Synthesis of 3-Hydroxyalkylbenzo[*b*]furans via the Palladium-Catalysed Heteroannulation of Silyl-Protected Alkynols with 2-Iodophenol

Brian C. Bishop,* Ian F. Cottrell, David Hands
Merck Sharp and Dohme Research Laboratories, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU, England
Fax +44(1992)470437
Received 11 December 1996; revised 30 April 1997

The palladium-catalysed annulation of silyl-protected alkynols with 2-iodophenol gives silyl-protected 3-hydroxyalkylbenzo[*b*]furans **3a–l**. The use of silyl-protected propynols bearing a free hydroxyl or an *O*-triethylsilyl protecting group resulted in the formation of 1-oxa-2-silacyclopent-3-enes **5a–d** as the major products. Removal of the silyl protecting groups from silyl benzo[*b*]furans **3c,3e** and **3i** affords 3-hydroxyalkylbenzo[*b*]furans **9a–c** in good yield.

The benzo[*b*]furan ring system occurs in a wide range of biologically active, naturally occurring, and synthetic compounds, and numerous methods for their synthesis are known.[1,2] 3-Substituted benzo[*b*]furans are useful intermediates for the synthesis of benzofuran isosteres of pharmacologically important indoles,[3] as well as benzofuran derivatives possessing analgesic,[4,5] narcotic,[4,5] antidiabetic,[6] and insecticidal activity.[7] However, the synthesis of 3-substituted benzo[*b*]furans is not as straightforward as the analogous benzo[*b*]thiophenes and indoles, since benzofuran undergoes electrophilic substitution predominantly at the 2-position.[2] In particular, there are only a few methods reported in the literature for the preparation of 3-hydroxyalkylbenzo[*b*]furans, most of which involve long reaction sequences[4,8,9] or harsh reaction conditions.[7,10]

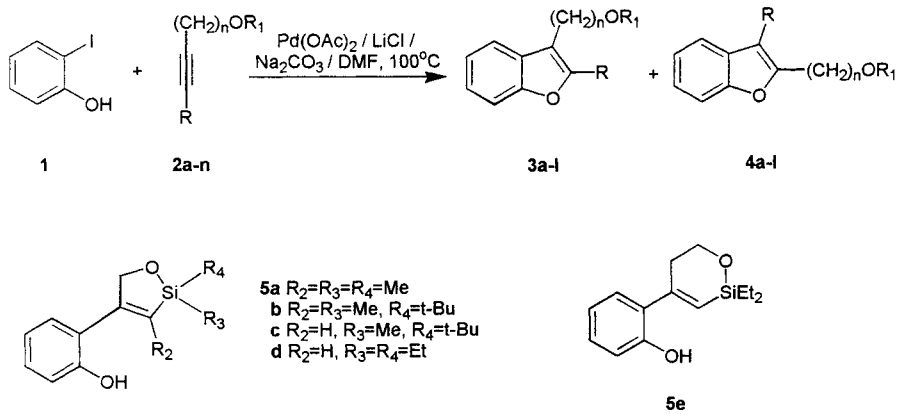
The synthesis of 2-substituted benzo[*b*]furans, including 2-hydroxyalkylbenzo[*b*]furans by the palladium-catalysed coupling of terminal acetylenes with 2-iodophenol has been reported.[11–13] More recently, the palladium-catalysed heteroannulation of internal alkynes has found application in the synthesis of an increasing number of heterocyclic compounds, including indoles,[14,15] tryptophans,[16] and heterocondensed pyrroles.[17] Larock and coworkers have reported the extension of this methodology to the synthesis of 1,2-dihydroisoquinolines, benzofurans, benzopyrans, and isocoumarins.[18] We now report our investigations on the synthesis of 3-hydroxyalkylbenzo[*b*]furans, via the palladium-catalysed annulation of silyl-protected alkynols with 2-iodophenol.

The palladium-catalysed coupling of 2-iodophenol with various silyl-protected alkynols was studied (Scheme 1, Table 1). The bis-silyl-protected alkynols **2,d,e,j,n** were prepared by formation of the dianion of the appropriate alkynol with BuLi followed by quenching with two equivalents of the trialkylsilyl chloride (Method A). A two-step protocol involving initial *O*-protection (imidazole/trialkylsilyl chloride/DMF) followed by protection of the terminal carbon (BuLi/trialkylsilyl chloride/THF) was more convenient for the preparation of the trialkylsilyl-protected alkynols **2c,i**, and **l** in high yield (Method B). The latter method was also used to prepare the differentially protected bis-trialkylsilylalkynols **2g** and **2h** in good yields. Selective *O*-desilylation (HCl/MeOH, Method C) provided the mono-silyl derivatives **2b,k** and **m**.

Initially, we studied the reactions of the silyl-protected propynols **2a–h**. We employed conditions similar to those used in other heteroannulations. Thus, 2-iodophenol and the silyl-protected alkynol (10–20% excess) were heated at 100°C in dimethylformamide in the presence of palladium acetate (5 mol%), lithium chloride (1.0 eq), and sodium carbonate (5.0 eq). The reaction of the mono-TMS-propynol **2a** with 2-iodophenol resulted in a complex mixture of products from which we were only able to isolate the 1-oxa-2-silacyclopent-3-ene **5a** in 6% yield. Similar products have been reported in other palladium-catalysed reactions of silyl-protected alkynols.[15,19,20] The formation of 1-oxa-2-silacyclopent-3-ene **5a** presumably results from reaction of the free hydroxy group on silicon in the intermediate vinylpalladium species **6** followed by transfer of a methyl group and finally reductive elimination of palladium (Scheme 2). The mono-TBDMS-protected propynol **2b** reacted similarly to give the 1-oxa-2-silacyclopent-3-ene **5b** isolated in 20% yield. The closely related 1-oxa-2-silacyclopent-3-ene **5c** resulting from loss of a methyl group was also isolated from this reaction in low yield. The bis-TES-propynol **2c** resulted in a low yield of 2-TES-3-hydroxymethylbenzo-[*b*]furan **3a**, the major product [**5d**; 45% by HPLC analysis (Method 1) of the reaction mixture, 10% yield] was the 1-oxa-2-silacyclopent-3-ene **5d**. Formation of **5d** was attributed to the instability of the O-TES group under the reaction conditions. Migration of an ethyl group is not observed in this case, presumably as a result of β-elimination from intermediate **8** (R = Et) with formation of ethene.

