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Concise Synthesis of (±)-Perrottetinene with Bibenzyl Cannabinoid

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Cannabinoids are widely distributed in nature and have been isolated from Indian hemp *Cannabis sativa,* which has been used as both a medicine and a psychotomimetic drug since ancient times (Figure 1).[1] These compounds possess analgesic, antiemetic, psychotropic, and anti-inflammatory properties.[2] They also have potential therapeutic applications in the treatment of asthma and glaucoma.[3] Among these, Δ^8-tetrahydrocannabinol (**1**) (Δ^8-THC) and Δ^9-tetrahydrocannabinol (**2**) (Δ^9-THC) are the major psychopharmacological active constituents of marijuana (hashish).[4] Their analogues have also attracted medical interest because of their promising biological and pharmacological activities including anthemetic, analgesic, and psychotropic effects.[5] Additionally, hexahydrocannabinol (**3**) has attracted considerable attention since clinical tests have shown that these compounds have a similar psychotropic activity to natural Δ^8-tetrahydrocannabinol (**1**).[6] Currently, synthesized Δ^9-tetrahydrocannabinol (**2**) (Δ^9-THC) and its derivatives have been used as the medicines, Marinol® and Cesamet,® for patients with chemotherapy-induced nausea and vomiting (CINV), who have failed to respond adequately to conventional antiemetic treatments.[7]

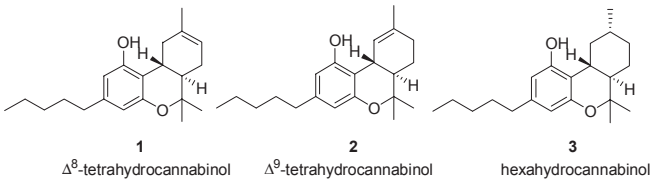


Figure 1. Naturally occurring cannabinoids **1-3** isolated from *Cannabis sativa*.

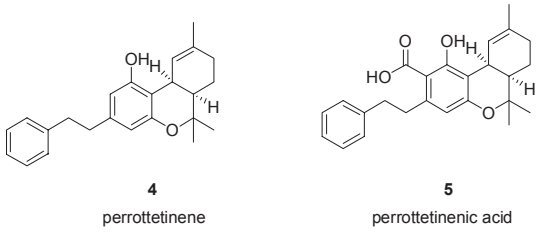


Figure 2. Naturally occurring bibenzyl cannabinoids **4-5** isolated from *Radula marginata*.

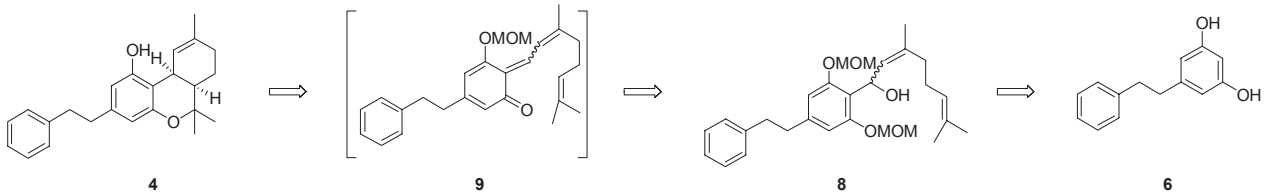
Structurally related perrottetinene (**4**) and perrottetinenic acid (**5**) with a bibenzyl cannabinoid nucleus were isolated from the extract of the New Zealand liverwort *Radula marginata* (Figure 2).[8] The structures of these natural products were determined using spectroscopic analysis.[8] Interestingly, most of the naturally occurring tetrahydrocannabinols **1-3** possessed a *trans*-fused ring junction between cyclohexene (or cyclohexane) and the pyranyl ring, whereas perrottetinene (**4**) and perrottetinenic acid (**5**) exhibited a *cis*-stereochemisty. Although the total synthesis of perrottetinene (**4**) has already been reported in a 9-step process,[9] simple and more concise synthetic approaches are still needed.

A new methodology was reported for synthesizing a variety of benzopyrans and canabinoid analogues starting from substituted resorcinols and α,β-unsaturated aldehydes utilizing ethylenediamine diacetate as a catalyst.[10] Naturally occurring hexahydrocannabinol (**3**) was synthesized using this methodology as a key step.[11] As an expansion of the synthesis of benzopyrans and cannabinoid, (±)-perrottetinene (**4**) was concisely synthesized in this study.

