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Enantioselective Synthesis of the Female Sex Pheromone of the Pink Hibiscus Mealybug, *Maconellicoccus hirsutus*

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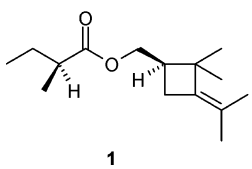
The pink hibiscus mealybug, *Maconellicoccus hirsutus* (Green), is an exotic insect pest and recently invaded Southern California and Florida. The female *M. hirsutus* releases the 2-methylbutanoate of a novel cyclobutanoid monoterpene alcohol (maconelliol) that together with lavandulyl 2-methylbutanoate constitutes the sex pheromone to attract males from a distance. Enantioselective syntheses of four different stereoisomers of the major component, maconelliyl 2-methylbutanoate **1**, from α-pinene are reported. Absolute configurations of both naturally occurring maconelliyl 2-methylbutanoate **1** and the minor component, lavandulyl 2-methylbutanoate **2**, have been established. Comparison of the analytical data of naturally occurring compounds with those of optically active synthetic isomers proved that both esters show the (*R*)-configuration at the alcohol and the (*S*)-configuration at acid moieties.

KEYWORDS: Sex pheromone; *Maconellicoccus hirsutus*; (*R*)-maconelliyl (*S*)-2-methylbutanoate; (*R*)-lavandulyl (*S*)-2-methylbutanoate; enantioselective synthesis

INTRODUCTION

The pink hibiscus mealybug, *Maconellicoccus hirsutus* (Green) (Homoptera: Pseudococcidae), is an exotic insect pest (*1*) to more than 200 agricultural and vegetable crops, forest trees, and ornamental plants (*2*−*5*) and recently invaded Southern California (*6*) and Florida (*4*). The sex pheromone of the *M. hirsutus* contains a novel cyclobutanoid monoterpene derivative (*7*). This compound, together with lavandulyl 2-methylbutanoate **2**, constitutes the female sex pheromone of the pink hibiscus mealybug. The structure of maconelliyl 2-methylbutanoate has been proposed as **1** (*7*). The cyclobutane carbon skeleton with a methylethylidene group on the ring ("maconelliane") has not previously been reported although the *Planococcus* alcohol isolated from the citrus mealybug is structurally close (*8*). An incompletely characterized ester of lavandulol with 2-methylbutanoic acid has been described by others (*9*, *10*), but the optically active esters have not previously been described. We now report the synthesis of **1**, as well as **2**, thereby confirming their structures, establishing their absolute configurations, and providing material for field biological testing (*11*).



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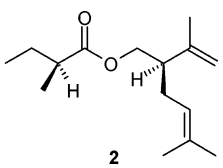

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MATERIALS AND METHODS

General. NMR spectra were recorded in C_6D_6 or $CDCl_3$ solution on a Bruker QE Plus spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C, respectively. The chemical shifts are expressed in ppm (δ scale) relative to the residual solvent for ^1H (C_6H_6 at δ 7.20 and $CHCl_3$ at 7.25 ppm) or to the central peak of solvent ^{13}C signal (C_6D_6 at 128.5 and $CDCl_3$ at 77.0 ppm). Low-resolution electron impact (EI) gas chromatography−mass spectrometry (GC-MS) was conducted on a Hewlett-Packard (HP) 6890 GC coupled to a HP 5973 Mass Selective Detector using a 60 m × 0.25 mm i.d., 0.25 μm film thickness DB-WAXETR capillary column (J&W Scientific Inc., Folsom, CA) with helium as the carrier gas (50 °C for 2 min and then programmed to 230 °C at 15 °C/min and held for 15 min). High-resolution EI-MS (HREIMS) was measured on a Shimadzu GC-17A GC coupled to a JEOL JMS-SX102A mass spectrometer using a 15 m × 0.25 mm i.d., 0.25 μm film thickness OV-5 capillary column (Ohio Valley Specialty Chemical, Marietta, OH) with helium as the carrier gas (50 °C and then programmed to 200 °C at 15 °C/min and held for 15 min). A 70 eV electron beam was employed for sample ionization. Enantiomeric excess (ee) data were obtained on a HP 6890 GC equipped with a 30 m × 0.25 mm i.d., 0.25 μm film thickness β-DEX 120 capillary column (Supelco, Inc., Bellefonte, PA) in the split mode (100:1) with hydrogen as the carrier gas (55 cm/s, 90 or 100 °C isothermal). Optical rotation was measured on a Perkin-Elmer 241 Polarimeter at 24 °C. Melting points were determined on a hot stage and are uncorrected. All reactions were performed under a nitrogen atmosphere with magnetic stirring unless otherwise indicated. All chemicals were obtained from Aldrich Chemical Co., and solvents were obtained from EM Science. Flash column chromatography was carried out on silica gel 60 (EM Science, 230−400 mesh), and solvents were evaporated using a Büchi RE 111 rotary evaporator.

