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CLAISEN REARRANGEMENTS—V[1]

SYNTHESIS OF THE COUMARINS, DENTATIN (PONCITRIN) AND GLABRALACTONE (ANGELICONE)

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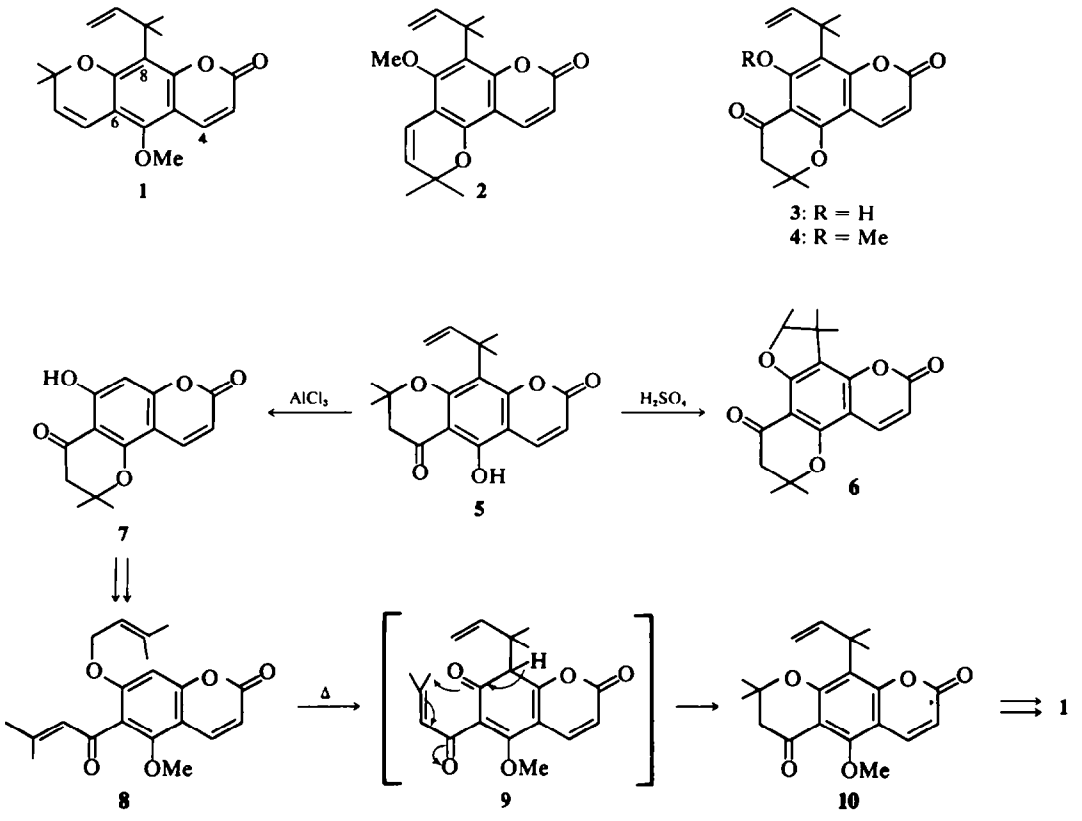
Abstract—Dentatin (= poncitrin) (**1**) has been synthesised from clausenidin methyl ether (**10**), the latter coumarin being obtained by Claisen rearrangement of the 3,3-dimethylallyl ether (**8**) derived from the chromanone (**7**). The synthesis of glabralactone (**17**) has been achieved from the methyl ether of **7** *via* retro-Michael chromanone ring opening, and coumarin ring isomerisation. The structure of angelicone is reassigned as **17**.

