Efficient Synthesis of Dihydrofurans with Sulfide Groups by Ceric(IV) Ammonium Nitrate-Mediated Oxidative Cycloaddition of 1,3-Dicarbonyl Compounds to Vinyl Sulfides. Application to the Synthesis of Benzo[b]naphtho[2,3-d]furan-6,11-dione and First Total Synthesis of Millettocalyxins C and Pongamol Methyl Ether

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Abstract: Ceric(IV) ammonium nitrate-mediated oxidative cycloaddition of 1,3-dicarbonyls to vinyl sulfides afforded substituted dihydrofurans with sulfide groups in moderate yields. This new synthetic method has been applied to the synthesis of benzo[b]naphtho[2,3-d]furan-6,11-dione and furanoflavone natural products such as millettocalyxins C and pongol methyl ether.

Key words: furans, natural products, cycloadditions, oxidations, millettocalyxins C, pongol methyl ether

Oxidative cycloaddition reactions mediated by metal salts (MnIII, CeIV, CoII, and VV) have received considerable attention in organic synthesis for the construction of carbon–carbon bonds. Among these, manganese(III) acetate and ceric(IV) ammonium nitrate (CAN) have been used most efficiently. CAN-mediated oxidative cycloaddition of 1,3-dicarbonyl compounds to alkenes, vinyl acetates, enol silyl ethers, and enol ethers has been studied extensively. We have reported on the CAN-mediated oxidative cycloaddition of 1,3-dicarbonyl compounds with conjugated compounds. While continuing our work based on the CAN-mediated oxidative cycloaddition, we have expanded this work to the synthesis of dihydrofurans with sulfide groups. In order to examine the breadth and generality of the reactions described in our preliminary results, we have reviewed additional reactions of a number of 1,3-dicarbonyl compounds and vinyl sulfides. Here, we report the efficient synthesis of a variety of substituted dihydrofurans and its application to the biologically interesting benzo[b]naphtho[2,3-d]furan-6,11-dione and furanoflavone natural products such as millettocalyxins C and pongol methyl ether.

The 1,3-dicarbonyl compounds used in this study included the commercially available cyclohexane-1,3-diones 1–4, ethyl acetooacetate (5), 2,4-pentanedione (6), 4-hydroxy-4H-coumarins 7–9, 3-hydroxy-1H-phenalen-1-one (10), and 2-hydroxy-1,4-naphthoquinone (11) (Figure 1). The vinyl sulfides 12–15 used to react with the dicarbonyl compounds were readily prepared with a known procedure (Figure 2).

Reaction of 1,3-dicarbonyl compound 1 with vinyl sulfide 13 was first examined utilizing the two oxidizing agents Mn(OAc)₃·2H₂O and Ce(NH₄)₂(NO₃)₆. Both manganese(III) acetate dihydrate (80 °C, 7 h) in HOAc and ceric(IV) ammonium nitrate (0 °C, 6 h) in acetonitrile provided the dihydrofuran 18 in 65 and 79% yields, respectively (Table 1). However, we found that ceric(IV) ammonium nitrate was a much superior reagent for this cycloaddition than manganese(III) acetate dihydrate, with the advantage of more mild reaction conditions and a higher yield. The formation of 18 was confirmed by the

Figure 1

Figure 2
In order to synthesize biologically interesting dihydrofurocoumarin derivatives, reaction of 4-hydroxycoumarins 7–9 with vinyl sulfides was next examined. Treatment of 7 with vinyl sulfide 12 in the presence of 2.2 equivalents of CAN(IV) in THF gave dihydrofurocoumarins 29 (42%), without any formation of possible regioisomers (entry 1, Table 3). Compound 29 has been clearly shown to be angular by spectral analysis and by comparison with reported data in the literature.10,11 With other vinyl sulfides 13 and 15, the expected dihydrofurocoumarins 30–32 were also obtained in 40–72% yields, respectively (entries 2–4). Similarly, reaction of 7 and 9 with acrylic vinyl sulfide 16 afforded cycloaducts 33 and 34 in 46% and 60% yields, respectively (entries 5, 6). The results are summarized in Table 3. These reactions provide a rapid route to the preparation of dihydrofurocoumarin derivatives which are known to have a number of biological activities such as anticoagulant, insecticidal, antihermophilic, hypnotic, and antifungal.12