(1*R*,3*S*)-(−)-3-(1-Hydroxy-1-methylethyl)-2,2-dimethylcyclobutanecarboxylic Acid (3a). To a solution of 11.0 g (0.065 mol) of pinononic acid in 200 mL of tetrahydrofuran (THF) was added dropwise 65 mL (0.195 mol) of methylmagnesium chloride (3.0 M THF). The reaction mixture was refluxed for 2 h on an 80 °C oil bath, then cooled, and treated with 50 g of ice water and 25 mL of concentrated HCl. The aqueous layer was separated and extracted with ether. The combined organic solutions were extracted with 1 N Na_2CO_3. After the solution was washed with ether, the Na_2CO_3 solution was acidified

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with concentrated HCl and extracted again with ether. The combined extracts were washed with brine, dried over MgSO4, and concentrated to give 10.5 g of white semisolid. Recrystallization of the crude product (1:8 = ethyl acetate:hexanes) gave 8.37 g (44 mmol) of pure **3a** in 67% yield. Optical purity: 80% ee; mp 98−99 °C; $[\alpha]_D^{24}$ −5.0 (*c* 0.1, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.10 (3H, s), 1.17 (3H, s), 1.22 (3H, s), 1.28 (3H, s), 1.8−2.0 (4H, bm), 2.1−2.4 (2H, m). ^{13}C NMR ($CDCl_3$): δ 176.26, 71.68, 51.88, 45.76, 44.39, 31.75, 29.06, 27.50, 19.71, 18.10. EI-MS *m*/*z* (%): 168 [M − H_2O] (3), 153 (21,) 128 (22), 123 (21), 110 (12), 101 (37), 99 (67), 83 (44), 71 (45), 69 (52), 59 (100), 56 (45), 43 (40).

(1*R*,5*S*)-(+)-4,4,6,6-Tetramethyl-3-oxabicyclo[3.1.1]heptan-2-one (4a). To a solution of 2.66 g (14.28 mmol) of alcohol **3a** in 15 mL of pyridine was added dropwise 1.40 mL (15.00 mmol) of phosphorus oxychloride at ice−water cooling. The mixture was stirred at room temperature for 24 h, poured onto 75 g of ice, and extracted with ether. The ether extracts were washed with water, 2 N hydrochloric acid, then water, saturated aqueous solution of sodium hydrogen carbonate, and brine. After it was dried over sodium sulfate, the solvent was removed, and the residue was purified by chromatography (30/70, ethyl acetate/hexanes) to afford 1.8 g (10.71 mmol) of pure lactone **4a** in 75% yield. Optical purity: 80% ee; $[\alpha]_D^{24}$ +5.0 (*c* 0.1, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.14 (3H, s), 1.37 (3H, s), 1.38 (3H, s), 1.49 (3H, s), 1.81 (1H, d, J = 10.59 Hz), 2.10 (1H, dd, J = 6.05, 5.67 Hz), 2.48 (1H, ddd, J = 10.59, 5.67, 5.30 Hz), 2.63 (1H, dd, J = 6.05, 5.30 Hz). ^{13}C NMR ($CDCl_3$): δ 175.04, 82.44, 50.34, 50.01, 40.91, 29.11, 26.11, 25.81, 25.27, 25.25. EI-MS *m*/*z* (%): 153 (26), 125 (20), 110 (40), 109 (55), 95 (100), 83 (27), 69 (72), 68 (78), 67 (60), 55 (42), 43 (35), 41 (38). HREIMS: obsd, 153.0911; calcd for $C_9H_{13}O_2$ (M^+ − CH_3), 153.0916.

