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CLAISEN REARRANGEMENTS—XII[1]

SYNTHESIS OF THE COUMARINS, 5-METHOXYSESELIN, TRACHYPHYLLIN, COUMURRAYIN AND XANTHOXYLETIN

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Abstract—The structure of the natural coumarins, 5-methoxyseselin **7** and trachyphyllin **14** have been confirmed by total syntheses from 7-acetoxy-5-prenyloxycoumarin **1** in good overall yields. Convenient synthetic routes to the natural coumarins, coumurrayin **4** and xanthoxyletin **10** have also been established.

Solvent extraction of *Eriostemon trachyphyllus* leaves by Lassak and Pinhey[2] in 1969 afforded the linear pyranocoumarin, xanthoxyletin **10**, the furanocoumarin, bergapten and a new coumarin, trachyphyllin. The linear pyranocoumarin structure **14** for this phenol was established from the marked similarity of the UV spectrum of its methyl ether **15** with that of xanthoxyletin and the observation that acetylation caused upfield shifts of the benzylic H-4 and H-4′ protons. The failure to obtain a cyclised product with acid precluded an ortho relationship of the hydroxyl and prenyl groups; accordingly the latter was placed at C-8.

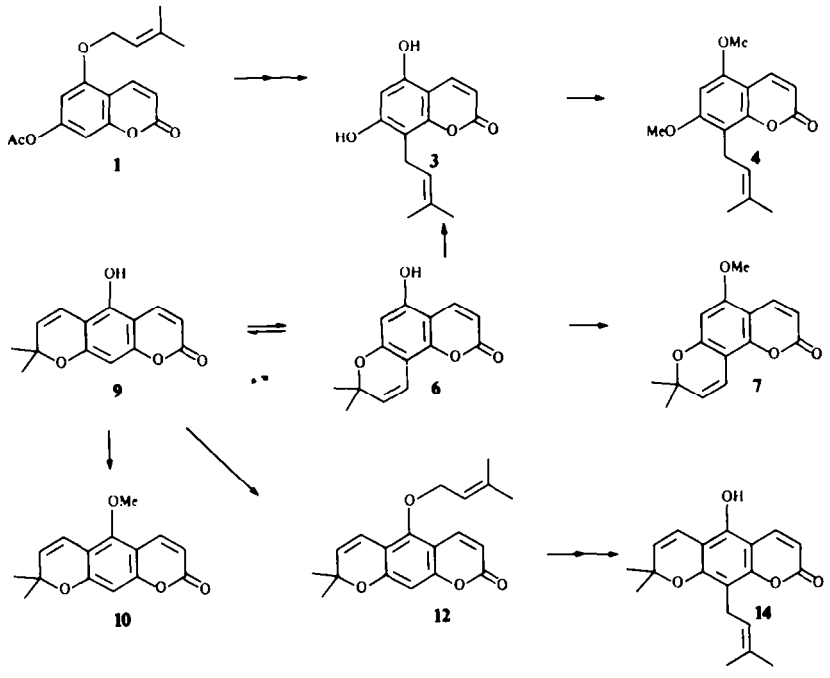
Only two syntheses of xanthoxyletin **10** have been recorded. The first,[3] from 5,7-dihydroxy-2,2-dimethylchroman-4-one, proceeds in poor yield, the chromen ring being obtained from the chromanone by a reduction-dehydration sequence. In the recent three-step, 25% overall, synthesis from 7-hydroxy-5-methoxycoumarin[4] the chromen ring was again introduced in the last step, by thermal rearrangement of the 1,1-dimethylpropargyl ether[5] of 8-iodo-7-hydroxy-5-methoxycoumarin in N,N-dimethylaniline. The iodine was present to exert a blocking effect and direct rearrangement to C-6. Neither of these routes involves the corresponding phenol **9**, a more versatile intermediate in that methylation should give xanthoxyletin while O-prenylation followed by Claisen rearrangement to the vacant para position should afford trachyphyllin. The desired linear pyranocoumarin **9** is a 5-hydroxycoumarin and thus derivable in principle from its angular isomer **6** by opening of the lactone ring followed by cyclisation of the coumarinic acid intermediate with the alternative ortho hydroxyl group.[6]

We previously observed[7,8] that 7-methoxy-5-prenyloxycoumarin underwent Claisen rearrangement in butyric anhydride and N,N-diethylaniline exclusively to the para position despite the presence of a vacant ortho position. The more readily available 7-acetoxy-5-prenyloxycoumarin[7] **1** gave complex mixtures when heated in N,N-diethylaniline containing either butyric anhydride or acetic anhydride. However the simple expedient of using only refluxing acetic anhydride resulted in a smooth para-Claisen rearrangement to 5,7-diacetoxy-8-prenylcoumarin **2**, the yield after three days being 98%.