These results contrast with the indole case in which 3-TMS-propynol coupled with 2-iodoaniline under similar conditions to give 3-hydroxymethylindole in 60% yield.[14] This difference is presumably a reflection of the lower nucleophilicity of the oxygen of the phenol compared to the nitrogen in aniline. Hence, formation of the 1-oxa-2-silacyclopent-3-enes **5a–d** is kinetically favoured over cyclisation to give benzofuran products. Much better yields of benzofurans were obtained when more stable *O*-silyl protecting groups were employed (Table 1, entries 4, 5, and 7). Thus, bis-TBDMS-propynol **2e** reacted with 2-iodophenol in 3 hours to afford 2-TBDMS-3-(TBDMSoxymethyl)benzo[*b*]furan **3c** in 85% yield while the 1-oxa-2-silacyclopent-3-ene **5b** was formed in <1% yield. The more bulky bis-TIPS-propynol **2d** coupled in 17 hours to afford 2-TIPS-3-(TIPSoxymethyl)-benzo[*b*]-furan **3b** in 57% yield.

The methodology was then applied to the annulation of silyl-protected butynols and pentynols (entries 9 to 14). In these cases it was found that *O*-protection was not essential in order to obtain 3-hydroxyalkylbenzo[*b*]furans

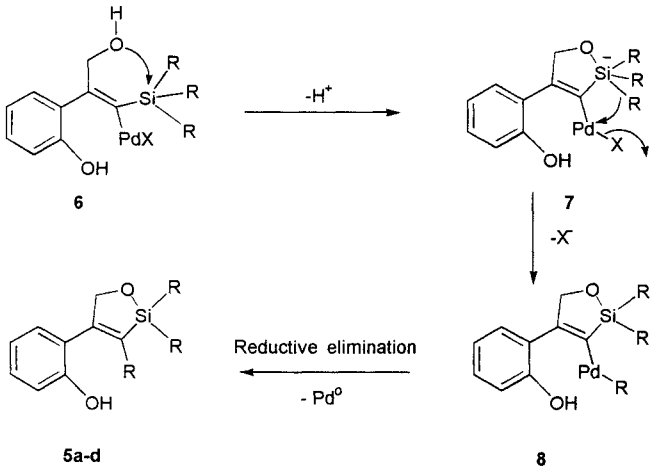


Scheme 1

Table 1. Synthesis of Benzo[*b*]furans **3** and 1-Oxa-2-silacyclopentenes **5** via Palladium-Catalysed Reaction of Silyl-Protected Alkynols **2** with 2-Iodophenol

Entry	2	n	R	R_1	Time (h)	Product (% isolated yield)[a]	
						3	5
1	**2a**	1	TMS	H	3	–	**5a** (6)
2	**2b**	1	TBDMS	H	65	–	**5b** (17) + **5c** (3)
3	**2c**	1	TES	TES	2	**3a**[b] (18)	**5d** (10)
4	**2d**	1	TIPS	TIPS	17	**3b** (57)	–
5	**2e**	1	TBDMS	TBDMS	3	**3c** (85)	–
6	**2f**	1	TMS	TBDMS	8	–[c]	–
7	**2g**	1	TES	TBDMS	3	**3d** (81)	–
8	**2h**	1	TBDMS	TES	3.5	–	**5b** + **5c**[d]
9	**2i**	2	TBDMS	TBDMS	7	**3e** (74)	–
10	**2j**	2	TES	TES	4	**3f** + **3g** (47)[e]	**5e** (4)
11	**2k**	2	TBDMS	H	23	**3h** (65)	–
12	**2l**	3	TBDMS	TBDMS	7	**3i** (75)	–
13	**2m**	3	TBDMS	H	24	**3j** (76)	–
14	**2n**	3	TES	TES	5	**3k** + **3l** (76)[f]	–

[a] Yields for compounds **3a–l** include the regioisomers **4a–l**.
[b] Product is 2-TES-3-hydroxymethylbenzo[*b*]furan (R^1 = H).
[c] A complex mixture was obtained from which no products were isolated.
[d] Products not isolated.
[e] Product is a 2 : 3 mixture of **3f** (R = R^1 = TES) and **3g** (R = TES, R^1 = H).
[f] Product is a 2 : 1 mixture of **3k** (R = R^1 = TES) and **3l** (R = TES, R^1 = H).

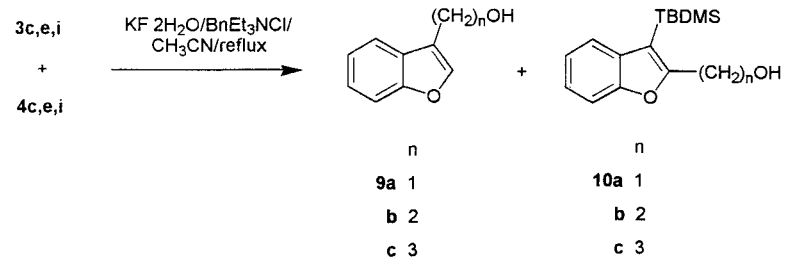


Scheme 2

as the major products (entries 11 and 13), presumably because formation of six- or seven-membered 1-oxa-2-silacycloalkenes by reaction of the free hydroxy group on silicon in the intermediate vinyl-palladium species is slower than cyclisation to give benzofuran products. However, the bis-TBDMS-alkynols again gave the best results with fewer side-products and shorter reaction times (entries 9 and 12). The bis-TES-butynol and -pentynol also gave the TES-protected-hydroxyethyl and -hydroxypropylbenzo[*b*]furans as the major products (entries 10 and 14) although annulation of bis-TES-butynol also resulted in the formation of some of the 1-oxa-2-silacyclohex-3-ene **5e** [8% by HPLC (Method 1) of the reaction mixture, 4% yield] as a side product.

