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4,6-Dimethoxy-3,7-Dimethylcoumarin from *Colchicum decaisnei*. Total Synthesis by Carbamoyl Baker-Venkataraman Rearrangement and Structural Revision to Isoeugenetin Methyl Ether

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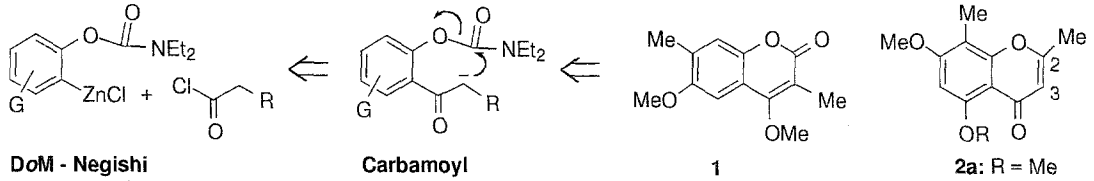
Abstract: Coumarin (**1**), the putative natural product isolated from *Colchicum decaisnei*, has been shown, by spectroscopic analysis and total synthesis, to be isoeugenetin methyl ether (**2a**), a synthetic derivative of the isoeugenetin (**2b**), isolated from *Eugenia caryophyllata*.

The discovery of the carbamoyl variation of the Baker-Venkataraman rearrangement as a general route to 4-hydroxycoumarins[1] invited its application to the total synthesis of coumarin natural products[1,2] not only because of their wide occurrence and diverse biological activities, but significantly as a result of the specific advantages of the retrosynthetic analysis whose basis is the Directed *ortho* Metalation (DoM) - Negishi cross coupling protocol (Scheme 1). This tactic allows regiospecific construction of the substituted coumarin heterocycle and the instalation of the C-3 substituent in a manner which is not dependent upon C vs O alkylation.[1,3] As a target, 4,6-dimethoxy-3,7-dimethylcoumarin (**1**), the unnamed natural product isolated from the tubers of *Colchicum decaisnei* whose structure was elucidated by extensive NMR analysis,[4] was chosen. Herein we report the synthesis of **1**, demonstrate that the proposed structure[4] is incompatible with that of the synthetic material, and show, by total synthesis, that the natural product is identical to isoeugenetin methyl ether (**2a**), a known derivative of isoeugenitin (**2b**), isolated from *Eugenia caryophyllata*.[5]

Scheme 1



DoM - Negishi cross coupling | **Carbamoyl Baker-Venkataraman** | **1** | **2a:** R = Me, **2b:** R = H

