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Biorational Synthesis of Iridomyrmecin Diastereomers from Catnip oil

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Abstract—4*S*,4a*S*,7*S*,7a*R*; 4*R*,4a*S*,7*S*,7a*R*; 4*S*,4a*S*,7*S*,7a*S* and 4*R*,4a*S*,7*S*,7a*S* diastereomers of iridomyrmecin have been prepared in 5 steps from 4a*S*,7*S*,7a*R* and 4a*S*,7*S*,7a*S*-nepetalactones, major components of catnip oil, major components of catnip oil. 4*S*,4a*S*,7*S*,7a*R* and 4*R*,4a*S*,7*S*,7a*R* - iridomyrmecin have been identified as a defensive compound from *Iridomyrmex* ants.

Families of cyclopentanoid monoterpenes, also known as iridoids are typical of the vegetable kingdom, but they are also present as defensive semiochemicals. Because of their potential application as biopesticides and semiochemicals, iridoids have attracted attention[1]. Iridomyrmecin, iridodials, actinidine, and dolichodial as a part of defensive compounds of *Iridomyrmex* ants are well documented iridoids[2] and led to numerous synthetic approaches for the synthesis[3]. In the quest of developing naturally occurring feeding deterrence against arthropod pest we are evaluating streospecific effects of known and modified iridoids. Having developed economical separation and isolation of pure nepetalactone isomers from catnip oil[4], we have diverted our attention of exploiting nepetalactones as chiral synthones[5,6]. Here we present the gram quantities preparation of enantiomerically pure iridomyrmecin, isoiridomyrmecin and two trans fused diastereomers of iridomyrmecin in 5 steps synthesis from nepetalactones without using chiral auxiliaries or catalysts. This simple approach could specifically be used for the synthesis of enantiomerically pure dihydronepetalactones and is applicable to chiral synthesis of numerous cyclopentanoid monoterpene analogues.

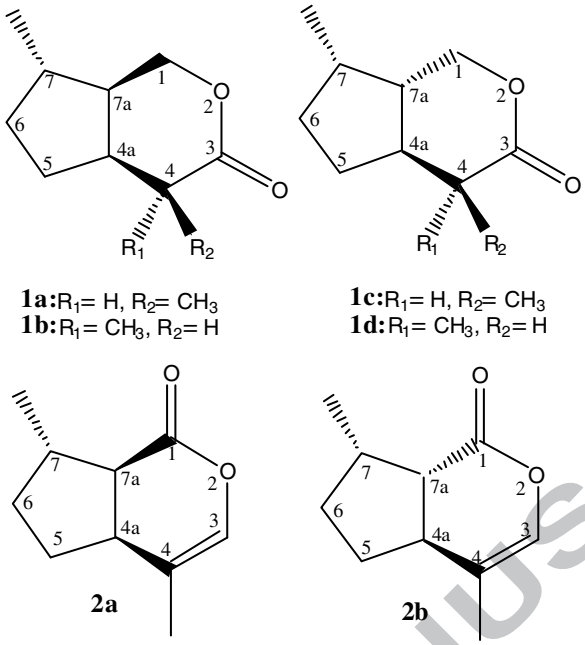

Figure 1. Monoterpene-iridomyrmecin: **1a**: 4*S*,4a*S*,7*S*,7a*R*-iridomyrmecin; **1b**: 4*R*,4a*S*,7*S*,7a*R* -isoiridomyrmecin*;* **1c**: 4*S*,4a*S*,7*S*,7a*S* (trans) iridomyrmecin; **1d**: 4*R*,4a*S*,7*S*,7a*S*- (trans) isoiridomyrmecin; **2a**: 4a*S*,7*S*,7a*R* (Z,E)-nepetalactone; **2b**: 4a*S*,7*S*,7a*S* (E,Z)-nepetalactone

Initial conversion to iridoid lactones, a surprise revelation from failed oxidation attempt to form iridodials from iridodiols led us to the development of this synthetic approach (Figure 2).

