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Alicyclic Terpenoids from Cyclocitryl Phenyl Sulfides. V. A Synthesis of Ferruginol

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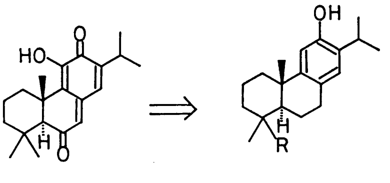
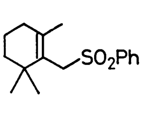
Synopsis. Ferruginol a precursor for taxodione synthesis, was prepared by the coupling of C(10) units between 2-(phenylsulfonylmethyl)-1,3,3-trimethylcyclohexane and 3-isopropyl-4-methoxybenzyl bromide followed by desulfonation and acid-catalyzed cyclization.

Taxodione (**1**), a tumor-inhibitory diterpene, has been isolated from *Taxodium distichum* Rich (Taxodiaceae) by Kupchan *et al.*[2)] Because of its significant tumor-inhibitory activity, its synthesis attracted our attention. Mori *et al.* succeeded the transformation of podocarpic acid into **1** *via* ferruginol (**2**) by several modifications on B and C rings.[3)] Matsumoto *et al.* prepared **1** starting from 2,3-dimethoxyisopropylbenzene by C→B →A ring construction[4a)] and also from abieta-8,11,13-trienoate (**3**).[4b)] Recently, the same authors reported a new route to **1** from methyl ether of **2**.[5)]



1   2 R=Me ; 3 R=CO_2H



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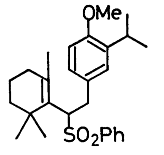

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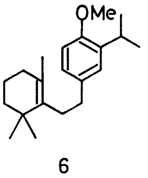

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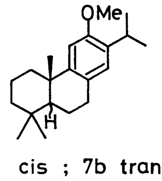

7a cis ; 7b trans

Considering the synthetic design of **1**, ferruginol (**2**) must be one of the desirable precursors of **1** and therefore should be prepared by a simple and practical method, since the reported syntheses involved many steps and unsatisfactory yields.[6)] Here, we describe an efficient synthesis of **2** by the coupling of C(10) units between 2-(phenylsulfonylmethyl)-1,3,3-trimethylcyclohexene (**4**) and 3-isopropyl-4-methoxybenzyl bromide followed by desulfonation and acid-catalyzed cyclization.

The sulfone, **4**, is a synthon of cyclocitral and can react effectively with carbonyls, halides, and epoxides[7)] as a nucleophile. Thus, the reaction of **4** with 3-isopropyl-4-methoxybenzyl bromide afforded **5** in 92% yield on treatment with butyllithium in THF at −70 C°. Desulfonation of **5** was accomplished selectively in 80% yield, without reducing the anisole ring, by the action of potassium in liquid ammonia at −65 °C. Cyclization of **6** thus obtained was performed quantitatively by stirring in AcOH–H_2SO_4 (9 : 1) to afford **7** as a mixture (6 : 4) of *cis*-**7a** and *trans*-**7b**. The isomers were separated by VPC and identified spectroscopically with those reported.[8)] Demethylation of *trans*-**7b** with boron tribromide in dichloromethane gave **2** as a sole product. The spectral data of **2** was consistent with those reported.[3,6g)]

Experimental

Melting point is uncorrected. IR spectra were determined with a JASCO IRA-1 infrared spectrophotometer. NMR spectra were obtained at 100 MHz with a JEOL FX-100 spectrometer and the chemical shift values are expressed in δ value (ppm) relative to Me_4Si in $CDCl_3$. The mass spectra were determined at 70 eV with a Finnigan 3300F.

