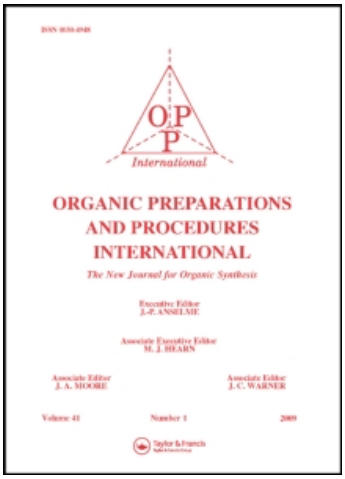

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METHYL 6-METHOXY-1-OXOINDAN-4-CARBOXYLATE

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OPPI BRIEFS

METHYL 6-METHOXY-1-OXOINDAN-4-CARBOXYLATE

Submitted by Martin G. Banwell* and Scott G. Stewart
(05/18/01)

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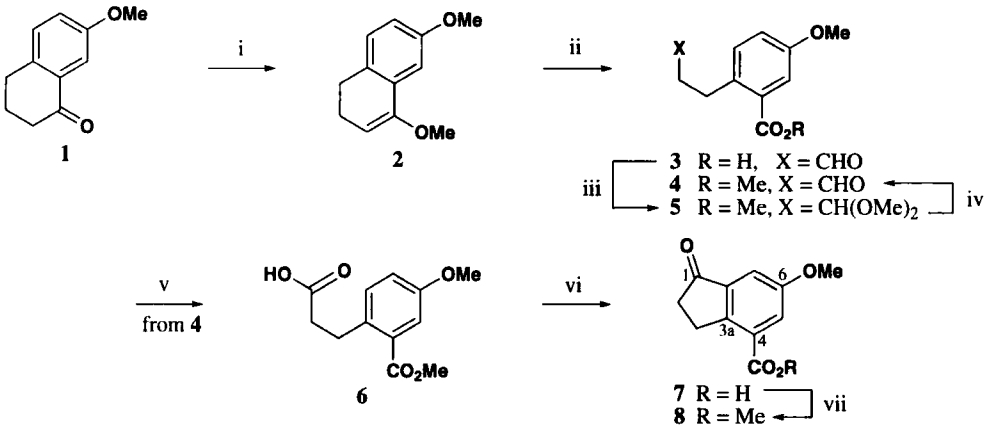
In connection with work directed towards the synthesis of taxoids,[1] we required samples of a 4,6-disubstituted-1-indanone wherein the C-4 substituent was carbon-based and the C-6 substituent was oxygen-based. However, such compounds appear to be unknown. Consequently, we now describe a short reaction sequence (Scheme 1) which allows for conversion of commercially available 7-methoxy-1-tetralone (**1**) into the title compound **8**.



Reagents and conditions; i) $HC(OMe)_3$, *p*-TsOH (cat.), 18°, 72 h; ii) $KMnO_4$, $NaIO_4$, *t*-BuOH, H_2O, buffer, 18°, 1.75 h; iii) MeOH, H_2SO_4 (cat.), reflux, 48 h; iv) AcOH, THF, H_2O, 45°, 12 h; v) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 18°, 36 h; vi) $MeSO_3H$, P_2O_5, 85°, 0.25 h; vii) MeOH, H_2SO_4 (cat.), reflux, 24 h.

Scheme 1

Thus, reaction of ketone **1** (*ex* Aldrich) with neat trimethyl orthoformate in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH)[2] afforded the corresponding enol ether **2** in 89%

