Total Synthesis of Pinguisone

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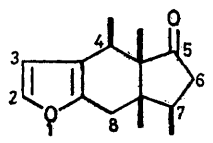
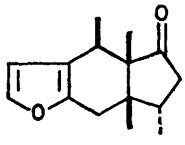
A stereoselective total synthesis of pinguisone (1) from the known (*S*)-(+)2,3,7,7a-tetrahydro-7a-methyl-6*H*-indene-1,5-dione (3) is described. The utilization of common intermediates in the synthesis of pinguisone-like and 7-*epi*-pinguisone-like compounds is discussed.

PINGUISONE (1),[1] a constituent of the crude extract of the liverwort *Aneura pinguis* (L.) Dum., is of particular interest in the total synthesis of natural products, because it possesses both the unusual tricyclic furan skeleton with a *cis*-junction between the five- and six-membered carbocyclic rings and four methyl groups, connected to four contiguous carbon atoms on the β-side of its structure, which produce strong distortions of the bond angles and lengths.[2]



(1)



(2)

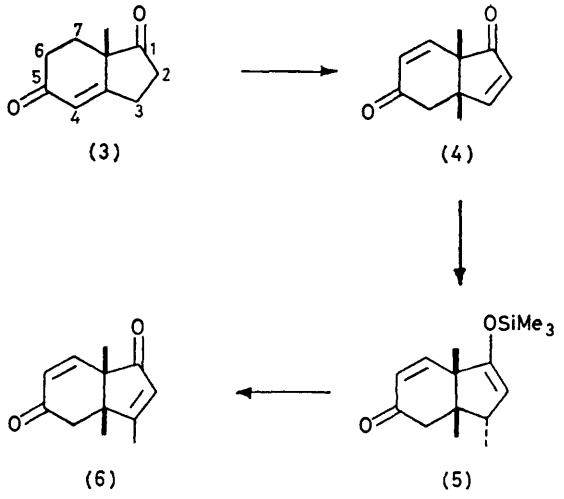
In view of the theoretical interest of such structures and the potential physiological activity of pinguisone-like substances, we developed a general scheme for their total synthesis. In a previous paper [3] we described the synthesis of 7-*epi*-pinguisone (2); in this paper the details of the complete synthesis of pinguisone, starting from the known and easily prepared [4] diketone (3), are given.

RESULTS AND DISCUSSION

The stereoselective synthesis of (+)-(3a*R*,7a*S*)-3a,7a-dihydro-3a,7a-dimethyl-4*H*-indene-1,5-dione (4) *via* the conjugated addition of lithium dimethylcuprate to the dione (3) and the bromination–dehydrobromination of the resulting (+)-(3a*R*,7a*S*)-3a,7a-dimethylindenedione has previously been described by us.[3] Moreover, we have demonstrated [3] that the conjugated addition of a nucleophile (1 mol equiv.) to the diene (4) is completely regioselective, the double bond in the five-membered ring being more reactive. With regard to the stereoselectivity of this reaction, very bulky nucleophiles such as lithium dimethylcuprate gave only one diastereoisomer resulting from an α-attack by the reagent, whereas other nucleophiles, such as the thiols, gave a mixture of the two diastereoisomers.

On the basis of these results we considered two routes for the stereoselective synthesis of pinguisone.

As shown in Scheme 1, the reaction of the diene (4) with lithium dimethylcuprate (1 mol equiv.) and the quenching of the resulting carbanion with trimethylsilyl chloride gave the trimethylsilyl enol ether (5) which was directly converted into the trimethyl diene (6) by dehydrosilylation with palladium diacetate.[5] Reduction of the five-membered ring double-bond with a bulky reagent inverts the α-methyl group at C-3 into the required β-configuration, but we abandoned this approach because of the low yields obtained in the preparation of the silyl enol ether (5) and because of its instability.



