at the 3-position of the benzoate ring (**7**–**10**). The substituent effects of these groups at the 3-position are compared with those at the 5-position to suggest that the activation mechanism of the methoxy substituent is different from that of the halo substituent; the ligating ability of the 3-methoxy group plays a crucial role in enhancing the reactivity of the 2-methoxy moiety, while the electron-withdrawing ability is more important in the case of the halo groups. It has also been found that introduction of an additional methoxy substituent at the *meta*-position (**33**, **34**) enables the S_NAr methoxy-displacement reaction even at the *para*-position to the ester activator. The accelerating effect of the 3-bromo substituent is advantageously utilized for regioselective allylation of 3-bromo-2,6-dimethoxybenzoic ester **55** at the 2-position to provide an easy access to a multisubstituted naphthol **59**, which is a key compound for the syntheses of michellamines A–C and the related naphthylisoquinoline alkaloids.

Aromatic syntheses have mostly relied on the introduction of a substituent into an aromatic ring followed by its conversion into other functionalities. Thus, a large number of methodologies have been developed for these transformations. However, regioselective syntheses of multifunctional aromatic compounds are frequently still difficult. Therefore, the regioselective functionalization of the aromatic ring continues to be an important problem in organic synthesis. Recently, we have reported that an ester group significantly activates an *ortho*-alkoxy substituent for the S_NAr reaction (*e.g.* Scheme 1, path



Scheme 1

a),[1] and thus, the oxazoline functionality required in the conventional Meyers reaction[2] can be replaced by a readily prepared and easily removable ester functionality. We have also reported that the 2,6-di-*tert*-butyl-4-methoxyphenyl (BHA) ester of 2-methoxybenzoic acid **1** on treatment with several organo-lithium and -magnesium reagents affords the conjugate addition products **3**, **4** to the benzoate ring (path b).[3] The dichotomy between the two reaction paths was found to depend mainly on the electron-donating ability of the carbanion species, the stronger electron donors preferring path b to path a. In our continuing efforts to extend the scope and utility of these reactions, we have found that the S_NAr reaction is greatly accelerated by introduction of a methoxy or halo substituent into the 3-position of the benzoate ring (Scheme 2).



	X	11–15	R
7, **12**	OMe	**a**	Ph
8, **13**	F	**b**	Bu
9, **14**	Cl	**c**	Pr^i
10, **15**	Br	**d**	allyl
		e	Bn
		f	Bu^t

Scheme 2 *Reagents*: i, Et_2O–PhH.

Close scrutiny of the literature revealed that Fuson *et al.* reported a similar accelerating effect of a *meta*-methoxy group in the S_NAr reaction of 2-methoxybenzonitriles with Grignard reagents as early as 1948.[4] They found that displacement of the 2-methoxy group occurs only if the 3-position is occupied by the second methoxy group. They also reported the 4-methoxy-substitution reaction of 3,4-dimethoxyphenyl mesityl ketone with benzylmagnesium chloride.[5] On the other hand, Meyers and co-workers have recently reported the regioselective 2-alkoxy-displacement reaction of [2,6-dialkoxy-3,4-(methylenedioxy)phenyl]oxazoline with an aryl Grignard reagent.[6] It is quite obvious that these accelerating effects of the adjacent substituent to the leaving group have great potential in the regioselective syntheses of multisubstituted aromatic compounds. However, research from such a view point is scarce in

Table 1 The substituent effect in the 2-methoxy-displacement reaction

Entry	Substrate	Nucleophile	*t*/h	Product	Yield (%)
1	**7**	**11a**	1[a]	**12a**	94
2	**7**	**11b**	1[a]	**12b**	95
3	**7**	**11c**	1[a]	**12c**	94
4	**7**	**11d**	1[a]	**12d**	97
5	**7**	**11e**	3[a]	**12e**	63[b]
6	**7**	**11e**	6[a]	**12e**	89
7	**7**	**11f**	48[a]	**12f**	22[c]
8	**8**	**11a**	1[a]	**13a**	92
9	**8**	**11d**	1[a]	**13d**	99
10	**8**	**11e**	3[a]	**13e**	55[d]
11	**9**	**11a**	1[a]	**14a**	98
12	**9**	**11d**	1[a]	**14d**	98
13	**9**	**11e**	3[a]	**14e**	45[e]
14	**10**	**11a**	1[a]	**15a**	89
15	**10**	**11d**	1[a]	**15d**	93
16	**10**	**11e**	3[a]	**15e**	65[f]
17	**20**	**11a**	1[a]	**13a**	94
18	**20**	**11d**	1[a]	**13d**	53
19	**20**	**11e**	24[a]→12[g]	**13e**	12[h]
20	**21**	**11a**[i]	1[a]	**22**	98
21	**21**	**11e**	3[a]	**23**	87
22	**24**	**11a**	24[a]	**25**	81[j]
23	**26**	**11a**	1.5[a]	**27**	90

[a] At room temp. [b] Ester **7** was recovered in 35% yield. [c] Ester **16** was obtained in 42% yield after treatment of the crude product with DDQ. [d] Phenol **17** was obtained in 9% yield. [e] Phenol **18** was obtained in 14% yield. [f] Phenol **19** was obtained in 8% yield. [g] At reflux. [h] Ester **20** was recovered in 57% yield. [i] 1.5 equiv. [j] Ester **24** was recovered in 12% yield.

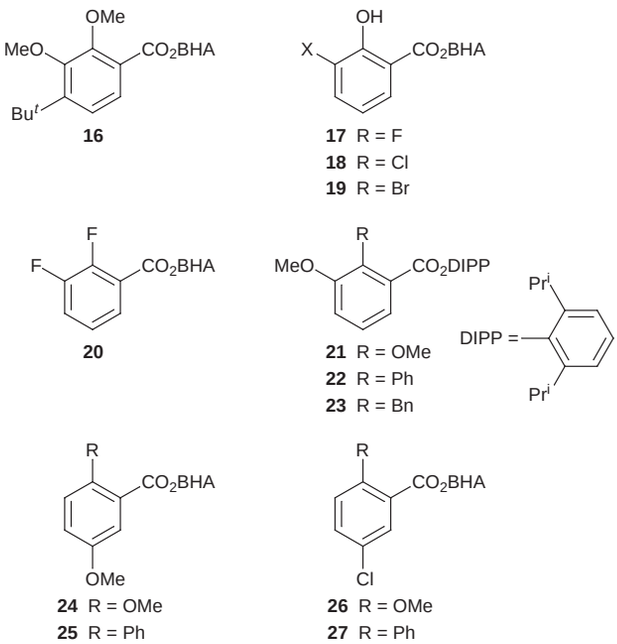
the literature, except the report by Wells *et al.* dealing with the regioselective 2-fluoro-displacement of 2,3,6-trifluorobenzonitrile by an alkoxide.[7] Herein, we report the accelerating effects of *meta* substituents in the ester-mediated S_NAr reaction and the application of the methodology to the regioselective synthesis of multisubstituted naphthol **59**, which is a key compound for the syntheses of naphthylisoquinoline alkaloids.

Results and discussion

ortho-Methoxy substitution of 2-methoxybenzoic esters promoted by a *meta* substituent

Before describing the results of the reactions of 3-substituted 2-methoxybenzoic esters **7**–**10** with Grignard reagents **11a**–**f** (Scheme 2), we would like to summarize briefly the previous results of the corresponding reactions of 2-methoxybenzoic ester **1** (Scheme 1).[3] Treatment of ester **1** with 2.5 equiv. of phenyl-, butyl- and isopropyl-magnesium bromide **11a**–**c** in diethyl ether–benzene at room temperature for 18–24 h and then, if necessary, at reflux for a further 1 h, afforded the methoxy-substitution products **2** in almost quantitative yields. On the other hand, benzyl- and *tert*-butyl-magnesium bromide **11e**,**f** were rather reluctant to react with ester **1** under the same reaction conditions, giving no S_NAr products in detectable amounts, but conjugate addition to the benzoate ring occurred to give cyclohexadienes **3** after prolonged reaction time (96 h). They were aromatized for quantification by treatment with DDQ to give 4-substituted benzoic esters **5** in 76 and 74% yields, respectively.

The results listed in Table 1 reveal the effects brought about by introducing a 3-methoxy or 3-halo substituent. Reactions of 2,3-dimethoxybenzoic ester **7** with phenyl-, butyl-, isopropyl- and allyl-magnesium bromide **11a-d** were completed in less than 1 h at room temperature, giving the S_NAr products **12a-d** in excellent yields (entries 1–4). It can be seen that the path of the reaction between ester **1** and benzylmagnesium bromide **11e** was completely changed from the conjugate addition to the S_NAr reaction by introduction of a methoxy group into the 3-position of the benzoate ring (**7**) (entries 5 and 6). On the other hand, the conjugate addition still predominated in the reaction of ester **7** with *tert*-butylmagnesium bromide **11f** to give, after aromatization by treatment with DDQ, 4-substituted benzoic ester **16** in 42% yield, while the S_NAr product **12f** was also obtained in 22% yield (entry 7).



Interestingly, a 3-halo substituent showed a similar accelerating effect, as can be seen in the reactions of 3-halo-2-methoxybenzoic esters **8**–**10** with Grignard reagents **11** (entries 8–16): esters **8**–**10** showed almost equal reactivity toward the S_NAr reaction with the phenyl and allyl Grignard reagents **11a**,**d** to that of 2,3-dimethoxybenzoic ester **7**, giving substitution products **13a**,**d**–**15a**,**d** within 1 h in excellent yields. Benzylmagnesium bromide **11e** also reacted with esters **8**–**10** to afford the methoxy-displacement products **13e**–**15e** in somewhat reduced yields, accompanied by demethylation of substrates **8**–**10** to give 2-hydroxybenzoic esters **17**–**19** in 8–14% yield. We attempted to replace the methoxy leaving group (**8**) with a fluoro moiety (**20**) to avoid the demethylation problem. Although the replacement did not appreciably alter the S_NAr reaction with the phenyl Grignard reagent **11a** (compare entry 17 with entry 8), it slowed down the reactions with allyl- and benzyl-magnesium bromide **11d**,**e** (entries 18 and 19).

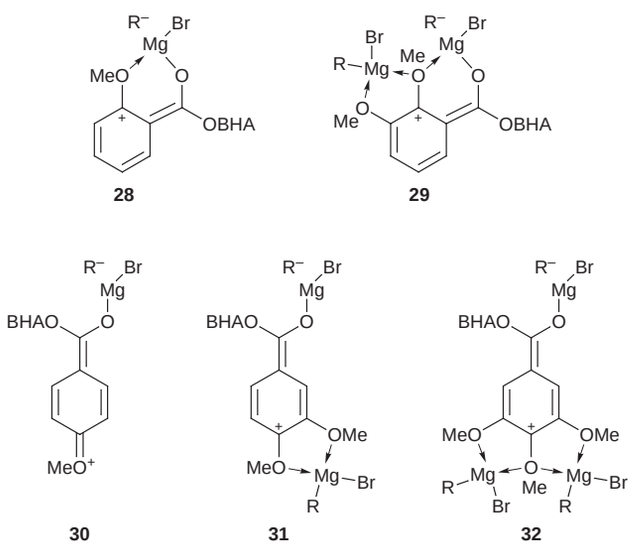
As has been reported previously, steric balance between the ester moiety and the nucleophile is crucial to proceed the ester-mediated S_NAr reaction of 2-methoxybenzoic esters while preventing nucleophilic attack at the ester carbonyl function.[8] Thus, 2,6-di-*tert*-butylphenyl esters (*e.g.* **1**) when treated with phenylmagnesium bromide **11a** gave the corresponding 1,1′-biphenyl-2-carboxylic esters in almost quantitative yields, while the reaction of the 2,6-diisopropylphenyl (DIPP) ester of 2-methoxybenzoic acid afforded the corresponding biphenyl in 71% yield, accompanied by a formation of the carbonyl addition product, (2-methoxyphenyl)diphenylmethanol, in 21% yield. On the other hand, the DIPP ester of 2,3-dimethoxybenzoic acid **21**, with the aid of the accelerating effect of the 3-methoxy moiety, exclusively underwent the S_NAr reaction when treated with the Grignard reagent **11a** (entry 20). It should be noted that the use of the less bulky DIPP rather than BHA as the carboxy protecting group shortened substantially the reaction time, as exemplified by comparing the result of entry 21 with that of entry 5.

