Total Synthesis of a Xanthonolignoid, Kielcorin

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The reaction of 3-benzyloxy-4-hydroxy-2-methoxyxanthone with ethyl 2-bromo-3-(4-benzyloxy-3-methoxyphenyl)-3-oxopropionate in the presence of potassium *tert*-butoxide afforded the condensation product (8) which was converted to the debenzylation product (9) by hydrogenolysis. Reduction of 9 with lithium borohydride followed by treatment of resulting alcohols (10a, b) with concentrated hydrochloric acid in acetic acid provided kielcorin.

Keywords xanthonolignoid; xanthone; kielcorin; benzodioxane; Guttiferae; *cis*-kielcorin

Xanthonolignoids are a new class of natural products and to data five compounds (kielcorin,[1a-c] kielcorin B,[1d] cadensin A,[1a,c] cadensin B,[1a,c] and cadensin C[1c]) have been isolated from the plant kingdom. These materials possess a novel skeleton in which a phenylpropane unit is linked to a xanthone nucleus through a dioxane bridge.[2] The xanthonolignoid, kielcorin (**1**), has been isolated[1a] from several species of *Kielmeyera* (*K. coriacea*, *K. corymbosa*, *K. speciosa*, *K. ferruginosa* and *K. rubriflora*) (Guttiferae) and has also been found[1b] in several *Hypericum* (*H. androsaemum*, *H. calycinum*, *H. maculatum* and *H. perforatum*) (Guttiferae). The structure was proposed[1b] (**1**) on the basis of spectroscopic studied. Gottlieb *et al.*[1d] have recently accomplished the synthesis of kielcorin in low yield by oxidative coupling of 3,4-dihydroxy-2-methoxyxanthone and coniferyl alcohol with silver oxide.

Herein, we wish to describe a facile synthesis of kielcorin (**1**) from readily available materials (3-benzyloxy-4-hydroxy-2-methoxyxanthone (**6**) and ethyl 2-bromo-3-(4-benzyloxy-3-methoxyphenyl)-3-oxopropionate (**7**)).

The starting material (**6**) was synthesized by benzylation of 4-formyl-3-hydroxy-2-methoxyxanthone (**4**),[4] followed by treatment with *m*-chloroperbenzoic acid in CH_2Cl_2 (the Baeyer–Villiger reaction). Compound **6** was then condensed with **7**[5] in acetonitrile in the presence of potassium *tert*-butoxide to give **8** in 74% yield; this product was subjected to catalytic hydrogenation, affording a debenzylation product (**9**). Reduction of **9** with lithium borohydride in tetrahydrofuran (THF) at 0 °C provided an inseparable mixture of alcohols (**10a**, **b**).[6]

Acetylation of the alcohols (**10a**, **b**) followed by separation of resulting tetraacetates (**11a**, **b**) using preparative high-performance liquid chromatography (HPLC) gave **11a** as the major product and **11b** as a minor product. The structural assignment of **11a**, **b** was made on the basis of their spectral data. The high-resolution mass spectra (MS) of **11a**, **b** indicated the same molecular formula $C_{32}H_{30}O_{13}$. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **11a**, the signal of the methine proton at the C-1″ position was observed as a doublet at δ 6.20, whose coupling constant was 4.4 Hz. On the other hand, the same proton signal in **11b** appeared as a doublet at δ 6.27 (J=7.1 Hz). It is known[7] that the vicinal coupling constant of the *threo* form is larger than that of the *erythro* form and hence the signal at δ 6.20 was attributed to the *erythro* isomer (**11a**), and **11b** was assigned as the *threo* isomer. The ratio of the *erythro* and *threo* isomers was about 8.3 : 1 on the basis of the ^{1}H-NMR spectral analysis (**11a**, **b**).

The mixture of **10a**, **b** cyclized upon heating in acetic acid in the presence of concentrated hydrochloric acid to furnish kielcorin (**1**) (30% yield) and *cis*-kielcorin (**3**) (3% yield).

