Full Paper

CSIRO PUBLISHING

Aust. J. Chem. **2008**, *61*, 350–358

www.publish.csiro.au/journals/ajc

Synthesis, and Cyclization to Aurones and Flavones, of Alkoxy-Substituted Aryl, Arylalkynyl Ketones

Penelope J. Kerr,[A] *Simon M. Pyke,*[A] *and A. David Ward*[A,B]

[A]School of Chemistry and Physics, University of Adelaide, Adelaide SA 5005, Australia.
[B]Corresponding author. Email: david.ward@adelaide.edu.au

Acylation of 1,3,5-tribenzyloxybenzene with alkoxy-substituted phenylpropioloyl chlorides provides the corresponding aryl alkoxylarylalkynyl ketones in which one of the benzyl groups has been removed. Cyclization of these phenolic ketones using basic reagents (potassium carbonate in acetone is best) provides the corresponding aurone system. When the phenolic group of the alkynyl ketones is protected as the *t*-butyldimethylsilyl ether followed by cyclization, using 18-crown-6 and potassium fluoride, mixtures of the corresponding aurones and flavones are produced. A by-product from the formation of the ketones is the corresponding β-chlorochalcone, which can also be cyclized to an aurone product using basic conditions. Similarly, the *t*-butyldimethylsilyl ethers of the HCl adducts can also be cyclized to a mixture of the corresponding aurones and flavones.

Manuscript received: 3 October 2007.
Final version: 1 April 2008.

Introduction

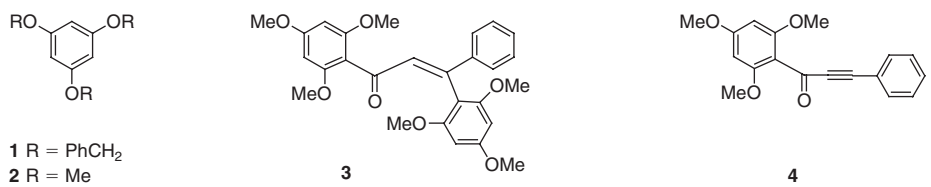
In recent years, the potential health benefits derived from the consumption of tea have received increased attention.[1–6] These health benefits have largely been attributed to the catechin and epicatechin components of tea, which have been shown to have considerable antioxidant activity, attributed to their free-radical scavenging activity. For some time, we have been interested in the development of a radioenzymatic assay for the measurement of tea catechins in biological samples as part of a collaboration with the CSIRO Division of Human Nutrition. Such an assay would require the availability of radiolabelled catechin components present in tea. Although the tea catechins are available from the extraction of tea, the process is tedious and time-consuming and the samples obtained are often difficult to purify completely. We have thus been interested in synthetic methodology that would lead to the synthesis of the tea catechins in pure form and in relatively large amounts as well as making it easier to insert a suitable and stable radiolabel. There has been little published on the synthesis of the epicatechin components of tea. The present paper describes our results from an investigation of the cyclization of alkoxy-substituted aryl, arylalkynyl ketones. We anticipated that if the cyclizations could be directed to yield flavone structures as a consequence of a 6-*endo*-digonal cyclization, rather than aurone structures arising from the alternative 5-*exo*-digonal process, then the sequence could, in principle, be used to develop syntheses of epicatechins and epigallocatechins.

Results and Discussion

Synthesis of Aryl, Arylalkynyl Ketones

The synthesis of the required aryl, arylalkynyl ketones was expected to be achieved by the direct acylation of suitably protected phloroglucinol systems (e.g. Scheme 1; **1** and **2**) with substituted aryl acetylenic anhydrides or acid chlorides. Acetylenic ketones have been prepared by the aluminium chloride-catalyzed acylation of protected di- and tri-hydric phenols with phenylpropioloyl chloride.[7] However, these reactions can be complicated by the simultaneous addition of HCl (generated during the course of the reaction) to the alkyne unit of the initially formed acetylenic ketone.[7] For this reason, we initially approached the acylation using a mixed anhydride method, which has successfully been used for the acylation of **1** with a substituted cinnamic acid.[8]

Acylation of the trimethyl ether **2** with phenylpropiolic acid and trifluoroacetic anhydride (TFAA) gave an unexpected product in 66% yield. This product proved to be **3**, which presumably arises from a further addition of trimethoxybenzene to the initial adduct, the expected acetylenic ketone **4**. The ^{1}H NMR spectrum of **3** showed a one-hydrogen singlet at δ 6.98 due to the alkene



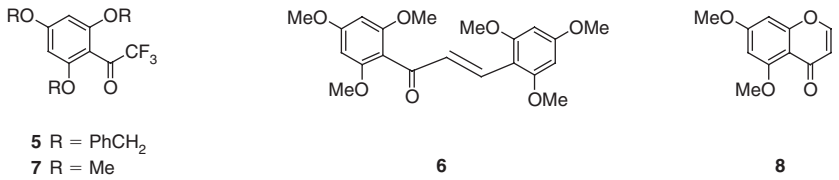
1 R = $PhCH_2$
2 R = Me

3

4

Scheme 1.

10.1071/CH07348 0004-9425/08/050350

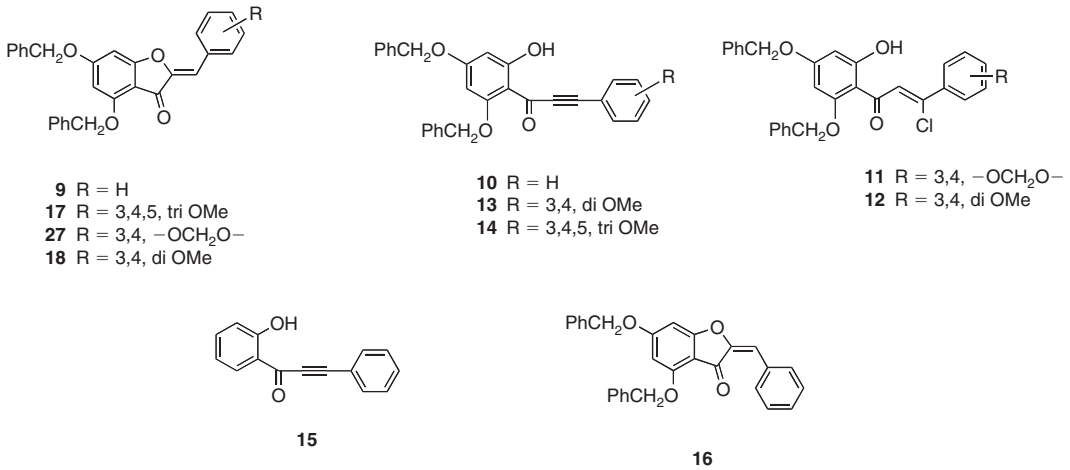


5 R = $PhCH_2$
7 R = Me

6

8

Scheme 2.



9 R = H
17 R = 3,4,5, tri OMe
27 R = 3,4, $-OCH_2O-$
18 R = 3,4, di OMe

10 R = H
13 R = 3,4, di OMe
14 R = 3,4,5, tri OMe

11 R = 3,4, $-OCH_2O-$
12 R = 3,4, di OMe

15

16

Scheme 3.

hydrogen, a total of 18 hydrogens in the region δ 3.56–3.78, representing six methoxyl groups, and nine aromatic hydrogens, four in the region δ 5.86–5.93 due to the four hydrogens *ortho* to two methoxyl groups, and five in the region δ 7.25–7.35. A relatively weak molecular ion at 464 was observed in the electron-impact mass spectrum (EI-MS) but the base peak was at 433 (M − 31). A rotating frame overhauser effect spectroscopy (ROESY) spectrum showed a correlation of the α-hydrogen to the hydrogens of the monosubstituted benzene ring. The ^{13}C NMR spectrum had no signals due to acetylenic carbons (in the region δ 80–100) but showed signals at δ 130.94 and 144.38 for the alkene α and β carbons, respectively. The signal at δ 130.94 correlated with the signal at δ 6.98 in a heteronuclear multiple-quantum coherence (HMQC) spectrum. The signal at δ 6.98 showed correlation with the carbonyl carbon, the β-carbon, the quaternary carbon of the phenyl ring and to two quaternary carbons of the trimethoxybenzene rings. Presumably the second trimethoxybenzene unit adds to the initial acetylenic ketone product in a Michael addition fashion, facilitated by the activation provided by the three methoxyl groups.

When tribenzyloxybenzene **1** was used in place of trimethoxybenzene, the only product obtained was the trifluoroacetyl ketone **5** (Scheme 2). Some of the starting material was recovered. This trifluoroacetylation may arise from a reaction of TFAA with **1** or from the reaction of an intermediate mixed anhydride with **1**. This result suggests that **1** is considerably more sterically hindered to ring acylation than **2**.

