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# CLAISEN REARRANGEMENTS—XIII[1]

## SYNTHESIS OF THE NATURAL COUMARINS, NORDENTATIN, DENTATIN AND CLAUSARIN

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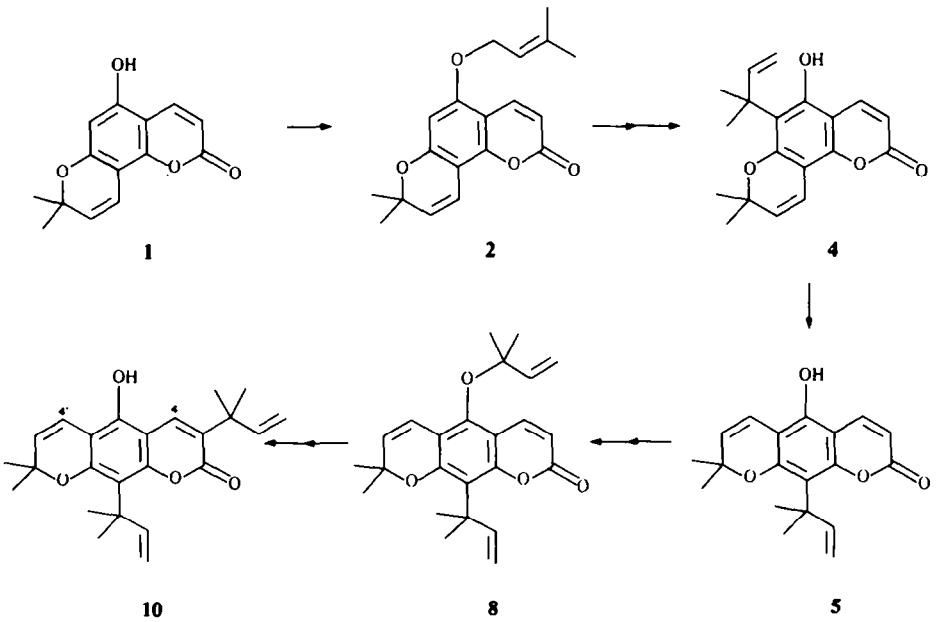
**Abstract**—The structure of the natural coumarin, clausarin **10** has been confirmed by an eight-step synthesis from 5-hydroxyseselin **1** in 56% overall yield. The efficient synthesis of its precursor, nordentatin **5** provides a convenient alternative synthetic route to dentatin **6**. The revised structure **13** is suggested for clausenidinaric acid.

In 1968 a new phenol, nordentatin and its methyl ether, dentatin were isolated from *Clausena dentata* rootbark.[2] The structures of these two coumarins followed from the preparation of the latter from the methyl ether of clausenidin, a phenol first isolated from *C. heptaphylla*[3] and later from *C. excavata*.[4] However, the structure of clausenidin was incorrectly deduced initially[3] but later revised to **12**, thereby leading to the now accepted structures **5** and **6** for nordentatin and dentatin. Recently, Wu and Furukawa[6] reinvestigated *C. excavata* and from the rootbark isolated three other known 5,7-dioxygenated coumarins, nordentatin, clausarin **10**[7] and xanthoxyletin.[1] The observation that nordentatin possesses important antibacterial properties prompted us to develop a route for its synthesis since our earlier synthesis of dentatin,[8] which had confirmed the revised structure **6**, was not amenable for the efficient synthesis of the corresponding phenol.