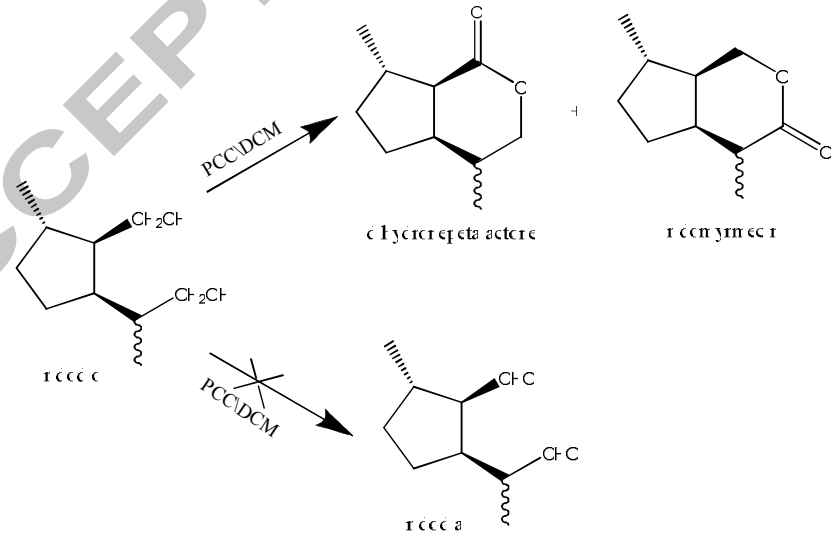

Figure 2: PCC oxidation of iridodiols

Availability of 4a*S*,7*S*,7a*R* (Z,E) **2a** and 4a*S*,7*S*,7a*S* (E,Z) **2b**-nepetalactone (major components of catnip oil (*Nepeta cataria*), quantitatively isolated by chemical separation) [4] was the key to this synthetic approach (Figure 3). Methanolysis of **2a** at room temperature in 5% methanolic $NaHCO_3$ solution (95:5 methanol/water) gave an isomeric mixture of methyl ester-aldehyde **3**, which was quantitatively protected to the cyclic acetals by azeotropic dehydration with ethane-1,2-diol and then followed by DIBAL reduction converting ester to hydroxyl moiety to 94% yield over the two steps. Cyclic acetals **4a** and **4b** were separated by flash column chromatography[7]. At this stage, the absolute configuration at the C-4 asymmetric center of each isomer was established by NMR spectroscopy (^1H, ^{13}C-APT, and COSEY)[5] of mono protected aldehyde.

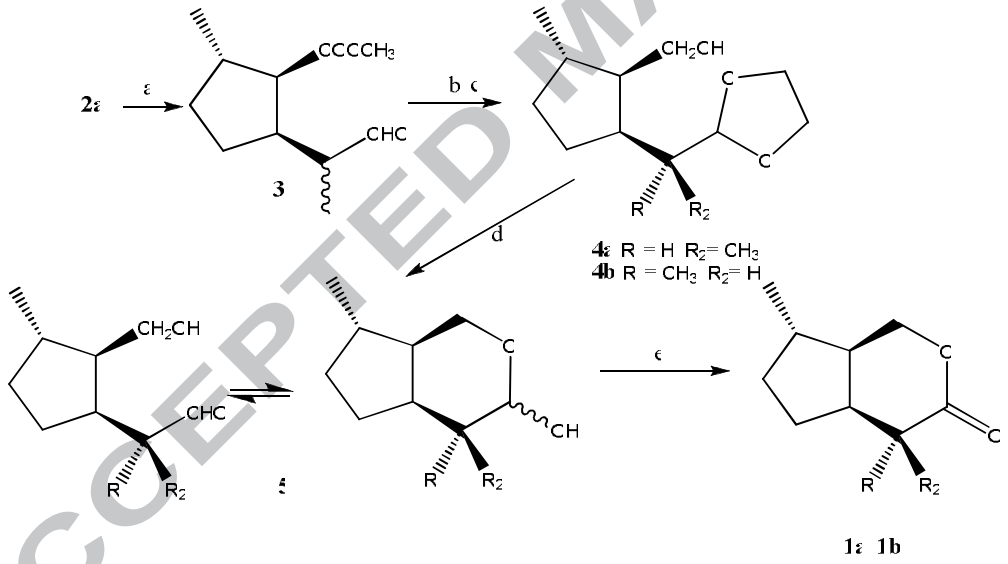

Figure 3: *Synthesis of iridomyrmecin* **1a/1b***; reagents and conditions.* (a) $NaHCO_3$ (5%), MeOH:H_2O (95:5), rt; (b) ethane-1,2-diol, toluene, cat. TsOH; (c) DIBAL, toluene, -78^{0}C to 0^{0}C; (d) THF:H2O (80:20), 2N HCl, rt (e) PDC, dry DCM, rt.