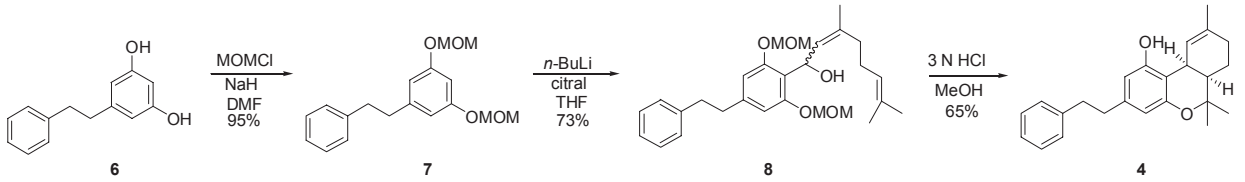
Results and Discussion

Scheme 1 shows the retrosynthetic analysis of (±)-perrottetinene (**4**). Compound **4** could be prepared from **8** through the hetero Diels-Alder reaction of quinine methide intermediate **9**. Compound **8** could be synthesized from readily available dihydropinosylvin (**6**).

Scheme 2 shows the synthetic approach for (±)-perrottetinene (**4**). The two phenolic hydroxyl groups of dihydropinosylvin (**6**) were first protected as MOM ethers to produce **7** in 95% yield. Treatment of **7** with *n*-butyl lithium in THF followed by addition of citral afforded compound **8** (73%) with a *E*:*Z* isomer ratio of 50:50. The cyclization of **8** with 3 N HCl in methanol



Scheme 1. Retrosynthetic analysis of (±)-perrottetinene (**4**)



Scheme 2. Synthesis of (±)-perrottetinene (**4**)

provided **4** in 65% yield and no other *trans*-fused adduct was detected. The formation of this type of *cis*-fused cycloadduct has already been described utilizing TMSCl and Et_4NBr by Snider.[12] The structure and the *cis*-stereochemistry of the synthetic material **4** were confirmed through a comparison with the reported data for the natural product.[8,9]

In conclusion, biologically interesting (±)-perrottetinene with bibenzyl cannabinoid structure was efficiently and concisely synthesized from the readily available dihydropinosylvin in an overall yield of 45% (3 steps).

Experimental Section

All of the experiments were carried out in a nitrogen atmosphere. Pre-coated silica gel plates (Art. 5554) with a fluorescent indicator were used for the TLC analysis. Flash column chromatography was performed using silica gel 9385 (Merck). The ^1H and ^{13}C NMR spectra were recorded using a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ as the solvent for the chemical shift. The IR spectra were recorded using a Jasco FTIR 5300 spectrophotometer.

Compound 7. Methoxymethyl chloride (0.51 g, 6.2 mmol) was added to a solution of **6** (0.514 g, 2.4 mmol) and NaH (0.288 g, 12.0 mmol) in DMF (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h and then water (40 mL) was added at 0 °C. The reaction mixture was extracted with ethyl acetate (3 × 30 mL) and the combined organic extracts were washed with saturated NH_4Cl solution (30 mL), water (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Flash column chromatography on silica gel using hexane/ethyl acetate (20:1) afforded **7** (0.689 g, 95%) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.24 (2H, m), 7.20-7.05 (3H, m), 6.58 (1H, d, J = 2.1 Hz), 6.60 (2H, d, J = 2.1 Hz), 5.18 (4H, s), 3.48 (6H, s), 2.85 (4H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 144.3, 141.6, 128.3, 125.8, 109.8, 102.4, 94.3, 56.0, 38.1, 37.6; IR (neat) 2951, 1597, 1456, 1400, 1282, 1215, 1147, 1084, 1037, 923, 848 cm^{-1}.

Compound 8. *n*-BuLi (0.8 mL, 2.5 M in hexane, 2.0 mmol) was added at 0 °C to a solution of **7** (0.514 g, 1.7 mmol) in THF (20 mL) and the resulting solution was stirred at 0 °C for 2 h. Citral (0.259 g, 1.7 mmol) was added dropwise to the reaction mixture at 0 °C, which was stirred at room temperature for 10 h. The reaction mixture was quenched with saturated NH_4Cl solution (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed water (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Flash column chromatography on silica gel using hexane/ethyl acetate (4:1) afforded **8** (0.564 g, 73%) as a *E*:*Z* isomer ratio of 50:50. ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.16 (2H, m), 7.19-7.15 (3H, m), 6.60 (2H, s), 5.92-5.86 (1H, m), 5.70 (0.5 H, d, J = 7.8 Hz), 5.67 (0.5 H, d, J = 8.7 Hz), 5.19-5.17 (4H, m), 5.05 (1H, t, J = 6.6 Hz), 3.47 (6H, s), 2.86 (4H, br s), 2.10-1.93 (4H, m), 1.79 (3H, s), 1.67 (3H, s), 1.62 (3H, m); IR (neat) 3566, 2928, 1608, 1583, 1452, 1388, 1155, 1105, 1045, 923, 823, 750, 700 cm^{-1}.