Mechanistic consideration of the accelerating effect of the *meta* substituent

From the view point of the steric effect, the 3-methoxy or halo

substituent of esters **7**–**10** should retard rather than promote the S_NAr displacement of the 2-methoxy group, as exemplified by the previously reported reaction of 3-methyl-substituted 2-alkoxybenzoic esters.[9] It has been a common understanding that an electron-withdrawing substituent usually facilitates conventional S_NAr reactions but a donating group retards them. Therefore, it is obvious that the electronic effect of the substituent at the 3-position does not solely explain the enhanced reactivity, considering the fact that both the electron-donating methoxy and electron-withdrawing halo substituents promoted the reaction. In fact, the 5-methoxy substituent of 2,5-dimethoxybenzoic ester **24**, which is expected to exert an electronic effect toward the 2-methoxy leaving group similar to that of the 3-methoxy substituent of 2,3-dimethoxybenzoic ester **7**, significantly retarded the S_NAr reaction with the phenyl Grignard reagent **11a** (entry 22). On the other hand, the 5-chloro substituent of 5-chloro-2-methoxybenzoic ester **26** actually promoted the S_NAr reaction (entry 23), but the accelerating ability of the 5-chloro substituent was to some extent inferior to that of the 3-chloro substituent (entry 11). Thus, the 3-chloro substituent seems to exert an electron-withdrawing effect enforced by a ligating effect (*vide infra*). Therefore, it may be concluded that, in the case of halogens, their inductive electron-withdrawing nature may be the principal rather than the only factor promoting the S_NAr reaction.

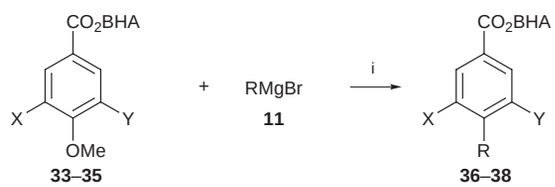
The ester-mediated S_NAr reaction has been considered to proceed through the strong ligations of both the 2-methoxy and carbonyl oxygen to the metal cation of the nucleophile to form a chelated complex **28**, the formation of which should facilitate



the conjugate addition of the anionic species to the *ipso*-carbon bearing the leaving group, followed by elimination of the metal alkoxide.[10] Based on this mechanism, another chelation between the 2- and 3-methoxy substituent or the 2-methoxy and 3-halo substituent in the substrates may play an important role in enhancing the reactivity of the 2-methoxy group, although the ligating abilities of the halo substituents may not be so strong compared to the methoxy substituent. Similar participation of the 3-methoxy substituent has been suggested by Hutchings and Meyers in a related oxazoline-mediated reaction.[6] A tentative chelated complex **29** formed from ester **7** and two molecules of Grignard reagents is suggested. The formation of the two chelate rings in complex **29** will more effectively prevent resonance stabilization of the aryl-oxygen linkage and polarize more effectively the bond between the 2-methoxy oxygen and the *ipso*-carbon than the single chelate structure in complex **28** does, to accelerate the addition of the anionic species to the *ipso*-carbon. The two-chelation mechanism may be supported by the fact that 2,6-di-*tert*-butyl-4-methylphenyl 2,3-(methylenedioxy)benzoate, which could not form the second chelate for steric reasons, did undergo the S_NAr displacement at the 2-position but did not show any enhanced reactivity toward the S_NAr reaction with the phenyl Grignard reagent **11a** as reported previously.[11]

para-Methoxy substitution of 4-methoxybenzoic esters induced by a *meta* substituent

Next, our interest was directed toward the possibility of whether the S_NAr reaction proceeds at the *para*-position to the ester activator by introduction of a *meta*-substituent with potential to ligate to metal cations in cooperation with the *para*-methoxy moiety (Scheme 3). Treatment of 4-methoxybenzoic

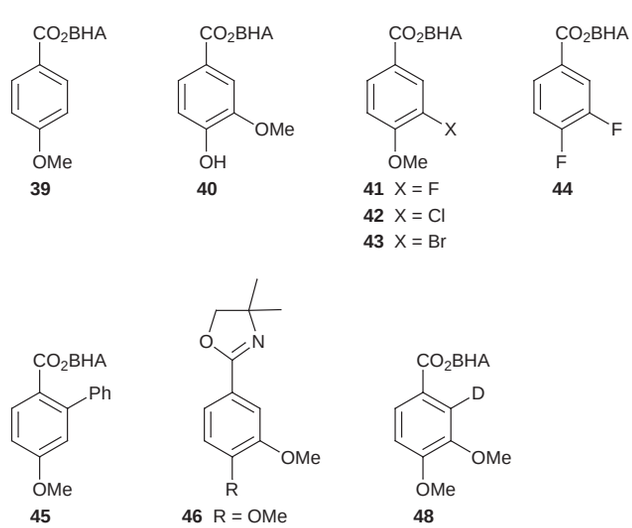


	X	Y	11, 36–38	R
33, 36	OMe	H	a	Ph
34, 37	OMe	OMe	b	Bu
35, 38	Pyr	H	c	Pr^i
			d	allyl
			e	Bn
			f	Bu^t

Pyr = —N

Scheme 3 *Reagents*: i, Et_2O–PhH.

ester **39** with 2.5 equiv. of phenyl- and benzyl-magnesium bromide **11a**,**e** in diethyl ether–benzene at reflux for 24 h did not afford the methoxy-substitution product but the substrate **39**

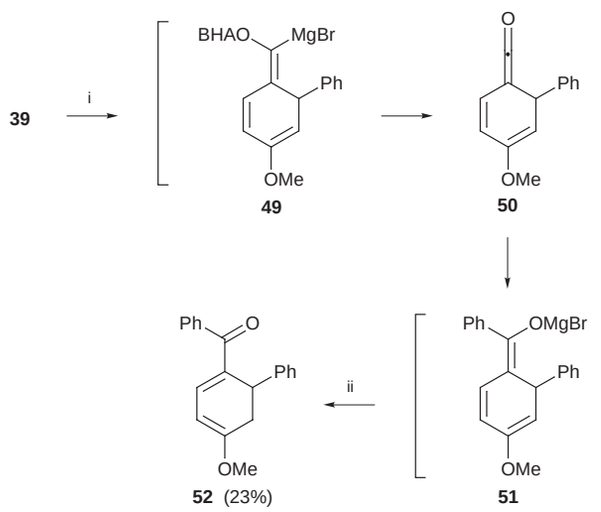


was recovered in 67 and 98%, respectively. In the case of the former reaction, ketone **52** was also isolated in 23% yield. The formation of ketone **52** can be rationalized by the sequential reactions: initial conjugate addition of Grignard **11a** to ester **39**, decomposition of the resulting enolate **49** to ketone **50**,[12] and 1,2-addition of Grignard **11a** to give the adduct **51** followed by aqueous work-up to afford ketone **52** (Scheme 4). On the other hand, 3,4-dimethoxybenzoic ester **33** was found to give the substitution products of the 4-methoxy moiety **36a**–**c**,**e** in good to excellent yields on treatment with the Grignard reagents **11a**–**c**,**e** under refluxing conditions (Table 2, entries 1–3, 5). The reaction of ester **33** with the allyl Grignard reagent **11d**, however, afforded a complex mixture which contained 2,6-di-*tert*-butyl-4-methoxyphenol in 62% yield (entry 4). No detectable amount of the S_NAr product **36f** was found in the

Table 2 The substituent effect in the 4-methoxy-displacement reaction

Entry	Substrate	Nucleophile	*t*/h	Product	Yield (%)
1	**33**	**11a**	5[a]	**36a**	93
2	**33**	**11b**	5[a]	**36b**	87
3	**33**	**11c**	3[a]	**36c**	97
4	**33**	**11d**	5[a]	**36d**	0[b]
5	**33**	**11e**	24[a]	**36e**	75
6	**33**	**11f**	72[a]	**36f**	0[c]
7	**34**	**11a**	6[d]	**37a**	91
8	**34**	**11e**	24[d]	**37e**	82
9	**35**	**11a**	24[a]	**38a**	21[e]
10	**46**	**11a**	24[a]	**47**	8[f]

[a] At reflux. [b] 2,6-Di-*tert*-butyl-4-methoxyphenol was obtained in 62% yield. [c] Phenol **40** was obtained in 21% yield along with ester **33** in 74% recovery. [d] At room temp. [e] Ester **35** was recovered in 69% yield. [f] Oxazoline **46** was recovered in 79% yield.



Scheme 4 *Reagents and conditions*: i, PhMgBr, Et_2O–PhH, reflux; ii, saturated aqueous NH_4Cl.

reaction of ester **33** with the *tert*-butyl Grignard reagent **11f** but the demethylation product **40** was obtained in 21% yield along with unchanged ester **33** (74% recovery) after prolonged heating at reflux (entry 6). It is of particular interest that 3,4,5-trimethoxybenzoic ester **34** showed reactivity toward the S_NAr reaction superior to that of ester **33**, affording the S_NAr products at room temperature (entries 7 and 8).

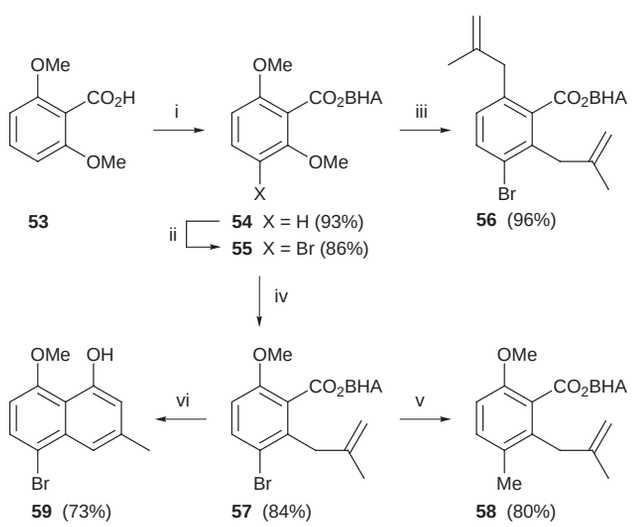
3-Halo-4-methoxybenzoic esters **41**–**43**, as well as 3,4-difluorobenzoic ester **44**, were left almost intact (88, 94, 92 and 79% recovery, respectively) with no detectable amounts of the S_NAr products, when treated with the benzyl Grignard reagent **11e** under the same reaction conditions as mentioned for 4-methoxybenzoic ester **39** (*vide supra*). Similar treatment of esters **41**–**44** with the phenyl Grignard reagent **11a** also left the starting esters **41**–**44** but in somewhat reduced recovery (60, 70, 54 and 58%, respectively). Conjugate addition of Grignard **11a** to ester **41**–**44** may be a plausible explanation of the reduced recovery. However, it should be noted that a small amount of 4-methoxy-2-phenylbenzoic ester **45** (21%) was isolated in the reaction of the bromo ester **43** with the latter Grignard reagent **11a**, suggesting the intermediary of a benzyne in the cine substitution. Therefore, when these halogenated benzoic esters **41**–**44** were treated with Grignard **11a**, directed metallation might have occurred at the 2-position of the benzoate rings with the aid of the *ortho*-alkoxycarbonyl and the *ortho'*-halo substituent, and the resulting species would greatly resist the methoxy-substitution reaction due to the negative charge. In line with these explanations, introduction of a pyrrolidinyl substituent, which is a good ligand to metal cations as well as an effective promotor for *ortho*-metallation, into the 3-position of the benzoate ring (**35**) actually induced the S_NAr reaction but the activating power was largely offset by the metallation preference as compared to that of the 3-methoxy moiety of ester **33** (entry 9). It is noteworthy that oxazoline **46** also afforded the methoxy-substitution product **47** in only a poor yield when treated with the Grignard regent **11a** (entry 10). In connection with these observations, it should be mentioned that treatment of ester **33** with 2.5 equiv. of phenyllithium in toluene at −45 °C for 3 h resulted in lithiation of ester **33** to afford, after deuterium oxide quenching, a deuterated compound **48** in 89% yield.

