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# Total synthesis of enokipodins A-D and cuparene-1,4-diol

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A Claisen rearrangement and RCM reaction based sequence has been developed for total synthesis of the antifungal sesquiterpenes enokipodins A-D and cuparene-1,4-diol starting from 2,5-dimethoxy-4-methylhydroquinone.

**Keywords**: Enokipodins, cuparenes, RCM reaction, Claisen rearrangement, sesquiterpenes

Among the natural products, terpenoids (isoprenoids) occupy a special position on account of their widespread occurrence and the bewildering array of carbocyclic skeleta that they embody. Sesquiterpenes comprising of three isoprene units, biogenetically derived from farnesyl pyrophosphate, holds special appeal to synthetic chemists as they are assembled in acyclic, monocyclic, bicyclic, tricyclic and even tetracyclic as well as spirofused structures containing small, medium and large rings with a wide range of functionalities[1,2]. *Flammulina velutipes* (Curt.: Fr.) Sing. (Enokitake in Japanese) is a fresh edible mushroom frequently consumed in Japan. The natural compounds (proteins, polysaccharides, glycolproteins, *etc.*) isolated from the body of *F. velutipes* are known to have potent antitumor and immunomodulatory activities. In 2000, Takahashi and coworkers reported[3] the bioassay guided isolation of four new sesquiterpenes enokipodins A-D **1-4** from the mycelial culture medium of *F. velutipes*, **Chart I**. Structurally, enokipodins A-D **1-4** are related to the less oxidised sesquiterpenes cuparene-1,4-diol **5** isolated[4] from the Japanese liverwort *Lejeunea aquatica*, HM-1 **6** isolated[5] from phytopathogenic fungus *Helicobasidium mompa* and the cuparene-1,4-quinone **7** isolated[6] from the liverwort *Radula javanica*, and more oxidised pigments lagopodins **8-10** isolated from the Basidiomycetes *Coprinus lagopus* and helicobasidins **11** and **12** isolated from the *Helicobasidium mompa*[6]. Enokipodins A-D exhibited significant antimicrobial activity against a fungus *Cladosporium herbarum* and Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* however, they were ineffective against Gram-negative bacteria.

Presence of a sterically crowded carbon framework coupled with biological properties made enokipodins **1-4** attractive synthetic targets. Since the first synthesis by us[7], there have been several reports[8] on the synthesis of enokipodins both in racemic as well as enantioselective manner. Recently, Mukherjee and coworkers[9] reported the first total synthesis of HM-1 methyl ether **13** and its conversion to cuparene-1,4-diol **5** and cuparene-1,4-quinone **7**. The interesting biological properties associated with the enokipodins **1-4** prompted us to investigate a Claisen rearrangement-RCM based methodology for the synthesis of enokipodins A-D **1-4** and cuparene-1,4-diol **5**, and herein we describe the details[7].

As the enokipodin A **1** is a hemiketal, retrosynthetic analysis (**Scheme I**) readily identified the cyclopentanone **14** as the ideal precursor for the generation of the enokipodins A **1** and B **2** as well as cuparene-1,4-diol **5**. It was envisaged that the cyclopentanone **14** could be obtained by RCM reaction of the hydroxydiene **15**. And the hydroxyldiene **15** could be obtained from 2,5-dimethoxy-4-methylacetophenone **17** *via* the allyl alcohol **16**.

The synthetic sequence is depicted in **Schemes II** and **III**. First attention was focused on the synthesis of the allyl alcohol **16**. Treatment of the acetophenone[10] **17** with sodium enolate of triethyl phosphonoacetate in refluxing THF for 5 hr furnished the *E*-cinnamate **18** in 88% yield, in a highly stereoselective manner, which on regioselective reduction at low temperature (–70°C) with LAH in dry ether furnished the allyl alcohol **16** in 91% yield. Thermal activation of the allyl alcohol **16** and ethyl vinyl ether in the presence of a catalytic amount of mercuric acetate at 175°C in a sealed tube[11], furnished the γ,δ-unsaturated

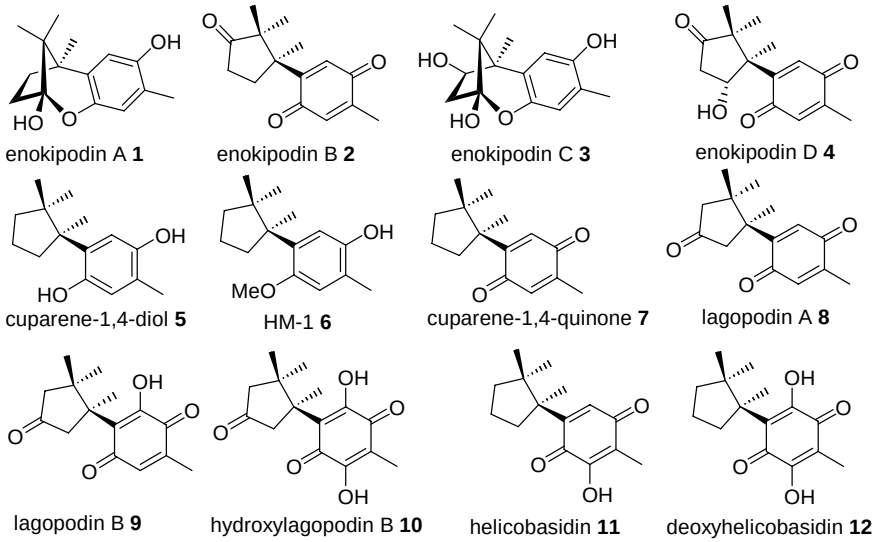
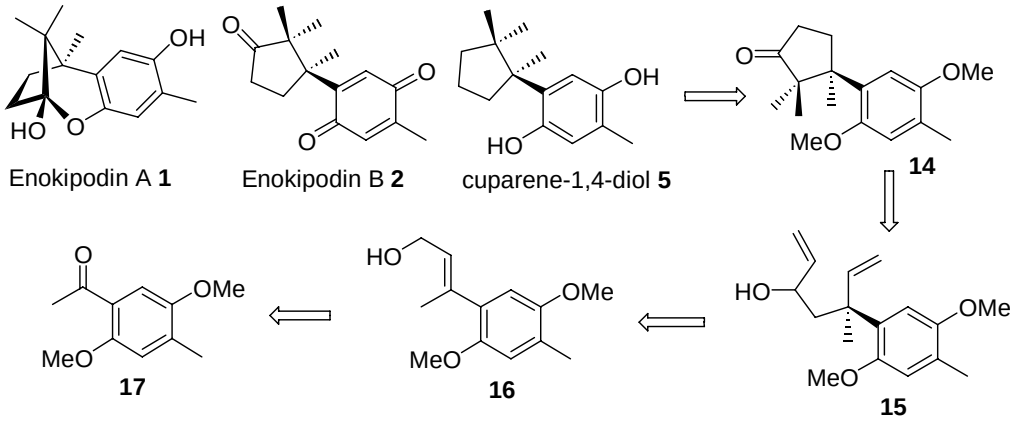



