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New syntheses of dalbergichromene and dalbergin from vanillin via neoflavene intermediate

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Abstract—In this Letter, naturally occurring dalbergichromene and dalbergin were synthesized from a common neoflavene intermediate, which was derived from vanillin. The giving neoflavene intermediate was debenzylated with $AlCl_3$ to yield dalbergichromene in 39% total yield, and it was oxidized by DDQ, and subsequently debenzylated by $Pd(OH)_2/C$ and cyclohexene in refluxing ethanol to give dalbergin in 31% total yield.

Plant *Dalbergia* species in China are known to be applied in traditional medicine as a remedy for blood disorders, ischemia, and inflammation.[1] Dalbergichromene, firstly isolated from the stembark of *Dalbergia sissoo*[2] and *Dalbergia latifolia*,[3] belongs to the neoflavene family. Moreover, Dalbergin isolated from *Dalbergia odorifera*,[1,4] belongs to neoflavonoids, and was investigated to have tumor-specific cytotoxicity.[5] Neoflavenes attract the attention of chemists because it was not only found to have various biological activities,[6] but also can be converted into other biological active coumarins.[7] In addition, neoflavenes can be transferred into chroman-3-ones which were the important intermediates for various biological and therapeutic agents.[8,9] Up to date, various strategies to deal with the syntheses of neoflavenes including the coupling reaction of 4-trifluoromethylsulfonyloxy-2*H*-chromenes with arylboronic acids,[10] a coupling reaction of the ligand with aryllead triacetates,[11] and so on[12] have been reported. However, there is no synthetic method for dalbergichromene disclosed. For the biological and chemical interest, we design a rational and simple synthetic strategy for both dalbergichromene (**8**) and dalbergin (**11**) through a common neoflavene intermediate **7**, which was prepared from vanillin via 6 steps. In addition, dihydrodalbergichromene (**9**) and *O*-benzyldalbergin (**10**) were also obtained in good yield, respectively (Scheme 1).

As a general procedure, vanillin (**1**) was treated with benzyl bromide to provide **2** in 98% yield which was subsequently oxidized with *m*-CPBA to give **3** in yield of 92%.[13] Followed by the reaction with allyl bromide, **4** was given in yield of 98%. Subsequently, **4** was reacted with benzoyl chloride in the presence of zinc oxide at room temperature to afford **5** in yield of 61%. Compound **5** was allowed to react with methylene triphenylphosphine to undergo the Wittig reaction to give **6** in yield of 88%. Then, compound **6** was reacted with Grubbs' catalyst (II) to undergo the ring-closing metathesis, resulting in the formation of neoflavene **7** in yield of 96% as the key intermediate,[14] and which was treated with $AlCl_3$ to undergo O-debenzylation to give dalbergichromene (**8**) in 85% yield. The ^1H NMR and other spectroscopic data reported for **8** either from the natural products[2] or semi-synthesis[15] were comparable and coincident with our synthetic one.[16] The reaction of compound **7** with cyclohexene and $Pd(OH)_2/C$ in refluxing ethanol gave dihydrodalbergichromene (**9**)[17] in yield of 95% via O-debenzylation and reduction. Moreover, the reaction of compound **7** with DDQ in dioxane to undergo allylic oxidation afforded *O*-benzyldalbergin **10** in 78% yield.[18] After debenzylation of **10** with $Pd(OH)_2/C$ and cyclohexene in refluxing ethanol,