The regioselectivity of the reactions was also investigated. The silyl-protected 3-hydroxyalkylbenzo[*b*]furans **3a–l** contained 2–10% of the regioisomers **4a–l** [by HPLC (Method 1) and NMR]. It was not possible to separate the regioisomers **4a–l** from the silyl-protected

benzo[*b*]furans **3a–l** by chromatography. However, the 2-regioisomers could be separated from the bis-TBDMS-3-hydroxymethylbenzo[*b*]furans **3c,3e**, and **3i** by subjecting the mixture to desilylation conditions ($BnEt_3NCl$/$KF{\cdot}2\,H_2O$/CH_3CN/reflux). The 2-regioisomers were isolated as the monosilyl derivatives **10a–c** whereas the 3-regioisomers **3c,3e**, and **3i** were fully deprotected to afford the 3-hydroxyalkylbenzo[*b*]furans **9a–c** in good yield. Separation at this point allowed quantification of the 2-regioisomers **10a–c** (Scheme 3).



n	HPLC ratio **3**:**4** (Method 2)	Isolated yield **9**	**10**
1	97.3 : 2.3	80	1.6
2	90.8 : 8.4	79	7.1
3	95.3 : 4.7	76	3.8

Scheme 3

All reactions were carried out under an atmosphere of dry N_2. Melting points (uncorrected) were measured with a Büchi 510 apparatus. NMR spectra were recorded on a Bruker DPX250 spectrometer. Chemical shifts were measured in ppm and coupling constants (J) in Hz. Infrared spectra were recorded on a Nicolet 510P

Table 2. NMR Data for Compounds **3**[a]

Product[b]	^1H NMR (CD_2Cl_2) δ, J (Hz)	^{13}C NMR (CD_2Cl_2) δ
3a	0.87–1.10 (15H, m, $SiEt_3$), 1.79 (1H, t, J = 5.4, OH), 4.85 (2H, d, J = 5.4, CH_2), 7.27 (2H, m, H-5 and H-6), 7.49 (1H, m, H-4), 7.72 (1H, m, H-7)	3.8, 7.5, 56.2, 111.5, 120.3, 122.6, 124.9, 128.5, 130.8, 158.4, 158.9
3b	1.15–1.59 (42H, m, 2 × Si-*i*Pr_3), 5.05 (2H, s, CH_2), 7.25 (2H, m, H-5 and H-6), 7.48 (1H, m, H-4), 7.85 (1H, m, H-7)	12.1, 12.5, 18.3, 18.9, 58.2, 111.3, 121.5, 122.2, 124.5, 129.0, 131.6, 156.2, 158.5
3c	0.2 (6H, s, $SiMe_2$), 0.43 (6H, s, $SiMe_2$), 0.98 (9H, s, Si-*t*-Bu), 1.00 (9H, s, Si-*t*-Bu), 4.94 (2H, s, CH_2), 7.28 (2H, m, H-5 and H-6), 7.50 (1H, m, H-4), 7.75 (1H, m, H-7)	17.6, 18.6, 26.1, 26.6, 56.9, 111.4, 120.9, 122.4, 124.8, 128.9, 131.1, 158.1, 158.3
3d	0.15 (6H, s, $SiMe_2$), 0.89–1.06 (24H, m, $SiEt_3$ and Si-*t*-Bu), 4.87 (2H, s, CH_2), 7.23 (2H, m, H-5 and H-6), 7.44 (1H, m, H-4), 7.70 (1H, m, H-7)	3.9, 7.6, 18.7, 26.1, 56.9, 111.4, 120.8, 122.4, 124.7, 128.9, 131.0, 157.8, 158.5
3e	0.02 (6H, s, $SiMe_2$), 0.41 (6H, s, $SiMe_2$), 0.89 (9H, s, Si-*t*-Bu), 0.99 (9H, s, Si-*t*-Bu), 3.04 (2H, t, J = 7.5, CH_2), 3.90 (2H, t, J = 7.5, CH_2), 7.26 (2H, m, H-5 and H-6), 7.47 (1H, m, H-4), 7.64 (1H, m, H-7)	17.8, 18.6, 26.0, 26.7, 28.9, 64.0, 111.4, 120.3, 122.1, 124.6, 128.3, 129.6, 157.6, 158.1
3f	0.56–1.08 (30H, m, 2 × $SiEt_3$), 3.01 (2H, t, J = 7.5, CH_2), 3.87 (2H, t, J = 7.5, CH_2), 7.25 (2H, m, H-5 and H-6), 7.48 (1H, m, H-4), 7.63 (1H, m, H-7)	3.8, 4.5, 6.9, 7.5, 28.8, 63.6, 111.3, 120.2, 122.1, 124.5, 128.1, 129.7, 157.4, 158.3
3g	0.93–1.15 (15H, m, $SiEt_3$), 1.90 (1H, brt, J = 5.0, OH), 3.09 (2H, t, J = 6.5, CH_2), 3.91 (2H, q, J = 5.0, 6.5, CH_2), 7.31 (2H, m, H-5, H-6), 7.55 (1H, m, H-4), 7.66 (1H, m, H-7)	3.9, 7.5, 28.5, 63.0, 111.5, 120.0, 122.3, 124.7, 127.6, 129.3, 158.0, 158.4
3h	0.44 (6H, s, $SiMe_2$), 1.02 (9H, s, Si-*t*-Bu), 1.77 (1H, br s, OH), 3.08 (2H, t, J = 6.7, CH_2), 3.90 (2H, t, J = 6.7, CH_2), 7.28 (2H, m, H-5 and H-6), 7.50 (1H, m, H-4), 7.64 (1H, m, H-7)	17.8, 26.7, 28.6, 63.0, 111.5, 120.1, 122.3, 124.8, 127.8, 129.4, 158.2, 158.2
3i	0.10 (6H, s, $SiMe_2$), 0.40 (6H, s, $SiMe_2$), 0.96 (9H, s, Si-*t*-Bu), 0.99 (9H, s, Si-*t*-Bu), 1.88 (2H, m, CH_2), 2.85 (2H, m, CH_2), 3.74 (2H, t, J = 6.3, CH_2), 7.24 (2H, m, H-5 and H-6), 7.45 (1H, m, H-4), 7.60 (1H, m, H-7)	17.8, 18.6, 21.6, 26.2, 26.7, 34.6, 63.3, 111.4, 120.1, 122.0, 124.5, 129.5, 131.7, 156.5, 158.2
3j	0.43 (6H, s, $SiMe_2$), 0.83 (9H, s, Si-*t*-Bu), 1.96 (3H, m, CH_2 and OH), 2.88 (2H, m, CH_2), 3.75 (2H, t, J = 6.4, CH_2), 7.26 (2H, m, H-5 and H-6), 7.48 (1H, m, H-4), 7.62 (1H, m, H-7)	17.8, 21.4, 26.7, 34.3, 62.9, 111.5, 120.1, 122.1, 124.6, 129.4, 131.4, 156.7, 158.2
3k	0.59–1.09 (30H, m, 2 × $SiEt_3$), 1.89 (2H, m, CH_2), 2.85 (2H, m, CH_2), 3.74 (2H, t, J = 6.4, CH_2), 7.25 (2H, m, H-5 and H-6), 7.47 (1H, m, H-4), 7.60 (1H, m, H-7)	3.8, 4.8, 7.0, 7.5, 21.4, 34.6, 62.8, 111.4, 120.0, 122.0, 124.4, 129.5, 131.5, 156.3, 158.4
3l	0.89–1.10 (15H, m, $SiEt_3$), 1.66 (1H, br s, OH), 1.95 (2H, m, CH_2), 2.87 (2H, m, CH_2), 3.73 (2H, t, J = 6.3, CH_2), 7.26 (2H, m, H-5 and H-6), 7.47 (1H, m, H-4), 7.63 (1H, m, H-7)	3.8, 7.5, 21.2, 34.3, 62.8, 111.4, 120.0, 122.1, 124.5, 129.4, 131.2, 156.5, 158.4

