J. Indian Inst. Sci., Mar.–Apr. 2001, **81**, 175–179.

Short Communication

Synthesis of 7-hydroxy-4-isopropyl-6-methylcoumarin: a bisnorsesquiterpene†

S. K. PAKNIKAR* AND K. P. P. FONDEKAR
Department of Chemistry, Goa University, Goa 403 206, India.
email: param@csino.ren.nic.in; Phone: 91-832-220601.

Received on October 23, 2000.

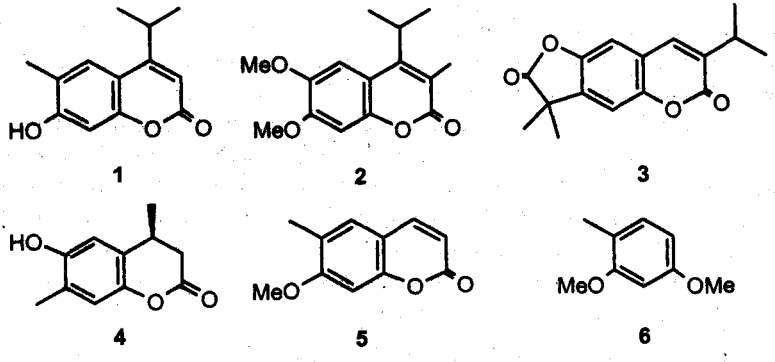
Abstract

We report herein a simple and straightforward synthesis of 7-hydroxy-4-isopropyl-6-methylcoumarin (**1**), a natural product isolated from the fronds of *Macrothelypteris torresiana* Ching var calvata Holtt (Murray, R. D. H., *Nat. Prod. Rep.*, 1995, **12**, 477–505). It is proposed that biogenetically **1** is a bisnorsesquiterpene and could be derived *in vivo* by loss of two carbon atoms of a cadinane precursor.

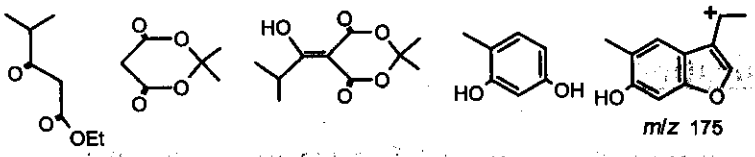
Keywords: 7-hydroxy-4-isopropyl-6-methylcoumarin, bisnorsesquiterpene, ethyl isobutyroylacetate, Meldrum's acid, isopropyl substituted coumarins.

Although a large number of coumarins having different substitution patterns occur in nature, only three have an isopropyl substituent in the α-pyrone ring, 7-hydroxy-4-isopropyl-6-methylcoumarin (**1**), 7-hydroxy-4-isopropyl-6-methyl-3-methoxycoumarin (**2**) and pygmaeoherin (**3**) and therefore are regarded as a rare group of natural coumarins.[1]

Satake and co-workers have reported the isolation of **1** and **2** from the fronds of *Macrothelypteris torresiana* Ching var valvata Holtt (Thelypteridaceae).[2] Subsequently, pygmeoherin (**3**) was isolated from the roots of *Pygmaeopremna herbacea*.[3] The relative disposition of methyl and isopropyl groups in **1** and **2** would indicate without doubt that these coumarins are



†Dedicated to Prof. S. C. Bhattacharyya.
*Author for correspondence.



7 8 9 10 11

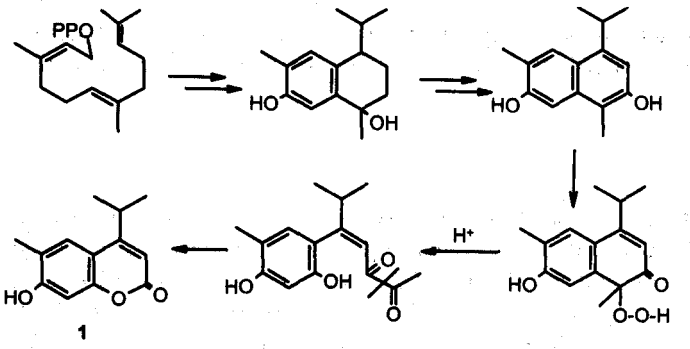
derived by the loss of two carbons of a regular cadinane precursor and therefore should be regarded as bisnorsesquiterpenoids. On the other hand, congeners of pygmeoherin would certainly suggest it to be a degraded diterpene. In spite of the well-established procedures for the synthesis of coumarins, no report has yet appeared describing their synthesis. We have been interested in the synthesis of modified terpenoids and earlier reported the synthesis of 6-hydroxy-4,7-dimethyl-3,4-dihydrocoumarin (**4**) and showed it to be the first well-characterized tetranorsesquiterpene.[4] Herein we report the synthesis of **1** and propose its likely biogenetic pathway.

