

Total Synthesis of (±)-Parvifoline and (±)-Isoparvifolinone

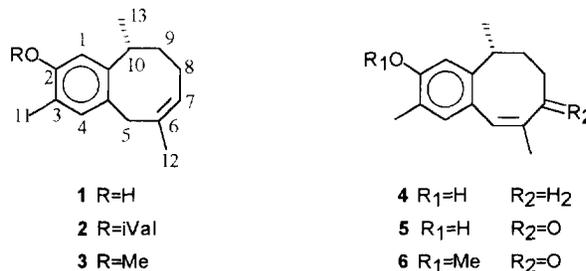
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Abstract. The total synthesis of the unusual trimethylbenzocyclooctenes (±)-parvifoline (**1**) and (±)-isoparvifolinone (**5**) have been achieved by using the Grob fragmentation reaction of mesylate **25** as the key step.

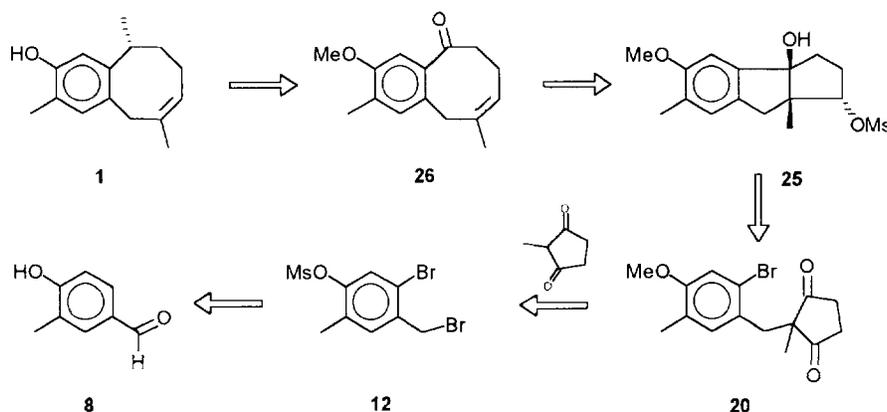
Parvifoline (**1**) and isoparvifolinone (**5**) are two unusual sesquiterpene derivatives isolated from the genera *Coreopsis*¹ and *Perezia*². These compounds, together with parvifoline isovalerate (**2**), are up to now the only natural substances which contain a trimethylbenzocyclooctane skeleton. The absolute configuration of parvifoline (**1**) was determined³ by chemical transformation into (–)-curcuquinone⁴ and the preferred conformation of four trimethylbenzocyclooctane derivatives prepared from **1** were deduced.^{3a}

The construction of an eight-membered ring⁵ and the presence of a double bond in a position which is next to conjugation are two structural features that challenge the synthesis of **1**. A previous attempt to synthesize parvifoline (**1**), which in fact afforded 2-hydroxycalamenene,⁶ as well as the synthesis of isoparvifoline⁷ (**4**) constitute the initial efforts for these molecules.



Recently, two total syntheses of parvifoline (**1**) were described. In the first⁸ of them, the key step was a modified Stork-Landesman ring expansion, while in the second⁹ case, the key step was an intramolecular cyclization of an ester sulfone to afford a ketosulfone. We now detail our total synthesis¹⁰ of (±)-parvifoline (**1**) and (±)-isoparvifolinone (**5**) from 4-hydroxy-3-methylbenzaldehyde (**8**) in which the key step is a stereospecific Grob fragmentation reaction.¹¹

As shown in the antithetic evaluation depicted in Scheme 1, parvifoline (**1**) would be obtained from benzocyclooctenone **26** by introduction of a methyl group using a Grignard type reagent (MeLi or MeMgI), followed by substitution of the resulting tertiary hydroxyl group by a hydrogen atom and removal of the ethereal protecting methyl group. Ketone **26** can in turn be prepared from mesylate **25** by means of the Grob fragmentation reaction.¹¹ This is considered the crucial step in the present synthesis, since the relative stereochemistry of the tertiary hydroxyl group and the leaving group induce the geometry of the double bond in the product. Mesylate **25** can be available from arylcyclopentanedione **20** by an intramolecular coupling reaction of the carbonyl group with the anion formed by treatment of halide **20** with lithium or magnesium. The construction of **20** can result from condensation of 2-methyl-1,3-cyclopentanedione with dihalide **12** which in turn is available from 4-hydroxy-3-methylbenzaldehyde (**8**) by protection of the hydroxyl group, conversion of the carbonyl group into a benzyl halide and reaction with bromine in the presence of iron.

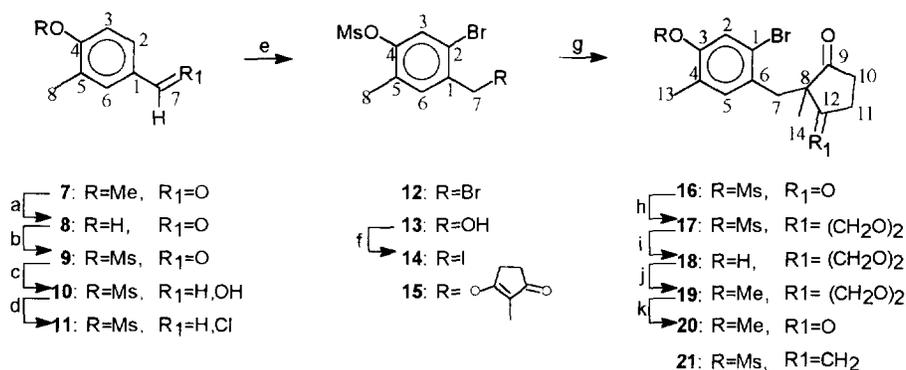


Scheme 1. Antithetic analysis for parvifoline (**1**).

Since an attempt to directly introduce a bromine atom at C-2 in 3-methyl-*p*-anisaldehyde (**7**) (Scheme 2)¹² failed, it was necessary to prepare mesylate **9** from **8**, followed by sodium borohydride in methanol reduction to afford compound **10**, which was then converted into chloride **11** by treatment with thionyl chloride in benzene and finally treated with bromine in the presence of iron to yield the desired dihalide **12** in 89% yield.

The reaction of dibromide **12** with 2-methyl-1,3-cyclopentanedione¹³ in dimethylformamide in the presence of potassium carbonate afforded the *O*-alkylated and the *C*-alkylated products **15** and **16**, respectively, in a 2.1:1.0 ratio. When instead of dimethylformamide a mixture of H₂O:*t*-BuOH (1.0:1.2) was used as the solvent, **15** and **16** were obtained in a 1.0:1.3 ratio, respectively. The protic solvent is a better solvating agent for the electronegative oxygen of the enol form of 2-methyl-1,3-cyclopentanedione, whereby the *O*-alkylation is difficultated. Compound **15** could be converted into **16** using the following procedure. Treatment of **15** with HBr (47 %) gave alcohol **13**, which was transformed into **14** by treatment with iodine and phosphorous in tetrahydrofuran. Finally, **14** reacted with 2-methyl-1,3-cyclopentanedione, under the same conditions as **12**, to

give **15** and **16** in a 1.1:1.0 ratio using dimethylformamide as solvent, and in a 1.0:1.4 ratio using H₂O:*t*-BuOH (1.0:1.2). The structure of **16** was confirmed by single crystal X-ray diffraction analysis.



Scheme 2. (a) BBr₃ in CH₂Cl₂, rt, 21 h, 87%. (b) MsCl, py, 4 °C, 15 h, 91%. (c) NaBH₄ in MeOH, 30 min, rt, 93%. (d) SOCl₂ in benzene, reflux, 2 h, 82%. (e) **11**→**12**, Fe, Br₂ in CHCl₃, rt, 8 h. (f) I₂, P (red), THF, rt, 19 h, 89%. (g) **12**→**15**(38%) + **16**(50%), 2-methyl-1,3-cyclopentanedione in *t*-BuOH:H₂O (1.2:1.0), K₂CO₃, reflux, 3 h. (h) *p*-TsOH in benzene, ethylene glycol, reflux, 4 h, 95%. (i) KOH in MeOH, reflux, 2 h, 74%. (j) Me₂SO₄, K₂CO₃, acetone, reflux, 4 h, 94%. (k) H₂SO₄, MeOH, rt, 0.5 h, 91%.

