Synthesis of Arylspiroketalis Related to the Papulacandins via Generation of Phthalide Oxycarbenium Ions

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Abstract: The nucleophilic addition of allylstannanes to oxycarbenium ions generated from phthalide acetate has been studied. The optimum conditions involve the use of trimethylsilyl trifluoromethanesulfonate in dichloromethane at –78°C. Hydroboration of the allylated products followed by oxidative cyclization provides an efficient synthesis of arylspiroketalis which are closely related to the papulacandins.

Key words: phthalides, oxycarbenium ions, papulacandins, spiroketals, allylstannanes

Spiroacetals are an important structural feature in many biologically active compounds such as the polyether antibiotics, marine and plant toxins, insect pheromones and antiparasitic agents.1 The papulacandins A 1, B 2, C 3, D 4 and E are a group of C-arylglycosyl spiroacetals antifungal agents isolated from Papularia spheropserma7 and Dictyochaeta simplex5 which exhibit potent in vitro activity against Candida albicans and related microorganisms. These compounds inhibit the enzymes involved in the biosynthesis of the fungal cell wall component, 1,3-β-d-glucan.4 The common opportunistic infection in AIDS patients, Pneumocystis carinii pneumonia, has also been effectively overcome5 by newer members of the papulacandin family, Mer-WF3010 5 and L-687–781 6.4 Papulacandin D 4 which lacks the short fatty acid and the galactose residue still exhibits antifungal activity, hence, our attention has focused on the synthesis of less complex arylspiroketalis which may also exhibit antifungal activity. The synthesis of these compounds also provides a better understanding of the elements required for activity.

Successful synthetic approaches to the C-arylglycosidic nucleus of the papulacandins have used a hetero Diels–Alder reaction,7 a palladium(0) catalysed coupling of an aryl halide with a stannyl glucal8 and the reaction of a 2-bromobenzyl ether with an appropriately protected D-glucose precursor9 or protected gluconolactone.10 Recently the [4.5]spiroacetal moiety of the papulacandins has been assembled by condensation of a D-arabino-1,4-lactone with an α-lithiated carbonyl of a β-phenylsulfonyldihydropyran,11 Achmatowicz oxidative ring expansion of a dihydroxylated aryfuran12 and the reductive aromatization of a quinol.13 To date the only total synthesis of a papulacandin is the synthesis of papulacandin D which has been achieved by Barrett et al.14

We have reported an efficient two step synthesis of a range of aryl spiroacetals related to the papulacandins, via the addition of ortho-lithiated tertiary benzamides 7 to lactones followed by acid-catalyzed cyclization of the resultant keto alcohols (Scheme 1).15 Difficulties were encountered when this methodology was applied to the synthesis of arylspiroketalis with a similar oxygenation pattern to that present in the papulacandins owing to steric hindrance by the neighboring methoxy group in the starting amides which hindered addition of the bulky lactone electrophile to the ortho position of amides 8,9. This problem prompted an alternative strategy for the synthesis of aryl spiroketalis in which the key step involved treatment of a phthalide acetate with an allylstannane.16 Whilst the use of glycosyl acetates as precursors to oxycarbenium ions in carbohydrate chemistry is well established, the use of phthalide acetates to generate oxycarbenium ions has not been studied. We therefore herein report the full details of our study of the addition of allylstannanes to phthalide acetates 10 and 11 in phthalide acetates to stabilize the oxycarben-
nium ion that forms upon treatment of 12 and 13 with a Lewis acid. In situ trapping of this oxycarbenium ion with an allylstannane provides an allyl group which can undergo further transformation. Phthalide acetates 12 and 13 were prepared (Scheme 2) by standard acetylation of hydroxyphthalides 10 and 11 respectively. The requisite hydroxyphthalides 10 and 11 were readily prepared via lithiation of \( N,N\)-diethyl-3,5-dimethoxybenzamide or \( N,N\)-diethyl-3-methoxybenzamide with tert-butyllithium at \(-78^\circ C\) using tetrahydrofuran/tetramethylethylenediamine as solvent and quenching with DMF. Subsequent hydrolysis with aqueous hydrochloric acid affords the desired hydroxyphthalides 10 and 11.