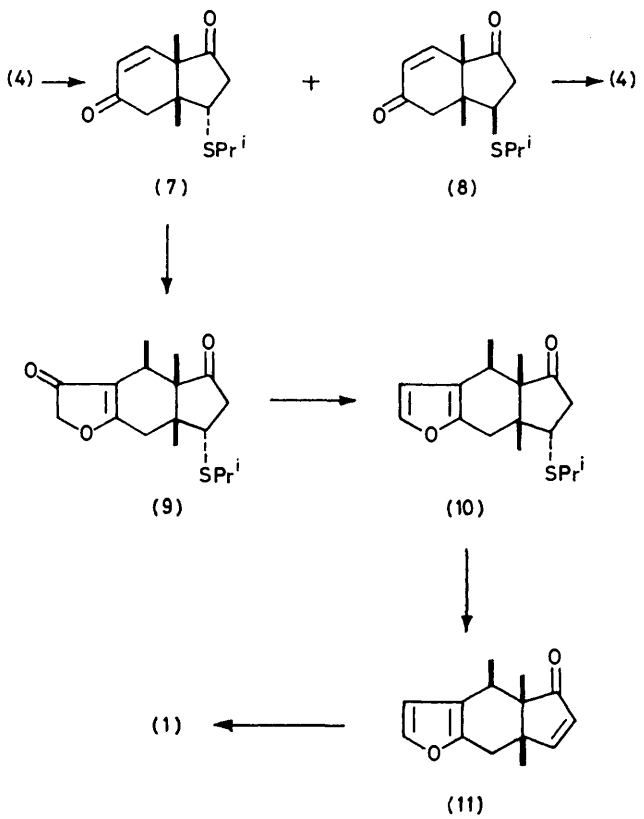
SCHEME 1

The approach which was adopted for the synthesis of pinguisone is shown in Scheme 2.

The reaction of the diene (4) with 1-methylethanethiol (1 mol equiv.) in a buffered solution afforded, cleanly and with high yields, a 3 : 2 mixture of two diastereoisomers (7) and (8) which were separated by chromatography.

The structures and the stereochemistries of these compounds were assigned from their u.v., i.r., ^{1}H n.m.r., ^{13}C n.m.r., and mass spectra. The diastereoisomer with higher polarity is crystalline while the less polar one is oily. In the ^{13}C n.m.r. spectrum, the crystalline compound shows a signal at δ_C 46.3 p.p.m., attributable to C-3, which shifts to δ_C 44.5 p.p.m. in the spectrum of the oily one. The C-7 (equivalent carbon) signal is at δ_C 35.7 in 7-*epi*-pinguisone and at 29.2 p.p.m. in the pinguisone spectrum. The pairs of epimers (at this carbon atom) synthesized by us always show the chemical shift of the α-epimer at δ_C 2—6 p.p.m. downfield with respect to the β-epimer. Hence, the crystalline and more-polar diastereoisomer is considered to possess the α-configuration at

C-3 (7) while the oily and less-polar diastereoisomer has the β-configuration (8). The u.v. spectra of compounds (7) and (8) in 2,2,4-trimethylpentane are different and indicative of anomalous cyclohexenone systems. The behaviour of the two diastereoisomers is understandable, however, in terms of the following factors. (1) The presence of both an α,β-unsaturated enone and a β,γ-unsaturated enone non-classical chromophore.[6] (2) The $\pi \rightarrow \pi^*$ transition of the cyclohexenone system may be



SCHEME 2

affected by second-order interactions [7] with the lone-pair electrons of the oxygen in the five-membered ring. (3) The loss of planarity associated with the α,β-unsaturated ketone chromophore and the six-membered ring conformation are strongly influenced by configuration of the substituent on C-3. In fact, the conformation of the six-membered ring, which is of the half-chair type in compounds of the pinguisone group, is boat-like in the 7-*epi*-pinguisone group, as demonstrated by *X*-ray analysis.[3] Pairs of C-3 epimers are also distinguished by their ^{1}H n.m.r. spectra, the doublet of the C-7 proton being deshielded in the α-epimers and the difference between the chemical shifts of the C-7 and C-6 protons being larger in the α-epimer spectra; thus, the ^{1}H n.m.r. spectrum of the diastereoisomer (7) shows two doublets at δ 6.57 and 6.03 (Δδ 0.54) attributable to the protons at C-7 and C-6, respectively, while the signals of the same protons in the spectrum of the diastereoisomer (8) appear as doublets at δ 6.35 and 6.06 (Δδ 0.29).