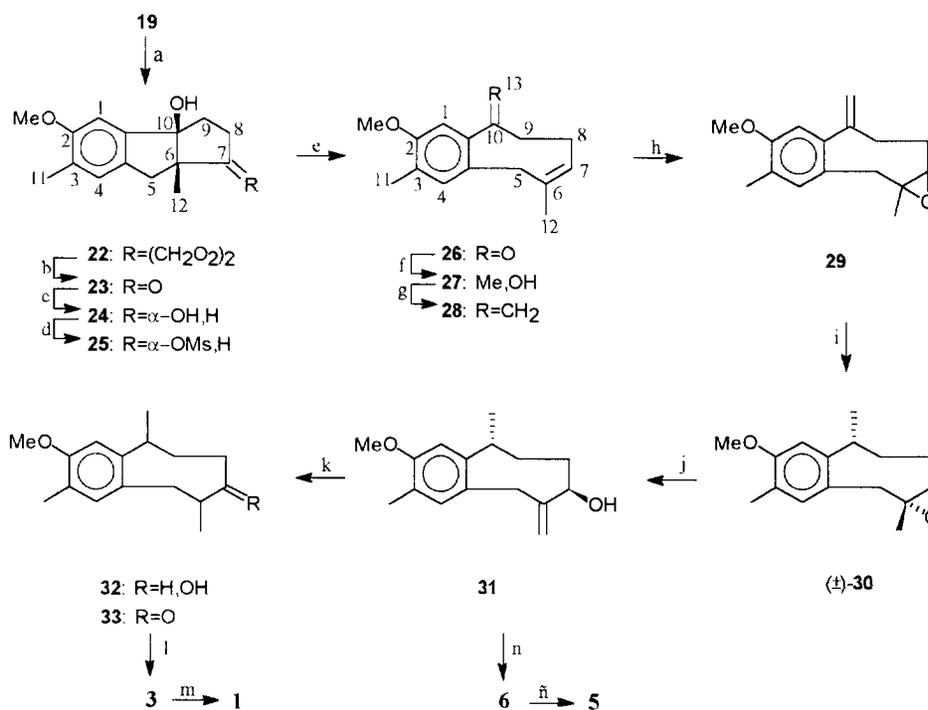
Treatment of **16** with lithium in tetrahydrofuran gave compound **21** in 10 % yield, but none of the desired tricyclic substance (analogue to **23**) was detected. The formation of **21** arises by intermolecular reaction of a mesyl group of one molecule of **16** with the carbonyl group of another molecule of **16**. Because attempts to cyclize **16** and **17** failed, it was decided to remove the mesyl ester. Thus, treatment of mesylate **17** with potassium hydroxide in methanol gave phenol **18**, which was treated with dimethylsulfate in the presence of potassium carbonate to produce **19** in 94% yield, which was easily converted (91% yield) into diketone **20** under acidic conditions.

While treatment of **20** with magnesium or lithium in tetrahydrofuran gave a complex mixture of unidentified compounds, ketal **19** afforded, after treatment with lithium in tetrahydrofuran, the expected cyclized compound **22** in 43% yield, which in turn easily gave ketone **23** under acidic conditions (Scheme 3). The structure of **23** was confirmed by single crystal X-ray diffraction analysis.

Reduction of **23** with sodium borohydride in methanol at room temperature followed by treatment of the resulting alcohol **24** with methanesulfonyl chloride in pyridine provided mesylate **25** as the only product. Mesylate **25** possesses the required relative stereochemistry at C-7 and C-10 to stereospecifically produce the *Z*-isomer in a Grob fragmentation reaction.¹¹ Indeed, when **25** was treated with sodium methoxide in methanol, benzocyclooctenone **26** was obtained in 80% yield.

Treatment of **26** with methyllithium (generated *in situ* with methyl iodide and lithium) at *ca.* -70°C gave benzocyclooctenol **27**. This compound was treated with triethylsilane and boron trifluoride in an attempt to obtain *O*-methylparvifoline (**3**) by substitution of the hydroxyl group by a hydrogen atom.¹⁴ The C-6–C-7 double bond reduction product was obtained instead of **3**. Therefore the C-6–C-7 double bond should be protected as an epoxide. In fact alcohol **27** underwent elimination of the hydroxyl group by treatment with

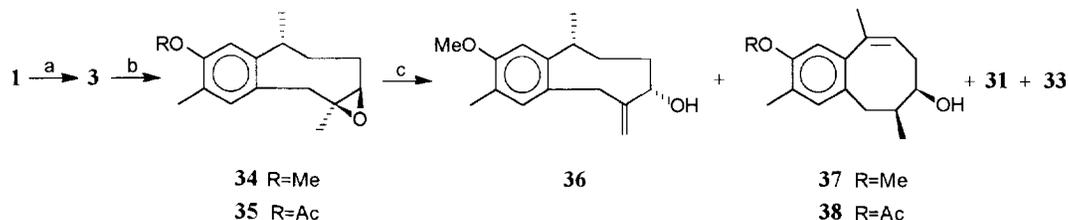
methanesulfonyl chloride in pyridine to produce diene **28** in 80% yield, which reacted with *m*-chloroperbenzoic acid in methylene chloride to give monoepoxide **29** in 77% yield. Hydrogenation of the exocyclic double bond in the presence of Pd/C (5%) in ethanol gave the isomer **30**. In addition, isomer **34** was prepared from parvifoline (**1**) by treatment with dimethyl sulfate in the presence of potassium carbonate in acetone to give *O*-methylparvifoline (**3**), which was treated with *m*-chloroperbenzoic acid in methylene chloride yielding only the isomer **34**. The stereochemistry of both compounds (**30** and **34**) was determined by comparison of their ¹H NMR spectral data with that of acetate **35**.¹



Scheme 3. (a) Li in THF, rt, 1 h, 43%. (b) H₂SO₄ in MeOH, rt, 0.5 h, 94%. (c) NaBH₄ in MeOH, rt, 1 h, 98%. (d) MsCl, py, -4 °C, overnight, 68%. (e) MeONa in MeOH, 2 h, reflux, 80%. (f) MeLi in THF, -78 °C → -70 °C, 3 h, 75%. (g) MsCl, py, -4 °C, overnight, 80%. (h) MCPBA in CH₂Cl₂, 40 min, 77%. (i) 5% Pd-C, H₂, EtOH, rt, 1 h, 95%. (j) *p*-TsOH in benzene, rt, 1 h, 70%. (k) 5% Pd/C, H₂, EtOH, rt, 1 h, 97%. (l) *p*-TsCl, py, -4 °C, 36 h, 83%. (m) EtSLi, DMF, 85 °C, 24 h, 98%. (n) CrO₃, Py, rt, 1 h, 80%. (ñ) BBr₃ in CH₂Cl₂, rt, 45 min, 54%.

Compound **30** was treated with *p*-toluenesulfonic acid in benzene yielding **31** in 70% yield. Both isomers (**31** and **36**) as well as **33** and **37** were obtained from **34** by treatment with *p*-toluenesulfonic acid in benzene (Scheme 4). The stereochemistry of isomers **31** and **36** was established on the basis of the nOe differential experiments carried out on **36**, and the stereochemistry of **37** was established on the basis of NMR spectral

data of **38**.¹ Irradiation of H-7 on **36** increased the signal of H-10 and vice versa. On the other hand, **31** was treated with chromium trioxide in pyridine yielding *O*-methylisoparvifolinone (**6**) which was demethylated with boron tribromide in methylene chloride to give isoparvifolinone (**5**).^{2a}



Scheme 4. (a) Me_2SO_4 , K_2CO_3 , acetone, reflux, 4 h, 94%. (b) MCPBA in CH_2Cl_2 , rt, 5 h, 98%. (c) *p*-TsOH, benzene, rt, 24 h.

Finally, **31** was hydrogenated in EtOH in the presence of Pd/C (5%) to give **32** (Scheme 3), which underwent elimination of the hydroxyl group, by treatment with *p*-toluenesulfonyl chloride in pyridine, to produce **3**. *O*-methylparvifoline (**3**) was treated with ethanethiol lithium salt (generated with ethanethiol and butyllithium) in *N,N*-dimethylformamide to give the desired (±)-parvifoline (**1**)² in 98% yield, while the reaction of *O*-methylparvifoline (**3**) with boron tribromide in methylene chloride only produced isoparvifoline (**4**).

Thus, we achieved a new total synthesis of (±)-parvifoline (**3**) and the first total synthesis of (±)-isoparvifolinone (**5**) by using a Grob fragmentation reaction of mesylate **25** as the key step. This transformation produced several new compounds whose structures were determined from their NMR spectra.

EXPERIMENTAL SECTION

Melting points, determined on a Fisher-Johns apparatus, are uncorrected. IR spectra were recorded in CHCl_3 , unless otherwise stated, on a Nicolet MX-1 spectrophotometer and UV spectra were recorded on a Unicam SP-800 instrument. Mass spectra were obtained on a Hewlett-Packard 5989-A spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian XL-300GS spectrometer with tetramethylsilane as the internal standard. Microanalyses were performed by the Alfred Bernhard Laboratories (Germany). X-ray data collections were obtained on a Nicolet R3m four circle diffractometer equipped with $\text{CuK}\alpha$ radiation. The diffractometer was operated in the $\theta.2\theta$ scanning mode. Organic layers were dried with anhydrous Na_2SO_4 . Column chromatographies (CC) were done with Merck silica gel 60 (230-400 mesh ASTM).

4-Hydroxy-3-methylbenzaldehyde mesylate (9). A cold solution of 4-hydroxy-3-methylbenzaldehyde (3 g, 20 mmol) in pyridine (8 ml) was treated with methanesulfonyl chloride (2 ml, 25.8 mmol). The mixture was kept for 15 h at 4 °C, poured over ice-water and extracted with EtOAc. The organic layer was washed with aqueous NaHCO_3 , water, diluted HCl and water, dried, filtered and evaporated under vacuum. The residue

was purified by CC (hexane-AcOEt 3:1) yielding **9** (4.3 g, 91%) as a white solid. After recrystallization from hexane/CHCl₃ mp 176-177 °C. IR (CHCl₃) ν_{\max} 1696 (C=O), 1376 cm⁻¹. UV (EtOH) λ_{\max} 209 (ϵ 2923), 232 (ϵ 7076), 270 nm (ϵ 846). ¹H NMR (300 MHz, CDCl₃): δ 7.76 (1H, s, H-5), 7.45 (1H, d, J=8.3 Hz, H-2), 7.71 (1H, dd, J_o=8.3 Hz, J_m=1.7 Hz, H-1), 9.91 (1H, s, H-7), 3.30 (3H, s, Ms), 2.40 ppm (3H, s, H-8). ¹³C NMR (75.4 MHz, CDCl₃), δ 191.1 (d, C-7), 151.9 (s, C-3), 134.7 (s, C-6), 132.9 (d, C-5), 132.4 (s, C-4), 130.3 (d, C-1), 122.6 (d, C-2), 38.4 (q, Ms) and 16.4 ppm (q, C-8).

