Enantioselective Synthesis of the 3C-Protease Inhibitor (−)-Thysanone by a Staunton–Weinreb Annulation Strategy

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Abstract: The total synthesis of (−)-thysanone is described. The key step involves the addition of an o-toluate anion to a lactone to create the naphthopyran framework (Staunton–Weinreb annulation). This synthesis further confirms the absolute stereochemistry of the natural product to be 1R,3S.

Key words: thysanone, Staunton–Weinreb annulation, total synthesis, natural products, polycycles

Human rhinoviruses (HRVs) are a leading cause of the common cold in the Western world. At present, only symptomatic treatments are available to treat the common cold and the search for pharmaceutical agents aimed at preventing HRV infections are of major pharmaceutical interest.1,2

Thysanone (1, Figure 1) is a pyranonaphthoquinone antibacterial that was discovered by chemists at Merck upon screening the fermentation broths of the fungus Thysanophora penicilloides.3 It was subsequently shown to be the first inhibitor of HRV-3C protease to be identified by screening (IC$_{50}$ = 13 μg/mL), hence making thysanone an ideal lead compound for the rational design of small molecule HRV-3C-protease inhibitors. Due to the interesting biological activity exhibited by thysanone together with our ongoing interest in the synthesis of pyranonaphthoquinone antibiotics,4 we aimed to execute an efficient synthesis of thysanone that would be amenable to the production of analogues.5-7

Figure 1 (−)-Thysanone, shown with 1R,3S stereochemistry

Our initial thoughts were focused on construction of the central ring of thysanone using a Hauser–Kraus annulation.8,9 Unfortunately, our initial work adopting this approach showed that the 4,6-dimethoxy substitution pattern on the cyanophthalide coupling partner prevented successful annulation with a variety of electrophiles.7e Upon further examination of this reaction, it was noted that a parallel annulation reaction was published in the same paper by Hauser,8a in which the annulation of 2-(ethoxycarbonyl)benzyl phenyl sulfoxide with several Michael acceptors was reported. A notable difference is the oxygenation pattern produced in the products using this method. In contrast to the naphthalenediol products that are produced by the reaction of stabilised phthalides with electrophiles (the Hauser–Kraus annulation), the reaction of sulfoxides with a variety of Michael acceptors furnishes naphthol products that are much more amenable to facile purification (Scheme 1). Based on these observations, our revised retrosynthesis hinged on the annulation between a sulfoxide 2 or sulfone 3 with the lactone (S)-parasorbic acid (4), a natural product isolated from mountain ash berries Sorbus aucuparia L.10 (Scheme 2).

Scheme 1 Hauser–Kraus annulation and variants
With this strategy in mind, the synthesis of both the sulf-
oxide 2 and sulfone 3 were conducted as follows: diphe-
nol 5 was prepared from methyl acetoacetate by slight modi-
fication of a route described by Jouillé. Facile di-
alkylation of diphenol 5 delivered aromatic 6, which un-
derwent smooth toluate anion addition to diphenyl di-
sulfide, furnishing the sulfide 7. Monooxidation was
accomplished with sodium periodate, to deliver sulfoxide
2, and further oxidation was achieved with catalytic quan-
tities of ammonium molybdate tetrahydrate in the pres-
ence of hydrogen peroxide, affording the desired sulfone
3 (Scheme 3).

With both sulfoxide 2 and sulfone 3 annulation partners in
hand, attention turned to the synthesis of (S)-parasorbic
acid (4) (Scheme 4). By modification of a literature syn-
thesis by Brown, commercially available (S)-pent-4-en-
2-ol was treated with acryloyl chloride to deliver the vol-
itile diene 8. Smooth ring-closing metathesis was
achieved with the Grubbs second generation catalyst, to
furnish (S)-parasorbic acid (4) in good overall yield
\([\alpha]_D^{24} +199.8 (c 2.5, \text{EtOH})\) (Scheme 4).

Unfortunately, attempted annulation of sulfone 2 or sul-
oxide 3 with lactone 4 by our standard cyanophthalide-
based Hauser–Kraus annulation conditions \((t\)-BuOK or\(t\)-BuOLi in DMSO) failed to deliver any of the desired an-
nulation product. Upon screening several reaction condi-
tions, it was found that upon treatment of sulfoxide 2 and
sulfone 3 with lithium disopropylamide, both species
formed a bright red colour, indicative of anion formation,
but only the sulfoxide 2 underwent successful annulation
with lactone 8 to deliver (S)-semivioxanthin methyl
ether\(16 \) (9) in a poor 29% yield (Scheme 5).