**Chart I**

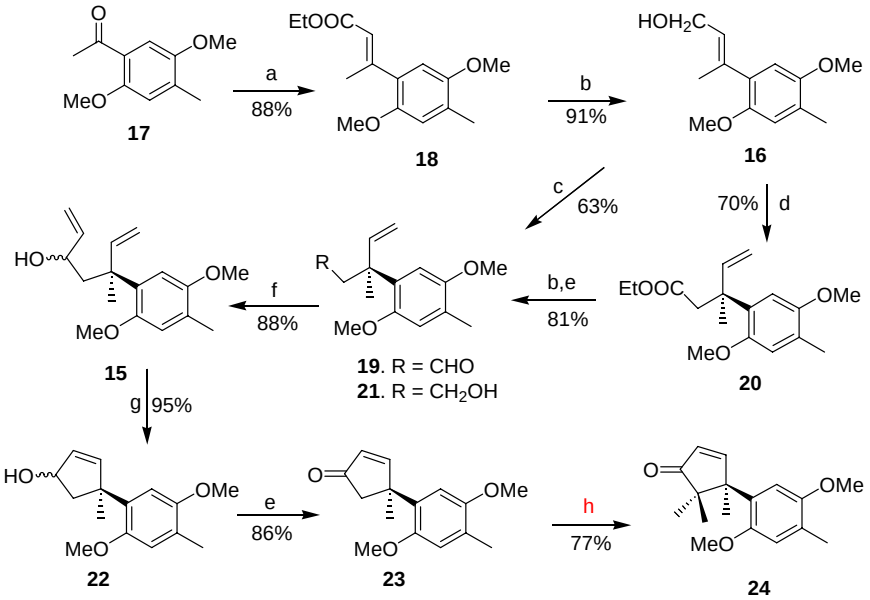
aldehyde **19** in 63% yield, whose structure was established from its spectral data. The pentenal **19** was also obtained *via* ortho ester variant[12] of the Claisen rearrangement with equal efficiency. Thermal activation of the allyl alcohol **16** with triethyl orthoacetate in the presence of a catalytic amount of propionic acid in a sealed tube at 180°C, generated the γ,δ-unsaturated ester **20** in 70% yield. Reduction of the ester **20** with LAH at –20°C furnished the alcohol **21** in 92% yield, which on oxidation using PCC and silica gel in methylene chloride for 1 hr furnished the aldehyde **19** in 87% yield. The aldehyde **19** was then converted into the cyclopentanone **14** employing the RCM based methodology. Thus, reaction of the aldehyde **19** with vinylmagnesium bromide in dry THF at RT for 1 hr furnished a 1:1 diastereomeric mixture of the hydroxydiene **15** in 88% yield. The RCM reaction[13] of the hydroxydiene **15** with 5 mole% of Grubbs' first generation catalyst in anhydrous methylene chloride for 4 hr at RT generated a 1:1 diastereomeric mixture of the cyclopentenol **22** in near quantitative yield. Oxidation of the cyclopentenol **22** using PCC and sodium acetate in methylene chloride at RT for 1 hr gave the cyclopentenone **23** in 86% yield, whose structure was established from its spectral data. Alkylation of the cyclopentenone **23** using sodium hydride and methyl iodide in dry THF and DMF created the second quaternary carbon and generated the enone **24** in 77% yield. Presence of three singlets at δ 1.48, 1.24 and 0.65 due to the tertiary methyl groups in the $^1$H NMR spectrum established the structure of the dialkylated cyclopentenone **24**, which was further confirmed by the $^{13}$C NMR spectrum. Hydrogenation of the enone **24** using 10% palladium over carbon as the catalyst at one atmosphere pressure (balloon) of hydrogen in ethanol for 1 hr furnished the cyclopentanone **14** in 92% yield.

It was obvious that hydrolysis of the two aromatic methoxy groups in the compound **14**, followed by formation of the hemiketal would generate enokipodin A **1**. As expected, demethylation of the compound **14** with boron tribromide in methylene chloride for 4 hr at 0°C to RT furnished directly enokipodin A **1** in 78% yield. As depicted in **Table I**, synthetic enokipodin A **1** exhibited $^1$H and $^{13}$C NMR spectral data[3a] identical to that of the natural compound. Even though it was clear that oxidation of enokipodin A **1** generates enokipodin B **2**, it was considered that direct oxidation of the dimethyl ether **14** would lead to enokipodin B **2**. Thus, reaction of the compound **14** with ceric ammonium nitrate (CAN) in aqueous acetonitrile for 1 hr at RT generated enokipodin B **2** in near quantitative yield. Comparision[3a] of the $^1$H and $^{13}$C NMR spectral data with that of the natural enokipodin B **2**, as given in the **Table II**, confirmed the structure of enokipodin B **2**. Since conversion of the enone **24** into enokipodins C **3** and D **4** has already been reported[8] via the corresponding epoxide, the present sequence also constitutes a formal total synthesis of enokipodins C and D.

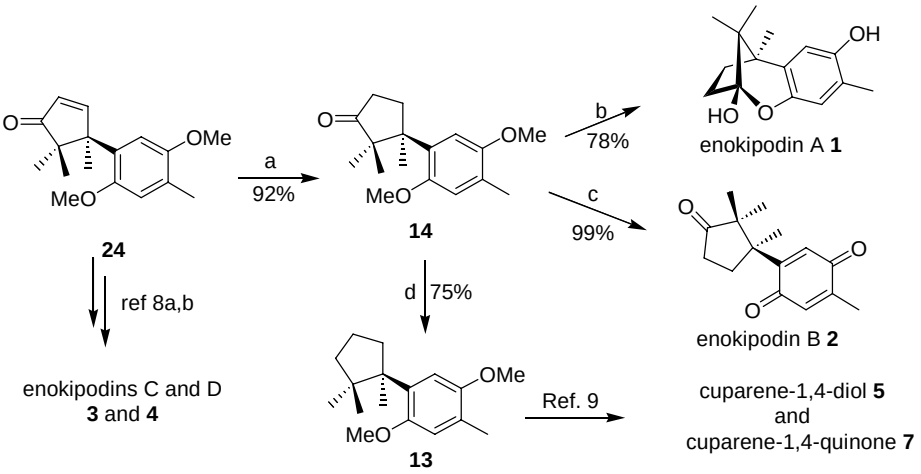
Wolff-Kishner reduction of the cyclopentanone **14** by treatment with hydrazine hydrate in digol for 3 hr




**Scheme I**




**Scheme II—** (a) NaH, $(EtO)_2P(O)CH_2COOEt$, THF; (b) LAH, $Et_2O$; (c) $CH_2$=CHOEt, $Hg(OAc)_2$; (d) $CH_3C(OEt)_3$, EtCOOH; (e) PCC, $CH_2Cl_2$; (f) $CH_2$=CHMgBr, THF; (g) $(Cy_3P)_2RuCl_2$=CHPh, $CH_2Cl_2$; (h) NaH, MeI, THF, DMF.




