

Articles

Concise Synthesis of Biologically Interesting (\pm)-Cannabichromene, (\pm)-Cannabichromenic Acid, and (\pm)-Daurichromenic Acid

Yong Rok Lee* and Xue Wang

School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Korea. *E-mail: yrlee@yu.ac.kr
Received September 7, 2005

Total synthesis of biologically interesting (\pm)-cannabichromene, (\pm)-cannabichromenic acid, and (\pm)-daurichromenic acid is described. The key step in the synthetic strategy involves the formation of benzopyrans by ethylenediamine diacetate-catalyzed reactions of resorcinols with α,β -unsaturated aldehydes.

Key Words : Benzopyran, Cannabichromene, Cannabichromenic acid, Daurichromenic acid

Introduction

Cannabichromene (**1**) and cannabichromenic acid (**2**) were isolated from *Cannabis sativa* L (Figure 1).¹ The resin of this plant has shown a variety of interesting pharmacological activities such as anti-inflammatory, anti-fungal, and anti-microbial effects.² They have been also used as a medicine and a psychotomimetic drug since ancient times.³

Daurichromenic acid (**3**) was recently isolated from *Rhododendron dauricum*, a plant found in areas of northern China, eastern Siberia, Mongolia, and Hokkaido, Japan.⁴ The dried leaves of this plant are known as "Manshanfong" in China and are used in medicines for treatment of an expectorant and an acute-chronic bronchitis.⁵ Daurichromenic acid (**3**) has shown highly potent anti-HIV activity in acutely infected H9 cells with an EC_{50} of 0.00567 $\mu\text{g}/\text{mL}$ and a therapeutic index (TI) of 3710.⁴ The absolute configuration of C-2 in daurichromenic acid (**3**) was known as S.⁴

Recently, we have developed a new methodology for the preparation of a variety of benzopyrans by using ethylenedi-

amine diacetate-catalyzed reactions of resorcinols to α,β -unsaturated aldehydes.⁶ Our efforts in developing these reactions led us to synthesis of natural products with benzopyran skeletons. We report herein on the concise synthesis of (\pm)-cannabichromene, (\pm)-cannabichromenic acid, and (\pm)-daurichromenic acid.

Results and Discussion

The one-step synthesis of (\pm)-cannabichromene (**1**) was first examined. Several synthetic approaches of (\pm)-cannabichromene have already been reported.⁷ However, this synthetic exploitation has been limited due to harsh reaction conditions and side reactions involving the *bis*-product.⁷ Our strategy is depicted in Scheme 1. Reaction of olivetol (**4**) with citral using 20 mol % of ethylenediamine diacetate in refluxing toluene for 6 h gave adduct **1** in a 40% yield. The spectroscopic data of our synthetic material **1** are in agreement with those reported in the literature.⁸

Next, the synthesis of (\pm)-cannabichromenic acid (**2**) was examined. The synthesis of cannabichromene has been