Due to the unpredictable nature of this annulation and its
poor yields, it was next decided to pursue an alternative
annulation to access thysanone. Thus, the addition of tol-
uate anions to enone electrophiles, also known as the
Staunton–Weinreb annulation\(7d,17 \) was deemed a viable al-
ternative to the Hauser–Kraus annulation (Scheme 6).
The revised aromatic annulation partner 6 was readily accessible, as it was an intermediate in the previous syntheses of sulfoxide 2 and sulfone 3. Lactone 10 was, in turn, obtained from commercially available (S)-ethyl-3-hydroxybutyrate by a three-step procedure reported by Müller. Gratifyingly, the o-toluate anion addition of 6 with lactone 10 proceeded smoothly, delivering (S)-semivioxanthin methyl ether (9) in an acceptable 56% yield, together with recovery of both starting materials (Scheme 7). At this stage, reduction of the lactone to the lactol 11 could not be achieved with diisobutylaluminum hydride, so complete reduction was envisaged, with the aim of installing the lactol at a later stage of the synthesis. Thus, treatment of lactone 9 with borane–dimethyl sulfide complex gave the reduced pyran 12 in moderate yield. Next, salcomine-mediated oxidation of naphthol 12 proceeded in excellent yield, delivering the pyranonaphthoquinone 13. Disappointingly, the seemingly straightforward removal of both methyl groups to give 14 was not successful. Despite subjecting 13 to a plethora of Lewis acid and nucleophile based deprotection conditions (e.g., BBr3, BCl3, AlCl3, TMSI, BF3·OEt2, MsOH/methionine, K2CO3/PhSH), only the monodeprotected product 15 was ever isolated, along with degradation being observed if the reaction was subjected to harsher conditions (Scheme 7). Disappointingly, at this stage a new protecting group strategy had to be implemented.

It is well established that isopropyl ethers are more labile than methyl ethers. Thus, it was decided to return to the start of the synthesis and use an isopropyl ether protecting group instead of a methyl ether. Treatment of diphenol 5 with 2-bromopropane in the presence of potassium carbonate delivered the dialkylated diol 16, which gratifyingly underwent smooth annulation with lactone 10 in the presence of lithium diisopropylamide, to deliver the naphthol 17 in moderate yield (Scheme 8). Smooth boron-mediated lactone reduction gave 18, which underwent oxidation in presence of salcomine and oxygen, delivering the pyranonaphthoquinone 19 in excellent yield. Gratifyingly, facile removal of both isopropyl protecting groups was easily achieved by treatment of 19 with aluminium trichloride in dichloromethane at room temperature, furnishing 14 in excellent yield. Boron trichloride only delivered moderate yields of 14 (45–55%) in this instance. Finally, following the procedure of Gill,6 a solution of 14 in carbon tetrachloride in the presence of molecular bromine was irradiated at 40 °C with a 60-watt desk lamp for one hour. Hydrolysis of the resulting diastereomeric bromides in aqueous tetrahydrofuran delivered (–)-thysanone 1, which was identical in all aspects to the synthetic thysanone obtained by Donner and Gill6b (Scheme 8, Figure 2, Table 1), and a similar anomaly in our recorded optical rotation [\([\alpha]_D^{24} = -21.2 \ (c 0.005, \text{MeOH})\)] was also evident. As noticed by Donner and Gill, the optical rotation of synthetic (1R,3S)-thysanone ([\([\alpha]_D^{24} = -29.7 \ (c 0.002, \text{MeOH})\] was of opposite sign to that reported in the isolation paper3 ([\([\alpha]_D^{25} = +29 \ (c 1.62, \text{MeOH})\]). By extensive comparison of their synthetic sample with an authentic sample of the natural product, Donner and Gill concluded that the optical rotation extensively fluctuates at higher concentrations, and hence was inaccurately recorded in the isolation paper. It was therefore concluded unequivocally that the stereochemistry of thysanone was, in fact, 1R,3S.6b Our own synthesis further confirms this observation.
In conclusion, we have achieved a convergent, enantioselective synthesis of (−)-thysanone with a longest linear sequence of eight steps, hence confirming the absolute stereochemistry of the natural product. We envisage this will provide a sound basis for the rapid synthesis of analogues, with the intention of increasing the HRV-3C protease activity of this class of pyranonaphthoquinones.

