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Isolation and synthesis of chalcones with different degrees of saturation

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Dedicated to Professor Dr. Peter Welzel on the occasion of his 65th birthday.

Abstract

Crotaoprostrin, a chalcone not yet known as a plant constituent, was isolated from the aerial parts of the Indian medicinal plant *Crotalaria prostrata*. The structures of the chalcone polyarvin and the partially hydrogenated naturally occurring derivatives crotaramin, crotaramosmin, and crotin were confirmed by chemical synthesis.

Keywords: *Crotalaria prostrata*; Chalcones; Chromenes; Isolation; Chemical synthesis; Hydrogenation

1. Introduction

In connection with the isolation of bioactive compounds from Indian medicinal plants, we investigated the aerial parts of *Crotalaria prostrata*. The genus *Crotalaria* belongs to the family Leguminosae, sub-family papilionaceae, tribe genistae and is essentially restricted to the tropical and subtropical areas of the world. About 15 species of *Crotalaria* have been reported to occur in India. The phytochemistry of this genus has been investigated quite well (Steglich et al., 1997) in view of its importance in Indian traditional medicine (the roots are used as purgative: Chopra et al., 1956). Our own studies of this genus have produced several chalcones (Rao et al., 1998a, b; Kumar et al., 1999). In addition to further isolation of secondary metabolites, we wanted to confirm the structures of several previously isolated chalcones, in particular the correct location of the double bonds or sites of hydrogenation. We also wanted to get sufficient material for further testing of the antioxidant (Cuendet et al., 2000), antifeedant (Barua et al., 1983), and antimicrobial (Ahluwalia et al., 1987) activities of these compounds.

2. Results and discussion

2.1. Isolation of crotaoprostrin

Compound **1**, $C_{18}H_{18}O_5$, was isolated as yellow crystals from the ethanolic extract of the aerial parts of *C. prostrata*. The UV spectrum of **1** showed absorptions at 271, 326 and 381 nm, indicating the presence of substituted aromatic rings and an α,β-unsaturated ketone, confirmed by a typical band at 1639 cm^{-1} in the IR spectrum. The ^1H NMR spectrum of **1** showed a signal for a chelated aromatic hydroxyl group at δ = 12.88, three aromatic methoxyl groups and seven aromatic protons. The resonances in the ^{13}C NMR spectrum for the aromatic carbons bearing the three methoxy groups at δ = 154.0 and δ = 141.2 are typical for three vicinal methoxy groups, as found for instance in 3,4,5-trimethoxybenzoic acid (Pouchet and Behnke, 1993). The magnetically equivalent carbons and hydrogens at positions 2 and 6 give rise to singlets at δ = 106.4 and δ = 6.92 in the ^{13}C and ^1H NMR spectra. The remaining vicinal aromatic protons H-3′ and H-6′ on ring B show a typical aromatic four-spin pattern with *ortho* (J = 8.1–8.5 Hz) and *meta* (J = 1.0–1.1 Hz) couplings in the ^1H NMR spectrum. Two sharp doublets at = 7.56 and 7.87 with J = 15.4 Hz are characteristic for the chalcone *trans* double bond. These data suggest structure **1** for the chalcone named crotaoprostrin. The compound is new

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as a natural product, but was mentioned as a synthetic material (Chaturvedi et al., 1992). However, no spectroscopic data have been published yet for **1** (Fig. 1).

2.2. Synthesis of chalcones

The aim of our synthetic study was to provide easy and unambiguous access to prenylated chalcones with different degrees of saturation in the chromene part as well as in the α,β-unsaturated side chain as represented by the compounds **9**, **11**, **12**, and **15** (Schemes 1–3). Our synthetic strategy was the construction of the acetylated chromene **4** by condensation of dihydroxyacetophenone (**3**) with 3-methyl-2-butenal (**2**) in pyridine, followed by condensation with different aldehydes (Narkhede et al., 1990). It was sufficient to use 1.2 equivalents of aldehyde **2** for complete conversion of acetophenone **3**. Careful analysis of the reaction mixture also revealed the formation of small amounts (5%) of the isomeric chromene **5**. This compound was identical to eupatoriochromene, isolated from the Brazilian plant *Calea serrata* (Steinbeck et al., 1997) and was recently also prepared by a different route (Nicolaou et al., 2000). For later construction of the 3′,4′-saturated compounds such as **12** (Scheme 3) the chromene **4** was hydrogenated quantitatively over palladium-charcoal to yield the saturated chromane **6**.