In 1968, the natural coumarin, dentatin, m.p. 95–96°, isolated from the root bark of *Clausena dentata* (Willd.) R. and S., was formulated[2] as the angular chromenocoumarin (**2**). The alternative linear possibility (**1**) was also considered but discounted since a direct relationship of dentatin with another natural coumarin, clausenidin (**3**) was established. The angular structure (**3**) was preferred[3] for clausenidin for two reasons. First, clausenidin on treatment with conc H_2SO_4, gave, in 30% yield, a dihydrofuran cycloclausenidin (**6**); consequently an *ortho* relationship of the phenolic OH and the 1,1-dimethylallyl group was inferred. It should be noted however that cyclisation of such groups normally proceeds in high yield under much milder acidic conditions even where the OH is chelated to a CO group.[4] Again, the $AlCl_3$ induced removal of the C_5H_9 side chain from clausenidin afforded the known[5] chromanocoumarin (**7**).

More recently, the deduction[6] from NMR and especially NOE that poncitrin, m.p. 93–94°, a new coumarin from the root of *Poncirus trifoliata* Rafinesque, was the linear chromenocoumarin (**1**), prompted a reinvestigation[7] of the structure of dentatin and, in particular that of clausenidin (**3**) on which the latter structure was based. NOE experiments on clausenidin methyl ether revealed the *peri* relationship of the OMe and the C-4 hydrogen which necessitated its reformulation as **10**. Consequently dentatin and poncitrin (**1**) must be identical and the chemical transformations of clausenidin, now **5**, must therefore proceed with isomerisation of the chromanone ring. Since the currently accepted structure (**1**) of dentatin-poncitrin is largely dependent on interpretation of spectroscopic data, we felt it would be useful to provide additional support of a synthetic nature.

We consider that the 1,1-dimethylallyl unit of dentatin could in principle be introduced[8,9] at C-8 by the *ortho*-Claisen rearrangement of a 7-O-(3,3-dimethylallyl) ether. However the yields in such a rearrangement can be low[9] since the newly formed phenolic OH can interact directly with the alkenyl double bond giving a dihydrofuran or indirectly *via* a spirocyclohexadienone intermediate leading to a 1,2-Me shift in the side chain. Both problems can be obviated by carrying out the pyrolysis in the presence of an anhydride thereby trapping the phenol as it is formed as an ester.[8] We envisaged that the intermediate phenol, or its cyclohexadienone precursor (**9**), could be trapped if a senecioyl group were placed at C-6, an added advantage being that the required linear framework would thereby be created at the same time. Thus from a synthetic viewpoint, the key intermediate was the bisether (**8**), in principle derivable from the synthetically available[5] phenol (**7**) if it were possible to etherify the C-7 OH and then effect a retro-Michael opening of the chromanone ring.

With this latter process in mind, we initially studied[12] the behaviour of the methyl ether (**11**) of **7** with base. When **11** was reacted with a 2-fold excess of NaOEt in EtOH at 40° for 5 hr and the mixture acidified, three isomeric coumarins could be isolated by preparative TLC. Apart from recovered chromanone (33%), two new phenols were produced; one, m.p. 152° (28%), formulated on the following evidence as **13**, was mobile on TLC ($CHCl_3$) while the other, **15**, m.p. 190° (dec) (39%) was extremely polar. Significantly, IR and NMR evidence reveals the presence of a senecioyl grouping in both phenols (Experimental). The less polar phenol also possesses a chelated OH (τ − 4·77) and must therefore be represented by **13**. Confirmation of this structure was obtained from the observation that **13** was quantitatively reconverted to the starting chromanone in acidified EtOH, albeit slowly at 20° but rapidly at 60°. The very insoluble polar phenol from its UV behaviour also possesses a 5-OH and, apart from the absence