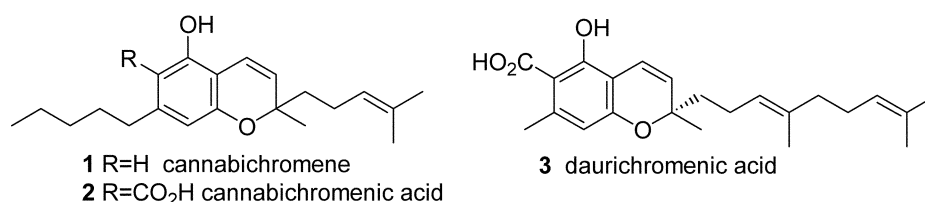
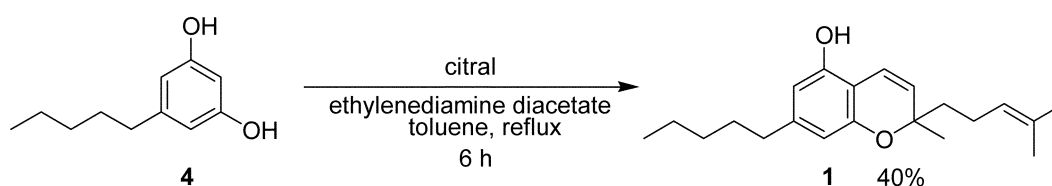
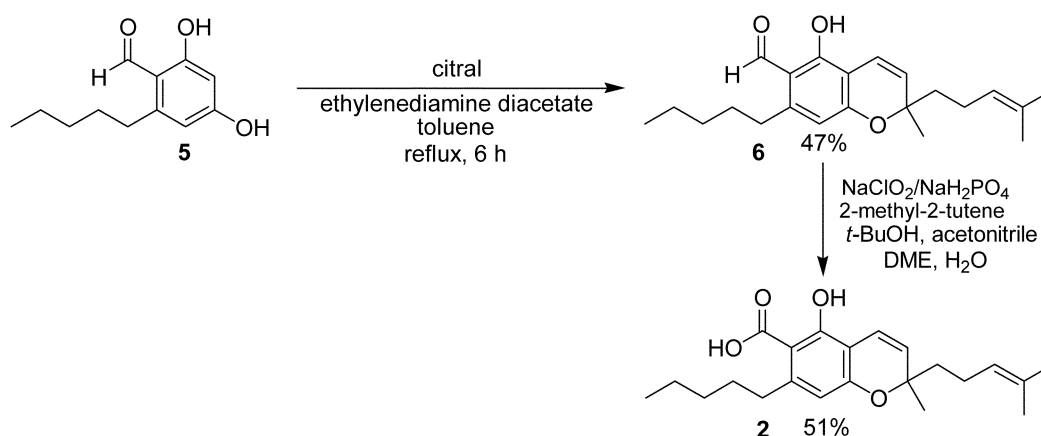


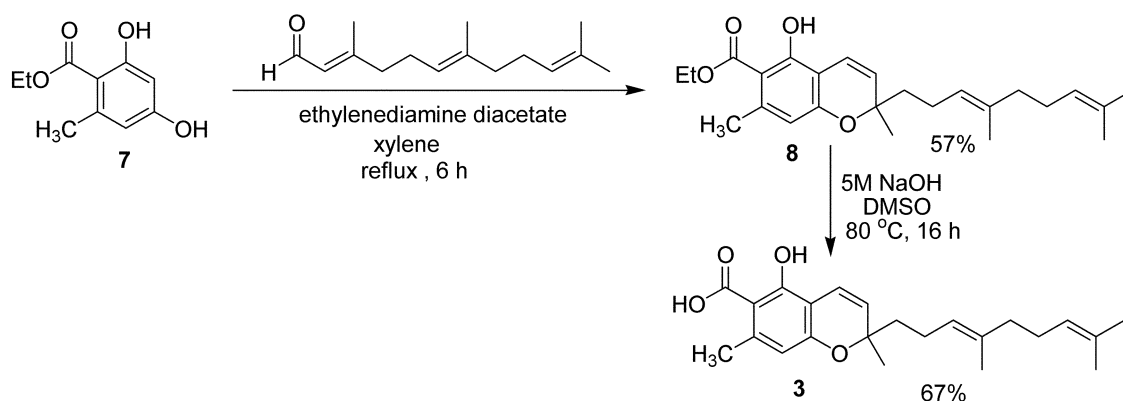
Figure 1



Scheme 1



Scheme 2



Scheme 3

attracted with considerable attention, whereas little was known about the total synthesis of cannabichromenic acid. Our synthetic route is outlined in Scheme 2. Reaction of **5** with citral in the presence of 20 mol % of ethylenediamine diacetate in refluxing toluene for 6 h afforded adduct **6** (47%), which was oxidized to the corresponding carboxylic acid **2** with NaClO₂/NaH₂PO₄ in 51% yield.⁹ The spectroscopic data of our synthetic cannabichromenic acid (**2**) are in agreement with those reported in the literature.^{1c}