yield. Oxidative cleavage of this latter compound with the Lemieux-von Rudloff reagent[3] at pH 7.5 then gave the acid-aldehyde **3** (32%) and the required ester **4** (40%). The former compound was converted into the latter by a two-step sequence involving initial treatment with acidic methanol then hydrolysis of the intermediate acetal **5**. Oxidation of compound **4** using Pinnick's sodium chlorite ($NaClO_2$) procedure[4] then gave the corresponding acid **6** (92%). The acid chloride derived from this latter compound failed to engage in an intramolecular Friedel-Crafts acylation reaction upon treatment with aluminium trichloride in refluxing benzene and other solvents.[5] However, treatment of carboxylic acid itself with phosphorous pentoxide/methanesulfonic acid[6] at 85° for 0.25 h gave the target indanone **8** as a crystalline solid in 32% yield. The spectral data obtained for this material were in full accord with the assigned structure. In particular, the 300 MHz ^1H NMR spectrum showed, *inter alia*, two *meta*-coupled doublets (J = 2.7 Hz) at δ 7.85 and 7.40 thus implying that there are substituents at C-4 and C-6 as required. A by-product observed during the latter cyclization was indanone-acid **7**, which was easily esterified using acidic methanol to give the indanone **8**. In this manner, the indanone **8** was obtained in 43% overall yield from precursor **6**.

The protocol described here has potential for application to the synthesis of a wide-variety of new indanones, a class of compound continuing to receive considerable attention because of their utility in both synthetic and medicinal chemistry.[7] Further examination of the scope and value of the procedures described above are currently being pursued in our laboratories.

EXPERIMENTAL SECTION

Melting points were determined on a hot-stage microscope and are uncorrected. Unless stated otherwise, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, at 300 and 75 MHz, respectively. Mass spectra were recorded at 70 eV on a three sector (E/B/E) double-focussing mass spectrometer while IR spectra were recorded on an FT Instrument. GC analyses of crude reaction mixtures were conducted on a SGE BPX5 capillary column using an injector temperature of 270°. The initial column temperature was 100°, which was held for 1 min and subsequently heated at 10° per min until a final temperature of 270° was attained. Compounds **3** and **4** were too unstable to allow acquisition of combustion analysis data.

4,6-Dimethoxy-1,2-dihydronaphthalene (2).- *p*-Toluenesulfonic acid (200 mg, 1.05 mmol) was added to a magnetically stirred solution of ketone **1** (10.0 g, 56.7 mmol) in trimethyl orthoformate (62.2 mL) maintained at 18° under an atmosphere of nitrogen. Stirring was continued for 16 h after which time GC analysis revealed a *ca.* 1:4 mixture of starting material (R_t 620 s) and the corresponding dimethyl acetal (R_t 660 s). To ensure complete reaction, 50 mg portions of *p*-TsOH were added every 24 h until complete conversion to the acetal was observed (total reaction time *ca.* 72 h). The resulting mixture was then heated at reflux for 0.5 h and the methanol by-product and excess trimethylorthoformate were removed by fraction distillation at 760 mm Hg. The residue was subjected to vacuum distillation to afford the enol ether **2** (9.45 g, 89%) as a clear, colorless oil, bp 96°/0.01 mm Hg. ^1H NMR (d_6-acetone): δ 6.95 (m, 2 H), 6.63 (dd, J = 8.2 and 2.7 Hz, 1 H), 4.95 (t, J = 4.7 Hz, 1

H), 3.65 (s, 3 H), 3.58 (s, 3 H), 2.55 (t, J = 7.3 Hz, 2 H), 2.15 (m, 2 H); ^{13}C NMR (d_6-acetone): δ 157.4 (C), 151.6 (C), 131.9 (C), 127.8 (C), 126.8 (CH), 111.6 (CH), 106.3 (CH), 94.4 (CH), 53.6 (CH_3), 52.9 (CH_3), 26.1 (CH_2), 20.9 (CH_2); IR (KBr): ν_{max} 2935, 1642, 1573 cm^{-1}; MS: *m/z* 190 ($M^{+\bullet}$, 92%), 175 [$(M-H_3C^{\bullet})^+$, 100], 159 [$(M-H_3CO^{\bullet})^+$, 28], 147 (35), 115 (44), 62 (44); HRMS: $C_{12}H_{14}O_2$ requires $M^{+\bullet}$, 190.0994. Found $M^{+\bullet}$, 190.0996.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.48; H, 7.35