Although the ratio (3 : 2) of the diastereoisomeric products (7) and (8) produced by the conjugated addition of 1-methylethanethiol to the diene (4) was not very favourable towards the useful diastereoisomer (7), we did not try to find more stereoselective and bulky thiols, as the diastereoisomer (8) could be quantitatively reconverted into the starting material (4) by oxidation to the sulphoxide with sodium metaperiodate and thermal elimination of sulphenic acid in the presence of calcium carbonate.[8]

Treatment of compound (7) with an excess of lithium dimethylcuprate gave only the β-C-4 methylated diastereoisomer as expected on the basis of the considerations and results discussed for the synthesis of 7-*epi*-pinguisone.[3] The quenching of the enolate anion resulting from the conjugated addition with chloroacetyl chloride, as previously described,[3] afforded directly, in one step, compound (9) containing three methyl groups at C-4, C-4a, and C-7a in the required β-configuration and a β-furanone system; the ^{1}H n.m.r. spectrum of compound (9) displayed, besides other signals, one doublet at δ 1.16 (*J* 8 Hz) due to the C-4 methyl group and one broad singlet at δ 4.40 due to C-2 protons.

The reduction of compound (9) with the very bulky hydride 9-borabicyclononane (9-BBN) was, as in the case of 7-*epi*-pinguisone, fully regioselective; after the reaction, compound (10) was isolated in high yield, the reduction of the furanone being followed by spontaneous elimination of borinic acid in the intermediate complex. In the ^{1}H n.m.r. of compound (10) the signal due to the C-4 methyl group was still present at δ 1.16 (*J* 7.5 Hz) whereas the signal due to the C-2 protons in the spectrum of compound (9) was replaced by a doublet at δ 6.21 (*J* 1.5 Hz) due to the proton at C-3 and a multiplet at δ 7.25 due to the proton at C-2, analogous with the low-field region of the pinguisone spectrum.[9]

Oxidation of compound (10) with sodium metaperiodate at room temperature and subsequent elimination of sulphenic acid by heating the resulting sulphoxide in carbon tetrachloride solution and in the presence of calcium carbonate,[8] afforded compound (11) in high yield. The i.r. spectrum of compound (11) showed absorptions at $\nu_{max.}$ 1 710, 1 605, and 1 500 cm^{-1}, typical of an α,β-unsaturated ketone in a five-membered ring and of a furan ring; its ^{1}H n.m.r. spectrum, besides the multiplet at δ 7.17 and the doublet at 6.18 due to the C-2 and C-3 protons, exhibited two new doublets at δ 7.18 and 5.91 (*J* 6 Hz) due to the C-7 and C-6 protons respectively.

Unlike compound (4), if a torsion angle between the two methyl groups at C-7a and C-4a of approximately 45° and a quasi-chair conformation for the six-membered ring are considered for compound (11), as occurs in the structure of pinguisone, the presence of two α-hydrogens at C-4 and C-8 produces a strong steric hindrance on the α-side of this molecule. In fact, conjugated addition of lithium dimethylcuprate to the enone (11) afforded, with high yields a 4 : 1 mixture of pinguisone (1) and 7-*epi*-pinguisone (2) which were separated by silica-gel

chromatography. The synthesized pinguisone was identical with the natural product and 7-*epi*-pinguisone was identical with the compound previously described by us.[3]

EXPERIMENTAL

M.p.s were determined with a Kofler block apparatus and are uncorrected. I.r. spectra were obtained for solutions in chloroform (unless otherwise indicated) with a Perkin-Elmer 257 spectrophotometer. U.v. spectra were run for iso-octane solutions on a Cary 118 spectrophotometer. ^1H and ^{13}C N.m.r. spectra were recorded for deuteriochloroform solutions with a Varian XL 100 instrument ($SiMe_4$ as internal standard). Mass spectra were obtained on a Varian Mat 112 spectrometer. Optical rotations were measured for benzene solutions with a Perkin-Elmer 141 polarimeter. Microanalysis were carried out in the microanalytical laboratory of our Department with a Perkin-Elmer 240 instrument. Light petroleum refers to the fraction of b.p. 40—60 °C. Solutions were dried over sodium sulphate and solvents were dried by standard procedures. All evaporations were carried out with a rotary evaporator under reduced pressure.

(3aS,7aS)-3a,7a-*Dihydro*-3,3a,7a-*trimethyl*-4H-*indene*-1,5-*dione* (6).—To a cooled (−25 °C) solution of lithium dimethylcuprate (0.22 mmol) in ether (2 ml), prepared as previously described,[3] a solution of the diene (4) (0.03 g, 0.16 mmol) in anhydrous ether (1 ml) was added; after 2 h at −25 °C, the reaction mixture was allowed to reach room temperature and was then treated with a solution of trimethylsilyl chloride (0.2 ml, 1.6 mmol) in anhydrous ether (1 ml). After being set aside overnight at room temperature the mixture was filtered and the solution evaporated to dryness. To the residue (which gas chromatography showed to be a mixture of 3,3a,7a-trimethyl-4*H*-indene-1,5-dione [3] and a new compound) dissolved in acetonitrile (1 ml) was added a solution of palladium diacetate (20 mg) and *p*-benzoquinone (10 mg) in acetonitrile (0.5 ml); the mixture was then stirred under argon for 6 h.