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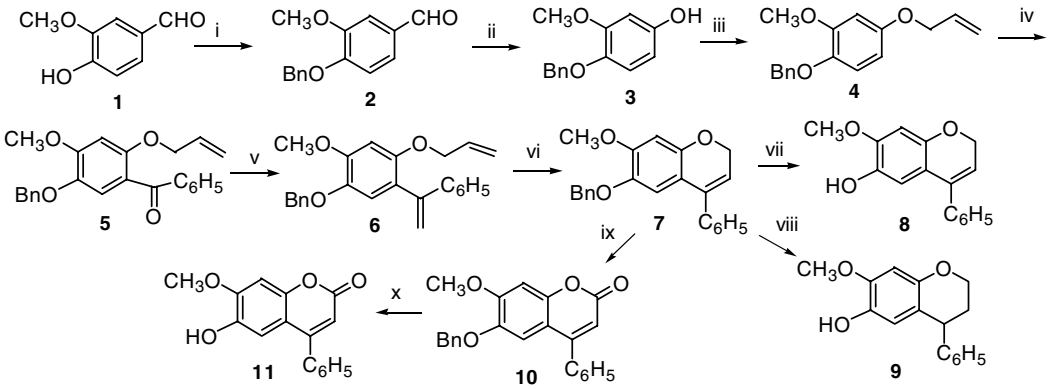

Scheme 1. Synthesis of dalbergichromene (**8**), dihydrodalbergichromene (**9**), *O*-benzyldalbergin (**10**), and dalbergin (**11**). Reagents and conditions: (i) $C_6H_5CH_2Br$, K_2CO_3, acetone, reflux 5 h, 98%; (ii) *m*-CPBA, CH_2Cl_2, 12 h, 6 N NaOH–MeOH, 3 h, HCl–H_2O, 92%; (iii) allyl bromide, K_2CO_3, acetone, reflux, 8 h, 98%; (iv) C_6H_5COCl, ZnO, rt, 61%; (v) $Ph_3P^+CH_3Br^-$, *tert*-BuO^-K^+, 88%; (vi) Grubbs' cat. (II), CH_2Cl_2, 96%; (vii) $AlCl_3$, CH_2Cl_2, 85%; (viii) $Pd(OH)_2$/C, cyclohexene, EtOH, reflux, 95%; (ix) DDQ, dioxane, 77%; (x) $Pd(OH)_2$/C, cyclohexene, EtOH, reflux, 87%.

dalbergin (**11**)[19] with spectral data identical to that reported,[1] was produced in 87% yield.

In conclusion, besides we have disclosed the first and an efficient method to prepare the naturally occurring dalbergichromene (**8**) in 39% total yield, the other naturally occurring compound dalbergin (**11**) was also prepared from the same common neoflavene (**7**) intermediate in 31% total yield.

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14. Synthesis of **7**: A solution of **6** (0.33 g, 0.89 mmol) in CH_2Cl_2 (60 mL) was stirred and Grubbs' catalyst (II) (0.05 g, 0.06 mmol) was added at rt under dry argon. The resulting mixture was continually stirred for 8 h. After work-up as general procedure, and chromatographic purification process (silica-gel, EtOAc–*n*-hexane = 1:15), pure **7** (0.29 g, 96%) was given as colorless liquid, R_f 0.35 (ethyl acetate–*n*-hexane = 1:10); UV (CH_2Cl_2) 211, 234, 320 nm; IR (KBr) 2924, 2352, 1612, 1503, 1454, 1379, 1271, 1193, 1017, 808, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.85 (s, 3H, OCH_3), 4.74 (d, $J = 4.0$ Hz, 2H, H-2), 4.94 (s, 2H, $CH_2C_6H_5$), 5.63 (t, 1H, $J = 4.0$ Hz, H-3), 6.53 (s, 1H, ArH), 6.56 (s, 1H, ArH), 7.16 (m, 2H, ArH), 7.28 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.94 (OCH_3), 65.26 (C-2), 71.84 ($OCH_2C_6H_5$), 100.93, 113.36, 115.42, 117.0, 127.45, 127,56, 127.61, 128.32, 136.93, 137.20, 138.12, 141.79, 149.94, 150.70; EI-MS (70 eV) *m*/*z* (intensity), 344 (M^+, 22), 281 (38), 254 (18), 253 (M^+-91, 100), 249 (23), 221 (22), 165 (26), 115 (14); HRMS calcd for $C_{23}H_{20}O_3$: 344.1412. Found: 344.1413.
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16. Dalbergichromene **8** was obtained as a colorless crystal, mp 99–101 °C (petroleum ether) [reported,[2] mp 99–100 °C], R_f 0.36 (EtOAc–*n*-hexane = 1:4), ^1H NMR ($CDCl_3$, 400 MHz) δ 3.86 (s, 3H, OCH_3), 4.76 (d, $J = 4.0$ Hz, 2H, H-2), 5.21 (s, 1H, OH), 5.69 (t, $J =$ 4.0 Hz, 1H, H-3), 6.51 (s, 1H, ArH), 6.62 (s, 1H, ArH), 7.31 (m, 5H, ArH), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.02 (OCH_3), 65.30 (C-2), 99.96, 111.53, 116.60, 117.52, 127.69, 128.32, 128.52, 137.13, 138.30, 139.59, 146.73, 148.51; HRMS (ESI) calcd for $C_{16}H_{14}O_3Na$ $[M+Na]^+$: 277.0841. Found: 277.0838.
17. Compound **9** was obtained as a colorless crystal, mp 96–97 °C (*n*-hexane); UV (CH_2Cl_2) λ_{max} 232, 300 nm; IR (KBr) 3500, 1631, 1499, 1451, 1387, 1349, 1261, 1161, 1132, 1063, 1027, 885, 806, 757, 702 cm^{-1}; ^1H NMR