The synthesis of chalcones generally uses the aldol condensation of acetophenones with aldehydes (Ahluwalia et al., 1987). First, the acylated chromene **4** was reacted with 4-methoxybenzaldehyde (**7**), using barium hydroxide in ethanolic solution as the base to test the reaction. In fact, the expected chalcone **9** was isolated in 77% yield. Recently, a chalcone monomethyl ether of structure **10**, named polyarvin, was isolated from *Polygala arvensis* (Rao et al., 1998b). The compound is identical with pongachalcone-II, isolated from *Pongamia glabra*, another Indian plant, but NMR data were not reported at the time (Subrahmanyam et al., 1977). Condensation of vanillin with chromene **4** yielded the chalcone **10**,

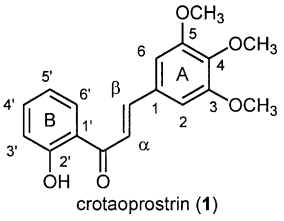
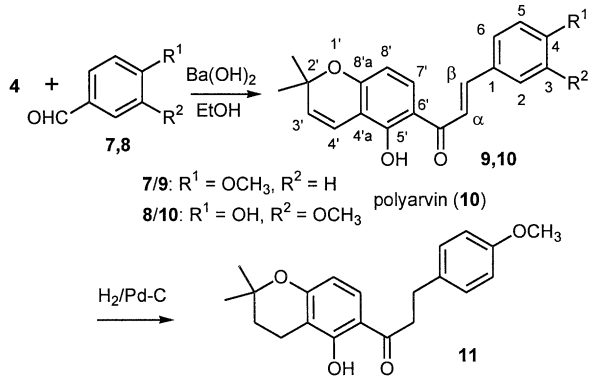
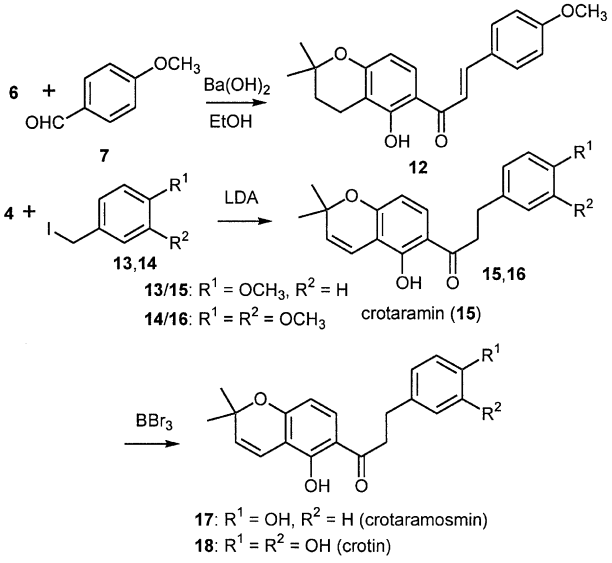


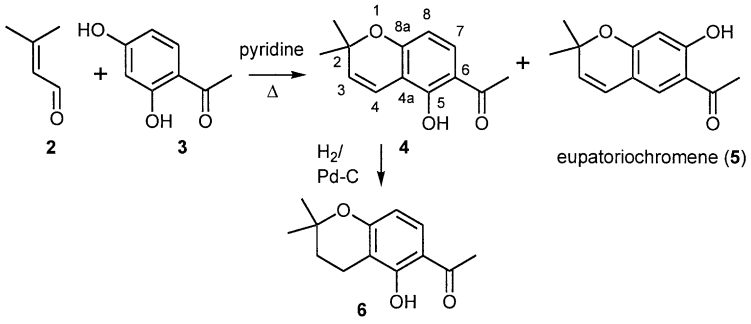
Fig. 1. Structure of crotaoprostrin (**1**).



Scheme 2. Condensation of acetophenone **4** with aldehydes to chalcones **9** and **10**, and their hydrogenation to **11**.



Scheme 3. Synthesis of 3′,4′- and α,β-saturated chalcones.



Scheme 1. Synthesis of chromenes **4** and **5** and hydrogenation of **4** to **6**.

having NMR data and melting point identical with those of the natural product polyarvin (Rao et al., 1998b), thus confirming the correct regiochemical position of the methoxy group at C-3.