This efficient and convenient reaction represents a dramatic improvement on the recently reported seven-step, 13% yield, procedure for effecting the same overall transformation where the prenyl ether was used to protect the 5-hydroxyl group and the 8-prenyl group was introduced by ortho-rearrangement of a 7-(1,1-dimethylallyloxy)coumarin, a route previously established by us for the synthesis of sesibiricin.[7] Deacetylation of **2** was effected quantitatively by exposure to Zn dust in MeOH for 48 h.[10] Confirmation that the prenyl group in **3** was indeed at C-8 and that no lactone-ring isomerisation had occurred during the mild deacetylation followed from the rapid formation of only one dihydropyran **5** with cold trifluoroacetic acid and methylation, which provided an attractive alternative synthetic route to coumurrayin[7,11] **4**.

Oxidative cyclisation of **3** with DDQ in ether[12] afforded the angular pyranocoumarin **6**, methylation of which gave 5-methoxyseselin **7**. The synthetic material was identical with a sample recently isolated for the first time as a natural product from *Citrus grandis* f. *hakunikuyu* rootbark[13] and with a sample obtained previously[11] as a by-product in the etherification of 7-hydroxy-5-methoxycoumarin with 3-chloro-3-methylbut-1-yne.[5] Treatment of 5-hydroxyseselin **6** with a tenfold excess of 8% NaOH in MeOH for 6 h gave an equilibrium mixture containing equimolar amounts of **6** and the slightly more polar linear isomer, 5-hydroxyxanthyletin **9** which were conveniently separated by column chromatography on silica. As expected, the ^{1}H NMR spectra of both these isomeric pyranocoumarins were similar but only the spectrum of the latter revealed long-range H_4–H_8 coupling[14] necessitating C-8 to be unsubstituted. Methylation of **9** completed a convenient alternative synthetic route to xanthoxyletin **10**.

5-Prenyloxyxanthyletin **12** rearranged smoothly in refluxing acetic anhydride[1] to give trachyphyllin acetate[2] **13** (82%) the prenyl moiety migrating with two inversions and thus net retention to the only available benzenoid position. Prenyl ether cleavage[15] to **11** (17%) accompanied the para rearrangement but could be prevented by carrying out the reaction in the presence of sodium acetate when a quantitative yield of trachyphyllin acetate was obtained. Trachyphyllin



Synthetic route to coumurrayin(**4**), 5 - methoxyseselin(**7**), xanthoxyletin (**10**) and trachyphyllin (**14**)

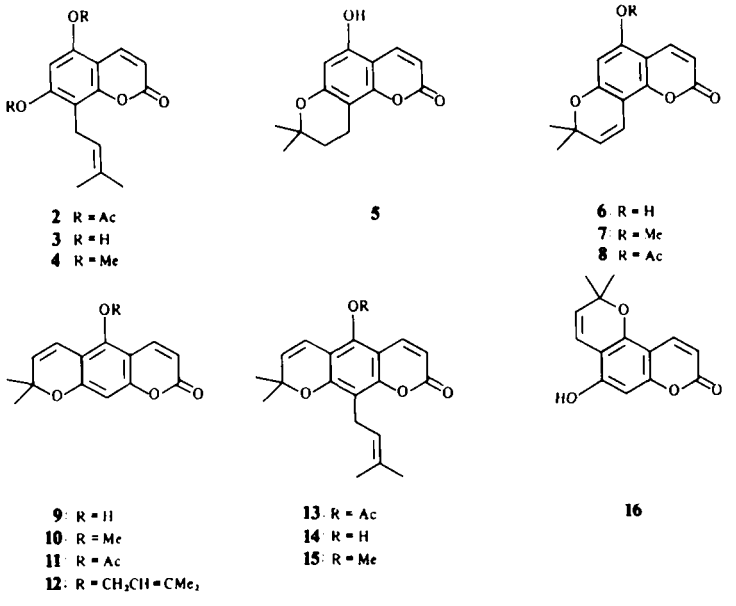
14, identical with a sample of natural provenance, was obtained quantitatively by deacetylation with Zn dust in MeOH for three days or 1% NaOH in MeOH for five minutes.