These results suggest that 4-methoxybenzoic esters undergo the methoxy-displacement reaction by Grignard reagents if the 3-position is occupied by a substituent which can ligate to the magnesium cations in cooperation with the 4-methoxy substituent but has rather low ability to promote *ortho*-metallation. A methoxy group is particularly desirable for this purpose to form a firm chelated complex **31**, to induce the *para*-methoxy substitution (compare complex **30** with **31**). The superior reactivity of 3,4,5-trimethoxybenzoic ester **34** to that of its 3,4-dimethoxy counterpart **33** may be explained by the formation of a magnesium complex **32** having a bis-chelated structure.

Regioselective synthesis of multisubstituted naphthol 59

The 1,8-dioxygenated 4-aryl-6-methylnaphthalene moiety is a structural unit of anti-HIV agents michellamines A–C[13] and the related naphthylisoquinoline alkaloids.[14] Thus, hydroxy-protected 4-bromo-1,8-dihydroxy-6-methylnaphthalenes are utilized as key compounds for the syntheses of these naphthylisoquinoline alkaloids *via* the Kharasch-type biaryl coupling reactions after conversion into proper organometallic species.[15] Therefore, several papers have dealt with strategies for the synthesis of multisubstituted naphthalenes, but the reported methods require many steps and/or suffer from low yields.[15–18]

It occurred to us that the 3-halo-promoted regioselective displacement of the 2-methoxy substituent of a 2,6-dimethoxybenzoic ester **55** could be advantageously utilized for the construction of the required naphthalene structure (**59**) (Scheme 5):



Scheme 5 *Reagents and conditions*: i, BHA-OH, TFAA, PhH, room temp.; ii, Br_2, AcOH, room temp.; iii, 2-methylprop-2-enylmagnesium chloride, Et_2O–PhH, room temp.; iv, 2-methylprop-2-enylmagnesium chloride, THF, room temp.; v, MeLi, Et_2O–THF, room temp.; vi, NaOMe, HMPA, 60 °C.

our synthetic strategy started from commercially available 2,6-dimethoxybenzoic acid **53**, which was esterified to ester **54** and then brominated to the prerequisite bromo ester **55**. Treatment of ester **55** with 2-methylprop-2-enylmagnesium chloride in diethyl ether–benzene at room temperature, however, afforded diallylated product **56** exclusively, even after a short time (see Experimental section), showing that the bromo substituent

substantially accelerated not only the *ortho*- but also the *para*-methoxy substitution by the inductive effect. We were pleased, however, to find that the regioselective substitution at the *ortho*-position could be conducted by changing the solvent from diethyl ether–benzene to THF to give monoallylated product **57** in a good yield. We next tried a base-catalyzed cyclization of ester **57** to naphthol **59**. Previously, Snieckus and co-workers reported that treatment of *N*,*N*-dimethyl-2-(prop-2-enyl)benzamide with methyllithium resulted in the formation of the allyl anion, which then cyclized intramolecularly between the allyl terminus at the 3′-position and the carbonyl carbon to afford 1-naphthol after aqueous work-up.[19] We tried to apply this procedure to ester **57**. However, it was found that the use of a strong base was incompatible with ester **57** because of the presence of the bromo substituent; the Wurtz-type coupling reaction occurred on treatment of ester **57** with methyllithium in diethyl ether–THF to give methylated product **58** in 80% yield. We found, however, that the desired naphthol **59** was obtained in a good yield when ester **57** was treated with sodium methoxide in HMPA. Changing the solvent from HMPA to DMF or 1,3-dimethylimidazolidin-2-one (DMI) caused isomerization of the terminal double bond of the allylic moiety and transesterification to the methyl ester, affording no cyclization product. Efforts are still in progress to replace HMPA with a more convenient solvent for the cyclization step.

In conclusion, we have shown here the exceptional substituent effects of methoxy and halo groups in the ester-mediated S_NAr reaction. These effects were effectively utilized to control the reactivities of the methoxy leaving groups at the 2,4,6-positions of a benzoate ring toward the S_NAr reaction, affording a convenient method for the regioselective synthesis of multisubstituted aromatic compounds.

Experimental

Mps were taken using a Mitamura Riken MP-P apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-460 or FT-IR 8300 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker DPX-400 or DRX-500 spectrometer using tetramethylsilane as the internal standard and $CDCl_3$ as the solvent. *J* Values are given in Hz. Microanalyses were carried out in the Microanalytical Laboratory of the Institute for Chemical Reaction Science, Tohoku University. Merck silica gel $60GF_{254}$ was used for analytical and preparative TLC (PLC). Silica gel columns were prepared by use of Merck silica gel 60 (63–200 μm). Alumina columns were prepared by use of Nacalai activated alumina 300 (300 mesh). Water- and air-sensitive reactions were routinely carried out under nitrogen. Diethyl ether, THF, benzene and toluene were distilled from sodium diphenyl ketyl just before use. Other solvents for experiments requiring anhydrous conditions were purified by usual methods. 3-Bromo-2-methoxybenzoic acid,[20] 3-chloro-4-methoxybenzoic acid,[21] 3-bromo-4-methoxybenzoic acid[21] and methyl 3-amino-4-methoxybenzoate[22] were prepared according to the literature procedures.

3-Chloro-2-methoxybenzoic acid

This compound was prepared according to the literature procedure for the preparation of 3-bromo-2-methoxybenzoic acid from 2-bromophenol.[20] 2-Chlorophenol (25.1 g, 195 mmol) was allylated with allyl bromide (25.6 g, 212 mmol) in the presence of K_2CO_3 (40.5 g, 293 mmol) in refluxing acetone (180 cm^3) for 3 h. After work-up, the crude product was distilled under reduced pressure (94 °C/1.07 kPa) to give 1-chloro-2-(prop-2-enyloxy)benzene (28.0 g, 85%) as an oil (Found: C, 63.8; H, 5.2; Cl, 20.7. C_9H_9ClO requires C, 64.1; H, 5.4; Cl, 21.0%); ν_{max}(neat)/cm^{-1} 1250 and 1057; δ_H(400 MHz) 4.59 (2 H, d, *J* 5.2, OCH_2), 5.30 [1 H, dd, *J* 10.6 and 1.2, CH=CH_2 (*trans*)], 5.46 [1 H, dd, *J* 17.3 and 1.2, CH=CH_2 (*cis*)], 6.06 (1 H, ddt, *J* 17.3, 10.6 and 5.2, C*H*=CH_2), 6.86–6.91 (2 H, m, ArH), 7.18 (1 H, td, *J* 7.8 and 1.1, ArH) and 7.35 (1 H, dd, *J* 7.8 and 1.1, ArH).

The allyl ether (26.5 g, 157 mmol) was heated at 200 °C for 6 h under nitrogen. The crude product was worked up and distilled under reduced pressure (72.5 °C/333 Pa) to give 2-chloro-6-(prop-2-enyl)phenol (23.5 g, 89%) as an oil (Found: C, 63.8; H, 5.3; Cl, 20.8. C_9H_9ClO requires C, 64.1; H, 5.4; Cl, 21.0%); ν_{max}(neat)/cm^{-1} 3535; δ_H(400 MHz) 3.43 (2 H, d, *J* 6.6, $ArCH_2$), 5.06–5.12 (2 H, m, CH=CH_2), 5.62 (1 H, s, OH), 5.94–6.04 (1 H, m, C*H*=CH_2), 6.80 (1 H, t, *J* 7.8, ArH), 7.04 (1 H, dd, *J* 7.8 and 1.6, ArH) and 7.18 (1 H, dd, *J* 7.8 and 1.6, ArH).

The phenol (22.6 g, 134 mmol) was methylated with iodomethane (38.3 g, 270 mmol) in the presence of K_2CO_3 (27.9 g, 202 mmol) in refluxing acetone (50 cm^3) for 1 h to give 1-chloro-2-methoxy-3-(prop-2-enyl)benzene (23.8 g) after usual work-up. The product was spectromerically pure enough to use in the following step without further purification, δ_H(400 MHz) 3.44 (2 H, dt, *J* 6.6 and 1.4, $ArCH_2$), 3.84 (3 H, s, OMe), 5.07 [1 H, dq, *J* 16.8 and 1.4, CH=CH_2 (*cis*)], 5.09 [1 H, dq, *J* 10.3 and 1.4, CH=CH_2 (*trans*)], 5.96 (1 H, ddt, *J* 16.8, 10.3 and 6.6, C*H*=CH_2), 6.99 (1 H, t, *J* 7.8, ArH), 7.09 (1 H, dd, *J* 7.8 and 1.7, ArH) and 7.24 (1 H, dd, *J* 7.8 and 1.7, ArH).

The crude terminal olefin (23.8 g, *ca.* 130 mmol) was isomerized to an (*E*)- and (*Z*)-mixture of the internal olefins by boiling with KOH (49.7 g) in a mixture of ethanol (120 cm^3) and water (15 cm^3) for 5 h. The mixture was worked up and the crude product was oxidized by $KMnO_4$ (61.0 g, 386 mmol) in acetone (1.4 dm^3) at 0 °C for 3 h. After work-up, recrystallization from ethanol–dichloromethane gave 3-chloro-2-methoxybenzoic acid (11.8 g). The mother liquor was evaporated and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (4:1) as the eluent to give an additional crop (1.44 g) for a total yield of 13.2 g [53% based on the 2-chloro-6-(prop-2-enyl)phenol] as crystals, mp 122–123 °C (Found: C, 51.4; H, 3.9; Cl, 19.0. $C_8H_7ClO_3$ requires C, 51.5; H, 3.8; Cl, 19.0%); ν_{max}(KBr)/cm^{-1} 2995 and 1674; δ_H(400 MHz) 4.06 (3 H, s, OMe), 7.21 (1 H, t, *J* 7.9, ArH), 7.63 (1 H, dd, *J* 7.9 and 1.7, ArH) and 7.99 (1 H, dd, *J* 7.9 and 1.7, ArH).

General procedure for esterification of mono-, di- and trimethoxybenzoic acids

Mono-, di- and tri-methoxybenzoic esters **7**, **21**, **24**, **33**, **34** and **39** were prepared by the same procedure as reported before,[23] unless otherwise noted. A mixture of the corresponding benzoic acid (40.0 mmol), the equimolar amount of 2,6-di-*tert*-butyl-4-methoxy- or 2,6-diisopropyl-phenol, TFAA (16.8 g, 80.0 mmol) and dry benzene (30 cm^3) was stirred at room temperature for 4 h to 5 d, while the reaction was monitored by TLC. After work-up, the crude product was purified by recrystallization from ethanol.

Ester 7. As crystals (63%), mp 144–145 °C (Found: C, 72.0; H, 7.8. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.1%); ν_{max}(KBr)/cm^{-1} 1735; δ_H(400 MHz) 1.35 (18 H, s, Bu^t × 2), 3.81 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.93 (3 H, s, OMe), 6.91 (2 H, s, ArH), 7.16 (1 H, dd, *J* 8.0 and 2.0, ArH), 7.19 (1 H, t, *J* 8.0, ArH) and 7.70 (1 H, dd, *J* 8.0 and 2.0, ArH).

Ester 21. As crystals (85%), mp 122–123 °C (Found: C, 73.5; H, 7.8. $C_{21}H_{26}O_4$ requires C, 73.7; H, 7.7%); ν_{max}(KBr)/cm^{-1} 1729; δ_H(400 MHz) 1.23 (12 H, d, *J* 6.9, $CHMe_2$ × 2), 3.11 (2 H, sept, *J* 6.9, C*H*Me_2 × 2), 3.93 (3 H, s, OMe), 3.95 (3 H, s, OMe), 7.14 (1 H, dd, *J* 7.6 and 1.8, ArH), 7.17–7.27 (4 H, m, ArH) and 7.50 (1 H, dd, *J* 7.6 and 1.8, ArH).