All reactions were carried out in oven-dried or flame-dried glassware under a N₂ atmosphere unless otherwise stated. Analytical TLC was performed on 0.2-mm Kieselgel F254 (Merck) silica plates and compounds were visualised under 365-nm UV irradiation followed by staining with either alkaline permanganate or ethanolic vanillin soln. IR spectra of samples prepared as thin films between NaCl plates were obtained on a Perkin-Elmer Spectrum One FT-IR spectrometer. Optical rotations were measured on a Perkin-Elmer 341 polarimeter at λ = 598 nm. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded on either a Bruker DRX-400 spectrometer (1H, 400 MHz; 13C, 100 MHz) or a Bruker Avance 300 spectrometer (1H, 300 MHz; 13C, 75 MHz). The 1H NMR chemical shifts are reported relative to the TMS peak recorded as δ = 0.00 in CDCl₃/TMS solvent, the residual CHCl₃ peak at δ = 7.25, or the residual acetone peak at δ = 2.05. The 13C NMR values were referenced to the residual CHCl₃ peak at δ = 77.0 or the residual acetone peak at δ = 29.8. Assignments are made with the aid of DEPT 135, COSY, NOESY, and HSQC experiments. HRMS was carried out on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70 eV. For all microwave-assisted reactions, the CEM Discover system with a circular single mode and focused waves was used, resulting in formation of a homogeneous field pattern surrounding the sample.

**Methyl 2,4-Dihydroxy-6-methylbenzoate (5)**

In a 500-mL round-bottom flask equipped with a condenser and side arm, a soln of a 60% dispersion of NaH in mineral oil (11 g, 258.4 mmol) in THF (100 mL) was cooled to 0 °C. A freshly distilled soln of methyl acetoacetate (21.6 mL, 172.2 mmol) in THF (25 mL) was added dropwise over 30 min. Upon completion of the addition, the resulting suspension was stirred at 0 °C for 30 min, and then cooled to –78 °C. A 1.6 M soln of n-BuLi in pentane (103 mL, 163.6 mmol) was added slowly via cannula over 30 min, and the resulting soln was allowed to reach r.t. over 20 h. The resulting bright red soln was then heated to reflux for 24 h and cooled to 0 °C, and its pH was adjusted to 1–2 by careful addition of concd aq HCl. The mixture was diluted with H₂O (300 mL) and then extracted with CH₂Cl₂ (3 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried (MgSO₄), filtered, and concentrated in vacuo. Purification by flash chromatography (pre-loading of sample onto silica; silica gel, hexanes–EtOAc, 5:1) gave 5.

Yield: 8.53 g (55%); strong-smelling beige solid; mp 131–132 °C (Lit. 136–138 °C).

The spectroscopic data were consistent with those previously reported in the literature. 1

**Methyl 2,4-Dimethoxy-6-methylbenzoate (6)**

K₂CO₃ (8.7 g, 63 mmol) and TBAI (100 mg, 0.3 mmol), followed by Me₂SO₄ (3.98 mL, 42 mmol), were added to a soln of diphenol 5 (1.6 g, 10.5 mmol) in acetone (40 mL) and DMF (2 mL), and the reaction mixture was heated to reflux for 16 h. A 1 M soln of aq HCl (100 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, hexanes–EtOAc, 4:1) gave 6.

Yield: 2.02 g (91%); colourless oil that crystallised upon standing; mp 39–40 °C (Lit. 41.6 °C).

**Scheme 8**

Reagents and conditions: (i) i-PrBr, K₂CO₃, TBAI, acetone–DMF, 60 °C, 16 h, 91%; (ii) LDA, THF, –78 °C to r.t., 1 h, 47%; (iii) BH₃·SMe₂, THF, 0 °C to r.t., 16 h, 61%; (iv) salcomine, MeCN, O₂, r.t., 16 h, 91%; (v) AlCl₃, CH₂Cl₂, r.t., 1 h, 95%; or BCl₃, CH₂Cl₂, –78 °C to r.t., 3 h, 53%; (vi) Br₂, Bz₂O₂, CCl₄, 60-W lamp, 40 °C, 1 h, then THF–H₂O, 45 min, 89%.
The spectroscopic data were consistent with those previously reported in the literature.\textsuperscript{12}

**Methyl 2,4-Dimethoxy-6-[[phenylsulfinyl]methyl]benzoate (2)**

A soln of 7 (2.3 g, 11 mmol) in THF (4.5 mL) was added dropwise over 5 min to a freshly prepared soln of LDA (20 mmol) in THF (20 mL) at –78 °C. The bright red mixture was stirred for 1 h at –78 °C. A soln of Ph\(_2\)S\(_2\) (2.6 g, 12 mmol) in THF (4 mL) was added and the reaction mixture was left to warm to r.t. overnight. The soln was quenched by the addition of H\(_2\)O (40 mL) and extracted with CH\(_2\)Cl\(_2\) (3 × 30 mL). The combined organic extracts were washed with sat. aq NaHCO\(_3\) (30 mL) and brine (30 mL), dried (MgSO\(_4\)), filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, hexanes–EtOAc, 9:1) gave 2.

Yield: 2.2 g (64%); yellow oil.