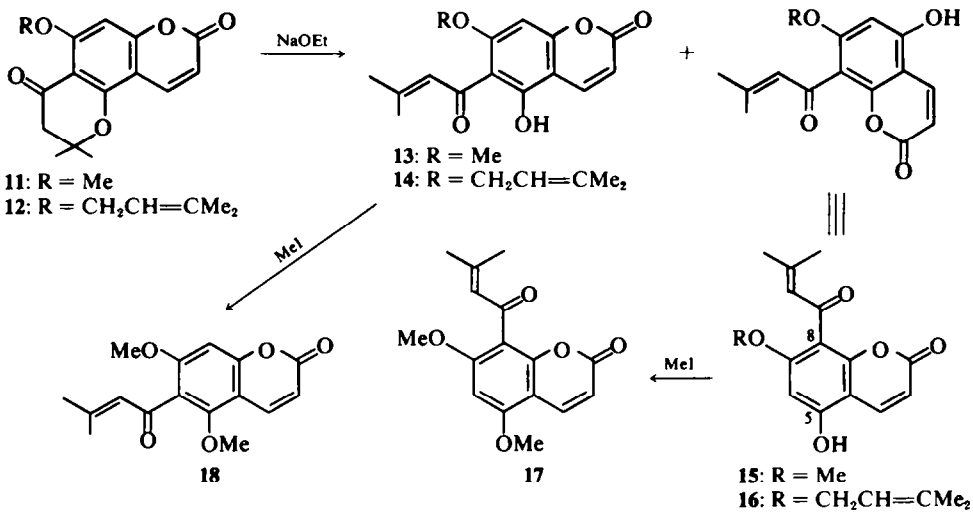


of chelation, shows similar spectral behaviour to **13**. This was therefore the isomer (**15**) having the senecioyl grouping at C-8, presumably arising from base-induced opening of the coumarin ring followed, on acidification, by lactonisation of the intermediate coumarinic acid with the alternative available *ortho* OH. Thus **15** was stable to cold acid, although prolonged warming in an acidic medium did result in its reconversion to the original chromanone (**11**). By utilising the simple separation procedure and resubmitting recovered **11** and either **13** or **15** to base, the overall yield of **15** or **13** could be optimised as desired.

With the isomeric phenols (**13** and **15**) to hand, syntheses of the natural coumarins, angelicone (**18**) and glabralactone (**17**) were now possible. The structure **17** of glabralactone has been assigned[13] on the basis of rigorous degradative evidence and, in complete accord, methylation of **15** with MeI and K_2CO_3 in acetone quantitatively afforded glabralactone, m.p. 128–130°. Similar methylation of **13** also quantitatively afforded the corresponding methyl ether which now possessed the structure **18** assigned[14] to angelicone. Compound **18** melted sharply at 120° in contrast to the reported[14] 130° for angelicone, while the UV and IR spectra of our synthetic glabralactone were identical with those published[14] for angelicone. Thus natural angelicone and glabralactone must be identical and an earlier, but somewhat inaccessible, publication[15] in which the structure of the angelicone retro-aldol product was revised from 6-acetyl to 8-acetyl-5,7-dimethoxycoumarin has been overlooked in the three most important reviews of natural coumarins[16] wherein angelicone and glabralactone are classified as discrete compounds.

For the synthesis of dentatin, the 3,3-dimethylallyl ether (**12**) was prepared (60%) from **7** and, in a similar manner to **11**, reacted with ethanolic NaOEt. Again preparative TLC was used to separate unreacted **12** (31%) from the two isomeric phenolic coumarins **14** and **16** which arose from retro-Michael opening of the chromanone ring. The structure **14** of the less polar phenol (34%), which possesses a chelated OH (τ −4·70) was confirmed by its quantitative reconversion to **12**, slowly on standing in EtOH but rapidly when warmed in acidified EtOH. The more polar phenol (34%) possesses a free phenolic OH ($\nu_{max}^{CHCl_3}$ 3590 cm^{-1}) which from UV evidence is located at C-5. The senecioyl group must therefore be at C-8, the result of lactone ring isomerisation. Conveniently, **16**, on resubjection to NaOEt/EtOH was also converted to the same readily separable mixture of **12**, **14** and **16**.