Next, reaction of 3-hydroxy-1H-phenalen-1-one (10) with vinyl sulfides was investigated. Treatment of 10 with vinyl sulfide 12 gave dihydrofuraphenalenone 35 with a yield of 87% (entry 1, Table 4). Similarly, reaction with sulfides 13 and 15 afforded dihydrofuraphenalenone derivatives 36 and 37 in 77 and 74% yields, respectively (entries 2, 3). Reaction with vinyl sulfide 17 afforded cycloaduct 39 (92%) with a 34:66 mixture of cis- and trans-isomers (entry 5). This reaction also affords the trans-compound as the major product, despite the fact that the cis-vinyl sulfide was the major reagent. The results are summarized in Table 4. Importantly, these reactions provide a rapid route for the synthesis of biologically interesting dihydrofuraphenalenone derivatives which are reported to have various biological activities such as antibacterial, antimicrobial, antifungal, and phytoalexin.13

Finally, the reaction of 2-hydroxy-1,4-naphtoquinone (11) with vinyl sulfides was investigated. Treatment of 11 with vinyl sulfide 12 resulted in dihydrofuraphnaphthoquinone 40 (30%) and 41 (19%) as a mixture of linear and angular regioisomers (entry 1, Table 5). The products were easily purified by column chromatography and the structures of the two isomers were determined by their spectroscopic data, and by comparison with data that had been reported in the literature.14 The clear assignments came from the IR carbonyl absorptions at 1690 and 1647 cm⁻¹ for the two carboxyls in 40 and at 1701 and 1653 cm⁻¹ in 41. Similarly, with other sulfides 13–16, cycloaducts 42–47 were obtained as a mixture of regioisomers (entries 2–4). However, reaction with vinyl sulfide 16 at room temperature in THF afforded solely dihydrofuraphnaphthoquinone 48 in 53% yield, without formation of the other possible regioisomer (entry 5). The results are summarized in Table 5. These reactions also provided a rapid entry to the synthesis of biologically active dihydrofuraphnaphthoquinone derivatives.15

As an application of this methodology, the synthesized adducts can be elaborated toward other biologically and
Table 2  Reaction of Cyclic and Acyclic 1,3-Dicarbonyl Compounds 1–6 with Vinyl Sulfides

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,3-Dicarbonyl compound</th>
<th>Vinyl sulfide</th>
<th>Solvent</th>
<th>Product</th>
<th>Yield (%)</th>
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<tr>
<td>10</td>
<td></td>
<td>17 (cis–trans, 60:40)</td>
<td>MeCN</td>
<td>28 (cis:trans = 32:68)</td>
<td>64</td>
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<tr>
<td>11</td>
<td></td>
<td>17 (cis–trans, 60:40)</td>
<td>THF</td>
<td>28 (cis:trans = 46:54)</td>
<td>71</td>
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</table>
pharmacologically interesting compounds. For example, dihydrofuran 42 can be readily converted to benzofuranonaphthoquinone derivative 50 which has been reported to have significant biological activities such as antipruritic, antitumor, topo II-mediate DNA cleavage.16 Although several synthetic methods for the preparation of benzofuranonaphthoquinone derivatives have been reported, their synthetic exploitation has been limited due to many reaction steps, low yield, and the difficulty in availability of the required starting materials.17 Reaction of 42 with MCPBA in CH₂Cl₂ at room temperature for 24 hours afforded the corresponding sulfoxide, which upon refluxing for 5 hours in xylene gave furan 49 in 70% yield (Scheme 1). When 49 was treated with Pd/C at reflux for 5 hours in phenyl ether, benzofuronaphthofurandione 50 was produced in 42% yield. The structural assignment of 50 was easily made with the new aromatic peaks in the ¹H NMR spectrum.