\(\text{1H NMR (300 MHz, CDCl}_3\):} \delta = 3.61 (s, 3 H, OMe), 3.70 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 4.10 (s, 2 H, S\(\text{CH}_2\)), 6.31 (m, 2 H, ArH), 7.17 (m, 3 H, ArH), 7.30 (m, 2 H, ArH).

The spectroscopic data were consistent with those previously reported in the literature.\textsuperscript{13}

**Table 1**  \(^1\)H and \(^{13}\)C NMR Data for Natural and Synthetic Thysanone (1)

<table>
<thead>
<tr>
<th>Position(^b)</th>
<th>Natural thysanone from (T.) penicilloides(^3)</th>
<th>Synthetic thysanone (ref. 6)</th>
<th>Synthetic thysanone (this work)</th>
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<tbody>
<tr>
<td>(^1)H ((\delta))</td>
<td>(^{13})C ((\delta))</td>
<td>(^1)H ((\delta))</td>
<td>(^{13})C ((\delta))</td>
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<tr>
<td>1</td>
<td>5.84 (s)</td>
<td>86.5</td>
<td>5.90 (s)</td>
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<td>3</td>
<td>4.21 (m)</td>
<td>62.0</td>
<td>4.30 (m)</td>
</tr>
<tr>
<td>(4_{ax})</td>
<td>2.05 (dd, (J = 19.4, 11.0) Hz)</td>
<td>29.9</td>
<td>2.10 (dd, (J = 19.4, 11.3) Hz)</td>
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<tr>
<td>(4_{eq})</td>
<td>2.62 (dd, (J = 19.4, 3.5) Hz)</td>
<td>2.65 (dd, (J = 19.4, 3.5) Hz)</td>
<td>2.66–2.73 (dd, (J = 18.1, 3.5) Hz)</td>
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<tr>
<td>4a</td>
<td>–</td>
<td>144.0</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>–</td>
<td>184.2</td>
<td>–</td>
</tr>
<tr>
<td>5a</td>
<td>–</td>
<td>134.6</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>6.97 (d, (J = 2.3) Hz)</td>
<td>108.7</td>
<td>7.02 (d, (J = 2.4) Hz)</td>
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<tr>
<td>7</td>
<td>–</td>
<td>165.2</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>6.53 (d, (J = 2.3) Hz)</td>
<td>108.4</td>
<td>6.57 (d, (J = 2.4) Hz)</td>
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<td>9</td>
<td>–</td>
<td>165.1</td>
<td>–</td>
</tr>
<tr>
<td>9a</td>
<td>–</td>
<td>109.5</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>–</td>
<td>187.3</td>
<td>–</td>
</tr>
<tr>
<td>10a</td>
<td>–</td>
<td>142.0</td>
<td>–</td>
</tr>
<tr>
<td>3-Me</td>
<td>1.25 (d, (J = 6.3) Hz)</td>
<td>21.4</td>
<td>1.28 (d, (J = 6.2) Hz)</td>
</tr>
<tr>
<td>1-OH</td>
<td>not observed</td>
<td>–</td>
<td>not observed</td>
</tr>
<tr>
<td>7-OH</td>
<td>not observed</td>
<td>–</td>
<td>not observed</td>
</tr>
<tr>
<td>9-OH</td>
<td>12.10 (s)</td>
<td>12.23 (s)</td>
<td>12.26 (s)</td>
</tr>
</tbody>
</table>

\(^a\) Solvent: acetone-\(d_6\).

\(^b\) See Figure 2 for the atom-numbering of compound 1.

Methyl 2,4-Dimethoxy-6-[[phenylsulfinyl]methyl]benzoate (2)

\(\text{NaO} \text{H} \text{(0.5 g, 2 mmol) was added in one portion to a soln of 7 (0.6 g, 2 mmol) in MeOH-H}_2\text{O (16 mL, 4:1). The reaction mixture was stirred overnight at r.t., concentrated in vacuo, and then diluted with H}_2\text{O (50 mL). The aqueous phase was extracted with CH}_3\text{Cl}_2 \text{(3 \times 30 mL). The combined organic phases were washed with brine (20 mL), dried (MgSO}_4\text{), filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, hexanes–EtOAc, 2:1) gave 2.}

Yield: 0.5 g (80%); colourless solid; mp 56–58 °C.

\(\text{IR (film):} \text{3053, 2985, 1710, 1604, 1461, 1433, 1331, 1265, 1204, 1163, 670 cm}^{-1}.\)

\(\text{1H NMR (300 MHz, CDCl}_3\):} \delta = 3.70 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 4.14 (s, 2 H, S\(\text{CH}_2\)), 6.12 (d, \(J = 2.1\) Hz, 1 H, ArH), 6.43 (d, \(J = 2.1\) Hz, 1 H, ArH), 7.46–7.55 (m, 5 H, ArH).