MeI methylation of **14** afforded the desired



bisether (**8**, 67%). As we had hoped, **8**, on heating to 180° in diethylaniline, smoothly rearranged with concomitant cyclisation giving clausenidin methyl ether (**10**) in 74% yield. The presence of added butyric anhydride had no effect on the course of the reaction which implies that the phenol derived from the cyclohexadienone (**9**) interacts very rapidly with the pendant *ortho* enone or alternatively that the phenol is not formed but that **9** cyclises spontaneously as shown. Reduction of **10** in EtOH to the corresponding alcohol (50%) was accomplished[5] by the portionwise addition of $NaBH_4$ at room temperature. Dehydration of the alcohol was smoothly effected[5] by sublimation from freshly fused $KHSO_4$ giving synthetic dentatin–poncitrin, m.p. 93–95° which was found to be identical with an authentic sample of natural dentatin.[2]

EXPERIMENTAL

M.ps were determined with a Kofler hot stage apparatus. IR spectra were recorded on a Perkin-Elmer 225 spectrophotometer. NMR spectra of solns in $CDCl_3$ with TMS as internal standard were recorded by Mr. A. Haetzman with a Varian T-60 spectrometer. Mass spectra were recorded by Mr. A. Ritchie with an AEI-GEC MS12 mass spectrometer. UV spectra were recorded on a Unicam SP800 spectrometer and refer to EtOH solns; λ_{max} (in base) refers to EtOH solns to which 2 drops of 4N NaOH were added. Microanalyses were performed by Miss F. G. Cowan and her staff. Kieselgel G (Merck) was used for preparative TLC; since most compounds were purified by preparative TLC in $CHCl_3$, yields refer to material which is homogeneous on TLC (using $CHCl_3$). Light petroleum refers to the fraction of b.p. 60–80°.

Preparation of the chromanone **7**. (i) 2,2-Dimethyl-5,7-dihydroxychroman-4-one (3 g), malic acid (2 g) and conc H_2SO_4 (8 ml) were heated at 125° for 1 hr[11] to give **7** (needles from EtOAc) (1 g, 27%), m.p. 215–220°, (lit.[11] 218–220°); (ii) 2,2-dimethyl-5,7-dihydroxychroman-4-one (2·15 g), $ZnCl_2$ (1·4 g) and ethyl propiolate (1 ml) were heated at 100° for 1·1/4 hr.[5] The cooled residue was extracted into EtOAc, washed with dil HCl, brine to neutrality and dried. Evaporation yielded a viscous gum which crystallised from EtOAc to give **7** (350 mg, 13%), m.p. 215–220°.

Methylation of **7**. K_2CO_3 (80 mg) was added to a soln of **7** (125 mg) in acetone (25 ml) and the mixture stirred for ½ hr. MeI (0·75 ml) was added and the mixture refluxed for 20 hr. After filtration and evaporation, the residue was extracted into EtOAc, washed with brine to neutrality and dried. Evaporation gave **11** (100 mg, 76%) as plates (from $CHCl_3$-ether), m.p. 190–191° (lit.[5] 193–194°); λ_{max} 230 (sh), 273 and 318 nm (log ε 3·80, 4·15 and 3·87).