5-Methoxy-2-(3'-oxopropyl)benzoic Acid (3) and Methyl 5-Methoxy-2-(3'-oxopropyl)benzoate (4).- Enol ether **2** (1.00 g, 5.26 mmol) was added dropwise to a magnetically stirred solution of potassium permanganate (20 mg, 0.13 mmol), sodium periodate (3.33 g, 0.02 mol) and *t*-butanol (50 mL) in water (100 mL) maintained at 18°. At all times, but especially during the addition of enol ether **2**, the pH of the pink-colored reaction mixture was maintained at *ca.* 7.5 by the appropriate addition of KH_2PO_4 (1 M aqueous solution) or K_2CO_3 (saturated aqueous solution). Stirring was continued for 1.75 h after which time GC analysis of the reaction mixture indicated that no starting material (R_t 660 s) was present. The reaction mixture was then placed on the rotary evaporator for 0.25 h to remove *t*-butanol. The resulting slurry was extracted with ether (3 × 100 mL) and the combined organic phases washed with K_2CO_3 (2 × 30 mL of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear, yellow oil (fraction A). The aqueous layer was acidified with HCl (2 M aqueous solution), then extracted with ether (3 × 50 mL) and the combined organic phases washed with brine (1 × 50 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford clear, light-yellow oil (fraction B).

Flash chromatography of fraction A (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f 0.3) furnished compound **4** (470 mg, 40%) as a clear, colorless oil. ^{1}H NMR: δ 9.79 (s, 1 H), 7.43 (d, J = 2.8 Hz, 1 H), 7.18 (d, J = 8.5 Hz, 1 H), 7.00 (dd, J = 8.5 and 2.8 Hz, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.19 (t, J = 7.5 Hz, 2 H), 2.76 (t, J = 7.5 Hz, 2 H); ^{13}C NMR: δ 201.9 (CH), 166.2 (C) 157.7 (C), 134.4 (C), 132.1 (CH), 129.7 (C), 118.4 (CH), 115.4 (CH), 55.3 (CH_3), 51.9 (CH_3), 45.6 (CH_2), 26.3 (CH_2).

Flash chromatography of fraction B (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f 0.3) provided compound **3** (403 mg, 32%) as a colorless, crystalline solid, mp 62-63°. ^{1}H NMR: δ 9.83 (s, 1 H), 7.60 (d, J = 2.8 Hz, 1 H), 7.23 (d, J = 8.4 Hz, 1 H), 7.05 (dd, J = 2.8 and 8.4 Hz, 1 H), 3.84 (s, 3 H), 3.28 (t, J = 7.4 Hz, 2 H), 2.81 (t, J = 7.4 Hz, 2 H) (CO_2H proton resonance not observed); ^{13}C NMR: δ 202.0 (CH), 172.4 (C), 157.8 (C), 135.5 (C), 132.5 (CH), 128.5 (C), 119.8 (CH), 116.1 (CH), 55.4 (CH_3), 45.5 (CH_2), 26.5 (CH_2); IR (KBr): ν_{max} 1714, 1688, 1609 cm^{-1}; MS: *m/z* 208 ($M^{+\bullet}$, 62%), 190 [$(M-H_2O)^{+\bullet}$, 34], 180 (37), 165 (100), 152 (47), 77 (39); HRMS: $C_{11}H_{12}O_4$ requires $M^{+\bullet}$, 208.0736. Found $M^{+\bullet}$ 208.0732.

Methyl 2-(3',3'-Dimethoxypropyl)-5-methoxybenzoate (5).- Sulfuric acid (259 mg, 98% w/w) was added to a magnetically stirred solution of acid **3** (4.00 g, 0.019 mol) in methanol (20 mL) maintained at ambient temperatures. The reaction mixture was heated at reflux for 48 h then cooled to 18°, treated with water (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were then

dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear colorless oil. Flash chromatography of this material (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f 0.8) then furnished dimethoxy acetal **5** (4.39 g, 86%) as a clear, colorless oil. ^{1}H NMR: δ 7.38 (d, *J* = 2.8 Hz, 1 H), 7.14 (d, *J* = 8.5 Hz, 1 H), 6.94 (dd, *J* = 8.5 and 2.8 Hz, 1 H), 4.36 (t, *J* = 5.8 Hz, 1 H), 3.85 (s, 3 H), 3.77 (s, 3 H), 3.30 (s, 6 H), 2.93-2.87 (m, 2 H), 1.89-1.82 (m, 2 H); ^{13}C NMR: δ 167.4 (C), 157.3 (C), 135.4 (C), 132.0 (CH), 129.9 (C), 118.1 (CH), 115.0 (CH), 103.8 (CH), 55.1 (CH_3), 52.3 (2 × CH_3), 51.7 (CH_3), 34.0 (CH_2), 28.6 (CH_2); IR (KBr): ν_{max} 2952, 2833, 1724, 1610 cm^{-1}; MS: *m/z* 268 ($M^{+\bullet}$, 23%), 236 [M-$CH_3OH)^{+\bullet}$, 70], 204 (70), 179 (91), 75 (100); HRMS: $C_{14}H_{20}O_5$ requires $M^{+\bullet}$, 268.1311. Found $M^{+\bullet}$, 268.1310.

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.83; H, 7.84

Hydrolysis of Acetal 5. Formation of Aldehyde 4.- Acetal **5** (3.00 g, 0.11 mmol) was added dropwise to a solution of THF (50 mL) and water (50 mL) in glacial acetic acid (150 mL) maintained at 18°. The resulting solution was heated at 45° for 12 h then cooled and extracted with ether (3 × 100 mL). The combined organic extracts were washed with water (3 × 50 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a colorless oil. Flash chromatography of this material (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f 0.3) then afforded aldehyde **4** (2.39 g, 96%) as a clear, colorless oil. This material was identical, in all respects, with samples obtained earlier.

3-(2'-Carbomethoxy-4'-methoxyphenyl)propanoic Acid (6).- A solution of sodium chlorite (3.37 g, 80%, 0.03 mol) and sodium dihydrogen phosphate monohydrate (3.43 g, 28 mmol) in water (30 mL) was added dropwise over 0.25 h to a magnetically stirred solution of 2-methyl-2-butene (18 mL of a 2 M solution in THF) and aldehyde **4** (920 mg, 4.14 mmol) in *t*-butanol (60 mL) maintained at 18°. Stirring was continued for 36 h and the yellow solution was concentrated under reduced pressure. The resulting residue was treated with water (70 mL) and washed with hexane (2 × 20 mL). The yellow-colored aqueous phase was acidified to pH 3 with HCl (1 M aqueous solution) then extracted with ether (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a colorless solid. Flash chromatography of this material (silica, 1:1 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f 0.5) then furnished acid **6** (910 mg, 92%) as a colorless, crystalline solid, mp 72-73°. ^{1}H NMR: δ 7.45 (d, *J* = 2.9 Hz, 1 H), 7.21 (d, *J* = 8.5 Hz, 1 H), 7.00 (dd, *J* = 8.5 and 2.9 Hz, 1 H), 3.90 (s, 3H), 3.83 (s, 3 H), 3.21 (t, *J* = 7.4 Hz, 2 H), 2.67 (t, *J* = 7.4 Hz, 2 H) (CO_2H proton resonance not observed); ^{13}C NMR: δ 179.3 (C), 167.3 (C), 157.7 (C), 134.0 (C), 132.1 (CH), 129.8 (C), 118.4 (CH), 115.4 (CH), 55.3 (CH_3), 52.0 (CH_3), 35.7 (CH_2), 28.8 (CH_2); IR (KBr): ν_{max} 2950, 1720, 1610 cm^{-1}; MS: *m/z* 238 ($M^{+\bullet}$, 34%), 206 [(M-$CH_3OH)^{+\bullet}$, 24], 192 (77), 178 (100), 149 (51); HRMS: $C_{12}H_{14}O_5$ requires $M^{+\bullet}$, 238.0841. Found $M^{+\bullet}$, 238.0841.