\(\text{13C NMR (75 MHz, CDCl}_3\):} \delta = 52.3 (OMe), 55.5 (OMe), 56.1 (OMe), 63.1 (S\(\text{CH}_2\)), 99.3 (CH), 107.8 (CH), 124.3 (2 CH), 129.0 (2 CH), 131.2 (C), 131.8 (C), 143.6 (C), 159.3 (C), 161.6 (C), 167.7 (C=O), 1 C not observed.

\(\text{MS–FAB: m/z} = 335 [\text{M} + \text{H}^+](29), 303 (30), 209 (42), 195 (3), 178 (14), 165 (6), 120 (12), 89 (21), 77 (21).\)
HRMS–FAB: m/z [M + H+] calcld for C17H19O5S: 335.0953; found: 335.0953.

Methyl 2,4-Dimethoxy-6-[(phenylsulfonyl)methyl]benzoate (3)
(NH4)2MoO4·4H2O (0.09 g, 0.07 mmol) was added to 27% aq H2O2 (400 mg, 1.2 mmol) to provide a freshly prepared soln of LDA (3 mmol) in THF (10 mL) at ~78 °C [prepared from 1.6 M n-BuLi in pentane (1.9 mL, 9 mmol) and i-Pr2NH (421 μL, 3 mmol) in THF (3 mL) at 0 °C]. The resulting bright red soln was stirred for 30 min, and then a soln of lactone 4 (134 mg, 1.2 mmol) in THF (1 mL) was added dropwise, before the reaction mixture was warmed to r.t. and stirred for 1 h. Sat. aq NH4Cl (20 mL) was added and the mixture was extracted with CH2Cl2 (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO4), filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, hexanes–EtOAc, 1:2) gave 3.

Yield: 0.3 g (56%); colourless solid; mp 146–148 °C.

IR (film): 1705, 1605, 1463, 1317, 1162 cm–1.

Yield: 2.02 g (60% over 2 steps); pale yellow oil; [a]24D +199.8 (c 2.5, EtOH).

1H NMR (300 MHz, CDCl3): δ = 2.36 (2 H, CH 2), 3.68 (s, 3 H, OMe), 4.40–4.51 (m, 1 H, CH), 6.47 (d, J = 2.3 Hz, 1 H, ArH), 6.58 (d, J = 2.3 Hz, 1 H, ArH), 6.85 (s, 1 H, ArH), 13.15 (s, 1 H, OH).

IR (neat): 3577, 2990, 1667, 1602, 1576, 1412, 1352, 1281, 1154, 1011, 910 cm–1.

(4) 2,4-Dimethoxy-6-[(phenylsulfonyl)methyl]benzoate (3)

A soln of sulfide 2 (400 mg, 1.2 mmol) in THF (2 mL) was added dropwise to a freshly prepared soln of LDA (3 mmol) in THF (10 mL) at ~78 °C [prepared from 1.6 M n-BuLi in pentane (1.9 mL, 9 mmol) and i-Pr2NH (421 μL, 3 mmol) in THF (3 mL) at 0 °C].

The resulting reaction mixture was stirred for 1 h and then warmed to r.t. and stirred for 4 h. The reaction mixture was warmed to reflux for 3 h. Concentration in vacuo followed by column chromatography (silica gel, hexanes–EtOAc, 1:1) gave 4.

Yield: 101 mg (29%); colourless solid; mp 104–106 °C (Lit. 16 130–131 °C); [a]24D +16.1 (c 0.5, CHCl3) [Lit. 16 [a]24D +18 (c 0.3, CHCl3)].

HRMS–FAB: m/z % = 289 [M + H+] (100), 271 (11), 154 (64), 136 (50), 107 (20), 99 (21), 77 (24).

HRMS–FAB: m/z [M + H+] calcld for C16H16O7S: 319.0786; found: 319.0781.

The spectroscopic data were consistent with those previously reported in the literature.16

(5) 4-Methoxy-3,6-dihydro-2H-pyrano[2,3-b]pyran-2-one (10)

Compound 10 was prepared by following a reported procedure.16

IR (neat): 3081, 1741, 1610, 1547, 1421, 1348, 1280, 1178, 1013, 876 cm–1.

IR (neat): 3577, 2990, 1667, 1602, 1576, 1412, 1352, 1281, 1154, 1011, 910 cm–1.

The spectroscopic data were consistent with those previously reported in the literature.16

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BH3·SMe2 (3.06 mmol, 300 mg) was added to a soln of lactone 9 (220 mg, 0.76 mmol) in THF (5 mL) at 0 °C, and the reaction mixture was warmed to r.t. over 1 h. Sat. aq NH4Cl soln (10 mL) was added and the mixture was extracted with CH2Cl2 (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO4), filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, hexanes–EtOAc, 5:1) gave 12.