**Scheme III—** (a) $H_2$, 10%Pd/C, EtOH; (b) $BBr_3$, $CH_2Cl_2$; (c) CAN, MeCN-$H_2O$; (d) $NH_2NH_2.H_2O$, KOH, digol.

**Table I —** NMR spectra of enokipodin A **1**

| $^{1}$H NMR | | $^{13}$C NMR | |
|---|---|---|---|
| Present study[a] (300 MHz) | Literature[3a] (500 MHz) | Present study[a] (75 MHz) | Literature[3a] (125 MHz) |
| 6.54 (1 H, s) | 6.55 (1 H, s) | 147.5 (C) | 147.4 (C) |
| 6.50 (1 H, s) | 6.50 (1 H, s) | 146.1 (C) | 146.1 (C) |
| 4.34 (1 H, s, OH) | 4.30 (1 H, s, OH) | 131.1 (C) | 131.1 (C) |
| 2.77 (1 H, s, OH) | 2.74 (1 H, s, OH) | 122.4 (C) | 122.5 (C) |
| 2.17 (3 H, s, $CH_3$) | 2.16 (3 H, s) | 116.9 (CH, C-5) | 116.9 (CH) |
| 2.25-2.00 (2 H, m) | 2.17 (1 H, ddd, | 111.0 (CH, C-2) | 111.0 (CH) |
| 1.87 (1 H, ddd, | *J* = 14.3, 9.7 | 109.6 (C) | 109.6 (C) |
| 12.3, 11.1 | and 6.5 Hz) | 47.3 (C) | 47.3 (C) |
| and 6.9 Hz) | 2.09 (1 H, ddd, | 43.3 (C) | 43.3 (C) |
| 1.76 (1 H, ddd, | *J* = 14.3, 11.9 | 38.2 ($CH_2$) | 38.2 ($CH_2$) |
| *J* = 12.3, 9.6 | and 3.7 Hz) | 34.8 ($CH_2$) | 34.8 ($CH_2$) |
| and 3.3 Hz) | 1.90 (1 H, ddd, | 18.5 ($CH_3$) | 18.5 ($CH_3$) |
| 1.23 (3 H, s) | *J* = 12.7, 11.9 | 16.0 ($CH_3$) | 16.0 ($CH_3$) |
| 1.09 (3 H, s) | and 6.5 Hz) | 15.5 (2 C, $CH_3$) | 15.5 ($CH_3$) |
| 0.80 (3 H, s) | 1.78 (1 H, ddd, | | 15.49 ($CH_3$) |
| | *J* = 12.7, 9.7 | | |
| | and 3.7 Hz) | | |
| | 1.24 (3 H, s) | | |
| | 1.09 (3 H, s) | | |
| | 0.80 (3 H, s) | | |

**Table II —** NMR spectra of Enokipodin B **2**

| $^{1}$H NMR | | $^{13}$C NMR | |
|---|---|---|---|
| Present study[a] (300 MHz) | Literature[3a] (500 MHz) | Present study[a] (75 MHz) | Literature[3a] (125 MHz) |
| 6.66 (1 H, s, H-5) | 6.69 (1 H, s) | 219.9 (C, C=O) | 220.9 (C) |
| 6.55 (1 H, q, | 6.56 (1 H, s) | 187.8 (C, C=O) | 188.2 (C) |
| *J* = 1.5 Hz) | 2.49 (1 H, ddd, | 187.5 (C, C=O) | 187.8 (C) |
| 2.55-2.20 (3 H, m) | *J* = 19.3, 9.8 | 153.5 (C) | 153.5 (C) |
| 2.04 (3 H, d, | and 2.4 Hz) | 144.4 (C) | 144.4 (C) |
| *J* = 1.5 Hz, | 2.44 (1 H, ddd, | 135.3 (CH) | 135.3 (CH) |
| *olefinic*-$CH_3$) | *J* = 19.3, 10.4 | 134.1 (CH) | 134.1 (CH) |
| 1.87 (1 H, ddd, | and 8.7 Hz) | 52.3 (C) | 52.3 (C) |
| *J* = 12.7, 8.0 | 2.27 (1 H, ddd, | 49.0 (C) | 49.0 (C) |
| and 3.0 Hz) | *J* = 12.8, 10.4 | 33.7 ($CH_2$) | 33.7 ($CH_2$) |
| 1.32 (3 H, s) | and 9.8 Hz) | 31.2 ($CH_2$) | 31.1 ($CH_2$) |
| 1.22 (3 H, s) | 2.04 (3 H, s) | 23.2 ($CH_3$) | 23.1 ($CH_3$) |
| 0.75 (3 H, s) | 1.88 (1 H, ddd, | 22.3 ($CH_3$) | 22.1 ($CH_3$) |
| | *J* = 12.8, 8.7 | 20.6 ($CH_3$) | 20.6 ($CH_3$) |
| | and 2.4 Hz) | 15.0 ($CH_3$) | 14.9 ($CH_3$) |
| | 1.32 (3 H, s) | | |
| | 1.23 (3 H, s) | | |
| | 0.76 (3 H, s) | | |

at 125°C followed by treatment of the hydrazone with potassium hydroxide in digol for 12 hr at 190°C furnished the deoxygenated compound, HM-1 methyl ether **13** in 75% yield. It is worth mentioning that deoxygenation of the ketone **14** at 220°C (instead of 190°C) for longer time (3 days) led to the formation of cuparene-1,4-diol **5**. Since, conversion of HM-1 methyl ether **13** to cuparene-1,4-diol **5** and cuparene-1,4-quinone **7** has already been reported by Mukherjee and coworkers[9], the present sequence constitutes a formal synthesis of these sesquiterpenes also.

In conclusion, total synthesis of the antimicrobial sesquiterpenes enokipodins A and B **1** and **2**, and formal total synthesis of enokipodins C and D **3** and **4**, cuparene-1,4-diol **5** and cuparene-2,4-dione **7** have been accomplished employing a combination of Claisen rearrangement and RCM reaction based methodology.