($CDCl_3$, 400 MHz) δ 2.05 (m, 1H, H-3a), 2.28 (m, 1H, H-3b), 3.85 (s, 3H, OCH_3), 4.07 (d, $J = 6.4$ Hz, 1H, H-4), 4.13 (m, 2H, H-2), 5.11 (s, 1H, OH), 6.37 (s, 1H, ArH), 6.42 (s, 1H, ArH), 7.11 (m, 2H, ArH), 7.21 (m, 1H, ArH), 7.28 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.97, 40.58, 51.91, 63.97, 99.73, 115.16, 116.25, 126.41, 128.41, 128.55, 139.36, 145.69, 146.09, 148.47; EI-MS (70 eV) *m*/*z* (intensity), 257 (M^++1, 19), 256 (M^+, 100), 240 (8), 239 (8), 228 (24), 227 (32); HRMS (ESI) calcd for $C_{16}H_{16}O_3Na$ $[M+Na]^+$: 279.0997. Found: 279.0996. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.71; H, 6.29.

18. Synthesis of **10**: **7** (0.15 g, 0.44 mmol) dissolved in 1,4-dioxane (5 mL) was reacted with DDQ (0.2 g, 0.88 mmol) at rt for 1 h. After usual work-up and chromatographic purification process (silica-gel, EtOAc–*n*-hexane = 1:4), **10** was produced (0.12 g, 77%) as pale yellow crystals, mp 119–120 °C (*n*-hexane), $R_f = 0.68$ (ethyl acetate–*n*-hexane = 1:2), ^1H NMR ($CDCl_3$, 200 MHz) δ 3.98 (s, 3H, OCH_3), 5.04 (s, 2H, $OCH_2C_6H_5$), 6.20 (s, 1H, H-3), 6.84 (s, 1H, H-5), 6.92 (s, 1H, H-8), 7.27 (m, 7H, ArH), 7.47 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.38 (OCH_3), 71.45 ($OCH_2C_6H_5$), 100.44, 110.97, 111.23, 112.12, 127.33, 128,00, 128.19, 128.57, 128.81 129.44, 135.51, 136.31, 144.53, 150.32, 153.57, 155.46, 161.30; EI-MS (70 eV) *m*/*z* (intensity), 358 (M^+, 5), 268 (20), 267 (100), 236 (30), 235 (69), 209 (24), 208 (21), 207 (45), 91 (72). Anal. Calcd for $C_{23}H_{18}O_4$: C, 77.08; H, 5.06. Found: C, 77.10; H, 5.09.

19. Dalbergin **11** was obtained as pale yellow crystals, mp 210–211 °C (EtOAc–*n*-hexane = 1:1) [reported,[1] mp 211–212 °C], $R_f = 0.58$ (ethyl acetate–*n*-hexane = 1:1), The spectral data such as ^1H NMR, ^{13}C NMR, EI-MS are all coincident to the reported dalbergin.