Yield: 121 mg (58%); colourless solid; mp 117–119 °C; [α]D 24 +9.9 (c 0.12, MeOH).

IR (neat): 3410, 1638, 1364, 1204, 829 cm–1.

1H NMR (400 MHz, CDCl3): δ = 1.37 (d, J = 6.2 Hz, 3 H, Me), 2.79 (m, 2 H, CH–4), 3.08–3.84 (m, 1 H, CH), 3.88 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 4.75 (dd, J = 15.2, 3.1 Hz, 1 H, Hax–1), 5.13 (dd, J = 15.2, 2.6 Hz, 1 H, H–1), 6.38 (d, J = 2.0 Hz, 1 H, ArH), 6.61 (d, J = 2.0 Hz, 1 H, ArH), 6.95 (s, 1 H, ArH), 9.20 (s, 1 H, OH).


13C NMR (100 MHz, CDCl3): δ = 21.6 (Me), 55.3 (OMe), 64.1 (OMe), 67.4 (CH2), 97.0 (CH), 98.6 (CH), 115.0 (C), 116.5 (CH), 135.0 (C), 135.6 (C), 149.2 (C), 157.1 (C), 157.2 (C), 1 C not observed.

MS (EI, 70 eV); m/z (%): 274 [M]+ (100), 259 (12), 245 (23), 230 (55), 212 (18), 122 (12), 43 (13).


1H and 13C NMR and MS data are consistent with those reported in the literature.6b

Methyl 2,4-Diisopropoxy-6-methylbenzoate (16)

K2CO3 (4.2 g, 30.3 mmol) and TBAI (100 mg, 0.3 mmol), followed by i-PrBr (8 mL, 86 mmol) were added to a soln of diphenol 5 (1.15 g, 7.57 mmol) in acetone (20 mL) and DMF (2 mL), and the reaction mixture was heated to reflux for 16 h. A 1 M soln of aq HCl (50 mL) was added and the mixture was extracted with CH2Cl2 (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO4), filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, hexanes–EtOAc, 4:1) gave 16.

Yield: 1.83 g (91%); colourless oil that crystallised upon standing; mp 29–32 °C.

IR (neat): 2976, 1724, 1600, 1430, 1383, 1372, 1316, 1265, 1182, 1178 cm–1.


1H NMR (400 MHz, CDCl3); δ = 1.42–1.46 (m, 12 H, 2 CH2Me), 3.98 (s, 3 H, Me), 4.57–4.67 (m, 2 H, 2 CH2Me), 6.43 (s, 2 H, ArH).

13C NMR (100 MHz, CDCl3); δ = 21.2 (Me), 55.9 (OMe), 64.1 (OMe), 67.4 (CH2), 97.0 (CH), 98.6 (CH), 115.0 (C), 116.5 (CH), 135.0 (C), 135.6 (C), 149.2 (C), 157.1 (C), 157.2 (C), 1 C not observed.

MS (EI, 70 eV); m/z (%): 266 [M]+ (22), 235 (12), 224 (10), 192 (28), 182 (16), 150 (100), 122 (11), 43 (16).


(S)-7,9-Dimethoxy-3-methyl-3,4-dihydro-1H-benzo[g]isochromene-5,10-dione (15)

Compound 15 was obtained from the reaction of 13 with BBr3, AlCl3, BCl3, or TMSI. The experimental details of the reaction with AlCl3 are provided, as this method afforded the best yield.

AlCl3 (144 mg, 1.08 mmol) was added to a soln of 13 (26 mg, 0.09 mmol) in CH2Cl2 (2 mL) at –78 °C, and the reaction mixture was warmed to r.t. for 6 h, before being heated to reflux for 4 h. Sat. aq NH4Cl (2 mL) was added and the mixture was extracted with CH2Cl2 (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (MgSO4), filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, hexanes–EtOAc, 5:1) gave 15.

Yield: 11 mg (48%); orange solid; mp 108–110 °C (Lit.6b 161–162 °C); [α]D 24 +60.5 (c 1.3, CHCl3).

IR (neat): 3090, 2980, 2936, 1686, 1618, 1442, 1393, 1349, 1289, 1233, 1204, 1053, 991, 856, 842 cm–1.