When **2** was treated with propiolic acid in TFAA at room temperature, the chalcone **6** was formed in 10% yield. Its structure was confirmed by an X-ray structure analysis.[9] The trifluoroacetyl-substituted product, **7**, was obtained as the major product (52%). Addition of trifluoroacetic acid to the reaction increased the yield of the chalcone to 15% and decreased the yield of **7** to 38%. 1,2,3-Trimethoxybenzene did not react with TFAA under these conditions or at elevated temperatures (50°C). Neither anisole nor 1,2- or 1,4-dimethoxybenzene reacted and 1,3-dimethoxybenzene gave a small amount (5%) of trifluoroacetylated product at either room temperature or 50°C. *m*-Anisidine gave the expected trifluoroacetamide (86%) and the propiolamide (9%).

As 1,3,5-trimethoxybenzene was the only material to react well under these acylation conditions, it was of interest to see whether other activated benzene rings would add to the initial product in a Michael fashion. When a mixture of 1,3,5- and 1,2,3-trimethoxybenzene was added to a solution of TFAA and propiolic acid, the only pure product obtained from reactions using different conditions and varying ratios of the two trimethoxybenzenes was **7** in low yield (up to 29%). Small amounts of the aromatic starting materials were recovered.

The formation of significant amounts of trifluoroacetylated material as well as poor yields of the desired acetylenic ketones from the reactions with TFAA prompted us to investigate other Friedel Craft acylation conditions. To minimize the HCl addition products obtained using aluminium chloride as the catalyst, we chose to investigate less reactive catalysts such as zinc chloride and ferric chloride. When **2** was treated with propiolic anhydride in the presence of zinc chloride, a complex mixture of products was obtained. Starting material (10%) and the chromone **8** (3%) were isolated from this mixture. The alkene hydrogens of this chromone appeared at δ 6.15 (α) and 7.98 (β) with a coupling constant of 9.6 Hz in the ^1H NMR spectrum. A later chromatographic fraction contained the chalcone **6** (14%). There was no reaction between 1,3-dimethoxybenzene and propiolic anhydride in the presence of zinc chloride.

The acylation of **1** with phenylpropioloyl chloride and aluminium chloride gave mainly polymeric material after 40 min in dichloromethane under reflux conditions, and no reaction at lower temperatures. When the catalyst was changed to ferric

chloride (catalytic amount) and the mixture was refluxed in dichloroethane for 1.5 h, a 30% yield of the aurone **9** (Scheme 3) was obtained, whose structure was confirmed by an X-ray structure analysis (E. R. T. Tiekink, pers. comm.). Presumably the aurone arises from the expected acylation product, followed by attack of the adjacent benzyloxy oxygen at the α position of the triple bond (5-*exo*-*dig*-cyclization) and consequential cleavage of the benzyl group. However, deprotection may have occurred before cyclization as a result of complexation between one of the adjacent benzyloxy oxygens, the ferric ion, and the carbonyl oxygen. When the reaction was conducted using a catalytic amount of zinc chloride in refluxing dichloroethane, the deprotected acetylenic ketone **10** was obtained in 18% yield. This structure was also confirmed by an X-ray structure analysis.[10]

Having established that phenylpropioloyl chloride could be used to acylate a protected phloroglucinol system, it was of interest to establish whether this acylation could be extended to alkoxy-substituted phenylpropiolic acids. 3,4-Methylenedioxyphenylpropioloyl chloride and zinc chloride (catalytic amount) were reacted with **1** in refluxing dichloroethane. The only pure material isolated from chromatography of the crude product was the HCl adduct **11** of the expected acetylenic ketone, which was obtained in 14% yield. The structure of this adduct was confirmed by an X-ray structure analysis.[11] The same reaction with 3,4-dimethoxyphenylpropiolyl chloride gave the corresponding HCl adduct **12** in 57% yield. To minimize the HCl generated in the preparation of the phenylpropioloyl chloride, the acid chloride was generated, using thionyl chloride, from the sodium salt of the acid rather than the acid itself. When the reaction was repeated using the acid chloride prepared from the sodium salt, only 5% of the HCl adduct was obtained, together with 13% of the desired acetylenic ketone **13**. In contrast, the reaction of 3,4,5-trimethoxyphenylpropioloyl chloride (prepared either from the acid or from the sodium salt) with **1** gave the acetylenic ketone **14** in 34 and 30% yields, respectively.

It is likely that the HCl addition occurred in the generation of the acid chloride and that the acylation occurs with the HCl adduct. However, it is possible that the acetylenic ketone product may also be reacting with the zinc chloride-containing solution to produce this adduct. Further work on this reaction may lead to considerably improved yields of the acetylenic ketones. It is also quite likely that any HCl adduct could be converted to the desired acetylenic ketone by treatment with a suitable base. The isolation of an HCl adduct from the aluminium chloride-catalyzed acylation of anisole with phenylpropioloyl chloride has been reported.[7]

Cyclization of the Acetylenic Ketones

The availability of the *o*-hydroxyaryl arylethynyl ketones **10**, **13**, **14**, and the formation of the aurone **9** from, apparently, the ketone **10** encouraged us to investigate their cyclization. Cyclizations of arylalkynyl ketones similar to these ketones that yield both flavone- and aurone-containing products have been reported and the mode of cyclization has been shown to be sensitive to the reagent,[12–22] the solvent[14] and the extent and type of substitution on either of the aryl rings.[18] *Ab initio* calculations have suggested that the transition state energies in 5-*exo*-digonal (leading to aurones) and 6-*endo*-digonal (leading to flavones) cyclizations may be very close.[21] They also support obtuse approach angles that would favour a 5-*exo*-*dig* cyclization mode.[17] It has been suggested that the formation of the carbanion leading to aurone products is the kinetic situation and that the presence of a suitable protic source leads to aurone formation.[14] In the absence of a protic material, the carbanion leading to the flavone is thermodynamically favoured.[14] However, an indication of the complexity of the cyclization process is provided by the results of Korshunov et al.[22] who showed that the ketone **15** cyclized to a flavone with a secondary amine as the reagent but gave an aurone when a tertiary amine was used.

Cyclizations of systems related to **10** to aurones and/or flavones have been reported by a variety of methods including potassium carbonate in refluxing acetone,[14] diethylamine in refluxing ethanol,[13] 4 M HBr in dioxane,[23] and the use of trifluoroacetic acid and *p*-toluenesulfonic acid as acidic catalysts.[17] Silyl-protected phenolic arylalkynyl ketones have been cyclized using potassium fluoride and 18-crown-6 in DMF[21] to give mixtures of aurone and flavone products.

Cyclization of **10**, using potassium carbonate in refluxing acetone,[14] gave the aurone **9** in 42% yield. When the reaction was repeated in [D_6]acetone at room temperature, the ^{1}H NMR spectrum after 23 h showed that a mixture of the aurone **9** and its *E*-isomer had been formed in a 2:1 ratio. The aurone was the only product observed when the reaction was monitored over the first hour, which indicates that the reaction does not take place by cyclization to the flavone followed by isomerization to the aurone. The *E*-isomer could not be obtained pure, possibly because of partial isomerization to a mixture of the two isomers on exposure to light. The aurone **9** was isolated in 64% yield from a reaction using **10** with diethylamine in refluxing ethanol,[13,20] with the *E*-isomer **16** (12%) also being formed. With the acidic reagents trifluoroacetic acid and *p*-toluenesulfonic acid,[17] no cyclization of **10** was observed and starting material was recovered. With 4 M HBr in dioxane,[23] an acetylene HBr addition product and ring-brominated starting material were the two main products suggested by the ^{1}H NMR data of chromatographic fractions obtained from the reaction mixture.

Literature reports[13,20] indicate that a flavone is the major cyclization product when the free phenolic group on the aryl ring is protected and then treated with diethylamine, apparently because this allows addition of the diethylamine to the alkyne to occur before cyclization occurs. However Sakamoto et al.[20] have also described the formation of both aurone- and flavone-type products using this diethylamine treatment. As we needed a sample of the flavone product from the cyclization of **10** to determine whether a cyclization process gave one or other or both of the aurone **9** or flavone **21** products, the phenolic ketone **10** was treated with trimethylsilyl chloride in pyridine with the expectation that the product would be the corresponding trimethylsilyl ether. However, the product was the *Z*-aurone **9**, in 55% yield, indicating that the silylating conditions were sufficiently basic to form the phenolate anion, which cyclized, as it does with potassium carbonate, to form the aurone. Protection of the phenolic group by formation of the *tert*-butyldimethylsilyl derivative **19**, and treatment of this product with 18-crown-6 and potassium fluoride[21] gave a mixture of the desired flavone **21** and the corresponding aurone **9**, which were separable by chromatography. These two products had surprisingly similar NMR spectra and it was apparent from their spectroscopic data that the easiest way to determine whether the product had an aurone or flavone structure was to compare their UV and IR spectra (Table 1). The highest wavelength absorption for flavones is below λ_{max} 354 nm but aurones show absorption at much higher values.[24] 6,8-Dimethylflavone has its highest wavelength band at 300 nm, whereas the highest wavelength band for 5,7-dimethylaurone is

at 380 nm. The aurone **9** showed an absorption peak at 367 nm, whereas the highest absorption peak of the flavone **21** was at 305 nm. The wavelength of the carbonyl group absorption in the IR was also quite different for the two isomers (Table 1).