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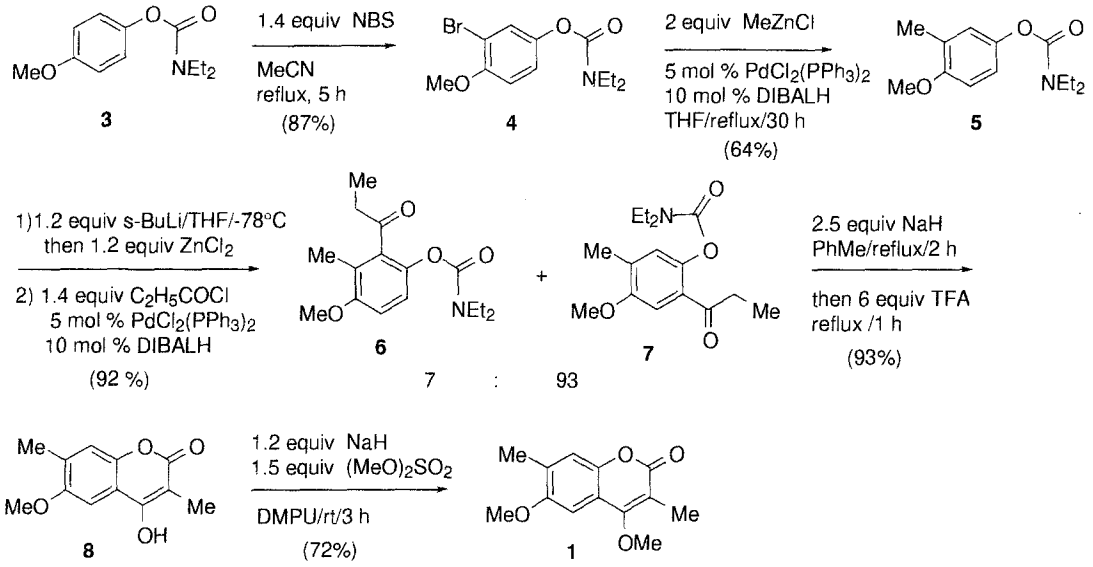
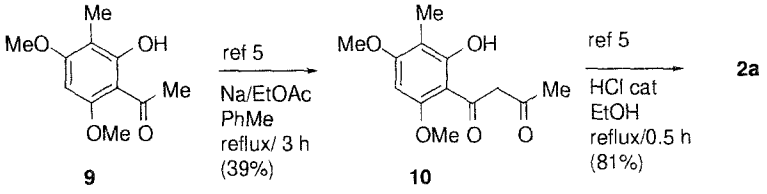
The synthesis of **1** (Scheme 2) was initiated by regiospecific electrophilic bromination of the aryl carbamate **3** with NBS followed by Pd-catalyzed Negishi cross-coupling[6] with MeZnCl to furnish the tolyl carbamate **5**.[7] Lithiation-zinc transmetalation of **5** followed by cross coupling with propionyl chloride resulted in the formation of a mixture of **6** and **7** in a 7:93 ratio. Although inseparable by column chromatography, the mixture was subjected to crystallization (hexanes/-20°C) to cleanly produce **7** in 76% yield.[8] The regioselectivity was expected on the basis of *meta*-methyl group effect in D*o*M reactions.[9] The carbamoyl Baker-Venkataraman rearrangement of **7** using NaH in refluxing toluene followed by TFA cyclization in one-pot reaction[1] proceeded smoothly to give coumarin **8** in excellent yield. Methylation under reported conditions,[3b] except in non-toxic DMPU rather than HMPA, concluded the synthesis of **1** in five steps and 28% overall yield, illustrating the efficiency of the new general 4-hydroxycoumarin construction method.[1]

Scheme 2



Examination of the spectral data,[10] especially the IR and NMR spectra, of synthetic **1** showed vast discrepencies with those reported[4] for the natural product isolated from *C. decaisnei* which was assigned the same structure. Analysis of the reported[4] NOE data and a characteristic difference in ^{1}H NMR of chemical shifts of vinylic proton in 2- and 3-methyl substituted chromen-4-ones[11] led to the proposal of an alternate chromen-4-one structure **2a**. Interestingly, compound **2a** had been previously synthesized to confirm the structure of isoeugenitin (**2b**), isolated from *Eugenia caryophyllata*.[5a] The lack of reported spectroscopic data for **2a** forced the repetition of its synthesis according to Schmid and Bolleter[5b] by Claisen condensation of the acetophenone **9**[12] to give **10** followed by acid-catalyzed cyclization (Scheme 3). The spectroscopic data (IR, ^{13}C, ^{1}H NMR, MS)[13] of synthetic **2a** was in full agreement with that reported[4] for the natural product isolated from *C. decaisnei* whose structure is duly revised from **1** to **2a**.

Scheme 3



In summary, the new synthetic protocol consisting of sequential Directed *ortho* Metalation, Negishi cross coupling, and carbamoyl Baker-Venkataraman reactions[1] has been applied to an efficient construction of 4,6-dimethoxy-3,7-dimethylcoumarin (**1**), a structure assigned[4] to a compound isolated from *Colchicum decaisnei*. The achievement of this unequivocal synthesis coupled with spectral data comparison led to the reassignment of structure **1** to **2a**, isoeugenetin methyl ether, a known derivative of isoeugenetin (**2b**)[5] isolated from *Eugenia caryophyllata*.[5a] This was confirmed by synthesis of **2a**. Thus, compound **1** is, to the best of our knowledge, not a natural product.[14]

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7. This route was chosen in lieu of a classical synthesis of the phenol corresponding to **5** by a terminal Baeyer-Villiger oxidation (see, Rathore, R.; Kochi, J. K. *J. Org. Chem.* **1995**, *60*, 7479-7490) in order to provide greater scope for substituent variation in the overall methodology for coumarins. Furthermore, experiments of metal-halogen exchange (n-BuLi/-78°C) and MeI or MeOTf quench on **4** led to complex mixtures containing minor amounts of **5**.