Diene **9** was ideally suited to test if selective hydrogenation of either double bond was possible in order to prepare some of the naturally occurring partially saturated chromenochalcones. Several methods were tested. First we tried hydrogenation in the aprotic solvent THF. However, analysis of the reaction mixtures, even at 50% conversion, showed that both double bonds were saturated. The fully saturated product **11** was isolated as the only product (98% after complete conversion). The reagent system $NaBH_4/NiCl_2$ (Dhawan and Grover, 1992) also did not show good selectivity with respect to 1,2 or 1,4 hydride addition to the unsaturated double bond in **9**. Evidently, reduction of the carbonyl group led to an unstable allylic alcohol. Suspensions of metals such as magnesium in methanol/THF are reported to reduce α,β-unsaturated ketones selectively (Zarecki and Wicha, 1996). When this was attempted, the reduction did take place in the desired sense, but the conversion was very sluggish.

Since easy ways for selective reduction of chalcones such as **9** failed, we changed our synthetic strategy. Thus, the readily available hydrogenation product 6-acetylchromane (**6**) was used for the aldol condensation with aldehyde **7** under the conditions described above to afford the partially saturated chalcone **12** in 77% yield (Barua et al., 1983).

A different method was used for the dihydrochalcones saturated at the α- and β-positions. In principle, alkylation of the acetophenone enolates with benzylic halides could be considered. One open question was whether the chelated hydroxyl group was also alkylated under the required basic reaction conditions. Initial attempts using benzylic bromide did not give the expected products in reasonable reaction times, and slow decomposition of the reaction mixture was observed. Fortunately, the corresponding iodides such as **13** or **14**, prepared from the corresponding benzylic alcohols by treatment with trimethylsilyl iodide in acetonitrile (Stoner et al., 1995), gave the expected alkylation products **15** and **16** in 95 and 75% yield. The spectroscopic data of the saturated monomethyl ether **15** corresponded to those of the natural product crotaramin, isolated from *Crotolaria ramosissima* (Kumar et al., 1999), thus unambiguously confirming the site of saturation in that compound. Cleavage of the methyl ethers **15** and **16**, using boron tribromide in dichloromethane, gave the bisphenol **17** and the trisphenol **18**, showing identical spectroscopic and physical data with crotaramosmin (**17**) and crotin (**18**), α,β-dihydrochalcones isolated from the same Indian medicinal plant (Kumar et al., 1999).

3. Experimental

3.1. General experimental procedures

Column chromatography was performed using silica gel (Merck, 100-200 mesh). Thin layer chromatography was carried out using Merck precoated silica gel sheets (0.25 mm, 60 F_{254}). UV spectra were recorded on a Hitachi UV 3200 spectrophotometer. IR spectra were recorded on a JASCO 302-A spectrophotometer. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. EI MS were recorded on a Varian MAT 311A mass spectrometer. ^1H and ^{13}C NMR spectra were recorded using a Bruker ARX-200 spectrometer.

3.2. Isolation of crotaoprostrin (*1*)

3.2.1. Plant material

Plant material was collected from Regional Engineering College campus, Warangal, India during October 1999, and was identified by Dr. V. S. Raju and Dr. A. Ragan, Department of Botany, Kakatiya University, Warangal, India. Voucher specimens (No. CP-25) are deposited in the Department of Botany, Kakatiya University, Warangal.