(*R*)-(−)-2,2-Dimethyl-3-(1-methylethylidene)cyclobutanecarboxylic Acid (5a). A solution of 3.68 g (21.9 mmol) of **4a** in 60 mL of benzene with 416 mg (2.19 mmol) of *p*-toluenesulfonic acid monohydrate was heated in an oil bath at 100−110 °C for 24 h. A mini Dean−Stark trap was used for azeotropic distillation. Benzene was evaporated on a rotary evaporator, and the residue was treated with 2 N aqueous Na_2CO_3 solution. The basic aqueous solution was washed with ether, then acidified to pH 2 with hydrochloric acid, and again extracted with ether. The combined ether extracts were washed with water and brine, dried, and concentrated to give 2.87 g (17.1 mmol, 78% yield) of **5a** as colorless oil after chromatography (silica gel, eluted with 20−25% of ethyl acetate in hexanes). Optical purity: 79% ee (after methylation); $[\alpha]_D^{24}$ −22.0 (*c* 0.1, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.19 (3H, s), 1.37 (3H, s), 1.48 (3H, s), 1.58 (3H, s), 2.55 (1H, m), 2.81 (2H, m). ^{13}C NMR (C_6D_6): δ 183.49, 135.57, 123.27, 47.47, 45.09, 28.15, 25.94, 22.09, 19.51, 18.52. EI-MS *m*/*z* (%): 168 $[M]^+$ (38), 153 (38), 135 (8), 125 (21), 123 (27), 107 (59), 93 (29), 81 (100), 67 (30), 53 (16), 41 (25). HREIMS: obsd, 168.1152; calcd for $C_{10}H_{16}O_2$ (M^+), 168.1150.

[(*R*)-(−)-2,2-Dimethyl-3-(1-methylethylidene)cyclobutyl]-methanol [(*R*)-(−)-Maconelliol] (6a). A solution of 2.1 g (12.5 mmol) of **5a** in 30 mL of dry ether was stirred under a nitrogen atmosphere and cooled with an ice bath, while 713 mg (18.8 mmol) of lithium aluminum hydride was added in portions. The mixture was then stirred at room temperature overnight. To decompose excess hydride, 0.8 mL of water was added dropwise at ice bath temperature and stirred for 15 min, followed by the addition of 0.8 mL of 10% aqueous sodium hydroxide solution and stirring for another 15 min. After the ice bath was removed, 2.4 mL of water was added and it was stirred for an additional 30 min, and then, the solid was filtered off and washed with ether. The combined ether solutions were dried over Na_2SO_4 and concentrated to afford 2.0 g of clear oil. Pure compound **6a** (1.7 g, 11 mmol, 88% yield) was obtained by chromatography (silica gel, eluted with 15−20% of ethyl acetate in hexanes). Optical purity: 78% ee; $[\alpha]_D^{24}$ −31.0 (*c* 0.1, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.15 (3H, s), 1.25 (3H, s), 1.38 (1H, br), 1.44 (3H, bs), 1.56 (3H, bs), 2.08 (2H, m), 2.58 (1H, bm), 3.62 (1H, dd, J = 17.0, 11.4 Hz), 3.75 (1H, dd, J = 17.0, 11.3 Hz). ^{13}C NMR ($CDCl_3$): δ 179.85, 135.57, 123.27, 47.48, 45.09, 28.14, 25.93, 22.09, 19.51, 18.52. EI-MS *m*/*z* (%): 154 (17), 139 (18), 136 (13), 121 (59), 111 (14), 105 (12), 95 (34), 93 (28), 91 (15), 81 (100), 67 (23), 55 (14), 41 (20). HREIMS: obsd, 154.1362; calcd for $C_{10}H_{18}O$ (M^+), 154.1358.