In an important publication in 1971, Crombie *et al.*[16] introduced 3-hydroxy-3-methyl-1, 1-dimethoxybutane as a new reagent for converting meta-dihydric phenols into 2,2-dimethylchromens and utilised it for the syntheses of a number of natural products. When the reagent was condensed with 5,7-dihydroxycoumarin, the major product, obtained in 45% yield, was believed to be 5-hydroxyseselin. Direct comparison has revealed that our 5-hydroxyseselin **6** is similar but not identical to the product from the above reaction, and Professor Crombie has informed us that the latter should be reoriented as in **16**.[17]

EXPERIMENTAL

For general experimental details see Ref. 6.

5,7-Diacetoxy-8-(3-methylbut-2-enyl)coumarin **2**. A soln of 7-acetoxy-5-(3-methylbut-2-enyloxy)coumarin[7] **1** (1.90 g) in Ac_2O (40 ml) was refluxed for 3 days. Evaporation under reduced pressure gave **2** (2.15 g, 99%) colourless needles, m.p. 133–135° (lit[9] 137–138°) (from EtOAc–light petroleum). Found: C, 65.35; H, 5.65. Calc for $C_{18}H_{18}O_6$: C,



2 R = Ac
3 R = H
4 R = Me

5

6 R = H
7 R = Me
8 R = Ac

9 R = H
10 R = Me
11 R = Ac
12 R = $CH_2CH=CMe_2$

13 R = Ac
14 R = H
15 R = Me

16

65.45; H, 5.5%. ν_{max}(CCl$_4$) 1778, 1750, 1628 and 1610 cm^{-1}; NMR signals at δ 1.68 (3H, bs), 1.81 (3H, bs), 2.31 (3H, s), 2.36 (3H, s), 3.47 (2H, bd, J 7.5 Hz), 5.14 (1H, bt, J 7.5 Hz), 6.36 (1H, d, J 9.5 Hz), 6.94 (1H, s) and 7.70 (1H, d, J 9.5 Hz).

5,7-*Dihydroxy*-8-(3-*methylbut*-2-*enyl*)*coumarin* **3**. A soln of **2** (1.51 g) in MeOH (35 ml) was stirred with activated Zn[10] (from 2.0 g Zn powder) at room temp. for 2 days. After filtration through Celite and washing with MeOH, the combined filtrates were evaporated under reduced pressure and the residue partitioned between EtOAc and dil HCl. The organic layer was washed with brine to neutrality, dried and evaporated to give 5,7-dihydroxy-8-(3-methylbut-2-enyl)coumarin **3** (1.13 g, 100%) tan-yellow needles, m.p. 240–242° (lit[18] 215–216°) (from EtOAc). Found: C, 68.3; H, 5.5. $C_{14}H_{14}O_4$ requires: C, 68.3; H, 5.75%. ν_{max}(KBr) 3300(b), 1690(b), 1610 and 1570 cm^{-1}; NMR signals (acetone-d$_6$) at δ 1.63 (3H, bs), 1.81 (3H, bs), 3.41 (2H, bd, J 7 Hz), 5.28 (1H, bt, J 7 Hz), 6.04 (1H, d, J 9.5 Hz), 6.46 (1H, s), 8.02 (1H, d, J 9.5 Hz) and 9.10 (2H, bs, 2 × OH).

5-*Hydroxydihydroseselin* **5**. A soln of **3** (130 mg) in CF_3CO_2H (0.5 ml) was kept for 10 min at room temperature. Evaporation under reduced pressure gave 5-hydroxydihydroseselin **5** (120 mg, 92%) colourless needles, m.p. 250–252° (from EtOAc). Found: C, 68.35; H, 5.8. $C_{14}H_{14}O_4$ requires: C, 68.3; H, 5.7%. ν_{max}(KBr) 3400(b), 3200(b), 1680, 1620, 1605 and 1570 cm^{-1}; NMR signals (DMSO-d$_6$) at δ 1.29 (6H, s), 1.78 (2H, t, J 7 Hz), 2.67 (2H, t, J Hz), 6.09 (1H, d, J 9.5 Hz), 6.19 (1H, s), 7.99 (1H, d, J 9.5 Hz) and 7.10 (1H, bs, OH).