3.2.2. Extraction and isolation

The fresh aerial plant material (1.5 kg) of *C. prostrata* was macerated with hot petroleum ether and then with ethanol and kept under this solvent for a period of 2 weeks. The petroleum ether extract gave cohesive material. The ethanol extract was concentrated at reduced pressure in a rotary evaporator to yield a viscous solid (1.2 g). Column chromatography on silica gel using petroleum ether/ethyl acetate (10–30% of ethyl acetate) as the eluant gave crotaoprostrin (**1**) as yellow crystals (24 mg), which were homogeneous on TLC [petroleum ether/ethyl acetate 7:3 (v/v), $R_f = 0.54$]. mp 147 °C (Chaturvedi et al., 1992): 152 °C); UV λ_{max} (MeOH): 381, 326, 271 nm; IR ν_{max} (KBr) cm^{-1}, 2938, 1639, 1581, 1504, 1489, 1297, 1263, 1025; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 3.95$ (*s*, 3H, OCH_3), 3.96 (*s*, 6H, $2\times OCH_3$), 6.92 (*s*, 2H, H-2, H-6), 6.98 (*dd*, $J = 8.1$, 1.1 Hz, 1H, H-5′), 7.06 (*dd*, $J = 8.5$, 1.1 Hz, 1H, H-3′), 7.53 (*m*, 1H, H-4′), 7.56 (*d*, $J = 15.4$ Hz, 1H, H-α), 7.87 (*d*, $J = 15.4$ Hz, 1H, H-β), 7.92 (*dd*, $J = 8.1$, 1.5 Hz, 1H, H-6′), 12.88 (*s*, 1H, OH); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 56.7$ (*q*, 3-,5-OCH_3), 61.4 (*q*, 4-OCH_3), 106.4 (*d*, C-2, C-6), 119.0 (*d*, C-3′), 119.2 (*d*, C-5′), 119.6 (*d*, C-α), 120.4 (*s*, C-1′), 130.0 (*d*, C-6′), 130.5, (*s*, C-1), 136.8 (*d*, C-4′), 141.2 (*s*, C-4), 146.1 (*d*, C-β), 154.0 (*d*, C-3, C-5), 164.0 (*d*, C-2′),193.9 (*s*, C=O); MS (EI, 70 eV, direct inlet) *m*/*z* 314 [M^+] (37), 279 (9), 212 (39), 181 (68), 149 (48), 84 (78).

3.3. Chemical synthesis

3.3.1. 6-Acetyl-5-hydroxy-2,2-dimethyl-2H-chromene (**4**) and 6-acetyl-7-hydroxy-2,2-dimethyl-2H-chromene (**5**)

A slightly modified procedure as described (Narkhede et al., 1990) was employed. To a solution of 2,4-dihydroxyacetophenone (6.08 g, 40 mmol) in dry pyridine (4 ml) was added 3-methylcrotonaldehyde (4.2 ml, 44 mmol). The solution was refluxed for 12 h, the pyridine was removed by distillation in vacuo and the black residue was separated by column chromatography on silica gel (gradients of petroleum ether/1–5% ethyl acetate) to afford **4** as yellow crystals (4.50 g, 20 mmol, 51%) and 6-acetyl-7-hydroxy-2,2-dimethyl-2*H*-chromene (**5**) (0.40 g, 2 mmol, 5%).

Data for **4**: mp 103 °C (Narkhede et al., 1990: 103–104 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.49 (*s*, 6H, 2×CH_3), 2.57 (*s*, 3H, $COCH_3$), 5.61 (*d*, *J* = 10.1 Hz, 1H, 3-H), 6.37 (*d*, *J* = 8.8 Hz, 1H, 8-H), 6.75 (*d*, *J* = 10.1 Hz, 1H, 4-H), 7.55 (*d*, *J* = 8.8 Hz, 1H, 7-H), 13.01 (*s*, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.8 (*q*, CH_3), 28.7 (*q*, 2×CH_3), 78.1 (*s*, C-2), 108.7(*d*, C-8), 109.6 (*s*, C-4a), 114.3 (*s*, C-6), 116.2 (*d*, C-4), 128.6 (*d*, C-3) 132.1 (*d*, C-7), 160.0 (*s*, C-5)*, 160.1 (*s*, C-8a)*, 203.0 (*s*, C = O).* asterisked values are interchangeable

Data for **5**: mp 79 °C (Steinbeck et al., 1997: 80 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.47 (*s*, 6H, 2×CH_3), 2.56 (*s*, 3H, CH_3), 5.60 (*d*, *J* = 9.9 Hz, 1H, 3-H), 6.30 (*d*, *J* = 9.9 Hz, 1H, 4-H), 6.35 (*s*, 1H, 8-H), 7.33 (*s*, 1H, 5-H), 12.74 (*s*, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.6 (*q*, CH_3), 29.0 (*q*, 2×CH_3), 78.4 (*s*, C-2), 104.9 (*d*, C-8), 114.0 (*s*, C-4a), 114.3 (*s*, C-6), 121.4 (*d*, C-4), 129.0 (*d*, C-5), 129.3 (*d*, C-3), 160.9 (*s*, C-7), 165.5 (*s*, C-8a), 202.8 (*s*, C = O).