## Experimental Section

IR spectra were recorded on a Jasco FTIR 410 spectrophotometer. $^1$H (300 MHz) and $^{13}$C NMR spectra (75 MHz) were recorded on a JNM λ-300 spectrometer. The chemical shifts (δ, ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for $^1$H) or the central line (77.0 ppm) of $CDCl_3$ (for $^{13}$C). In the $^{13}$C NMR spectra, the nature of the carbons (C, CH, $CH_2$ or $CH_3$) was determined by recording the DEPT-135 spectra, and is given in parentheses. Low-resolution mass spectra were recorded using a Shimadzu QP-5050A GCMS instrument using direct inlet mode. Relative intensities are given in parentheses. High-resolution mass spectra were recorded using Micromass Q-TOF micro mass spectrometer using electro-spray ionisation.

### Ethyl 3-(2,5-dimethoxy-4-methylphenyl)but-2-enoate, 18

A suspension of sodium hydride (185 mg, 60% dispersion in oil, 4.63 mmoles) in hexanes under nitrogen atmosphere was magnetically stirred for 10 min and the solvent was syringed out. The oil free NaH was then suspended in dry THF (3 mL) and cooled in an ice bath. Triethyl phosphonoacetate (1.08 mL, 5.40 mmoles) was added drop wise and the reaction-mixture was stirred for 30 min at RT. A solution of the ketone **17** (500 mg, 2.57 mmoles) in dry THF (3 mL) was added drop wise to the reaction-mixture and stirred for 12 hr at RT. The reaction was then quenched by careful addition of saturated aqueous $NH_4Cl$ solution and extracted with ether (3 × 4 mL). The combined ether extract was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the *E*-cinnamate **18** (598 mg, 88%), containing a small amount of *Z*-isomer, as oil[10]. IR (neat): 2979, 2935, 2850, 1715 (OC=O), 1632, 1505, 1464, 1397, 1374, 1335, 1273, 1234, 1212, 1166, 1142, 1044, 862, 808 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$ + $CCl_4$): δ 6.66 (1 H, s) and 6.58 (1 H, s) [Ar-H], 5.84 (1 H, br s, H-2), 4.18 (2 H, q, *J* = 6.9 Hz, $OCH_2CH_3$), 3.78 (3 H, s) and 3.76 (3 H, s) [2 × $OCH_3$], 2.47 (3 H, s, H-4), 2.20 (3 H, s, $ArCH_3$), 1.32 (3 H, t, *J* = 6.9 Hz, $OCH_2CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$ + $CCl_4$): δ 165.3 (C, OC=O), 152.9 (C), 151.5 (C), 148.9 (C, C-3), 127.9 (C), 126.5 (C), 118.9 (CH, C-2), 114.4 (CH, C-6'), 110.5 (CH, C-3'), 59.3 ($CH_2$, $OCH_2CH_3$), 56.2 ($CH_3$) and 55.7 ($CH_3$) [2 × $OCH_3$], 26.3 ($CH_3$, C-4), 16.5 ($CH_3$, $ArCH_3$), 14.2 ($CH_3$, $OCH_2CH_3$).

### 3-(2,5-Dimethoxy-4-methylphenyl)but-2-enol, 16

To a cold (–70°C) magnetically stirred solution of the ester **18** (550 mg, 2.08 mmoles) in dry ether (5 mL) was added LAH (39 mg, 1.04 mmoles) in one portion. The reaction-mixture was stirred at the same temperature for 2 hr and allowed to warm to –20°C over a period of 30 min. Ethyl acetate (2 mL) was carefully introduced to consume the excess reagent and the reaction was quenched with ice-cold water (5 mL). The solution was filtered through a sintered funnel and the residue thoroughly washed with ether (3 × 5 mL). The ether layer was separated, washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:5) as eluent furnished the cinnamyl alcohol **16** (420 mg, 91%) as oil[10]. IR (neat): 3365 (OH), 2929, 2852, 1648, 1500, 1464, 1396, 1375, 1210, 1178, 1043, 1001, 864, 811, 759, 758, 697 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$ + $CCl_4$): δ 6.61 (1 H, s) and 6.55 (1 H, s) [Ar-H], 5.62 (1 H, t, *J* = 6.9 Hz, H-2), 4.27 (2 H, d, *J* = 6.9 Hz, $CH_2OH$), 3.76 (3 H, s) and 3.73 (3 H, s) [2 × $OCH_3$], 2.18 (3 H, s, $ArCH_3$), 1.99 (3 H, s, H-4), 1.61 (1 H, br s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$ + $CCl_4$): δ 151.6 (C), 150.1 (C), 138.5 (C), 131.7 (C), 128.2 (CH, C-2), 126.0 (C), 114.3 (CH, C-6'), 111.8 (CH, C-3'), 59.5

($CH_2$, C-1), 56.1 ($CH_3$) and 55.8 ($CH_3$) [2 × $OCH_3$], 17.5 ($CH_3$, C-4), 16.4 ($CH_3$, $ArCH_3$); MS: *m/z* (%) 222 ($M^+$, 70), 207 (22), 191 (16), 189 (17), 179 (100), 175 (20), 164 (20), 149 (16), 103 (15), 91 (30), 84 (30); HRMS: *m/z* Calcd. for $C_{13}H_{18}O_3Na$ (M+Na): 245.1154. Found: 245.1145.

**Ethyl 3-methyl-3-(2,5-dimethoxy-4-methylphenyl)-pent-4-enoate, 20**

A solution of the allyl alcohol **16** (400 mg, 1.80 mmoles), triethyl orthoacetate (4.5 mL, 24.6 mmoles) and a catalytic amount (*ca* 5 μL) of propionic acid was placed in a Carius tube under nitrogen atmosphere and heated to 180°C for 48 hr. The reaction-mixture was cooled, diluted with ether (3 × 4 mL), washed with 0.5 *N* aqueous HCl followed by saturated aqueous $NaHCO_3$ solution and brine, and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:10) as eluent gave the ester **20** (370 mg, 70%) as oil. IR (neat): 3080, 2979, 2940, 2838, 1733 (OC=O), 1635, 1502, 1467, 1392, 1369, 1309, 1212, 1125, 1046, 915 ($CH=CH_2$), 867, 798, 692 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.70 (1 H, s) and 6.63 (1 H, s) [Ar-H], 6.32 (1 H, dd, *J* = 17.1 and 10.5 Hz, C*H*=$CH_2$), 5.04 (1 H, d, *J* = 10.5 Hz) and 4.99 (1 H, d, *J* = 17.1 Hz) [CH=C$H_2$], 3.94 (2 H, q, *J* = 7.0 Hz, OC$H_2$$CH_3$), 3.78 (3 H, s) and 3.76 (3 H, s) [2 × $OCH_3$], 3.05 and 2.85 (2 H, 2 × d, *J* = 14.4 Hz, H-2), 2.17 (3 H, s, $ArCH_3$), 1.56 (3 H, s, *tert*-$CH_3$), 1.08 (3 H, t, *J* = 7.0 Hz, $OCH_2CH_3$); $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$): δ 171.4 (C, OC=O), 151.6 (C), 151.3 (C), 145.9 (CH, C-4), 131.7 (C), 125.2 (C), 115.0 (CH, C-6'), 111.4 ($CH_2$, C-5), 111.0 (CH, C-3'), 59.5 ($CH_2$, $OCH_2CH_3$), 55.7 (2 C, $CH_3$), 43.8 ($CH_2$, C-2), 42.9 (C, C-3), 24.8 ($CH_3$, *tert*-$CH_3$), 16.2 ($CH_3$, $ArCH_3$), 14.3 ($CH_3$, $OCH_2CH_3$); MS: *m/z* (%) 292 ($M^+$, 38), 205 (100), 190 (15), 174 (23); HRMS: *m/z* Calcd. for $C_{17}H_{24}O_4Na$ (M+Na): 315.1572. Found: 315.1569.