When **19** was refluxed with diethylamine in ethanol for 24 h, the product appeared to be mainly the deprotected material resulting from addition of diethylamine to the triple bond.

Cyclization of the ketone **14** using potassium carbonate in acetone gave the aurone **17** in quantitative yield. With trifluoroacetic acid as the reagent, a complex mixture was obtained. With diethylamine, the aurone **17** was obtained in 20% yield, and with 18-crown-6 and potassium fluoride in DMF, the aurone **17** was the major product.

The reaction of the ketone **13** with potassium carbonate in acetone gave a quantitative yield of a product that was also obtained in quantitative yield from the cyclization of the β-chlorochalcone **12** using sodium hydride. It is possible that sodium hydride converts **12** to the acetylene **13**, which then cyclizes to this product. When the chalcone **12** was treated with the milder base triethylamine, this product and starting material were the only compounds observed in the ^{1}H NMR spectrum of the reaction product. The product had a strong molecular ion at 494 (corresponding to that expected for the aurone or the flavone). Its UV spectra showed a peak at λ_{max} 397 nm, supporting an aurone structure for **18**. This conclusion was further supported by the NMR data; an alkene hydrogen signal at δ 6.66 (singlet) correlated with a signal at δ 111.21 in the ^{13}C NMR spectrum using HMQC conditions. The signal at δ 6.66 showed heteronuclear multiple-bond correlation (HMBC) correlations with six carbons (at δ 113.64, 125.27, 125.56, 146.89, 149.00, and 180.35). These signals correspond to carbons C2′, C6′, C1′, C2, C3′, and C=O, respectively. These correlations would require $^nJ_{CH}$, where n is the number of bonds over which the coupling interaction is observed, of 3, 3, 2, 2, 4, and 3 for the aurone structure and 4, 4, 3, 2, 5, and 2 for the flavone structure.

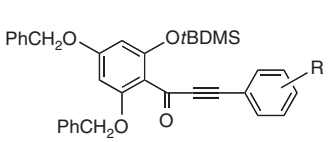
Table 1. Spectroscopic data for aurones and flavones
For each pair, the aurone is listed first

Compound	UV λ_{max} (log ε)		δ_H		IR ν_{max}/cm^{-1}
9	367 (4.5)	Δ 62 nm	6.76	Δ 0.10 ppm	1693
21	305 (4.0)		6.66		1655
17	384 (3.9)	Δ 63 nm	6.69	Δ 0.08 ppm	1693
22	321 (4.1)		6.61		1644
27	400 (4.2)	Δ 68 nm	6.68	Δ 0.13 ppm	1697
25	332 (4.0)		6.55		1652
18	398 (4.2)	Δ 66 nm	6.74	Δ 0.14 ppm	1695
26	332 (4.1)		6.60		1652

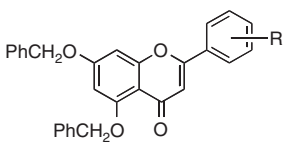
Clearly the correlation data support the aurone structure more strongly as $^nJ_{CH}$ are typically $n = 2$ and 3.[25] A wide variety of aurones and flavones have been examined[26] by ^{13}C NMR spectroscopy, from which it has been concluded that C2 is in the range δ 160.5–163.2 for flavones and 146.1–147.7 for aurones, that C3 is in the range δ 104.7–111.8 for flavones and 111.6–111.9 for aurones and that C4 (C=O) is in the range δ 176.3–178.3 for flavones and 182.5–182.7 for aurones. The corresponding values for the product are 146.88, 111.21 and 180.35. These NMR values, particularly those for C2 and C4, as well as the UV and IR data (Table 1) strongly support the aurone structure **18**.

Several reports, as well as theoretical calculations,[21] have highlighted the fact that an important factor in deciding the mode of cyclization for systems such as **12**, **13**, and **14** may well be whether the cyclization conditions are protic or not. If the phenolic molecule is used as the starting material for cyclization, then the presence of the phenol in the starting material ensures that the solution is at least slightly protic. For this reason, we investigated further the cyclization of the protected phenolic compounds using 18-crown-6 and potassium fluoride that gave a mixture of the flavone and aurone products with **19** (Scheme 4). The phenolic ketone **14** was converted to its *tert*-butyldimethylsilyl ether (*t*BDMS) derivative **20**. This derivative was obtained as an unstable gum that showed only the one spot on TLC and was used immediately. Treatment of **20** with 18-crown-6 and potassium fluoride gave a mixture of the flavone **22** and the corresponding aurone **14**, which were separable by chromatography. The HCl adducts **11** and **12** were also converted to their *t*BDMS derivatives, **23** and **24** respectively, and subjected to the same cyclization conditions. In both cases, a flavone was obtained, **25** and **26** respectively, together with some of the corresponding aurone, **27** or **18**.

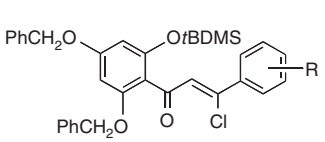
The data displayed in Table 1 show that the aurones are most easily distinguished from their flavone isomers by both their UV and IR spectra. The aurones absorb further into the visible region of the UV-visible than the corresponding flavone, with the difference between the highest wavelength absorption peak of the aurones being consistently ∼65 nm higher compared with that of the corresponding flavone. This difference is also notable when the reaction product containing both cyclized materials is chromatographed using TLC, with the aurone product being noticeably more yellow than the flavone. In addition, the isomers can be easily distinguished by their IR spectra, with the aurones showing a carbonyl absorption between 1690 and 1700 cm^{-1}, whereas the carbonyl stretching frequency of the corresponding flavone is in the region 1644–1655 cm^{-1} (Table 1). Although the δ value of the olefinic proton of the aurones is consistently higher than that of the corresponding flavone, the difference is not enough to be definitive (Table 1).



19 R = H
20 R = 3,4,5, tri OMe



21 R = H
22 R = 3,4,5, tri OMe
25 R = 3,4, $-OCH_2O-$
26 R = 3,4, di OMe



23 R = 3,4, $-OCH_2O-$
24 R = 3,4, di OMe

Scheme 4.

In summary, the cyclizations of alkoxy-substituted aryl arylalkynyl ketones to either flavones or aurones appear to be controlled by subtle factors that are not entirely clear. Comparison with other cyclizations described in the literature suggests that substitution (both position and type of group) may have considerable significance. Whether the conditions are aprotic or protic also appears to be an important factor for the course of the reaction. Given the difficulty in determining whether the product is an aurone or a flavone, it is possible that some products may have been assigned the wrong structure in the literature. Cyclization of the phenolic aryl arylalkynyl ketones described in the present paper yields the aurone product using a variety of conditions. Only the cyclization of the *t*BDMS-protected phenols yields significant amounts of the corresponding flavones. Further work will be necessary to clarify these factors and to maximize the yields of flavones. The availability of flavones such as **22**, **25**, and **26** opens the way for investigations into their conversion into the corresponding catechin and epicatechin structures.

Experimental

General

Melting points were determined on a Kofler hot stage apparatus equipped with a Reichert microscope and are uncorrected. Ultraviolet (UV) spectra were recorded on a Varian Cary 300 bio UV-Visible spectrophotometer using methanol solutions. Infrared (IR) spectra were recorded on a Hitachi 270-30, a Perkin–Elmer Spectrum BX or an ATI Mattson Genesis FTIR spectrometer. ^{1}H NMR (δ_H) and ^{13}C NMR (δ_C) spectra were recorded on Varian Gemini-2000 (^{1}H: 300.13 MHz; ^{13}C: 74.47 MHz) and Varian INOVA (^{1}H: 599.95 MHz; ^{13}C: 150.87 MHz) instruments as solutions in $CDCl_3$ unless indicated otherwise. Chemical shifts are quoted as δ in parts per million and coupling constants (J) are given in Hertz (Hz). Electron impact and fast atom bombardment mass spectra were recorded at 70 eV on a Vacuum Generators ZAB 2HF mass spectrometer. High resolution accurate mass measurements were obtained from the University of Tasmania mass spectrometric service. Elemental analyses were performed at the University of Otago, New Zealand. Chromatography refers to flash chromatography[27] conducted using Merck Silica Gel 60.