Ester 24. The crude product was chromatographed on a silica gel column with hexane–ethyl acetate (19:1 to 6:1) as the eluent; crystals (96%), mp 91.4–92.3 °C (Found: C, 71.8; H, 8.0. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.1%); ν_{max}(KBr)/cm^{-1} 1711;

δ_H(400 MHz) 1.34 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 3.83 (3 H, s, OMe), 3.87 (3 H, s, OMe), 6.90 (2 H, s, ArH), 7.00 (1 H, d, *J* 9.1, ArH), 7.13 (1 H, dd, *J* 9.1 and 3.2, ArH) and 7.67 (1 H, d, *J* 3.2, ArH).

Ester 33. The reaction was carried out by using 4.0 equiv. of TFAA. Recrystallization of the crude product gave ester **33** (6.93 g). The mother liquor was evaporated and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (7:1) as the eluent to give an additional crop (1.17 g) for a total yield of 8.10 g (51%) as crystals, mp 141–142 °C (Found: C, 71.8; H, 8.2. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.1%); ν_{max}(KBr)/cm^{-1} 1725; δ_H(400 MHz) 1.33 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 3.97 (3 H, s, OMe), 3.98 (3 H, s, OMe), 6.91 (2 H, s, ArH), 6.99 (1 H, d, *J* 8.5, ArH), 7.69 (1 H, d, *J* 2.0, ArH) and 7.90 (1 H, dd, *J* 8.5 and 2.0, ArH).

Ester 34. The reaction was carried out by using 4.0 equiv. of TFAA. The crude product was chromatographed on a silica gel column with hexane–ethyl acetate (19:1) as the eluent; crystals (35%), mp 159–160 °C (Found: C, 69.7; H, 7.9. $C_{25}H_{34}O_6$ requires C, 69.7; H, 8.0%); ν_{max}(KBr)/cm^{-1} 1726; δ_H(400 MHz) 1.33 (18 H, s, Bu^t × 2), 3.83 (3 H, s, OMe), 3.94 (6 H, s, OMe × 2), 3.97 (3 H, s, OMe), 6.91 (2 H, s, ArH) and 7.48 (2 H, s, ArH).

Ester 39. The reaction was conducted in TFAA (40 cm^3) without the use of benzene; crystals (63%), mp 140–141 °C (Found: C, 74.4; H, 8.0. $C_{23}H_{30}O_4$ requires C, 74.6; H, 8.2%); ν_{max}(KBr)/cm^{-1} 1732; δ_H(400 MHz) 1.32 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 3.90 (3 H, s, OMe), 6.90 (2 H, s, ArH), 7.00–7.03 (2 H, m, ArH) and 8.18–8.20 (2 H, m, ArH).

General procedure for esterification of halo-substituted benzoic acid

Halogenated benzoic esters **9**, **10**, **20** and **42**–**44** were prepared by a similar procedure to that described in the previous paper.[24] The corresponding acid (12.0 mmol) was boiled in thionyl chloride (10 cm^3) for 3 h and then volatiles were removed under reduced pressure to give the acid chloride. This was dissolved in dry benzene (20 cm^3) and the solution was added to a mixture of 2,6-di-*tert*-butyl-4-methoxyphenol (2.55 g, 10.8 mmol), 4-pyrrolidinylpyridine (4-PPy) (1.78 g, 12.0 mmol), pyridine (4.0 cm^3) and benzene (30 cm^3). The mixture was refluxed for 24 h and worked up. The crude product was purified by chromatography on a silica gel column using the indicated eluent, unless otherwise noted.

Ester 9. Hexane–ethyl acetate (19:1) as the eluent; crystals (48%), mp 141–142 °C (Found: C, 68.35; H, 7.1; Cl, 9.0. $C_{23}H_{29}ClO_4$ requires C, 68.2; H, 7.2; Cl, 8.8%); ν_{max}(KBr)/cm^{-1} 1740; δ_H(400 MHz) 1.34 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 3.96 (3 H, s, OMe), 6.92 (2 H, s, ArH), 7.23 (1 H, t, *J* 8.0, ArH), 7.66 (1 H, dd, *J* 8.0 and 1.7, ArH) and 8.11 (1 H, dd, *J* 8.0 and 1.7, ArH).

Ester 10. The crude product was recrystallized from hexane–ethanol to give ester **10** (1.75 g). The mother liquor was evaporated and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (19:1) as the eluent to give an additional crop (2.04 g) for a total yield of 3.79 g (78%) as crystals, mp 162–164 °C (Found: C, 61.35; H, 6.45; Br, 17.6. $C_{23}H_{29}BrO_4$ requires C, 61.5; H, 6.5; Br, 17.8%); ν_{max}(KBr)/cm^{-1} 1739; δ_H(400 MHz) 1.34 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 3.95 (3 H, s, OMe), 6.91 (2 H, s, ArH), 7.17 (1 H, t, *J* 7.9, ArH), 7.84 (1 H, dd, *J* 7.9 and 1.7, ArH) and 8.18 (1 H, dd, *J* 7.9 and 1.7, ArH).

Ester 20. The crude product was recrystallized from ethanol to give ester **20** (1.97 g). The mother liquor was evaporated and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (14:1) as the eluent to give an additional crop (465 mg) for a total yield of 2.44 g (60%) as crystals, mp 119–120 °C (Found: C, 70.35; H, 6.7. $C_{22}H_{26}F_2O_3$ requires C, 70.2; H, 7.0%); ν_{max}(KBr)/cm^{-1} 1734; δ_H(400 MHz) 1.33 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 6.91 (2 H, s, ArH), 7.25 (1 H, tdd, *J* 8.0, 4.6 and 1.7, ArH), 7.42–7.49 (1 H, m, ArH) and 7.93 (1 H, ddt, *J* 8.0, 6.1 and 1.8, ArH).

Ester 42. Hexane–ethyl acetate (9:1 to 4:1) as the eluent; crystals (85%), mp 133–135 °C (Found: C, 67.9; H, 7.1; Cl, 9.0. $C_{23}H_{29}ClO_4$ requires C, 68.2; H, 7.2; Cl, 8.8%); ν_{max}(KBr)/cm^{-1} 1727; δ_H(400 MHz) 1.31 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 4.01 (3 H, s, OMe), 6.90 (2 H, s, ArH), 7.05 (1 H, d, *J* 8.7, ArH), 8.14 (1 H, dd, *J* 8.7 and 2.1, ArH) and 8.23 (1 H, d, *J* 2.1, ArH).

Ester 43. Hexane–ethyl acetate (6:1) as the eluent; crystals (47%), mp 169–170 °C (Found: C, 61.4; H, 6.5; Br, 17.5. $C_{23}H_{29}BrO_4$ requires C, 61.5; H, 6.5; Br, 17.8%); ν_{max}(KBr)/cm^{-1} 1731; δ_H(400 MHz) 1.31 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 4.00 (3 H, s, OMe), 6.90 (2 H, s, ArH), 7.02 (1 H, d, *J* 8.7, ArH), 8.18 (1 H, dd, *J* 8.7 and 2.1, ArH) and 8.40 (1 H, d, *J* 2.1, ArH).

Ester 44. Hexane–ethyl acetate (24:1) as the eluent; crystals (74%), mp 103–105 °C (Found: C, 70.2; H, 7.0. $C_{22}H_{26}F_2O_3$ requires C, 70.2; H, 7.0%); ν_{max}(KBr)/cm^{-1} 1733; δ_H(400 MHz) 1.31 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 6.91 (2 H, s, ArH), 7.30–7.37 (1 H, m, ArH) and 8.00–8.07 (2 H, m, ArH).

2,6-Di-*tert*-butyl-4-methoxyphenyl 3-fluoro-2-methoxybenzoate 8

This compound was found to be readily prepared from 2,3-difluorobenzoic ester **20** *via* the ester-mediated 2-fluoro-displacement reaction by sodium methoxide in THF.[7,9,25] To dry methanol (16 cm^3) was added sodium (800 mg, 34.8 mmol) and the mixture was stirred at room temperature until hydrogen evolution ceased. The excess of methanol was distilled off and the residue was heated at 110 °C under reduced pressure for 2 h to give sodium methoxide. This was suspended in dry THF (45 cm^3) and a solution of ester **20** (1.66 g, 4.41 mmol) in THF (20 cm^3) was added. The mixture was stirred at room temperature for 1 h and then poured into 2 mol dm^{-3} HCl (150 cm^3). After the two layers had been separated, the aqueous layer was extracted with diethyl ether and the combined organic layer was washed successively with 1 mol dm^{-3} Na_2CO_3 and water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on a silica gel column eluting with hexane–ethyl acetate (14:1) to give ester **8** (1.49 g, 87%) as crystals, mp 81.0–82.5 °C (Found: C, 71.4; H, 7.25. $C_{23}H_{29}FO_4$ requires C, 71.1; H, 7.5%); ν_{max}(KBr)/cm^{-1} 1744; δ_H(400 MHz) 1.35 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 4.01 (3 H, s, OMe), 6.91 (2 H, s, ArH), 7.17 (1 H, td, *J* 8.1 and 4.8, ArH), 7.35 (1 H, ddd, *J* 10.9, 8.1 and 1.7, ArH) and 7.91 (1 H, ddd, *J* 8.1, 1.7 and 1.5, ArH).

2,6-Di-*tert*-butyl-4-methoxyphenyl 5-chloro-2-methoxybenzoate 26

This compound was prepared by esterification of 2,5-dichlorobenzoic acid with 2,6-di-*tert*-butyl-4-methoxyphenol, followed by the nucleophilic 2-chloro-displacement reaction by sodium methoxide as mentioned for the preparation of ester **9** and **8**. The acid chloride prepared from 2,5-dichlorobenzoic acid (6.94 g, 36.3 mmol) and thionyl chloride (20 cm^3) was treated with 2,6-di-*tert*-butyl-4-methoxyphenol (7.73 g, 32.7 mmol) in benzene (75 cm^3)–pyridine (15 cm^3) in the presence of 4-PPy (5.38 g, 36.3 mmol) under reflux for 15 h. The crude product was recrystallized from ethanol to give 2,6-di-*tert*-butyl-4-methoxyphenyl 2,5-dichlorobenzoate (7.34 g). The mother liquor was evaporated and the residue was chromato-

graphed on a silica gel column eluting with hexane–ethyl acetate (12:1) to give an additional crop (3.01 g) for a total yield of 10.4 g (77%) as crystals, mp 108–109 °C (Found: C, 64.7; H, 6.3; Cl, 17.4. $C_{22}H_{26}Cl_2O_3$ requires C, 64.6; H, 6.4; Cl, 17.3%); ν_{max}(KBr)/cm^{-1} 1751; δ_H(400 MHz) 1.34 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 6.91 (2 H, s, ArH), 7.50 (2 H, d, *J* 1.4, ArH) and 8.24 (1 H, t, *J* 1.4, ArH).

Sodium methoxide prepared from sodium (1.15 g, 50.0 mmol) and methanol (30 cm^3) was suspended in THF (40 cm^3) and a solution of the dichloro ester (2.05 g, 5.00 mmol) in THF (40 cm^3) was added. The mixture was stirred at room temperature for 5 h and worked up. The crude product was chromatographed on a silica gel column with hexane–ethyl acetate (10:1) as the eluent to give ester **26** (367 mg, 18%) as crystals, mp 82.1–83.3 °C (Found: C, 68.3; H, 7.2; Cl, 8.65. $C_{23}H_{29}ClO_4$ requires C, 68.2; H, 7.2; Cl, 8.8%); ν_{max}(KBr)/cm^{-1} 1732; δ_H(400 MHz) 1.33 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 3.91 (3 H, s, OMe), 6.90 (2 H, s, ArH), 7.01 (1 H, d, *J* 8.9, ArH), 7.53 (1 H, dd, *J* 8.9 and 2.8, ArH) and 8.09 (1 H, d, *J* 2.8, ArH).