Based on our observations during the synthesis of 6-methyl-7-methoxycoumarin,[5] we envisaged the synthesis of methyl ether derivative of **1** by condensation of 2,4-dimethoxytoluene (**6**) with ethyl isobutyroylacetate (**7**) under Pechmann conditions. Ethyl isobutyroylacetate (**7**) was prepared earlier by Kroeker and McElvain[6] and following their procedure, we could get it in very poor yields. This led us to look for an alternate and simple synthesis of **7**. Yonemitsu and coworkers[7] prepared several β-keto esters using Meldrums's acid (**8**) which appeared to be suitable for our work.

The base-catalyzed acylation of Meldrum's acid (**8**) with isobutyroyl chloride resulted in the formation of **9** in almost quantitative yield, which without further purification was refluxed with ethanol for 3 h and usual work up afforded **7** as a colourless oil (56%), whose IR spectrum showed bands at 1745 and 1710 cm^{-1} for an ester and ketonic carbonyl, respectively. The ^1H NMR spectrum showed doublets at δ 1.13 and δ 1.16 (J = 7Hz) and a clean septet at δ 2.62 (J = 7Hz) confirming the presence of the isopropyl group. A three-proton triplet at δ 1.26 (J = 8 Hz) and a two-proton quartet at δ 4.17 (J = 8 Hz) belongs to the ester function. The methylene protons appeared as a clear singlet at δ 3.48. ^1H NMR spectrum also showed the presence of the enol tautomer.

The Pechmann condensation of **7** with 2,4-dimethoxytoluene (**6**) using conc. sulfuric acid afforded a complex mixture. The major product was isolated as a colourless oil and its spectral data showed it to be different from the methyl ether of **1**. Replacement of **6** by 2,4-dihydroxytoluene (**10**) seemed the logical alternative. Though **10** can be prepared by Clemmensen reduction of β-resorcyl aldehyde,[8] we prepared it by BBr_3 demethylation[9] of **6** in 40% yield as a white solid, m. p. 102°C (lit[8]. 104°C). The condensation of 2,4-dihydroxytoluene (**10**) with **7** using conc. sulfuric acid at 0°C for 1 h and then at room temperature for 16 h followed by usual work-up afforded an yellowish solid which on repeated crystallization from chloroform–petroleum ether afforded colourless needles of 7-hydroxy-4-isopropyl-6-methylcoumarin (**1**) in 52% yield, m. p. 197°C (lit[1]. 198°C).

Direct comparison of the spectral data (IR, ^1H NMR, ^{13}C NMR and MS) measured on the synthetic **1** with those recorded on the natural product established their identity beyond doubt.



Scheme 1.

The base peak at *m/z* 175 in the mass spectrum of **1** is due to the fragment ion (**11**), derived by the loss of carbon monoxide followed by a CH_3 radical.

The biogenetic origin of 7-hydroxy-4-isopropyl-6-methylcoumarin (**1**) and (**2**) is interesting. The location of isopropyl, methyl and the hydroxy substituents suggests that these are derived by the loss of two carbon atoms of a sesquiterpene precursor (Scheme 1).