3.3.2. 1-(5-Hydroxy-2,2-dimethylchroman-6-yl)-ethanone (**6**)

Palladium on charcoal (10%, 20 mg) was added to a yellow solution of chromene **4** (1.10 g, 5 mmol) in methanol (15 ml) stirred under argon. Hydrogen was then bubbled through the solution until it became colorless. The palladium was filtered off and the solvent was evaporated to dryness to yield oily **6** in 98% yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 (*s*, 6H, 2×CH_3), 1.84 (*t*, *J* = 6.5 Hz, 2H, 3-H), 2.57 (*s*, 3H, CH_3), 2.72 (*t*, *J* = 6.5 Hz, 2H, 4-H), 6.37 (*d*, *J* = 8.9 Hz, 1H, 8-H), 7.52 (*d*, *J* = 8.9 Hz, 1H, 7-H), 13.15 (*s*, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.7 (*t*, C-4), 26.5 (*q*, CH_3), 27.1 (*q*, CH_3), 32.0 (*t*, C-3), 76.1 (*s*, C-2), 109.45 (*s*, C-4a), 109.5 (*d*, C-7/8), 113.0 (*s*, C-6), 123.0 (*d*, C-8/7), 161.1 (*s*, C-5) 163.1 (*s*, C-8a), 203.0 (*s*, C = O).

3.3.3. 1-(5-Hydroxy-2,2-dimethyl-2H-chromen-6-yl)-3-(4-methoxyphenyl)-propenone (**9**)

$Ba(OH)_2$ (150 mg, 0.9 mmol) was added to a solution of chromene **4** (218 mg, 1 mmol) and 4-methoxybenzaldehyde (**7**) (204 mg, 1.5 mmol) in dry ethanol (7 ml). The suspension was refluxed for 6 h, the reaction mixture was concentrated in vacuo, and the red residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate 9/1 as the eluant to afford orange crystals of **9** (252 mg, 77%), The data of **9** were identical with those described in the literature (Bandaranayake et al., 1971).

3.3.4. 1-(5-Hydroxy-2,2-dimethyl-2H-chromen-6-yl)-3-(4-hydroxy-3-methoxyphenyl)-propenone (**10**)

A solution of KOH (2 g) in ethanol (5 ml) was added to a solution of chromene **4** (218 mg, 1 mmol) and vanillin (304 mg, 2 mmol). Yield: 71 mg (20%). The data of **10** were identical with those of polyarvin (Rao et al., 1998b).

3.3.5. 1-(5-Hydroxy-2,2-dimethylchroman-6-yl)-3-(4-methoxyphenyl)-propan-1-one (**11**)

Palladium on charcoal (10%, 5 mg) was added to an orange solution of **9** (672 mg, 2 mmol) in methanol (10 ml) stirred under argon. Then hydrogen was bubbled through the solution until it became colorless. The palladium was filtered off and the solvent was evaporated to dryness to yield **11** (662 mg, 98%); mp: 116 °C (Ahluwalia et al., 1987: 117–118 °C). The spectroscopic data corresponded to those described (Ahluwalia et al., 1987). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39 (*s*, 6H, 2×CH_3), 1.85 (*t*, *J* = 6.8 Hz, 2H, 3′-H), 2.73 (*t*, *J* = 6.8 Hz, 2H, 4′-H), 3.03 (*t*, *J* = 7.4 Hz, 2H, α-CH_2), 3.23 (*t*, *J* = 7.4 Hz, 2H, β-CH_2), 3.83 (*s*, 3H, OCH_3), 6.36 (*d*, *J* = 9.0 Hz, 1H, 8′-H), 6.88 (*d*, *J* = 8.6 Hz, 2H, 3-H, 5-H), 7.20 (*d*, *J* = 8.6 Hz, 2H, 2-H, 6-H), 7.54 (*d*, *J* = 9.0 Hz, 1H, 7′-H), 13.23 (*s*, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.7 (*t*, C-4′), 27.1 (*q*, CH_3), 30.1 (*t*, β-CH_2), 32.2 (*t*, C-3′), 40.2 (*t*, α-CH_2), 55.7 (*q*, OCH_3), 76.1 (*s*, C-2′), 109.57 (*d*, C-8′), 109.58 (*d*, C-4′a), 112.5 (*s*, C-6′) 114.4 (*d*, C-3, C-5), 129.2 (*d*, C-7′), 129.7 (*d*, C-2, C-6), 133.4 (*s*, C-1), 158.4 (*s*, C-4), 161.0 (*s*, C-5′), 163.2 (*s*, C-8′a), 204.2 (*s*, C-1). MS (70 eV, 200 °C): *m*/*z* (%) = 341 [M^+ + H] (17), 323 [M^+ − OH] (4), 205 (6), 178 (10), 149 (12), 134 (8), 121 (20), 49 (100).