Gas chromatography of the solution indicated the presence of a mixture of two compounds, the most abundant of which showed the same retention time as 3,3a,7a-trimethyl-4*H*-indene-1,5-dione. Any attempt to isolate, by chromatography, the silyl enol ether before the dehydrosilylation was unfruitful and resulted in hydrolysis of the compound; attempts to improve the yields of enolsilylation were unsuccessful. Thin-layer chromatography of the reaction mixture [light petroleum–ether (6 : 4) as eluant] gave the pure dione (6), isolated in poor yields; δ_H 6.58 (1 H, d, *J* 10 Hz, 7-H), 5.98 (1 H, d, *J* 10 Hz, 6-H), 5.80 (1 H, m, 2-H), 2.60 (2 H, m, 4-H), 2.10 (3 H, d, *J* 1.5 Hz, 3-Me), 1.30 (3 H, s, Me), and 1.21 (3 H, s, Me).

(+)-(3S,3aR,7aS)- and (+)-(3R,3aR,7aS)-2,3,3a,7a-*Tetrahydro*-3-*isopropylthio*-3a,7a-*dimethyl*-4H-*indene*-1,5-*diones* (7) *and* (8).—1-Methylethanethiol (0.194 g, 2.56 mmol) was added in drops to a magnetically stirred tetrahydrofuran (THF) solution (15 ml) of the dione (4) (0.45 g, 2.56 mmol), buffered at pH 9 with sodium tetraborate solution (0.1 M). After 1 h at room temperature the mixture was concentrated to dryness under reduced pressure and the residue was partitioned between water and dichloromethane. Evaporation of the organic extract gave a crude mixture of diastereoisomeric adducts (0.63 g) which was separated by silica-gel chromatography. Elution with benzene gave the pure *dione* (8) (0.198 g, 30.7%), as an oil which was purified by thin-layer chromatography; $[\alpha]_D^{25}$ +407 (*c*,1); $\nu_{max.}$ 1 750, 1 680, and 1 620 cm^{-1}; $\lambda_{max.}$ 215 (10 g ε 3.94), shoulders 238 (3.61) and 222 nm (3.87); δ_H 6.35 (1 H, d, *J* 10 Hz, 7-H), 6.06 (1 H, d, *J* 10 Hz, 6-H), 1.22 (3 H, d, *J* 6 Hz, MeCS), 1.21 (3 H, d, *J* 6 Hz, MeCS), 1.19 (3 H, s, Me), and 1.01 (3 H, s, Me); δ_C 214.155 (s, C-1), 196.940 (s, C-5), 148.840 (d, C-7), 128.825 (d, C-6), 57.261 (s, C-7a), 45.640 (s, C-3a), 45.283 (t, C-2), 44.552 (d, C-3), 42.506 (t, C-4), 36.308 (d, CH of Pr^i), 24.234 (q, C-7a-Me), 23.706 (q, C-3a-Me), 19.026 (q, Me of Pr^i), and 17.274 p.p.m. (q, Me of Pr^i); *m/e* 176 (8%), 134 (19), 133 (18), 106 (97), 105 (63), 91 (100), 79 (61), and 77 (58) (Found: C, 66.45; H, 7.9. $C_{14}H_{20}O_2S$ requires C, 66.66; H, 7.93%).