**3-Methyl-3-(2,5-dimethoxy-4-methylphenyl)pent-4-enol, 21**

Reduction of the pentenoate **20** (350 mg, 1.20 mmoles) in dry ether (4 mL) using LAH (23 mg, 0.60 mmole) at –20°C for 2 hr, and work up as described for the alcohol **16**, followed by purification on a silica gel column using ethyl acetate-hexane (1:5) as eluent furnished the primary alcohol **21** (275 mg, 92%) as oil. IR (neat): 3366 (OH), 3082, 2934, 1634, 1504, 1463, 1391, 1211, 1044, 915 ($CH=CH_2$), 864, 816, 764, 701 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.68 (1 H, s) and 6.64 (1 H, s) [Ar-H], 6.22 (1 H, dd, *J* = 17.4 and 10.5 Hz, C*H*=$CH_2$), 5.01 (1 H, d, *J* = 10.5 Hz) and 4.97 (1 H, d, *J* = 17.4 Hz) [CH=C$H_2$], 3.76 (6 H, s, 2 × $OCH_3$), 3.60-3.40 (2 H, m, $CH_2OH$), 2.33 and 2.07 (2 H, t of AB q, *J* = 12.9 and 7.0 Hz, H-2), 2.16 (3 H, s, $ArCH_3$), 1.44 (3 H, s, *tert*-$CH_3$), 1.20 (1 H, br s, OH); $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$): δ 151.8 (C), 151.5 (C), 147.1 (CH, C-4), 132.4 (C), 125.2 (C), 115.4 (CH, C-6'), 111.0 (CH, C-3'), 110.9 ($CH_2$, C-5), 60.4 ($CH_2$, C-1), 55.8 (2 C, $CH_3$), 43.1 (C, C-3), 41.7 ($CH_2$, C-2), 25.0 ($CH_3$, *tert*-$CH_3$), 16.1 ($CH_3$, $ArCH_3$); MS: *m/z* (%) ($C_{15}H_{22}O_3$) 250 ($M^+$, 43), 206 (16), 205 (100), 190 (17), 175 (19), 174 (24), 91 (13).

**3-Methyl-3-(2,5-dimethoxy-4-methylphenyl)pent-4-enal, 19**

**Method 1**

To a magnetically stirred suspension of PCC (447 mg, 2.08 mmoles) and silica gel (447 mg) in dry $CH_2Cl_2$ (2 mL) was added a solution of the primary alcohol **21** (260 mg, 1.04 mmoles) in $CH_2Cl_2$ (2 mL) and stirred vigorously for 1 hr at RT. The reaction-mixture was then filtered through a small silica gel column, and the column eluted with more $CH_2Cl_2$. Evaporation of the solvent furnished the aldehyde **19** (225 mg, 87%) as oil.

**Method 2**

A solution of the allyl alcohol **16** (200 mg, 0.90 mmole), ethyl vinyl ether (1.3 mL, 13.5 mmoles) and mercuric acetate (20 mg) was heated to 175°C for 48 hr in a Carius tube under nitrogen atmosphere. The reaction-mixture was then cooled, diluted with ether, washed with aqueous $NaHCO_3$ solution and brine, and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the aldehyde **19** (140 mg, 63%) as oil. IR (neat): 2968, 2840, 2730 (H-C=O), 1721 (C=O), 1635, 1495, 1456, 1394, 1212, 1042, 918 ($CH=CH_2$), 763, 701 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): δ 9.46 (1 H, t, *J* = 2.7 Hz, $CH_2$C*H*O), 6.70 (1 H, s) and 6.67 (1 H, s) [Ar-H], 6.22 (1 H, dd, *J* = 17.4 and 10.5 Hz, C*H*=$CH_2$), 5.10 (1 H, d, *J* = 10.5 Hz) and 5.02 (1 H, d, *J* = 17.4 Hz) [CH=C$H_2$], 3.77 (3 H, s) and 3.76 (3 H, s) [2 × $OCH_3$], 3.02 and 2.85 (2 H, d of AB q, *J* = 15.6 and 2.7 Hz, H-2), 2.17 (3 H, s, $ArCH_3$), 1.53 (3 H, s, *tert*-$CH_3$); $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$): δ 202.3

(CH, CHO), 151.6 (C), 151.3 (C), 145.5 (CH, C-4), 130.6 (C), 125.9 (C), 115.2 (CH, C-6'), 112.1 ($CH_2$, C-5), 110.8 (CH, C-3'), 55.8 ($CH_3$) and 55.6 ($CH_3$) [2 × $OCH_3$], 51.8 ($CH_2$, C-2), 42.3 (C, C-3), 25.6 ($CH_3$, *tert*-$CH_3$), 16.1 ($CH_3$, $ArCH_3$); MS: *m/z* (%) 248 ($M^+$, 50), 205 (100), 190 (22), 175 (22), 174 (33); HRMS: *m/z* Calcd. for $C_{15}H_{20}O_3Na$ (M+Na): 271.1310. Found: 271.1300.

