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NEW COUMARINS FROM *SESELI SIBIRICUM*

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Key Word Index—*Seseli sibiricum*; Umbelliferae; coumarins; sesebrin; sesebrinol; sibiricol; isobergapten; phellopterin; bergapten; sibiricin; sesibiricin; coumurrayin; osthenol; meranzin hydrate; sitosterol.

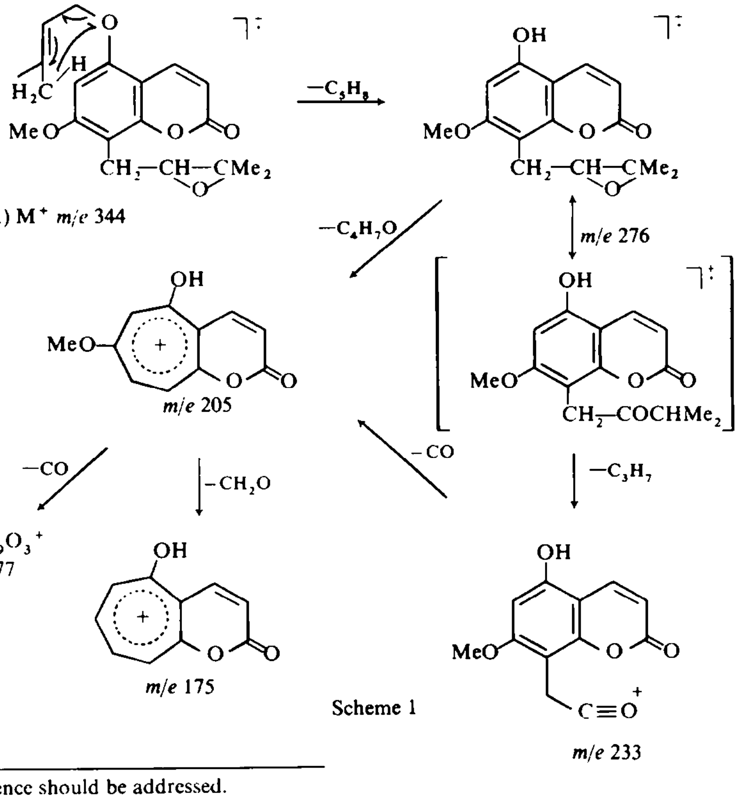
Abstract—Three new coumarins, sesebrin(7-methoxy-5-[3-methylbut-2-enyloxy]-8-[3-methyl-2,3-epoxybutyl] coumarin), sesebrinol(7-methoxy-5-[3-methylbut-2-enyloxy]-8-[3-methyl-2,3-dihydroxybutyl] coumarin) and sibiricol (7-methoxy-5-hydroxy-8-[3-methylbut-2-enyl] coumarin) have been isolated from the roots of *Seseli sibiricum*, in addition to sitosterol and 7 known coumarins, isobergapten, bergapten, phellopterin, sibiricin, coumurrayin, osthenol and meranzin hydrate.

INTRODUCTION

Seseli sibiricum Benth. is an odorous perennial glabrous herb growing in Jammu and Kashmir at altitudes of 2500–3500 m [1]. Its roots are rich in essential oils which yield a number of monoterpenes [2]. Four coumarins viz. osthol, imperatorin, bergapten and sibiricin have been isolated from its umbels [3]. From the roots of the plant, isolation of two coumarins, osthol and sesibiricin have been reported [4, 5]. In the course of our researches on the Umbelliferae plants of the north western Himalayan region, we undertook a detailed chemical examination of the roots which resulted in the isolation of 10 coumarins, in addition to osthol and sesibiricin. Of the 10 coumarins, 3 are new.

RESULTS AND DISCUSSION

The roots of *S. sibiricum* were successively extracted with hexane and benzene. The hexane extract on chromatography yielded sesibiricin [5], osthol[4], isobergapten,