(*S*)-(+)-Maconelliol (6b). Optical purity: 70% ee; $[\alpha]_D^{24}$ +22.0 (*c* 0.1, MeOH).

[(*R*)-2,2-Dimethyl-3-(1-methylethylidene)cyclobutyl]methyl (*S*)-2-Methylbutanoate [(*R*)-Maconelliyl (*S*)-2-Methylbutanoate] (1a). To a solution of 2.2 mL (20.1 mmol) of (*S*)-(+)-2-methylbutanoic acid {Aldrich, 99% ee, $[\alpha]_D^{24}$ +24.0 (*c* 0.1, MeOH)} in 15 mL of benzene was treated with 2.2 mL (25.2 mmol) of oxalyl chloride and 10 μL of dimethyl formamide (DMF). After 1.5 h at room temperature, the benzene and excess oxalyl chloride were removed followed by the addition of another 15 mL portion of benzene. The acid chloride residue was dissolved in 15 mL of benzene, and then, a solution of 1.65 g (10.7 mmol) of **6a** and 1.8 mL (22.2 mmol) of pyridine in 15 mL of benzene was added dropwise. After it was stirred at room temperature for 1 h, the solvent was removed. The residue was treated with 20 mL of water and extracted with ether. The organic solution was washed with water, 1 N hydrochloric acid, 1 N aqueous sodium bicarbonate, and brine, dried over sodium sulfate, and concentrated to afford yellow oil. Pure **1a** (2.0 g, 79% yield) was obtained by chromatography (silica gel, 2% of ethyl acetate in hexanes). Optical purity: 99% ee; $[\alpha]_D^{24}$ −0.79 (*c* 2.03, MeOH). ^{1}H NMR (C_6D_6): δ 0.84 (3H, t, J = 7.19 Hz), 1.08 (3H, d, J = 6.82 Hz), 1.12 (3H, s), 1.24 (3H, s), 1.36 (1H, m), 1.40 (3H, bs), 1.51 (3H, t, J = 1.89 Hz), 1.67 (2H, m), 2.05 (1H, m), 2.17 (1H, m), 2.27 (1H, m), 2.48 (1H, ddt, J = 14.75, 8.79, 1.52 Hz), 4.15 (2H, d, J = 7.57 Hz). ^{13}C NMR (C_6D_6): δ 175.76, 137.48, 122.55, 65.30, 44.43, 41.39, 39.71, 28.62, 27.79, 27.13, 21.17, 19.60, 18.64, 16.85, 11.80. EI-MS *m*/*z* (%): 238 $[M]^+$ (2), 136 (29), 121 (100), 107 (12), 93 (20), 81 (26), 67 (5), 57 (16), 41 (10). HREIMS: obsd, 238.1929; calcd for $C_{15}H_{26}O_2$ (M^+), 238.1933.

[(*R*)-2,2-Dimethyl-3-(1-methylethylidene)cyclobutyl]methyl (*R*)-2-Methylbutanoate [(*R*)-Maconelliyl (*R*)-2-Methylbutanoate] (1b). (*R*)-(−)-2-Methylbutyric acid (*13*) {99% ee, $[\alpha]_D^{24}$ −24.0 (*c* 0.1, MeOH)}. Optical purity: 99% ee; $[\alpha]_D^{24}$ −24.0 (*c* 0.1, MeOH). ^{1}H NMR (C_6D_6): δ 0.84 (3H, t, J = 7.51 Hz), 1.08 (3H, d, J = 7.01 Hz), 1.12 (3H, s), 1.23 (3H, s), 1.33 (1H, m), 1.40 (3H, bs), 1.51 (3H, t, J = 2.00 Hz), 1.67 (2H, m), 2.05 (1H, m), 2.17 (1H, m), 2.26 (1H, m), 2.48 (1H, ddt, J = 14.77, 9.01, 1.50 Hz), 4.15 (2H, m). ^{13}C NMR (C_6D_6): δ 175.74, 137.47, 122.55, 65.28, 44.41, 41.38, 39.75, 28.61, 27.80, 27.09, 27.18, 19.60, 18.63, 16.88, 11.80. MS (EI): *m*/*z* 238 $[M]^+$ (2), 136 (27), 121 (100), 107 (11), 93 (19), 81 (27), 67 (5), 57 (19), 41 (12).