5,7-*Dimethoxy*-8-(3-*methylbut*-2-*enyl*)*coumarin* (*coumurrayin*) **4**. A mixture of **3** (20 mg), K_2CO_3 (100 mg), MeI (0.5 ml) and acetone (8 ml) was refluxed with stirring for 30 min. After evaporation, the residue was partitioned between EtOAc and brine, the organic layer washed with brine, dried and evaporated to give coumurrayin **4** (20.5 mg, 92%) colourless needles, m.p. 155–157° (lit[11] 155–157°) (from EtOAc–light petroleum) identical (m.m.p., NMR and TLC) with an authentic sample.[7,11]

5-*Hydroxyseselin* **6**. A solution of DDQ (500 mg, 2.2 mmol) in anhydrous ether (100 ml) was added dropwise over 1 h at room temperature to a rapidly stirred suspension of **3** (541 mg, 2.2 mmol) in anhydrous ether (100 ml). After stirring overnight, the solvent was evaporated and the residue chromatographed on silica gel (Fluka HF 254). Elution with EtOAc–light petroleum (3:7) afforded 5-hydroxyseselin **6** (336 mg, 63%) tan yellow needles, m.p. >210° (dec.) (from EtOAc). Found: C, 68.8; H, 5.0. $C_{14}H_{12}O_4$ requires: C, 68.85; H, 4.95%. λ_{max}(MeOH) 350 (log ϵ 3.98), 318 (4.24), 288 (4.42) and 279 (4.44) nm; ν_{max}(KBr) 3310(b), 1705, 1640, 1620, 1605 and 1570 cm^{-1}; NMR signals (acetone-d$_6$) at δ 1.41 (6H, s), 5.67 (1H, d, J 10 Hz), 6.07 (1H, d, J 9.5 Hz), 6.25 (1H, s), 6.69 (1H, d, J 10 Hz) and 7.98 (1H, d, J 9.5 Hz).

(i) 5-*Methoxyseselin* **7**. A mixture of **6** (22 mg), K_2CO_3 (100 mg), MeI (0.5 ml) and acetone (10 ml) was refluxed for 1 h. Work-up gave 5-methoxyseselin **7** (21 mg, 95%) colourless needles, m.p. 160–161.5° (lit[13] 162–164°) (from EtOAc–pentane) identical (m.m.p., NMR, IR and TLC) with synthetic[11] and natural[13] samples.

(ii) 5-*Acetoxyseselin* **8**. A solution of **6** (20 mg), Ac_2O (1 ml) and pyridine (0.5 ml) was kept at room temperature for 20 min. Evaporation under reduced pressure gave 5-acetoxyseselin **8** (22.5 mg, 96%) colourless needles, m.p. 172–174° (from EtOAc–light petroleum). Found: C, 66.9; H, 4.9. $C_{16}H_{14}O_5$ requires: C, 67.1; H, 4.95%. ν_{max}(CHCl$_3$) 1770, 1730, 1640, 1620 and 1600 cm^{-1}; NMR signals at δ 1.43 (6H, s), 2.32 (3H, s), 5.68 (1H, d, J 10 Hz), 6.21 (1H, d, J 9.5 Hz), 6.56 (1H, s), 6.91 (1H, d, J 10 Hz) and 7.59 (1H, d, J 9.5 Hz).

Isomerisation of 5-hydroxyseselin **6** *to 5-hydroxyxanthyletin* **9**. A solution of **6** (336 mg, 1.38 mmol) in MeOH (5 ml) and 8% NaOH–MeOH (7 ml, 14 mmol) was stirred at room temperature and monitored by TLC. After 6 h, equilibrium was reached and the solution was neutralised with dil HCl, the MeOH evaporated under reduced pressure and the residue worked up as for **4** and chromatographed on silica gel (Merck 60, 0.063–0.200 mm). Elution with EtOAc–light petroleum (3:7) gave **6** (170 mg, 50.6%) and 5-hydroxyxanthyletin **9** (166 mg, 49.4%) colourless plates, m.p. >200° (dec.) (from EtOAc). Found: C, 68.95; H, 5.1. $C_{14}H_{12}O_4$ requires: C, 68.85; H, 4.95%. λ_{max}(MeOH) 322 (log ϵ 4.09), 270 (4.43), 262 (4.4), 256 (4.43) and 250 (4.40) nm; ν_{max}(KBr) 3320(b), 1695, 1620, 1600 and 1570 cm^{-1}; NMR signals (acetone-d$_6$) at δ 1.42 (6H, s), 5.66 (1H, d, J 10 Hz), 6.12 (1H, d, J 9.5 Hz), 6.30 (1H, s), 6.80 (1H, d, J 10 Hz) and 8.08 (1H, d, J 9.5 Hz).