4-Mesyloxy-3-methylbenzyl alcohol (10). A solution of **9** (3.7 g, 17.2 mmol) in methanol (40 ml) was treated with NaBH₄ (740 mg, 19.5 mmol) during 30 min. The mixture was stored at room temperature for 30 min, concentrated under vacuum and extracted with EtOAc. The organic layer was dried and then evaporated under vacuum. The residue was purified by CC (hexane-AcOEt 1.5:1.0) yielding **10** (3.5 g, 93%) as a white solid. Recrystallization from CH₂Cl₂/hexane provided the pure sample: mp 72-73 °C. IR (CHCl₃) ν_{\max} 3608 (OH), 1494 (C=C). UV (EtOH) λ_{\max} 214 (ϵ 5000), 262 nm (ϵ 434). MS: *m/z* 216 (88%) for C₉H₁₂O₄S (low resolution), 137 (52%), 109 (79%), 81 (100%). ¹H NMR (300 MHz, CDCl₃): δ 7.22 (1H, d, J_o=8.1 Hz, J_m=2.0 Hz, H-1), 7.23 (1H, br s, H-5), 4.58 (2H, s, H-7), 3.14 (3H, s, Ms) 2.32 (3H, s, H-8) and 2.60 ppm (1H, s, exchangeable with D₂O). ¹³C NMR (75.4 MHz, CDCl₃), δ 146.9 (s, C-3), 140.0 (s, C-6), 131.3 (s, C-4), 130.2 (d, C-5), 125.6 (d, C-1), 122.0 (d, C-2), 64.1 (t, C-7), 38.0 (q, Ms) and 16.5 ppm (q, C-8). *Anal.* calcd for C₉H₁₂O₄S: C, 49.98; H, 5.59; O, 29.59; S, 14.82. Found: C, 49.81; H, 5.52.

4-Mesyloxy-3-methylbenzyl chloride (11). A solution of **10** (12 g, 55.5 mmol) in benzene (42 ml) was treated with a solution of SOCl₂ (4.1 ml, 56.1 mmol) in benzene (8 ml). The mixture was heated under reflux for two hours, neutralized with saturated aq. NaHCO₃ and extracted with EtOAc. The extracts were dried filtered and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 3:1) yielding **11** (10.7 g, 82%) as a white solid. Recrystallization from CH₂Cl₂/hexane provided the pure sample: mp 45-47 °C. IR (CHCl₃) ν_{\max} 1495 (C=C), 1371 cm⁻¹. UV (EtOH) λ_{\max} 222 (ϵ 7000), 265 nm (ϵ 600). MS: *m/z* 234.3 (45.3%) for C₉H₁₁O₃SCl (low resolution), 155.3 (61.9%), 121.3 (59.6%), 91.2 (100.0%). ¹H NMR (300 MHz, CDCl₃): δ 7.28 (1H, d, J=10.1 Hz, H-2), 7.30 (1H, br s, H-5), 7.24 (1H, dd, J_o=8.5 Hz, J_m=2.1 Hz, H-1), 4.54 (2H, s, H-7), 3.19 (3H, s, Ms), 2.36 ppm (3H, s, H-8). ¹³C NMR (75.4 MHz, CDCl₃), δ 147.5 (s, C-3), 136.5 (s, C-6), 132.0 (d, C-5), 131.8 (s, C-4), 127.4 (d, C-1), 122.3 (d, C-2), 45.2 (q, C-7), 38.1 (q, Ms) and 16.6 ppm (q, C-8). *Anal.* calcd for C₉H₁₁O₃SCl: C, 46.05; H, 4.72; S, 13.66; Cl, 15.10; O, 20.45. Found: C, 45.81; H, 4.68; S, 13.83; Cl, 15.02; O, 20.66.

2-Bromo-4-mesyloxy-5-methylbenzyl bromide (12). A cold solution of **11** (6.0 g, 25.5 mmol) in chloroform (30 ml) was treated with bromine (1.5 ml, 29.0 mmol) and iron (powder, 1.5 g). The mixture was covered from light and stirred for 8 h at room temperature. Sodium bisulfite and H₂O were added and the solvent evaporated under vacuum. The mixture was extracted with EtOAc and the extracts were washed with saturated aq. NaHCO₃, dried and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 3:1) yielding **12** (8.1 g, 89%), as a white solid. The analytical sample of **12** was recrystallized from CHCl₃/hexane, mp 135-137 °C. IR (CHCl₃) ν_{\max} 1576, 1480 (C=C), 1359 cm⁻¹. UV (EtOH) λ_{\max} 211 nm (ϵ 4727), λ_{\max} 237 nm (ϵ 2545). MS: *m/z* 355.9 (5.2%) for C₉H₁₀O₃Br₂S, (low resolution), 358.0 (10.2%), 359.9

(5.6%), 277.0 (91.1%), 279.0 (100.0%), 199.2 (78.4%), 201.2 (72.1%). ^1H NMR (300 MHz, CDCl_3) δ 7.52 (1H, s, H-2), 7.37 (1H, s, H-5), 4.54(2H, s, H-7), 3.22(3H, s, Ms), 2.31 ppm (3H, s, H-8). ^{13}C NMR (75.4 MHz, CDCl_3) δ 145.7 (s, C-3), 136.0 (s, C-6), 133.8 (d, C-5), 131.5 (s, C-4), 126.7 (d, C-2), 121.3 (s, C-1), 38.4 (q, Ms), 32.1 (t, C-7) and 16.1 ppm (q, C-8). *Anal.* calcd for $\text{C}_9\text{H}_{10}\text{O}_3\text{Br}_2\text{S}$: C, 30.19; H, 2.81; Br, 44.63; S, 8.95; O, 13.40. Found: C, 30.29; H, 2.77; S, 9.01.

Treatment of 2-bromo-4-mesyloxy-5-methylbenzyl bromide (12) with 2-methyl-1,3-cyclopentane-dione.

A solution of **12** (7.3 g, 20.3 mmol) in *t*-BuOH (87 ml) and H_2O (73 ml) was treated with 2-methyl-1,3-cyclopentanedione (2.3 g, 20.4 mmol) in the presence of K_2CO_3 (3.0 g, 21.7 mmol). The mixture was stirred and heated under reflux during 3 h, extracted with EtOAc and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 2:1) yielding **16** (4.0 g, 50%) as colorless crystals and **15** (hexane-AcOEt 1:2) (3 g, 38%) as pale yellow amorphous solid. Compound **16** was recrystallized from CHCl_3 /hexane, mp 107-109 °C. UV (EtOH) λ_{max} 215 nm (ϵ 9285), 271 nm (ϵ 714). IR (CHCl_3) ν_{max} 1722 (C=O), 1479 (arom C=C), 1371 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 7.46 (1H, s, H-2), 7.04 (1H, s, H-5), 3.22 (3H, s, Ms), 3.07 (2H, s, H-7), 2.66 (4H, AA'BB', H-9, H-10) 2.27 (3H, s, Me-13), 1.18 ppm (3H, s, Me-14). ^{13}C NMR (75.4 MHz, CDCl_3) δ 215.3 (s, C-9), 215.3 (s, C-12), 146.6 (s, C-3), 134.3 (s, C-6), 134.2 (d, C-5), 130.8 (s, C-4), 126.4 (d, C-2), 122.2 (q, C-1), 56.7 (s, C-8), 39.7 (t, C-7), 38.3 (q, Ms), 35.5 (t, C-10), 35.5 (t, C-11), 18.7 (q, C-14) and 16.3 ppm (q, C-13). Compound **15** was recrystallized from CHCl_3 /hexane mp 107-109 °C. UV (MeOH), λ_{max} 204 (ϵ 12666), 249 nm (ϵ 20333). IR (CHCl_3) ν_{max} 1636 (C=O), 1118 cm^{-1} (C-O). ^1H NMR (300 MHz, CDCl_3) δ 7.55 (1H, s, H-2), 7.36 (1H, s, H-5), 5.23 (2H, s, H-7), 3.25 (3H, s, Ms), 2.71 (2H, m, H-12), 2.48 (2H, m, H-11), 2.35 (3H, s, Me-13) and 1.71 ppm (3H, s, Me-14). ^{13}C NMR (75.4 MHz, CDCl_3) δ 147.3 (s, C-3), 134.2 (s, C-6), 131.4 (s, C-4), 131.3 (d, C-5), 126.4 (d, C-2), 119.0 (s, C-1), 69.5 (t, C-7), 38.4 (q, Ms) and 16.5 ppm (q, C-8).

X-Ray analysis for 16. Single crystals of **16** were grown by slow crystallization from CHCl_3 /hexane. They were monoclinic P, space group $\text{P}2_1/\text{c}$ with $a = 9.275(2)$, $b = 8.144(2)$, $c = 21.916(5)$ Å and $d_{\text{calc}} = 1.554\text{g}/\text{cm}^3$ for $Z = 4$ (M, 389). The size of the crystal used for data collection was $0.28 \times 0.26 \times 0.02$ mm. No absorption correction was applied ($\mu = 47.55\text{ cm}^{-1}$). A total of 2423 reflections were measured for $3^\circ \leq \theta \leq 110^\circ$ of which 1791 reflections were considered to be observed [$I \geq 2.5\sigma(I)$]. The final discrepancy indices were $R = 5.77\%$ using 1618 reflections in the final refinement. The final difference Fourier map was essentially featureless, the highest residual peaks having densities of $0.5490\text{ e}/\text{Å}^3$.