As another application, a synthetic route to furanoflavone natural products starting from the obtained dihydrofuran was next investigated (Scheme 2). Furanoflavones are an abundant subclass of the flavonoid and are widely distributed in nature.18 Members of the furanoflavones have been associated with a wide variety of biological activities such as insecticide, pesticidal, anticancer and antiulcer,19 and are used in traditional medicines for the treatment of

### Table 3 Reaction of 4-Hydroxycoumarins 7–9 with Vinyl Sulfides

<table>
<thead>
<tr>
<th>Entry</th>
<th>4-Hydroxycoumarin</th>
<th>Vinyl sulfide</th>
<th>solvent</th>
<th>Product</th>
<th>Yield (%)</th>
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Scheme 1
Dihydrofurans by Oxidative Cycloaddition of 1,3-Dicarbonyl Compounds to Vinyl Sulfides

1981

PAPER


Table 4 Reaction of 3-Hydroxy-1H-phenalen-1-one (10) with Vinyl Sulfides

<table>
<thead>
<tr>
<th>Entry</th>
<th>3-Hydroxy-1H-phenalen-1-one</th>
<th>Vinyl sulfide</th>
<th>Solvent</th>
<th>Product</th>
<th>Yield (%)</th>
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<tr>
<td>2</td>
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<td><img src="36" alt="13" /></td>
<td>THF</td>
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<td><img src="15" alt="10" /></td>
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<td>THF</td>
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<tr>
<td>5</td>
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<td><img src="39" alt="17" /></td>
<td>THF</td>
<td><img src="92" alt="39" /></td>
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In conclusion, CAN-mediated oxidative cycloaddition of 1,3-dicarbonyls to vinyl sulfides is described. This method provides a simple and efficient synthesis of substituted dihydrofurans. As an application of this methodology, the synthesis of benzofuranaphthoquinone and the natural furanoflavones is carried out starting from obtained dihydrofurans.

All experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). Mps were determined with microcover glasses on a Fisher–Johns apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Bruker Model ARX (300 MHz) spectrometer. $^{13}$C NMR spectra were recorded on a Bruker Model ARX (75 MHz) spectrometer in CDCl$_3$ using $\delta = 77.0$ as the solvent chemical shift. IR spectra were recorded on a JASCO FTIR 5300 spectrophotometer. Mass and high resolution mass spectra were obtained with a JEOL JMS-700 spectrometer at the Korea Basic Science Institute (Daegu). Elementary analyses were performed by the Korea Basic Science Institute (Daegu).

Dihydrofurans; General Procedure

To a solution of 1,3-dicarbonyl compound (1.0 mmol) and vinyl sulfide (2.0 mmol) in MeCN (20 mL) or THF (20 mmol) was added CAN (1.206 g, 2.2 mmol) and NaHCO$_3$ (420 mg, 5.0 mmol) at 0 °C

tumours, piles, skin diseases, wounds, ulcers, etc. Very recently, new furanoflavones, millettocalyxins C 55 and pongol methyl ether 56, were isolated from the stem bark of Millettia erythrocalyx. Currently, the bark of this plant has been used by the local people in Thailand for treating stomach pain. However, the total synthesis of millettocalyxins C 55 and pongol methyl ether 56 has not been reported.

The conversion of dihydrofuran 27 to both of these natural products 55 and 56 was begun by syn-elimination with MCPBA to give compound 51 (70%). Transformation of 51 into the sodium enolate with an excess of NaH in the presence of a catalytic amount of KH was followed by treatment with dimethyl carbonate to form 52 in 90% yield. The DDQ-mediated oxidation of 52 in refluxing dioxane gives the compound 53 (85%), which was treated with the dimsyl anion in benzene to form the $\beta$-keto sulfoxide 54 (83%). The $\beta$-keto sulfoxide 54 is easily converted by treatment with 2,5-dimethoxybenzaldehyde and 3-methoxybenzaldehyde in the presence of piperidine, first at 40 °C and then at 110 °C, to the corresponding furanoflavones 55 and 56 in 78% and 88% yield, respectively. The spectroscopic properties of our synthetic materials agreed well with those reported in the literature.

All experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). Mps were determined with microcover glasses on a Fisher–Johns apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Bruker Model ARX (300 MHz) spectrometer. $^{13}$C NMR spectra were recorded on a Bruker Model ARX (75 MHz) spectrometer in CDCl$_3$ using $\delta = 77.0$ as the solvent chemical shift. IR spectra were recorded on a JASCO FTIR 5300 spectrophotometer. Mass and high resolution mass spectra were obtained with a JEOL JMS-700 spectrometer at the Korea Basic Science Institute (Daegu). Elementary analyses were performed by the Korea Basic Science Institute (Daegu).
or r.t. The reaction mixture was stirred for 6 h at 0 °C in MeCN or for 6 h at r.t. in THF. The mixture was diluted with H2O and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried (MgSO4), and evaporated under reduced pressure to give the residue. The residue was purified by flash column chromatography on silica gel to give product.