Isomerisation of the chromanone (**11**). A soln of **11** (100 mg) in EtOH (15 ml) was added to a soln (5 ml) of ethanolic NaOEt [made from Na (100 mg) and EtOH (15 ml)], and stirred at 40° for 4·3/4 hr. After dilution with water and acidification with dil HCl, the mixture was extracted with EtOAc. Work up gave a solid which was separated by TLC into, in order of decreasing chromatoplate mobility, (i) the *phenol* (**13**; 28 mg, 28%), yellow needles, m.p. 151–153° (from MeOH). (Found: C, 65·75; H, 5·3. $C_{15}H_{14}O_5$ requires: C, 65·7; H, 5·15%); $\nu_{max}^{CHCl_3}$ 1741 (lactone), 1620 (chelated enone) and 1610 cm^{-1}; λ_{max} 235 (sh) and 300 nm (log ε 3·78 and 3·54), (after 3 days at room temp or 3 hr at 65°, this spectrum changed to that of **11**), λ_{max} (in base) 240, 313 and 392 nm (log ε 3·73, 3·56 and 3·39); mass spectral peaks at *m/e* 274 (5%, M^+), 259 (100), 189 (19), and 54 (25); NMR signals at τ 8·00 and 7·80 (each 3H, bs, vinyl Me), 6·07 (3H, s, OMe), 3·82 (1H, d, J = 10 Hz), 3·72 (1H, s), 3·13 (1H, bs, vinyl H), 1·97 (1H, d, J = 10 Hz) and −4·77 (1H, s, disappears on addition of D_2O): (ii) recovered starting material (33 mg, 33%): and (iii) a polar *phenol* (**15**) (39 mg, 39%), prisms, m.p. 203–206° (from EtOAc-light petroleum) (Found: C, 65·55; H, 5·3. $C_{15}H_{14}O_5$ requires: C, 65·7; H, 5·15%); $\nu_{max}^{CHCl_3}$ 1735 (lactone), 1670 (enone) and 1612 cm^{-1}; λ_{max} 218 (sh), 251 and 318 nm (log ε 4·13, 4·08 and 4·00), λ_{max} (in base) 255, 325 and 360 nm (log ε 4·05, 3·91 and 3·83); mass spectral peaks at *m/e* 274 (25%, M^+), 243 (70), 150 (40), 83 (60), 55 (100), 43 (85) and 41 (70); NMR signals (deuteroacetone) at τ 8·15 and 7·92 (each 3H, d, J = 1 Hz, vinyl Me), 6·25 (3H, s), 3·97 (1H, d, J = 10 Hz), 3·75 (1H, m), 3·50 (1H, s) and 2·02 (1H, d, J = 10 Hz).

Methylation of **13**. K_2CO_3 (80 mg) was added to a soln of **13** (40 mg) in acetone (15 ml) and the mixture stirred at room temp for 15 min. MeI (0·6 ml) was added and the mixture refluxed for 3 hr. After filtration and evaporation, the residue was extracted into EtOAc, washed with brine to neutrality and dried. Evaporation afforded the *ether* (**18**), plates, m.p. 120° (from ether-light petroleum) (40 mg, 97%) (Found: C, 66·6; H, 5·7. $C_{16}H_{16}O_5$ requires: C, 66·65; H, 5·6%); ν_{max}^{KBr} 1740, 1670 and 1610 cm^{-1}; λ_{max} 218 (sh), 247, 268 (sh) and 332 nm (log ϵ 4·09, 4·16, 4·09 and 4·1); mass spectral peaks at *m/e* 288 (26%, M^+), 257 (10), 149 (40), 83 (50), 69 (40) and 55 (100%); NMR signals at τ 8·05 (3H, d, J = 1·5 Hz), 7·77 (3H, d, J = 1·5 Hz), 6·17 (6H, s), 3·78 (1H, d, J = 10 Hz), 3·70 (1H, m, J = 1·5 Hz), 3·40 (1H, s) and 2·15 (1H, d, J = 10 Hz).

Methylation of **15**. Similar methylation of **15** (40 mg) and purification of the crude product by TLC gave **17**, m.p. 128–130° (lit.[13] 127–129°) (33 mg, 75%) (Found: C, 66·6; H, 5·6. Calc. for $C_{16}H_{16}O_5$: C, 66·65; H, 5·6%); ν_{max}^{KBr} 1730, 1660, 1615 and 1595 cm^{-1}; λ_{max} 221, 247 and 320 nm (log ϵ 4·13, 4·21 and 4·18); mass spectral peaks at *m/e* 288 (20%, M^+), 257 (100), 83 (50) and 55(50); NMR signals at τ 8·05 and 7·75 (each 3H, d, J = 1·5 Hz), 6·10 and 6·05 (each 3H, s), 3·90 (1H, d, J = 10 Hz), 3·68 (2H, bs) and 2·10 (1H, d, J = 10 Hz). The IR and UV spectra were identical with those published[14] for natural angelicone, m.p. 130°.