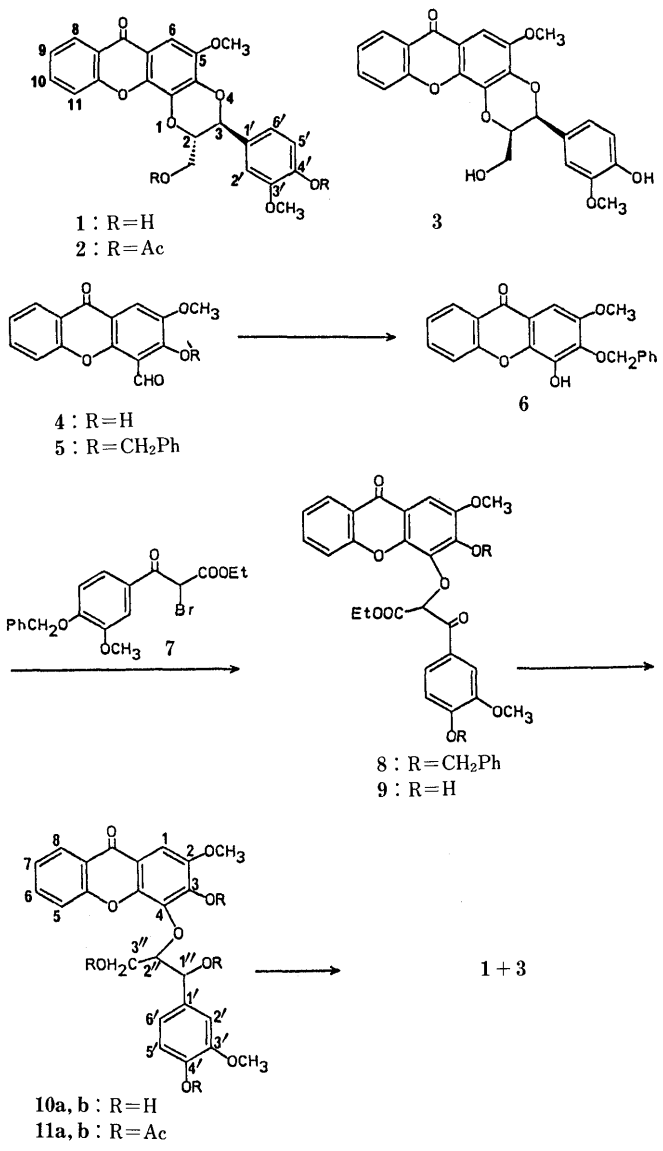

Chart 1

This synthetic kielcorin (**1**) was identical with an authentic specimen[1d] by direct comparison of the spectral data (infrared (IR), MS, ^{1}H-NMR and ^{13}C-NMR). The IR and MS spectra of *cis*-kielcorin were similar to those of kielcorin (**1**). However, in the ^{1}H-NMR spectrum, the methine proton signal at C-3 was observed as a doublet at δ 5.42 with 3.0 Hz, demonstrating *cis* orientation of the benzo-

dioxane moiety and therefore this compound is represented by the formula **3**.

Experimental

All melting points are uncorrected. Column chromatography was run on Merck silica gel 60 (70—230 mesh). Thin layer chromatography (TLC) was performed on glass plates precoated with Kieselgel 60 F_{254} (Merck). MS were recorded on a Hitachi M-52 spectrometer and high-resolution MS on a Hitachi M-80 spectrometer. IR spectra were obtained on a JASCO IR-810 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GX-270 and ^{13}C-NMR spectra on a JEOL JNM-FX-100 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad).

4-Formyl-3-benzyloxy-2-methoxyxanthone (5) A mixture of **4**[4] (540 mg), benzyl chloride (455 mg), and anhydrous K_2CO_3 (966 mg) in dry dimethylformamide (DMF) (20 ml) was heated with stirring at 140 °C for 1 h. After cooling, the reaction mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4, and evaporated. The crude solid was recrystallized from MeOH–$CHCl_3$ to give **5** as colorless needles (527 mg, 73%). mp 159 °C. *Anal.* Calcd for $C_{22}H_{16}O_5$: C, 73.33; H, 4.48. Found: C, 73.02; H, 4.53. MS *m/z*: 360 (M^+), 332, 269, 268, 254, 240, 226, 213, 170. IR ($CHCl_3$): 1700, 1650, 1620, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.05 (3H, s, OCH_3), 5.36 (2H, s, OCH_2Ph), 7.33—7.45 (6H, m, C_7-H and 5 × aromatic protons), 7.56 (1H, dd, J = 0.7, 8.4 Hz, C_5-H), 7.72 (1H, ddd, J = 1.7, 7.4, 8.4 Hz, C_6-H), 8.00 (1H, s, C_1-H), 8.30 (1H, dd, J = 1.7, 8.1 Hz, C_8-H), 10.49 (1H, s, CHO).