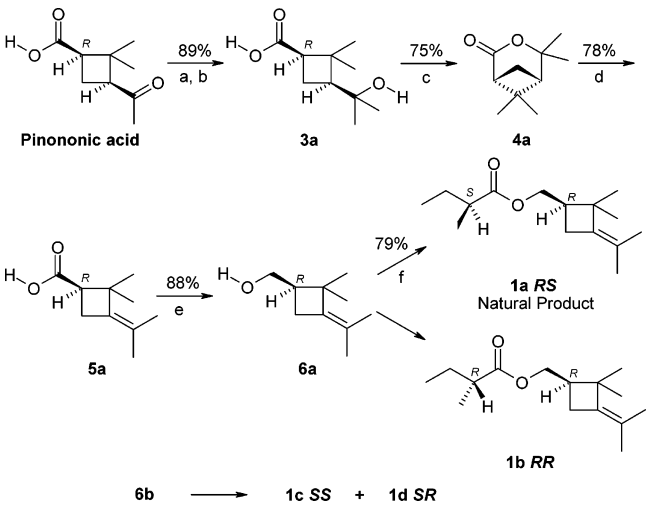
[(*S*)-2,2-Dimethyl-3-(1-methylethylidene)cyclobutyl]methyl (*S*)-2-Methylbutanoate [(*S*)-Maconelliyl (*S*)-2-Methylbutanoate] (1c). Optical purity: 97% ee; $[\alpha]_D^{24}$ +16.0 (*c* 0.1, MeOH).

[(*S*)-2,2-Dimethyl-3-(1-methylethylidene)cyclobutyl]methyl (*R*)-2-Methylbutanoate [(*S*)-Maconelliyl (*R*)-2-Methylbutanoate] (1d). Optical purity: 99% ee; $[\alpha]_D^{24}$ −0.2 (*c* 2.03, MeOH).

(*R*)-2-Isopropenyl-5-methylhex-4-enyl (*S*)-2-Methylbutanoate [(*R*)-Lavandulyl (*S*)-2-Methylbutanoate] (2a). Esterification of (*R*)-(−)-lavandulol {(86% ee, $[\alpha]_D^{24}$ −9.6 (*c* 0.1, MeOH), prepared according to the method described by Cardillo et al. (*14*)} with (*S*)-(+)-2-methylbutanoic acid using the same procedures as compound **1a** gave 75 mg (75% yield) of **2a** as a clear oil. Optical purity: 99% ee; $[\alpha]_D^{24}$ +5.0 (*c* 0.1, MeOH). ^{1}H NMR (C_6D_6): δ 0.83 (3H, t, J = 7.29 Hz), 1.08 (3H, d, J = 7.0 Hz), 1.35 (1H, m), 1.50 (3H, s), 1.59 (3H, t, J = 0.80 Hz), 1.61 (3H, d, J = 1.13 Hz), 1.68 (1H, m), 2.06 (2H, m), 2.28 (1H, sextet, 6.85 Hz), 2.42 (1H, quintet, 7.00 Hz), 4.12 (2H, m), 4.79 (1H, m), 4.83 (1H, quintet, J = 1.51 Hz), 5.11 (1H, t, quintet, J = 7.19, 1.52 Hz). ^{13}C NMR (C_6D_6): δ 175.88, 146.31, 132.70, 122.00, 112.50, 66.68, 45.41, 41.22, 29.13, 26.00, 25.80, 20.00, 17.80, 16.50, 11.52. EI-MS *m*/*z* (%): 238 $[M]^+$ (1), 169 (2), 156 (3), 136 (15), 121 (39), 107 (11), 93 (100), 85 (23), 80 (25), 69 (75), 57 (59), 41 (40). HREIMS: obsd, 238.1934; calcd for $C_{15}H_{16}O_2$ (M^+), 238.1933.