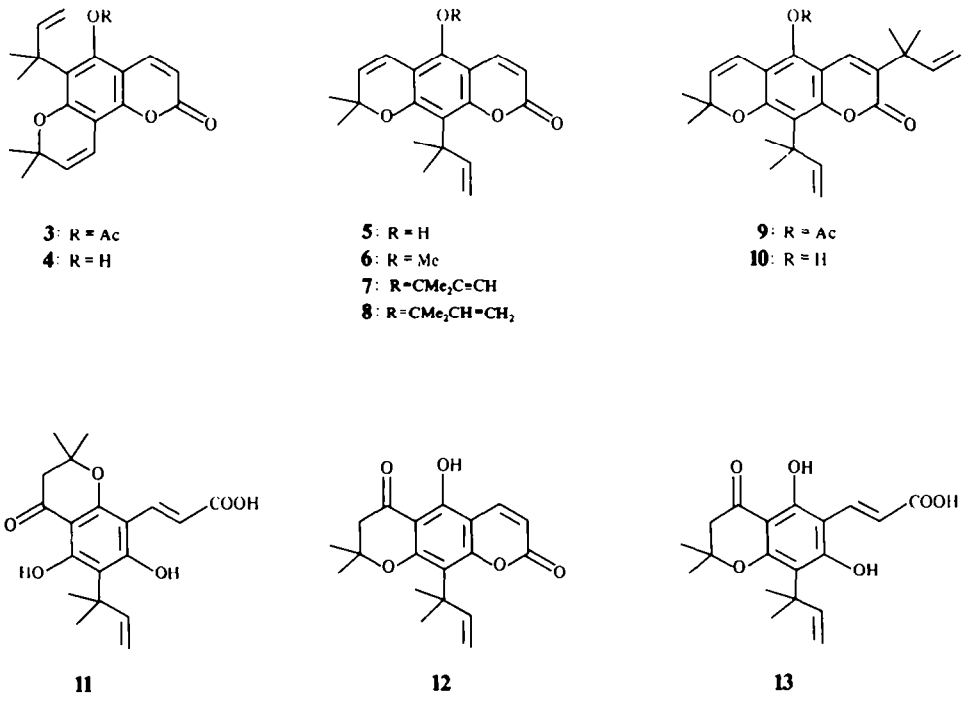

Scheme 1. Synthetic route to nordentatin **5** and clausarin **10**.

Our new approach was based upon the recognition that nordentatin **5** is a 5-hydroxycoumarin and thus theoretically derivable from its isomer **4**, in which only the C–6 and C–8 substituents are interchanged, by base-induced lactone-ring opening followed by lactonisation with the original phenolic hydroxyl group. The phenol **4** was conveniently obtained by a modified ortho-Claisen rearrangement of the prenyl ether **2** of the readily accessible 5-hydroxyseselin **1**.[1]

Claisen rearrangements of prenyloxycoumarins are frequently attended by abnormal Claisen rearrangements, cyclisations and prenyl ether cleavage to the parent hydroxycoumarin.[9] However, the simple expedient of trapping the first-formed product as its acetate, developed for the synthesis of hortiolone,[10] followed by mild hydrolysis, provides an efficient two-step route to the desired ortho-(1,1-dimethylallyl)hydroxycoumarin.[10,11] Thus 5-prenyloxyseselin **2** was found to rearrange smoothly in refluxing acetic anhydride containing sodium acetate to **3** in 97% yield, introducing the potential C–8 1,1-dimethylallyl group at C–6. Exposure of the acetate to two equivalents of 1% NaOH in cold MeOH for 3 h quantitatively afforded the corresponding phenol **4**. Consistent with the introduction of the dimethylallyl group at C-6, the solution IR spectrum of **4** shows a band at 3400 $cm^{-1}$ indicative of strong intramolecular OH-$\pi$ H-bonding. Base-induced lactone-ring isomerisation of **4** to the more polar nordentatin **5**, in which the bulky 1,1-dimethylallyl group is in the slightly less crowded C-8 position since both ortho oxygen functions are incorporated into ring systems, was accomplished by treatment with five equivalents of 1% NaOH in MeOH and was complete in 50 h. Significantly, the dilute solution IR spectrum of nordentatin shows only a free OH stretching frequency at 3600 $cm^{-1}$. Conveniently, nordentatin could be obtained directly from **3** in almost quantitative yield by treatment with ten equivalents of base for 20 h. Methylation completed an effective alternative synthetic route[8] to dentatin **6**.

The novel coumarin clausarin[7] was isolated in 1977 from *C. pentaphylla* roots where it occurs with dentatin. More recently, clausarin has been reported[6] as a constituent of *C. excavata* rootbark where it is accompanied by nordentatin. Clausarin was assigned the linear pyranocoumarin structure **10** on spectroscopic evidence.[6] Three six-proton singlets were observed in the high-field region of its $^1H$ NMR spectrum, substitution at C–3 being revealed by the singlet H-4 resonance which, like H-4′ of the chromene, moved upfield on acetylation of the phenolic hydroxyl which was thus placed at C-5. The two 1,1-dimethylallyl groups were therefore placed at C-3 and C-8. Clausarin is unique not only in possessing two 1,1-dimethylallyl groups but also in being the only natural coumarin in which each position on the coumarin nucleus apart from C-4 bears a substituent. Synthetic confirmation for structure **10** was thus desirable but posed considerable problems, not least the regiospecific introduction of the two 1,1-dimethylallyl groups at C-3 and C-8. With the efficient synthesis of nordentatin **5** established (91% from **1**) it was of interest to determine whether the further 1,1-dimethylallyl group could be introduced at C-3.