Scheme 1

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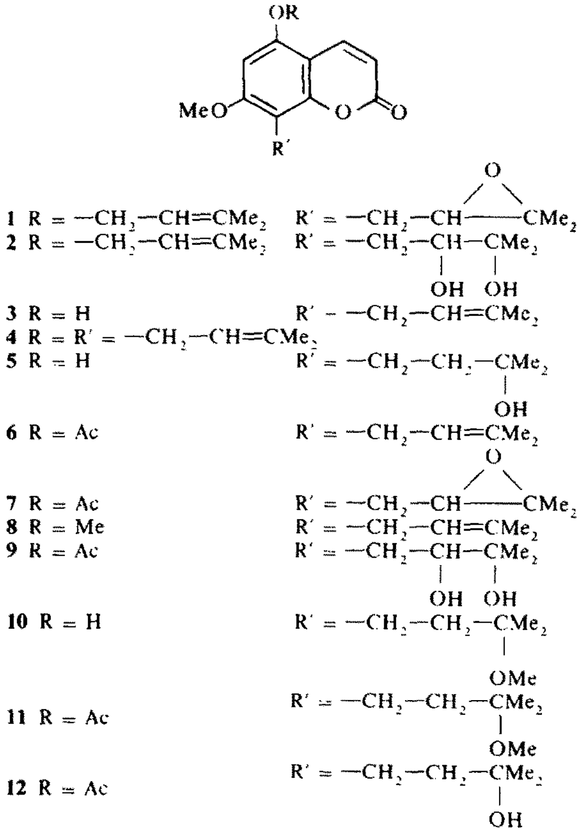
bergapten, coumurrayin, phellopterin, sibiricin, sitosterol and two new coumarins for which we propose the names sesebrin and sesebrinol.

Sesebrin (M$^+$ 344), mp 112–113° has been characterized as 7-methoxy-8-(3-methyl-2,3-epoxybutyl)-5-(3-methylbut-2-enyloxy) coumarin (**1**) on the basis of following evidence. In the PMR spectrum (100 MHz) a pair of doublets at δ 6 and 7.9 were assigned to H-3 and H-4, respectively. H-6 appeared as a singlet at 6.26. The olefinic proton at δ 5.4 was a triplet whilst the methoxy protons resonated at δ 3.85. A doublet at δ 4.57 was assigned to the *O*-methylene. The benzylic methylene and epoxymethine protons appeared as a multiplet between δ 2.6–3.2. The two methyls of the epoxyprenyl chain appeared as singlets at δ 1.23 and 1.44 whilst the methyls of the prenyloxy chain at C-5 showed up as a singlet at 1.74. The MS of sesebrin (**1**) showed significant peaks at *m/e* 276 (base peak), 233, 218, 205, 177, 175 which may be rationalized as in Scheme 1. The structure for sesebrin is confirmed by its synthesis from sesibiricin [6]. Sesibiricin (**4**) was readily dealkylated with 1% aqueous methanolic HCl to the phenol (**3**), the acetate (**6**) of which on epoxidation with perbenzoic acid gave the epoxide (**7**) which, on *trans*-prenylation with isoprenyl chloride in acetone solution in the presence of anhydrous K_2CO_3 and a crown-ether, afforded sesebrin (**1**).

Sesebrinol (M$^+$ 362), mp 114°, has been assigned the structure, 7-methoxy-8-(3-methyl-2,3-dihydroxybutyl)-5-(3-methylbut-2-enyloxy) coumarin (**2**). In its PMR spectrum H-3 and H-4 appeared as a pair of doublets at δ 5.97 and 7.88. The methoxy protons resonated at δ 3.83 and the methyls of the isopentenyloxy chain at C-5 appeared at δ 1.72 and 1.76. A coupled triplet at δ 5.38 is assigned to the olefinic proton whilst the *O*-methylene showed up as a doublet at δ 4.51. A multiplet centred at δ 2.78 and integrating for 4 protons was assigned to the benzylic methylene and the hydroxyl groups because on D_2O exchange the multiplet integrated for only two protons. A pair of doublets at δ 3.49 is for the methine in $-CH_2-\underline{CH}(OH)-$ (X part of ABX system, AB part being the benzylic methylene). The methyls in the dihydroxyisopentyl chain showed up as a singlet at δ 1.26. In the MS of **2**, prominent peaks are observed at *m/e* 294, 276, 236, 235, 205, 177, 175 and 59 (Scheme 2) which are in accordance with the structure (**2**). Synthesis of sesebrinol (**2**) from the acetate (**6**) was achieved by treating (**6**) with OsO_4, decomposing the osmate to obtain **9** followed by *trans*-prenylation. Sesebrinol (**2**) is also formed amongst other products by heating **1** with aqueous oxalic acid.