Incidentally, 1,7-dihydroxycalamenene (**12**), 2,7-dihydroxycadalene (**13**), 2-hydroxy-7-methoxycadalene (**14**) and lancinelene (**15**) have been isolated as natural products.[10–12] Moreover, (**13**) and (**14**) have been known to autooxidise rapidly to give (**15**) and its 7-methyl ether derivative.[11] In fact, we anticipate the presence of (**1**) in *Gossypium hirsutum*.[11]

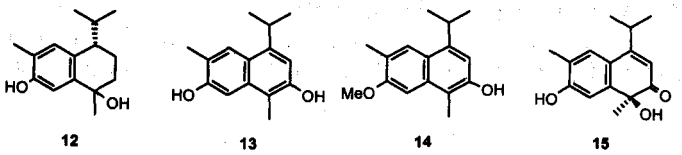
The natural occurrence of **12**, **13**, **14** and **15**, together with the reported rapid autooxidation of 1-alkyl-2-naphthols to the corresponding 1-alkyl-1-hydroperoxy-2-naphthalenones,[13] lends support to our biogenetic proposal. We therefore conclude that **1** and **2** are biosynthetically not derived by shikimic acid–phenyl alanine–tyrosine pathway, a common biosynthetic sequence for coumarins, but are degraded sesquiterpenoids.

Experimental

All melting points are uncorrected. Petroleum ether refers to the fraction of b. p. 60–80°C.

2-Isobutyroyl-Meldrums acid (9)

To a stirred solution of Meldrums acid (**8**) (1.44 g, 0.01 mol) in dry CH_2Cl_2 (10 ml) at 0°C, dry pyridine (1.6 ml, 0.02 mol) was added under nitrogen atmosphere, followed by the addition of isobutyroyl chloride (1.2 ml, 0.011 mole). After stirring the reaction mixture for 1 h at 0°C and 2 h at room temperature, it was decomposed on ice containing 2N HCl and diluted with CH_2Cl_2 (30 ml). The organic layer was then separated, washed with dil. HCl (2 × 20 ml), water



and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 2-isobutyroyl-Meldrums acid (**9**) as yellow oil in quantitative yield, which was used in the following experiment without further purification.

Ethyl isobutyroylacetate (7)

A solution of 2-isobutyroyl–Meldrums acid (**8**) (1.93 g, 0.01 mol) in ethanol (20 ml) was refluxed for 3 h and then ethanol was distilled under reduced pressure. The concentrated product was chromatographed over silica gel and eluted with EtOAc–pet. ether (1:9) to yield **7** (0.88 g, 56%) as colourless oil. IR : ν max (film): 2990, 1745, 1710, 1620, 1470, 1310, 1220, 1055 cm^{-1}. ^1H NMR (δ ppm, $CDCl_3$, 300 MHz): 1.13 (3H, d, $J = 7.0$ Hz), 1.16 (3H, d, $J = 7.0$ Hz), 1.26 (3H, t, $J = 8$ Hz), 2.62 (1H, septet), 3.48 (2H, s), 4.17 (2H, q, $J = 8$ Hz).

2,4-Dihydroxytoluene (10)

To a stirred solution of 2,4-dimethoxytoluene (**6**) (1.0 g, 6.5 mmol) under nitrogen atmosphere in dry CH_2Cl_2 (25 ml) was added BBr_3 (4 ml, 26 mmol) in dry CH_2Cl_2 (45 ml) over a period of 45 min. After stirring for 1½ h at room temperature, the reaction mixture was refluxed for 30 min, decomposed with moist EtOAc, ice and extracted with 2N NaOH. The aqueous layer was neutralized with dil. HCl and extracted with ethyl acetate (3 × 25 ml). The combined organic extract was washed with brine, water and dried over anhydrous sodium sulfate. Removal of the solvent yielded dark oil, which was chromatographed over silica gel and eluted with EtOAc–pet. ether (4:6) to give white solid. Recrystallization from $CHCl_3$ afforded 2, 4-dihydroxytoluene (**10**) (0.325 g, 40%), m. p. 102°C (lit.[8] 104°C). IR: ν_{max} (KBr): 3420, 1620, 1520, 1470, 1300, 1245, 1150, 1110, 1000, 960, 840, 790 and 620 cm^{-1}. ^1H NMR (δ ppm, $CDCl_3$, 300 MHz): 2.15 (3H, s), 4.75 (2H, brs), 6.37 (2H, m), 6.88 (1H, d, $J = 6$ Hz).