(i) 5-*Methoxyxanthyletin* (*xanthoxyletin*) **10**. Methylation of **9** (20 mg), as for **6**, gave xanthoxyletin **10** (20.7 mg, 98%) colourless plates, m.p. 134–135° (lit[14] 131–132°) (from EtOAc) identical (m.m.p., NMR, IR and TLC) with a natural sample.[7]

(ii) 5-*Acetoxyxanthyletin* **11**. Acetylation of **9** (22 mg), as for **6**, gave 5-acetoxyxanthyletin **11** colourless plates, m.p. 146–147° (from EtOAc–light petroleum). Found: C, 67.1; H, 4.95. $C_{16}H_{14}O_5$ requires: C, 67.1; H, 4.95%. ν_{max}(CHCl$_3$) 1772, 1730, 1625, 1605 and 1565 cm^{-1}; NMR signals at δ 1.46 (6H, s), 2.43 (3H, s), 5.74 (1H, d, J 10 Hz), 6.24 (1H, d, J 9.5 Hz), 6.29 (1H, d, J 10 Hz), 6.68 (1H, s) and 7.51 (1H, d, J 9.5 Hz).

(iii) 5-(3-*Methylbut*-2-*enyloxy*)*xanthyletin* **12**. A mixture of **9** (105 mg), K_2CO_3 (500 mg), 1-bromo-3-methylbut-2-ene (102 mg) and acetone (15 ml) was refluxed for 30 min. Work up as for **4** gave 5-(3-methylbut-2-enyloxy)xanthyletin **12** (126 mg, 97%) as a colourless oil. Found: M$^+$ 312.1365. $C_{19}H_{20}O_4$ requires M$^+$ 312.1361. ν_{max}(film) 1730, 1610 and 1560 cm^{-1}; NMR signals at δ 1.42 (6H, s), 1.59 (3H, bs), 1.74 (3H, bs), 4.48 (2H, bd, J 7 Hz), 5.50 (1H, bt, J 7 Hz), 5.68 (1H, d, J 10 Hz), 6.16 (1H, d, J 9.5 Hz), 6.53 (1H, s), 6.58 (1H, d, J 10 Hz) and 7.82 (1H, d, J 9.5 Hz).

Claisen rearrangement of **12**. (i) A solution of **12** (69 mg) in Ac_2O (3 ml) was refluxed for 2.5 h. Evaporation under reduced pressure followed by chromatography of the residue on silica gel G (Merck) and elution with EtOAc–light petroleum (3:17) gave (a) trachyphyllin acetate **13** (64 mg, 82%) colourless needles, m.p. 119–120° (lit[2] 121–122°) (from EtOAc–light petroleum). Found: C, 71.2; H, 6.45. Calc for $C_{21}H_{22}O_5$: C, 71.15; H, 6.25%. ν_{max}(CHCl$_3$) 1770, 1720 1620, 1600 and 1570 cm^{-1}; NMR signals at δ 1.43 (6H, s), 1.65 (3H, bs), 1.83 (3H, bs), 2.40 (3H, s), 3.47 (2H, bd, J 7 Hz), 5.24 (1H, bt, J 7 Hz), 5.71 (1H, d, J 10 Hz), 6.21 (1H, d, J 9.5 Hz), 6.26 (1H, d, J 10 Hz) and 7.50 (1H, d, J 9.5 Hz); (b) **11** (11 mg, 17%).

(ii) A mixture of **12** (30 mg), NaOAc (40 mg) and Ac_2O (1.5 ml) was refluxed for 24 h. The cooled mixture was filtered and the solid washed with EtOAc. The combined filtrates were evaporated under reduced pressure to give **13** (34 mg, 100%). No trace of **11** could be detected by TLC or NMR.

Trachyphyllin **14**. (i) A solution of **13** (20.4 mg) in MeOH (5 ml) was stirred with activated Zn (from 300 mg Zn powder) at room temperature for 3 days. Work up as for **3** gave trachyphyllin **14** (18 mg, 100%) colourless plates, m.p. 213–215° (lit[2] 213–214°) (from MeOH) identical (m.m.p., NMR, IR and TLC) with a natural sample. Methylation of **14** (15 mg), as for **6**, gave trachyphyllin methyl ether **15** (15.5 mg, 98%) colourless plates, m.p. 113–114° (lit[2] 114°) (from MeOH) having identical NMR signals to those quoted.[2]

(ii) A solution of **13** (40 mg, 0.13 mmol) in MeOH (10 ml) was treated with 1% NaOH/MeOH (2.5 ml, 0.62 mmol) for 5 min. Neutralisation with dil HCl and work up as for **9** gave **14** (35 mg, 100%).

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