Isomers 15 and 16 from 12 using DMF as solvent. A solution of **12** (7.3 g, 20.3 mmol) in DMF (130 ml) was treated with 2-methyl-1,3-cyclopentanedione (2.3 g, 20.4 mmol) and K_2CO_3 (3.0 g, 21.7 mmol). The mixture was heated at 60 °C during 6 min, extracted with EtOAc and concentrated under vacuum. The residue was purified by CC yielding **15** (2.0 g, 61%) and **16** (0.92 g, 28%).

Reaction of 14 with 2-methyl-1,3-cyclopentanedione. Compounds **15** and **16** were prepared by treatment of **14** with 2-methyl-1,3-cyclopentanedione in the presence of K_2CO_3 as above. When DMF was used as solvent, yields of 37% of **16** and 44% of **15** were obtained and when *t*-BuOH/ H_2O (1.2:1.0) was used as solvent, yields of 44% of **16** and 31% of **15** were obtained, respectively.

Preparation of 16 from 17. A solution of 17 (300 mg, 0.69 mmol) in MeOH (3 ml) was treated with H₂SO₄ (catalytic amounts). The mixture was allowed to stand at room temperature for 1 h, neutralized with saturated aq. NaHCO₃ and extracted with EtOAc. The organic layer was dried, filtered and concentrated under vacuum. The residue was purified by CC yielding 16 (260 mg, 97%).

2-Bromo-4-mesyloxy-5-methylbenzyl alcohol (13). A solution of 15 (10.0 g, 25.7 mmol) in EtOH (57 ml) was treated with HBr (47%, 8 ml), heated under reflux during 3 min, neutralized with saturated aq. NaHCO₃, extracted with EtOAc, dried, filtered and evaporated under vacuum. The residue was purified by CC (hexane-AcOEt 2:1) yielding 13 (6.4 g, 84%) as a white solid. Recrystallization from CHCl₃/hexane provided 13 mp 83-85 °C. IR (CHCl₃) ν_{\max} 3602, 3412 cm⁻¹ (OH free and associated). ¹H NMR (300 MHz, CDCl₃), δ 7.45 (1H, s, H-2), 7.39 (1H, s, H-5), 4.65 (2H, s, H-7), 3.19 (3H, s, Ms), 2.30 (3H, s, Me-8) and 2.60 ppm (1H, br s, OH). ¹³C NMR (75.4 MHz, CDCl₃), δ 146.6 (s, C-3), 138.8 (s, C-6), 131.2 (d, C-5), 130.8 (s, C-4), 125.9 (d, C-2), 118.8 (s, C-1), 64.0 (t, C-7), 38.2 (q, Ms) and 16.3 ppm (q, C-8).

2-Bromo-4-mesyloxy-5-methylbenzyl iodide (14). A solution of 13 (2.0 g, 6.7 mmol) in THF (22 ml) was treated with iodine (1.7 g, 6.7 mmol) and phosphorous (red, 210 mg, 6.7 mmol). The mixture was stirred at room temperature during 19 h, treated with NaHSO₃ and extracted with EtOAc. The residue was purified by CC (hexane-AcOEt 3:1) yielding 14 (2.35 g, 86 %) as a white solid. Recrystallized, acetone/hexane. mp 150-152 °C, UV (EtOH) λ_{\max} 214 nm (ϵ 6734). IR (CHCl₃) ν_{\max} 1478, 1375, 1131, 967, 855 cm⁻¹. ¹H NMR (300 MHz, CDCl₃), δ 7.47 (1H, s, H-2), 7.35 (1H, s, H-5), 4.47 (2H, s, H-7), 3.22 (3H, s, Ms) and 2.29 ppm. (3H, s, Me-8). ¹³C NMR (75.4 MHz, CDCl₃), δ 146.9 (s, C-3), 137.4 (s, C-6), 133.0 (d, C-5), 131.5 (s, C-4), 126.8 (d, C-2), 120.9 (s, C-1), 38.3 (q, Ms), 16.2 (q, C-8) and 4.1 ppm (t, C-7).

Compound 17 from 16. A solution of 16 (7.3 g, 18.7 mmol) in benzene (50 ml) was treated with *p*-toluenesulfonic acid (300 mg) and ethylene glycol (1.2 ml, 19.3 mmol). The mixture was heated under reflux for 4 h. The water generated in the reaction was eliminated by a Dean-Stark apparatus. The mixture was neutralized with saturated aq. NaHCO₃ and extracted with EtOAc. The organic layer separated, dried and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 2:1) yielding 17. Recrystallization from CHCl₃/hexane gave ketal 17 (7.7 g, 95%), mp = 113-115 °C. UV (MeOH) λ_{\max} 215 nm (ϵ 6086). IR (CHCl₃) ν_{\max} 1743 cm⁻¹ (C=O), MS: *m/z* 432.0 (8%), for C₁₇H₂₁O₆BrS, 434.0 (9%), 353.2 (3%), 325.2 (18%), 99.1 (100%). ¹H NMR (300 MHz, CDCl₃), δ 7.45 (1H, s, H-2), 7.18 (1H, s, H-5), 4.05 (4H, m, OCH₂CH₂O), 3.10, 2.94 (2H, dd, AB, J=14.3 Hz, H-7), 2.58 (1H, m, H-10), 2.10 (1H, m, H-11), 2.45-2.24 (2H, m, H-10', H-11'), 3.19 (3H, s, Ms), 2.28 (3H, s, Me-13), 0.99 ppm (3H, s, Me-14). ¹³C NMR (75.4 MHz, CDCl₃), δ 216.6 (s, C-9), 146.2 (s, C-3), 136.0 (s, C-6), 135.1 (d, C-5), 129.9 (s, C-4), 125.8 (d, C-2), 122.9 (s, C-1), 115.8 (s, C-12), 65.1 (t, CH₂O), 64.8 (t, CH₂O), 55.1 (s, C-8), 38.1 (q, Ms), 36.5 (t, C-7), 35.4 (t, C-10), 29.8 (t, C-11), 16.3 (q, C-13) and 14.9 ppm (q, C-14). *Anal.* calcd for C₁₇H₂₁O₆BrS C, 47.12; H, 4.88; O, 22.15; Br, 18.44; S, 7.39. Found: C, 47.04; H, 4.72; O, 22.18; Br, 18.60; S, 7.46.

Compound 21. A solution of 16 (1.0 g, 2.5 mmol) in anhydrous THF (5 ml) was treated with lithium (18 mg, 2.6 mmol). The mixture was heated under reflux overnight, treated with H₂O and extracted with EtOAc.

The residue was purified by CC (hexane-AcOEt 3:1) yielding **21** (100 mg, 10 %) as colorless oil. IR (CHCl₃) ν_{\max} 1737 (C=O) 1650, 1587 cm⁻¹ (C=C). ¹H NMR (300 MHz, CDCl₃) δ 7.45 (1H, s, H-2), 7.03 (1H, s, H-5), 5.11 (1H, br s, H-15), 4.77 (1H, br s, H-15'), 3.21 (3H, s, Ms), 2.95, 2.89 (2H, dd, AB, H-7), 2.27 (3H, s, Me-13), 1.15 ppm (3H, s, Me-14). ¹³C NMR (75.4 MHz, CDCl₃) δ 220.5 (s, C-9), 151.9 (s, C-12), 146.2 (s, C-3), 135.7 (s, C-6), 134.3 (d, C-5), 130.0 (s, C-4), 126.1 (d, C-2), 122.8 (s, C-1), 110.2 (t, CH₂), 53.7 (s, C-8), 41.5 (t, C-7), 38.3 (q, Ms), 37.1 (t, C-10), 28.0 (t, C-11), 21.3 (q, C-14) and 16.3 ppm (q, C-13).

Compound 18. A solution of **17** (5 g, 11.5 mmol) in MeOH (30 ml) was treated with KOH (1.1 g, 16.6 mmol). The mixture was heated under reflux for 2 h, extracted with EtOAc, dried and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 1:1) yielding **18** (2.96 g, 74%). Recrystallization from CHCl₃/hexane provided the pure sample mp 144-146 °C. UV (MeOH) λ_{\max} 218 nm (ϵ 6567) λ_{\max} 286 nm (ϵ 1492). IR (CHCl₃) ν_{\max} 3616, 3339 (OH free and associated, respectively), 1735 (C=O), 1604 cm⁻¹ (C=C, arom). ¹H NMR (300 MHz, CDCl₃) δ 6.85 (1H, s, H-2), 6.76 (1H, s, H-5) 4.03 (4H, m, OCH₂CH₂O), 3.15 (1H, d, J=14.2 Hz, H-7) and 2.78 (1H, d, J=14.2 Hz, H-7') AB system, 2.80 (1H, m, H-10), 2.44 (2H, m, H-10',11), 2.12 (1H, m, H-11'), 2.08 (3H, s, Me-13) and 1.03 ppm (3H, s, Me-14). ¹³C NMR (75.4 MHz, CDCl₃) δ 219.8 (s, C-9), 154.1 (s, C-3), 134.1 (d, C-5), 123.3 (s, C-6), 122.4 (s, C-1), 122.4 (s, C-4), 118.7 (d, C-2), 116.1 (s, C-12), 65.6 (t, CH₂O), 64.7 (t, CH₂O), 56.1 (s, C-8), 37.9 (t, C-7), 36.1 (t, C-10), 30.0 (t, C-11), 15.5 (q, C-13) and 14.0 ppm (q, C-14). *Anal.* calcd for C₁₆H₁₉O₄Br: C, 54.09; H, 5.39; O, 18.01; Br, 22.49. Found: C, 54.21; H, 5.47.