1 R = $-CH_2-CH{=}CMe_2$ R′ = $-CH_2-CH\overset{O}{\frown}CMe_2$

2 R = $-CH_2-CH{=}CMe_2$ R′ = $-CH_2-\underset{OH}{CH}-\underset{OH}{CMe_2}$

3 R = H R′ = $-CH_2-CH{=}CMe_2$

4 R = R′ = $-CH_2-CH{=}CMe_2$

5 R = H R′ = $-CH_2-CH_2-\underset{OH}{CMe_2}$

6 R = Ac R′ = $-CH_2-CH{=}CMe_2$

7 R = Ac R′ = $-CH_2-CH\overset{O}{\frown}CMe_2$

8 R = Me R′ = $-CH_2-CH{=}CMe_2$

9 R = Ac R′ = $-CH_2-\underset{OH}{CH}-\underset{OH}{CMe_2}$

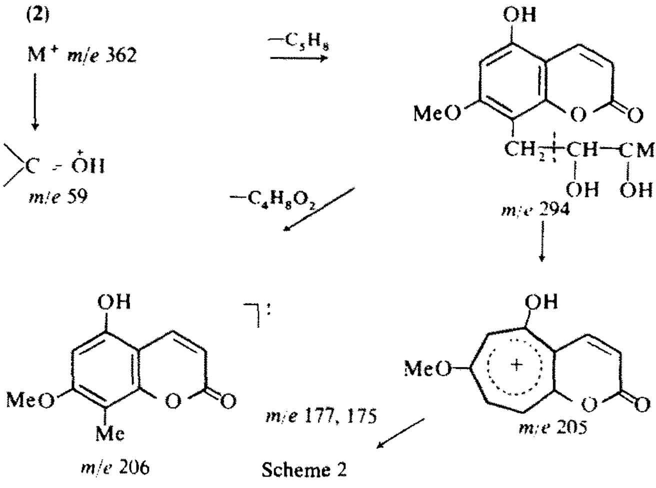
10 R = H R′ = $-CH_2-CH_2-\underset{OMe}{CMe_2}$

11 R = Ac R′ = $-CH_2-CH_2-\underset{OMe}{CMe_2}$

12 R = Ac R′ = $-CH_2-CH_2-\underset{OH}{CMe_2}$

The benzene extract of the roots on chromatography yielded a new coumarin, named sibiricol besides **2** and meranzin hydrate.

Sibiricol (M$^+$ 260), mp 194° has been characterized as 5-hydroxy-7-methoxy-8-(3-methylbut-2-enyl) coumarin (**3**). It shows a greenish yellow fluorescence in UV



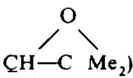
Scheme 2

light. It has a phenolic hydroxyl group and gives a positive $FeCl_3$ test. In the PMR spectrum of **3**, H-3 and H-4 appeared as a pair of doublets at δ 6.03 and 7.77. A singlet integrating for two protons represents H-6 and the hydroxyl since on D_2O exchange the signal integrates for one proton. The prenyl side chain at C-8 was discernible from the singlets at δ 1.58 and 1.73 (methyls), a doublet at δ 3.35 and a triplet at δ 5.13 ($—CH_2—CH=$). The methoxy protons resonated at δ 3.77. The identity of sibiricol with the acid hydrolysis product (**3**) from sesibiricin became evident at this stage. Final proof of the structure was obtained by comparing their physical data as well as comparing the data of sibiricol acetate with those of the acetate of the acid hydrolysis product from sesibiricin and also by converting sibiricol into coumurrayin (**8**) [7] and **4**. It is interesting to note that the dealkylation of **4** with methanolic HCl gives **3** in *ca* 5% yield, the major products being the hydroxyprenyl (**5**) and methoxyprenyl (**10**) derivatives. These results are the outcome of experiments designed to prepare sibiricol (**3**) in high yield, required for the synthesis of **1** and **2**.

EXPERIMENTAL

Mps are uncorr. PMR spectra were recorded at 100 MHz in $CDCl_3$ unless otherwise stated. R_f values refer to TLC on Si gel plates using C_6H_6-Me_2CO (9:1) as solvent. The plant materials (roots) were collected from Kashmir (voucher specimen No. 7124 deposited at the Plant Survey Division of R.R.L., Jammu). The identity of the known products was established by comparison of their physical data with those of their authentic samples. These include mps, UV fluorescence, R_f values, NMR and MS. The new coumarins were characterized on the basis of chemical evidence and spectral data.