[a] Signals due to the regioisomers **4a–l** are not reported.
[b] All compounds gave satisfactory microanalysis (C ± 0.40, H ± 0.1, O ± 0.2) or HRMS.

series FTIR. UV spectra were recorded on a Hewlett Packard HP 8452A diode array. Column chromatography was carried out on silica gel (70–230 mesh, E. Merck) and on neutral aluminium oxide (150 mesh, Brockmann I). Reversed phase HPLC analyses were obtained with a Hewlett Packard 1050 HPLC instrument using a Zorbax RX C8 column: A = 0.1% H_3PO_4, B = MeCN; gradient operation 50% A to 5% A in 10 min, 5% A for 15 min; 1.0 mL/min; 40 °C; 220 nm (Method 1) or using a Hypersil ODS 3 column: 5% H_2O, 95% MeCN isocratic, 1.0 mL/min, 40 °C, 220 nm (Method 2).

1-*tert*-Butyldimethylsilyl-3-(*tert*-butyldimethylsilyloxy)prop-1-yne (2e); Typical Procedure (Method A):

A solution of propargyl alcohol (5.0 g, 90 mmol) in THF (250 mL) was cooled to −30 °C and *n*-BuLi (74.9 mL of 2.5 M in hexane, 187 mmol) was added over 45 min (temp. ≤ −20 °C). The mixture was stirred at −20 °C for 1 h, cooled to −30 °C, and treated with a solution of *tert*-butyldimethylsilyl chloride (28.2 g, 187 mmol) in THF (50 mL) over 30 min (temp. ≤ −20 °C). The mixture was allowed to warm to r.t. and stirred overnight. The resulting solution was cooled to −6 °C and treated with 1% aqueous Na_2CO_3 (200 mL) over 15 min (temp. ≤ 0 °C). The mixture was extracted with hexane (2 × 100 mL) and the combined hexane extracts were washed with water (100 mL) and saturated brine (100 mL). The hexane phase was dried (Na_2SO_4) and evaporated to afford crude **2e**; yield: quantitative. Kugelrohr distillation (110 °C, 0.3 mbar) afforded pure **2e** as a colourless crystalline solid; yield: 19.24 g (76%); mp 58–60 °C (MeOH).

^{1}H NMR (CD_2Cl_2): δ = 0.1 (6H, s, $SiMe_2$), 0.12 (6H, s, $SiMe_2$), 0.91 (9H, s, Si-*t*-Bu), 0.94 (9H, s, Si-*t*-Bu), 4.31 (2H, s, CH_2).

1-*tert*-Butyldimethylsilyl-4-(*tert*-butyldimethylsilyloxy)but-1-yne (2i); Typical Procedure (Method B):

A solution of but-3-yn-1-ol (20.0 g, 285 mmol) and imidazole (21.4 g, 314 mmol) in DMF (120 mL) was treated with *tert*-butyldimethylsilyl chloride (43.0 g, 285 mmol) at r.t. After stirring for 1 h the mixture was partitioned between 1% aqueous Na_2CO_3 (400 mL) and hexane (400 mL). The hexane phase was washed with 1% aqueous Na_2CO_3 (200 mL) and saturated brine (200 mL), dried (Na_2SO_4), filtered and evaporated to afford 4-(*tert*-butyldimethylsilyloxy)but-1-yne as a colourless liquid; yield: 46.8 g (89%).