Compound 19. A solution of **18** (1.0 g, 2.8 mmol) in acetone (19 ml) was treated with K₂CO₃ (0.4 g, 2.8 mmol) and Me₂SO₄ (0.3 ml, 3.0 mmol). The mixture was heated under reflux for 4 h, concentrated under vacuum, extracted with EtOAc, dried and evaporated under vacuum. The residue was purified by CC (hexane-AcOEt 2:1) yielding **19** (0.98 g, 94%) as a white solid. Recrystallization from CHCl₃/hexane provided the pure sample mp 136-138 °C. UV (1,4-dioxane) λ_{\max} 245 (ϵ 571), λ_{\max} 279 nm (ϵ 2000), λ_{\max} 285 nm (ϵ 2000). IR, (CHCl₃) ν_{\max} 1738 (C=O), 1605 cm⁻¹ (C=C, arom). MS: *m/z* 368 (40%) for C₁₇H₂₁O₄Br (low resolution), 370 (40%), 269 (14%), 203 (100%) and 188 (26%). ¹H NMR (300 MHz, CDCl₃) δ 6.92 (1H, s, H-2), 6.95 (1H, s, H-5), 4.00 (4H, m, OCH₂CH₂O), 3.76 (3H, s, CH₃O), 3.05 and 2.90 (2H, dd, AB, J=14.3 Hz, H-7), 2.12 (1H, m, Me-13) and 0.98 ppm (3H, s, Me-14). ¹³C NMR (75.4 MHz, CDCl₃) δ 216.6 (s, C-9), 156.7 (s, C-3), 133.9 (d, C-5), 127.7 (s, C-6), 125.4 (s, C-4), 123.0 (s, C-1), 116.1 (s, C-12), 114.0 (d, C-2), 65.4 (t, CH₂O), 64.7 (t, CH₂O), 55.5 (s, C-8), 55.4 (q, OMe), 36.9 (t, C-7), 35.5 (t, C-10), 29.9 (t, C-11), 15.9 (q, C-13) and 14.5 ppm (q, C-14). *Anal.* calcd for C₁₇H₂₁O₄Br: C, 55.29; H, 5.73; O, 17.33; Br, 21.63. Found C, 55.09; H, 5.61; O, 17.43; Br, 21.87.

Compound 20. A solution of **19** (250 mg) in MeOH (3 ml) was treated with H₂SO₄ (catalytic amounts). The mixture was stirred at room temperature during 0.5 h, neutralized with saturated aq. NaHCO₃, concentrated, extracted with EtOAc, dried, filtered and evaporated under vacuum. The residue was purified by CC (hexane-AcOEt 3:1) to give **20** (200 mg, 91 %) as a white solid. Recrystallization from CHCl₃/hexane provided the pure sample mp 135-137 °C. UV (MeOH) λ_{\max} 216 (ϵ 9672), 285 nm (ϵ 1475). IR ν_{\max} 1726 (C=O), 1604, 1495 cm⁻¹ (C=C). MS: *m/z* 324.2 (11%) for C₁₅H₁₇O₃Br (low resolution), 326.2 (11%),

213.0 (100%), 215.2 (95%), 91.1 (15%). ^1H NMR (300 MHz, CDCl_3) δ 6.93 (1H, s, H-2), 6.86 (1H, s, H-5), 3.78 (3H, s, MeO), 3.03 (2H, s, H-7), 2.58 (4H, AA'BB', H-10, H-11), 2.10 (3H, s, Me-13) and 1.17 ppm (3H, s, Me-14). ^{13}C NMR (75.4 MHz, CDCl_3) δ 215.9 (s, C-9), 215.9 (s, C-12), 157.2 (s, C-3), 133.0 (d, C-5), 126.2 (s, C-6), 126.2 (s, C-4), 122.2 (s, C-1), 114.4 (d, C-2), 57.3 (s, C-8), 55.5 (q, OMe), 40.9 (t, C-7), 35.7 (t, C-10), 35.7 (t, C-11), 18.2 (q, C-14) and 15.8 ppm (q, C-13).

Compound 22. A solution of **19** (2.35 g, 6.3 mmol) in anhydrous THF (15 ml) was treated with lithium (excess 20%, in small fragments) under an argon atmosphere. The mixture was stirred at room temperature for 1 h, decanted to remove the excess of lithium, treated with water, extracted with EtOAc, dried and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 1:1) yielding **22** (800 mg, 43%) as a white solid. Recrystallization from CHCl_3 /hexane provided the pure sample mp 74–76 °C. UV (MeOH) λ_{max} 220 (ϵ 5609), 581 (ϵ 3902) and 587 nm (ϵ 3658). IR (CHCl_3) ν_{max} 3575 (OH). MS: m/z 290.4 (100%) for $\text{C}_{17}\text{H}_{22}\text{O}_4$, 204.4 (28%), 186.4 (82%). ^1H NMR (300 MHz, CDCl_3) δ 6.89 (1H, s, H-4), 6.85 (1H, s, H-1), 4.00 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.82 (3H, s, MeO), 3.19 and 2.60 (2H, 2d, AB, $J=16.8$, H-5), 2.18 (3H, s, Me-11), 2.10 (2H, m, H-9, H-8), 1.79 (1H, ddd, $J=2.4$, $J=7.3$, $J=12.8$, H-9 β or H-8 α), 1.64 (1H, ddd, $J=8.4$, $J=12.2$, $J=12.2$, H-9 α or H-8 β) and 1.07 ppm (3H, s, Me-12). ^{13}C NMR (75.4 MHz, CDCl_3) δ 157.7 (s, C-2), 145.9 (s, C-7), 132.1 (s, C-10a), 127.2 (s, C-4a), 127.2 (s, C-3), 126.3 (d, C-4), 104.3 (d, C-1), 90.1 (s, C-10), 65.1 (t, CH_2O), 65.0 (t, CH_2O), 57.3 (s, C-6), 55.4 (q, OMe), 42.2 (t, C-5), 39.2 (t, C-9), 32.4 (t, C-8), 16.4 (q, C-11) and 16.1 ppm (q, C-12). *Anal.* calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4$: C, 70.32; H, 7.64; O, 22.04. Found: C, 70.10; H, 7.61; O, 22.29.

Compound 23. A solution of **22** (1 g, 4.0 mmol) in MeOH (13 ml) was treated with H_2SO_4 (catalytic amounts). The mixture was stored at room temperature for 0.5 h, neutralized with saturated aq. NaHCO_3 , concentrated, extracted with EtOAc, dried and evaporated under vacuum. The residue was purified by CC (hexane-AcOEt 2:1) to give **23** (789 mg, 94%) as a white solid. Recrystallization from CHCl_3 /hexane provided the pure sample mp 136–138 °C. UV (MeOH), λ_{max} 222 (ϵ 5432), 285 nm (ϵ 3456). IR (CHCl_3) ν_{max} 3587, 3465 (OH, free and associated), 1735 cm^{-1} (C=O). MS: m/z 246.4 (66%) for $\text{C}_{15}\text{H}_{18}\text{O}_3$, 218.4 (34%), 189.2 (100%), 175.2 (37%). ^1H NMR (300 MHz, CDCl_3) δ 6.91 (1H, s, H-4), 6.88 (1H, s, H-1), 3.83 (3H, s, MeO), 3.08 (1H, d, $J=16.1$, H-5), 2.75 (1H, d, $J=16.0$ Hz, H-5'), 2.54 (1H, dd, $J=12.6$, $J=8.9$, $J=2.1$ Hz, H-8), 2.24 (1H, ddd, $J=14.9$, $J=8.9$, $J=12.6$, H-8'), 2.44 (1H, ddd, $J=18.5$, $J=8.9$, $J=2.1$, H-9), 1.92 (1H, ddd, $J=8.8$, $J=18.5$, $J=11.8$, H-9'), 2.17 (3H, s, Me-11) and 1.17 ppm (3H, s, Me-12). ^{13}C NMR (75.4 MHz, CDCl_3) δ 221.7 (s, C-7), 157.9 (s, C-2), 143.0 (s, C-10a), 133.5 (s, C-4a), 128.7 (s, C-3), 126.7 (d, C-4), 104.1 (d, C-1), 88.6 (s, C-10), 59.2 (s, C-6), 55.4 (q, OMe), 40.4 (t, C-5), 36.7 (t, C-9), 31.2 (t, C-8), 16.4 (q, C-11) and 15.6 ppm (q, C-12).

X-Ray analysis for 23. Single crystals of **23** were grown by slow crystallization from CHCl_3 -hexane. They were monoclinic P, space group $\text{P}2_1/a$ with $a = 1.362(6)$, $b = 6.829(4)$, $c = 18.02(1)$ Å and $d_{\text{calc}} = 1.205\text{g}/\text{cm}^3$ for $Z = 4$ (M, 246). The size of the crystal used for data collection was 0.20x0.30x0.20 mm. No absorption correction was necessary ($\mu = 6.39\text{ cm}^{-1}$). A total of 2030 reflections were measured for $3^\circ \leq \theta \leq 110^\circ$ of which 1350 reflections were considered to be observed [$I \geq 2.5\sigma(I)$]. The final discrepancy indices were $R =$

4.86% using 1340 reflections in the final refinement. The final difference Fourier map was essentially featureless, the highest residual peaks having densities of 0.15 e/Å³.