Extraction and isolation. Dried and ground roots (4.5 kg) of *S. sibiricum* were extracted successively with hexane and C_6H_6 (Soxhlet) for 48 hr. The hexane extract on removal of solvent yielded a brown residue (280 g) which was chromatographed over neutral Al_2O_3 (5 kg) deactivated with H_2O (10%). 46 fractions (2 l. each) were collected, fractions 1–36, 37–40, 41–45 and 46 having been eluted with hexane, C_6H_6, $CHCl_3$ and EtOAc, respectively. Fractions 5–6 afforded sesibiricin (10 g), mp 122°, R_f 0.76. Fractions 7–13 (95 g) on rechromatography over Si gel gave sesibiricin (14 g), a mixture (21 g) of sesibiricin and osthol, osthol (29 g), mp 84°, R_f 0.68 and a mixture (21 g) of osthol and isobergapten from which isobergapten (800 mg), mp 216–217°, R_f 0.72, was separated by fractional crystallization from C_6H_6. Fractions 14–17 (12 g) were rechromatographed over Si gel (400 g). Elution with hexane–C_6H_6 (1:1) gave coumurrayin (**8**) (300 mg), mp 155–156°, R_f 0.58. C_6H_6 eluted sitosterol (520 mg), mp 137°. Fractions 18–36 (30 g) were rechromatographed over Si gel (1 kg). C_6H_6 eluted phellopterin (2 g), mp 102°, R_f 0.54 and bergapten (4.7 g), mp 188°, R_f 0.52. Elution with C_6H_6-$CHCl_3$ (1:1) gave a fraction which on crystallization from Me_2CO-hexane afforded sesebrin (**1**) as needles (830 mg), mp 112–113°. Later C_6H_6-$CHCl_3$ eluates yielded sibiricin (630 mg), mp 153°, R_f 0.40. Fractions 36–46 (16 g) were chromatographed over Si gel (500 g). The $CHCl_3$ eluate on rechromatography over Si gel gave osthenol (2.1 g), mp 128–129° (needles from EtOAc-hexane), blue fluorescence in UV light, R_f 0.41. Elution with $CHCl_3$-EtOAc (4:1) gave a fraction which on crystallization from EtOAc-hexane yielded sesbrinol (**2**) as needles (1.6 g), mp 114–115°. The C_6H_6 extract of the hexane extracted roots yielded on removal of the solvent a dark brown residue (185 g). This was chromatographed over Al_2O_3 (3 kg, grade IV). The C_6H_6 eluate was rechromatographed over Si gel. The C_6H_6–$CHCl_3$ (1:1) eluate gave a greenish yellow fluorescent compound which on crystallization from EtOAc hexane afforded sibiricol (**3**) as needles (310 mg), mp 193–194°. $CHCl_3$ eluted a mixture of 2 blue fluorescent compounds which was rechromatographed over Si gel. Earlier $CHCl_3$–EtOAc (4:1) eluates gave sesebrinol (200 mg), mp 115°, whilst later fractions yielded meranzin hydrate (1 1 g), mp 128–129°, needles from EtOAc–hexane, R_f 0.05.

Sesebrin (**1**). Mp 112–113°. $[\alpha]_D$ + 15° (*c* 1%, EtOH). Blue fluorescence in UV light. R_f 0.51 λ_{max} nm: 327, 261, 253 (*sh*), 239 (*sh*). PMR (δ ppm): 1.23 (*s*) and 1.44 (*s*) (Me's epoxyprenyl), 1.74 (6H, *s*, Me's of prenyloxy), 2.6–3.2 (3H, *m*, Ar—$\underline{CH}_2$—  $\overset{\quad O}{\overbrace{\underline{C}H—C}}\ Me_2$), 3.85 (3H, *s*, OMe), 4.57 (2H, *d*, *J* = 7 Hz, —O— $\underline{CH}_2$—CH=), 5.4 (1H, coupled *t*, *J* = 7 Hz, —O—CH_2— $\underline{CH}$=), 6 (1H, *d*, *J* = 9.5 Hz, H-3), 6.26 (1H, *s*, H-6) and 7.9 (1H, *d*, *J* = 9.5 Hz, H-4). MS: *m/e* 344 (M^+), 276, 233, 218 (*m/e* 233-Me), 205, 177, 175, 161, 147, 91.