3.3.6. 1-(5-Hydroxy-2,2-dimethylchroman-6-yl)-3-(4-methoxyphenyl)-propenone (**12**)

$Ba(OH)_2$ (150 mg, 0.9 mmol) was added to a solution of chromane **6** (220 mg, 1 mmol) and 4-methoxybenzaldehyde (**7**) (204 mg, 1.5 mmol) in dry ethanol (7 ml). The suspension was refluxed for 6 h, the reaction mixture was concentrated in vacuo, and the red residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate 9/1 as the eluant to afford 260 mg of orange crystals of **12** (77%), mp: 119 °C (Barua et al., 1983: 120 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.40 (*s*, 6H, 2×CH_3), 1.86 (*t*, *J* = 6.8 Hz, 2H, CH_2), 2.76 (*t*, *J* = 6.8 Hz, 2H, CH_2), 3.88 (*s*, 3H,

OCH_3), 6.42 (*d*, $J=9.0$ Hz, 1H), 6.96 (*d*, $J=8.7$ Hz, 2H), 7.50 (*d*, $J=15.4$ Hz, 1H), 7.63 (*d*, $J=8.7$ Hz, 2H), 7.73 (*d*, $J=9.0$ Hz, 1H), 7.88 (*d*, $J=15.4$ Hz, 1H), 14.01 (*s*, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=16.8$ (*t*), 27.2 (*q*), 32.3 (*t*), 55.8 (*q*), 76.2 (*s*), 109.5 (*s*, 109.7 (*s*), 113.3 (*s*), 114.8 (*d*), 118.5 (*d*), 128.1 (*s*), 128.9 (*d*), 130.7 (*d*), 144.1 (*d*), 161.1 (*s*), 162.1 (*s*), 164.5 (*s*), 192.3 (*s*).

3.3.7. 1-Iodomethyl-4-methoxybenzene (**13**) and 4-Iodomethyl-1,2-dimethoxybenzene (**14**)

1-Iodomethyl-4-methoxybenzene (**13**) and 4-Iodomethyl-1,2-dimethoxybenzene (**14**) were prepared as described in the literature (Stoner et al., 1995).

3.3.8. 1-Iodomethyl-4-methoxybenzene (**13**)

^{1}H NMR (200 MHz, $CDCl_3$): $\delta=3.84$ (*s*, 3H, OCH_3), 4.52 (*s*, 2H, CH_2), 6.86 (*d*, $J=8.7$ Hz, 2H, 3-H, 5-H), 7.36 (d, $J=8.7$ Hz, 2H, 2-H, 6-H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=7.1$ (*t*, CH_2), 55.8 (*q*, OCH_3), 114.7 (d, C-3, C-5), 130.5 (d, C-2, C-6), 131.8 (*s*, C-1), 159.6 (*s*, C-4).

3.3.9. 4-Iodomethyl-1,2-dimethoxybenzene (**14**)

^{1}H NMR (200 MHz, $CDCl_3$) $\delta=3.90$ (*s*, 3H, OCH_3), 3.92 (*s*, 3H, OCH_3), 4.51 (*s*, 2H, CH_2I), 6.80 (d, $J=8.2$ Hz, 1H, 6-H), 6.93 (*s*, 1H, 3-H), 6.99 (d, $J=8.2$ Hz, 1H, 5-H). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta=7.6$ (*t*, CH_2), 56.3 (*q*, OCH_3), 111.5 (d, C-3), 112.2 (d, C-6), 121.5 (*d*, C-5), 132.1 (*s*, C-4), 149.2 (*s*, C-1), 149.4 (*s*, C-2).