E-*3-Phenyl-1,3-di(2,4,6-trimethoxyphenyl)-2-propen-1-one* ***3***

Trifluoroacetic anhydride (0.49 g, 2.34 mmol) was added to a solution of phenylpropiolic acid (0.17 g, 1.17 mmol) in CH_2Cl_2 (1.7 mL). The solution was cooled to 0°C and 1,3,5-trimethoxybenzene **2** (0.30 g, 1.78 mmol) in CH_2Cl_2 (1.8 mL) was added. After stirring at room temperature for 1 h, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added to the stirred mixture. The mixture was extracted with CH_2Cl_2 (2 × 5 mL) and dried over Na_2SO_4. After concentration under reduced pressure, the residual oil was chromatographed (silica, 50% ethyl acetate in hexane) to give the *title compound*, **3**, as a beige solid (0.02 g, 66%). mp 167–170°C. (Found: *m*/*z* 464.1834. $C_{27}H_{28}O_7$ requires 464.1834.) ν_{max}(Nujol)/cm^{-1} 1590, 1130, 831. δ_H (600 MHz) 3.56 (6H, s, OMe), 3.66 (6H, s, OMe), 3.75 (3H, s, OMe), 3.78 (3H, s, OMe), 5.86 (2H, s, ArH), 5.93 (2H, s, ArH), 6.98 (1H, s, H2), 7.25 (3H, m, ArH), 7.35 (2H, m, ArH). δ_C 55.03, 89.99, 108.99, 113.70, 126.91, 128.07, 128.32, 130.94, 140.78, 144.38, 158.08, 158.47, 160.97, 161.70, 194.23. *m*/*z* 464 (M, 7%), 433 (100), 417 (5), 375 (3), 341 (6), 297 (3), 255 (3), 195 (12), 151 (2), 91 (4).

When the reaction was conducted as above, except that 1,3,5-tribenzyloxybenzene **1** replaced 1,3,5-trimethoxybenzene, only one product was obtained after chromatography (silica; 20% ethyl acetate in hexane) apart from starting material. 2,2,2-Trifluoro-1-[2,4,6-tri(benzyloxy)phenyl]ethan-1-one **5** was obtained as a yellow oil (0.12 g, 25%). (Found: C 70.7, H 4.8. $C_{29}H_{23}F_3O_4$ requires C 70.7, H 4.7%.) ν_{max}(Nujol)/cm^{-1} 1714, 1606, 1339, 1159, 696. δ_H 4.96 (2H, s, benzyl), 5.03 (4H, s, benzyl), 6.23 (2H, s, ArH), 7.34–7.38 (15H, m, ArH). δ_C 71.03, 71.40, 93.86, 111.13 (q), 118.19, 127.69–129.37 (overlapping signals), 136.46, 136.58, 159.84, 164.14, 181.12. *m*/*z* 493 (M, 30%), 424 (21), 402 (4), 182 (3), 126 (4), 91 (100).

E-*1,3-Di(2,4,6-trimethoxyphenyl)-2-propen-1-one* ***6***

1,3,5-Trimethoxybenzene (0.30 g, 1.78 mmol) was added all at once to a solution of trifluoroacetic anhydride (0.56 g, 2.70 mmol) and propiolic acid (0.12 g, 1.78 mmol). The solution was stirred at room temperature for 3 h. Saturated aqueous $NaHCO_3$ solution (5 mL) was added to the reaction mixture, which was then extracted with CH_2Cl_2 (2 × 10 mL) and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification using chromatography (silica; 50% ethyl acetate in hexane) gave 2,2,2-trifluoro-1-(2,4,6-trimethoxyphenyl)ethan-1-one **7** as a white solid (0.24 g, 52%). mp 58–59°C (lit.[28] 59–60°C). ν_{max}(Nujol)/cm^{-1} 1720, 1606, 1340, 737. δ_H 3.80 (6H, s, OMe), 3.84 (3H, s, OMe), 6.12 (2H, s, ArH). δ_C 55.22, 55.61, 90.37, 105.24, 115.04 (q), 160.37, 164.73, 180.23. *m*/*z* 264 (M, 19%), 249 (1), 221 (1), 195 (100), 165 (2), 152 (10), 109 (3).

The *title compound* **6** was obtained as a yellow solid (66.5 mg, 10%), mp 151–152°C. (Found: C 65.0, H 6.4; *m*/*z* 388.1533. $C_{21}H_{24}O_7$ requires C 64.9, H 6.2%; *m*/*z* 388.1522.) ν_{max}(Nujol)/cm^{-1} 1626, 1602, 1120. δ_H 3.75 and 3.81 (both 6H, s, OMe), 3.83 and 3.85 (both 3H, s, OMe), 6.08 (2H, s, ArH), 6.15 (2H, s, ArH), 7.29 (1H, d, *J* 16.2, H2), 7.79 (1H, d, *J* 16.2, H3). δ_C 55.96–56.56 (six signals), 91.21, 91.54, 107.15, 113.51, 129.90, 137.01, 159.29, 162.04, 162.47, 163.55, 189.96. *m*/*z* 388 (M, 22%), 357 (40), 195 (78), 91 (100), 68 (24).

The reaction was repeated except with the addition of trifluoroacetic acid (0.02 g, 0.18 mmol) at the beginning of the reaction. On workup, **7** (38%) and **6** (15%) were obtained.

Reactions of Propiolic Acid with Aromatic Ethers

(a) 1,3-Dimethoxybenzene (0.30 g, 2.19 mmol) was added to TFAA (0.61 g, 2.90 mmol) and propiolic acid (0.10 g, 1.46 mmol) and the mixture was stirred at room temperature for 4.5 h. Chromatography of the reaction product (silica; 20% ethyl acetate in hexane) gave starting material and 2,2,2-trifluoro-1-(2,4-dimethoxyphenyl)ethan-1-one (0.02 g, 5%), mp 47–49°C (lit.[29] 52°C). ν_{max}(Nujol)/cm^{-1} 1703, 1605, 1286, 1165, 721. δ_H 3.89 and 3.91 (both 3H, s, OMe), 6.48 (1H, d, *J* 2.4, ArH), 6.57 (1H, dd, *J* 2.4, 8.7, ArH), 7.77 (1H, dq, J_{HF} 1.2, 8.7, ArH). δ_C 56.39, 56.56, 99.41, 106.43, 118.17 (q), 119.23, 134.85, 153.87, 167.02. *m*/*z* 234 (M, 16%), 165 (100), 151 (6), 135 (4), 122 (17), 107 (10).

(b) *m*-Anisidine (0.30 g, 2.40 mmol) was added to a solution of TFAA (0.68 g, 3.20 mmol) and propiolic acid (0.11 g, 1.60 mmol) and the mixture was stirred at room temperature for 18 h. Chromatography (silica; 40% ethyl acetate in hexane) yielded two products: *N*-(3-methoxyphenyl)prop-2-ynamide was obtained as a white solid (0.03 g, 9%), mp 81–82°C. (Found: C 68.5, H 5.1. $C_{10}H_6NO_2$ requires C 68.6,

H 5.2%.) ν_{max}(Nujol)/cm^{-1} 3270, 3100, 2110, 1656, 1596, 1154, 1047. δ_H 2.92 (1H, s, alkyne-H), 3.79 (3H, s, OMe), 6.70 (1H, dd, *J* 2.4, 8.1, ArH), 7.01 (1H, dd, *J* 1.5, 8.1, ArH), 7.22 (1H, dd, *J* 8.1, ArH), 7.25 (1H, d, *J* 2.4, ArH), 7.76 (1H, bs, NH). δ_C 55.99, 74.77, 78.27, 106.67, 111.65, 112.86, 130.45, 138.81, 150.39, 160.83. *m/z* 175 (M, 35%), 146 (14), 132 (58), 104 (31), 53 (100). 2,2,2-Trifluoro-*N*-(3-methoxyphenyl)acetamide (0.30 g, 86%). mp 71–72°C (lit.[30] 73–74°C). ν_{max}(Nujol)/cm^{-1} 3284, 3214, 3116, 1707, 1624, 1289, 1048, 683. δ_H 3.74 (3H, s, OMe), 6.75 (1H, dt, *J* 1.5, 2.4, 8.1, ArH), 7.12 (1H, dd, *J* 1.5, 8.1, ArH), 7.22 (1H, dd, *J* 8.1, ArH), 7.26 (1H, d, *J* 2.4, ArH), 8.92 (1H, br s, NH). δ_C 56.02, 107.09, 112.86, 113.35, 116.77 (q), 130.73, 136.88, 155.17, 160.97. *m/z* 219 (M, 100%), 150 (41), 122 (19), 107 (75), 92 (28), 77 (43).

(c) With anisole, 1,2-dimethoxybenzene, and 1,4-dimethoxybenzene, starting material was recovered.