2,6-Di-*tert*-butyl-4-methoxyphenyl 4-methoxy-3-pyrrolidinylbenzoate 35

To a solution of methyl 3-amino-4-methoxybenzoate (4.66 g, 25.7 mmol) in xylene (10 cm^3)–pyridine (5.0 cm^3) was added butane-1,4-diyl bis(methanesulfonate) (12.7 g, 51.6 mmol) at 120 °C, and the mixture was stirred at this temperature for 6 h. After cooling, the mixture was poured into saturated aqueous Na_2CO_3 (20 cm^3) and extracted with diethyl ether. The extract was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (6:1 to 3:1) as the eluent to give methyl 4-methoxy-3-pyrrolidinylbenzoate (3.07 g, 51%) as an oil; ν_{max}(neat)/cm^{-1} 1715; δ_H(400 MHz) 1.91–1.97 (4 H, m, NCH_2CH_2 × 2), 3.29–3.34 (4 H, m, NCH_2 × 2), 3.87 (3 H, s, OMe), 3.89 (3 H, s, OMe), 6.83 (1 H, d, *J* 8.4, ArH), 7.44 (1 H, d, *J* 1.9, ArH) and 7.56 (1 H, dd, *J* 8.4 and 1.9, ArH).

A sample of the pyrrolidinyl ester (74.8 mg, 318 μmol) was boiled with KOH (35.6 mg) in a mixture of ethanol (400 mm^3) and water (40 mm^3) for 2 h. After most of the ethanol had been evaporated, the mixture was slightly acidified by the addition of 2 mol dm^{-3} HCl, the pH value being adjusted to around 4.5. The acidic mixture was extracted with ethyl acetate and the extract was dried ($MgSO_4$) and evaporated. The residue was purified by PLC with hexane–ethyl acetate (3:1) as the developer to give 4-methoxy-3-pyrrolidinylbenzoic acid (45.4 mg, 65%) as crystals, mp 146–147 °C (Found: C, 65.3; H, 7.1; N, 6.2. $C_{12}H_{15}NO_3$ requires C, 65.1; H, 6.8; N, 6.3%); ν_{max}(KBr)/cm^{-1} 2968 and 1680; δ_H(400 MHz) 1.92–1.99 (4 H, m, NCH_2CH_2 × 2), 3.31–3.37 (4 H, m, NCH_2 × 2), 3.91 (3 H, s, OMe), 6.87 (1 H, d, *J* 8.4, ArH), 7.50 (1 H, d, *J* 2.0, ArH) and 7.66 (1 H, dd, *J* 8.4 and 2.0, ArH). Application of this procedure to the pyrrolidinyl ester (2.77 g, 11.8 mmol) gave the acid (2.45 g), which was used without purification for the following reaction.

The crude acid (2.45 g, *ca.* 11.1 mmol) was boiled in thionyl chloride (12 cm^3) for 2 h and then volatiles were removed under reduced pressure to give the acid chloride. This was dissolved in dry benzene (12 cm^3) and the solution was added to a mixture of 2,6-di-*tert*-butyl-4-methoxyphenol (2.89 g, 12.2 mmol), 4-PPy (1.82 g, 12.3 mmol), DMAP (1.49 g, 12.2 mmol), pyridine (6.0 cm^3) and benzene (12 cm^3). The mixture was refluxed for 24 h. After cooling, the resulting mixture was poured into saturated aqueous Na_2CO_3 (35 cm^3) and the two layers were separated. The organic layer was extracted with diethyl ether and the combined organic layer was washed with water, dried ($MgSO_4$) and evaporated. Chromatography on a silica gel with hexane–ethyl acetate (6:1) as the eluent gave ester **35** (436 mg, 8% based on the methyl 4-methoxy-3-pyrrolidinylbenzoate) as crystals, mp 151–153 °C (Found: C, 73.7; H, 8.3; N, 3.1. $C_{27}H_{37}NO_4$ requires C, 73.8; H, 8.5; N, 3.2%); ν_{max}(KBr)/cm^{-1} 1723; δ_H(400 MHz) 1.32 (18 H, s, Bu^t × 2), 1.93–1.97 (4 H, m, NCH_2CH_2 × 2), 3.35–3.39 (4 H, m, NCH_2 × 2), 3.82 (3 H, s, OMe), 3.92 (3 H, s, OMe), 6.90 (2 H, s, ArH), 6.92 (1 H, d, *J* 8.5, ArH), 7.57 (1 H, d, *J* 2.1, ArH) and 7.75 (1 H, dd, *J* 8.5 and 2.1, ArH).

2,6-Di-*tert*-butyl-4-methoxyphenyl 3-fluoro-4-methoxybenzoate 41

This compound was prepared by the same procedure as mentioned for the preparation of ester **8**. Sodium methoxide prepared from sodium (1.85 g, 80.5 mmol) and methanol (30 cm^3) was suspended in THF (80 cm^3) and a solution of ester **44** (3.02 g, 8.02 mmol) in THF (40 cm^3) was added. The mixture was stirred at room temperature for 5 h and worked up. The crude product was recrystallized from ethanol to give ester **41** (1.33 g). The mother liquor was evaporated and the residue was chromatographed on a silica gel column eluting with hexane–ethyl acetate (14:1) to give an additional crop (1.50 g) for a total yield of 2.83 g (91%) as crystals, mp 150–151 °C (Found: C, 71.1; H, 7.5. $C_{23}H_{29}FO_4$ requires C, 71.1; H, 7.5%); ν_{max}(KBr)/cm^{-1} 1728; δ_H(400 MHz) 1.31 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 3.99 (3 H, s, OMe), 6.90 (2 H, s, ArH), 7.08 (1 H, t, *J* 8.4, ArH), 7.93 (1 H, dd, *J* 11.6 and 2.1, ArH) and 8.02 (1 H, ddd, *J* 8.4, 2.1 and 1.2, ArH).

2-(3,4-Dimethoxyphenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole 46

This method is essentially the same as reported by Meyers *et al.*[26] The acid chloride prepared from 3,4-dimethoxybenzoic acid (1.00 g, 5.49 mmol) and thionyl chloride (3.0 cm^3) was dissolved in dry dichloromethane (4.0 cm^3) and the solution was added to a solution of 2-amino-2-methylpropan-1-ol (1.03 g, 11.6 mmol) in dichloromethane (6.0 cm^3) at 0 °C. The mixture was stirred at room temperature for 2.5 h and then filtered. The filtrate was evaporated and the residue was dissolved in dry benzene (6.0 cm^3). The solution was cooled in an ice bath and thionyl chloride (3.0 cm^3) was added. The mixture was stirred at room temperature overnight, quenched with water (20 cm^3) and made alkaline by addition of 2 mol dm^{-3} NaOH (30 cm^3). The mixture was extracted with diethyl ether and the extract was washed with water, dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (5:2) as the eluent to give oxazoline **46** (1.20 g, 93%) as crystals, which melt near room temperature (Found: C, 66.1; H, 7.3; N, 5.95. $C_{13}H_{17}NO_3$ requires C, 66.4; H, 7.3; N, 6.0%); ν_{max}(KBr)/cm^{-1} 1651; δ_H(400 MHz) 1.38 (6 H, s, Me × 2), 3.92 (3 H, s, OMe), 3.93 (3 H, s, OMe), 4.09 (2 H, s, OCH_2), 6.87 (1 H, d, *J* 8.4, ArH), 7.47 (1 H, d, *J* 1.9, ArH) and 7.53 (1 H, dd, *J* 8.4 and 1.9, ArH).

General procedure for the S_NAr reaction

A mixture of magnesium turnings (100 mg), a few drops of 1,2-dibromoethane and dry diethyl ether (1.0 cm^3) was irradiated with ultrasound for 10 min. To the activated magnesium was added dropwise a solution of a pertinent bromide (2.50 mmol) in diethyl ether (2.5 cm^3) under sonication over a controlled period of time (30 min for phenyl, butyl and isopropyl bromide, 3 h for allyl and benzyl bromide and 6 h for *tert*-butyl bromide). After the mixture had been sonicated under gentle reflux for a further 2 h, dry benzene (3.5 cm^3) was added, and the resulting mixture was sonicated for 15 min to give the Grignard solution. After cooling, this was added to a solution of a substrate (1.00 mmol) in benzene (3.5 cm^3) and the mixture was stirred at an appropriate temperature for 1–72 h. The mixture was poured into saturated aqueous NH_4Cl (15 cm^3) and the two layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic layer was washed with water, dried ($MgSO_4$) and evaporated. See Tables 1 and 2 for reaction condi-

tions and the yield of the corresponding product. Chromatography on a silica gel column was used for purification of the products using the indicated eluent, unless otherwise noted.

Compound 12a. Hexane–ethyl acetate (8:1) as the eluent; crystals, mp 148–149 °C (Found: C, 77.9; H, 7.6. $C_{29}H_{34}O_4$ requires C, 78.0; H, 7.7%); ν_{max}(KBr)/cm^{-1} 1746; δ_H(400 MHz) 1.28 (18 H, s, Bu^t × 2), 3.73 (3 H, s, OMe), 3.74 (3 H, s, OMe), 6.79 (2 H, s, ArH), 7.10–7.13 (2 H, m, ArH), 7.22–7.33 (4 H, m, ArH), 7.53 (1 H, td, *J* 8.1 and 1.0, ArH) and 8.06 (1 H, dd, *J* 7.8 and 1.0, ArH).

Compound 12b. Hexane–ethyl acetate (20:1) as the eluent; crystals, mp 102–104 °C (Found: C, 76.1; H, 8.9. $C_{27}H_{38}O_4$ requires C, 76.0; H, 9.0%); ν_{max}(KBr)/cm^{-1} 1729; δ_H(400 MHz) 0.86 [3 H, t, *J* 7.2, $(CH_2)_3$*Me*], 1.33 (18 H, s, Bu^t × 2), 1.34–1.42 [2 H, m, $(CH_2)_2CH_2$Me], 1.44–1.52 (2 H, m, CH_2CH_2Et), 3.05–3.09 (2 H, m, CH_2Pr), 3.81 (3 H, s, OMe), 3.87 (3 H, s, OMe), 6.91 (2 H, s, ArH), 7.11 (1 H, dd, *J* 8.1 and 1.0, ArH), 7.32 (1 H, t, *J* 8.1, ArH) and 7.97 (1 H, dd, *J* 8.1 and 1.0, ArH).

Compound 12c. Hexane–ethyl acetate (20:1) as the eluent; crystals, mp 106–107 °C (Found: C, 75.8; H, 8.85. $C_{26}H_{36}O_4$ requires C, 75.7; H, 8.8%); ν_{max}(KBr)/cm^{-1} 1734; δ_H(400 MHz) 1.30 (6 H, d, *J* 7.0, CHMe_2), 1.35 (18 H, s, Bu^t × 2), 3.81 (3 H, s, OMe), 3.87 (3 H, s, OMe), 4.13 (1 H, sept, *J* 7.0, C*H*Me$_2$), 6.91 (2 H, s, ArH), 7.09 (1 H, d, *J* 8.1, ArH), 7.31 (1 H, t, *J* 8.1, ArH) and 7.81 (1 H, d, *J* 8.1, ArH).

Compound 12d. Hexane–ethyl acetate (19:1) as the eluent; crystals, mp 124–125 °C (Found: C, 76.05; H, 8.3. $C_{26}H_{34}O_4$ requires C, 76.1; H, 8.3%); ν_{max}(KBr)/cm^{-1} 1731; δ_H(400 MHz) 1.32 (18 H, s, Bu^t × 2), 3.81 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.92 (2 H, ddd, *J* 6.3, 1.5 and 1.3, ArCH_2), 4.88 [1 H, ddt, *J* 10.1, 2.1 and 1.3, CH=CH_2 (*trans*)], 4.98 [1 H, ddt, *J* 17.1, 2.1 and 1.5, CH=CH_2 (*cis*)], 5.97 (1 H, ddt, *J* 17.1, 10.1 and 6.3, C*H*=CH$_2$), 6.91 (2 H, s, ArH), 7.14 (1 H, dd, *J* 8.1 and 1.1, ArH), 7.37 (1 H, t, *J* 8.1, ArH) and 8.00 (1 H, dd, *J* 8.1 and 1.1, ArH).