3-Benzyloxy-4-hydroxy-2-methoxyxanthone (6) A mixture of **5** (1.0 g) and *m*-chloroperbenzoic acid (720 mg) in CH_2Cl_2 (60 ml) was refluxed under a nitrogen atmosphere for 6 h. After cooling, the solvent was removed and the residue was dissolved in AcOEt. The AcOEt solution was washed with 5% $NaHCO_3$ and brine, and evaporated to afford an ester compound as a pale yellow solid. The ester compound was dissolved in a mixture of 10% KOH (5.0 ml), MeOH (120 ml) and $CHCl_3$ (30 ml). The mixture was heated at 90 °C for a few minutes, and then ice-water was added. The reaction mixture was neutralized with HCl and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The crude solid was recrystallized from benzene to give **6** as colorless needles (802.6 mg, 83%). mp 177 °C. *Anal.* Calcd for $C_{21}H_{16}O_5$: C, 72.41; H, 4.63. Found: C, 72.37; H, 4.59. MS *m/z*: 348 (M^+), 333, 258, 243, 229, 215. IR ($CHCl_3$): 3520, 1660, 1620, 1615, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.02 (3H, s, OCH_3), 5.27 (2H, s, OCH_2Ph), 5.96 (1H, s, OH), 7.34—7.45 (7H, m, C_1-H, C_7-H and 5 × aromatic protons), 7.55 (1H, dd, J = 0.7, 8.4 Hz, C_5-H), 7.70 (1H, ddd, J = 1.7, 7.4, 8.4 Hz, C_6-H), 8.34 (1H, dd, J = 1.7, 8.1 Hz, C_8-H).

Ethyl 2-[3-Benzyloxy-2-methoxy-9-oxo-4-xanthenyloxy]-3-(4-benzyloxy-3-methoxyphenyl)-3-oxopropionate (8) A solution of **7**[5] (234 mg) in acetonitrile (5.0 ml) was added dropwise to a mixture of **6** (100 mg) and potassium *tert*-butoxide (96.6 mg) in acetonitrile (20 ml). The mixture was stirred at room temperature for 50 min and then poured into ice-water. The reaction mixture was extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (benzene–AcOEt (10 : 1)) to give **8** as a yellow oil (143.3 mg, 74%). High-resolution MS *m/z*: 674.2150 Calcd for $C_{40}H_{34}O_{10}$ (M^+). Found: 674.2148. MS *m/z*: 674 (M^+), 583, 417, 416, 414, 371, 346, 331, 328, 269, 258, 241, 225. IR ($CHCl_3$): 3030, 1715, 1680, 1650, 1615, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t, J = 7.1 Hz, OCH_2CH_3), 3.89, 3.94 (6H, 2 × s, 2 × OCH_3), 4.17 (2H, q, J = 7.1 Hz, OCH_2CH_3), 5.19, 5.20 (4H, 2 × s, 2 × OCH_2Ph), 5.81 (1H, s, $C_{2''}$-H), 6.84 (1H, d, J = 8.4 Hz, $C_{5'}$-H), 7.07 (1H, dd, J = 0.7, 8.4 Hz, C_5-H), 7.27—7.45 (11H, m, C_7-H and 10 × aromatic protons), 7.54 (1H, s, C_1-H), 7.60 (1H, ddd, J = 1.7, 7.4, 8.4 Hz, C_6-H), 7.64 (1H, d, J = 2.0 Hz, $C_{2'}$-H), 7.75 (1H, dd, J = 2.0, 8.4 Hz, $C_{6'}$-H), 8.28 (1H, dd, J = 1.7, 8.1 Hz, C_8-H).

Ethyl 2-[3-Hydroxy-2-methoxy-9-oxo-4-xanthenyloxy]-3-(4-hydroxy-3-methoxyphenyl)-3-oxopropionate (9) A mixture of **8** (22 mg) and 5% Pd–C (2 mg) in MeOH (4.0 ml) was stirred under a hydrogen atmosphere at room temperature for 3 h. Then the catalyst was filtered off and the filtrate was evaporated. The residue was recrystallized from benzene to give **9** as colorless needles (14.4 mg, 89%). mp 127—128 °C. *Anal.* Calcd for $C_{26}H_{22}O_{10}$: C, 63.16; H, 4.48. Found: C, 63.95; H, 4.46. MS *m/z*: 494 (M^+), 448, 258, 243, 238, 215. IR ($CHCl_3$): 3520, 1710, 1680, 1650, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J = 7.1 Hz, OCH_2CH_3), 4.00 (6H, s, 2 × OCH_3), 4.34 (2H, q, J = 7.1 Hz, OCH_2CH_3), 5.75 (1H, s, $C_{2''}$-H), 6.27 (1H, s, OH), 7.01 (1H, d, J = 8.4 Hz, $C_{5'}$-H), 7.22 (1H, dd, J = 0.7, 8.4 Hz, C_5-H), 7.37 (1H, ddd, J = 0.7, 7.4, 8.1 Hz, C_7-H), 7.54 (1H, s, C_1-H), 7.65 (1H, ddd, J = 1.7, 7.4, 8.4 Hz, C_6-H), 7.74 (1H, d, J = 2.0 Hz, $C_{2'}$-H), 7.82 (1H, dd, J = 2.0, 8.4 Hz, $C_{6'}$-H), 8.31 (1H, dd, J = 1.7, 8.1 Hz, C_8-H), 9.03 (1H, s, OH).

