

# 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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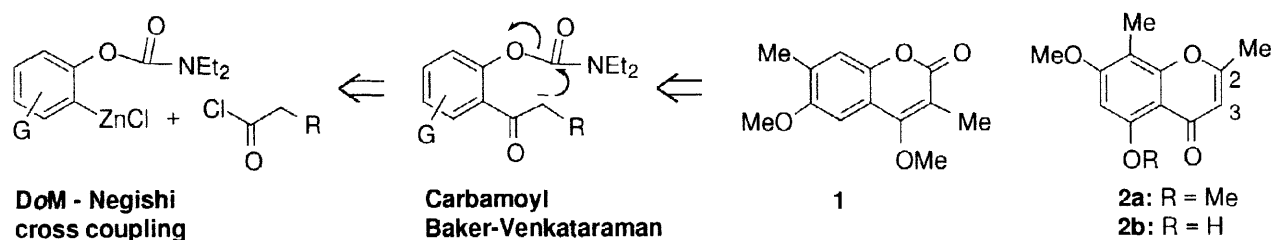
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**Abstract:** Coumarin (**1**), the putative natural product isolated from *Colchicum decaisnei*, has been shown, by spectroscopic analysis and total synthesis, to be isoeugenetin methyl ether (**2a**), a synthetic derivative of the isoeugenetin (**2b**), isolated from *Eugenia caryophyllata*. © 1998 Elsevier Science Ltd. All rights reserved.

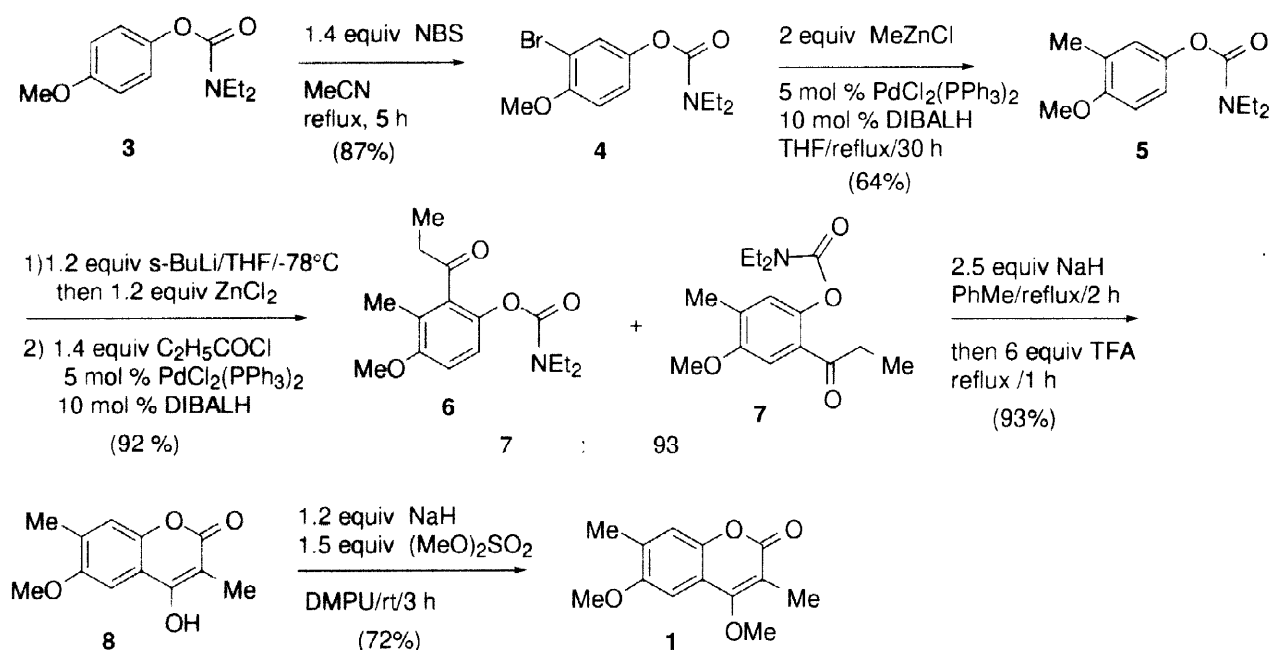
The discovery of the carbamoyl variation of the Baker-Venkataraman rearrangement as a general route to 4-hydroxycoumarins<sup>1</sup> invited its application to the total synthesis of coumarin natural products<sup>1,2</sup> not only because of their wide occurrence and diverse biological activities, 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 installation of the C-3 substituent in a manner which is not dependent upon C vs O alkylation.<sup>1,3</sup> 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,<sup>4</sup> was chosen. Herein we report the synthesis of **1**, demonstrate that the proposed structure<sup>4</sup> 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 isoeugenetin (**2b**), isolated from *Eugenia caryophyllata*.<sup>5</sup>