Deprotection of the cyclic acetal was carried out under mild acidic hydrolysis at room temperature to quantitative yields of free hydroxyl aldehyde **5**, which was oxidized to conclude the synthesis of iridomyrmecin **1a** in 62% and **1b** in 58% overall yields[8,9].

Repetition of the foregoing sequence using 4a*S*,7*S*,7a*S*-nepetalactone **2b** proceeded analogously and with comparable yields to give **1c** and **1d** (Fig. 1). Spectral data, and physiochemical parameters for **1a** and **1b** were confirmed[10] with authentic samples of iridomyrmecin and isoiridomyrmecin. Two trans fused iridomyrmecin diastereomers **1c** and **1d** synthesized from E,Z-nepetalactone were analyzed and reported[11].

In conclusion, 1*R*,2*S*,5*R*,8*R*-iridomyrmecin **1a**, along with three isomeric iridomyrmecin, have been conveniently prepared in five steps from readily available starting materials. Iridomyrmecin enantiomer **1a** and **1b** are present as defense compounds in many hemepterea insects and widely used as natural product insecticides. The availability of iridomyrmecin diastereomers in absolute purity with economically viable synthesis will facilitate identification of iridoid presence as semiochemicals in insect and plants. Ease of preparation of racemic iridomyrmecin and isomers will open exploration of these defensive compounds as biopesticide as well as insect repellents[12].

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7. 5% Ethyl acetate in hexane as mobile phase and 230-400-mesh silica gel as stationary phase.

8. 4*S*,4a*S*,7*S*,7a*R*-iridomyrmecin **1a**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.29 (dd, J = 3.8, 11.5 Hz, 1H,1-Ha), 4.16 (d, J = 11.8 Hz, 1-Hb), 2.74 (q, J = 6.8 Hz, 1H, 7-H), 2.62 (dddq, J = 7.6 Hz, 1H, 4-H), 2.01-1.88 (m, 3H, 6-Ha,7a-H, 5-Ha), 1.82-1.69 (m, 1H, 5-Hb), 1.33-1.35 (m, 1H, 6-Hb), 1.23 (d, J= 7.6 Hz, 3H, 7-CH3), 0.97 (d, J = 7.3 Hz, 3H, 4-CH3), 0.89-0.90 (m, 1H, 4a-H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.00, 68.01, 45.53, 43.30, 37.70, 37.21, 34.19, 29.65, 18.29, 12.70 ppm. MS *m/z* (%): 168 (8) [M]+, 153 (2), 109 (45), 95 (100), 82 (29), 81 (59), 67 (68), 55 (23), 53 (15), 41 (55), 39 (41)

4*R*,4a*S*,7*S*,7a*R* -isoiridomyrmecin **1b**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.38 (dd, J = 6.1, 11.6 Hz, 1-Ha), 4.01 (dd, J = 11.4, 11.6 Hz, 1-Hb), 2.35-2.38 (m, 1H, 4-H), 2.12 (dq, J = 7.0, 11.2 Hz, 1H, 7-H), 2.05-1.98 (m, 2H, 6-Ha, 5-Ha), 1.90-1.91 (m, 1H, 6Hb), 1.68 (dddd, J = 5.8 Hz, 1H, 7a-H), 1.28-1.32 (m, 2H, 4a-H, 5-Hb), 1.21 (d, J = 7.1 Hz, 3H, 4-CH3), and 1.06 (d, J = 7.1 Hz, 3H, 7-CH3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.96, 69.0, 45.22, 43.16, 39.11, 38.25, 35.60, 33.1, 19.12, 13.76 ppm. MS *m/z* (%): 168 (33) $[M]_+$, 109 (52), 95 (100), 82 (26), 81 (86), 67 (84), 55 (29), 53 (11), 41 (64), 39 (40)