Allylstannanes 14–16 were prepared following the method reported by Naruta et al.\(^{19}\) and allylstannane 17 was prepared following the procedure of Weigand and Bruckner.\(^{20}\) The optimum procedure for reaction of phthalide acetates 12, 13 with allyltributylstannanes 14–17 involved the use of trimethylsilyl trifluoromethanesulfonate (TM-SOTf) as the Lewis acid in dichloromethane at \(-78^\circ C\) using 2 equivalents of the stannane (Scheme 3). Alternative Lewis acids (e.g. boron trifluoride, titanium tetrachloride and tin tetrachloride) were less effective as was the use of allyltrimethylsilanes rather than the more nucleophilic allyltributylstannanes.

The presence of a substituent at C-2 on the allylstannane 15 did not affect the outcome of the allylation reaction however a lower yield was obtained when allylstannane 16 (bearing a substituent at C-3) was used (Table, Entry 4). Allylstannane 17 which contains a protected hydroxyethyl side chain at C-2 was also converted to isobenzofuranone 30 which is an important precursor to the arylspiroketal nucleus present in the papulacandins.

Having established conditions for the successful allylation of phthalide acetates 12 and 13, our next goal was to convert the allylated 1(3\(^H\))-isobenzofuranones to aryl spiroketals. Hydroboration of alkenes 18, 21, 24, 27 with borane –tetrahydrofuran cleanly afforded the primary alcohols 19, 22, 25, 28, respectively. Conversion of these primary alcohols to aryl spiroketals 20, 23, 26, 29, respectively, was then effected by oxidative cyclization using iodobenzene diacetate and iodine under photolytic
Similar oxidative cyclizations have been used by this research group as a method to prepare bis-spiroacetals. Methyl substituted arylspiroketals and were obtained as a 1:1 mixture of diastereomers. Whilst oxidative cyclization of alcohols led to formation of a spiro[1(3H)isobenzofuran, 2'-tetrahydrofuran] ring system, the homologous spiro[1(3H)isobenzofuran, 2'-tetrahydropyran] ring system that is present in the papulacandins was formed by oxidative cyclization of alcohol . Alcohol was obtained by desilylation of silyl ether which in turn was prepared via treatment of phthalide acetate with function-alized allylstannane. The exocyclic double bond present in arylspiroketal offers potential for further functionalization of the spiroketal ring system. For example the exocyclic olefin can be further transformed into a hydroxyl group via hydroboration which can then be used to introduce fatty acid side chains thus providing analogues of papulacandin D.

In conclusion, we have developed an efficient procedure for the synthesis of arylspiroacetals similar to those present in the potent antifungal agents, the papulacandins. The methodology combines the use of a novel allylation of an oxycarbenium ion derived from phthalide-acetates and a Barton-type oxidative cyclization.

Melting points were determined using a Riechert Kofler block and are uncorrected. IR spectra were recorded with a Perkin Elmer 1600 series Fourier-transform IR spectrometer as thin films between NaCl plates. H and C NMR spectra were obtained using a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. All chemical shifts are given in parts per million (ppm) downfield from TMS as internal standard and J values are given in Hz. Both H and C NMR spectra were interpreted with the aid of COSY, HETCOR and DEPT 135 experiments. HRMS were recorded using a VG7070 spectrometer operating at a nominal accelerat-

### Table: Products of Allylation of Phthalide Acetates 12,13 and their Conversion to Arylspiroacetals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Materials</th>
<th>Allylated Product (%)</th>
<th>Alcohol (%)</th>
<th>Arylspiroacetal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12,14</td>
<td>18 (71)</td>
<td>19 (67)</td>
<td>20 (78)</td>
</tr>
<tr>
<td>2</td>
<td>13,14</td>
<td>21 (98)</td>
<td>22 (50)</td>
<td>23 (83)</td>
</tr>
<tr>
<td>3</td>
<td>13,15</td>
<td>24 (72)</td>
<td>25 (58)</td>
<td>26 (83)</td>
</tr>
<tr>
<td>4</td>
<td>13,16</td>
<td>27 (43)</td>
<td>28 (51)</td>
<td>29 (72)</td>
</tr>
<tr>
<td>5</td>
<td>13,17</td>
<td>30 (4); R=SiPh₂Bu-₁</td>
<td>31 (80)</td>
<td>32 (4)</td>
</tr>
</tbody>
</table>
ing voltage of 70eV. THF was dried using Na/benzophenone and distilled prior to use. Cyclohexane, CH₂Cl₂, DMF and Et₂N were distilled from CaH₂ and used immediately. Flash chromatography was performed by using Merck Kieselgel 60 or Riedel de Haen Kieselgel Si gelica gel (both 230-400 mesh) with the indicated solvents. TLC was carried out on precoated silica gel plates (Merck Kieselgel 60F₂₅₄u) and compounds were visualized by UV fluorescence or vanillin in methanolic H₂SO₄. 3-Methoxybenzoic acid, 3,5-dimethoxybenzoic acid and allyltributylstannane (14) were purchased from Aldrich Chemical Co. Allylstannanes 15 and 16 were prepared according to the method of Naruta et al.²⁹ and their ⁱH NMR spectra were in agreement with the literature.²⁹ Allyltributylstannane 17 was prepared according to the method of Weigand and Brückner.²⁹