Compound 12e. Hexane–ethyl acetate [9:1 (entry 5 in Table 1) or 20:1 (entry 6 in Table 1)] as the eluent; crystals, mp 106–107 °C (Found: C, 78.4; H, 7.8. $C_{30}H_{36}O_4$ requires C, 78.2; H, 7.9%); ν_{max}(KBr)/cm^{-1} 1728; δ_H(400 MHz) 1.24 (18 H, s, Bu^t × 2), 3.79 (3 H, s, OMe), 3.85 (3 H, s, OMe), 4.61 (2 H, s, CH_2Ph), 6.86 (2 H, s, ArH), 7.02–7.06 (1 H, m, ArH), 7.09–7.15 (4 H, m, ArH), 7.18 (1 H, d, *J* 8.1, ArH), 7.42 (1 H, t, *J* 8.1, ArH) and 8.06 (1 H, d, *J* 8.1, ArH).

Compound 13a. Hexane–ethyl acetate (19:1) (entry 8 in Table 1) or hexane–benzene (1:1) (entry 17 in Table 1) as the eluent; crystals, mp 224–225 °C (Found: C, 77.1; H, 7.3. $C_{28}H_{31}FO_3$ requires C, 77.4; H, 7.2%); ν_{max}(KBr)/cm^{-1} 1741; δ_H(400 MHz) 1.28 (18 H, s, Bu^t × 2), 3.74 (3 H, s, OMe), 6.81 (s, 2 H, ArH), 7.18–7.21 (2 H, m, ArH), 7.29–7.35 (3 H, m, ArH), 7.41 (1 H, td, *J* 8.1 and 1.2, ArH), 7.55 (1 H, td, *J* 8.1 and 5.4, ArH) and 8.25 (1 H, dt, *J* 8.1 and 1.2, ArH).

Compound 13d. Hexane–ethyl acetate [14:1 (entry 9 in Table 1) or 19:1 (entry 18 in Table 1)] as the eluent; crystals, mp 86.6–87.7 °C (Found: C, 75.2; H, 7.8. $C_{25}H_{31}FO_3$ requires C, 75.3; H, 7.8%); ν_{max}(KBr)/cm^{-1} 1730; δ_H(400 MHz) 1.32 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 3.91 (2 H, ddd, *J* 6.4, 2.8 and 1.4, ArCH_2), 4.94 [1 H, ddt, *J* 10.2, 1.5 and 1.4, CH=CH_2 (*trans*)], 5.01 [1 H, dtd, *J* 17.0, 2.8 and 1.5, CH=CH_2 (*cis*)], 5.97 (1 H, ddt, *J* 17.0, 10.2 and 6.4, C*H*=CH$_2$), 6.91 (2 H, s, ArH), 7.33 (1 H, ddd, *J* 9.5, 8.0 and 1.3, ArH), 7.40 (1 H, td, *J* 8.0 and 5.6, ArH) and 8.19 (1 H, d, *J* 8.0, ArH).

Compound 13e (entry 10 in Table 1). The crude product was chromatographed on a silica gel column with hexane–ethyl acetate (19:1) as the eluent to give a mixture of compounds **13e** and **17**, which was then chromatographed on an alumina column with hexane–benzene (1:1) as the eluent; crystals, mp 108–109 °C (Found: C, 77.45; H, 7.6. $C_{29}H_{33}FO_3$ requires C, 77.6; H, 7.4%); ν_{max}(KBr)/cm^{-1} 1733; δ_H(400 MHz) 1.24 (18 H, s, Bu^t × 2), 3.80 (3 H, s, OMe), 4.59 (2 H, d, *J* 2.3, CH_2Ph), 6.87 (2 H, s, ArH), 7.06–7.10 (1 H, m, ArH), 7.12–7.19 (4 H, m, ArH), 7.37 (1 H, ddd, *J* 9.4, 8.0 and 1.4, ArH), 7.43 (1 H, td, *J* 8.0 and 5.6, ArH) and 8.25 (1 H, dt, *J* 8.0 and 1.4, ArH).

Compound 13e (entry 19 in Table 1). Hexane–ethyl acetate (9:1) as the eluent; crystals, the spectral data of which were identical with those of compound **13e** obtained from the reaction of ester **8** with benzylmagnesium bromide.

Compound 14a. Hexane–benzene (1:1) as the eluent; crystals, mp 194–195 °C (Found: C, 74.65; H, 6.95; Cl, 8.0. $C_{28}H_{31}ClO_3$ requires C, 74.6; H, 6.9; Cl, 7.9%); ν_{max}(KBr)/cm^{-1} 1741; δ_H(400 MHz) 1.27 (18 H, s, Bu^t × 2), 3.74 (3 H, s, OMe), 6.79 (2 H, s, ArH), 7.09–7.12 (2 H, m, ArH), 7.24–7.38 (3 H, m, ArH), 7.52 (1 H, t, *J* 8.0, ArH), 7.75 (1 H, dd, *J* 8.0 and 1.2, ArH) and 8.38 (1 H, dd, *J* 8.0 and 1.2, ArH).

Compound 14d. Hexane–ethyl acetate (12:1) as the eluent; crystals, mp 107–108 °C (Found: C, 72.6; H, 7.45; Cl, 8.6. $C_{25}H_{31}ClO_3$ requires C, 72.4; H, 7.5; Cl, 8.5%); ν_{max}(KBr)/cm^{-1} 1735; δ_H(400 MHz) 1.32 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 4.07 (2 H, ddd, *J* 6.1, 1.6 and 1.5, ArCH_2), 4.97 [1 H, ddt, *J* 10.2, 1.7 and 1.5, CH=CH_2 (*trans*)], 5.01 [1 H, ddt, *J* 17.2, 1.7 and 1.6, CH=CH_2 (*cis*)], 5.94 (1 H, ddt, *J* 17.2, 10.2 and 6.1, C*H*=CH$_2$), 6.91 (2 H, s, ArH), 7.37 (1 H, t, *J* 8.0, ArH), 7.67 (1 H, dd, *J* 8.0 and 1.3, ArH) and 8.34 (1 H, dd, *J* 8.0 and 1.3, ArH).

Compound 14e. The crude product was chromatographed on a silica gel column with hexane–ethyl acetate (40:1) as the eluent to give a mixture of compounds **14e** and **18**, which was then chromatographed on an alumina column with hexane–benzene (1:2) as the eluent; crystals, mp 117–118 °C (Found: C, 74.65; H, 7.0; Cl, 7.5. $C_{29}H_{33}ClO_3$ requires C, 74.9; H, 7.2; Cl, 7.6%); ν_{max}(KBr)/cm^{-1} 1734; δ_H(400 MHz) 1.22 (18 H, s, Bu^t × 2), 3.78 (3 H, s, OMe), 4.78 (2 H, s, CH_2Ph), 6.85 (2 H, s, ArH), 7.01–7.16 (5 H, m, ArH), 7.43 (1 H, t, *J* 8.0, ArH), 7.73 (1 H, dd, *J* 8.0 and 1.3, ArH) and 8.41 (1 H, dd, *J* 8.0 and 1.3, ArH).

Compound 15a. Hexane–ethyl acetate (19:1 to 12:1) as the eluent; crystals, mp 184–185 °C (Found: C, 68.0; H, 6.2; Br, 16.4. $C_{28}H_{31}BrO_3$ requires C, 67.9; H, 6.3; Br, 16.1%); ν_{max}(KBr)/cm^{-1} 1741; δ_H(400 MHz) 1.27 (18 H, s, Bu^t × 2), 3.74 (3 H, s, OMe), 6.79 (2 H, s, ArH), 7.06–7.09 (2 H, m, ArH), 7.27–7.36 (3 H, m, ArH), 7.44 (1 H, t, *J* 8.0, ArH), 7.94 (1 H, dd *J* 8.0 and 1.2, ArH) and 8.25 (1 H, dd, *J* 8.0 and 1.2, ArH).

Compound 15d. Hexane–ethyl acetate (9:1) as the eluent; crystals, mp 134–135 °C (Found: C, 65.5; H, 6.8; Br, 17.2. $C_{25}H_{31}BrO_3$ requires C, 65.4; H, 6.8; Br, 17.4%); ν_{max}(KBr)/cm^{-1} 1734; δ_H(400 MHz) 1.31 (18 H, s, Bu^t × 2), 3.81 (3 H, s, OMe), 4.10 (2 H, ddd, *J* 6.1, 1.6 and 1.5, ArCH_2), 4.98 [1 H, ddt, *J* 10.2, 1.7 and 1.5, CH=CH_2 (*trans*)], 5.02 [1 H, ddt, *J* 17.2, 1.7 and 1.6, CH=CH_2 (*cis*)], 5.94 (1 H, ddt, *J* 17.2, 10.2 and 6.1, C*H*=CH$_2$), 6.91 (2 H, s, ArH), 7.29 (1 H, t, *J* 8.0, ArH), 7.87 (1 H, dd, *J* 8.0 and 1.3, ArH) and 8.39 (1 H, dd, *J* 8.0 and 1.3, ArH).

Compound 15e. The crude product was chromatographed on a silica gel column with hexane–ethyl acetate (40:1) as the eluent to give a mixture of compounds **15e** and **19**, which was then chromatographed on an alumina column with hexane–benzene (1:1) as the eluent; crystals, mp 122–123 °C (Found: C, 68.3; H,

6.35; Br, 15.8. $C_{29}H_{33}BrO_3$ requires C, 68.4; H, 6.5; Br, 15.7%); ν_{max}(KBr)/cm^{-1} 1733; δ_H(400 MHz) 1.21 (18 H, s, Bu^t × 2), 3.78 (3 H, s, OMe), 4.82 (2 H, s, CH_2Ph), 6.85 (2 H, s, ArH), 7.00 (2 H, d, *J* 7.3, ArH), 7.07 (1 H, t, *J* 7.3, ArH), 7.14 (2 H, t, *J* 7.3, ArH), 7.35 (1 H, t, *J* 8.0, ArH), 7.92 (1 H, d, *J* 8.0, ArH) and 8.46 (1 H, d, *J* 8.0, ArH).

Compound 17. This compound was separated from compound **13e** as mentioned above; crystals, mp 111–112 °C (Found: C, 70.5; H, 7.25. $C_{22}H_{27}FO_4$ requires C, 70.6; H, 7.3%); ν_{max}(KBr)/cm^{-1} 3140 and 1684; δ_H(400 MHz) 1.32 (18 H, s, Bu^t × 2), 3.83 (3 H, s, OMe), 6.92 (2 H, s, ArH), 6.96 (1 H, td, *J* 8.2 and 4.6, ArH), 7.37 (1 H, ddd, *J* 10.2, 8.2 and 1.7, ArH), 7.89 (1 H, dt, *J* 8.2 and 1.7, ArH) and 10.82 (1 H, s, OH).

Compound 18. This compound was separated from compound **14e** as mentioned above; crystals, mp 118–119 °C (Found: C, 67.5; H, 6.9; Cl, 9.4. $C_{22}H_{27}ClO_4$ requires C, 67.6; H, 7.0; Cl, 9.1%); ν_{max}(KBr)/cm^{-1} 3105 and 1684; δ_H(400 MHz) 1.32 (18 H, s, Bu^t × 2), 3.83 (3 H, s, OMe), 6.92 (2 H, s, ArH), 6.99 (1 H, t, *J* 7.9, ArH), 7.66 (1 H, dd, *J* 7.9 and 1.5, ArH), 8.05 (1 H, dd, *J* 7.9 and 1.5, ArH) and 11.38 (1 H, s, OH).