5a-Phenylsulfanyl-3,4,5a,6,7,8,9,9a-octahydro-2H-dibenzo-furan-1-one (18)
Reaction of 1,3-cyclohexanedione (11) (112 mg, 1 mmol) with vinyl sulfide 13 (381 mg, 2 mmol) in THF (20 mL) afforded 18. Yield: 258 mg (86%); solid; mp 96–97 °C.
IR (KBr): 3057, 2946, 2866, 1638, 1474, 1454, 1439, 1399, 1248, 1181, 1136, 1061, 999 cm⁻¹.

Table 5 Reaction of 2-Hydroxy-1,4-naphthoquinone (11) with Vinyl Sulfides

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Hydroxy-1,4-naphthoquinone</th>
<th>Vinyl sulfide</th>
<th>Solvent</th>
<th>Product</th>
<th>Yield (%)</th>
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<td><img src="image1" alt="image" /></td>
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<td>THF</td>
<td><img src="image15" alt="image" /></td>
<td>53</td>
</tr>
</tbody>
</table>

Scheme 2

1H NMR (300 MHz, CDCl3): \( \delta = 7.58–7.53 \) (2, H, m), 7.37–7.29 (3 H, m), 3.16 (1 H, dd, \( J = 6.7, 5.9 \) Hz), 2.41–2.37 (2 H, m), 2.27–2.18 (2 H, m), 1.98–1.89 (4 H, m), 1.60–1.41 (6 H).

HRMS: m/z calcd for \( C_{15}H_{26}O_2S \) (M+): 255.1280; found: 255.1279.

9a-Phenylsulfanyl-1,2,3,4b,5,6,7,8,9a-decahydro-10-oxabenzo[a]julolid-4-one (23)

Reaction of 1,3-cyclohexanediene (1) (112 mg, 1 mmol) with vinyl sulfide 15 (409 mg, 2 mmol) in THF (20 mL) afforded 23 (255 mg, 81%).

Solid: mp 80–81 °C.

IR (KBr): 3059, 2930, 2853, 1642, 1453, 1439, 1397, 1362, 1277, 1256, 1225, 1179, 1136, 1063, 995, 984 cm⁻¹.

1H NMR (300 MHz, CDCl3): \( \delta = 7.55–7.51 \) (2 H, m), 7.42–7.29 (3 H, m), 3.21 (1 H, d, \( J = 9.2 \) Hz), 2.43–2.38 (2 H, m), 2.32–2.16 (2 H, m), 2.04–1.89 (4 H, m), 1.76–1.35 (8 H, m).

MS (EI): m/z = 204 (M+ – PhSH) (100), 189 (30), 176 (63), 175 (46), 148 (43), 125 (20), 105 (17), 91 (20), 77 (14), 55 (18).

HRMS: m/z calcd for \( C_{13}H_{14}O_2S \) (M+ – PhSH): 204.1150; found: 204.1152.

Reaction of 4-hydroxycoumarin (7) (162 mg, 1 mmol) with vinyl sulfide 12 (353 mg, 2 mmol) in THF (20 mL) afforded 29.

Yield: 141 mg (42%); solid; mp 62–64 °C.

IR (KBr): 3057, 2932, 2855, 1707, 1645, 1607, 1570, 1499, 1440, 1439, 1404, 1327, 1275, 1235, 1196, 1165, 1094, 1028, 983, 895 cm⁻¹.

HRMS: m/z calcd for C₁₉H₁₈O₂S (M⁺ - PhSH): 336.0821; found: 336.0824.

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10a-Phenylsulfanyl-6h,7,8,9,10a-hexahydrobenzo[4,5]fluor[3,2-c]chromen-6-one (30)

Reaction of 4-hydroxycoumarin (7) (162 mg, 1 mmol) with vinyl sulfide 13 (381 mg, 2 mmol) in THF (20 mL) afforded 30.