N,N-Diethyl-3-methoxybenzamide; Typical Procedure

3-Methoxybenzoic acid (30 g, 197.6 mmol) was heated at reflux under N₂ for 1.5 h with SOCl₂ (51.7 g, 434 mmol). Benzene (100 mL) was added and the excess SOCl₂ removed under reduced pressure. This procedure was repeated with additional benzene (2 × 100 mL). The residue was dissolved in CH₂Cl₂ (100 mL), cooled to 0 °C, and a solution of diethylamine (28.8 g, 394 mmol) in CH₂Cl₂ (150 mL) was slowly added. The reaction mixture was stirred for 12 h under N₂, then poured into CH₂Cl₂ (500 mL), washed with 10% aq NaHCO₃ solution (3 × 100 mL) and brine (3 × 50 mL). The organic extract was dried (MgSO₄) and concentrated under reduced pressure to afford a pale yellow oil that was further purified by distillation under reduced pressure to give N,N-diethyl-3-methoxybenzamide (40.1 g, 98%) as a pale yellow oil; bp 176 °C/760 Torr (Lit.²³ bp 177 °C/760 Torr).

N,N-Diethyl-3,5-dimethoxybenzamide

Using the procedure described above for the preparation of N,N-diethyl-3-methoxybenzamide, 3,5-dimethoxybenzoic acid (36 g, 197.6 mmol) was treated with SOCl₂ (51.7 g, 434 mmol) and diethylamine (28.8 g, 394 mmol) to afford N,N-diethyl-3,5-dimethoxybenzamide (41 g, 87%) as a pale yellow oil; bp 163 °C (9.9 g, 67%) as a colorless solid; mp 154–156 °C. This procedure was repeated with additional benzene (2 × 100 mL) and the resultant residue was dissolved in EtOAc (1:1) as eluent to afford 18a (11.1 g, 90%) as a colorless solid; mp 158–159°C.

IR (nujol); v=1785 (s), 1743 (s) cm⁻¹.
³¹H NMR (200 MHz CDCl₃); δ=2.18 (3 H, s, CH₂CO), 3.87 (3 H, s, OCH₃), 4.30 (2 H, d, J=8.0 Hz, 6-H), 6.70 (1 H, d, J=8.0 Hz, 5-H), 7.40 (1 H, s, 3-H).

HRMS (EI): m/z calcd for C₁₁H₁₀O₅ [M⁺]: 222.0528. Found: 222.0528. ¹³C NMR (100 MHz CDCl₃): δ=121.6 (quat, C=O), 129.5 (quat, C-7a), 155.8 (quat, C-4), 69.5, 66.1, 55.8, (OCH₃), 56.0

3-Hydroxy-4-methoxy-1(3H)-isobenzofuranone (11); Typical Procedure

To a vigorously stirred solution of N,N-diethyl-3-methoxybenzamide (17 g, 82.0 mmol) and tetramethylethylenediamine (10.8 g, 92.7 mmol), t-BuLi (59.4 mL of a 1.6 mol/L solution in hexanes, 101.1 mmol) was slowly added. The reaction mixture was heated at reflux for 0.5 h, then warmed to r.t. and stirred for 15 h. The mixture was extracted with Et₂O (100 mL) and the excess SOCl₂ removed under reduced pressure. The resultant residue was dissolved in CH₂Cl₂ (2 × 30 mL) and dried (MgSO₄). Removal of solvent under reduced pressure gave a pale pink solid that was purified by flash chromatography using hexane–EtOAc (1:1) as eluent to afford 11 (11.1 g, 63%) as a colorless solid; mp 163–164°C (Lit.¹⁸ mp 165 °C).