Sesebrinol (**2**). Mp 114–115°. $[\alpha]_D$ + 56° (*c* 1%, EtOH). Blue fluorescence in UV light. R_f 0.07. λ_{max} nm: 330, 262, 256 (*sh*), 238 (*sh*). PMR (δ in ppm): 1.26 (6H, *s*, Me's of hydroxyprenyl), 1.72 and 1.76 (3H each, *s*, =CMe_2), 2.76 (4H, *m*, on D_2O exchange 2 H, *m*, Ar—$\underline{CH}_2$—CH($\underline{OH}$)—C ($\underline{OH}$) Me_2), 3.49 (1H, *dd*—on removal of OH coupling by D_2O exchange—*J* = 3.5, 7.5 Hz, —CH_2—$\underline{CH}$(OH)—), 3.83 (3H, *s*, OMe), 4.51 (2H, *d*, *J* = 7 Hz, Ar—O—$\underline{CH}_2$—CH=), 5.38 (1H, coupled *t*, *J* = 7 Hz, —O—CH_2—$\underline{CH}$=), 5.97 (1H, *d*, *J* = 10 Hz, H-3), 6.24 (1H, *s*, H-6), 7.88 (1H, *d*, *J* = 10 Hz, H-4). MS: *m/e* 362 (M^+), 294, 276 (*m/e* 294-H_2O), 236 (*m/e* 294 − Me_2CO), 235 (*m/e* 294 − Me_2COH), 206, 205, 177, 175, 161, 147, 91, 59.

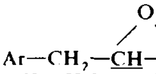
Sibiricol (**3**). Mp 193–194°. Greenish yellow fluorescence in UV light. R_f 0.23. $FeCl_3$ test -green. λ_{max} nm: 327, 266. PMR (δ in ppm, 90 MHz): 1.58 (3H, *s*, Me), 1.73 (3H, *s*, Me), 3.35 (2H, *d*, *J* = 7 Hz, Ar—$\underline{CH}_2$—CH=), 3.77 (3H, *s*, OMe), 5.13 (1H, *t*, *J* = 7 Hz, Ar—CH_2—$\underline{CH}$=), 6.03 (1H, *d*, *J* = 10 Hz, H-3), 7.17 (2H, *s*, on D_2O exchange 1H, *s*, H-6 and phenolic OH), 7.77 (1H, *d*, *J* = 10 Hz, H-4). MS: *m/e* 260 (M^+), 245 (*m/e* 260 − Me), 217 (*m/e* 245 − CO), 189 (*m/e* 217 − CO). On treatment with Ac_2O–C_5H_5N **3** gave the acetate (**6**), mp 124–125°. PMR (δ in ppm, CCl_4, 60 MHz): 2.3 (3H, *s*, OCOMe), 6.55 (1H, *s*, H-6), no D_2O exchangeable peak, rest of signal similar to that of **3**.

Methylation. Sibiricol (**3**) (100 mg) in MeOH (5 ml) was treated with an Et_2O soln of CH_2N_2. After 24 hr the soln was evapd to dryness and the residue crystallized from Me_2CO hexane when coumurrayin (**8**) was obtained as needles, mp 156°, identical with natural coumurrayin (mmp, Co-TLC, PMR).

Prenylation. **3** (100 mg) in dry Me_2CO (10 ml) and prenyl chloride (0.2 ml) were refluxed in the presence of dry K_2CO_3. After 2 hr the mixture was filtered and the filtrate evapd to dryness. The residue was crystallized from Me_2 CO–hexane when sesibiricin (**4**) was obtained as needles, mp 121 122° (mmp, Co-TLC, PMR).

Acid hydrolysis of **4** *in* MeOH: *formation of* **3**, **5** *and* **10**. **4** (1 g) in 5% HCl-MeOH (30 ml) was refluxed under N_2 for 3 hr. After removal of MeOH, the residue was taken up in $CHCl_3$. Usual work up gave a gummy mass which on separation by PLC gave 3 phenolic products. The least polar phenol was characterized as **3** (50 mg), mp 193°, on the basis of physical data including mmp, R_f, PMR and MS. The middle one, characterized as **10** was crystallized from EtOAc hexane as needles (360 mg), mp 148°, acetate (**11**), prepared by treating **10** with Ac_2O–C_5H_5N, mp 112°. PMR of **11** (δ in ppm, CCl_4, 60 MHz): 1.32 (6H, *s*, Me's), 1.45–2 (2H, *m*, Ar— CH_2—$\underline{CH}_2$—), 2.42 (3H, *s*,—O COMe), 2.6–3.1 (2H, *m*, Ar— $\underline{CH}_2$ —CH_2—), 3.3 (3H, *s*, OMe in the side chain), 4 (3H, *s*, Ar—OMe), 6.16 (1H, *d*, *J* = 10 Hz, H-3), 6.65 (1H, *s*, H-6), 7.62 (1H, *d*, *J* = 10 Hz, H-4). The most polar phenol (**5**) was crystallized from EtOAc-hexane as colourless needles (130 mg), mp 195–196°, which on treatment with Ac_2O–C_5H_5N gave the acetate (**12**), mp 146–147°. PMR of **12** (δ in ppm, 90 MHz): 1.32 (6H, *s*, Me's), 1.5–2 (3H, *m*, on D_2O exchange 2H, *m*, —CH_2—$\underline{CH}_2$—C ($\underline{OH}$)Me_2), 2.41 (3H, *s*, — OCOMe), 2.7–3.1 (2H, coupled *t*, Ar— $\underline{CH}_2$—CH_2—), 3.91 (3H, *s*, OMe), 6.25 (1H, *d*, *J* = 10 Hz, H-3), 6.69 (1H, *s*, H-6), 7.65 (1H, *d*, *J* = 10 Hz, H-4).