In 1964, Nickon and Aaronoff[12] showed that a propenyl group could serve as an allyl receptor in an out-of-ring Claisen rearrangement. Pyrolysis of the allyl ether of 2,6-dimethyl-4-propenylphenol followed by catalytic hydrogenation gave 2,6-dimethyl-4-




Scheme 2.

(2-methylpentyl)phenol in 32% yield. Although a phenyl group was found not to act as an allyl receptor in such a rearrangement, it was suggested that similar rearrangements might proceed to ring systems having less aromatic character than phenyl. The first example of such a rearrangement was utilised[9] for the synthesis of rutacultin [6,7-dimethoxy-3-(1,1-dimethylallyl)-coumarin]. The 1,1-dimethylallyl group was introduced by the triple rearrangement, albeit in low yield, of 7-prenyloxy-6-methoxycoumarin, the 3,3-dimethylallyl group migrating to C-3 with three inversions of configuration of the ends of attachment of the allyl group, and hence overall inversion. Although an identical approach is not possible for clausarin since the oxygen atom at C-7 is part of the chromene ring, it was envisaged that a double rearrangement of nordentatin 1,1-dimethylallyl ether **8** might result in a similar out-of-ring migration to C-3 since rearrangement to give an ortho- or para-substituted phenol is precluded.

Reaction of nordentatin with 3-chloro-3-methylbut-1-yne gave the 1,1-dimethylpropargyl ether **7** which was partially hydrogenated to the requisite 1,1-dimethylallyl ether **8** over 5% Pd–$BaSO_4$. The novel out-of-ring rearrangement of **8** was accomplished in high yield (82%) in refluxing acetic anhydride containing sodium acetate for 2 h giving clausarin acetate **9** which was readily deacetylated to clausarin **10** with two equivalents of 1% NaOH in MeOH for one minute.

During their studies[6] on *C. excavata* rootbark, Wu and Furukawa isolated a new compound, clausenidinaric acid. Structure **11** was proposed since the coumaric acid could be obtained from lactone-ring opening of clausenidin with methanolic KOH followed by cis to trans inversion. However the original[3] and not the revised[5] structure **12** of clausenidin was the basis for the assignment. Consequently, unless chromanone-ring isomerisation has also intervened, clausenidinaric acid should be reformulated as **13**. This problem is currently being reinvestigated.[13]

## EXPERIMENTAL

For general experimental details see Ref. 10. IR spectra were recorded for solutions in $CHCl_3$.

*5-Prenyloxyseselin* **2**. A mixture of 5-hydroxyseselin[1] **1** (196 mg), $K_2CO_3$ (500 mg), 3-methylbut-2-enyl bromide (150 mg) and acetone (20 ml) was refluxed with stirring for 1 h. The solvent was evaporated and the residue partitioned between EtOAc and brine, the organic layer washed with 5% $Na_2CO_3$, brine, dried and evaporated. The residue was chromatographed on silica gel G. Elution with EtOAc–light petroleum (1:4) gave 5-(3-methylbut-2-enyloxy)seselin **2** (245 mg, 98%) colourless needles, m.p. 107–108° (from MeOH). Found: C, 73.1; H, 6.25. $C_{19}H_{20}O_4$ requires: C, 73.05; H, 6.45%. $\nu_{max}$ 1720, 1640, 1622 and 1595 $cm^{-1}$; NMR signals at $\delta$ 1.42 (6H, s), 1.72 (3H, bs), 1.79 (3H, bs), 4.55 (2H, bd, *J* 7 Hz), 5.50 (1H, bt, *J* 7 Hz), 5.55 (1H, d, *J* 10 Hz), 6.10 (1H, d, *J* 9.5 Hz), 6.22 (1H, s), 6.78 (1H, d, *J* 10 Hz) and 7.94 (1H, d, *J* 9.5 Hz).