**5-Methyl-5-(2,5-dimethoxy-4-methylphenyl)hepta-1,6-dien-3-ol, 15**

To a magnetically stirred solution of the aldehyde **19** (200 mg, 0.80 mmole) in THF (2 mL) was added vinylmagnesium bromide [prepared from magnesium (88 mg, 3.66 mmoles) and bromoethylene (0.5 mL, 7.3 mmoles) in THF (2 mL)] and stirred for 1 hr at RT. The reaction was quenched with aqueous $NH_4Cl$ solution and extracted with ether (3 × 4 mL). The organic layer was washed with water and brine, and dried (anhyd. $Na_2SO_4$). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished a 1:1 diastereomeric mixture of the hydroxydiene **15** (196 mg, 88%) as oil. IR (neat): 3446 (OH), 3080, 2933, 2843, 1635, 1503, 1464, 1391, 1373, 1211, 1044, 994, 916 ($CH=CH_2$), 864, 793, 702 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ + $CCl_4$, 1:1 mixture of diastereomers): δ 6.72 and 6.71 (1 H, s), 6.64 and 6.63 (1 H, s), 6.33 and 6.29 (1 H, 2 × dd, *J* = 17.7 and 11.1 Hz, H-6), 5.82-5.65 (1 H, m, H-2), 5.15-4.85 (4 H, m, H-1 and 7), 4.10-3.75 (1 H, m, C*H*OH), 3.76 (3 H, s) and 3.75 (3 H, s) [2 × $OCH_3$], 2.26 (1 H, m), 2.14 (3 H, s, $ArCH_3$), 2.00 (1 H, m), 1.50 and 1.44 (3 H, s, *tert*-$CH_3$), 1.42 (1 H, br s, OH); $^{13}C$ NMR (75 MHz, $CDCl_3$ + $CCl_4$, 1:1 mixture of diastereomers): δ 151.6 (C), 151.5 (C), 147.5 & 147.4 (CH, C-6), 142.4 & 142.3 (CH, C-2), 132.2 & 132.1 (C), 125.4 & 125.3 (C), 115.3 (CH, C-6'), 113.0 & 112.9 ($CH_2$), 111.2 (CH, C-3'), 110.8 ($CH_2$), 70.9 & 70.8 (CH, C-3), 55.8 ($CH_3$) and 55.7 ($CH_3$) [2 × $OCH_3$], 46.4 & 46.0 ($CH_2$, C-4), 43.6 (C, C-5), 25.5 ($CH_3$), 16.1 ($CH_3$); MS: *m/z* (%) 276 ($M^+$, 39), 206 (23), 205 (100), 190 (23), 175 (25), 174 (35), 153 (28), 135 (15), 91 (20); HRMS: *m/z* Calcd. for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623. Found: 299.1630.

**4-Methyl-4-(2,5-dimethoxy-4-methylphenyl)cyclo-pent-2-enol, 22**

To a magnetically stirred solution of a 1:1 diastereomeric mixture of the hydroxydiene **15** (50 mg, 0.18 mmole) in anhydrous $CH_2Cl_2$ (2 mL) was added a solution of Grubbs' first generation catalyst (7 mg, 6 mole%) in anhydrous $CH_2Cl_2$ (3 mL) and the reaction-mixture was stirred at RT for 4 hr. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column by using ethyl acetate-hexane (1:5) as eluent furnished a 1:1 diastereomeric mixture of the cyclopentenol **22** (43 mg, 95%) as oil. IR (neat): 3383 (OH), 3048, 2930, 2866, 1501, 1465, 1392, 1371, 1210, 1180, 1044, 881, 861, 781 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ + $CCl_4$, 1:1 mixture of diastereomers): δ 6.69 (1 H, s, Ar-H), 6.68 and 6.61 (1 H, s, Ar-H), 6.25 (1 H, d, *J* = 5.4 Hz, H-3), 5.90-5.80 (1 H, m, H-2), 4.90-4.75 (1 H, m, H-1), 3.83 (3 H, s, $OCH_3$), 3.81 and 3.79 (3 H, s, $OCH_3$), 2.70-2.60 (1 H, m), 2.21 and 2.20 (3 H, s, $ArCH_3$), 2.18-1.85 (1 H, m), 1.75 (1 H, br s, OH), 1.56 & 1.44 (3 H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$ + $CCl_4$, 1:1 mixture of diastereomers): δ 151.2 (C), 151.0 (C), 142.6 (CH, C-3), 135.2 & 134.7 (C), 132.1 & 131.9 (CH, C-2), 124.8 & 124.7 (C), 115.3 & 114.8 (CH), 109.5 & 109.3 (CH), 77.2 (CH, C-1), 55.8 ($CH_3$) and 55.6 ($CH_3$) [2 × $OCH_3$], 51.6 & 50.4 (C, C-4), 49.4 & 48.8 ($CH_2$, C-5), 29.5 & 28.1 ($CH_3$, *tert*-$CH_3$), 16.1 ($CH_3$, $ArCH_3$); MS: *m/z* (%) 248 ($M^+$, 48), 234 (9), 233 (100), 231 (18), 152 (17); HRMS: *m/z* Calcd. for $C_{15}H_{19}O_2$ (M–OH): 231.1385. Found: 231.1399.

**4-Methyl-4-(2,5-dimethoxy-4-methylphenyl)cyclo-pent-2-enone, 23**

To a magnetically stirred suspension of PCC (73 mg, 0.34 mmole) and sodium acetate (28 mg, 0.34 mmole) in $CH_2Cl_2$ (2 mL) was added a solution of a 1:1 diastereomeric mixture of the alcohol **22** (42 mg, 0.17 mmole) in $CH_2Cl_2$ (2 mL) in one portion. The reaction-mixture was stirred at RT for 1 hr, filtered through a silica gel column, and the column eluted with more $CH_2Cl_2$. Evaporation of the solvent furnished the enone **23** (35 mg, 86%) as oil. IR (neat): 2930, 2846, 1714 (C=O), 1589, 1503, 1465, 1394, 1212, 1042, 859, 798 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ + $CCl_4$): δ 7.70 (1 H, d, *J* = 6.9 Hz, H-3), 6.63 (1 H, s) and 6.56 (1 H, s) [Ar-H], 6.09 (1 H, d, *J* = 6.9 Hz, H-2), 3.75 (3 H, s) and 3.73 (3 H, s) [2 × $OCH_3$], 2.70 and 2.50 (2 H, AB q, *J* = 18.6 Hz, H-5), 2.15 (3 H, s, $ArCH_3$), 1.54 (3 H, s, *tert*-$CH_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$ + $CCl_4$): δ 208.7 (C, C=O), 169.8 (CH, C-3), 151.3 (C), 151.1 (C), 131.3 (CH, C-2), 131.0 (C), 125.8 (C), 114.8 (CH, C-6'), 109.6 (CH, C-3'),

55.9 ($CH_3$) and 55.5 ($CH_3$) [2 × $OCH_3$], 50.3 ($CH_2$, C-5), 47.1 (C, C-4), 27.6 ($CH_3$, *tert*-$CH_3$), 16.1 ($CH_3$, $ArCH_3$); MS: *m/z* (%) 246 ($M^+$, 96), 231 (100), 216 (16), 203 (15), 188 (14), 173 (15), 128 (12), 115 (19), 91 (18); HRMS: *m/z* Calcd. for $C_{15}H_{19}O_3$ (M+1): 247.1334. Found: 247.1337.