3.4. Crotaramin (**15**)

A solution of LDA (2.2 equiv in 5 ml THF) was added dropwise within 10 min to a solution of 6-acetyl-5-hydroxy-2,2-dimethyl-2*H*-chromene (**4**) (218 mg, 1 mmol) in THF at −30 °C. The yellow solution was stirred for 30 min at −30 °C and a solution of the iodomethylbenzene **13** (496 mg, 2 mmol) in THF (5 ml) was then added. The solution was stirred for 3 h at −30 °C and was then allowed to warm to 0 °C. HCl solution (10%, 10 ml) was added, the organic phase was separated, and the aqueous phase extracted with ethyl acetate (2×10 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by column chromatography using petroleum ether and ethyl acetate 9:1 as the eluant to yield 271 mg (80%) of **15** as colorless crystals. mp: 48 °C. ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=1.49$ (*s*, 6H, 2×CH_3), 3.03 (*m*, 2H, β-CH_2), 3.22 (*m*, 2H, α- CH_2), 3.83 (*s*, 3H, 4-OCH_3), 5.62 (*d*, $J=10.1$ Hz, 1H, 3′-H), 6.35 (*d*, $J=9.0$ Hz, 1H, 8′-H), 6.76 (*d*, $J=10.1$ Hz, 1H, 4′-H), 6.88 (*d*, $J=8.6$ Hz, 2H, 3-H, 5-H), 7.19 (*d*, $J=8.6$ Hz, 2H, 2-H, 6-H), 7.56 (*d*, $J=9.0$ Hz, 1H, 7′-H), 13.07 (*s*, 1H, 5′-OH). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta=28.4$ (*q*, 2×CH_3), 29.7 (*t*, C-β), 40.0 (*t*, C-α), 55.4 (*q*, OCH_3), 77.8 (*s*, C-2′), 108.4 (*d*, C-8′), 109. 4 (*s*, C-4′a), 113.5 (*s*, C-6′), 114.1 (*d*, C-3, C-5), 115.9 (*d*, C-4′), 128.3 (*d*, C-3′), 129.4 (*d*, C-2, C-6), 131.0 (*d*, C-7′), 133.0 (*s*, C-1), 158.2 (*s*, C-4), 159.7 (*s*, C-8′a), 159.8 (*s*, C-5′), 204.0 (*s*, C=O).

3.4.1. 3-(3,4-Dimethoxyphenyl)-1-(5-hydroxy-2,2-dimethyl-2H-chromen-6-yl)-propanone (**16**)

Mp: 120 °C. IR (KBr) cm^{-1}: 3092, 2956, 2923, 1618, 1514 1291, 1259 1118, 1026. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=1.48$ (*s*, 6H, 2×CH_3), 3.02 (*m*, 2H, 3-H), 3.23 (*m*, 2H, 2-H), 3.88 (*s*, 3H, OCH_3), 3.90 (*s*, 3H, OCH_3), 5.61 (*d*, $J=10.1$ Hz, 1H, 3′-H), 6.34 (*d*, $J=8.9$ Hz, 1H, 8′-H), 6.74 (*d*, $J=10.1$ Hz, 1H, 4′-H), 6.79–6.81 (*m*, 3H, 2-H, 5-H, 6-H), 7.55 (*d*, $J=8.9$ Hz, 1H, 7′-H), 13.08 (*s*, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=28.4$ (*q*, CH_3), 30.2 (*t*, C-3), 49.9 (*t*, C-2), 55.95 (*q*, OCH_3), 56.04 (*q*, OCH_3), 77.9 (*s*, C-2′), 108.4 (*d*, C-8′), 109.4 (*s*, C-4′a), 111.4 (*d*, C-2), 111.9 (*d*, C-5), 113.5 (*s*, C-6′), 115.9 (*d*, C-4′), 120.3 (*d*, C-6), 128.3 (*d*, C-3′), 131.0 (*d*, C-7′), 133.6 (*s*, C-1), 147.6 (*s*, C-4), 149.0 (*s*, C-3′), 159.7 (*s*, C-8′a), 159.8 (*s*, C-5′), 204.0 (*s*, C=O). Elemental analysis: calcd for $C_{22}H_{24}O_5$: C, 71.72%, H; 6.57%. Found: C, 71.34%; H, 6.60%.