(*R*)-2-Isopropenyl-5-methylhex-4-enyl (*R*)-2-Methylbutanoate [(*R*)-Lavandulyl (*R*)-2-Methylbutanoate] (2b). Optical purity: 99% ee; $[\alpha]_D^{24}$ −11.0 (*c* 0.1, MeOH). ^{1}H NMR (C_6D_6): δ 0.83 (3H, t, J = 7.57 Hz), 1.08 (3H, d, J = 7.19 Hz), 1.35 (1H, m), 1.50 (3H, s), 1.59 (3H, q, J = 0.76 Hz), 1.61 (3H, d, J = 1.10 Hz), 1.69 (1H, m), 2.07 (2H, m), 2.28 (1H, sextet, 6.81 Hz), 2.43 (1H, quintet, 7.00 Hz), 4.12 (2H, m), 4.79 (1H, m), 4.83 (1H, m), 5.12 (1H, t, quintet, J = 7.00, 1.51

Scheme 1[a]



[a] (a) MeLi/ether, 1.0 equiv, THF, –20 °C, 15 min; (b) MeMgCl/THF, 1.6 equiv, –10 °C, 30 min, room temperature, 1 h; (c) $POCl_3$/pyridine, room temperature, 24 h; (d) *p*-TsOH/C_6H_6, reflux, 24 h; (e) $LiAlH_4$/ether, room temperature, overnight; (f) EtCHMECOOH, ClCOCOCl/DMF/C_6H_6, room temperature, 1.5 h.

Hz). ^{13}C NMR (C_6D_6): δ 175.74, 145.22, 132.62, 122.38, 112.69, 65.50, 46.84, 41.41, 28.99, 27.08, 25.79, 19.87, 17.78, 16.91, 11.79. MS (EI): *m/z* 238 $[M]^+$ (1), 169 (2), 156 (4), 136 (17), 121 (42), 107 (11), 93 (100), 85 (22), 80 (25), 69 (72), 57 (53), 41 (35).

(*S*)-2-Isopropenyl-5-methylhex-4-enyl (*S*)-2-Methylbutanoate [(*S*)-Lavandulyl (*S*)-2-Methylbutanoate] (2c). {(*S*)-(+)-lavandulol, 81% ee, $[\alpha]_D^{24}$ +10.0 (*c* 0.1, MeOH), prepared according to the method described by Cardillo et al. (*14*)}. Optical purity: 98% ee; $[\alpha]_D^{24}$ +10.0 (*c* 0.1, MeOH).

(*S*)-2-Isopropenyl-5-methylhex-4-enyl (*R*)-2-Methylbutanoate [(*S*)-Lavandulyl (*R*)-2-Methylbutanoate] (2d). Optical purity: 99% ee; $[\alpha]_D^{24}$ −8.0 (*c* 0.1, MeOH).

RESULTS AND DISCUSSION

Pinononic acid is a suitable intermediate for the preparation of novel **1** because it can be easily obtained from α-pinene through the intermediate verbenone and contains the required cyclobutane skeleton and useful functional groups. Allylic oxidation of (1*R*)-(+)-α-pinene (94% ee) at C_4 using molecular oxygen afforded (1*R*)-(+)-verbenone in moderate yield (*15*). Subsequently, oxidative cleavage of double bond in verbenone by using ruthenium trichloride/$NaIO_4$ (*16*) resulted in the target compound pinononic acid without epimerization.