1H NMR (300 MHz, CDCl3); δ = 1.29 (d, J = 6.3 Hz, 3 H, Me), 2.20–2.25 (dd, J = 18.9, 9.2, 3.8, 2.6 Hz, 1 H, H–1), 2.59–2.66 (dd, J = 18.9, 3.8, 2.6 Hz, 1 H, H–4), 3.57 (m, 1 H, CH), 3.82 (s, 3 H, OMe), 4.39–4.46 (dd, J = 18.8, 4.3, 3.3 Hz, 3 H, CH–1), 4.72–4.80 (dd, J = 18.8, 2.8 Hz, 1 H, H–1), 6.53 (d, J = 2.5 Hz, 1 H, ArH), 7.10 (d, J = 2.5 Hz, 1 H, ArH), 12.04 (s, 1 H, OH).

13C NMR (100 MHz, CDCl3): δ = 21.2 (Me), 29.6 (CH), 56.0 (OMe), 63.0 (CH2), 69.6 (CH2), 106.0 (CH), 108.1 (CH), 133.4 (C), 142.3 (C), 142.8 (C), 164.3 (C), 166.0 (C), 182.9 (C=O), 186.7 (C=O), 1 C not observed.

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Yield: 630 mg (47%); colourless solid; mp 48–50 °C; [α]D^24 +26.4 (c 2.5, CHCl₃).

IR (neat): 3558, 2978, 1631, 1576, 1373, 1332, 1289, 1272, 1187, 1114, 1030, 910, 831 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.29–1.55 (m, 15 H, 2 CHMe₂, 3-Me), 2.97–2.90 (m, 2 H, CH₂-4), 6.40–6.72 (m, 3 H, 2 CHMe₂, CH₂-1), 6.46 (d, J = 2.4 Hz, 1 H, ArH), 6.55 (d, J = 2.4 Hz, 1 H, ArH), 6.78 (s, 1 H, ArH), 12.79 (s, 1 H, OH).

13C NMR (75 MHz, CDCl₃): δ = 20.7 (Me), 21.9 (4 Me), 35.2 (CH₂), 69.9 (CH), 72.3 (CH), 75.4 (CH), 100.6 (C), 101.0 (CH), 102.5 (CH), 111.4 (C), 115.0 (CH), 134.2 (C), 141.3 (C), 158.9 (C), 159.8 (C), 164.1 (C), 170.4 (C=O).

MS (El, 70 eV); m/z (%) = 344 [M⁺] (51), 302 (39), 260 (100), 242 (36), 216 (26), 213 (19), 43 (32).


(5S,7S)-Dihydroxy-3-methyl-3,4-dihydro-1H-benzo[g]isochroman-5,10-dione (14)

A solution of lactone 17 (80 mg, 0.23 mmol) in THF (4 mL) was cooled to 0 °C. BH₃·SMe₂ (50 μL, 0.48 mmol, 2 equiv) was added dropwise and the reaction mixture was warmed to r.t. with stirring for 16 h. The reaction mixture was diluted with CH₂Cl₂ (5 mL), sat. aq NH₄Cl (10 mL) was added, and the organic layer was removed. The aqueous layer was extracted with CH₂Cl₂ (2 × 3 mL) and the combined organic extracts were washed with brine (2 mL), dried (MgSO₄), filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, hexanes–EtOAc, 3:1) gave 18 as a viscous oil.

Yield: 46 mg (61%); [α]D^24 +14.2 (c 0.06, CHCl₃).

IR (neat): 3383, 2974, 2932, 1617, 1614, 1582, 1467, 1362, 1308, 1183, 1153, 1135, 1108, 1021, 906, 848, 824 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 1.37–1.39 (m, 9 H, CHMe₂, 3,Me). 1.49 (m, 6 H, CH₂Me₂). 2.79 (m, 2 H, CH₂-4). 3.75–3.83 (m, 1 H, CHMe₂). 4.61–4.67 (m, 1 H, CHMe₂). 4.75–4.82 (m, 2 H, Hax-1, CH-3). 5.13–5.10 (dt, J = 18.8, 2.6 Hz, 1 H, ArH-1). 6.37 (d, J = 1.7 Hz, 1 H, ArH). 6.60 (d, J = 1.7 Hz, 1 H, ArH). 6.90 (s, 1 H, ArH). 9.65 (s, 1 H, OH).

13C NMR (100 MHz, CDCl₃): δ = 21.6 (Me), 21.98 (2 Me), 22.01 (2 Me), 36.1 (CH₂), 64.8 (CH₃), 69.7 (CH), 70.5 (CH), 72.5 (CH), 100.2 (CH), 100.7 (CH), 109.5 (C), 114.5 (C), 116.3 (CH), 134.7 (C), 135.8 (C), 149.5 (C), 155.2 (C), 155.3 (C).

MS (El, 70 eV); m/z (%) = 330 [M⁺] (100), 314 (101), 288 (50), 246 (52), 202 (95), 186 (20), 173 (20), 43 (42).