8. *Typical Procedure for DoM - Negishi Cross Coupling Reaction:* To a cooled (-78°C) solution of **5** (1.187 g, 5 mmol) in THF (10 mL) was added s-BuLi (4.5 mL, 6 mmol, 1.34 M cyclohexane solution) maintaining the internal temperature <-72 °C. After stirring for 1 h at - 78 °C, $ZnCl_2$ (6.2 mL, 1 M THF solution) was added in the same manner and, in 30 min, the reaction mixture was brought to 0 °C followed by addition of C_2H_5COCl (0.61 mL, 7 mmol) and a solution of Pd-catalyst

[prepared by addition of DIBALH (0.5 ml, 1 M solution in hexane) to a stirred suspension $PdCl_2(PPh_3)_2$ (176 mg, 0.25 mmol) in 5 mL of PhMe at 0 °C with further stirring for 15 min at 0 °C and 15 min at rt]. The reaction mixture was stirred for 30 min at 0 °C and 2 h at rt, before 25 mL of sat NH_4Cl solution was added. The organic phase was separated, the aq phase was extracted with Et_2O (2 x 20 mL), the combined organic extract was filtered through Celite, the filtrate was concentrated in vacuum, and the residue was diluted with Et_2O, dried (Na_2SO_4), and purified by column chromatography on silica gel (EtOAc-hexanes, 1:4) providing 1.36 g (4.62 mmol, 92% yield) of a 93:7 mixture of **7** and **6**, which was dissolved in hexanes (20 mL) and cooled to - 20 °C resulting in crystallization of **7** (1.12 g, 3.80 mmol, 76% yield) as colorless needles, mp 67-68 °C; IR (KBr) 1716, 1684 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.88 (s, 1H), 3.85 (s, 3H), 3.53-3.35 (m, 4H), 2.88 (q, 2H, J = 7.3 Hz), 2.23 (s, 3H), 1.30-1.13 (m, 9H); ^{13}C NMR (62.9 MHZ, $CDCl_3$) δ 200.5, 154.9, 154.1, 143.3, 132.5, 129.7, 125.7, 109.9, 55.7, 42.2, 41.8, 35.1, 16.1, 14.1, 13.3, 8.2; EI MS *m/z* (rel intensity) 293 (M, 25), 264 (2), 237 (4), 165 (10), 135 (3), 101 (9), 100 (100); EI HRMS Calcd for $C_{16}H_{23}NO_4$: 293.1627. Found 293.1619. Coumpound **6:** ^1H NMR (250 MHz, $CDCl_3$) δ 6.98 (d, 1H, J = 8.6 Hz), 6.81 (d, 1H, J = 8.6 Hz), 3.82 (s, 3H), 3.56-3.30 (m, 4H), 2.71 (q, 2H, J = 7.2 Hz), 2.07 (s, 3H), 1.30-1.05 (m, 9H).

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10. Compound **1:** colorless needles, mp 141-142 °C (EtOAc-hexanes); IR (KBr) 1704, 1634, 1620, 1575, 1331, 1257, 1202 cm^{-1}; ^1H NMR (250MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.00 (s, 1H), 4.00 (s, 3H), 3.89 (s, 3H), 2.30 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 164.6, 163.7, 154.5, 146.6, 132.1, 118.4, 115.3, 111.3, 101.9, 61.0, 55.8, 16.6, 10.7; EI MS *m/z* (rel intensity) 234 (M, 100), 219 (46), 206 (17), 205 (15), 191 (69), 175 (14), 91 (28), 77 (27), 65 (19), 63 (19). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.49; H, 6.10.

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13. Isoeugenetin methyl ether (**2a**): yellowish needles, mp 173-174 °C (benzene-hexanes) [lit[5b] mp 173.5-174.5 °C]; IR (KBr) 1661, 1628, 1602, 1388, 1323, 1131, 841 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.38 (s, 1H), 6.00 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 2.30 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 177.6, 162.6, 160.7, 158.5, 156.5, 110.9, 108.0, 105.3, 91.1, 56.0, 55.4, 19.4, 7.3; EI MS *m/z* (rel intensity) 234 (100), 233 (40), 205 (68), 188 (56), 161 (51), 149 (13), 103 (17), 69 (47); EI HRMS Calcd for $C_{13}H_{14}O_4$: 234.0892. Found 234.0888.

14. All new compounds show analytical and spectra (IR, NMR, HRMS) data consistent with the given structures.