**4-(2,5-Dimethoxy-4-methylphenyl)-4,5,5-trimethyl-cyclopent-2-enone, 24**

To a magnetically stirred suspension of NaH (34 mg, 60% dispersion in oil, 0.84 mmole, washed with dry hexanes) in THF (1 mL) was added a solution of the ketone **23** (35 mg, 0.14 mmole) in THF (2 mL) and DMF (2 mL), and stirred for 40 min at RT. To the reaction-mixture was added methyl iodide (0.05 mL, 0.84 mmole) and stirred for 12 hr at RT. It was then quenched with water (3 mL) and extracted with ether (3 × 3 mL). The combined ether extract was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the ketone **24** (30 mg, 77%) as oil. IR (neat): 2963, 1707 (C=O), 1600, 1505, 1465, 1393, 1375, 1213, 1044, 861, 834, 789 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ + $CCl_4$): δ 7.84 (1 H, d, *J* = 6.0 Hz, H-3), 6.66 (1 H, s) and 6.45 (1 H, s) [Ar-H], 6.10 (1 H, d, *J* = 6.0 Hz, H-2), 3.78 (3 H, s) and 3.76 (3 H, s) [2 × $OCH_3$], 2.19 (3 H, s, $ArCH_3$), 1.48 (3 H, s), 1.24 (3 H, s) and 0.65 (3 H, s) [3 × *tert*-$CH_3$]; $^{13}C$ NMR (75 MHz, $CDCl_3$ + $CCl_4$): δ 214.2 (C, C=O), 170.2 (CH, C-3), 151.6 (C), 151.5 (C), 129.8 (C), 127.0 (CH, C-2), 125.8 (C), 114.6 (CH, C-6'), 111.2 (CH, C-3'), 56.0 ($CH_3$) and 55.4 ($CH_3$) [2 × $OCH_3$], 54.8 (C, C-5), 50.9 (C, C-4), 25.8 ($CH_3$), 20.1 ($CH_3$), 16.2 (2 C, $CH_3$); MS: *m/z* (%) 274 ($M^+$, 42), 260 (17), 259 (100), 244 (13), 229 (12), 216 (10); HRMS: *m/z* Calcd. for $C_{17}H_{22}O_3Na$ (M+Na): 297.1467. Found: 297.1466.

**3-(2,5-Dimethoxy-4-methylphenyl)-2,2,3-trimethyl-cyclopentanone, 14**

To the activated 10% Pd-C (5 mg) was added a solution of the enone **24** (25 mg, 0.09 mmole) in ethanol (2 mL). The reaction-mixture was stirred for 1 hr at RT in an atmosphere of hydrogen, created by evacuative replacement of air (balloon) and then the catalyst was filtered off. Evaporation of the solvent furnished the cyclopentanone **14** (23 mg, 92%) as oil. IR (neat): 2960, 2930, 2847, 1735 (C=O), 1505, 1464, 1391, 1372, 1213, 1043, 859, 787 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ + $CCl_4$): δ 6.78 (1 H, s) and 6.62 (1 H, s) [Ar-H], 3.78 (3 H, s) and 3.70 (3 H, s) [2 × $OCH_3$], 2.65-2.30 (3 H, m), 2.18 (3 H, s, $ArCH_3$), 2.15-1.90 (1 H, m), 1.37 (3 H, s), 1.20 (3 H, s) and 0.67 (3 H, s) [3 × *tert*-$CH_3$]; $^{13}C$ NMR (75 MHz, $CDCl_3$ + $CCl_4$): δ 221.4 (C, C=O), 151.9 (C), 151.4 (C), 132.5 (C), 125.2 (C), 114.4 (CH, C-6'), 111.2 (CH, C-3'), 56.0 ($CH_3$) and 54.8 ($CH_3$) [2 × $OCH_3$], 52.7 (C, C-2), 48.9 (C, C-3), 34.3 ($CH_2$), 32.7 ($CH_2$), 23.7 ($CH_3$), 21.9 ($CH_3$) and 21.7 ($CH_3$) [3 × *tert*-$CH_3$], 16.0 ($CH_3$, $ArCH_3$); MS: *m/z* (%) 276 ($M^+$, 92), 261 (28), 227 (16), 205 (100), 192 (27), 177 (32), 175 (24), 174 (22), 149 (24), 105 (15), 91 (28); HRMS: *m/z* Calcd. for $C_{17}H_{25}O_3$ (M+1): 277.1803. Found: 277.1803.

**1,5,12,12-Tetramethyl-8-oxatricyclo[7.2.1.0$^{2,7}$]dodeca-2,4,6-trien-4,9-diol (Enokipodin A 1)**

A solution of $BBr_3$ (0.12 mL, 1 *M* $CH_2Cl_2$ solution, 0.12 mmole) was added drop wise to a magnetically stirred solution of the ketone **14** (8 mg, 0.03 mmole) in $CH_2Cl_2$ (2 mL) at 0°C and the reaction-mixture was stirred for 2 hr at RT. It was then quenched with saturated aqueous $NaHCO_3$ solution and extracted with $CH_2Cl_2$ (3 × 3 mL). The combined $CH_2Cl_2$ extract was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:5) as eluent furnished enokipodin A **1** (5.5 mg, 78%), which was recrystallized from ether. m.p. 135-136°C. (lit.[3a] 138.5-138.9°C); IR (neat): 3390 (OH), 2928, 1494, 1288, 1194, 1146, 1036, 992, 943, 905, 871, 853 $cm^{-1}$; $^1H$ and $^{13}C$ NMR spectra are given in **Table I**; MS: *m/z* (%) 248 ($M^+$, 37), 178 (9), 177 (100), 162 (32), 149 (67); HRMS: *m/z* Calcd. for $C_{15}H_{20}O_3Na$ (M+Na): 271.1310. Found: 271.1307.

**5-Methyl-2-(3-oxo-1,2,2-trimethylcyclopentyl)benzoquinone (Enokipodin B 2)**

To a magnetically stirred solution of the ketone **14** (7 mg, 0.02 mmole) in $CH_3CN$ (0.6 mL) and $H_2O$ (0.6 mL) was added CAN (27 mg, 0.05 mmole). The reaction-mixture was stirred at RT for 1 hr and extracted with $CH_2Cl_2$ (3 × 3 mL). The combined $CH_2Cl_2$ layer was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the enokipodin B **2** (5.7 mg, 95%) as a semi solid. IR (neat): 2964, 1732 (C=O), 1650 (C=O), 1456, 1346, 1251, 1066, 998, 932, 842 $cm^{-1}$; $^1H$ and $^{13}C$ NMR spectra are given in **Table II**; MS: *m/z* (%) 246 ($M^+$,

3), 231 (8), 218 (20), 203 (12), 191 (16), 190 (47), 175 (100), 161 (21), 147 (16), 133 (5); HRMS: *m/z* Calcd. for $C_{15}H_{18}O_3Na$ (M+Na): 269.1154. Found: 269.1166.