3-Acetoxy-4-methoxy-1(3H)-isobenzofuranone (12); Typical Procedure

To a solution of 10 (1.0 g, 5.55 mmol) in CH₂Cl₂ (30 mL) was added Et₃N (1.7 g, 16.6 mmol), Ac₂O (1.13 g, 11.1 mmol) and 4-dimethylaminopyridine (10 mg). The reaction mixture was allowed to stand at r.t. for 2 h, then quenched with H₂O (2.0 mL), extracted with CH₂Cl₂ (2 × 30 mL) and dried (MgSO₄). Removal of solvent under reduced pressure gave a pale pink solid that was purified by flash chromatography using hexane–EtOAc (1:1) as eluent to afford 12 (11.1 g, 90%) as a colorless solid; mp 158–159°C.

IR (nujol); v=1785 (s), 1743 (s) cm⁻¹.
³¹H NMR (200 MHz CDCl₃); δ=2.18 (3 H, s, CH₂CO), 3.87 (3 H, s, OCH₃), 4.30 (2 H, d, J=8.0 Hz, 6-H), 6.70 (1 H, d, J=8.0 Hz, 5-H), 7.40 (1 H, s, 3-H).

HRMS (EI): m/z calcd for C₁₁H₁₀O₅ [M⁺]: 222.0528. Found: 222.0528. ¹³C NMR (100 MHz CDCl₃): δ=121.6 (quat, C=O), 129.5 (quat, C-7a), 155.8 (quat, C-4), 69.5, 66.1, 55.8, (OCH₃), 56.0

3-Acetoxy-4,6-dimethoxy-1(3H)-isobenzofuranone (13)

Using the procedure described above for the preparation of 12, 3-acetoxy-4,6-dimethoxy-1(3H)-isobenzofuranone (13) was prepared from 11 (1.5 g, 7.14 mmol) using Et₃N (2.17 g, 21.4 mmol) and Ac₂O (1.46 g, 14.3 mmol). Purification by flash chromatography using hexane–EtOAc (1:1) as eluent afforded 13 (1.76 g, 98%) as a colorless solid; mp 154–155°C.

IR (nujol); v=1785 (s), 1744 (s) cm⁻¹.
³¹H NMR (200 MHz CDCl₃); δ=2.17 (3 H, s, COCH₃), 3.87 (3 H, s, OCH₃), 3.88 (3 H, s, OCH₃), 4.30 (2 H, d, J=8.0 Hz, 6-H), 6.70 (1 H, d, J=1.8 Hz, 5-H), 6.92 (1 H, d, J=1.8 Hz, 7-H), 7.40 (1 H, s, 3-H).

¹³C NMR (100 MHz CDCl₃); δ=20.7 (CH₃CO), 55.9, (OCH₃), 56.0 (CH₂), 91.2 (CH, C-3), 99.1 (CH, C-5 or C-7), 105.2 (CH, C-7 or C-5), 124.2 (quat, C-3a), 129.8 (quat, C-7a), 155.8 (quat, C-4), 164.2 (quat, C-6), 168.0 (quat, C=O), 169.3 (C=O).

LRMS (EI): m/z (%)=252 [M⁺] (1%), 209 (18), 193 (100), 164 (43), 43 (27), 28 (100).


3-Acetoxy-4,6-dimethoxy-1(3H)-isobenzofuranone (18); Typical Procedure

To a solution of 12 (500 mg, 2.25 mmol) in anhyd CH₂Cl₂ (10 mL) at ~78°C under N₂, was added allyltributylstannane (14) (1.1 g, 3.35 mmol) followed by trimethylsilyl trifluoromethanesulphonate (0.2 mL) and the reaction mixture warmed to r.t. over 16 h. The mixture was quenched with aq sat. NH₄Cl solution (1.0 mL), extracted with CH₂Cl₂ (3 × 30 mL) and the combined organic extracts were dried (MgSO₄). Removal of the solvent at reduced pressure afforded a yellow solid that was purified by flash chromatography using hexane–EtOAc (1:1) as eluent to afford 18 (326 mg, 71%) as a colorless solid; mp 78–80°C.
IR (nujol): ν=1761 (s), 1051 (s), 976 (s) cm⁻¹.