^{1}H NMR (CD_2Cl_2): δ = 0.07 (6H, s, $SiMe_2$), 0.89 (9H, s, Si-*t*-Bu), 1.99 (1H, t, *J* = 2.5, C≡CH), 2.38 (2H, dt, *J* = 2.5, 7.0, CH_2), 3.73 (2H, t, *J* = 7.0, CH_2).

A solution of the crude 4-(*tert*-butyldimethylsilyloxy)but-1-yne (10.0 g, 54.2 mmol) in THF (100 mL) was cooled to −60 °C and treated with *n*-BuLi (21.7 mL of 2.5 M in hexane, 54.2 mmol) over 15 minutes (temp. ≤ −40 °C). The solution was kept at −20 °C for 1 h cooled to −40 °C, and treated with a solution of *tert*-butyldimethylsilyl chloride (8.2 g, 54.2 mmol) in THF (30 mL) over 15 min. The resulting solution was allowed to warm to r.t. and stirred for 1 h. The mixture was partitioned between 1% aqueous Na_2CO_3 (200 mL) and hexane (200 mL). The hexane phase was washed with water (200 mL) and saturated brine (100 mL), dried (Na_2SO_4), filtered, and evaporated. Purification by Kugelrohr distillation (0.2–0.3 mbar, 120 °C) afforded **2i** as a colourless liquid; yield: 11.6 g (72%).

^{1}H NMR (CD_2Cl_2): δ = 0.07 (12H, s, 2 × $SiMe_2$), 0.89 (9H, s, Si-*t*-Bu), 0.92 (9H, s, Si-*t*-Bu), 2.43 (2H, t, *J* = 6.7, CH_2), 3.71 (2H, t, *J* = 6.7, CH_2).

4-*tert*-Butyldimethylsilylbut-3-yn-1-ol (2k); Typical Procedure (Method C):

1-*tert*-Butyldimethylsilyl-4-(*tert*-butyldimethylsilyloxy)but-1-yne (3.7 g, 12.4 mmol) was dissolved in methanol (60 mL) and the solution was treated with conc. HCl (1.20 mL, 13.9 mmol). The solution was stirred for 2 h at r.t. and then partitioned between hexane (100 mL) and water (100 mL). The aqueous phase was extracted with hexane (100 mL) and the combined hexane phases were washed with water (100 mL) and saturated brine (100 mL). The hexane solution was dried (Na_2SO_4), filtered and evaporated to give a colourless liquid. Kugelrohr distillation (105 °C, 0.5 mbar) gave **2k** as a colourless liquid; yield: 1.63 g (71.5%).

^{1}H NMR (CD_2Cl_2): δ = 0.08 (6H, s, $SiMe_2$), 0.92 (9H, s, Si-*t*-Bu), 2.09 (1H, br s, OH), 2.47 (2H, t, *J* = 6.4, CH_2), 3.67 (2H, br t, *J* = 6.4, CH_2).

2,2,3-Trimethyl-4-(2-hydroxyphenyl)-1-oxa-2-silacyclopent-3-ene (5a):

2-Iodophenol (2.0 g, 9.1 mmol), 3-trimethylsilylpropargyl alcohol (1.28 g, 10 mmol), palladium acetate (0.05 g, 0.223 mmol), and sodium carbonate (4.8 g, 45.5 mmol) were heated together in DMF (25 mL) at 100 °C for 3 h. The mixture was cooled to r.t. and filtered through Hyflo. The Hyflo was rinsed through with isopropyl acetate (25 mL) and water (25 mL) and the filtrate diluted further with isopropyl acetate (25 mL) and water (25 mL). The phases were separated and the aqueous phase was extracted with isopropyl acetate (50 mL). The combined organic phases were washed with water (50 mL) and saturated brine (50 mL), dried (Na_2SO_4), filtered and evaporated to a residual oil that partially crystallised on standing. The residue was extracted with hot hexane (100 mL) and the hexane extract was evaporated to a pale brown solid which was recrystallised from EtOAc/hexane to afford **5a** as a beige solid; yield: 122 mg (6%); mp 148–152 °C.

IR (Nujol): ν = 3192, 1593, 1255, 1082, 1025, 820 cm^{-1}.

UV (CH_3CN): λ_{max} = 196, 281 nm.

^{1}H NMR (CD_2Cl_2): δ = 0.32 (6H, s, $SiMe_2$), 1.71 (3H, t, *J* = 2.1 Hz, CH_3), 4.70 (2H, q, *J* = 2.1 Hz, CH_2), 5.24 (1H, br s, OH), 6.90–7.28 (4H, m, Ar–H).

^{13}C NMR (CD_2Cl_2): δ = 13.1, 75.2, 115.6, 120.7, 122.8, 125.5, 129.1, 129.6, 136.9, 148.5, 152.6.

2-*tert*-Butyl-4-(2-hydroxyphenyl)-2,3-dimethyl-1-oxa-2-silacyclopent-3-ene (5b) and 2-*tert*-butyl-2-methyl-4-(2-hydroxyphenyl)-1-oxa-2-silacyclopent-3-ene (5c):

2-Iodophenol (2.20 g, 10 mmol) and 3-*tert*-butyldimethylsilylpropargyl alcohol (2.04 g, 12 mmol) were dissolved in DMF (25 mL). Sodium carbonate (5.3 g, 50 mmol) and lithium chloride (0.424 g, 10 mmol) were added and the mixture was evacuated and flushed with nitrogen three times. Palladium acetate (112 mg, 0.5 mmol) was added and the mixture was evacuated and flushed with nitrogen once more. The mixture was heated at 100 °C for 65 hours after which time HPLC (Method 1) showed < 1% iodophenol remaining. The mixture was cooled to r.t. diluted with EtOAc (100 mL) and water (100 mL) and filtered through Hyflo. The phases were separated and the aqueous phase was extracted with EtOAc (50 mL). The combined organic phases were washed with water (2 × 50 mL) and saturated brine (50 mL), dried (Na_2SO_4), filtered and evaporated to give a brown oil. The crude product was subjected to column chromatography on silica gel (80 g) eluting with 9:1 hexane/EtOAc to afford a yellow oil that partially crystallised. Trituration with hexane and filtration (filtrate A) gave crude **5b** as a cream solid; crude yield: 0.76 g (29%).