Dimethylallylation of the chromanone (**7**). K_2CO_3 (1 g) was added to a soln of **7** (1·1 g) in acetone (100 ml) and the mixture stirred at room temp for 1 hr. Freshly distilled dimethylallyl bromide (1 g) was added and the mixture refluxed for 20 hr. After filtration and evaporation, the residue was extracted into EtOAc, the organic layer washed with brine to neutrality and dried. Evaporation gave an oil which, after purification by TLC, afforded the *ether* (**12**; 0·8 g, 60%), needles, m.p. 128–129° from ether. (Found: C, 69·25; H, 6·15. $C_{19}H_{20}O_5$ requires: C, 69·5; H, 6·15%); ν_{max}^{Nujol} 1740, 1690 and 1610 cm^{-1}; λ_{max} 235, 274 and 325 nm (log ϵ 3·76, 4·37 and 4·09); mass spectral peaks at *m/e* 328 (5%, M^+), 260 (52), 245 (100), 205 (33), 69 (28) and 41 (55); NMR signals at τ 8·50 (6H, s), 8·23 (6H, bs), 7·24 (2H, s), 5·27 (2H, d, J = 6 Hz), 4·36 (1H, bt, J = 6 Hz), 3·80 (1H, d, J = 10 Hz), 3·60 (1H, s) and 2·05 (1H, d, J = 10 Hz).

Ring opening of the chromanone (**12**). A soln of **12** (350 mg) in EtOH (25 ml) was added to a stirred soln of NaOEt [made from Na (65 mg) in EtOH (25 ml)] at 45°. After 3 hr, the yellow soln was diluted with cold water, acidified with dil HCl and extracted thoroughly with EtOAc. The organic layer was washed with brine to neutrality, dried and the residue from evaporation separated by TLC into (i) the *phenol* (**14**; 120 mg, 34%), yellow needles, m.p. 136–138° from MeOH. (Found: C, 69·25; H, 6·2. $C_{19}H_{20}O_5$ requires: C, 69·5; H, 6·15%); $\nu_{max}^{CHCl_3}$ 1739, 1617 (chelated enone) and 1608 cm^{-1}; λ_{max} 239 and 302 nm (log ϵ 3·52 and 4·31), λ_{max} (in base) 240, 315 and 393 nm (log ϵ 4·20, 4·13 and 3·93); mass spectral peaks at *m/e* 328 (5%, M^+), 260 (17), 245 (82), 69 (100) and 41 (50); NMR signals at τ 8·22 (6H, s), 8·03 and 7·83 (each 3H, d, J = 1 Hz), 5·40 (2H, bd, J = 6 Hz), 4·48 (1H, bt, J = 6 Hz), 3·87 (1H, d, J = 10 Hz), 3·75 (1H, s), 3·10 (1H, m, J = 1 Hz), 1·97 (1H, d, J = 10 Hz) and −4·70 (1H, s, disappears on addition of D_2O); (ii) recovered **12** (110 mg, 31%); and (iii) the *phenol* (**16**; 120 mg, 34%), m.p. 137–140° (from EtOAc-light petroleum) (Found: M^+ 328 by mass spec. $C_{19}H_{20}O_5$ requires: M^+ 328); $\nu_{max}^{CHCl_3}$ 3590, 1734, 1670 (enone) and 1611 cm^{-1}; λ_{max} 220 (sh), 250 and 320 nm (log ϵ 4·30, 4·28 and 4·25), λ_{max} (in base) 258, 326 and 360 nm (log ϵ 4·29, 4·23 and 4·15); mass spectral peaks at *m/e* 328 (12%), 313 (70), 257 (45), 245 (100), 217 (23), 205 (18) and 83 (30); NMR signals at τ 8·37 and 8·30 (each 3H, s), 8·05 and 7·80 (each 3H, bs), 5·78 (2H, bd, J = 6 Hz), 4·70 (1 H, bt, J = 6 Hz), 8·95 (1 H, d, J = 10 Hz), 3·63 (2 H, m) and 2·05 (1 H, d, J = 10 Hz).