Finally, the synthesis of the biologically interesting (\pm)-daurichromenic acid (**3**) was examined. Recently, the total synthesis of daurichromenic acid (**3**) has been reported by three groups.¹⁰⁻¹² Hsung and co-worker have reported the total synthesis of the methyl ester of **3** starting from 5-methyl-1,3-cyclohexanedione in 3-steps (22%, overall yields).¹⁰ Other synthetic approach of daurichromenic acid (**3**) was accomplished by Jin and co-workers starting from orcinol in 5-steps (49%, overall yields).¹¹ More recently, another concise synthesis of **3** has been reported by Wilson and co-workers from ethyl acetoacetate in 4-steps (6%, overall yields).¹² Although there are currently several methods available to synthesize daurichromenic acid (**3**), general and efficient concise synthetic routes are still more desired. Our concise synthetic approach is outlined in Scheme 3. Reaction of **7** with *trans,trans*-farnesal in the presence of 20

mol % of ethylenediamine diacetate at refluxing xylene for 6 h gave adduct **8** in 57% yield. Hydrolysis of **8** with 5 M NaOH at 80 °C for 16 h in DMSO afforded daurichromenic acid (**3**) in a 67% yield. The spectroscopic data of our synthetic material **3** are in agreement with those reported in the literature.⁴

In conclusion, as an application of the methodology developed previously by our group, we have described the synthesis of the biologically interesting cannabichromene (**1**), cannabichromenic acid (**2**), and daurichromenic acid (**3**).

Experimental Section

All experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ¹H NMR spectra were recorded on a Bruker Model ARX (300 MHz) spectrometer in CDCl₃ using 7.24 ppm as the solvent chemical shift. ¹³C NMR spectra were recorded on a Bruker Model ARX (75 MHz) spectrometer in CDCl₃ using 77.0 ppm as the solvent chemical shift. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS mass spectra were carried out on JEOL JMS-700 spectrometer by Korea Basic Science Institute (Daegu).

(\pm)-Cannabichromene (**1**). Olivetol (**4**) (360 mg, 2.0 mmol) and citral (365 mg, 2.4 mmol) were dissolved in toluene (20 mL), and ethylenediamine diacetate (72 mg, 0.4 mmol) was added at room temperature. The mixture was refluxed for 6 h and then cooled to room temperature. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (10 : 1) to give product **1** (252 mg, 40%) as a yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 6.59 (1H, d, $J = 10.0$ Hz), 6.23 (1H, s), 6.10 (1H, s), 5.47 (1H, d, $J = 10.0$ Hz), 5.07 (1H, t, $J = 7.1$ Hz), 4.72 (1H, s), 2.42 (2H, t, $J = 7.5$ Hz), 2.15-2.04 (2H, m), 1.73-1.60 (2H, m), 1.63 (3H, s), 1.58-1.48 (2H, m), 1.55 (3H, s), 1.36 (3H, s), 1.30-1.20 (4H, m), 0.86 (3H, t, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 154.3, 151.5, 145.2, 132.0, 127.6, 124.6, 117.4, 109.4, 108.3, 107.5, 78.7, 41.4, 36.3, 31.9, 31.1, 26.6, 26.1, 23.1, 23.0, 18.0, 14.5; IR (neat) 3416, 2963, 2928, 2859, 1624, 1576, 1431, 1377, 1343, 1144, 1084, 1053, 833 cm^{-1} .

5-Hydroxy-2-methyl-2-(4-methylpent-3-enyl)-7-pentyl-2H-chromene-6-carbaldehyde (6). 2,4-Dihydroxy-6-pentylbenzaldehyde (**5**) (208 mg, 1.0 mmol) and citral (183 mg, 1.2 mmol) were dissolved in toluene (20 mL), and ethylenediamine diacetate (36 mg, 0.2 mmol) was added at room temperature. The mixture was refluxed for 6 h and then cooled to room temperature. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (20 : 1) to give product **6** (168 mg, 47%) as a yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 12.66 (1H, s), 10.0 (1H, s), 6.68 (1H, d, $J = 10.1$ Hz), 6.16 (1H, s), 5.47 (1H, d, $J = 10.1$ Hz), 5.06 (1H, t, $J = 7.0$ Hz), 2.75 (1H, t, $J = 7.6$ Hz), 2.07-2.02 (2H, m), 1.82-1.55 (4H, m), 1.63 (3H, s), 1.54 (3H, s), 1.39 (3H, s), 1.35-1.29 (4H, m), 0.85 (3H, t, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 193.1, 161.2, 160.0, 149.4, 132.3, 126.8, 124.2, 116.3, 112.7, 110.4, 107.3, 81.0, 42.2, 32.7, 32.4, 32.0, 27.7, 26.1, 23.0, 22.9, 18.0, 14.4; IR (neat) 2928, 1628, 1568, 1453, 1383, 1294, 1252, 1157, 808 cm^{-1} ; HRMS m/z (M^+) calcd for $\text{C}_{22}\text{H}_{30}\text{O}_3$: 342.2195. Found: 342.2194.