Scheme 1

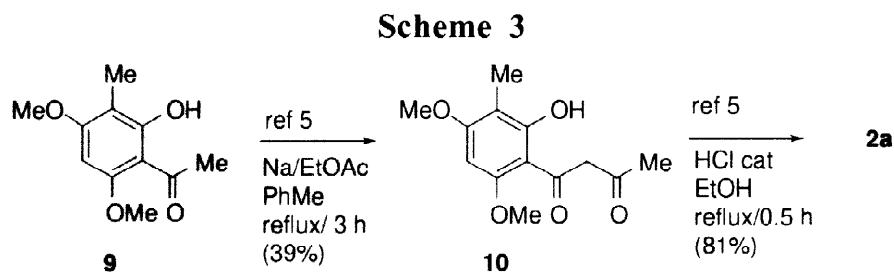


The synthesis of **1** (Scheme 2) was initiated by regioselective electrophilic bromination of the aryl carbamate **3** with NBS followed by Pd-catalyzed Negishi cross-coupling<sup>6</sup> with MeZnCl to furnish the tolyl carbamate **5**.<sup>7</sup> Lithiation-zinc transmetalation of **5** followed 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/ $-20^{\circ}\text{C}$ ) to cleanly produce **7** in 76% yield.<sup>8</sup> The regioselectivity was expected on the basis of *meta*-methyl group effect in DoM reactions.<sup>9</sup> The carbamoyl Baker-Venkataraman rearrangement of **7** using NaH in refluxing toluene followed by TFA cyclization in one-pot reaction<sup>1</sup> proceeded smoothly to give coumarin **8** in excellent yield. Methylation under reported conditions,<sup>3b</sup> 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.<sup>1</sup>

### Scheme 2



Examination of the spectral data,<sup>10</sup> especially the IR and NMR spectra, of synthetic **1** showed vast discrepancies with those reported<sup>4</sup> for the natural product isolated from *C. decaisnei* which was assigned the same structure. Analysis of the reported<sup>4</sup> NOE data and a characteristic difference in  $^1\text{H}$  NMR of chemical shifts of vinylic proton in 2- and 3-methyl substituted chromen-4-ones<sup>11</sup> 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*.<sup>5a</sup> The lack of reported spectroscopic data for **2a** forced the repetition of its synthesis according to Schmid and Bolleter<sup>5b</sup> by Claisen condensation of the acetophenone **9**<sup>12</sup> to give **10** followed by acid-catalyzed cyclization (Scheme 3). The spectroscopic data (IR,  $^{13}\text{C}$ ,  $^1\text{H}$  NMR, MS)<sup>13</sup> of synthetic **2a** was in full agreement with that reported<sup>4</sup> for the natural product isolated from *C. decaisnei* whose structure is duly revised from **1** to **2a**.



In summary, the new synthetic protocol consisting of sequential Directed *ortho* Metalation, Negishi cross coupling, and carbamoyl Baker-Venkataraman reactions<sup>1</sup> has been applied to an efficient construction of 4,6-dimethoxy-3,7-dimethylcoumarin (**1**), a structure assigned<sup>4</sup> 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**)<sup>5</sup> isolated from *Eugenia caryophyllata*.<sup>5a</sup> This was confirmed by synthesis of **2a**. Thus, compound **1** is, to the best of our knowledge, not a natural product.<sup>14</sup>

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#### References and Footnotes:

1. Kalinin, A. V.; da Silva A. J. M.; Lopes, C. C.; Lopes, R. S. C.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4995-4998.
2. Estevez-Braun, A.; Gonzalez, A. G. *Nat. Prod. Repts.* **1997**, *14*, 465-475.
3. a) Tabakovic, I.; Tabakovic, K.; Gaon, I. *Org. Prep. Proc. Int.* **1997**, *29*, 223-226 and refs cited therein; b) Suzuki, E.; Katsuragawa, B.; Inoue, S. *Synthesis* **1978**, 144-146 and refs cited therein; c) Bohlmann, F.; Steinmeyer, A. *Tetrahedron Lett.* **1986**, *27*, 5359-5362.
4. Al-Tel, T. H.; Zarga, M. H. A.; Sabri, S. S.; Feroz, M.; Fatima, N.; Shah, Z.; Atta-ur-Rahman *Phytochemistry* **1991**, *30*, 3081-3086.
5. a) Schmid, H.; Bolleter, A. *Helv. Chim. Acta* **1949**, *32*, 1358-1360; b) Schmid, H.; Bolleter, A. *Helv. Chim. Acta* **1950**, *33*, 917-922.
6. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117-2188; Erdik, E. *Tetrahedron* **1992**, *48*, 9577-9648.
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<sub>2</sub> (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<sub>2</sub>H<sub>5</sub>COCl (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<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (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<sub>4</sub>Cl solution was added. The organic phase was separated, the aq phase was extracted with Et<sub>2</sub>O (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<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), 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<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>) 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<sub>16</sub>H<sub>23</sub>NO<sub>4</sub>: 293.1627. Found 293.1619. Compound **6**: <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) 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).

9. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933.
10. Compound **1**: colorless needles, mp 141-142 °C (EtOAc-hexanes); IR (KBr) 1704, 1634, 1620, 1575, 1331, 1257, 1202 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>) 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<sub>13</sub>H<sub>14</sub>O<sub>4</sub>: C, 66.65; H, 6.02. Found: C, 66.49; H, 6.10.
11. Eguchi, S. *Org. Mass Spectrom.* **1979**, *14*, 345-349.
12. Tada, A.; Saiton, T.; Shoji, J. *Chem. Pharm. Bull.* **1980**, *28*, 2487-2493.
13. Isoeugenetin methyl ether (**2a**): yellowish needles, mp 173-174 °C (benzene-hexanes) [lit<sup>5b</sup> mp 173.5-174.5 °C]; IR (KBr) 1661, 1628, 1602, 1388, 1323, 1131, 841 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>) 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<sub>13</sub>H<sub>14</sub>O<sub>4</sub>: 234.0892. Found 234.0888.
14. All new compounds show analytical and spectra (IR, NMR, HRMS) data consistent with the given structures.