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.22; H 5.90

6-Methoxy-1-oxoindan-4-carboxylic Acid (7) and Methyl 6-Methoxy-1-oxoindan-4-carboxylate (8).- A magnetically stirred mixture of freshly distilled and dry methanesulfonic acid (10 mL) and

phosphorous pentoxide (1.0 g, 3.5 mmol) was heated at 85° under a nitrogen atmosphere for 0.5 h at which point the mixture became homogeneous. The resulting solution was treated, in one portion, with acid **6** (100 mg, 0.42 mmol) and the mixture stirred at 85° for 0.25 h. The reaction mixture was then poured, while still hot (CAUTION!), into ice-cold water (20 mL), cooled to 18° and extracted with $CHCl_3$ (4 × 70 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-orange solid. Flash chromatography of this material (silica,1:3 v/v ethyl acetate/hexane elution) provided two fractions, A and B. Concentration of fraction A (R_f <0.1) afforded a mixture (~50 mg) that contained small amounts of carboxylic acid **7**, as judged by ^1H NMR spectroscopic analysis. This material was immediately subjected to the esterification procedure detailed below. Concentration of fraction B (R_f 0.3) afforded indanone **8** (30 mg, 32%) as a colorless, crystalline solid, mp 124-126°. ^1H NMR: δ 7.85 (d, *J* = 2.7 Hz, 1 H), 7.40 (d, *J* = 2.7 Hz, 1 H), 3.95 (s, 3 H), 3.87 (s, 3 H), 3.41-3.38 (complex m, 2 H), 2.73-2.70 (m, 2 H); ^{13}C NMR: δ 206.4 (C), 165.9 (C), 159.2 (C), 148.7 (C), 139.5 (C), 128.8 (C), 124.5 (CH), 110.3 (CH), 55.8 (CH_3), 52.1 (CH_3), 36.5 (CH_2), 26.3 (CH_2); IR (KBr): ν_{max} 1717 cm^{-1}; MS: *m/z* 220 ($M^{+\bullet}$, 100%), 205 [$(M-H_3C^{\bullet})^+$, 89], 188 (48), 177 (30), 161 (52); HRMS: $C_{12}H_{12}O_4$ requires $M^{+\bullet}$, 220.0736. Found $M^{+\bullet}$, 220.0734.

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.43; H, 5.50. Found: C, 65.24; H, 5.38

Methylation of Carboxylic acid 7. Formation of Ester 8.- Sulfuric acid (1 mL, 98% w/w) was added to a magnetically stirred solution of the above-mentioned sample of carboxylic acid **7** in methanol (10 mL) maintained at 18°. The resulting solution was heated at reflux for 24 h then cooled, diluted with water (10 mL) and extracted with $CHCl_3$ (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear, yellow oil. Flash chromatography of this material (silica, 1:3 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f 0.3) then provided indanone **8** (10 mg, 11% from **6**) as a colorless, crystalline solid. This material was identical, in all respects, with the samples obtained earlier.

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AN EFFICIENT ONE-STEP CONVERSION OF BILIVERDINS TO 14-FORMYLTRIPYRRINONES

Submitted by (05/08/01)

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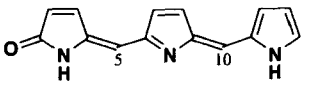
The tripyrrinone skeleton (**I**) is a fully conjugated linear tripyrrolic system and a structural part of biliverdins, phycocyanobilins,[1] pentapyrrins,[2] and hexapyrrins.[3] It is an important precursor for the synthesis of linear tetrapyrroles[4] and oligopyrrole pigments such as 15-thia- and 15-norhexapyrrins.[3] A 9,10-dihydrotripyrrinone analog was recently synthesized and used as a bilirubin model compound to investigate the spectroscopic, solution, and metabolic properties of bilirubin.[5] Although 14-formyltripyrrinones have been known for many years,[1] larger scale and efficient synthetic methods are still not available. Multiple-step syntheses starting from pyrroles could in principle lead to the desired 14-formyltripyrrinones.



I Tripyrrinone Skeleton

14-Formyltripyrrinones, such as compound **2a**, were first found in the mixture of the oxidation of bilirubins with nitric acid,[6,7] a reaction characteristic of bilirubins. Compound **2a** was also obtained by treatment of biliverdins with iodine in the presence of Zn(II) and ethanol,[8] with thallium(III) triacetate, lead(IV) tetraacetate,[9] and bromine.[10] These reactions afforded only low yields and were not synthetically useful. The importance of 14-formyltripyrrinones in the synthesis of linear oligopyrroles and other polypyrrolic pigments prompted us to explore facile, efficient and synthetic useful procedures to 14-formyltripyrrinones. In 1990, our group briefly reported that treatment of