Elution with more benzene and crystallization from diisopropyl ether–2,2,4-trimethylpentane gave the pure *dione* (7) (0.34 g, 52.7%), m.p. 86—86.5 °C, $[\alpha]_D^{25}$ +326 (*c*, 1); $\nu_{max.}$ 1 745, 1 685, and 1 630 cm^{-1}; $\lambda_{max.}$ 233 nm (lg ε 3.62); δ_H 6.57 (1 H, d, *J* 10 Hz, 7-H), 6.03 (1 H, d, *J* 10 Hz, 6-H), 1.30 (6 H, d, *J* 7 Hz, Me_2CS), 1.23 (3 H, s, Me), and 1.18 (3 H, s, Me); δ_C 214.310 (s, C-1), 197.067 (s, C-5), 148.638 (d, C-7), 128.384 (d, C-6), 55.461 (s, C-7a), 48.644 (s, C-3a), 46.319 (d, C-3), 45.203 (t, C-2), 43.260 (t, C-4), 36.101 (d, CH of Pr^i), 24.071 (q, C-7a-Me), 23.658 (q, C-3a-Me), and 19.514 p.p.m. (q, Me_2 of Pr^i); *m/e* 176 (8%), 134 (21), 133 (16), 106 (83), 105 (60), 91 (100), 79 (54), and 77 (55) (Found: C, 66.6; H, 7.9. $C_{14}H_{20}O_2S$ requires C, 66.66; H, 7.93%).

2,3-*Dihydro*-7-*isopropylthio*-3-*oxo*-7-*norpinguisone* (9).—To a cooled (−25 °C) solution of lithium dimethylcuprate in ether (2.25 mmol, 10 ml), a solution of compound (7) (0.188 g, 0.75 mmol) in anhydrous ether (5 ml) was added in drops during 5 min. After stirring at −25 °C for 1 h in an argon atmosphere, the reaction mixture was brought to room temperature and then a solution of chloroacetyl chloride (1.02 g, 9 mmol) in anhydrous ether (5 ml) was added during 10 min. The reaction mixture was magnetically stirred for 30 min at room temperature and then poured into concentrated ammonia–crushed ice (v/w 1/2) and extracted three times with ether. On evaporation of the combined extracts (washed with cold, diluted ammonia and water, and then dried) the crude norpinguisone (9) (0.231 g) was obtained, a sample of which was purified by thin-layer silica-gel chromatography [benzene–ethyl acetate (3 : 1) as eluant]; $\nu_{max.}$ 1 745, 1 705, and 1 645 cm^{-1}; δ_H 4.40 (2 H, br s, 2-H), 2.40 (2 H, br s, 8-H), 1.30 (6 H, d, *J* 6 Hz, Me_2CS), 1.32 (3 H, s, Me), 1.16 (3 H, d, *J* 8 Hz, 4-Me), and 1.08 (3 H, s, Me); *m/e* 308 (M^+, 24%), 265 (55), 233 (22), 232 (27), 217 (34), 189 (47), 177 (76), 163 (40), 135 (29), 124 (31), 109 (100), 105 (32), and 81 (24).

7-*Isopropylthio*-7-*norpinguisone* (10).—Borabicyclononane (9-BBN) (0.093 g, 0.76 mmol) was added under nitrogen to a magnetically stirred solution of the crude compound (9) (0.22 g, 0.72 mmol) in anhydrous THF (5 ml) at 0 °C. The mixture was left for 2 h at 0 °C and then for 1 h at room temperature after which methanol (0.3 ml) was added. The solution was then evaporated to dryness and the residue was treated with 2-aminoethanol (0.456 g, 0.76 mmol) in n-pentane (5 ml). The mixture was filtered off and the precipitate was washed three times with n-pentane (5 ml each). On evaporation of the combined extracts, a crude product (0.2 g) was obtained which was purified by silica-gel chromatography. Elution with benzene afforded pure 7-*isopropylthio*-7-*norpinguisone* (10) (0.15 g, 71%) as an oil which crystallized with time in a refrigerator. An analytical sample was obtained by thin-layer chromatography as an

oil; $\nu_{max.}$ 1 750 and 1 515 cm^{-1}; δ_H 7.25 (1 H, m, 2-H), 6.21 (1 H, d, *J* 1.5 Hz, 3-H), 1.28 (6 H, d, *J* 7 Hz, Me_2CS), 1.27 3 H, s, Me), 1.16 (3 H, d, *J* 7.5 Hz, 4-Me), and 1.05 (3 H, s, Me); δ_C 215.138 (s, C-5), 146.540 (s, C-8a), 140.998 (d, C-2), 119.973 (s, C-3a), 109.310 (d, C-3), 56.017 (s, C-4a), 47.730 (d, C-7), 46.447 (s, C-7a), 43.912 (t, C-6), 36.292 (d, Me_2CS), 30.396 (d, C-4), 29.903 (t, C-8), 24.250 (q, C-4a-Me) 23.769 (q, C-7a-Me), 22.049 (q, C-4-Me), 17.246 (q, Me at Pr^i) and 15.990 p.p.m. (q, Me at Pr^i); *m/e* 292 (M^+, 24%), 216 (35), 108 (100), 107 (31), 85 (58), 83 (60), 79 (35), and 71 (97) (Found: C, 69.8; H, 8.2. $C_{17}H_{24}O_2S$ requires C, 69.86; H, 8.22%).