(\pm)-Cannabichromenic acid (**2**). To a solution of the aldehyde **6** (140 mg, 0.4 mmol) in *t*-butanol (3 mL), acetonitrile (3 mL), 2-methyl-2-butene (2 mL), and DME (1 mL) was added NaH_2PO_4 (336 mg, 2.80 mmol) and NaClO_2 (253 mg, 2.80 mmol, dissolved in 1 mL of water) at 0 $^\circ\text{C}$. The resulting mixture was warmed slowly to room temperature and stirred for 12 h. Brine (15 mL) was added, and the resultant solution was extracted with ethyl acetate (20 mL \times 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous MgSO_4 , and concentrated *in vacuo*. The crude product was then purified by flash chromatography using hexane/ethylacetate (5 : 1) as the eluant to afford **2** (74 mg, 51%) as a liquid: ^1H NMR (300 MHz, CDCl_3) δ 11.8 (1H, s), 6.71 (1H, s, 10.1 Hz), 6.21 (1H, s), 5.46 (1H, d, $J = 10.1$ Hz), 5.07 (1H, t, $J = 7.2$ Hz), 2.85 (2H, d, $J = 7.6$ Hz), 2.11-2.03 (2H, m), 1.80-1.57 (4H, m), 1.65 (3H, s), 1.54 (3H, s), 1.40 (3H, s), 1.33-1.27 (4H,

m), 0.85 (3H, t, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 176.2, 161.0, 159.2, 149.8, 132.2, 126.7, 124.3, 117.2, 111.8, 107.5, 103.6, 80.3, 42.1, 37.1, 32.4, 31.7, 27.5, 26.0, 23.1, 22.9, 18.0, 14.4; IR (neat) 2928, 1618, 1453, 1373, 1264, 1168, 908 cm^{-1} .

5-Hydroxy-2,7-dimethyl-2-(4,8-dimethyl-3E,7-nonadienyl)-2H-chromene-6-carboxylic acid ethyl ester (8). Ethyl 2,4-dihydroxy-6-methylbenzoate (**7**) (235 mg, 1.2 mmol) and *trans,trans*-farnesal (330 mg, 1.5 mmol) were dissolved in xylene (20 mL), and ethylenediamine diacetate (43 mg, 0.2 mmol) was added at room temperature. The mixture was refluxed for 6 h and then cooled to room temperature. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (15 : 1) to give product **8** (272 mg, 57%) as a yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 12.05 (s, 1H), 6.71 (d, 1H, $J = 10.1$ Hz), 6.17 (s, 1H), 5.46 (d, 1H, $J = 10.1$ Hz), 5.09-5.05 (m, 2H), 4.37 (q, 2H, $J = 7.1$ Hz), 2.45 (s, 3H), 2.11-1.93 (m, 6H), 1.78-1.65 (m, 2H), 1.65 (s, 3H), 1.57 (3H, s), 1.56 (s, 3H), 1.38 (t, 3H, $J = 7.1$ Hz), 1.36 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.1, 159.9, 157.9, 142.9, 135.6, 131.5, 126.4, 124.5, 123.9, 117.0, 111.8, 107.2, 105.2, 79.8, 61.3, 41.7, 39.8, 27.1, 26.8, 25.8, 24.7, 22.7, 17.8, 16.1, 14.4; IR (neat) 3316, 2971, 2925, 1650, 1568, 1447, 1379, 1265, 1169, 1023, 914, 811 cm^{-1} ; HRMS m/z (M^+) calcd for $\text{C}_{25}\text{H}_{34}\text{O}_4$: 398.2457. Found: 398.2455.