### 1-(2,5-Dimethoxy-4-methylphenyl)-1,2,2-trimethyl-cyclopentane (HM-1 methyl ether 13)

A solution of the ketone **14** (8 mg, 0.03 mmole), KOH (17 mg, 0.3 mmole) and $NH_2NH_2.H_2O$ (0.03 mL, 0.6 mmole) in digol (2 mL) was taken in a sealed tube and heated to 125°C for 3 hr and then to 190°C for 12 hr. The reaction-mixture was then cooled, acidified with 3 *N* aqueous HCl (5 mL) and extracted with $CH_2Cl_2$ (3 × 3 mL). The combined $CH_2Cl_2$ extract was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished HM-1 methyl ether **13** (5.7 mg, 75%) as oil[9]. IR (neat): 2954, 2872, 1504, 1463, 1389, 1372, 1260, 1212, 1181, 1048, 861, 808, 704 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.77 (1 H, s) and 6.60 (1 H, s) [Ar-H], 3.77 (3 H, s) and 3.73 (3 H, s) [2 × $OCH_3$], 2.55-2.40 (1 H, m), 2.17 (3 H, s, $ArCH_3$), 1.85-1.50 (5 H, m), 1.34 (3 H, s), 1.14 (3 H, s) and 0.70 (3 H, s) [3 × *tert*-$CH_3$]; $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$): δ 152.6 (C), 151.1 (C), 133.9 (C), 124.4 (C), 115.0 (CH, C-6'), 112.1 (CH, C-3'), 56.0 ($CH_3$) and 55.5 ($CH_3$) [2 × $OCH_3$], 51.4 (C), 44.6 (C), 41.9 ($CH_2$), 40.0 ($CH_2$), 27.6 ($CH_3$), 26.0 ($CH_3$), 23.4 ($CH_3$), 20.8 ($CH_2$, C-4), 16.0 ($CH_3$, $ArCH_3$); MS: *m/z* (%) 262 ($M^+$, 91), 248 (15), 205 (21), 192 (45), 191 (23), 179 (100), 177 (30), 165 (33), 152 (32), 149 (26).

## References


1 (a) Fraga B M, *Nat Prod Rep*, 2, **1985**, 147; (b) *ibid* 3, **1986**, 273; (c) *ibid* 4, **1987**, 473; (d) *ibid* 5, **1988**, 497; (e) *ibid* 7, **1990**, 61 and 515; (f) *ibid* 9, **1992**, 217 and 557; (g) *ibid* 10, **1993**, 397; (h) *ibid* 11, **1994**, 533; (i) *ibid* 12, **1995**, 303; (j) *ibid* 13, **1996**, 307; (k) *ibid* 14, **1997**, 145; (l) *ibid* 15, **1998**, 73; (m) *ibid* 16, **1999**, 21 and 711; (n) *ibid* 17, **2000**, 483; (o) *ibid* 18, **2001**, 650; (p) *ibid* 19, **2002**, 650; (q) *ibid* 20, **2003**, 392; (r) *ibid* 21, **2004**, 669; (s) *ibid* 22, **2005**, 465; (t) *ibid* 23, **2006**, 943; (u) *ibid* 24, **2007**, 1350; (v) *ibid* 25, **2008**, 1180; (w) *ibid* 26, **2009**, 1125.

2 (a) Heathcock C H, *The Total Synthesis of Natural Products*, Vol. 2, edited by J ApSimon, (Wiley, New York) **1973**, pp. 197-558; (b) Heathcock C H, Graham S L, Pirrung M C, Plavac F & White C T, *The Total Synthesis of Natural Products*, Vol. 5, edited by J ApSimon, (Wiley, New York) **1983**; (c) *The Total Synthesis of Natural Products*, Vol. 10, Acyclic and Monocyclic Sesquiterpenes, part A, edited by M C Pirrung & A T Morehead, (Wiley, New York) **1997**; (d) *The Total Synthesis of Natural Products*, Vol. 11, Bicyclic and Tricyclic Sesquiterpenes, part B, edited by M C Pirrung, A T Morehead & B G Young, (Wiley, New York) **1999**.

3 (a) Ishikawa N K, Yamaji K, Taharab S, Fukushi Y & Takahashi K, *Phytochemistry*, 54, **2000**, 777; (b) Ishikawa N K, Fukushi Y, Yamaji K, Tahara S & Takahashi K, *J Nat Prod*, 64, **2001**, 932.

4 Toyota M, Koyama H & Asakawa Y, *Phytochemistry*, 46, **1997**, 145.

5 Kajimoto T, Yamashita M, Imamura Y, Takahashi K, Nohara T & Shibata M, *Chem Lett*, **1989**, 527.

6 Asakawa Y, Kondo K & Tori M, *Phytochemistry*, 30, **1991**, 325.

7 Preliminary communication: Srikrishna A & Srinivasa Rao M, *Synlett*, **2004**, 374.

8 (a) Kuwahara S & Saito M, *Tetrahedron Lett*, 45, **2004**, 5047; (b) Kuwahara S & Saito M, *Biosci Biotechnol Biochem*, 69, **2005**, 374; (c) Srikrishna A, Lakshmi B V & Ravikumar P C, *Tetrahedron Lett*, 47, **2006**, 1277; (d) Secci F, Frongia A, Ollivier J & Piras P P, *Synthesis*, **2007**, 999; (e) Yoshida M, Shoji Y & Shishido K, *Org Lett*, 11, **2009**, 1441; (f) Luján-Montelongo J A & Ávila-Zárraga J G, *Tetrahedron Lett*, 51, **2010**, 2232.

9 (a) Pal A, Gupta P D, Roy A & Mukherjee D, *Tetrahedron Lett*, 40, **1999**, 4733; (b) Paul T, Pal A, Gupta P D & Mukherjee D, *Tetrahedron Lett*, 44, **2003**, 737.

10 Fuganti C & Serra S, *J Chem Soc, Perkin Trans 1*, **2000**, 3758.

11 (a) Claisen L, *Chem Ber*, 45, **1912**, 3157; (b) McKenzie T C, *Org Prep Proc Int*, **1987**, 435.

12 Johnson W S, Werthemann L, Bartlett W R, Brocksom T J, Li T T, Faulkner D J & Petersen R, *J Am Chem Soc*, 92, **1970**, 741.

13 (a) Grubbs R H & Chang S, *Tetrahedron*, 54, **1998**, 4413; (b) Fürstner A, *Angew Chem Int Ed (Engl)*, 39, **2000**, 3013; (c) Trnka T M & Grubbs R H, *Acc Chem Res*, 34, **2001**, 18; (d) Grubbs R H, *Handbook of Metathesis*, Vol. 2 (Wiley-VCH), **2003**.