6,7-*Didehydro-7-norpinguisone* (11).—To a magnetically stirred, saturated solution of sodium metaperiodate (0.105 g, 0.49 mmol) in water was added in drops a solution of compound (10) (0.130 g, 0.44 mmol) in methanol (8 ml). After the mixture had been stirred at room temperature for 6 h, the solvent was evaporated and the residue was extracted with dichloromethane. On evaporation of the extract, a crude sulphoxide (0.13 g) was obtained which was dissolved in carbon tetrachloride (10 ml) and, after addition of calcium carbonate (0.042 g), was refluxed for 2 h with stirring. The mixture was then filtered off and the solid was washed several times with carbon tetrachloride. Evaporation of the combined extracts gave a crude product (0.085 g) which was purified by silica-gel chromatography. Elution with benzene and crystallization from di-isopropyl ether–2-methylheptane gave pure 6,7-*didehydro-7-norpinguisone* (11) (0.075 g, 83%), m.p. 82—83 °C; $[\alpha]_D^{25}$ +28.3 (*c* 2); $\nu_{max.}$ 1 710, 1 605, and 1 500 cm^{-1}; $\lambda_{max.}$ 213 nm (lg ε, 3.82); δ_H 7.18 (1 H, d, *J* 6 Hz, 7-H), 7.17 (1 H, m, 2-H), 6.18 (1 H, d, *J* 1.8 Hz, 3-H), 5.91 (1 H, d, *J* 6 Hz, 6-H), 3.11 (1 H, q, *J* 7 Hz, 4-H), 2.86 (1 H, d, *J* 16 Hz, 8-H_A), 2.72 (1 H, d, *J* 16 Hz, 8-H_B), 1.34 (3 H, s, Me), 1.11 (3 H, d, *J* 7 Hz, 4-Me), and 1.09 (3 H, s, Me); δ_C 206.357 (s, C-5), 168.335 (d, C-7), 146.154 (s, C-8a), 139.516 (d, C-2), 134.168 (s, C-3a), 127.831 (d, C-6), 108.154 (d, C-3), 54.154 (s, C-4a), 48.906 (s, C-7a), 33.483 (t, C-8), 33.058 (d, C-4), 23.598 (q, Me), 18.748 (q, Me), and 14.481 p.p.m. (q, Me); *m/e* 216 (M^+, 12%), 201 (7), 108 (100), 107 (26), 81 (13), 79 (59), and 65 (20) (Found: C, 77.7; H, 7.4. $C_{14}H_{16}O_2$ requires C, 77.77; H, 7.41%).

(+)-*Pinguisone* (1).—To a cooled (−25 °C) solution of lithium dimethylcuprate, prepared as described before from methyl-lithium in ether (0.82 ml; 2M) and cuprous iodide (0.157 g, 0.82 mmol), was added, during 5 min, a solution of the norpinguisone (11) (0.06 g, 0.27 mmol) in anhydrous ether (5 ml). After 1.5 h at −25 °C, the reaction was brought to room temperature and then poured into a saturated solution of ammonium chloride (4 ml). The ethereal layer was separated, the water phase was extracted three more times with ether, and the combined organic extracts were washed with dilute aqueous ammonium chloride and water, and then dried. Evaporation of the solvent afforded a crude mixture of two products (0.059 g) which were separated by silica-gel chromatography. Elution with light petroleum–ether (8 : 2) gave pure pinguisone (1) (0.045 g, 70%) which was crystallized from 2,2,4-trimethylpentane, m.p. 63 °C (undepressed in mixture with the natural compound), $[\alpha]_D^{25}$ +63.9 (*c* 1) (natural product $[\alpha]_D^{25}$ +64.3). The synthetic sample showed i.r., u.v., ^1H n.m.r., ^{13}C n.m.r., and mass spectra identical with those of the natural compound.[2] Further elution with light petroleum–ether (8 : 2) afforded pure 7-epipinguisone (2) (0.01 g, 15.5%) identical with the compound previously described.[3]

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