*Modified Claisen rearrangement of* **2**. (i) A mixture of **2** (220 mg), NaOAc (300 mg) and $Ac_2O$ (10 ml) was refluxed with stirring for 20 h. The cooled mixture was filtered and washed with EtOAc. The combined filtrates were evaporated under reduced pressure to give 5-acetoxy-6-(1,1-dimethylallyl)seselin **3** (235 mg, 97%) colourless needles, m.p. 115–117° (from EtOAc–light petroleum). Found: C, 71.2; H, 6.35. $C_{21}H_{22}O_5$ requires: C, 71.15; H, 6.25%. $\nu_{max}$ 1765, 1725, 1645 and 1595 $cm^{-1}$; NMR signals at $\delta$ 1.47 (6H, s), 1.50 (6H, s), 2.28 (3H, s), 4.90 (1H, dd, *J* 10 and 2 Hz), 4.96 (1H, dd, *J* 17.5 and 2 Hz), 5.71 (1H, d, *J* 10 Hz), 6.23 (1H, d, *J* 9.5 Hz), 6.28 (1H, dd, *J* 17.5 and 10 Hz), 6.88 (1H, d, *J* 10 Hz) and 7.44 (1H, d, *J* 9.5 Hz).

(ii) A soln of **3** (40 mg, 0.113 mmol) in MeOH (5 ml) and 1% NaOH–MeOH (0.9 ml, 0.225 mmol) was stirred at room temperature and monitored by TLC. After 3 h, all the starting material had been transformed to a less polar product. The solution was carefully neutralised with dil HCl, the MeOH evaporated under reduced pressure and the residue partitioned between EtOAc and brine. The EtOAc layer was washed with brine, dried and evaporated to give 5-hydroxy-6-(1,1-dimethylallyl)seselin **4** (35 mg, 99%) tan yellow needles, m.p. 133–136° (from MeOH). Found: C, 73.1; H, 6.3. $C_{19}H_{20}O_4$ requires: C, 73.05; H, 6.45%. $\nu_{max}$ 3400, 1720, 1640, 1615 and 1595 $cm^{-1}$; NMR signals at $\delta$ 1.49 (6H, s), 1.58 (6H, s), 5.43 (1H, dd, *J* 10 and 2 Hz), 5.49 (1H, dd, *J* 17.5 and 2 Hz), 5.59 (1H, d, *J* 10 Hz), 6.13 (1H, d, *J* 9.5 Hz), 6.50 (1H, dd, *J* 17.5 and 10 Hz), 6.82 (1H, d, *J* 10 Hz), 7.36 (1H, bs, OH) and 7.95 (1H, d, *J* 9.5 Hz).

*Nordentatin* **5**. (i) A soln of **4** (16 mg, 0.045 mmol) in MeOH (3 ml) and 1% NaOH–MeOH (1 ml, 0.25 mmol) was stirred at room temp and monitored by TLC. After 50 h, transformation to a more polar product was complete. Work up as for **4** gave nordentatin **5** (15.5 mg, 96%) tan yellow plates, m.p. 183–184° (lit[2] 182°) (from EtOAc–light petroleum); $\nu_{max}$ 3600, 1720, 1615, 1600 and 1560 $cm^{-1}$; NMR signals at $\delta$ 1.41 (6H, s), 1.61 (6H, s), 4.75 (1H, dd, *J* 10 and 2 Hz); 4.80 (1H, dd, *J* 17.5 and 2 Hz); 5.66 (1H, d, *J* 10 Hz), 6.13 (1H, d, *J* 9.5 Hz), 6.28 (1H, dd, *J* 17.5 and 10 Hz), 6.55 (1H, bs, OH), 6.57 (1H, d, *J* 10 Hz) and 8.05 (1H, d, *J* 9.5 Hz) identical (m.m.p., IR, NMR and TLC) with a natural sample.[6]

(ii) A soln of **3** (166 mg, 0.47 mmol) in MeOH (5 ml) and 1% NaOH–MeOH (20 ml, 5 mmol) was stirred at room temp and monitored by TLC. After 3 min, no starting material could be detected and the main product was **4**. Work up after 20 h as above gave **5** (140 mg, 96%).

*Dentatin* **6**. A mixture of **5** (27 mg), $K_2CO_3$ (200 mg), MeI (0.3 ml) and acetone (10 ml) was refluxed with stirring for 30 min. Work up as for **2** gave dentatin **6** (28 mg, 99%) colourless plates, m.p. 93–94° (lit[2] 95°; lit[8] 93–94°) (from light petroleum) identical (m.m.p., IR, NMR and TLC) with synthetic[8] and natural[6] samples.