7-Hydroxy-4-isopropyl-6-methylcoumarin (1)

To vigorously stirred conc. H_2SO_4 (1.0 ml) at 0° C, a solution of 2,4-dihydroxytoluene (**10**) (0.124 g, 0.1 mmol) and ethyl isobutyroylacetate (**7**) (0.158 g, 0.1 mmol) was added slowly. After stirring for 1 h at room temperature, the reaction mixture was diluted with cold water and extracted with EtOAc (3 × 20 ml). The combined organic extracts were washed with sat. $NaHCO_3$ solution, brine, water and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded crude yellow solid which was recrystallized from $CHCl_3$–pet. ether to give colourless needles of 7-hydroxy-4-isopropyl-6-methylcoumarin (**1**) (0.113 g, 52%), m.p. 197° C (lit.[1] 198°C). UV: λ_{max} (CH_3OH): 330, 220, 204 nm. UV : λ_{max} (CH_3OH + NaOAc): 375, 220 nm; IR : ν_{max} (KBr) : 3120, 1680, 1608, 1530, 1400, 1390, 1315, 1285, 1270, 1155, 1105 cm^{-1}. ^1H NMR (δ ppm, $CDCl_3$, 300 MHz): 1.27 (6 H, d, $J = 7$ Hz, both C_9-CH_3), 2.27 (3H, s, C_6-CH_3), 2.45 (1H, brs, exchanges with D_2O, C_7-OH), 3.25 (1H, septet, C_9-H), 6.10 (1H, s, C_3-H), 6.90 (1H, s, C_8-H), 7.38 (1H, s, C_5-H). ^{13}C NMR: (δ ppm, $CDCl_3$, 75 MHz, APT): 16.0 (q, C_6-CH_3), 21.9 (2C, q, C_9-CH_3), 28.6 (d, C_9), 102.3 (d, C_8), 106.4 (d, C_3), 111.1 (s, C_{4a}), 122.6 (s, C_6), 125.2 (d, C_5), 153.5 (s, C_{8a}), 158.9 (s, C_4), 163.5 (2 C, s, C_2,C_7). HRMS: (*m/z*) 218 (M^+), 190, 175 (100%).

Acknowledgement

We thank Prof. G. Rucker and Dr R. Mayer, Pharmeceutical Institute, Bonn University, for recording the spectral data. We also thank Prof. T. Satake for providing copies of IR, UV, ^{1}H NMR and MS of natural **1**, Dr R. D. H. Murray for his interest and the Council of Scientific and Industrial Research (CSIR), India, for financial support to KPPF.

References

1. Murray, R. D. H. — *Nat. Prod. Rep.*, 1995, **12**, 477–505.
2. Hori, K., Satake, T., Saiki, Y., Murakami, T. and Chen, C. — *Yakugaku Zasshi*, 1987, **107**, 491–494.
3. Meng, Q. and Chen, W. — *Planta Med.*, 1988, **54**, 88–90.
4. Nadkarni, K. K., Kamat, S. P. and Paknikar, S. K. — *Indian J. Chem. B*, 1994, **33**, 432–435.
5. Malik, B. L. — *Transformation studies of terpenoids and new synthesis of benzofurobenzofurans*, Ph. D. Thesis, Goa University, 1995.
6. Kroeker, E. M. and McElvain, J. M. — *J. Am. Chem. Soc.*, 1934, **56**, 1171–1173.
7. Oikawa, Y., Sugano, K. and Yonemitsu, O. — *J. Org. Chem.*, 1978, **43**, 2087–2088.
8. Yanagita, M. — *Chem. Ber.*, 1938, **71**, 2269–2273.
9. McOmie, J. F. W., Watts, M. L. and West, D. E. — *Tetrahedron*, 1968, **24**, 2289–2292.
10. Stipanovic, R. D., Greenblatt, G. A., Beier, R. C. and Bell, A. L. — *Phytochemistry*, 1981, **20**, 729–730.
11. Jeffs, P. W. and Cynn, D. G. — *J. Org. Chem.*, 1975, **40**, 2958–2960.
12. El-Seedi, H., Ghia, F. and Torssell, K. B. G. — *Phytochemisty*, 1994, **35**, 1495–1497.
13. Carnduff, J. and Leppard, D. J. — *Chem. Communn.*, 1967, 829–830.