1H NMR (200 MHz CDCl₃): δ=2.55 (1 H, ddd, J=9.9, 6.3, 1.9 Hz), 3.00 (1 H, ddd, J=14.5, 6.9, 1.9 Hz), 5.02 (1 H, ddd, J=9.9, 6.3, 1.9 Hz). Purification by flash chromatography using hexane–EtOAc (1:1) as eluent afforded compound 24 (1.4 g, 72%) as a colorless solid; mp 121–123.5°C.

IR (nujol): ν=1765(s), 1049(s), 982(s) cm⁻¹.

1H NMR (200 MHz CDCl₃): δ=1.72 (3 H, s, CH₃), 2.29 (1 H, ddd, J=9.9, 6.3, 1.9 Hz), 2.95 (1 H, ddd, J=14.5, 6.3, 1.9 Hz). Purification by flash chromatography using hexane–EtOAc (1:1) as eluent afforded compound 24 (1.4 g, 72%) as a colorless solid; mp 121–123.5°C.

IR (nujol): ν=1766(s), 1031(s) cm⁻¹.

1H NMR (200 MHz CDCl₃): δ=7.09 (1 H, d, J=1.9 Hz, 5-H), 6.87 (1 H, d, J=1.9 Hz, 7-H).

13C NMR (100 MHz CDCl₃): δ=170.5 (quat, C=O), 128.3 (quat, C-3a), 130.9 (quat, C-7a), 131.7 (quat, C-3'), 154.3 (quat, C-4 or C-6), 162.4 (quat, C-6 or C-4), 171.1 (quat, C=O).

HRMS (ESI): m/z (%)=249 [M + 1]+ (40%), 198 (100), 195 (17), 193 (45), 118 (2), 83 (8).


Anal. Caled for C₁₂H₁₂O₃: C, 70.29; H, 5.90. Found: C, 70.76; H, 5.92.

4,6-Dimethoxy-3-(2-methylprop-2-enyl)-1(3H)-isobenzofuranone (27)

Using the procedure described above for the preparation of 18, 4,6-dimethoxy-3-(1-methyl-2-propenyl)-1(3H)-isobenzofuranone (27) was prepared from 13 (2.0 g, 7.8 mmol) using allyltrimethylstannane 16 (5.38 g, 15.6 mmol) and trimethylsilyl trifluoromethanesulfonate (0.2 mL). Purification by flash chromatography using hexane–EtOAc (1:1) as eluent afforded 27 (834 mg, 43%) as a colorless oil; mp 69–70°C.

IR (nujol): ν=1758(s), 1038(s), 977(s) cm⁻¹.

1H NMR (200 MHz CDCl₃): δ=5.99 (3 H, d, J=7.0 Hz, CH₃), 1.01 (3 H, d, J=6.8 Hz, CH₃). Purification by flash chromatography using hexane–EtOAc (1:1) as eluent afforded 27 (834 mg, 43%) as a colorless oil; mp 69–70°C.

HRMS (ESI): m/z (%)=249 [M + 1]+ (40%), 198 (100), 195 (17), 193 (45), 118 (2), 83 (8).


Anal. Caled for C₁₂H₁₂O₃: C, 70.29; H, 5.90. Found: C, 70.76; H, 5.92.

3-[2-(2-tert-Butydiphenylsilyloxy)ethyl]-4,6-dimethoxyprop-2-en-1(3H)-isobenzofuranone (30)

Using the procedure described above for the preparation of 18, compound 30 was prepared from 13 (100 mg, 0.4 mmol) using allyltrimethoxysilane 17 (709 mg, 3.1 mmol) and trimethylsilyl trifluoromethanesulfonate (0.2 mL). Purification by flash chromatography using hexane–EtOAc (1:1) as eluent afforded 30 (206 mg, 94%) as a colorless oil.

IR (film): ν=2966(s), 1628(s), 1510(s), 1462(s), 1427(s), 1381(s), 1255(s), 1192(s).
3-(3-Hydroxypropyl)-4-methoxy-1(3H)-isobenzofuranone (19); Typical Procedure

To a solution of 18 (200 mg, 1.0 mmol) in anhyd THF (20 mL) under N₂ at 0 °C was added a solution of BH₃·THF (10 mL of a 1.0 M solution in THF, 10 mmol). The resultant solution was allowed to stir at 0 °C for 5 h, then NaOH (5 mL of a 3 M solution) was added followed by H₂O₂ (10 mL of a 35% w/w solution in H₂O) and the resultant suspension stirred at 0 °C for a further 0.5 h. K₂CO₃ (200 mg) was added and the mixture extracted with EtOAc (3 × 50 mL). The combined extracts were washed with H₂O (10 mL) and dried (MgSO₄). Removal of the solvent at reduced pressure afforded a colourless oil that was purified by flash chromatography using hexane-EtOAc (1:1) as eluent to afford 19 (140 mg, 67%) as a colourless oil.