(\pm)-Daurichromenic Acid (**3**). To a solution of the ester **8** (200 mg, 0.5 mmol) in DMSO (6 mL) was added aqueous solution of NaOH (5 M, 1.6 mL, 8.0 mmol) at room temperature. The reaction was then heated at 80 $^\circ\text{C}$ for 16 h. After cooling, water (10 mL) was added, and the resultant solution was acidified with 2 N-HCl to pH \sim 2 and extracted with ethyl acetate (20 mL \times 3). The combined organic layer was washed with water and brine, dried over anhydrous MgSO_4 , and concentrated *in vacuo*. The crude product was then purified by flash chromatography using hexane/ethylacetate (1 : 1) as the eluant to afford **3** (125 mg, 67%): ^1H NMR (300 MHz, CDCl_3) δ 11.72 (s, 1H), 6.71 (d, 1H, $J = 10.1$ Hz), 6.23 (s, 1H), 5.46 (d, 1H, $J = 10.1$ Hz), 5.10-5.03 (m, 2H), 4.37 (q, 2H, $J = 7.1$ Hz), 2.51 (s, 3H), 2.12-1.86 (m, 6H), 1.80-1.70 (m, 2H), 1.65 (s, 3H), 1.57 (3H, s), 1.55 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.3, 160.7, 159.1, 144.5, 135.6, 131.4, 129.9, 126.5, 124.5, 116.7, 112.3, 103.6, 80.3, 41.7, 39.7, 27.2, 26.8, 25.7, 24.6, 22.6, 17.7, 16.1; IR (neat) 2926, 1620, 1454, 1381, 1269, 1177, 908 cm^{-1} .

Acknowledgement. This work was supported by grant No. RTI04-01-04 from the Regional Technology Innovation Program of the Ministry of Commerce, Industry, and Energy (MOCIE).

References

- (a) Claussen, U.; Spulak, F. v.; Korte, F. *Tetrahedron* **1966**, *22*, 1477. (b) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1971**, *93*, 217. (c) Shoyama, Y.; Fujita, T.; Yamauchi, T.; Nishioka, I. *Chem.*

- Pharm. Bull.* **1968**, *16*, 1157.
- (a) ElSohly, H. N.; Turner, C. E.; Clark, A. M.; ElSohly, M. A. *J. Pharm. Sci.* **1982**, *71*, 1319. (b) Wirth, P. W.; Watson, E. S.; ElSohly, M.; Turner, C. E.; Murphy, J. C. *Life Sci.* **1980**, *26*, 1991.
 - Bouquet, R. J. *Bull. Narcotics* **1951**, *3*, 22.
 - Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamasibi, T.; Fujioka, T.; Milashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559.
 - (a) *Chinese Mareria Medica*; Jiangsu New Medical College: Shanghai People's Pub. House, Shanghai, 1977; p 2506 (b) Yasuda, M.; Igarashi, H.; Kano, Y.; Konoshima, M. *Shoyakugaku Zasshi* **1984**, *38*, 346.
 - Lee, Y. R.; Choi, J. H.; Yoon, S. H. *Tetrahedron Lett.* in press.
 - (a) Mechoulam, R.; Yagnitinsky, B.; Gaoni, Y. *J. Am. Chem. Soc.* **1968**, *90*, 2418. (b) Kane, V. V.; Razdan, R. K. *J. Am. Chem. Soc.* **1968**, *90*, 6551. (c) Crombie, L.; Crombie, M. L. *Phytochemistry* **1975**, *14*, 213.
 - Kane, V. V.; Martin, A. R.; Peters, J. A. *J. Org. Chem.* **1984**, *49*, 1793.
 - Paquette, L. A.; Efremov, I. *J. Org. Chem.* **2005**, *70*, 510.
 - Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935.
 - Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481.
 - Hu, Y.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782.
-