9. a) Since iridomyrmecin isomers were derived from nepetalactone 2a and 2b, the absolute configuration remain intact for 1 (7a), 2 (7) and 5 (4a) positions of origin

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11. 4*S*,4a*S*,7*S*,7a*S* (trans) iridomyrmecin **1c**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.47 (dd, J = 4.9, 10.4 Hz, 1H), 4.21 (dd, J = 10.5, 11.8 Hz, 1H,), 3.01 (dq, J = 7.6 Hz, 1H, 4-H), 2.34 (dddq, J = 7.6 Hz, 1H, 7-H), 2.19 (dddd, J = 6.3 Hz, 1H, 4a-H), 2.09-2.14(m, 1H, 6-Ha), 2.02-2.09 (m, 1H, 7a-H), 1.71-1.72 (m, 1H, 5-Ha), 1.41-1.44 (m, 1H, 5-Hb), 1.31-1.37 (m, 1H, 6-Hb), 1.23 (d, J= 7.6 Hz, 3H, 4-CH3), and 0.87 (d, J = 7.3 Hz, 3H, 7-CH3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.1, 72.5, 41.0, 38.9, 37.3, 34.1, 31.8, 26.1, 17.1, 13.2 ppm. MS *m/z* (%): 168 (1) $[M]_+$, 95 (43), 82 (29), 81 (100), 69 (10), 68 (58), 67 (*100*), 55 (32), 53 (17), 41 (66), 39 (47)

4*R*,4a*S*,7*S*,7a*S*- (trans) isoiridomyrmecin **1d**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.50 (dd, J = 5.6, 10.8 Hz, 1Ha), 4.23 (dd, J = 10.8, 12.2 Hz, 1Hb), 2.37 (dddq, J = 7.6 Hz, 1H, 7-H), 2.25 (dq, J = 7.1, 11.2 Hz, 1H, 4-H), 2.12-2.16 (m, 1H, 6-Ha), 2.01-2.06 (m, 1H, 5-Hb), 1.91 (br dddd, 1H, 7a-H), 1.79 (br dddd, 1H, 4a-H), 1.35-1.41 (m, 1H, 6-Hb), 1.31 (d, J = 7.1 Hz, 3H, 4-CH3), 1.18 (d, J = 3.7 Hz,1H, 5-Ha), and 0.85 (d, J = 7.6 Hz, 3H, 7-CH3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.0, 72.2, 44.6, 44.5, 44.2, 33.7, 32.6, 30.3, 17.2, 15.7ppm. MS *m/z* (%):168 (1) $[M]_+$, 109 (15), 95 (33), 82 (25), 81 (100), 79 (18), 69 (23), 68 (48), 67 (94), 55 (32), 54 (11), 53 (28), 41 (68), 39 (48)

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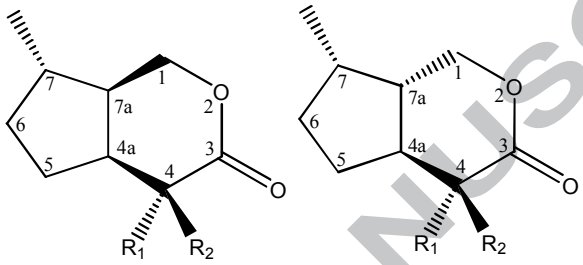
4*S*,4a*S*,7*S*,7a*R*; 4*R*,4a*S*,7*S*,7a*R*; 4*S*,4a*S*,7*S*,7a*S* and 4*R*,4a*S*,7*S*,7a*S* diastereomers of iridomyrmecin have been prepared in 5 steps from 4a*S*,7*S*,7a*R* and 4a*S*,7*S*,7a*S*-nepetalactones, major components of catnip oil.



1a: R_1= H, R_2= CH_3 **1c:** R_1= H, R_2= CH_3
1b: R_1= CH_3, R_2= H **1d:** R_1= CH_3, R_2= H