IR (film): ν = 3438–3105 (S), 1731 (s) cm⁻¹.

¹H NMR (200 MHz CDCl₃): δ = 1.51–1.75 (2 H, m, 2'-H), 2.92–2.51 (2 H, m, 1'-H), 3.65–3.69 (2 H, m, 3'-H), 3.84 (3 H, s, OCH₃), 5.47 (1 H, dd, J₃,₁ = 4.3, J₁,₁ = 4.2 Hz, 3-H), 6.65 (1 H, d, J = 7.9 Hz, 5'-H), 6.88 (1 H, d, J = 7.9 Hz, 7-H), 7.45 (1 H, t, J = 7.9 Hz, 6-H).

¹C NMR (100 MHz CDCl₃): δ = 28.0 (CH₂, C-2'), 29.4 (CH₂, C-1'), 55.9 (OCH₃), 62.5 (CH₂, C-3'), 90.4 (CH, C-3), 98.5 (CH, C-5), 104.4 (CH, C-7), 114.9 (quat, C-3a), 117.0 (quat, C-6), 130.8 (quat, C-7a), 161.8 (quat, C-4), 170.6 (quat, C=O).

LRMS (EI): m/z (%) = 222 [M⁺] (40%), 198 (100), 195 (17), 193 (45), 118 (2), 83 (8).

HRMS (LSIMS): m/z calcd for C₁₃H₁₆O₃ [M⁺]: 222.0892. Found: 222.0899.

Anal. Calcd for C₁₃H₁₆O₃: C, 64.85; H, 6.35. Found: C, 64.66; H, 6.10.

4,6-Dimethoxy-3-(3-hydroxypropyl)-1(3H)-isobenzofuranone (28)

Using the procedure described above for the preparation of 19, 4,6-dimethoxy-3-(1-methyl-3-hydroxypropyl)-1(3H)-isobenzofuranone (28) was prepared from 27 (500 mg, 2 mmol) and BH₃·SMEO₂ (4.0 mL of a 2.0 M solution in THF, 8 mmol). Purification by flash chromatography using hexane–EtOAc (1:1) as eluent afforded 28 (276 mg, 51%) as a colorless oil.

IR (film): ν = 3600–3200 (S), 1751 (s) cm⁻¹.

¹H NMR (200 MHz CDCl₃): δ = 6.04–6.48 (3 H, d, J₁ = 4.6 Hz, CH₃), 1.12–1.98 (3 H, m, 1'H–2'), 1.51–2.85 (2 H, m, 1'H–2'), 3.70–3.92 (2 H, m, 2-H, 3'-H), 3.85 (3 H, s, OCH₃), 3.86 (3 H, s, OCH₃), 5.47 (1 H, dd, J₁ = 4.1 Hz, 1-H), 6.66 (1 H, d, J = 1.9 Hz, 5'-H), 6.90 (1 H, d, J = 1.9 Hz, 7'-H).

¹C NMR (100 MHz CDCl₃): δ = 28.1 (CH₂, C-2'), 29.5 (CH₃, C-1'), 55.7 (OCH₃), 55.9 (OCH₃), 62.4 (CH₂, C-3'), 80.4 (CH, C-3), 98.5 (CH, C-5), 104.9 (CH, C-7), 128.7 (quat, C-3a), 131.0 (quat, C-7a), 155.0 (quat, C-4), 162.2 (quat, C-6), 168.3 (quat, C=O).

LRMS (EI): m/z (%) = 252 [M⁺] (20%), 206 (13), 193 (M⁻–CH₂CO₂H, 100), 165 (21), 28 (100), 18 (22).


4,6-Dimethoxy-3-(3-hydroxy-2-methylpropyl)-1(3H)-isobenzofuranone (25)

Using the procedure described above for the preparation of 19, 4,6-dimethoxy-3-(2-methyl-3-hydroxypropyl)-1(3H)-isobenzofuranone (25) was prepared from 24 (750 mg, 3.0 mmol) and BH₃·SMEO₂ (6.0 mL of a 2.0 M solution in THF, 12 mmol). Purification by flash chromatography using hexane–EtOAc (1:1) as eluent afforded 25 (460 mg, 58%) as a colorless solid; mp 110–112 °C.