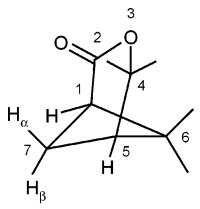
Pursuing the synthesis of structure **1**, the required methylethylidene group was introduced by treating pinononic acid with a nucleophilic reagent to form the tertiary alcohol **3** and then introduce the double bond upon dehydration. Reaction of pinononic acid (94% ee) with 3 mol of Grignard reagent, CH_3MgCl, in THF resulted in the formation of a crude semisolid, which could be recrystallized from ethyl acetate and hexanes to get pure **3a** (80% ee). Partial loss of enantiomeric purity is due to double epimerization during nucleophilic addition. Conversion of pinononic acid to hydroxyacid **3** without epimerization at both stereogenic centers was achieved later in a small-scale reaction at different conditions. When the pinononic acid (>96% ee) reacted with 1.0 equiv of MeLi at −20 °C, a THF soluble carboxylate solution was formed. Following an addition of 1.6 equiv of CH_3MgCl, **3a** was isolated in 89% yield with virtually no change of chirality (96% ee) (**Scheme 1**).

With the geminal dimethyl tertiary alcohol **3a** available, the immediate aim of the present synthesis was to attempt dehydration of the alcohol to the desired methylethylidene product by standard methods. To prevent decarboxylation during dehydration, **3a** was first converted into its methyl ester using thionyl chloride in absolute methanol (*17*, *18*). Among many reported dehydration catalysts and reagents, we felt that the best chance of success for this transaction would involve use of a copper(II) triflate [$Cu(OTf)_2$] catalyst (*19*). It was reported to dehydrate a number of alcohols to olefins under mild conditions. Unfortunately, treatment of **3a** with 0.1 mol equiv of $Cu(OTf)_2$ under conditions previously reported gave no useful result, even after extended periods of time at elevated temperatures.

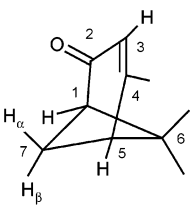
Therefore, more conventional dehydration catalysts were deployed. Approaches were made by treating the methyl ester of **3a** with different reagents under the following conditions: (a) 1.05 mol of $POCl_3$ in pyridine at room temperature for 24 h (*20*); (b) 1.1 mol of *p*-TsCl with equal amounts of DMAP in CH_2Cl_2 at room temperature for 6 h (*21*); and (c) 0.03 mol of *p*-TsOH in benzene at 100−110 °C refluxing for 22 h (*22*−*24*). In none of the cases could the desired compound be obtained exclusively. In experiment (a), a mixture of isopropenyl (56%) and methylethylidene compounds (44%) was obtained. In (b), no dehydration product was isolated. In (c), about 90% desired methylethylidene product was obtained but it still contained 10% of the isopropenyl isomer as a byproduct. The separation of these two isomers by column chromatography was difficult, because of the similarity of chemical and physical properties. From the above experiments, it was concluded that it is impossible to prepare the required methylethylidene product solely by the above methods.

Successful dehydration was ultimately realized through a key intermediate **4**. When the same experimental reagents and conditions were conducted with free acid **3**, lactone **4** was obtained as a sole product in experiments (a) and (b). However, experiment (c) still gave the same mixture as reacting with methyl ester. Surprisingly, the lactone **4a** was found to be easily converted to the desired methylethylidene compound **5** exclusively by the same reagent and conditions as described for experiment (c); refluxing lactone **4** in benzene with a catalytic amount of *p*-TsOH gave pure **5**. Sole formation of the methylethylidene compound **5** without its isopropenyl isomer as a byproduct by the above dehydration process could be confirmed by the absence of geminal olefinic resonance in the ^1H NMR spectrum from δ 4.4−6.6 ppm.

The identity of lactone **4a** was established on the basis of observed $^3J_{H-H}$ values between axial methylene hydrogen H-7α (δ 1.81, $J_{7\alpha,1} = 0$ Hz, $J_{7\alpha,5} = 0$ Hz) and vicinal H-1, H-5 (δ 2.63, $J_{1,7\alpha} = 0$ Hz; δ 2.10, $J_{5,7\alpha} = 0$ Hz). Through this analysis, it was deduced that the dihedral angle between H-7α and two vicinal protons, H-1and H-5, is about 90°; therefore, the coupling constants are zero, and only a doublet resonance with J_{gem} is observed ($J_{7a,7\beta} = 10.59$ Hz). This coupling pattern is similar to that of bicyclic precursor, (1*R*)-(+)-verbenone, for which a doublet resonance of axial geminal hydrogen H-7α is observed at δ 2.06 ppm with $J_{gem} = 9.08$ Hz (*25*) (1.76 ppm in C_6D_6) (*26*). A long-range coupling with $^4J_{H-H} = 6.05$ Hz between H-1 and H-5 is also observed because of the "W" configuration in the molecule **4a**.