Acid hydrolysis of **4** *in aq.* MeOH. **4** (3 g) was treated with 1% HCl in 50% aq. MeOH (150 ml) for 30 min under reflux under N_2. It was diluted with H_2O (150 ml) and dist. *in vacuo* at 50° to collect about 100 ml. The solid which separated was collected by filtration, washed with H_2O and dried. This on crystallization from EtOAc–hexane afforded **3** as colourless needles (1.6 g), mp 193°, identical with natural sibiricol (mmp, Co-TLC).

Synthesis of sesebrin (**1**). To a soln of sibiricol acetate (**6**) (600 mg) in $CHCl_3$ (15 ml) was added a soln of perbenzoic acid (400 mg) in $CHCl_3$ (5 ml). After being left for 2 hr at room temp. the soln was washed with aq. $NaHCO_3$ and H_2O, dried (Na_2SO_4) and evapd to dryness *in vacuo*. The residue on crystallization from EtOAc–hexane afforded **3** as colourless needles (1.6 g), needles (570 mg), mp 157–158°. PMR (δ in ppm, 60 MHz): 1.27, 1.45 (3H each, *s*, Me's), 2.34 (3H, *s*, OCOMe), 2.6–3.2 (3H, *m*,  $\mathrm{Ar{-}CH_2{-}}\overset{\overset{\displaystyle \mathrm{O}}{\diagup\quad\diagdown}}{\underline{\mathrm{CH}}{-}\mathrm{C}}$), 3.92 (3H, *s*, OMe), 6.15 (1H, *d*, $J = 10$ Hz, H-3), 6.64 (1H, *s*, H-6), 7.57 (1H, *d*, $J = 10$ Hz, H-4). The epoxide (**7**) (200 mg) in dry Me_2CO (30 ml) was refluxed with dry K_2CO_3 (1 g) and 18-Crown-6 (40 mg) under N_2. After 1 hr prenyl chloride (1 ml) was added to this and the mixture refluxed for a further 30 min. The mixture was cooled and the solid filtered off. The filtrate was evapd to dryness *in vacuo*. Crystallization of the residue from Me_2CO–hexane afforded needles (160 mg), mp 107–109°. The product was found to be identical with sesebrin (**1**) on comparison of PMR, MS, TLC and mmp.

Synthesis of sesebrinol (**2**). To sibiricol acetate (**6**) (450 mg) in thiophene free Na-dried C_6H_6 (20 ml) was added OsO_4 (400 mg). After leaving the mixture 18 hr, C_6H_6 was removed *in vacuo* at room temp. The black osmate ester was suspended in aq. EtOH (50 ml) and decomposed by refluxing with $NaHSO_3$ (1.5 g) for 30 min. It was cooled, filtered and the residue washed with EtOH. The combined filtrate and washings were diluted with H_2O (50 ml). EtOH was removed *in vacuo* and the residue taken up in EtOAc. Evapn of EtOAc gave a solid which on crystallization from Me_2CO–hexane afforded the diol (**9**) (320 mg), mp 194–196°. (PMR in agreement with the structure (**9**)). The diol (**9**) (200 mg) in dry Me_2CO (40 ml) was *trans*-prenylated with prenyl chloride and worked up as in the synthesis of **1** when a product (140 mg) was obtained as needles, mp 120–121°. This was found to be identical with natural sesebrinol (**2**) on the basis of fluorescence, mmp, R_f, PMR and MS data.

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