Compound 19. This compound was separated from compound **15e** as mentioned above; crystals, mp 122–123 °C (Found: C, 60.9; H, 6.5; Br, 18.5. $C_{22}H_{27}BrO_4$ requires C, 60.7; H, 6.3; Br, 18.4%); ν_{max}(KBr)/cm^{-1} 3105 and 1674; δ_H(400 MHz) 1.31 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 6.92 (2 H, s, ArH), 6.94 (1 H, t, *J* 7.9, ArH), 7.83 (1 H, d, *J* 7.9, ArH), 8.09 (1 H, d, *J* 7.9, ArH) and 11.49 (1 H, s, OH).

Compound 22. Hexane–ethyl acetate (14 : 1) as the eluent; an oil (Found: C, 80.5; H, 7.6. $C_{26}H_{28}O_3$ requires C, 80.4; H, 7.3%); ν_{max}(neat)/cm^{-1} 1744; δ_H(400 MHz) 1.10 (12 H, d, *J* 6.9, CH*Me*$_2$ × 2), 2.75 (2 H, sept, *J* 6.9, C*H*Me$_2$ × 2), 3.75 (3 H, s, OMe), 7.07–7.18 (4 H, m, ArH), 7.27–7.38 (5 H, m, ArH), 7.47 (1 H, t, *J* 8.0, ArH) and 7.67 (1 H, dd, *J* 8.0 and 1.0, ArH).

Compound 23. Hexane–ethyl acetate (19 : 1) as the eluent; crystals, mp 96.2–97.4 °C (Found: C, 80.7; H, 7.6. $C_{27}H_{30}O_3$ requires C, 80.6; H, 7.5%); ν_{max}(KBr)/cm^{-1} 1726; δ_H(400 MHz) 1.11 (12 H, d, *J* 6.9, CH*Me*$_2$ × 2), 2.84 (2 H, sept, *J* 6.9, C*H*Me$_2$ × 2), 3.85 (3 H, s, OMe), 4.56 (2 H, s, CH_2Ph), 7.08–7.23 (9 H, m, ArH), 7.40 (1 H, t, *J* 8.0, ArH) and 7.83 (1 H, d, *J* 8.0, ArH).

Compound 25. Hexane–ethyl acetate (9 : 1) as the eluent; crystals, mp 110–112 °C (Found: C, 78.0; H, 7.8. $C_{29}H_{34}O_4$ requires C, 78.0; H, 7.7%); ν_{max}(KBr)/cm^{-1} 1743; δ_H(400 MHz) 1.30 (18 H, s, Bu^t × 2), 3.75 (3 H, s, OMe), 3.93 (3 H, s, OMe), 6.81 (2 H, s, ArH), 7.17 (1 H, dd, *J* 8.5 and 2.7, ArH), 7.19–7.29 (6 H, m, ArH) and 7.97 (1 H, d, *J* 2.7, ArH).

Compound 27. Hexane–ethyl acetate (10 : 1) as the eluent; crystals, mp 143–144 °C (Found: C, 74.4; H, 6.9; Cl, 8.0. $C_{28}H_{31}ClO_3$ requires C, 74.6; H, 6.9; Cl, 7.9%); ν_{max}(KBr)/cm^{-1} 1747; δ_H(400 MHz) 1.30 (18 H, s, Bu^t × 2), 3.75 (3 H, s, OMe), 6.82 (2 H, s, ArH), 7.17–7.20 (2 H, m, ArH), 7.25–7.30 (4 H, m, ArH), 7.60 (1 H, dd, *J* 8.2 and 2.2, ArH) and 8.37 (1 H, d, *J* 2.2, ArH).

Compound 36a. Hexane–ethyl acetate (14 : 1) as the eluent; crystals, mp 195–197 °C (Found: C, 78.25; H, 7.7. $C_{29}H_{34}O_4$ requires C, 78.0; H, 7.7%); ν_{max}(KBr)/cm^{-1} 1727; δ_H(400 MHz) 1.36 (18 H, s, Bu^t × 2), 3.83 (3 H, s, OMe), 3.90 (3 H, s, OMe), 6.92 (2 H, s, ArH), 7.36–7.40 (1 H, m, ArH), 7.43–7.48 (3 H, m, ArH), 7.57–7.60 (2 H, m, ArH), 7.80 (1 H, d, *J* 1.5, ArH) and 7.93 (1 H, dd, *J* 7.9 and 1.5, ArH).

Compound 36b. Hexane–ethyl acetate (14 : 1) as the eluent; crystals, mp 154–156 °C (Found: C, 76.0; H, 9.0. $C_{27}H_{38}O_4$ requires C, 76.0; H, 9.0%); ν_{max}(KBr)/cm^{-1} 1730; δ_H(400 MHz) 0.96 [3 H, t, *J* 7.3, (CH$_2$)$_3$*Me*], 1.33 (18 H, s, Bu^t × 2), 1.34–1.48 [2 H, m, (CH$_2$)$_2$CH_2Me], 1.58–1.65 (2 H, m, CH$_2$CH_2Et), 2.69 (2 H, t, *J* 7.8, CH_2Pr), 3.82 (3 H, s, OMe), 3.90 (3 H, s, OMe), 6.91 (2 H, s, ArH), 7.28 (1 H, d, *J* 7.8, ArH), 7.64 (1 H, d, *J* 1.5, ArH) and 7.79 (1 H, dd, *J* 7.8 and 1.5, ArH).

Compound 36c. Hexane–ethyl acetate (14 : 1) as the eluent; crystals, mp 188–190 °C (Found: C, 75.9; H, 8.8. $C_{26}H_{36}O_4$ requires C, 75.7; H, 8.8%); ν_{max}(KBr)/cm^{-1} 1728; δ_H(400 MHz) 1.26 (6 H, d, *J* 6.9, CH*Me*$_2$), 1.33 (18 H, s, Bu^t × 2), 3.39 (1 H, sept, *J* 6.9, C*H*Me$_2$), 3.82 (3 H, s, OMe), 3.91 (3 H, s, OMe), 6.91 (2 H, s, ArH), 7.35 (1 H, d, *J* 8.0, ArH), 7.64 (1 H, d, *J* 1.6, ArH) and 7.83 (1 H, dd, *J* 8.0 and 1.6, ArH).

Compound 36e. Hexane–ethyl acetate (8 : 1) as the eluent; crystals, mp 156–157 °C (Found: C, 78.1; H, 7.85. $C_{30}H_{36}O_4$ requires C, 78.2; H, 7.9%); ν_{max}(KBr)/cm^{-1} 1730; δ_H(400 MHz) 1.31 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 3.92 (3 H, s, OMe), 4.04 (2 H, s, CH_2Ph), 6.90 (2 H, s, ArH), 7.18–7.33 (6 H, m, ArH), 7.67 (1 H, d, *J* 1.5, ArH) and 7.77 (1 H, dd, *J* 7.8 and 1.5, ArH).

Compound 37a. Hexane–ethyl acetate (19 : 1 to 9 : 1) as the eluent; crystals, mp 152–153 °C (Found: C, 75.6; H, 7.75. $C_{30}H_{36}O_5$ requires C, 75.6; H, 7.6%); ν_{max}(KBr)/cm^{-1} 1737; δ_H(400 MHz) 1.37 (18 H, s, Bu^t × 2), 3.82 (6 H, s, OMe × 2), 3.84 (3 H, s, OMe), 6.93 (2 H, s, ArH), 7.34–7.40 (3 H, m, ArH), 7.42–7.47 (2 H, m, ArH) and 7.52 (2 H, s, ArH).

Compound 37e. Hexane–ethyl acetate (19 : 1 to 6 : 1) as the eluent; crystals, mp 130–131 °C (Found: C, 75.9; H, 8.1. $C_{31}H_{38}O_5$ requires C, 75.9; H, 7.8%); ν_{max}(KBr)/cm^{-1} 1729; δ_H(400 MHz) 1.32 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 3.90 (6 H, s, OMe × 2), 4.07 (2 H, s, CH_2Ph), 6.90 (2 H, s, ArH), 7.14–7.18 (1 H, m, ArH), 7.22–7.27 (2 H, m, ArH), 7.32–7.35 (2 H, m, ArH) and 7.42 (2 H, s, ArH).

Compound 38a. Hexane–ethyl acetate (10 : 1) as the eluent; crystals, mp 129–130 °C (Found: C, 79.1; H, 8.1; N, 2.8. $C_{32}H_{39}NO_3$ requires C, 79.1; H, 8.1; N, 2.9%); ν_{max}(KBr)/cm^{-1} 1721; δ_H(400 MHz) 1.36 (18 H, s, Bu^t × 2), 1.76–1.81 (4 H, m, NCH$_2$CH_2 × 2), 2.94–2.99 (4 H, m, NCH_2 × 2), 3.83 (3 H, s, OMe), 6.92 (2 H, s, ArH) and 7.28–7.71 (8 H, m, ArH).

Compound 40. Hexane–ethyl acetate (14 : 1) as the eluent; crystals, mp 170–172 °C (Found: C, 71.3; H, 7.6. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%); ν_{max}(KBr)/cm^{-1} 3395 and 1697; δ_H(400 MHz) 1.32 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 3.98 (3 H, s, OMe), 6.11 (1 H, s, OH), 6.90 (2 H, s, ArH), 7.03 (1 H, d, *J* 8.3, ArH), 7.69 (1 H, d, *J* 1.9, ArH) and 7.86 (1 H, dd, *J* 8.3 and 1.9, ArH).

Compound 45. Hexane–ethyl acetate (19 : 1) as the eluent; crystals, mp 140–142 °C (Found: C, 78.0; H, 7.7. $C_{29}H_{34}O_4$ requires C, 78.0; H, 7.7%); ν_{max}(KBr)/cm^{-1} 1732; δ_H(400 MHz) 1.30 (18 H, s, Bu^t × 2), 3.74 (3 H, s, OMe), 3.89 (3 H, s, OMe), 6.81 (2 H, s, ArH), 6.83 (1 H, d, *J* 2.7, ArH), 7.05 (1 H, dd, *J* 8.8 and 2.7, ArH), 7.20–7.30 (5 H, m, ArH) and 8.40 (1 H, d, *J* 8.8, ArH).

The regiochemistry of the sample was confirmed by comparison of its spectral data with that of an authentic sample which had been prepared from the reaction of 2,6-di-*tert*-butyl-4-methoxyphenyl 2,4-dimethylbenzoate with phenylmagnesium bromide.

Compound 47. Hexane–ethyl acetate (10 : 1 to 2 : 1) as the eluent, crystals, mp 82.5–83.6 °C (Found: C, 76.9; H, 7.1; N, 4.9. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%); ν_{max}(KBr)/cm^{-1}

1645; δ_H(400 MHz) 1.40 (6 H, s, Me × 2), 3.87 (3 H, s, OMe), 4.12 (2 H, s, OCH_2), 7.31–7.36 (2 H, m, ArH), 7.38–7.43 (2 H, m, ArH), 7.52–7.56 (3 H, m, ArH) and 7.60 (1 H, dd, *J* 7.8 and 1.5, ArH).

Compound 52. Hexane–ethyl acetate (15:1) as the eluent, an oil, ν_{max}(neat)/cm^{-1} 1620; δ_H(400 MHz) 2.56 (1 H, dd, *J* 17.3 and 2.1, CH_2), 3.09 (1 H, ddd, *J* 17.3, 9.8 and 1.9, CH_2), 3.67 (3 H, s, OMe), 4.43 (1 H, dd, *J* 9.8 and 2.1, CHPh), 5.18 (1 H, dd, *J* 6.7 and 1.9, C*H*=COMe), 6.98 (1 H, d, *J* 6.7, C*H*=CBz), 7.16–7.20 (1 H, m, ArH), 7.23–7.27 (2 H, m, ArH), 7.30–7.32 (2 H, m, ArH), 7.37–7.41 (2 H, m, ArH), 7.44–7.48 (1 H, m, ArH) and 7.56–7.58 (2 H, m, ArH).