Yield: 140 mg (40%); solid; mp 125–126 °C.

IR (KBr): 3061, 2942, 2865, 1725, 1647, 1609, 1566, 1499, 1456, 1406, 1306, 1161, 1028, 943, 883, 845 cm⁻¹.

HRMS: m/z calcd for C₁₉H₁₈O₃S (M⁺): 350.0977; found: 350.0975.

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2-Chloro-10a-phenylsulfanyl-6b,7,8,9,10a-hexahydrobenzo[4,5]fluor[3,2-c]chromen-6-one (31)

Reaction of 6-chloro-4-hydroxycoumarin (8) (197 mg, 1 mmol) with vinyl sulfide 13 (381 mg, 2 mmol) in THF (20 mL) afforded 31.

Yield: 158 mg (41%); solid; mp 126–128 °C.

IR (KBr): 3069, 2961, 2940, 2870. 1726, 1651, 1564, 1493, 1431, 1391, 1265, 1123, 1065, 1011, 966, 939, 827 cm⁻¹.

HRMS: m/z calcd for C₁₉H₁₈ClOS (M⁺): 384.0588; found: 384.0589.

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11a-Phenylsulfanyl-7,8,9,10,11a-hexahydro-6b-5,12-di-oxanaphtho[2,1-e]azulen-6-one (32)

Reaction of 4-hydroxycoumarin (7) (162 mg, 1 mmol) with vinyl sulfide 15 (409 mg, 2 mmol) in THF (20 mL) afforded 32.

Yield: 262 mg (72%); solid; mp 116–118 °C.

IR (KBr): 3057, 2932, 2855, 1707, 1645, 1607, 1570, 1499, 1474, 1439, 1404, 1327, 1275, 1235, 1196, 1165, 1094, 1028, 983, 895 cm⁻¹.

HRMS: m/z calcd for C₁₉H₁₈O₃S (M⁺ - PhSH): 254.0943; found: 254.0948.

Anal. Calcd for C₁₉H₁₈O₃S: C, 72.50; H, 5.53; S, 8.80. Found: C, 72.21; H, 5.42; S, 8.75.

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2-Phenylsulfanyl-2,3-dihydrofuro[3,2-c]chromen-4-one (33)

Reaction of 4-hydroxycoumarin (7) (162 mg, 1 mmol) with phenyl vinyl sulfide 16 (272 mg, 2 mmol) in THF (20 mL) afforded 33.

Yield: 136 mg (46%); solid; mp 125–126 °C.

IR (KBr): 3061, 2926, 2865, 1724, 1649, 1608, 1570, 1498, 1440, 1410, 1344, 1325, 1269, 1207, 1157, 1091, 1028, 941, 895, 860 cm⁻¹.

HRMS: m/z calcd for C₁₉H₁₈O₃S (M⁺): 296.0508; found: 296.0505.

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8-Methyl-2-phenylsulfanyl-2,3-dihydrofuro[3,2-c]chromen-4-one (34)

Reaction of 4-hydroxy-6-methylcoumarin (7) (176 mg, 1 mmol) with phenyl vinyl sulfide 16 (272 mg, 2 mmol) in THF (20 mL) afforded 34.

Yield: 186 mg (60%); solid; mp 109–110 °C.
HRMS: m/z calcd for C_{18}H_{14}O_{3}S (M+): 310.0661; found: 310.0661.

HRMS: m/z calcd for C_{24}H_{18}O_{2}S: 370.1027; found: 370.1027.

HRMS: m/z calcd for C_{20}H_{16}O_{2} (M+–PhSH): 288.1147; found: 288.1147.

HRMS: m/z calcd for C_{21}H_{16}O_{3}S (M+): 348.0821; found: 348.0821.

HRMS: m/z calcd for C_{21}H_{14}O_{2}S (M+): 330.0714; found: 330.0714.

HRMS: m/z calcd for C_{22}H_{16}O_{2}S (M+): 344.0870; found: 344.0870.

HRMS: m/z calcd for C_{18}H_{14}O_{3}S: 310.0663; found: 310.0663.

HRMS: m/z calcd for C_{24}H_{18}O_{2}S: 370.1023; found: 370.1023.

HRMS: m/z calcd for C_{21}H_{16}O_{3}S: 348.0817; found: 348.0817.