Diol 24. A solution of **23** (500 mg, 2.0 mmol) in MeOH (10 ml) was treated with NaBH₄ (80 mg, 2.1 mmol) at room temperature for 1 h. The mixture was concentrated to remove MeOH, extracted with EtOAc, dried and evaporated under vacuum. The residue was purified by CC (hexane-AcOEt 1:2) yielding **24** (494 mg, 98.0%), which was recrystallized from CHCl₃/hexane mp 95-97 °C. UV (MeOH) λ_{max} 220 nm (ε 5000), λ_{max} 282 (ε 3600) and λ_{max} 287 nm (ε 3200). IR (CHCl₃) ν_{max} 3592 (OH), 1022 cm⁻¹ (C-O). MS: *m/z* 248.4 (72%) for C₁₅H₂₀O₃ (low resolution), 230.4 (36%), 215.4 (20%), 190.2 (100%), 175.2 (46%). ¹H NMR (300 MHz, CDCl₃) δ 6.92 (1H, s, H-4), 6.81 (1H, s, H-1) 3.96 (1H, dd, J=5.1 Hz, J=10.1 Hz, H-7), 3.82 (3H, s, MeO), 3.22, 2.40 (2H, 2d, AB, J=16.8, H-5), 2.12 (1H, m, H-9), 1.90 (2H, m, H-9', 8), 1.28 (1H, m, H-8'), 2.18 (3H, s, Me-11), 1.17 (3H, s, Me-12) y 1.80 (1H, OH, interchanged with D₂O). ¹³C NMR (75.4 MHz, CDCl₃), δ 157.7 (s, C-2), 145.9 (s, C-10a), 132.8 (s, C-4a), 127.6 (s, C-3), 126.4 (d, C-4), 104.2 (d, C-1), 90.9 (s, C-10), 80.4 (s, C-7), 55.4 (q, OMe), 54.8 (s, C-6), 37.9 (t, C-4), 37.4 (t, C-9), 31.3 (t, C-8), 21.4 (q, C-12) and 16.4 ppm (q, C-11). *Anal.* calcd for C₁₅H₂₀O₃: C, 72.55; H, 8.12; O, 19.33. Found: C, 72.74; H, 8.17; O, 19.11.

Mesylate 25. A cold solution of **24** (200 mg, 0.8 mol) in pyridine (2 ml) was treated with methanesulfonyl chloride (0.07 ml, 0.9 mmol). The mixture was kept at -4 °C overnight, extracted with EtOAc, washed successively with HCl (10%), NaHCO₃/H₂O and water. The organic layer was dried, filtered and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 2:1) yielding **25** (180 mg, 68 %) as colorless oil. UV (MeOH) λ_{max} 287 nm (ε 2000). IR (CHCl₃) ν_{max} 3585 cm⁻¹ (OH). ¹H NMR (300 MHz, CDCl₃) δ 6.92 (1H, s, H-4), 6.80 (1H, s, H-1), 4.80 (1H, dd, J=6.1, J=10.3 Hz, H-7), 3.82 (3H, s, MeO), 3.03 (3H, s, Ms), 3.22 (1H, d, J=16.8 Hz, H-5), 2.51 (1H, d, J=16.8 Hz, H-5'), 2.19 (3H, s, Me-11), 1.24 (3H, s, Me-12), 2.20 (2H, m, H-8, H-9), 1.97 (1H, ddd, J=6.8, J=11.8, H-9') and 1.60 ppm (1H, m, H-8'). ¹³C NMR (75.4 MHz, CDCl₃) δ 157.9 (s, C-2), 145.0 (s, C-10a), 131.9 (s, C-4a), 128.0 (s, C-3), 126.4 (d, C-4), 104.0 (d, C-1), 90.9 (s, C-10), 88.2 (d, C-7), 55.4 (q, OMe), 54.5 (s, C-6), 39.0 (t, C-5), 38.3 (q, Ms), 37.1 (t, C-9), 29.1 (t, C-8), 21.0 (q, C-12) and 16.4 ppm (q, C-11).

3,6-Dimethyl-2-methoxy-6-benzocycloocten-10-one (26). A solution of **25** (850 mg, 2.6 mmol) in MeOH (10 ml) was treated with sodium methoxide (1 equiv) in methanol (3 ml). The mixture was refluxed for 2 h, concentrated to remove MeOH and extracted with EtOAc, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 3:1) yielding **26** (478 mg, 80%) as a white solid. Recrystallization from CHCl₃/hexane provided the pure sample mp 106-108 °C. UV (EtOH) λ_{max} 227 (ε 21470), 260 (ε 7058), 310 nm (ε 2941). IR (CHCl₃), ν_{max} 1669 (C=O), 1605 (C=C). MS: *m/z* 230.4 (80%,) for C₁₅H₂₀O₃ (low resolution), 202.4 (100%), 187.2 (48%), 149.2 (46%), 91.1 (24%). ¹H NMR (300 MHz, CDCl₃) δ 7.20 (1H, s, H-1), 7.00 (1H, s, H-4), 5.31 (1H, tq, J_{7,11}=1.55 Hz, J_{7,8α} = J_{7,8β} = 5.2 Hz, H-7). 3.83 (3H, s, OMe), 3.54 (2H, s, H-5), 3.09 (2H, t, J=7.5, H-9), 2.53 (2H, q, H-8), 2.23 (3H, s, Me-11), and 1.63 ppm (3H, q, J=1.5 Hz, Me-12). ¹³C NMR (75.4 MHz, CDCl₃) δ 205.6 (s, C-10), 156.3 (s, C-2), 138.4 (s, C-10a), 138.4 (s, C-6), 133.3 (d, C-4), 133.1 (s, C-3), 130.5 (s, C-4a), 122.1 (d, C-7), 110.5

(d, C-1), 55.5 (q, OMe), 40.3 (t, C-9), 39.3 (t, C-5), 24.8 (t, C-8), 24.8 (q, C-12) and 16.1 ppm (q, C-11). *Anal.* calcd for C₁₅H₂₀O₃: C, 78.23; H, 7.88; O, 13.89. Found: C, 78.10; H, 7.86; O, 13.82.

Compound 27. A solution of **26** (250 mg, 1.0 mmol) in anhydrous THF (5 ml) was treated with methylolithium (generated from MeI and lithium at *ca* -70 °C) at -78 °C. The temperature of the reaction was varied (-78→-70 °C) several times until **26** reacted (3 h). The mixture was treated with water and extracted with CH₂Cl₂. The residue was purified by CC (hexane-AcOEt 2:1) yielding **27** as a colorless oil (200 mg, 75 %). UV (MeOH) λ_{max} 213 (ε 5145), λ_{max} 280 nm (ε 1566). IR (CHCl₃) ν_{max} 3589, 3516 (OH free and associated, respectively), 1613, 1571 cm⁻¹ (C=C). MS: *m/z* 246 (21%) for C₁₆H₂₂O₂, 203 (13%), 200 (100%). ¹H NMR (300 MHz, CDCl₃) δ 7.21 (1H, s, H-4), 6.85 (1H, s, H-1), 5.32 (1H, br t, H-7), 3.82 (3H, s, MeO), 3.54 (1H, br s, Me-12), 1.61 (3H, s, Me-13) and 2.00-2.40 ppm (4H, br signals, H-8 and H-9). ¹³C NMR (75.4 MHz, CDCl₃), δ 155.9 (s, C-2), 143.4 (s, C-10a), 137.8 (s, C-6), 132.8 (d, C-4), 128.5 (s, C-4a), 125.1 (s, C-3), 123.8 (d, C-7), 109.0 (d, C-1), 76.4 (s, C-10), 55.4 (q, OMe), 42.2 (t, C-5), 38.4 (t, C-9), 32.1 (q, C-13), 25.7 (q, C-12), 23.6 (t, C-8) and 15.5 ppm (q, C-11).

Compound 28. A solution of **27** (200 mg, 0.81 mmol) in pyridine (1ml), was treated with MsCl (1equiv). The mixture was kept at -4 °C overnight, extracted with CH₂Cl₂, washed with HCl (10%) and aq. NaHCO₃. The residue was purified by CC (hexane-AcOEt 3:1) yielding **28** (148 mg, 80%) as a colorless oil UV. (EtOH) λ_{max} 223 (ε 7090), λ_{max} 238 (ε 6181) λ_{max} 286 nm (ε 3272). IR (CHCl₃) ν_{max} 1609 (C=C), 1080 cm⁻¹ (C-O). MS: *m/z* 228 (100%) for C₁₆H₂₀O, 212 (5%), 198 (18%), 187 (25%), 159 (34%). ¹H NMR (300 MHz, CDCl₃), δ 6.90 (1H, s, H-4), 6.59 (1H, s, H-1), 5.32 (1H, br s, H-7), 5.15 (1H, d, J=2.3 Hz, H-13), 4.97 (1H, d, J=2.3 Hz, H-13'), 3.78 (3H, s, MeO), 3.16 (2H, br s, H-5), 2.35 (4H, br s, H-8 and H-9), 2.18 (3H, s, Me-11) and 1.76 ppm (3H, br s, Me-12). ¹³C NMR (75.4 MHz, CDCl₃), δ 155.8 (s, C-2), 153.9 (s, C-10), 142.2 (s, C-10a), 140.3 (s, C-6), 130.9 (d, C-4), 130.0 (s, C-4a), 124.5 (s, C-3), 123.1 (d, C-7), 116.1 (t, C-13), 111.3 (d, C-1), 55.3 (s, OMe), 37.6 (t, C-5), 37.6 (t, C-9), 29.4 (t, C-8), 23.3 (q, C-12) and 15.7 ppm (q, C-11).