Recrystallisation from EtOAc/hexane gave **5b** as colourless crystals; yield: 0.46 g (17.5%); mp 126–128 °C.

IR (Nujol): ν = 3169, 1593, 1255, 1082, 1033, 750 cm^{-1}.

UV (CH_3CN): λ_{max} = 196, 280 nm.

^{1}H NMR (CD_2Cl_2): δ = 0.31 (3H, s, SiMe), 1.00 (9H, s, Si-*t*-Bu), 1.74 (3H, t, *J* = 2.2, CH_3), 4.61 (1H, dq, *J* = 15.3, 2.2, CH), 4.72 (1H ,dq, *J* = 15.3, 2.2, CH), 5.34 (1H, s, OH), 6.89–7.25 (4H, m, Ar-H).

^{13}C NMR (CD_2Cl_2): δ = 14.3, 19.6, 25.8, 75.6, 115.6, 120.7, 122.9, 129.2, 129.6, 133.9, 149.8, 152.6.

The filtrate from isolation of **5b** (filtrate A) was evaporated to a residue and the residual yellow/brown oil was purified by column chromatography on neutral alumina (Brockmann I) eluting initially with 3:1 hexane/EtOAc and then with 9:1 EtOAc/MeOH to afford **5c** as a yellow/brown oil that crystallised on standing. Trituration with hexane gave **5c** as a pale beige solid; yield: 65 mg (2.6%); mp 154–156 °C.

IR (Nujol): ν = 3176, 1577, 1543, 1243, 1016, 750 cm^{-1}.

UV (CH_3CN): λ_{max} = 192, 210, 248, 294 nm.

HRMS: *m/z* calc. for $C_{14}H_{20}O_2Si$: 248.1233 (M^+); found: 248.1243.

Table 3. NMR Data for Compounds **9** and **10**[a]

Product[a]	^{1}H NMR (CD_2Cl_2) δ, J (Hz)	^{13}C NMR (CD_2Cl_2) δ
9a	2.34 (1H, t, J = 5.5, OH), 4.74 (2H, d, J = 5.5, CH_2), 7.26 (2H, m, H-5 and H-6), 7.46 (1H, m, H-4), 7.55 (1H, t, J = 1, H-2), 7.62 (1H, m, H-7)	56.0, 111.8, 120.4, 121.1, 123.1, 124.9, 127.2, 142.7, 156.0
9b	1.98 (1H, br t, J = 4.0, OH), 2.89 (2H, dt, J = 1.0, 6.5, CH_2), 3.86 (2H, br q, J = 4.0, 6.5, CH_2), 7.25 (2H, m, H-5 and H-6), 7.45 (1H, m, H-4), 7.49 (1H, t, J = 1.0, H-2), 7.55 (1H, m, H-7)	27.4, 62.0, 111.7, 117.5, 120.0, 122.8, 124.7, 128.5, 142.6, 155.7
9c	2.02 (3H, m, CH_2 and OH), 2.83 (2H, dt, J = 1.0, 6.5, CH_2), 3.76 (2H, t, J = 6.5, CH_2), 7.35 (2H, m, H-5 and H-6), 7.55 (2H, m, H-2 and H-4), 7.67 (1H, m, H-7)	20.1, 32.3, 62.4, 111.7, 120.0, 120.5, 122.6, 124.5, 128.6, 141.6, 155.8
10a	0.47 (6H, s, $SiMe_2$), 0.96 (9H, s, Si-*t*-Bu), 2.16 (1H, br d, J = 4.5, OH), 4.78 (2H, d, J = 4.5, CH_2), 7.29 (2H, m, H-5 and H-6), 7.52 (1H, m, H-4), 7.71 (1H, m, H-7)	17.9, 26.6, 58.6, 109.6, 111.2, 122.8, 123.6, 124.5, 133.6, 155.4, 162.1
10b	0.42 (6H, s, $SiMe_2$), 0.95 (9H, s, Si-*t*-Bu), 1.90 (1H, br t, J = 3.0, OH), 3.09 (2H, t, J = 6.3, CH_2), 3.99 (2H, br q, J = 3.0, 6.3, CH_2), 7.22 (2H, m, H-5 and H-6), 7.45 (1H, m, H-4), 7.64 (1H, m, H-7)	18.3, 26.8, 33.4, 61.6, 108.0, 110.7, 122.6, 122.9, 123.6, 134.0, 155.3, 162.2
10c	0.42 (6H, s, $SiMe_2$), 0.94 (9H, s, Si-*t*-Bu), 1.57 (1H, br s, OH), 2.00 (2H, m, CH_2), 2.91 (2H, m, CH_2), 3.72 (2H, br t, J = 6.3, CH_2), 7.18 (2H, m, H-5 and H-6), 7.42 (1H, m, H-4), 7.61 (1H, m, H-7)	18.3, 26.4, 26.7, 32.3, 62.5, 106.3, 110.6, 122.4, 122.8, 123.3, 134.2, 155.2, 165.0

[a] All compounds gave satisfactory microanalysis (C ± 0.40, H ± 0.1, O ± 0.2) or HRMS.