HRMS: m/z calcd for C_{21}H_{14}O_{2}S: 330.0713; found: 330.0713.

HRMS: m/z calcd for C_{22}H_{16}O_{2}S: 344.0871; found: 344.0871.

HRMS: m/z calcd for C_{22}H_{16}O_{3}S: 348.0819; found: 348.0819.

HRMS: m/z calcd for C_{24}H_{18}O_{2}S: 370.1025; found: 370.1025.

IR (KBr): 3063, 2946, 2864, 1628, 1589, 1508, 1468, 1433, 1418, 1383, 1318, 1292, 1225, 1194, 1150, 1101, 1020, 937, 887, 860, 839 cm⁻¹.

IR (KBr): 3057, 2928, 1714, 1649, 1610, 1577, 1494, 1439, 1394, 1271, 1203, 1095, 1035, 1006, 914, 858, 829, 798 cm⁻¹.

IR: 296 mg (77%); solid; mp 154–156 °C.

IR: 295 mg (87%); solid; mp 157–159 °C.

IR: 322 mg (87%); solid; mp 157–159 °C.

IR: 397 mg (92%).

IR: 317 mg (92%).

IR: 397 mg (92%).
IR (KBr): 3065, 2951, 1682, 1651, 1624, 1595, 1574, 1541, 1385, 1329, 1279, 1236, 1208, 1148, 990, 953, 930, 823 cm⁻¹.

Yield: 163 mg (53%); mp 151–152 °C.

HRMS: m/z calcd for C₂₂H₁₈O₃S (M⁺): 362.0979; found: 362.0979.

HRMS: m/z calcd for C₂₅H₂₀O₃S (M⁺ – PhSH): 308.0508; found: 308.0508.

Yield: 41 mg (42%); mp 247 °C.

HRMS: m/z calcd for C₂₃H₂Ο₃S (M⁺): 248.0476; found: 248.0476.

Yield: 248.0476; found: 248.0476.
6.7-Dihydro-5H-benzoefuran-4-one (51)\textsuperscript{24}

To a solution of 27 (2.10 g, 8.52 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (50 mL) was added MCPBA (1.54 g, 70%, 10.4 mmol) at 0 °C. The reaction mixture was stirred for 24 h at r.t., and then poured into sat. aq Na\textsubscript{2}CO\textsubscript{3}. The mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 50 mL), washed with brine, and dried (MgSO\textsubscript{4}). Evaporation of solvent gave an oil which was purified by chromatography (silica gel) to give the 51.

Yield: 812 mg (70%); liquid.

IR (KBr): 3500, 3071, 2950, 1677, 1617, 1441, 1433, 1276, 1208, 1164, 1122, 935, 903, 861 cm\textsuperscript{-1}.

1\textsuperscript{H} NMR (300 MHz, CDCl\textsubscript{3}): \(\delta = 7.32 (1 \text{ H, d, } J = 2.0 \text{ Hz}), 6.67 (1 \text{ H, d, } J = 2.0 \text{ Hz}), 2.89 (2 \text{ H, m}), 2.50 (2 \text{ H, m}), 2.18 (2 \text{ H, m}).\)

13\textsuperscript{C} NMR (75 MHz, CDCl\textsubscript{3}): \(\delta = 193.9, 166.7, 142.2, 120.6, 105.9, 37.2, 22.8, 22.2.\)

MS (EI): 136 (M\textsuperscript{+}), 121, 108, 94, 80, 77, 63, 55, 52.

4-Oxo-4,5,6,7-tetrahydrobenzofuran-5-carboxylic Acid Methyl Ester (52)

To a stirred suspension of Na\textsubscript{2}H\textsubscript{2}O\textsubscript{2} (1.175 g, 29.4 mmol, 60%) and KH (50 mg, 35 wt% dispersion in oil) in anhyd THF (50 mL) under N\textsubscript{2} (40 mL) were added carefully dropwise and the mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 50 mL), washed with brine, dried (MgSO\textsubscript{4}). Evaporation of solvent gave an oil which was purified by chromatography (silica gel) to give the 52.

Yield: 130 g (90%).

IR (neat): 3131, 2948, 1677, 1595, 1516, 1447, 1414, 1294, 1242, 1184, 1119, 1026 cm\textsuperscript{-1}.