Isomerisation of the phenol (**16**). **16** (100 mg) was added to a stirred soln of NaOEt [made from Na (20 mg) in EtOH (25 ml)]. The soln was kept at room temp for 1 hr and at 40° for 2½ hr. After cooling, the soln was diluted with water, acidified with dil HCl and extracted with EtOAc. The organic layer was washed with brine to neutrality and dried. Evaporation yielded an oil which was separated by TLC into (i) **14** (31 mg, 31%); (ii) **12** (30 mg, 30%); and (iii) **16** (39 mg, 39%).

Methylation of **14**. K_2CO_3 (110 mg) was added to a soln of **14** (80 mg) in acetone (30 ml) and the mixture stirred at room temp for 1 hr. MeI (1 ml) was added and the mixture refluxed for 1 hr, when more MeI (0·5 ml) was added and refluxing continued for a further 2 hr. After filtration and evaporation, the residue was extracted into EtOAc, washed with K_2CO_3 aq (0·5%, w/v), with brine to neutrality and dried. Evaporation gave an oil which was purified by TLC and crystallisation from CCl_4 to give the *ether* (**8**), m.p. 57–60° (83 mg, 67%) (Found: C, 70·0; H, 6·65. $C_{20}H_{22}O_5$ requires: C, 70·2; H, 6·5%); $\nu_{max}^{CCl_4}$ 1749, 1615 and 1602 cm^{-1}; λ_{max} 246, 270 (sh) and 324 nm (log ϵ 4·08, 3·95 and 4·05); mass spectral peaks at *m/e* 342 (5%, M^+), 274 (10), 259 (100), 69 (50) and 41 (40); NMR peaks at τ 8·23 (6H, bs), 8·05 and 7·78 (each 3H, d, J = 1 Hz), 6·15 (3H, s), 5·44 (2H, bd, J = 6 Hz), 4·65 (1H, bt, J = 6 Hz), 3·82 (1H, d, J = 10 Hz), 3·72 (1H, bs), 3·47 (1H, bs) and 2·15 (1H, d, J = 10 Hz).

Claisen rearrangement of **8**. A soln of **8** (243 mg) in N,N-diethylaniline (1 ml) was heated at 180° for 3 hr under N_2. The cooled soln was poured into ice-water, extracted into EtOAc, washed with dil HCl to pH 1, brine to neutrality, dried and evaporated. The residual oil was purified by TLC to give **10** (183 mg, 75%), m.p. 87–88° (lit.[3] 86–87°); λ_{max} 269, 290 (sh), 320 and 335 (sh) nm log ϵ 4·39, 4·13, 4·11 and 4·00); mass spectral peaks at *m/e* 342 (40%, M^+), 327 (23), 272 (100), 243 (30) and 230 (28). When the reaction was repeated in the presence of butyric anhydride, no trace of any butyrate ester could be detected while the yield of **10** was the same.

Dentatin⇌Poncitrin (**1**). $NaBH_4$ was added portionwise over 1 hr to a soln of **10** (180 mg) in EtOH (15 ml), the reaction being monitored by TLC until all **10** had been consumed. The soln was then diluted with dil HCl, extracted with EtOAc and the organic layer washed with brine to neutrality and dried. Evaporation afforded a solid which was purified by TLC to give the desired alcohol (90 mg, 50%) which crystallised from EtOAc-light petroleum as colourless plates, m.p. 155–158° (lit.[2] 157–158°); $\nu_{max}^{CHCl_3}$ 3570, 1720 and 1595 cm^{-1}; λ_{max} 228, 257, 266 and 332 nm (log ϵ 4·03, 3·84, 3·92 and 4·14). An intimate mixture of the alcohol (20 mg) and freshly fused $KHSO_4$ (45 mg) was heated at 105°/0·01 mm for 6 hr. The colourless solid, m.p. 93–95° (17 mg, 85%) (Found: C, 73·6; H, 6·9. Calc. for $C_{20}H_{22}O_4$: C, 73·6; H, 6·8%) which sublimed from the mixture was identical (mixed m.p., TLC, IR, UV and mass spectra) with an authentic sample of natural dentatin, m.p. 93–95°.[2] The NMR spectra of the synthetic material was identical with the values quoted in the literature.[2,6]

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