1-(4-Hydroxy-3-methoxyphenyl)-2-[3-hydroxy-2-methoxy-9-oxo-4-xanthenyloxy]propane-1,3-diol (10a, b) A solution of $LiBH_4$ (90 mg) in dry THF (15 ml) was added gradually to a solution of **9** (300 mg) in dry THF (15 ml) at 0 °C. The mixture was stirred at room temperature for 15 min and then poured into ice-water. The reaction mixture was neutralized with dilute HCl, and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH (10 : 1)) to give **10a**, **b** as an amorphous powder (100.6 mg, 37%). IR (KBr): 3300, 1650, 1620 cm^{-1}.

1,3-Diacetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-[3-acetoxy-2-methoxy-9-oxo-4-xanthenyloxy]propane (11a, b) A mixture of **10a**, **b** (24.5 mg), acetic anhydride (2.0 ml), and pyridine (2.0 ml) was stirred at room temperature for 4 h. The reaction mixture was poured into ice-water and then extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (benzene–AcOEt (10 : 1)) and recrystallized from MeOH to give **11a** (11.5 mg). The mother liquid gave two peaks at t_R 22.8 min (**11b**) and 23.6 min (**11a**) on HPLC [conditions: column, YMC-Pack A-302 (ODS), 4.6 × 150 mm: flow rate, 1.0 ml/min; detector, UV 254 nm; solvent, acetonitrile–MeOH–water (2 : 1.5 : 2); instrument, JASCO TRI ROTAR-II] yielding *erythro*-1,3-diacetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-[3-acetoxy-2-methoxy-9-oxo-4-xanthenyloxy]propane (**11a**) (9.6 mg) and *threo*-1,3-diacetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-[3-acetoxy-2-methoxy-9-oxo-4-xanthenyloxy]propane (**11b**) (2.2 mg)].

11a: Colorless prisms. mp 148—150 °C (from MeOH). High-resolution MS *m/z*: 622.1684 Calcd for $C_{32}H_{30}O_{13}$ (M^+). Found: 622.1657. MS *m/z*: 622 (M^+), 580, 520, 478, 418, 343, 323, 301, 300, 258, 222. IR ($CHCl_3$): 1760, 1740, 1660, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.86, 2.21, 2.25, 2.30 (12H, 4 × s, 4 × OAc), 3.80, 3.93 (6H, 2 × s, 2 × OCH_3), 4.15 (1H, dd, J = 4.0, 12.1 Hz, $C_{3''}$-H), 4.49 (1H, dd, J = 6.1; 12.1 Hz, $C_{3''}$-H), 5.07 (1H, ddd, J = 4.0, 4.4, 6.1 Hz, $C_{2''}$-H), 6.20 (1H, d, J = 4.4 Hz, $C_{1''}$-H), 7.01—7.07 (3H, m, $C_{2'}$-H, $C_{5'}$-H and $C_{6'}$-H), 7.41 (1H, ddd, J = 0.7, 7.4, 8.1 Hz, C_7-H), 7.44 (1H, dd, J = 0.7, 8.4 Hz, C_5-H), 7.59 (1H, s, C_1-H), 7.75 (1H, ddd, J = 1.7, 7.4, 8.4 Hz, C_6-H), 8.34 (1H, dd, J = 1.7, 8.1 Hz, C_8-H).