(5S,7S)-Diospropoxy-3-methyl-3,4-dihydro-1H-benzo[g]isochromene-5,10-dione (19)

Salcombe (12 mg, 15 mol%) was added to a solution of napthol 18 (96 mg, 0.29 mmol) in MeCN (3 mL), and the reaction mixture was stirred under an atmosphere of O₂ for 4 h. Concentration in vacuo followed by flash chromatography (silica gel, hexanes–EtOAc, 1:1) gave 19.

Yield: 89 mg (91%); orange solid; mp 127–128 °C; [α]D^24 +102.2 (c 0.09, CHCl₃).

IR (neat): 2976, 1654, 1590, 1555, 1431, 1305, 1275, 1164, 1104, 1038, 908, 843, 724 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 1.33–1.46 (m, 15 H, 2 CHMe₂, 3-Me), 2.19–2.27 (m, 1 H, Hax-1), 2.62–2.67 (m, 1 H, Hax-1). 3.60–3.65 (m, 1 H, H-3). 4.43–4.50 (dd, J = 19.0, 3.4 Hz, 1 H, Hax-1). 4.57–4.63 (m, 1 H, CHMe₂), 4.70–4.76 (m, 1 H, CCH₃). 4.80–4.86 (dd, J = 2.0, 18.9 Hz, 1 H, H-3). 6.65 (d, J = 2.3 Hz, 1 H, ArH). 7.20 (d, J = 2.3 Hz, 1 H, ArH).

13C NMR (100 MHz, CDCl₃): δ = 21.2 (Me), 21.9 (2 CHMe₂), 29.1 (CH₂), 63.8 (CH₃), 69.5 (CH), 70.7 (CH), 71.2 (CH), 104.9 (CH), 107.7 (CH), 114.4 (CH₃), 135.9 (C), 138.7 (C), 144.3 (C), 160.6 (C), 162.9 (C), 181.5 (C=O), 184.1 (C=O).

MS (El, 70 eV); m/z (%) = 344 [M⁺] (70), 329 (12), 302 (34), 261 (15), 260 (95), 245 (22), 224 (23), 213 (24), 216 (100), 200 (11), 188 (15), 43 (49).


(5S)-Thyssamenone (10)

A 1 M soln of Cr₂O₃ in CHCl₃ (30 μL, 0.030 mmol) and Br₂O (1 crystal) were added to a soln of quinone 14 (8 mg, 0.030 mmol) in CHCl₃ (7 mL) and the reaction mixture was irradiated with a 60-W lamp at 40 °C for 1 h. The cooled reaction mixture was concentrated in vacuo and taken up in THF (2 mL). H₂O (1 mL) was added and the reaction mixture was stirred for 1 h before being diluted with CH₂Cl₂ (8 mL). H₂O (5 mL) was added and the organic layer was removed. The aqueous layer was extracted with CH₂Cl₂ (2 × 5 mL) and the combined organic extracts were washed with brine (2 mL), dried (MgSO₄), filtered, and concentrated in vacuo. Purification by preparative TLC (silica gel, hexanes–EtOAc, 1:1, then 1:2) gave 10.

Yield: 7 mg (89%); orange solid; mp 201–202 °C (Lit. isolation 3100–320 °C).


The spectroscopic data were consistent with those previously reported in the literature.

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1H NMR (300 MHz, acetone-\(d_{6}\)): \(\delta = 1.30\) (d, \(J = 6.5\) Hz, 3 H, 3-Me), 2.11–2.17 (dd, \(J = 19.4, 3.5\) Hz, 1 H, \(H_2\)), 4.30–4.36 (m, 1 H, H-3), 5.93 (s, 1 H, H-1), 6.62 (d, \(J = 2.3\) Hz, 1 H, ArH), 7.07 (d, \(J = 2.3\) Hz, 1 H, ArH), 9.73–10.31 (br s, 1 H, OH), 12.26 (s, 1 H, OH).

13C NMR (75 MHz, acetone-\(d_{6}\)): \(\delta = 21.6\) (Me), 62.2 (CH), 86.8 (CH), 108.5 (CH), 108.8 (CH), 109.5 (C), 135.1 (C), 142.0 (C), 144.5 (C), 165.4 (C), 165.8 (C), 184.2 (C=O), 187.6 (C=O), 1 CH2 obscured by acetone.

MS (EI, 70 eV): \(m/z (\%) = 276\) [M+4 (4), 258 (50), 229 (10), 129 (10), 97 (40), 83 (50), 55 (100).

HRMS (EI): \(m/z \) [M+4] calcd for C\(_{14}\)H\(_{12}\)O\(_6\): 276.0634; found: 276.0634.

The spectroscopic data were consistent with those previously reported in the literature (see Table 1).\(^{1,6b}\)

Acknowledgment

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References


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