(±)-Perrottetinene (4). Aqueous 3 N HCl (1.0 mL) was added dropwise to a solution of **8** (0.501 g, 1.0 mmol) in methanol (10 mL) at room temperature. The reaction mixture was heated at 60 °C for 3 h and cooled to room temperature. The reaction was quenched with saturated sodium bicarbonate (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed water (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Flash column chromatography on silica gel using hexane/ethyl acetate (4:1) afforded **4** (0.227 g, 65%) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.19 (2H, m), 7.14-7.11 (3H, m), 6.26 (1H, s), 6.16 (1H, br s), 6.11 (1H, s), 4.98 (1H, br s), 3.51 (1H, br s), 2.83-2.78 (2H, m), 2.71-2.65 (2H, m), 1.96-1.82 (3H, m), 1.73-1.66 (1H, m), 1.64 (3H, s), 1.50-1.38 (1H, m), 1.34 (3H, s), 1.22 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 153.9, 142.0, 141.2, 134.9, 128.3, 125.8, 121.9, 109.9, 109.8, 107.9, 76.3, 40.0, 37.4, 37.3, 31.5, 29.7, 25.9, 25.2, 23.6, 20.7; IR (neat) 3388, 2928, 1622, 1577, 1496, 1427, 1367, 1265, 1157, 1055, 891, 821, 737, 700 cm^{-1}.

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References

1. Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc*. **1964**, *86*, 1646.
2. (a) Porter, A. C.; Felder, C. C. *Pharmacol. Ther*. **2001**, *90*, 45. (b) Williamson, E. M.; Evans, F. J. *Drugs* **2000**, *60*, 1303. (c) Hollister, L. E. *Pharmacol. Rev*. **1986**, *38*, 1.
3. Razdan, R. K. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1981; Vol. 4, p 185.
4. (a) Consroe, P.; Fish, B. S. *Med. Hypotheses* **1981**, *7*, 1079. (b) Consroe, P.; Fish, B. S. *Commun. Psychopharmacol*. **1980**, *4*, 287. (c) Fish, B. S.; Consroe, P. *Experientia* **1981**, *37*, 295.
5. (a) Razdan, R. K. *Pharmacol. Rev*. **1986**, *38*, 75. (b) Ben-Zvi, Z.; Mechoulam, R.; Edery, H.; Porath, G. *Science* **1971**, *174*, 951. (c) Mechoulam, R.; Varconi, H.; Ben-Zvi, Z.; Edery, H.; Grunfeld, Y. *J. Am. Chem. Soc.* **1972**, *94*, 7930. (d) Martin, P.; Consroe, P. *Science* **1976**, *194*, 965. (e) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature* **1990**, *346*, 561. (f) Munro, S.; Thomas, K. L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61.
6. Edery, H.; Grunfeld, Y.; Nen-Zvi, Z.; Mechoulam, R. *Ann. N.Y. Acad. Sci*. **1971**, *191*, 40.
7. (a) Mendizabal, V. E.; Adler-Graschinsky, E. *British J. Pharmacol*. **2007**, *151*, 427. (b) Ashton, C. H.; Moore, P. B.; Gallagher, P.;

Young, A. H. *J. Psychopharmaol*. **2005**, *19*, 293.
8. Toyata, M.; Shimamura, T.; Ishii, H.; Renner, M.; Braggins, J.; Asakawa, Y. *Chem. Pharm. Bull*. **2002**, *50*, 1390.
9. Song, Y.; Hwang, S.; Gong, P.; Kim, D.; Kim, S. *Org. Lett*. **2008**, *10*, 269.
10. (a) Lee, Y. R.; Choi, J. H.; Yoon, S. H. *Tetrahedron Lett*. **2005**, *46*, 7539. (b) Lee, Y. R.; Lee, W. K.; Noh, S. K.; Lyoo, W. S. *Synthesis* **2006**, 853. (c) Lee, Y. R.; Kim, D. H. *Synthesis* **2006**, 603. (d) Lee, Y. R.; Kim, J. H. *Synlett* **2007**, 2232. (e) Wang, X.; Lee, Y. R. *Tetrahedron Lett*. **2007**, *48*, 6275. (f) Wang, X.; Lee, Y. R. *Synthesis* **2007**, 3044. (g) Lee, Y. R.; Xia, L. *Synthesis* **2007**, 3240. (h) Lee, Y. R.; Kim, Y. M. *Helv. Chim. Acta* **2007**, *90*, 2401. (i) Lee, Y. R.; Li, X.; Kim, J. H. *J. Org. Chem*. **2008**, *73*, 4313. (j) Xia, L.; Lee, Y. R. *Synlett* **2008**, 1643. (k) Lee, Y. R.; Hung, T. V. *Tetrahedron* **2008**, *64*, 7338. (l) Lee, Y. R.; Wang, X. *Tetrahedron* **2009**, *65*, 10125. (m) Lee, Y. R.; Kim, Y. M.; Kim, S. H. *Tetrahedron* **2009**, *65*, 101. (n) Jung, D. H.; Lee, Y. R.; Kim, S. H. *Helv. Chim. Acta* **2010**, *93*, 635.
11. Lee, Y. R.; Xia, L. *Tetrahedron Lett*. **2008**, *49*, 3283.
12. Snider, B. B.; Lobera, M. *Tetrahedron Lett*. **2004**, *45*, 5015.