11b: Colorless prisms. mp 168—170 °C (from MeOH). High-resolution MS *m/z*: 622.1684 Calcd for $C_{32}H_{30}O_{13}$ (M^+). Found: 622.1711. MS *m/z*: 622 (M^+), 580, 520, 478, 418, 343, 323, 301, 300, 258, 222. IR ($CHCl_3$): 1760, 1740, 1660, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.87, 1.94, 2.31, 2.32 (12H, 4 × s, 4 × OAc), 3.83, 3.95 (6H, 2 × s, 2 × OCH_3), 4.14 (1H, dd, J = 5.7, 12.1 Hz, $C_{3''}$-H), 4.37 (1H, dd, J = 3.7, 12.1 Hz, $C_{3''}$-H), 4.92 (1H, ddd, J = 3.7, 5.7, 7.1 Hz, $C_{2''}$-H), 6.27 (1H, d, J = 7.1 Hz, $C_{1''}$-H), 7.03 (3H, br s, $C_{2'}$-H, $C_{5'}$-H and $C_{6'}$-H), 7.41 (1H, ddd, J = 0.7, 7.4, 8.1 Hz, C_7-H), 7.52 (1H, dd, J = 0.7, 8.4 Hz, C_5-H), 7.60 (1H, s, C_1-H), 7.76 (1H, ddd, J = 1.7, 7.4, 8.4 Hz, C_6-H), 8.35 (1H, dd, J = 1.7, 8.1 Hz, C_8-H).

(2*S,3*S**)-2-Hydroxymethyl-3-(4-hydroxy-3-methoxyphenyl)-5-methoxydioxano[2,3-*c*]xanthen-7-one (Kielcorin (1)) and (2*R**,3*S**)-2-Hydroxymethyl-3-(4-hydroxy-3-methoxyphenyl)-5-methoxydioxano[2,3-*c*]xanthen-7-one (*cis*-Kielcorin (3))** A mixture of **10a**, **b** (110 mg) and 35% HCl (6.0 ml) in acetic acid (6.0 ml) was heated at 60 °C for 5 min. After cooling, the reaction mixture was poured into ice-water, and then extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated to give a pale yellow oil. The oil was chromatographed on a silica gel column using $CHCl_3$–MeOH (10 : 1) to give **1** (32 mg, 30%) and **3** (2.7 mg, 3%).

1: Colorless needles. mp 250—251 °C (from MeOH–$CHCl_3$) (lit.,[1d] mp 250—251 °C). High-resolution MS *m/z*: 436.1157 Calcd for $C_{24}H_{20}O_8$ (M^+). Found: 436.1131. This compound was identical with an authentic sample[1d] by direct comparison of various spectra (IR, MS and ^{1}H-NMR).

3: Amorphous powder. High-resolution MS *m/z*: 436.1157 Calcd for $C_{24}H_{20}O_8$ (M^+). Found: 436.1184. MS *m/z*: 436 (M^+), 418, 299, 258, 243, 228, 215, 180. IR ($CHCl_3$): 3550, 1650, 1620, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (1H, m, CH_2OH), 3.85 (1H, m, CH_2OH), 3.89, 3.99 (6H, 2 × s, 2 × OCH_3), 4.73 (1H, ddd, J = 3.0, 4.0, 8.4 Hz, C_2-H), 5.42 (1H, d, J = 3.0 Hz, C_3-H), 5.68 (1H, s, OH), 6.92—6.94 (3H, m, $C_{2'}$-H, $C_{5'}$-H and $C_{6'}$-H), 7.40 (1H, ddd, J = 0.7, 7.4, 8.1 Hz, C_9-H), 7.41 (1H, s, C_6-H), 7.59 (1H, dd, J = 0.7, 8.4 Hz, C_{11}-H), 7.72 (1H, ddd, J = 1.7, 7.4, 8.4 Hz, C_{10}-H), 8.37 (1H, dd, J = 1.7, 8.1 Hz, C_8-H).

(2*S,3*S**)-2-Acetoxymethyl-3-(4-acetoxy-3-methoxyphenyl)-5-methoxydioxano[2,3-*c*]xanthen-7-one (Diacethylkielcorin (2))** A mixture of kiel-

corin (**1**) (30 mg), acetic anhydride (1.0 ml), and pyridine (1.0 ml) was stirred at room temperature overnight. The reaction mixture was poured into ice-water and then extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$–hexane–acetone (20 : 10 : 1)) and recrystallized from MeOH–$CHCl_3$ to give **2** as colorless needles (35 mg, 98%). mp 204—206 °C (lit.,[1c] mp 203—206 °C). High-resolution MS *m/z*: 520.1368 Calcd for $C_{28}H_{24}O_{10}$ (M^+). Found 520.1357. This compound was identical with an authentic sample[1c] by direct comparison (TLC and various spectra).

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References and Notes

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