Acylation of 1,3,5-Trimethoxybenzene with Propiolic Anhydride and Zinc Chloride

Zinc chloride (0.28 g, 2.06 mmol) was added to 1,3,5-trimethoxybenzene (0.17 g, 1.03 mmol) in dichloroethane (5 mL). Propiolic anhydride (0.13 g, 1.03 mmol) in dichloroethane (10 mL) was added dropwise to the stirred solution, which was then refluxed for 2 h. The cooled reaction mixture was poured into a mixture of hydrochloric acid (1 M, 10 mL) and ice and then extracted with CH_2Cl_2 (2 × 10 mL). The extracts were dried (Na_2SO_4) and concentrated to give an oil, which was chromatographed (silica; 40% ethyl acetate in hexane) to give 1,3,5-trimethoxybenzene (0.02 g, 10% recovery), followed by 5,7-dimethoxychromone **8** (6.3 mg, 3%), mp 132–135°C (lit.[31] 128–130°C). (Found: *m/z* 206.0588. $C_{11}H_{10}O_4$ requires 206.0579.) ν_{max}(Nujol)/cm^{-1} 1650, 1605, 1210. δ_H 3.83 and 3.91 (both 3H, s, OMe), 6.15 (1H, d, *J* 9.6, H3), 6.28 (1H, d, *J* 2.1, ArH), 6.42 (1H, d, *J* 2.1, ArH), 7.96 (1H, d, *J* 9.6, H2). δ_C 56.47, 56.71, 93.50, 95.51, 109.97, 111.65, 139.37, 157.66, 162.16, 164.39, 193.79. *m/z* 206 (M, 69%), 178 (100), 163 (68), 135 (49), 120 (12), 92 (18). Compound **6** (56 mg, 14%) was also isolated.

(2Z)-2-Benzylidene-4,6-di(benzyloxy)-1-benzofuran-3(2H)-one ***9***

1,3,5-Tribenzyloxybenzene, **1**, (0.03 g, 0.76 mmol), phenylpropioloyl chloride (0.11 g, 0.69 mmol), and ferric chloride (0.2 mg, 1.1×10^{-3} mmol) were suspended in dichloroethane (4 mL) and heated at reflux for 1.5 h. A 10% aqueous solution of sodium hydroxide solution (10%, 10 mL) was added to the cooled solution, which was then stirred at room temperature for 18 h. The two phases were then separated and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The organic extracts were washed with water (5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide an oil that was purified by chromatography (silica; 20% ethyl acetate in hexane) to give the aurone **9** as a yellow solid (0.03 g, 30%), mp 161–163°C. (Found: C 80.4, H 5.2. $C_{29}H_{22}O_4$ requires C 80.2, H 5.1%.) λ_{max} 367 (log ε 4.46). ν_{max}(Nujol)/cm^{-1} 1693, 1590, 1157, 1086. δ_H 5.08 and 5.25 (both 2H, s, benzyl), 6.22 (1H, d, *J* 1.4, ArH), 6.43 (1H, d, *J* 1.4, ArH), 6.76 (1H, s, H1′), 7.15–7.49 (13H, m, ArH), 7.82–7.89 (2H, m, ArH). δ_C 71.35, 91.27, 95.47, 106.47, 112.14, 127.32–131.74 (3 signals), 133.24, 136.14, 136.65, 148.55, 157.35, 169.40, 169.59. *m/z* 435 (MH, 12%), 345 (8), 326 (4), 238 (3), 129 (2), 91 (100), 43 (11).

1-[2,4-Di(benzyloxy)-6-hydroxyphenyl]-3-phenylprop-2-yn-1-one ***10***

1,3,5-Tribenzyloxybenzene **1** (0.20 g, 0.50 mmol), phenylpropioloyl chloride (0.07 g, 0.42 mmol), and zinc chloride (1 mg) were heated at reflux in dichloroethane (5 mL) for 1 h. A saturated solution of $NaHCO_3$ (5 mL) was added to the cooled solution and the mixture was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Chromatography (silica; 20% ethyl acetate in hexane) of the residual oil yielded the title ketone **10** as yellow solid (0.03 g, 18%), mp 121–122°C. (Found: C 80.1, H 5.1. $C_{29}H_{22}O_4$ requires C 80.2, H 5.1%.) ν_{max}(Nujol)/cm^{-1} 2720, 2410, 1618, 1577, 1160. δ_H 5.06 and 5.13 (both 2H, s, benzyl), 6.10 (1H, d, *J* 2.4, ArH), 6.16 (1H, d, *J* 2.4, ArH), 7.05–7.46 (15H, m, ArH). δ_C 71.10, 71.85, 90.50, 93.45, 95.37, 96.17, 107.99, 121.52, 128.32–129.41 (two signals), 130.65, 133.35, 136.25, 136.35, 162.47, 166.89, 168.97, 178.42. *m/z* 434 (M, 27%), 344 (20), 325 (4), 306 (2), 254 (3), 237 (2), 192 (2), 181 (4), 129 (3), 105 (2), 91 (100).

1-[1-Hydroxy-3,5-di(benzyloxy)phenyl]-3-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one ***14***

3,4,5-Trimethoxyphenylpropioloyl chloride (prepared from sodium 3,4,5-trimethoxyphenylpropiolate and thionyl chloride) (0.11 g, 4.21 mmol), 1,3,5-tribenzyloxybenzene **1** (0.20 g, 0.50 mmol), and zinc chloride (~2 mg) were refluxed in dichloroethane (5 mL) for 1 h. A saturated solution of $NaHCO_3$ (10 mL) was added to the cooled mixture, which was then extracted with CH_2Cl_2 (2 × 10 mL). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed (silica; CH_2Cl_2) to give the *title compound* **14** as a yellow solid (0.06 g, 30%), mp 110–115°C. (Found: *m/z* 524.1826. $C_{32}H_{28}O_7$ requires 524.1834.) ν_{max}(Nujol)/cm^{-1} 3395, 2197, 1651, 1637, 1618, 1577, 1267, 1127. δ_H 3.66 (6H, s, OMe), 3.86 (3H, s, OMe), 5.05 and 5.21 (both 2H, s, benzyl), 6.06 (1H, d, *J* 2.1, ArH), 6.16 (1H, d, *J* 2.1, ArH), 6.52 (2H, s, ArH), 7.17–7.46 (10H, m, ArH). δ_C 56.72, 61.58, 71.08, 71.47, 89.99, 93.42, 95.39, 96.53, 107.88, 110.81, 116.28, 127.50–129.37, 136.14 and 136.77 (benzyl aromatic carbons), 137.48, 153.60, 162.82, 166.95, 168.57, 178.27. *m/z* 524 (M, 58%), 493 (2), 433 (31), 384 (4), 327 (3), 282 (1), 243 (3), 193 (1), 91 (100).

3-(1,3-Benzodioxol-5-yl)-3-chloro-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]pro-2-en-1-one ***11***

3,4-Methylenedioxyphenylpropioloyl chloride (prepared from 3,4-methylenedioxyphenylpropiolic acid and thionyl chloride) (0.09 g, 0.42 mmol), 1,3,5-tribenzyloxybenzene **1** (0.20 g, 0.50 mmol), and zinc chloride (~2 mg) were refluxed in dichloroethane (5 mL) for 1 h. After workup as above, the residue was chromatographed (silica; CH_2Cl_2), to give the *title compound* **11** as yellow crystals (0.03 g, 14%), mp 115–6°C. (Found: C 69.9, H 4.5. $C_{30}H_{23}ClO_6$ requires C 70.0, H 4.5%.) ν_{max}(Nujol)/cm^{-1} 1624, 1599, 1580, 1169, 968, 722. δ_H (600 MHz) 4.98 and 5.09 (both 2H, s, benzyl), 5.98 (2H, s, OCH_2O), 6.13 (1H, d, *J* 2.4, ArH), 6.22 (1H, d, *J* 2.4, ArH), 6.58 (1H, d, *J* 7.8, ArH), 6.80 (1H, dd, *J* 1.8, 7.8, ArH), 6.82 (1H, d, *J* 1.8, ArH), 7.09–7.44 (10H, m, ArH), 7.28 (1H, s, H2). δ_C 71.08, 72.25, 93.41, 95.77, 102.22, 107.71, 108.01, 108.61, 122.26, 125.92, 128.33–129.43, 135.80 and 136.49 (benzyl aromatic carbons), 131.81, 140.14, 148.38, 149.72, 162.17, 166.26, 170.93,

192.82. *m/z* 479 (M − Cl, 2%), 388 (29), 371 (46), 277 (2), 215 (17), 131 (7), 91 (100), 73 (45).