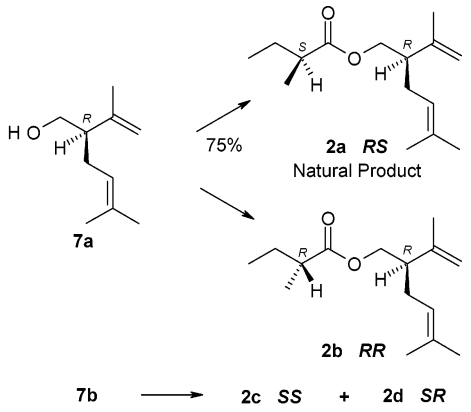


4a



(1*R*)-(+)-Verbenone

Scheme 2



With methylethylidene compound **5** in hand, the remaining steps were straightforward. The resulting acid **5a** was treated with $LiAlH_4$ in ether (*27*, *28*) to furnish the (*R*)-(−)-maconelliol **6a** {$[\alpha]_D^{24}$ −31.0 (*c* 0.1, MeOH)} in good yield, and its enantiomeric purity was determined to be 78% ee. Similarly, (1*S*)-(−)-verbenone (80% ee, commercially available) was also converted into (*S*)-(+)-maconelliol **6b** {70% ee, $[\alpha]_D^{24}$ +22.0 (*c* 0.1, MeOH)}. The various spectral and GC data of synthetic (*R*)-(−)-**6a** are in good agreement with those of the natural product (*7*). Thus, we were able to determine the absolute configuration of the naturally occurring maconelliol **6** to be *R*.

(*S*)-(+)-2-Methylbutyric acid was commercially available (>99% ee), and (*R*)-(−)-2-methylbutyric acids (*13*) was prepared in good yield and with high ee (>99%) according to the method described by Cardillo et al. (*14*). Both MS and chiral GC data of synthetic (*S*)-(−)-2-methylbutyric acid are in good agreement with those of the natural product (*7*). Therefore, the absolute configuration of the naturally occurring acid was determined to be *S*.

Condensation of (*S*)-(+)- and (*R*)-(−)-2-methylbutyric acids with (*R*)-maconelliol **6a** by using 1.25 mol of oxalyl chloride and catalytic amounts of DMF in benzene (*28*) gave the esters **1a** (*RS*) and **1b (***RR*) in good yields. Similarly, two other isomeric esters (*SS* and *SR*) were synthesized in this manner by using (*S*)-maconelliol **6b**. Only one isomer, (*R*)-maconelliyl (*S*)-2-methylbutanoate **1a**, was found to be indistinguishable from the natural product on the basis of both ^1H NMR spectra (*7*), MS, and enantioselective chromatography criteria.

The minor pheromone component **2** was also prepared. (*R*)- and (*S*)-Lavandulols **7** were enantioselectively synthesized according to the method described by Cardillo et al. (*14*). After esterification (**Scheme 2**), only *RS* ester **2a** was found to be indistinguishable from the natural product on the basis of ^1H NMR spectra, MS, and enantioselective chromatographic data. As a result, the sex pheromone of the pink hibiscus mealybug, *M. hirsutus*, was identified to be a mixture of (*R*)-maconelliyl (*S*)-2-methylbutanoate and (*R*)-lavandulyl (*S*)-2-methylbutanoate. The absolute configuration of the pheromone components has been established by comparison of the naturally occurring compounds with the optically active isomers derived from the enantioselective syntheses.

In conclusion, the most intriguing result of this study so far has been the synthesis of the 2,2-dimethyl-3-(1-methylethylidene)cyclobutane ("maconelliane") nucleus. To our knowledge, this cyclobutanoid monoterpene represents a heretofore undescribed natural product and has never been prepared synthetically.

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