A sample of ketone **52** (230 mg, 792 μmol) was aromatized by treatment with DDQ (450 mg, 1.98 mmol) in toluene (5.0 cm^3) at 80 °C for 12 h. The cooled mixture was poured into 2 mol dm^{-3} NaOH (15 cm^3) and extracted with diethyl ether. The extract was washed successively with 2 mol dm^{-3} NaOH and water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (5:1) as the eluent to give 5-methoxybiphenyl-2-yl phenyl ketone as crystals (215 mg, 94%), mp 82.7–83.6 °C (Found: C, 83.4; H, 5.65. $C_{20}H_{16}O_2$ requires C, 83.3; H, 5.6%); ν_{max}(KBr)/cm^{-1} 1655; δ_H(400 MHz) 3.91 (3 H, s, OMe), 6.97 (1 H, dd, *J* 9.4 and 2.5, ArH), 6.98 (1 H, s, ArH), 7.12–7.21 (3 H, m, ArH), 7.23–7.27 (4 H, m, ArH), 7.35–7.40 (1 H, m, ArH), 7.50–7.53 (1 H, m, ArH) and 7.61–7.64 (2 H, m, ArH).

Reaction of ester 7 with *tert*-butylmagnesium bromide 11f (entry 7 in Table 1)

The Grignard reaction was conducted by the general procedure for the S_NAr reaction. After the usual work-up, the crude mixture was treated with DDQ (749 mmol, 3.30 mmol) in dry toluene (15 cm^3) by the same procedure as mentioned for aromatization of ketone **52.** Chromatography on a silica gel column with hexane–ethyl acetate (20:1) as the eluent gave the following products.

Compound **12f** (94.9 mg, 22%) as crystals, mp 197–198 °C (Found: C, 76.0; H, 8.9. $C_{27}H_{38}O_4$ requires C, 76.0; H, 9.0%); ν_{max}(KBr)/cm^{-1} 1728; δ_H(400 MHz) 1.34 (18 H, s, Bu^t × 2), 1.52 (9 H, s, Bu^t), 3.81 (3 H, s, OMe), 3.85 (3 H, s, OMe), 6.90 (2 H, s, ArH), 7.11 (1 H, dd, *J* 8.0 and 1.3, ArH), 7.27 (1 H, t, *J* 8.0, ArH) and 8.06 (1 H, dd, *J* 8.0 and 1.3, ArH).

Compound **16** (192 mg, 42%) as crystals, mp 156–158 °C (Found: C, 73.4; H, 8.85. $C_{28}H_{40}O_5$ requires C, 73.7; H, 8.8%); ν_{max}(KBr)/cm^{-1} 1742; δ_H(400 MHz) 1.35 (18 H, s, Bu^t × 2), 1.42 (9 H, s, Bu^t), 3.82 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.96 (3 H, s, OMe), 6.91 (2 H, s, ArH), 7.19 (1 H, d, *J* 8.6, ArH) and 7.85 (1 H, d, *J* 8.6, ArH).

Reaction of ester 33 with phenyllithium

To a solution of ester **33** (401 mg, 1.00 mmol) in dry toluene (4.0 cm^3) was added dropwise phenyllithium (1.04 mol dm^{-3} in cyclohexane–diethyl ether; 2.4 cm^3, 2.50 mmol) at −45 °C and the mixture was stirred at this temperature for 3 h. The reaction was quenched with deuterium oxide (1.0 cm^3) and the mixture was diluted with saturated aqueous NH_4Cl (15 cm^3). The resulting mixture was extracted with diethyl ether and the extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (14:1) as the eluent to give deuterated compound **48** (359 mg, 89%) as crystals, mp 141–142 °C; ν_{max}(KBr)/cm^{-1} 1726; δ_H(400 MHz) 1.33 (18 H, s, Bu^t × 2), 3.82 (3 H, s, OMe), 3.96 (3 H, s, OMe), 3.98 (3 H, s, OMe), 6.91 (2 H, s, ArH), 6.99 (1 H, d, *J* 8.5, ArH) and 7.90 (1 H, d, *J* 8.5, ArH).

Synthesis of naphthol 59

Esterification of acid 53 to ester 54. This compound was prepared by the same procedure as reported before.[23] A mixture of acid **53** (9.63 g, 52.9 mmol), 2,6-di-*tert*-butyl-4-methoxyphenol (12.5 g, 52.9 mmol), TFAA (22.2 g, 106 mmol) and dry benzene (40 cm^3) was stirred at room temperature for 3 h. After work-up, the crude product was recrystallized from ethanol to give ester **54** (19.7 g, 93%) as crystals, mp 143–144 °C (Found: C, 71.9; H, 8.1. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.1%); ν_{max}(KBr)/cm^{-1} 1728; δ_H(400 MHz) 1.38 (18 H, s, Bu^t × 2), 3.81 (3 H, s, OMe), 3.85 (6 H, s, OMe × 2), 6.62 (2 H, d, *J* 8.4, ArH), 6.90 (2 H, s, ArH) and 7.85 (1 H, t, *J* 8.4, ArH).

Bromination of ester 54 to bromide 55. Ester **54** (4.01 g, 10.0 mmol) was dissolved in acetic acid (20 cm^3) by heating at 60 °C. To the cooled solution was added dropwise a solution of bromine (*d* 3.11; 560 mm^3, 10.9 mmol) in acetic acid (10 cm^3) over a period of 1 h with stirring and the mixture was stirred for a further 1 h. After the mixture had been poured into 10 wt% Na_2SO_3 (200 cm^3) in an ice bath, the resulting mixture was extracted with diethyl ether and the extract was washed successively with 1 mol dm^{-3} Na_2CO_3 and water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (10:1) to give bromide **55** (4.12 g, 86%) as crystals, mp 124–125 °C (Found: C, 59.9; H, 6.3; Br, 16.5. $C_{24}H_{31}BrO_5$ requires C, 60.1; H, 6.5; Br, 16.7%); ν_{max}(KBr)/cm^{-1} 1734; δ_H(400 MHz) 1.38 (18 H, s, Bu^t × 2), 3.81 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.95 (3 H, s, OMe), 6.71 (1 H, d, *J* 9.0, ArH), 6.91 (2 H, s, ArH) and 7.64 (1 H, d, *J* 9.0, ArH).

Allylation of bromide 55 to monoallylated compound 57. A mixture of magnesium turnings (1.15 g), 1,2-dibromoethane (50 mm^3) and THF (3.0 cm^3) was stirred at room temperature for 3 h. To the activated magnesium was added dropwise a solution of 3-chloro-2-methylpropene (660 mg, 7.29 mmol) in THF (7.0 cm^3) over a period of 6 h with stirring, while the reaction vessel was cooled in an ice bath. After being stirred for a further 2 h in the ice bath, the mixture was added dropwise to a solution of bromide **55** (1.41 g, 2.94 mmol) in THF (20 cm^3) over a period of 5 min at room temperature. The mixture was stirred for 10 min and poured into saturated aqueous NH_4Cl (100 cm^3). After the two layers had been separated, the aqueous layer was extracted with diethyl ether and the combined organic layer was washed with water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (10:1) as the eluent to give compound **57** (1.25 g, 84%) as crystals, mp 163–164 °C (Found: C, 64.2; H, 6.9; Br, 15.7. $C_{27}H_{35}BrO_4$ requires C, 64.4; H, 7.0; Br, 15.9%); ν_{max}(KBr)/cm^{-1} 1720; δ_H(400 MHz) 1.32 (18 H, s, Bu^t × 2), 1.78 (3 H, br, C*Me*=CH_2), 3.67 (2 H, br, ArCH_2), 3.80 (3 H, s, OMe), 3.91 (3 H, s, OMe), 4.10–4.11 (1 H, m, CMe=CH_2), 4.69–4.70 (1 H, m, CMe=CH_2), 6.87 (1 H, d, *J* 9.0, ArH), 6.88 (2 H, s, ArH) and 7.71 (1 H, d, *J* 9.0, ArH).

Cyclization of monoallylated compound 57 to naphthol 59. Sodium methoxide prepared from sodium (92.0 mg, 4.00 mmol) and methanol (2.0 cm^3), as mentioned for the preparation of ester **8**, was suspended in dry HMPA (2.0 cm^3). To the suspension was added compound **57** (100 mg, 199 μmol) and the mixture was stirred at 60 °C for 1 h. After cooling, the mixture was poured into 2 mol dm^{-3} HCl (30 cm^3) and the resulting mixture was extracted with diethyl ether. The extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (9:1) as the eluent to give naphthol **59** (38.8 mg, 73%) as crystals, mp 105–106 °C (lit.,[27] 100–102 °C); ν_{max}(KBr)/cm^{-1} 3327; δ_H(500 MHz) 2.47 (3 H, s, Me), 4.01 (3 H, s, OMe), 6.55 (1 H, d, *J* 8.3, ArH), 6.80 (1 H, s, ArH), 7.47 (1 H, s, ArH), 7.56 (1 H, d, *J* 8.3, ArH) and 9.31 (1 H, s, OH).

Reaction of bromide 55 with 2-methylprop-2-enylmagnesium bromide in diethyl ether–benzene

A mixture of magnesium turnings (1.26 g), 1,2-dibromoethane

(50 mm^3) and diethyl ether (3.0 cm^3) was stirred at room temperature for 3 h. To the activated magnesium was added dropwise a solution of 3-chloro-2-methylpropene (680 mg, 7.51 mmol) in diethyl ether (7.5 cm^3) over a period of 6 h with stirring, while the reaction vessel was cooled in an ice bath. After being stirred for a further 2 h in the ice bath, the mixture was diluted with benzene (10.5 cm^3) and the resulting mixture was added dropwise to a solution of bromide **55** (1.44 g, 3.00 mmol) in benzene (10.5 cm^3) over a period of 5 min at room temperature. After the addition, the mixture was poured into saturated aqueous NH_4Cl (100 cm^3) and the two layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic layer was washed with water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (9 : 1) as the eluent to give diallylated compound **56** (1.52 g, 96%) as an oil (Found: C, 68.1; H, 7.3; Br, 15.3. $C_{30}H_{39}BrO_3$ requires C, 68.3; H, 7.5; Br, 15.1%); ν_{max}(neat)/cm^{-1} 1732; δ_H(400 MHz) 1.30 (18 H, s, Bu′ × 2), 1.68 (3 H, br, C*Me*=CH_2), 1.84 (3 H, br, C*Me*=CH_2), 3.73 (2 H, br, $ArCH_2$), 3.81 (3 H, s, OMe), 3.94 (2 H, br, $ArCH_2$), 4.05–4.06 (1 H, m, CMe=CH_2), 4.58–4.59 (1 H, m, CMe=CH_2), 4.74–4.76 (1 H, m, CMe=CH_2), 4.89–4.90 (1 H, m, CMe=CH_2), 6.90 (2 H, s, ArH), 7.16 (1 H, d, *J* 8.4, ArH) and 7.70 (1 H, d, *J* 8.4, ArH).

Reaction of monoallylated compound 57 with methyllithium

To a solution of compound **57** (503 mg, 0.999 mmol) in dry THF (4.0 cm^3) was added dropwise methyllithium (1.05 mol dm^{-3} in diethyl ether; 2.1 cm^3, 2.21 mmol) at −78 °C, and the mixture was allowed to warm to room temperature. After being stirred for 1 h, the mixture was poured into saturated aqueous NH_4Cl (30 cm^3) and the two layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic layer was washed with water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (9 : 1) as the eluent to give methylated compound **58** (350 mg, 80%) as crystals, mp 124–126 °C (Found: C, 76.7; H, 8.4. $C_{28}H_{38}O_4$ requires C, 76.7; H, 8.7%); ν_{max}(KBr)/cm^{-1} 1717; δ_H(400 MHz) 1.33 (18 H, s, Bu′ × 2), 1.73–1.74 (3 H, m, C*Me*=CH_2), 2.23 (3 H, s, Me), 3.52 (2 H, br, $ArCH_2$), 3.80 (3 H, s, OMe), 3.89 (3 H, s, OMe), 4.14–4.15 (1 H, m, CMe=CH_2), 4.64–4.65 (1 H, m, CMe=CH_2), 6.88 (2 H, s, ArH), 6.88 (1 H, d, *J* 8.1, ArH) and 7.29 (1 H, d, *J* 8.1, ArH).

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