2-[1-Phenylsulfonyl-2-(3-isopropyl-4-methoxyphenyl)ethyl]-1,3,3-trimethylcyclohexane (5). To a solution of 181 mg (0.65 mmol) of **4** in 2 ml of dry THF was added 0.63 ml (0.98 mmol) of BuLi–ether at −70 °C under N_2. After 5 min tsirring, the reaction mixture was treated with 3-isopropyl-4-methoxybenzyl bromide (221 mg, 0.91 mmol) dissolved in 2 ml of dry THF and stirred at −70 °C for 2 h. After adding 2 ml of saturated NH_4Cl, the organic substances were extracted three times with ethyl acetate. The combined extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (SiO_2, benzene–AcOEt/10 : 1) to afford **5** (359 mg, 92%) as colorless crystals: mp 116—117 °C; IR (Nujol) 1506 (Ar), 1306, 1156 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 7.82—7.30 (5H, m, $ArSO_2$), 6.80—6.52 (3H, m, Ar), 3.98 (1H, dd, J=6 and 8 Hz, $CHSO_2$), 3.75 (3H, s, CH_3O), 3.55—3.00 (3H, m, CH_2Ar, CH), 2.30—1.92 (2H, m, CH_2C=), 2.14 (3H, s, CH_3), 1.70—1.18 (4H, m, CH_2), 1.11 (3H, d, J=7 Hz, CH_3), 1.08 (3H, d, J=7 Hz, CH_3), 0.99 (3H, s, CH_3), 0.36 (3H, s, CH_3); MS *m/e* (rel. intensity) 440 (m^+, 1), 299 (M^+−SO_2Ph, 69), 163 (81), 137 (71), 123 (100). Found: C, 73.66; H, 8.08%. Calcd for $C_{27}H_{36}O_3S$: C, 73.60; H, 8.24%.

2-[2-(3-Isopropyl-4-methoxyphenyl)ethyl]-1,3,3-trimethylcyclohexene (6). To a solution of 132 mg of **5** in 2 ml of dry THF and 20 ml of liq. NH_3 was added 100 mg of potassium at −70 °C and the mixture was vigorously stirred at −70—−65 °C for 2 h. After quenching with 1 ml of EtOH and evaporating the solvent under reduced pressure, 2 ml of saturated NH_4Cl was added to the residue and the organic substance was extracted with ether. The combined ether extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (SiO_2, hexane–benzene/10 : 1), affording **6** (72 mg, 80%). Subsequent elution with hexane–AcOEt (10 : 1) provided **5** (10 mg, 8%): IR (neat) 2840 (MeO), 1610 (Ar), 1500, 1460, 1240 cm^{-1}; NMR ($CDCl_3$) δ 7.02 (1H, d, J=2 Hz, ArH), 7.00 (1H, dd, J=9 and 2 Hz, ArH), 6.75 (1H, d, J=9 Hz, ArH), 3.80 (3H, s, CH_3O), 3.28 (1H, sept, J=7 Hz, CH), 2.44—2.70 (2H, m, CH_2Ar), 2.10—2.37 (2H, m, CH_2), 1.82—2.02 (2H, m, CH_2), 1.67 (3H, s, CH_3C=), 1.30—1.72 (4H, m, CH_2), 1.22 (6H, d, J=7 Hz, CH_3), 1.05 (6H, s, CH_3); MS m/e 300 (M^+, 8), 163 (100). Found: C, 84.04; H, 10.76%. Calcd for $C_{21}H_{32}O$: C, 83.94: H, 10.73%.

12-Methoxyabieta-8,11,13-triene (7). Into 46 mg of **6** was added a mixture of AcOH (1.8 ml) and concd H_2SO_4 (0.2 ml) under ice cooling. The reaction mixture was stirred vigorously at 5 °C for 5 min and at 15—18 °C for 20 h. After adding 5 ml of ice water, the organic substance was extracted with hexane–ether (1 : 5). The combined extracts were washed with saturated $NaHCO_3$ and saturated NaCl, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (SiO_2, hexane–benzene 10 : 1), affording **7** (45 mg, 99%) as a mixture (6 : 4) of *cis*-**7a** and *trans*-**7b**. Both isomers were separated by VPC (SE-30, 3 m, 4ϕ, 210 °C) and identified in comparison with the reported spectral data.

Ferruginol (2). To a solution of 1.4 mg of **7b** in 1.5 ml of dry CH_2Cl_2 was added 10 mg of BBr_3 at −70 °C under stirring. The mixture was stirred for 1 h while the reaction temperature was allowed to rise to −30 °C and then at 15—18 °C for additional 1 h. After adding 0.02 ml of saturated $NaHCO_3$, the mixture was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed (SiO_2, benzene), affording **2** (1.1 mg, 84%) as a sole product. The NMR and IR spectra were consistent with those reported.

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