IR (nujol): ν = 3600–3200 (s), 1752 (s) cm⁻¹.

¹H NMR (200 MHz CDCl₃): δ = 0.98 (3 H, d, J₃a,₂ = 6.8 Hz, CH₃), 1.07 (3 H, d, J₃b,₂ = 6.8 Hz, CH₃), 1.52–2.21 (4 H, m, 1'-CH-2'-H and 2'-H*), 3.50 (2 H, d, J₁,₁ = 6.7 Hz, 3'-CH₃), 3.52 (2 H, d, J₁,₁ = 6.7 Hz, 3'-CH₃), 3.79 (3 H, s, OCH₃), 3.85 (3 H, s, OCH₃), 5.52 (1 H, t, J₁,₁ = 4.6 Hz, 3'-H), 6.67 (1 H, d, J = 1.9 Hz, 5'-H), 6.90 (1 H, d, J = 1.9 Hz, 7'-H).

¹C NMR (100 MHz CDCl₃): δ = 17.0 (CH₃), 18.2 (CH₂*), 33.5 (CH, C-2'), 33.8 (CH, C-2*), 37.7 (CH₃, C-1'), 56.4 (OCH₂), 56.8 (OCH₂), 68.2 (CH₂, C-3'), 79.6 (CH, C-3), 80.1 (CH, C-3*), 99.2 (CH, C-5), 105.6 (CH, C-7), 128.9 (quat, C-3a), 132.2 (quat, C-7a), 155.5 (quat, C-4), 163.1 (quat, C-6), 171.3 (quat, C=O).

LRMS (CI, NH₃): m/z (%) = 267 [M + 1]⁺ (70%), 251 (55), 235 (30), 219 (15), 193 (30), 179 (100), 153 (20), 135 (35), 120 (50), 108 (29).


Anal. Calcd for C₁₄H₁₈O₅: C, 63.15; H, 6.35. Found: C, 63.01; H, 6.11.

3-(2-Hydroxyethyl)-4,6-dimethoxy-2-ethyl-1(3H)-isobenzofuranone (31)

To a solution of 30 (56 mg, 0.11 mmol) in anhyd THF (5 mL) at -0 °C was added a solution of Bu₄NF (1 mL of a 1.0M solution in THF). The resultant mixture was stirred at 0 °C for 2 h then the mixture was extracted with EtOAc (3 × 50 mL). The combined extract was washed with H₂O (10 mL) and dried (MgSO₄). Removal of solvent at reduced pressure afforded an oil that was purified by flash chromatography using hexane–EtOAc (1:1) as eluent to afford 31 (276 mg, 51%) as a colorless solid (24 mg, 80%); mp 76–77 °C.
SPIRO[2-tetrahydrofuran, 7-methoxy-1(3'H)-isobenzofuran]-3-one (20); Typical Procedure
A solution of 19 (71 mg, 0.34 mmol), I₂ (171 mg, 0.67 mmol), and iodobenzene diacetate (644 mg, 2.0 mmol) was purged with Ar and irradiated with a 500 W tungsten filament lamp. After 6 h, during which time the temperature was maintained at 23 °C using a waterbath, the solution was diluted with Et₂O (25 mL) and washed with 10% aq Na₂S₂O₃ solution (5.0 mL), H₂O (5.0 mL), brine (3.0 mL) and dried (MgSO₄). The solvent was removed under reduced pressure and the resultant oil was purified by flash chromatography using hexane–EtOAc (4:1) as eluent to afford 20 (58 mg, 78%) as a colorless oil.

IR (film): ν = 1763 (s) cm⁻¹.

1H NMR (200 MHz CDCl₃): δ = 2.06–2.20 (8 H, 3'-H and 4'-H), 3.93 (3 H, s, OCH₃), 4.16–4.43 (2 H, m, 5'-H), 6.38 (1 H, d, J = 7.9 Hz, 6'-H), 6.80 (1 H, d, J = 7.9 Hz, 4'-H), 7.48 (1 H, t, J = 7.9 Hz, 5-H).

13C NMR (100 MHz CDCl₃): δ = 26.4 (CH₂, C-2'), 34.6 (CH₂, C-3'), 55.9 (OCH₃), 70.5 (CH, C-5'), 98.6 (CH, C-6), 105.1 (CH, C-5), 113.7 (CH, C-4), 116.9 (quat, C-1'), 132.3 (quat, C-7a), 154.8 (quat, C-5a), 163.7 (quat, C-7), 168.1 (quat, C=O).