3,6-Dimethyl-6,7-epoxy-2-methoxy-10-methylenebenzocyclooctane (29). A solution of **28** (200 mg, 0.87 mmol) in CH₂Cl₂ was treated with *m*-chloroperbenzoic acid at room temperature. After stirring for 40 min, the suspension was filtered and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 2:1) yielding **29** (160 mg, 77%) as colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 6.58 (1H, s, H-1), 6.91 (1H, s, H-4), 4.90 (1H, br s, H-13), 5.17 (1H, d, J=2.1 Hz, H-13'), 3.81 (3H, s, Me-O) 2.84 (1H, d, H-5), 2.78 (1H ddd, J=1.0 Hz, J=8.3, J=5.9 Hz, H-7), 2.64 (1H, m, H-9), 2.67 (1H, d, H-5'), 2.47 (1H, m, H-8'), 1.63 (1H, m, H-8), 2.20 (1H, m, H-9'), 2.19 (3H, s, Me-11), 1.26 ppm (3H, s, Me-12). ¹³C NMR (75.4 MHz, CDCl₃), δ 156.3 (s, C-2), 152.9 (s, C-10), 142.9 (s, C-10a), 132.5 (d, C-4), 126.2 (s, C-4a), 125.1 (s, C-3), 116.4 (t, C-13), 111.2 (d, C-1), 63.1 (d, C-7), 62.3 (s, C-6), 55.3 (q, OMe), 38.8 (t, C-5), 33.5 (t, C-9), 31.2 (t, C-8), 22.4 (q, C-12) and 15.7 ppm (q, C-11).

cis-6,7-Epoxy-2-methoxy-3,6α,10β-trimethylbenzocyclooctane (30). A solution of **29** (100 mg, 0.4 mmol) in EtOH (2 ml) was stirred in the presence of Pd/C (5%, 15 mg) under a hydrogen atmosphere for 1 h,

filtered and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 3:1) yielding **30** (95 mg, 95%) as colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 6.93 (1H, s, H-4), 6.78 (1H, s, H-1), 3.83 (3H, s, MeO), 2.85 (1H, d, $J=13.1$, H-5), 2.76 (1H, d, H-5'), 2.19 (3H, s, Me-11), 1.40 (3H, d, $J=7.2$ Hz, Me-13), 1.19 (3H, s, Me-12), 2.64 (1H, ddd, $J=1.0$, $J=6.6$ Hz, $J=8.00$ Hz, H-7) and 2.45 ppm (1H, m, H-10). ^{13}C NMR (75.4 MHz, CDCl_3), δ 157.4 (s, C-2), 142.9 (s, C-10a), 132.8 (d, C-4), 127.1 (s, C-4a), 123.5 (s, C-3), 106.2 (d, C-1), 63.4 (d, C-7), 61.9 (s, C-6), 55.3 (q, OMe), 39.0 (t, C-5), 35.2 (t, C-9), 33.0 (d, C-10), 26.3 (q, C-12), 26.2 (t, C-8), 19.5 (q, C-13) and 15.5 ppm (q, C-11).

trans-3,10-Dimethyl-2-methoxy-6-methylenebenzocyclooctan-7-ol (31). A solution of **30** (100 mg) in benzene (2 ml) was treated with *p*-toluenesulfonic acid (catalytic amounts). After stirring for 1 h at room temperature, the mixture was neutralized with saturated aq. NaHCO_3 , extracted with EtOAc, dried and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 2:1) to give **31** (70 mg, 70%) as colorless oil. UV (EtOH) λ_{max} 230 nm (ϵ 4692), λ_{max} 280 nm (ϵ 1615). IR (CHCl_3), ν_{max} 3602, 3462 (OH, free and associated), 1710, 1638, 1510 (C=C) 1272 cm^{-1} (C-O). MS: m/z 246.4 (100%) for $\text{C}_{16}\text{H}_{22}\text{O}_2$ (low resolution), 200.3 (75.4%) 162.3 (98.3%), 115.2 (23.4%). ^1H NMR (300 MHz, CDCl_3) δ 6.66 (1H, s, H-1), 6.90 (1H, s, H-4), 4.85 (1H, br s, H-12), 4.93 (1H, br s, H-12'), 4.16 (1H, d, $J=8.5$ Hz, H-7), 3.84 (1H, d H-5), 3.17 (1H, d, H-5'), 3.81 (3H, s, Me-O), 3.35 (1H, m, H-10), 2.16 (3H, s, Me-11), 1.34 (3H, d, $J=6.8$ Hz, Me-13), 1.30 (2H, m, H-8, H-9), 1.88 (1H, m, H-8'), 2.07 (1H, m, H-9') and 1.69 ppm (1H, br s, OH). ^{13}C NMR (75.4 MHz, CDCl_3), δ 156.8 (s, C-2), 153.7 (s, C-6), 142.2 (s, C-10a), 131.3 (d, C-4), 130.4 (s, C-4a), 124.1 (s, C-3), 110.2 (t, C-12), 106.5 (d, C-1), 74.0 (d, C-7), 55.4 (q, OMe), 36.8 (t, C-5), 36.3 (t, C-9), 33.8 (d, C-10), 33.0 (t, C-8), 21.1 (q, C-13) and 15.6 ppm (q, C-11).

2-Methoxy-3,6,10-trimethylbenzocyclooctan-7-ol (32). A solution of **31** (100 mg) in EtOH (3 ml) was stirred in the presence of Pd/C (5%, 20 mg) under a hydrogen atmosphere for 1 h, filtered and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 3:1) yielding **32** (98 mg, 97%) as colorless oil. UV (MeOH), λ_{max} = 225 (ϵ 5714), λ_{max} 271 (ϵ 2040) and λ_{max} 277 nm (ϵ 2040). IR (CHCl_3), ν_{max} 3616, 3454 (OH free and associated), 1614, 1578 cm^{-1} (C=C, arom). MS: m/z 248.4 (100%) for $\text{C}_{16}\text{H}_{24}\text{O}_2$, 215.4 (12%), 202.4 (80%), 187.2 (73%). ^1H NMR (300 MHz, CDCl_3), δ 6.84 (1H, s, H-4), 6.69 (1H, s, H-1), 3.82 (3H, s, MeO), 3.28 (1H, dd, $J=3.5$ Hz, $J=14$ Hz, H-5), 2.23 (1H, dd, $J=14$ Hz, $J=3.5$ Hz, H-5'), 3.15 (1H, m, H-10), 3.20 (1H, t, $J=8.0$ Hz, H-7), 2.17 (3H, s, Me-11), 1.32 (3H, d, $J=6.9$ Hz, Me-13), 0.96 (3H, d, $J=6.9$ Hz, Me-12), 1.40 (H, br s OH, D_2O exchangeable), 1.20-2.00 ppm (4H, m, H-8, H-9). ^{13}C NMR (75.4 MHz, CDCl_3), δ 156.5 (s, C-2), 143.2 (s, C-10a), 132.2 (d, C-4), 128.5 (s, C-4a), 122.7 (s, C-3), 106.7 (d, C-1), 75.4 (d, C-7), 55.3 (q, OMe), 41.6 (d, C-6), 37.1 (t, C-9), 34.7 (d, C-10), 33.1 (t, C-5 or C-8), 32.5 (t, C-8 or C-5), 21.7 (q, C-13), 17.3 (q, C-12) and 15.6 ppm (q, C-11).

Methylation of parvifoline (1). A solution of parvifoline (**1**) (217 mg, 1.0 mmol) in acetone (3 ml) was treated with Me_2SO_4 (0.1 ml, 1.0 mmol) in the presence of K_2CO_3 (200 mg, 1.4 mmol). The mixture was stirred under reflux for 4 h, filtered and concentrated. The residue was purified by CC (hexane-AcOEt 8:1) yielding *O*-methylparvifoline (**3**) (219 mg, 94%) as colorless oil. UV (EtOH), λ_{max} 223 (ϵ 4210), 281 nm (ϵ 2105). IR (CHCl_3), ν_{max} 1614, 1577, 1500 (C=C), 1000, 1187 cm^{-1} (C-O-Ar). MS: m/z 230.3 (70%) for

$C_{16}H_{22}O$ (low resolution), 201.4 (32%), 187.2 (28%), 149.2 (100%). 1H NMR (300 MHz, $CDCl_3$) δ 6.64 (1H, s, H-1), 6.90 (1H, s, H-4), 5.36 (1H, t, $J=7.2$, H-7), 3.81 (3H, s, MeO), 3.54 (1H, d, $J=18.1$ Hz, H-5), 3.04 (1H, d, $J=18.2$, H-5'), 3.20 (1H, m, H-10), 2.16 (3H, s, Me-11), 1.75 (3H, s, Me-12) and 1.36 ppm (3H, d, $J=6.8$ Hz, Me-10). ^{13}C NMR (75.4 MHz, $CDCl_3$), δ 157.0 (s, C-2), 143.4 (s, C-10a), 137.8 (s, C-6), 131.7 (d, C-4), 130.2 (s, C-4a), 123.3 (d, C-7), 123.1 (s, C-3), 106.3 (d, C-1), 55.4 (q, OMe), 41.6 (t, C-5), 40.0 (t, C-9), 33.4 (d, C-10), 26.3 (q, C-12), 23.7 (t, C-8), 19.4 (q, C-13) and 15.6 ppm (q, C-11).

cis-6,7-Epoxy-2-methoxy-3,6 α ,10 α -trimethylbenzocyclooctane. (34). A solution of *O*-methylparvifoline (**3**) (4 g, 17.3 mmol) in CH_2Cl_2 was treated with *m*-chloroperbenzoic acid (3 g, 17.3 mmol) for 5 h (*ca.* 0.5 g each 30 min) at room temperature. The mixture was filtered and concentrated, treated with hexane, filtered and evaporated. The residue was purified by CC (hexane-AcOEt 3:1) to give **34** (4.1 g, 98%) as white crystals. Recrystallization from hexane provided the pure sample mp 95-97 °C. UV (EtOH), λ_{max} 228 (ϵ 5617), λ_{max} 278 nm (ϵ 2471). IR ($CHCl_3$) ν_{max} 1708, 1614 (C=C, arom), 1281 cm^{-1} (C-O, epoxide). MS: m/z 246.3 (71%) for $C_{16}H_{22}O_2$, 203.4 (34%), 189.4 (100%), 161.2 (34%). 1H NMR (300 MHz, $CDCl_3$) δ 6.87 (1H, s, H-4), 6.57 (1H, s, H-1), 3.79 (3H, s, MeO), 3.02 (1H, d, $J=15.9$ Hz, H-5), 3.23 (1H, d, H-5') AB, 2.73 (1H, dd, $J_{7,8\alpha} = 8.7$, $J_{7,8\beta} = 6.2$ Hz, H-7), 2.13 (3H, s, Me-11), 1.36 (3H, d, $J=6.8$ Hz, Me-13), 1.39 (3H, s, Me-6), 3.05 (1H, m, H-10) 0.69 (1H, m, H-8), 1.80 (1H, m, H-8'), 1.20 (1H, m, H-9) and 1.93 ppm (1H, m, H-9').