Table 4. IR and UV Data for Compounds **3**, **5**, **9** and **10**

Compound	IR ν (cm^{-1}) (film)	UV λ_{max} (nm) (acetonitrile)
3a	3324, 2986, 1593, 1560, 1453, 1412, 1230, 1005, 750	209, 256, 279, 287
3b[a,b]	1560, 1239, 1132, 1099, 1046, 1023, 880, 750	226, 259, 280, 288
3c[a]	1560, 1255, 1230, 1132, 1099, 1050, 840, 780, 750	210, 257, 279, 287
3d	3069, 1560, 1462, 1442, 1259, 1230, 1128, 1099, 1049, 840, 750	212, 256, 279, 287
3e	3060, 1560, 1445, 1415, 1236, 1099, 1008, 750	215, 259, 281, 288
3f	3069, 1560, 1445, 1412, 1230, 1099, 1066, 1008, 750	215, 259, 281, 288
3g	3340, 3060, 1560, 1552, 1445, 1412, 1230, 1132, 1099, 1008, 820, 750	216, 259, 281, 288
3h	3340, 3060, 1560, 1470, 1445, 1250, 1230, 1123, 1099, 1008, 830, 750	214, 259, 281, 288
3i	3060, 1552, 1470, 1445, 1387, 1363, 1250, 1230, 1102, 840, 750	217, 260, 281, 288
3j	3340, 3060, 1560, 1470, 1445, 1250, 1230, 1122, 1099, 1008, 830, 750	216, 259, 281, 288
3k	3052, 1560, 1445, 1409, 1230, 1099, 1005, 750	217, 259, 281, 288
3l	3332, 3060, 1550, 1445, 1412, 1230, 1124, 1099, 1008, 750	217, 259, 281, 288
9b	3357, 3052, 1709, 1577, 1453, 1272, 1181, 1097, 1048, 750	209, 248, 275, 282
10a[a]	3258, 1560, 1247, 1164, 1016, 750	207, 252, 276, 284
10b[a]	3291, 3192, 1557, 1247, 1153, 1135, 1035, 1012, 750	193, 208, 251, 276
5a[a]	3192, 1593, 1255, 1082, 1025, 820	196, 281
5b[a]	3169, 1593, 1255, 1082, 1033, 750	196, 280
5c[a]	3176, 1577, 1543, 1243, 1016, 750	192, 210, 248, 294
5d[a]	3176, 1601, 1552, 1135, 1040, 750	211, 248, 294
5e	3340, 1602, 1445, 1230, 1082, 1033, 750	196, 280

[a] IR recorded as Nujol mull.
[b] UV recorded in dichloromethane.

^{1}H NMR (CD_2Cl_2): δ = 0.31 (3H, s, SiMe), 0.97 (9H, s, Si-*t*-Bu), 4.88 (2H, m, CH_2), 5.82 (1H, s, OH), 6.27 (1H, t, J = 2.0, olefinic-H), 6.88–7.24 (4H, m, Ar-H).

^{13}C NMR (CD_2Cl_2): δ = 19.4, 25.7, 75.3, 116.3, 120.7, 123.2, 124.0, 128.0, 129.8, 153.3, 159.0.

3-Hydroxymethyl-2-triethylsilylbenzo[*b*]furan (3a) and 2,2-Diethyl-4-(2-hydroxyphenyl)-1-oxa-2-silacyclopent-3-ene (5d):

A mixture of 2-iodophenol (4.40 g, 20 mmol), 1-triethylsilyl-3-(triethylsilyloxy)prop-1-yne (6.83 g, 24 mmol), lithium chloride (0.848 g, 20 mmol), and sodium carbonate (10.6 g) in DMF (50 mL) was evacuated and flushed with nitrogen three times. Palladium acetate (225 mg, 1.0 mmol) was added and the mixture was evacuated and flushed with nitrogen once more. The mixture was heated at 100 °C for 2 h and then cooled to r.t. The mixture was diluted with EtOAc (150 mL) and water (150 mL) and filtered through Hyflo. The phases were separated and the aqueous phase was extracted with EtOAc (50 mL). The combined organic phases were washed with water (2 × 100 mL) and saturated brine (100 mL), dried (Na_2SO_4), filtered, and evaporated to a dark brown oil. The crude product was purified by column chromatography on silica gel (200 g) eluting with 3:1 hexane/EtOAc followed by removal of excess acetylene side chain by Kugelrohr distillation (120 °C, 0.2 mbar) and column chromatography on neutral alumina (Brockmann I) eluting initially with neat hexane, then with hexane/EtOAc mixtures and finally with neat EtOAc to afford **3a** as a yellow oil; yield: 0.96 g (18%) (Table 2).

Also isolated was crude **5d** as a yellow/brown oil that crystallised on standing. Trituration with hexane afforded **5d** as a pale beige solid; yield: 0.46 g (10%); mp 93–94 °C.

IR (Nujol): ν = 3176, 1601, 1552, 1135, 1040, 750 cm^{-1}.

UV (CH_3CN): λ_{max} = 211, 248, 294 nm.

^{1}H NMR (CD_2Cl_2): δ = 0.66–1.03 (10H, m, $SiEt_2$), 4.95 (2H, d, J = 2.0, CH_2), 6.26 (1H, t, J = 2.0, olefinic-H), 6.34 (1H, s, OH), 6.90 (2H, m, Ar-H), 7.21 (2H, m, Ar-H).

^{13}C NMR (CD_2Cl_2): δ = 6.7, 7.6, 75.3, 116.3, 120.6, 122.7, 124.1, 128.2, 129.9, 153.6, 159.3.