(2Z)-1-[2,4-Di(benzyloxy)-6-hydroxyphenyl]-3-chloro-3-(3,4-dimethoxyphenyl)prop-2-en-1-one ***12***

3,4-Dimethoxyphenylpropioloyl chloride (prepared from 3,4-dimethoxyphenylpropiolic acid and thionyl chloride) (0.10 g, 0.45 mmol), 1,3,5-tribenzyloxybenzene **1** (0.18 g, 0.45 mmol), and zinc chloride (∼2 mg) were heated in refluxing dichloroethane (5 mL) for 1 h. After workup as above, yellow crystals after chromatography (silica; 80% ethyl acetate in hexane) gave the *title compound* **12**, as yellow crystals (0.14 g, 57%), mp 110–120°C. (Found: *m/z* 530.1473. $C_{31}H_{27}O_6Cl$ requires 530.1496.) ν_{max}(Nujol)/cm^{-1} 3190, 1627, 1580, 1556, 1103, 738. δ_H 3.74 and 3.94 (both 3H, s, OMe), 4.99 and 5.08 (both 2H, s, benzyl), 6.12 (1H, d, *J* 2.4, ArH), 6.22 (1H, d, *J* 2.4, ArH), 6.65 (1H, d, *J* 8.7, ArH), 6.91 (1H, dd, *J* 2.1, 8.7, ArH), 6.97 (1H, d, *J* 2.1, ArH), 7.07–7.42 (10H, m, ArH), 7.41 (1H, s, H2). δ_C 55.76, 56.01, 70.39, 71.44, 92.77, 95.06, 107.71, 110.03, 110.59, 120.06, 124.93, 128.28–129.38, 135.83 and 136.45 (benzyl aromatic carbons), 130.29, 139.98, 149.22, 151.28, 162.09, 166.78, 169.26, 192.73. *m/z* 530 (M, 2%), 495 (25), 404 (5), 314 (2), 285 (2), 243 (1), 165 (2), 91 (100), 65 (8).

1-[2,4-Di(benzyloxy)-6-hydroxyphenyl]-3-(3,4-dimethoxyphenyl)prop-2-yn-1-one ***13***

3,4-Dimethoxyphenylpropioloyl chloride (prepared from sodium 3,4-dimethoxyphenylpropiolate and thionyl chloride) (0.11 g, 0.49 mmol), 1,3,5-tribenzyloxybenzene **1** (0.19 g, 0.49 mmol), and zinc chloride (∼2 mg) were refluxed in dichloroethane (3 mL) for 1 h. After workup as above, the residue was purified by chromatography (silica; CH_2Cl_2) to give two fractions. The first was a yellow solid (21 mg, 4%) whose spectroscopic data were identical with those of the chloride **12**. The second fraction gave the alkyne **13** as a yellow solid (30 mg, 13%), mp 140–145°C. (Found: *m/z* 494.1709. $C_{31}H_{26}O_6$ requires 494.1729.) ν_{max}(Nujol)/cm^{-1} 2181, 1655, 1615, 1580, 1541, 1259, 1100. δ_H 3.69 and 3.88 (both 3H, s, OMe), 5.06 and 5.19 (both 2H, s, benzyl), 6.08 (1H, d, *J* 2.1, ArH), 6.25 (1H, d, *J* 2.1, ArH), 6.66 (2H, br s, ArH), 6.82 (1H, br s, ArH), 7.22–7.49 (10H, m, ArH). δ_C 56.50, 56.60, 70.97, 71.08, 90.29, 93.53, 95.38, 97.42, 108.04, 111.48, 113.46, 116.10, 127.57–129.40, 136.36 and 136.49 (benzyl aromatic carbons), 149.26, 151.93, 162.31, 166.80, 168.84, 180.20. *m/z* 494 (M, 8%), 463 (1), 403 (5), 354 (1), 297 (1), 189 (1), 155 (1), 127 (1), 91 (100), 69 (15).

Cyclization of 1-[2,4-Di(benzyloxy)-6-hydroxyphenyl]-3-phenylprop-2-yn-1-one ***10***

(a) The ketone **10** (0.04 g, 0.01 mmol), potassium carbonate (0.02 g, 0.15 mmol), and acetone (1 mL) were heated at reflux for 2.5 h. The carbonate was removed by filtration, and the acetone solution concentrated under reduced pressure. Recrystallization of the residue (hexane/ethyl acetate, 5:1) gave the aurone **9** (0.02 g, 42%).

(b) The ketone **10** (3.6 mg, 8.29×10^{-3} mmol), potassium carbonate (1.4 mg, 9.95×10^{-3} mmol) and [D_6]acetone (1 mL) were mixed together in an NMR tube and placed immediately in the spectrometer. After 15 min, the presence of one new compound, **9**, together with the starting phenol was apparent (δ_H for **9** (600 MHz, [D_6]acetone), 5.32 and 5.36 (both 2H, s, benzyl), 6.53 (1H, d, *J* 1.8, ArH), 6.73 (1H, d, *J* 1.8, ArH), 7.31–7.57 (13H, m, ArH), 7.94 (2H, m, ArH)). The β-hydrogen was not present in the spectrum presumably owing to deuteration. No signals for other compounds were observed over 42 h, by which time no starting phenol could be observed. The NMR tube was left on the bench, in the presence of light for 23 h, after which time a spectrum was run. This showed the presence of another product, together with the *Z*-aurone, in a ratio of 1:2, respectively. NMR data indicated[32] that the minor product could be the aurone *E*-isomer, **16** (δ_H (600 MHz, [D_6]acetone), 5.26 and 5.29 (both 2H, s, benzyl), 6.49 (1H, d, *J* 2.1, ArH), 6.66 (1H, d, *J* 2.1, ArH), 7.31–7.57 (13H, m, ArH), 8.22–8.26 (2H, m, ArH)). Again the β-H was not observed. Attempts to isolate the purported *E*-isomer obtained from other cyclizations were frustrated by its apparent ability to partially isomerize to the *Z*-isomer after separation by chromatography.

(c) The ketone **10** (0.01 g, 2.3×10^{-2} mmol) was dissolved in [D_6]benzene (1 mL) to which was added trifluoroacetic acid (0.5 mL). ^{1}H NMR (300 MHz) spectra were run every 5 min for 1 h. Within this time there was no change to the spectrum.

(d) The ketone **10** (10 mg) was dissolved in 1,4-dioxane (1 mL) to which was added hydrobromic acid (4 M, 10 mL) at room temperature. The reaction mixture was stirred at 65°C for 3.5 h, cooled to room temperature, and diluted with ethyl acetate (8 mL). The mixture was poured onto ice and the aqueous phase was extracted with additional ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The ethyl acetate was removed under reduced pressure to give an oil that was largely two products by TLC. Chromatography separated the two products; the major product had a ^{1}H NMR spectrum that was consistent with it being mainly *Z*-3-bromo-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-3-phenylprop-2-en-1-one (δ_H 5.07 and 5.12 (2H, s, benzyl), 6.13 (1H, d, *J* 2.1, ArH), 6.22 (1H, d, *J* 2.1, ArH), 7.12–7.50 (16H, m, Ar-H and H2)), and the minor product had a ^{1}H NMR spectrum that was consistent with it being mainly 1-[2,4-di(benzyloxy)-3-bromo-6-hydroxyphenyl]-3-phenylprop-2-yn-1-one (δ_H 4.99 and 5.10 (both 2H, s, benzyl), 6.15 (1H, s, ArH), 7.14–7.52 (15H, m, ArH)). The two products were not further identified owing to the small amount of material involved.

(e) The ketone **10** (5.0 mg) was dissolved in CH_2Cl_2 (1 mL) to which was added *p*-toluenesulfonic acid (1.0 mg). The reaction mixture was heated at reflux for 30 min. After this time, only starting alkyne was visible by TLC. TEMPO (1 mg) was added to the reaction mixture, which was left at reflux for a further 23 h. The solution was cooled and concentrated under reduced pressure to give a gum that was the starting alkyne when analyzed by ^{1}H NMR spectroscopy and TLC.

(f) The ketone **10** (20 mg) was dissolved in ethanol (1 mL) to which was added diethylamine (30 mg) and the solution was heated at reflux for 24 h. The solution was evaporated under reduced pressure to give a yellow solid. Chromatography (silica; CH_2Cl_2) gave the aurone isomers **9** (12 mg, 64%) and **16** (2.4 mg, 12%).

Attempted Trimethylsilylation of ***10***

The ketone **10** (10 mg, 2.60×10^{-2} mmol) was dissolved in pyridine to which was added trimethylsilyl chloride (3.0 mg, 2.60×10^{-2} mmol). The mixture was stirred at 35°C for 12 h. The solution was diluted with ethyl acetate (3 mL) and washed successively with hydrochloric acid (5%, 5 mL) and water (5 mL). The organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a gum (6.1 mg, 55%) that was identified as **9** by ^{1}H NMR spectroscopy.