3.4.2. Crotaramosmin (**17**)

A solution of BBr_3 in CH_2Cl_2 (1 mol/l, 1 ml, 1 mmol) was added to a solution of **15** (135 mg, 0.4 mmol) in dry CH_2Cl_2 (8 ml) at −40 °C. The yellow solution was allowed to warm up to 0 °C and stirred for 3 h. HCl solution (10%, 10 ml) was added, the organic phase was separated, and the aqueous phase extracted with CH_2Cl_2 (2×5 ml). The combined organic phases were dried over $MgSO_4$, filtered and evaporated. The crude material was purified by preparative thin layer chromatography using petroleum ether and ethyl acetate 7:3 as eluant to yield 30 mg (23%) of **17** identical with crotaramosmin (Kumar et al., 1999). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=1.49$ (*s*, 6H, 2×CH_3), 3.01 (*m*, 2H, β-H), 3.21 (*m*, 2H, α-H), 5.62 (br *s*, 1H, 4-OH), 5.62 (*d*, $J=10.1$ Hz, 1H, 3′-H), 6.35 (*d*, $J=8.9$ Hz, 1H, 8′-H), 6.76 (*d*, $J=10.1$ Hz, 1H, 4′-H), 6.80 (*d*, $J=8.5$ Hz, 2H, 3-H, 5-H), 7.13 (*d*, $J=8.5$ Hz, 2H, 2-H, 6-H), 7.56 (*d*, $J=8.9$ Hz, 1H, 7′-H), 13.08 (*s*, 1H, 5′-OH). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=28.4$ (*q*, CH_3), 29.8 (*t*, C-β), 40.0 (*t*, C-α), 77.9 (*s*, C-2′), 108.5 (*d*, C-8′), 109. 4 (*s*, C-4′a), 113.5 (*s*, C-6′), 115.5 (*d*, C-3, C-5), 115.9 (*d*, C-4′), 128.4 (*d*, C-3′), 129.6 (*d*, C-2, C-6), 131.0 (*d*, C-7′), 133.0 (*s*, C-1), 154.2 (*s*, C-4), 159.7 (*s*, C-8′a), 159.8 (*s*, C-5′), 204.2 (*s*, C=O).

3.4.3. Crotin (**18**)

A solution of BBr_3 in CH_2Cl_2 (1 mol/l, 1.5 ml, 1.5 mmol) was added to a solution of **15** (147 mg 0.4 mmol) in dry CH_2Cl_2 (8 ml) at −40 °C. The yellow solution was allowed to warm to 0 °C and was stirred for 3 h. HCl solution (10%, 10 ml) was added, the organic phase separated, and the aqueous phase extracted with

CH_2Cl_2 (2×5 ml). The combined organic phases were dried over $MgSO_4$, filtered and evaporated. The crude material was purified by preparative thin layer chromatography using petroleum ether and ethyl acetate 7:3 as the eluant to yield 33 mg (24%) of **17**. mp: 106 °C (105 °C) (Kumar et al., 1999). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.48 (*s*, 6H, 2×CH_3), 2.93 (*m*, 2H, β-H), 3.17 (*m*, 2H, α-H), 5.61 (*d*, *J* = 10.1 Hz, 1H, 3′-H), 5.80 (br *s*, 1H, OH), 5.94 (br *s*, 1H, OH), 6.35 (*d*, *J* = 8.9 Hz, 1H, 8′-H), 6.74 (*d*, *J* = 10.1 Hz, 1H, 4′-H), 6.66 (*dd*, *J* = 8.0 Hz, *J* = 2.1 Hz, 1H, 6-H), 6.74 (*d*, *J* = 10.1 Hz, 1H, 4′-H), 6.77 (*d*, *J* = 2.1 Hz, 1H, 2-H), 6.81 (*d*, *J* = 8.0 Hz, 1H, 5-H), 7.55 (*d*, *J* = 8.9 Hz, 1H, 7′-H), 13.05 (*s*, 1H, 5′-OH). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 28.4 (*q*, 2×CH_3), 30.0 (*t*, C-β), 39.8 (*t*, C-α), 77.9 (*s*, C-2′), 108.5 (*d*, C-8′), 109.4 (*s*, C-4′a), 113.4 (*s*, C-6′), 115.53 (*d*, C-2)*, 115.54 (*d*, C-5)*, 120.7 (*d*, C-6), 128.3 (*d*, C-3′), 131.1 (*d*, C-7′), 133.8 (*s*, C-1), 142.0 (*s*, C-4′), 143.7 (*s*, C-3), 159.7 (*s*, C-8′a), 159.8 (*s*, C-5′), 204.3 (*s*, C=O). * Asterisked values are interchangeable.

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