2-*tert*-Butyldimethylsilyl-3-(*tert*-butyldimethylsilyloxymethyl)-benzo-[*b*]furan (3c); Typical Procedure:

2-Iodophenol (11.0 g, 50 mmol) and 1-*tert*-butyldimethylsilyl-3-(*tert*-butyldimethylsilyloxy)prop-1-yne (17.1 g, 60 mmol) were dis-

solved in DMF (125 mL). Lithium chloride (2.12 g, 50 mmol) and sodium carbonate (26.5 g, 250 mmol) were added and the mixture was evacuated and flushed with nitrogen three times. Palladium acetate (0.56 g, 2.5 mmol) was added, the mixture was evacuated and flushed with nitrogen once more and then heated to 100 °C for 3 hours when HPLC (Method 1) showed <1 % 2-iodophenol remaining. The mixture was cooled and diluted with hexane (350 mL) and water (350 mL). The mixture was filtered through a pad of Hyflo and the pad rinsed through with hexane (100 mL). The phases were separated and the aqueous phase was extracted with hexane (200 mL). The combined hexane phases were washed with water (2 × 250 mL) and saturated brine (250 mL). The hexane solution was then treated with silica gel (15 g) and stirred for 10 min. The silica gel was removed by filtration and the filtrate was evaporated to give crude **3c** as a yellow oil in quantitative yield. Purification by removal of excess silyl alkynol on a Kugelrohr apparatus (120 °C, 0.2 mbar) gave **3c** as a yellow oil that crystallised on standing; yield: 16.1 g (85 %); mp 43–45 °C (from methanol) (Table 2).

3-Hydroxymethylbenzo[*b*]furan (9a) and 2-Hydroxymethyl-3-*tert*-butyldimethylsilylbenzo[*b*]furan (10a); Typical Procedure:

To a solution of **3c** {15.0 g, 39.8 mmol [contains ca 2 % **4c** by HPLC (Method 2)]} in acetonitrile (300 mL) was added potassium fluoride dihydrate (7.87 g, 83.6 mmol) and benzyltriethylammonium chloride (9.98 g, 43.8 mmol) and the mixture heated at reflux for 4 h. The mixture was cooled to r.t. and filtered to remove solids. The filtrate was washed with hexane (2 × 200 mL) and evaporated to give a residual brown oil. The residue was partitioned between EtOAc (250 mL) and water (250 mL). The aqueous phase was extracted with EtOAc (150 mL) and the combined organic phases were washed with water (100 mL) and saturated brine (100 mL). The EtOAc solution was evaporated to give the crude product as a brown oil. The crude product was subjected to column chromatography on silica gel (180 g) eluting with 9:1 hexane/EtOAc to give **10a** as a yellow oil that crystallised on standing; yield: 0.17 g (1.6 %) (Table 3).

The column was then eluted with 3:1 hexane/EtOAc to give **9a** as a yellow oil that crystallised on standing; yield: 4.7 g (80 %); mp 47–48 °C (from hexane); lit.[8] mp 46–47 °C (Table 3).

We wish to thank Dr. D.J. Kennedy for assistance in obtaining NMR data and Mr. A. Kirtley for recording the IR and UV spectra.

(1) Donnelly, D.M.X.; Meegan, M.J. In *Comprehensive Heterocyclic Chemistry*, Vol. 4; Katritzky, A.R.; Rees, C.W., Eds.; Pergamon Press: Oxford, 1984; pp 657–712.
(2) Mustafa, A. *Benzofurans*; Wiley-Interscience: New York, 1974.
(3) Tomaszewski, Z.; Johnson, M.P.; Huang, X.; Nichols, D.E. *J. Med. Chem.* **1992**, *35*, 2061.
(4) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261.
(5) Ciganek, E. *Eur. Pat. Appl. EP* 9780, 1980; *Chem. Abstr.* **1980**, *93*, 220720.
(6) Komatsu, M.; Sato, H.; Taira, S.; Miyake, M.; Mayata, K.; Yoshida, H.; Ueyama, A.; Nishi, T. *PCT int. Appl. WO* 9509159, 1995; *Chem. Abstr.* **1995**, *123*, 112079.
(7) Fanta, W.I. *U.S. Patent* 3816469, 1974, *Chem. Abstr.* **1974**, *81*, 120817.
(8) Shafiee, A.; Mohamadpour, M. *J. Heterocycl. Chem.* **1978**, *15*, 481.
(9) Pearson, J.R.; Porter, Q.N. *Aust. J. Chem.* **1991**, *44*, 907.
(10) Trahanovsky, W.S.; Amah, A.N.; Cassady, T.J. *J. Am. Chem. Soc.* **1984**, *106*, 2696.
(11) Arcadi, A.; Marinelli, F. *Synthesis* **1986**, 749.
(12) Torii, S.; Yu, L.H.; Okumoto, H. *Synlett.* **1992**, 515.
(13) Kundu, N.G.; Pal, M.; Mahanty, J.S.; Dasgupta, S.K. *J. Chem. Soc., Chem. Commun.* **1992**, 41.
(14) Larock, R.C.; Yum, E.K. *J. Am. Chem. Soc.* **1991**, *113*, 6689.
(15) Chen, C.; Lieberman, D.R.; Larsen, R.D.; Reamer, R.A.; Verhoeven, T.R.; Reider, P.J.; Cottrell, I.F.; Houghton, P.G. *Tetrahedron Lett.* **1994**, *35*, 6981.
(16) Wensbo, D.; Eriksson, J.T.; Annby, U.; Gronowitz, S.; Cohen, L.A. *Tetrahedron Lett.* **1993**, *34*, 6471.
(17) Wensbo, D.; Eriksson, J.T.; Annby, U.; Gronowitz, S.; Cohen, L.A. *Tetrahedron Lett.* **1993**, *34*, 2823.
(18) Larock, R.C.; Yum, E.K.; Doty, M.J.; Sham, K.K.C. *J. Org. Chem.* **1995**, *60*, 3270.
(19) Ohta, T.; Shinoda, J.; Somei, M. *Chem. Lett.* **1993**, *5*, 797.
(20) Chauhan, B.P.S.; Tanaka, Y.; Yamashita, H.; Tanaka, M. *Chem. Commun.* **1996**, 1207.