*Reaction of **19** with Diethylamine*

The ketone **19** (12.0 mg, 0.02 mmol), diethylamine (16.0 mg, 0.22 mmol), and ethanol (1 mL) were heated together at reflux for 22 h. The solvents were removed under reduced pressure to give a yellow gum in quantitative yield that was mainly (2*Z*)-1-[2,4-di(benzyloxy)-6-hydroxyphenyl]-3-(diethylamino)-3-phenylprop- 2-en-1-one, as indicated by its ^{1}H NMR spectrum. δ_H 2.90 (3H, m, ethyl CH_3), 3.09 (3H, m, ethyl CH_3), 3.72 (2H, m, ethyl CH_2), 3.91 (2H, m, ethyl CH_2), 4.86 and 4.88 (both 2H, s, benzyl), 5.63 (1H, s, 1H, H2), 5.66 (1H, d, *J* 1.2, ArH), 5.84 (1H, s, *J* 1.2, ArH), 6.99–7.12 (5H, m, ArH), 7.25–7.42 (10H, m, ArH).

*Cyclization Reactions of **14***

(a) The ketone **14** (17 mg, 0.03 mmol) was dissolved in acetone (2 mL) to which was added potassium carbonate (7.0 mg, 0.05 mmol). The mixture was heated to reflux for 40 min, cooled, then filtered to remove the carbonate. The acetone was removed under reduced pressure to give (2*Z*)-4,6-di(benzyloxy)-2-(3,4,5-trimethoxybenzylidene)-1-benzofuran-3(2*H*)-one **17** in quantitative yield, mp 175–177°C. (Found: *m*/*z* 524.1830. $C_{32}H_{28}O_7$ requires 524.1835.) λ_{max} 384 (log ε 3.91). ν_{max}(Nujol)/cm^{-1} 1700, 1652, 1588, 1157, 1083. δ_H 3.91 (3H, s, OMe), 3.94 (6H, s, OMe), 5.10 and 5.28 (both 2H, s, benzyl), 6.24 (1H, d, *J* 1.5, ArH), 6.42 (1H, d, *J* 1.5, ArH), 6.69 (1H, s, H2′), 7.13 (2H, s, ArH), 7.30–7.49 (10H, m, ArH). δ_C 54.54, 56.94, 70.81, 71.52, 91.40, 97.14, 109.35, 111.59, 127.50–129.46, 136.14 and 136.68 (benzyl aromatic carbons), 140.89, 148.10, 153.99, 159.16, 168.38, 169.39. *m*/*z* 524 (M, 87%), 493 (12), 433 (73), 402 (14), 384 (30), 358 (11), 327 (15), 296 (4), 243 (15), 193 (9), 135 (2), 91 (100), 65 (13).

(b) The ketone **14** (20 mg, 38 μmol) was dissolved in trifluoroacetic acid (2 mL) and heated at 50°C for 1.5 h. After the usual workup, a gum was obtained that appeared to be a complex mixture by TLC and NMR spectroscopy.

(c) The ketone **14** (10 mg, 19 μmol) was dissolved in ethanol (1 mL) and diethylamine added (10 mg). The mixture was heated at reflux for 24 h and then cooled. The solvents were removed under reduced pressure and the residue chromatographed to give the aurone **17** (2.0 mg, 20%).

(d) The ketone **14** (10 mg, 19 μmol) was dissolved in DMF (1 mL), to which were added 18-crown-6 (10 mg, 38 μmol) and potassium fluoride (2 mg, 38 μmol) at 0°C. The mixture was stirred at ambient temperature for 2 h, then diluted with a saturated solution of ammonium chloride (2 mL) and extracted with ethyl acetate (2 × 2 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give an oil that appeared (^{1}H NMR) to contain mainly the *Z*-aurone **17** and a minor product that could not be further identified.

*Cyclization Reactions of **12***

(a) The ketone **12** (10 mg, 0.02 mmol) was dissolved in dichloroethane (1 mL), and sodium hydride (50%, 1 mg, 0.02 mmol) added. The reaction mixture was heated at reflux for 30 min, then cooled to room temperature, and more sodium hydride was added (50%, 1 mg, 0.02 mmol). The reaction mixture was stirred for a further 10 min and then washed with water (2 mL). The organic layer was removed, dried (Na_2SO_4), and concentrated under reduced pressure to give (2*Z*)-4,6-di(benzyloxy)-2-(3,4-dimethoxybenzylidene)-1-benzofuran-3(2*H*)-one **18** as yellow crystals in quantitative yield, mp 128–130°C. λ_{max} 398 (log ε 4.22). δ_H 3.94 and 3.97 (both 3H, s, OMe), 5.10 and 5.28 (both 2H, s, benzyl), 6.23 (1H, d, *J* 1.8, ArH), 6.42 (1H, d, *J* 1.8, ArH), 6.74 (1H, s, H2′), 6.93 (1H, d, *J* 9.0, ArH), 7.31–7.49 (12H, m, ArH). δ_C 55.93, 55.98, 70.76, 70.84, 90.60, 96.38, 106.07, 111.13, 111.21, 113.64, 125.27, 125.58, 126.79–128.77, 135.51 and 136.05 (benzyl aromatic carbons), 146.89, 149.00, 150.39, 158.35, 167.50, 168.61, 180.35. *m*/*z* 494 (M, 6%), 404 (11), 314 (2), 285 (2), 256 (2), 202 (3), 151 (7), 129 (26), 91 (68), 41 (100).

(b) The ketone **12** (6.0 mg, 0.01 mmol) was dissolved in acetone (1 mL) to which was added anhydrous potassium carbonate (3.0 mg, 0.02 mmol). The mixture was heated to reflux for 30 min, cooled, and filtered. The solution was concentrated under reduced pressure to give the aurone **18** (7.0 mg, 100%).

(c) The ketone **12** (10 mg, 0.02 mmol) was dissolved in triethylamine (0.5 mL) and stirred at room temperature for 40 min, in which time a bright yellow precipitate was evident in the reaction mixture. The reaction was then heated at 80°C for 30 min, then at reflux for 15 min, which did not dissolve the precipitate. Dichloroethane (1 mL) was added to the mixture, which was heated at reflux for 45 min. The solvents were evaporated under reduced pressure to give a gum that was a mixture of starting material and the aurone **18** according to TLC and ^{1}H NMR analysis, in a 2:1 ratio respectively.

*Preparation of the t**BDMS** Derivatives **19**, **20**, **23**, and **24***

These silyl ethers were prepared using a literature procedure.[21] The phenol (1 equiv.) and 2,6-lutidine (2 equiv.) were dissolved in dichloromethane (5 mL) and cooled to −60°C, *tert*-butyldimethylsilyl triflate[33] (1.5 equiv.) was added, and the mixture was allowed to warm to room temperature and then stirred at room temperature for a further 30 min. Water (5 mL) and ethyl acetate (5 mL) were added to the mixture, the organic layer was separated and washed with potassium hydrogen sulfate solution (0.3 M, 10 mL) then water (5 mL), followed by brine (5 mL). The dried organic extracts were evaporated under reduced pressure and the residue was chromatographed with petroleum spirits and ethyl acetate (3:2) as eluent. The silyl ethers were obtained as unstable gums that were initially one spot on a TLC plate but that slowly degraded as spectroscopic data were being obtained. For this reason, they were used immediately after preparation and initial purification.

^{1}H NMR data for 1-(2,4-di(benzyloxy)-6-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3-phenylprop-2-yn-1-one **19** obtained as a pale yellow gum: δ_H 0.30 (6H, s, SiMe), 1.15 (9H, s, Bu^{t}Si), 5.25 and 5.32 (both 2H, s, benzyl), 6.28 (1H, d, *J* 2.0, ArH), 6.48 (1H, d, *J* 2.0, ArH), 7.47–7.17 (15H, m, ArH).

*Cyclization of the t**BDMS** Ethers **19**, **20**, **23**, and **24***

The cyclizations were conducted using a literature procedure.[21] The *t*BDMS ether (1 equiv.) was dissolved in DMF (3 mL) and potassium fluoride (2 equiv.) and 18-crown-6 (2 equiv.) were added. The mixture was stirred at room temperature for 2 h, a saturated solution of ammonium chloride in water was then added, and the mixture was extracted with ethyl acetate (2 × 10 mL). The dried organic extracts were evaporated under reduced pressure and the residue was chromatographed on silica, with ethyl acetate/petroleum spirits (2:3) as eluent. In each case, the flavone was eluted after the corresponding aurone.

The following flavones were obtained:

5,7-Di(benzyloxy)flavone **21** (29%), mp 154–158°C, from the silyl ether **19**. (Found: *m*/*z* 434. $C_{29}H_{22}O_4$ requires 434.) δ_H 5.13, 5.24 (both 2H, s, benzyl), 6.52, 6.68 (both 1H, d, *J* 2.4,

H6, H8), 6.66 (1H, s, H3), 7.2–7.9 (15H, m, ArH). The aurone **9** (30%) was also obtained.