*Conversion of nordentatin to clausarin* **10** (i) *Nordentatin 1,1-dimethylpropargyl ether* **7**. A mixture of **5** (140 mg), $K_2CO_3$ (750 mg), KI (300 mg), 3-chloro-3-methylbut-1-yne (2 ml) and acetone (20 ml) were refluxed with stirring for 7 h. Work up as for **2**, chromatography of the residue on silica gel G and elution with EtOAc–light petroleum (1:4) gave nordentatin 1,1-dimethylpropargyl ether **7** (131 mg, 77%) tan yellow plates, m.p. 79–80° (from MeOH). Found: $M^+$ 378.1840, $C_{24}H_{26}O_4$ requires: $M^+$ 378.1831. $\nu_{max}$ 3300, 1720, 1640, 1610, 1580 and 1560 $cm^{-1}$; NMR signals at $\delta$ 1.42 (6H, s), 1.64 (6H, s), 1.65 (6H, s), 2.48 (1H, s), 4.90 (1H, dd, *J* 10 and 2 Hz), 4.95 (1H, dd, *J* 18 and 2 Hz), 5.62 (1H, d, *J* 10 Hz), 6.13 (1H, d, *J* 9.5 Hz), 6.33 (1H, dd, *J* 18 and 10 Hz), 6.67 (1H, d, *J* 10 Hz) and 8.06 (1H, d, *J* 9.5 Hz).

(ii) *Nordentatin 1,1-dimethylallyl ether* **8**. A solution of **7** (61 mg) in EtOAc (10 ml) was hydrogenated over 5% Pd–$BaSO_4$ (25 mg) and monitored by TLC for 12 h until transformation to a slightly less polar product was complete. Filtration through celite and evaporation under reduced pressure gave nordentatin 1,1-dimethylallyl ether **8** (61.5 mg, 100%) as a yellow semi-solid. Found: $M^+$ 380.1991; $C_{24}H_{28}O_4$ requires: $M^+$ 380.1988. $\nu_{max}$ 1720, 1690, 1610, 1580 and 1560 $cm^{-1}$; NMR signals at $\delta$ 1.42 (12H, s), 1.68 (6H, s), 4.92 (1H, dd, *J* 10 and 2 Hz), 4.96 (1H, dd, *J* 17.5 and 2 Hz), 5.13 (1H, dd, *J* 10 and 2 Hz), 5.23 (1H, dd, *J* 17.5 and 2 Hz), 5.63 (1H, d, *J* 10 Hz), 6.08 (1H, dd, *J* 17.5 and 10 Hz), 6.14 (1H, d, *J* 9.5 Hz), 6.35 (1H, dd, *J* 17.5 and 10 Hz), 6.65 (1H, d, *J* 10 Hz) and 7.92 (1H, d, *J* 9.5 Hz).

(iii) *Clausarin acetate* **9**. A mixture of **8** (45 mg), NaOAc

(100 mg) and $Ac_2O$ (2 ml) was refluxed with stirring for 30 min. Work up as for **3** gave clausarin acetate **9** (41 mg, 82%) colourless plates, m.p. 123–124° (lit[7] 120°) (from EtOAc–light petroleum). Found: C, 73.95; H, 7.1. Calc for $C_{26}H_{30}O_5$: C, 73.9; H, 7.15%. $\nu_{max}$ 1775, 1715, 1645, 1638, 1620, 1605 and 1565 $cm^{-1}$; NMR signals at $\delta$ 1.42 (12H, s), 1.66 (6H, s), 2.40 (3H, s), 4.92 (1H, dd *J* 10 and 2 Hz), 4.93 (1H, dd, *J* 17.5 and 2 Hz), 5.05 (1H, dd, *J* 17.5 and 2 Hz), 5.12 (1H, dd, *J* 10 and 2 Hz), 5.69 (1H, d, *J* 10 Hz), 6.12 (1H, dd, *J* 17.5 and 10 Hz), 6.25 (1H, d, *J* 10 Hz), 6.32 (1H, dd, *J* 17.5 and 10 Hz) and 7.34 (1H, s).

(iv) *Clausarin* **10**. A solution of **9** (25 mg, 0.06 mmol) in MeOH (5 ml) and 1% NaOH–MeOH (0.5 ml, 0.12 mmol) was stirred at room temp. Work up as for **4** after 1 min gave clausarin **10** (22 mg, 98%) colourless needles, m.p. 202–204° (lit[7] 208°) (from MeOH) identical (m.m.p., IR, NMR and TLC) with a natural sample.[6]

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