Treatment of 34 with *p*-toluenesulfonic acid. A solution of **34** (4 g) in benzene (60 ml) was treated with *p*-toluenesulfonic acid (300 mg). The mixture was stirred at room temperature during 24 h, neutralized with saturated aq. $NaHCO_3$ and washed with water. The organic layer was dried and evaporated under vacuum. The residue was purified by CC yielding **37** (hexane-AcOEt 4:1) (70 mg, 2.3%), **36** (hexane-AcOEt 3:1) (120 mg, 3.0%), **31** (hexane-AcOEt 3:1) (100 mg, 2.5%) and **33** (hexane-AcOEt 2:1) (50 mg, 1.2%). **Isomer 36**, mp 84-86 °C, IR ($CHCl_3$) ν_{max} 3598, 3461 (OH, free and associated), 1638, 1612, 1502 (C=C), 1274 cm^{-1} (C-O). 1H NMR (300 MHz, $CDCl_3$) δ 6.62 (1H, s, H-1), 6.93 (1H, s, H-4), 5.02 (1H, br s, H-12), 4.97 (1H, br s, H-12'), 4.20 (1H, d, $J=8.5$ Hz, H-7), 3.80 (3H, s, MeO), 3.43 (1H, d, $J=14.4$, H-5), 3.54 (1H, d, H-5'), 3.27 (1H, m, H-10), 2.16 (3H, s, Me-11), 1.35 (3H, d, $J=6.7$ Hz, Me-13), 1.68 and 1.20 (1H each signal, 2m, H-8), 1.94 and 1.20 ppm (1H each signal, m, H-9). The stereochemistry was deduced by nOe differential experiments. ^{13}C NMR (75.4 MHz, $CDCl_3$), δ 156.9 (s, C-2), 153.7 (s, C-6), 141.1 (s, C-10a), 131.6 (d, C-4), 130.2 (s, C-4a), 124.4 (s, C-3), 108.4 (t, C-12), 106.5 (d, C-1), 75.6 (d, C-7), 55.4 (q, OMe), 39.2 (t, C-5), 36.8 (t, C-9), 35.0 (t, C-8), 32.9 (d, C-10), 20.6 (q, C-13) and 15.6 ppm (q, C-11). **Isomer 33**, colorless oil UV (EtOH) λ_{max} 223 (ϵ 5230), λ_{max} 283 nm (ϵ 1846). IR ($CHCl_3$) ν_{max} 1690 cm^{-1} (C=O), 1272 (C-O). 1H NMR (300 MHz, $CDCl_3$) δ 6.86 (1H, s, H-4), 6.70 (1H, s, H-1), 3.82 (3H, s, MeO), 3.26 (1H, dd, $J=4.1$, $J=14.2$, H-5), 2.51 (1H, dd, $J=4.1$, $J=14.2$, H-5'), 2.84 (2H, m, H-6, H-10), 2.18 (3H, s, Me-11), 2.00 (3H, m, H-8, H-9'), 1.30 (1H, m, H-9), 1.33 (3H, d, $J=6.8$ Hz, Me-13) and 1.04 ppm (3H, d, $J=7.0$ Hz, Me-12). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 217.0 (s, C-7), 157.2 (s, C-2), 142.2 (s, C-10a), 133.6 (d, C-4), 127.0 (s, C-4a), 123.5 (s, C-3), 106.7 (d, C-1), 55.3 (q, OMe), 50.4 (d, C-6), 36.1 (t, C-8), 35.6 (t, C-9), 35.0 (t, C-5), 33.7 (d, C-10), 20.8 (q, C-13), 15.6 (q, C-11) and 14.2 ppm (q, C-12). **Isomer 37**, colorless oil, IR ($CHCl_3$), ν_{max} 3612, 3462 (OH, free and associated), 1610, 1506 (C=C) and 1260 cm^{-1} (C-O). 1H NMR (300 MHz, $CDCl_3$), δ 6.99 (1H, s, H-4), 6.61 (1H, s, H-1), 5.65 (1H, tq, $J_{9,11} = 1.4$ Hz, $J_{9,8} = 7.1$ Hz, H-9), 3.81 (3H,

s, MeO), 3.72 (1H, m, H-7), 2.64 (1H, dd, $J=13.8$, $J=10.6$, H-5 α), 1.78 (1H, dd, $J=13.7$, $J=8.7$, $J=8\beta$), 2.49 (1H, ddd, $J_{8,9} = 7$ Hz, $J_{8\alpha,8\beta} = 13.3$ Hz, $J_{8\alpha,7} = 8.8$, H-8 α), 2.17 (1H, d, $J=13.3$ Hz, H-5 β), 1.64 (1H, m, H-6), 2.19 (3H, s, Me-11), 2.07 (3H, br s, Me-13) and 1.12 ppm. (3H, d, $J=7.1$ Hz, Me-12). ^{13}C NMR (75.4 MHz, CDCl_3) δ 155.7 (s, C-2), 139.1 (s, C-10a), 138.2 (s, C-10), 132.8 (s, C-4a), 131.8 (d, C-4), 125.7 (s, C-3), 121.1 (d, C-9), 107.9 (d, C-1), 69.7 (d, C-7), 55.3 (q, OMe), 41.4 (d, C-6), 34.0 (t, C-8), 33.4 (t, C-5), 24.9 (q, C-13), 19.6 (q, C-2) and 15.9 ppm (q, C-11).

***O*-Methylisoparvifolinone (6).** A solution of **31** (100 mg, 0.40 mmol) in pyridine (3 ml) was treated with CrO_3 (62 mg, 0.62 mmol), stirred at room temperature for 1 h, extracted with EtOAc, washed successively with HCl (10%), water, saturated aq. NaHCO_3 and water. The organic layer was dried and concentrated under vacuum. The residue was purified by CC (hexane-AcOEt 9:1) yielding *O*-methylisoparvifolinone (**6**) (70 mg, 80%) as pale yellow oil. IR (CHCl_3) ν_{max} 1648, 1610 cm^{-1} (C=C=O). ^1H NMR (300 MHz, CDCl_3) δ 6.77 (1H, s, H-1), 7.08 (1H, br s, H-5), 7.03 (1H, s, H-4), 3.87 (3H, s, MeO), 3.01 (1H, m, H-10), 2.50 (2H, m, H-8, H-9), 2.18 (1H, m, H-8'), 1.58 (1H, m, H-9'), 2.21 (3H, s, Me-11), 2.02 (3H, d, $J=1.4$ Hz, Me-12), and 1.32 ppm (3H, d, $J=6.7$ Hz, Me-13). ^{13}C NMR (75.4 MHz, CDCl_3) δ 203.9 (s, C-7), 158.3 (s, C-2), 143.6 (s, C-10a), 139.0 (d, C-5), 136.4 (s, C-6), 132.7 (d, C-4), 128.8 (s, C-4a), 124.2 (s, C-3), 105.9 (d, C-1), 55.2 (q, OMe), 41.9 (t, C-9), 39.0 (t, C-8), 33.7 (d, C-10), 20.5 (q, C-12), 19.5 (q, C-13) and 15.5 (q, C-11). Compound **36** was treated as above to give **6** in an 85 % yield.

Isoparvifolinone (5). A solution of *O*-methylisoparvifolinone (**6**) (90 mg, 0.3 mmol) was treated with BBr_3 (2 ml, 1.0 M in CH_2Cl_2), stirred at room temperature for 45 min, treated with a saturated aq. NaHCO_3 solution, concentrated and extracted with EtOAc, dried and evaporated under vacuum. The residue, isoparvifolinone (**5**) was purified by CC (hexane-AcOEt 8:1) (46 mg, 54%), showed the same mp and ^1H NMR spectrum as the natural product.

***O*-Methylparvifoline (3) from 32.** A cold solution of **32** (70 mg, 0.28 mmol) in pyridine (1 ml) was treated with *p*-TsCl (70 mg, 0.36 mmol). The mixture was kept at -4 °C for 36 h. The solution was extracted with EtOAc, washed with HCl (10%), aqueous NaHCO_3 and water. The organic layer was dried and evaporated under vacuum. The residue was purified by CC yielding *O*-methylparvifoline (**3**) (54 mg, 83%).

Parvifoline (1). Ethanethiol (1 ml) was treated with butyllithium (5 ml, 1.6 M in hexane) at -78 °C. The white solid (EtSLi) (63 mg, 0.9 mmol) was added to a solution of *O*-methylparvifoline (**3**) (109 mg, 0.4 mmol) in DMF (5 ml). The mixture was stirred at 85 °C for 24 h, extracted with EtOAc, dried and evaporated under vacuum to give parvifoline (**1**) (100 mg, 98%), identical with the natural product.²

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