1\textsuperscript{H} NMR (300 MHz, CDCl\textsubscript{3}): \(\delta = 3.76 (3 \text{ H, s}), 3.52 (1 \text{ H, t, } J = 4.8 \text{ Hz}), 3.05–2.91 \text{ (5 H, m)}, 2.79 (3 \text{ H, s}).\)

13\textsuperscript{C} NMR (75 MHz, CDCl\textsubscript{3}): \(\delta = 193.9, 166.7, 142.2, 120.6, 105.9, 37.2, 22.8, 22.2.\)

HRMS: m/z calcd for C\textsubscript{11}H\textsubscript{10}O\textsubscript{4}S\textsuperscript{+}: 238.0316. Found: 238.0316.

Millettocalixynes C (55)\textsuperscript{21}

2,5-Dimethoxybenzaldehyde (0.157 g, 0.94 mmol) in anhyd toluene (3 mL) was slowly added to a warm solution (40 °C) of 54 (0.150 g, 0.63 mmol) in anhyd toluene (20 mL) containing a catalytic amount of piperidine (4 drops) and the resulting mixture was allowed to reflux for 3 h. After distillation of the solvent, the residue was purified by flash column chromatography (silica gel; hexane-EtOAc, 6:1) to give the 55.

Yield: 0.158 g (78%); solid; mp 167–168 °C.

IR (KBr): 3021, 2998, 2938, 2836, 1628, 1589, 1574, 1505, 1466, 1410, 1362, 1263, 1238, 1184, 1146, 1074, 1053, 852, 839, 814 cm\textsuperscript{-1}.

1\textsuperscript{H} NMR (300 MHz, CDCl\textsubscript{3}): \(\delta = 8.15 (1 \text{ H, d, } J = 8.8 \text{ Hz}), 7.73 (1 \text{ H, d, } J = 2.1 \text{ Hz}), 7.54 (1 \text{ H, d, } J = 8.8 \text{ Hz}), 7.50 (1 \text{ H, d, } J = 2.9 \text{ Hz}), 7.21 (1 \text{ H, s}), 7.15 (1 \text{ H, d, } J = 2.1 \text{ Hz}), 7.02 (1 \text{ H, dd, } J = 8.8, 2.9 \text{ Hz}), 6.99 (1 \text{ H, d, } J = 8.8 \text{ Hz}), 3.90 (3 \text{ H, s}), 3.84 (3 \text{ H, s}).\)

Pongol Methyl Ether (56)\textsuperscript{12}

3-Methoxybenzaldehyde (0.129 g, 0.94 mmol) in anhyd toluene (3 mL) was slowly added to a warm solution (40 °C) of 54 (0.150 g, 0.63 mmol) in anhyd toluene (20 mL) containing a catalytic amount of piperidine (4 drops) and the resulting mixture was allowed to reflux for 3 h. After distillation of the solvent, the residue was purified by flash column chromatography (silica gel; hexane-EtOAc, 6:1) to give the 56.

Yield: 0.162 g (88%); solid; mp 156–157 °C.

IR (KBr): 3055, 2988, 2949, 2843, 1651, 1607, 1491, 1451, 1433, 1402, 1358, 1296, 1273, 1254, 1215, 1165, 1067, 1043, 1030 cm\textsuperscript{-1}.

1\textsuperscript{H} NMR (300 MHz, CDCl\textsubscript{3}): \(\delta = 8.16 (1 \text{ H, d, } J = 8.8 \text{ Hz}), 7.76 (1 \text{ H, d, } J = 2.2 \text{ Hz}), 7.57 (1 \text{ H, d, } J = 8.8 \text{ Hz}), 7.54 (1 \text{ H, d, } J = 7.8 \text{ Hz}), 7.48 (1 \text{ H, d, } J = 3.0 \text{ Hz}), 7.46 (1 \text{ H, dd, } J = 7.8, 7.8 \text{ Hz}), 7.20 (1 \text{ H, d, } J = 2.2 \text{ Hz}), 7.11 (1 \text{ H, dd, } J = 7.8, 3.0 \text{ Hz}), 6.86 (1 \text{ H, s}), 3.90 (3 \text{ H, s}).\)

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References