LRMS (EI); m/z (%) = 220 [M + 1]+ (10%), 219 (94), 206 (68), 113 (47), 91 (100). Found: 219.0736.

HRMS (EI); m/z calcd for C₁₂H₁₀O₄ [M]+: 220.0736. Found: 220.0740.


SPIRO[2-tetrahydrofuran, 5,7-dimethoxy-1(3'H)-isobenzofuran]-3-one (23)
Using the procedure described above for the preparation of 20, spiro[2-tetrahydrofuran, 5,7-dimethoxy-1(3'H)-isobenzofuran]-3-one (23) was prepared from 22 (250 mg, 1.0 mmol) using I₂ (507 mg, 2.0 mmol) and iodobenzene diacetate (644 mg, 2.0 mmol). Purification by flash chromatography using hexane–EtOAc (4:1) as eluent afforded 23 (207 mg, 83%) as a colorless solid; mp 119–120 °C.

IR (nujol): ν = 1739 (s) cm⁻¹.

1H NMR (200 MHz CDCl₃): δ = 2.10–2.27 (4 H, 3'-H and 4'-H), 3.83 (3 H, s, OCH₃), 3.85 (3 H, s, OCH₃), 4.12–4.33 (2 H, m, 5'-H), 6.65 (1 H, d, J = 1.9 Hz, 6'-H), 6.80 (1 H, d, J = 1.9 Hz, 4'-H).

13C NMR (100 MHz CDCl₃): δ = 24.6 (CH₂, C-2'), 34.7 (CH₂, C-3'), 55.9 (OCH₃), 70.4 (CH, C-5'), 98.4 (CH, C-6), 104.9 (CH, C-4), 114.2 (quat, C-1'), 125.7 (quat, C-7a), 130.9 (quat, C-3a), 155.3 (quat, C-7), 163.6 (quat, C-5), 167.9 (quat, C=O).

LRMS (EI); m/z (%) = 250 [M⁺] (51%), 206 (46), 164 (100), 106 (31), 28 (100).

HRMS (EI); m/z calcd for C₁₅H₁₄O₅ [M⁺]: 250.0841. Found: 250.0843.


SPIRO[5,7-dimethoxy-1(3'H)-isobenzofuran, 4-methyl-2-tetrahydrofuran]-3-one (26)
Using the procedure described above for the preparation of 20, spiro[5,7-dimethoxy-1(3'H)-isobenzofuran, 4-methyl-2-tetrahydrofuran]-3-one (26) was prepared from 25 (250 mg, 1.0 mmol) using I₂ (507 mg, 2.0 mmol) and iodobenzene diacetate (644 mg, 2.0 mmol). Purification by flash chromatography using hexane–EtOAc (4:1) as eluent afforded 26 (219 mg, 83%) as a colorless solid; mp 119–120 °C.

IR (nujol): ν = 1763 (s) cm⁻¹.

1H NMR (200 MHz CDCl₃): δ = 3.83 (3 H, s, OCH₃), 3.85 (3 H, s, OCH₃), 4.12 (1 H, d, J = 17.0 Hz, 6'-H), 4.47 (1 H, s, 1'H a), 5.49 (1 H, s, 1'H b), 6.70 (1 H, d, J = 2.4 Hz, 6-H), 7.18 (1 H, d, J = 2.4 Hz, 4-H).

13C NMR (100 MHz CDCl₃): δ = 55.7 (OCH₃), 55.9 (OCH₃), 70.4 (CH₂, C-5'), 98.4 (CH, C-6), 104.9 (CH, C-4), 114.2 (quat, C-1'), 125.7 (quat, C-7a), 130.9 (quat, C-3a), 155.3 (quat, C-7), 163.6 (quat, C-5), 167.9 (quat, C=O).

LRMS (EI); m/z (%) = 277 [M + 1]+ (3%), 265 (10), 91 (100).

HRMS (CI, NH₃); m/z calcd for C₁₅H₁₄O₅ [M + 1]+: 277.0176. Found: 277.0176.
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References and Notes


(22) For a review on the synthesis of bis-spiroacetals see: Brimble, M. A.; Fares, F. A. Tetrahedron 1999, 55, 7661.