5,7-Di(benzyloxy)-3′,4′,5′-trimethoxyflavone **22** (17%), mp 131–134°C (lit.[34] 135–136°C), from the silyl ether **20**. (Found: *m*/*z* 524.1832. $C_{32}H_{28}O_6$ requires 524.1835.) δ_H 3.93 (3H, s, OMe), 3.96 (6H, s, OMe), 5.12, 5.26 (both 2H, s, benzyl), 6.51, 6.67 (both 1H, d, *J* 2.2), 6.61 (1H, s, H3), 7.08 (2H, s, H2′, H6′), 7.30–7.63 (10H, m, ArH). The aurone **17** (17%) was also obtained.

5,7-Di(benzyloxy)-3′,4′-methylenedioxyflavone **25** (17%), mp 201–202°C, from the silyl ether **23**. (Found: *m*/*z* 478.1427. $C_{30}H_{22}O_6$ requires 478.1416.) δ_H 5.12, 5.24 (both 2H, s, benzyl), 6.04 (2H, s, OCH_2O), 6.50, 6.64 (both 1H, d, *J* 2.1, H6, H8), 6.55 (1H, s, H3), 6.92 (1H, d, *J* 8.4, H2′), 7.30–7.63 (12H, m, ArH).

*(2Z)-4,6-Di(benzyloxy)-2-(3,4-methylenedioxybenzylidene)-1-benzofuran-3(2*H*)-one* **27** (38%), mp 194–196°C. (Found: *m*/*z* 478. $C_{30}H_{22}O_6$ requires 478.1416.) δ_H 5.08, 5.25 (both 2H, s, benzyl), 6.00 (2H, s, OCH_2O), 6.21, 6.41 (both 1H, d, *J* 1.6, H6, H8), 6.68 (1H, s, H3), 6.84 (1H, d, *J* 8.2, H5′), 7.22–7.51 (12H, m, ArH) was also obtained.

5,7-Di(benzyloxy)-3′,4′-dimethoxyflavone **26** (8%), as a pale yellow gum from the silyl ether **24**. (Found: *m*/*z* 494. $C_{31}H_{26}O_6$ requires 494.1729.) δ_H 3.96, 3.98 (both 3H, s, OMe), 5.13, 5.26 (both 2H, s, benzyl), 6.50, 6.67 (both 1H, d, *J* 2.4, H6, H8), 6.60 (1H, s, H3), 6.97 (1H, d, *J* 8.7, H5′), 7.22–7.63, (12H, m, ArH). Signals for the aurone **18** were evident in other chromatographic fractions.

*Cyclization of the Ketone **13***

The ketone **13** (6.0 mg, 0.01 mmol) was dissolved in acetone (1 mL) to which was added anhydrous potassium carbonate (3.0 mg, 0.02 mmol). The mixture was heated to reflux for 30 min, cooled, and filtered. The solution was concentrated under reduced pressure to give the aurone **26** (6.0 mg).

References

[1] W. Tuckmantel, A. P. Kozikowski, L. J. Romanczyk, Jr, *J. Am. Chem. Soc.* **1999**, *121*, 12073. doi:10.1021/JA993020D

[2] E. Haslam, *Practical Polyphenolics – From Structure to Molecular Recognition and Physiological Action* **1998** (Cambridge University Press: Cambridge, UK).

[3] *Flavonoids in Health and Disease, 2nd edn* (Eds C. A. Rice-Evans, L. Packer) **2003** (Marcel Dekker: New York, NY).

[4] *Phenolic Compounds in Foods and their Effects on Health, II: Antioxidants and Cancer Prevention*; ACS Symposium Series No. 507 **1992** (Eds M.-T. Huang, C.-T. Ho, C. Y. Lee) (American Chemical Society: Washington, DC).

[5] *Food Phytochemicals for Cancer Prevention II: Teas, Spices and Herbs*; ACS Symposium Series No. 547 **1994** (Eds C.-T. Ho, T. Osawa, M.-T. Huang, R. T. Rosen) (American Chemical Society: Washington, DC).

[6] H. N. Graham, *Prev. Med.* **1992**, *21*, 334. doi:10.1016/0091-7435(92)90041-F

[7] K. M. Johnston, R. G. Shotter, *J. Chem. Soc. (C)* **1967**, 2476.

[8] B. Nay, V. Arnaudinaud, J.-F. Peyrat, A. Nuhrich, G. Deffieux, J.-M. Merillon, J. Vercauteren, *Eur. J. Org. Chem.* **2000**, 1279. doi:10.1002/1099-0690(200004)2000:7<1279::AID-EJOC1279>3.0.CO;2-D

[9] P. J. Kerr, S. M. Pyke, A. D. Ward, E. R. T. Tiekink, *Z. Krist–New Cryst. St.* **2001**, *216*, 567.

[10] P. J. Kerr, S. M. Pyke, A. D. Ward, E. R. T. Tiekink, *Z. Krist–New Cryst. St.* **2001**, *216*, 565.

[11] P. J. Kerr, S. M. Pyke, A. D. Ward, E. R. T. Tiekink, *Z. Krist–New Cryst. St.* **2001**, *216*, 558.

[12] D. Pflieger, B. Muckensturm, *Tetrahedron Lett.* **1990**, *31*, 2299. doi:10.1016/0040-4039(90)80211-4

[13] A. S. Bhat, J. L. Whetstone, R. W. Bruggemeier, *Tetrahedron Lett.* **1999**, *40*, 2469. doi:10.1016/S0040-4039(99)00279-8

[14] H. Garcia, S. Iborra, J. Primo, *J. Org. Chem.* **1986**, *51*, 4432. doi:10.1021/JO00373A016

[15] A. J. Luxen, L. E. E. Christiaens, M. J. Renson, *J. Organomet. Chem.* **1985**, *287*, 81. doi:10.1016/0022-328X(85)80070-X

[16] S. Torii, H. Okumoto, L. H. Xu, M. Sadakane, M. V. Shostakovsky, A. B. Ponomaryov, V. N. Kalinin, *Tetrahedron* **1993**, *49*, 6773. doi:10.1016/S0040-4020(01)80421-X

[17] M. Alvaro, H. Garcia, S. Iborra, M. A. Miranda, J. Primo, *Tetrahedron* **1987**, *43*, 143. doi:10.1016/S0040-4020(01)89940-3

[18] L. W. McGarry, M. R. Detty, *J. Org. Chem.* **1990**, *55*, 4349. doi:10.1021/JO00301A027

[19] P. G. Ciattini, E. Morera, G. Ortar, S. S. Rossi, *Tetrahedron* **1991**, *47*, 6449. doi:10.1016/S0040-4020(01)86572-8

[20] K. Sakamoto, E. Honda, N. Ono, H. Uno, *Tetrahedron Lett.* **2000**, *41*, 1819. doi:10.1016/S0040-4039(00)00037-X

[21] (a) K. Nakatani, A. Okamoto, I. Saito, *Tetrahedron* **1996**, *52*, 9427. doi:10.1016/0040-4020(96)00480-2
(b) K. Nakatani, A. Okamoto, M. Yamanuki, I. Saito, *J. Org. Chem.* **1994**, *59*, 4360. doi:10.1021/JO00095A003

[22] S. P. Korshunov, N. V. Korzova, V. M. Kazantseva, V. L. Krasnov, N. V. Utekhina, I. V. Bodrikov, *Zh. Org. Khim* **1986**, *22*, 1847.

[23] D. Obrecht, *Helv. Chim. Acta* **1989**, *72*, 447. doi:10.1002/HLCA.19890720305

[24] B. Voirin, *Phytochemistry* **1983**, *22*, 2107. doi:10.1016/S0031-9422(00)80133-8

[25] D. H. Williams, I. Fleming, *Spectroscopic Methods in Organic Chemistry* **1995** (McGraw-Hill: London).

[26] A. Pelter, R. S. Ward, T. I. Gray, *J. Chem. Soc., Perkin Trans. 1* **1976**, 2475. doi:10.1039/P19760002475

[27] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

[28] E. G. Sundholm, *Tetrahedron* **1977**, *33*, 991. doi:10.1016/0040-4020(77)80213-5

[29] W. B. Whalley, *J. Chem. Soc.* **1951**, 665. doi:10.1039/JR9510000665

[30] G. Heinecke, T. V. Hung, R. H. Prager, A. D. Ward, *Aust. J. Chem.* **1984**, *37*, 831.

[31] J. A. Donnelly, D. E. Maloney, *Tetrahedron* **1979**, *35*, 2883. doi:10.1016/S0040-4020(01)99503-1

[32] J. S. Hastings, H. G. Heller, *J. Chem. Soc. Perkin Trans. 1* **1972**, *1*, 2128. doi:10.1039/P19720002128

[33] A. J. Corey, H. Cho, C. Rucker, H. D. Hua, *Tetrahedron Lett.* **1981**, *22*, 3455. doi:10.1016/S0040-4039(01)81930-4

[34] M. T. Briggs, G. L. S. Duncan, C. W. Thornber, C. R. Cooper, *J. Chem. Res. (M)* **1982**, 2461.