Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 9401–9403

Chiral synthesis of maconelliol: a novel cyclobutanoid terpene alcohol from pink hibiscus mealybug, *Maconellicoccus hirsutus*

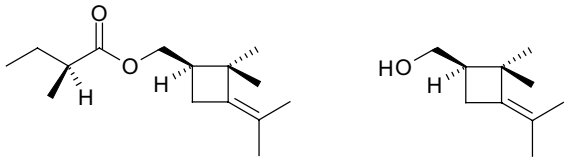
Aijun Zhang,* Junying Nie and Ashot Khrimian

USDA-ARS Chemicals Affecting Insect Behavior Laboratory, Beltsville Agriculture Research Center-West, Beltsville, MD 20705, USA

Received 14 September 2004; revised 13 October 2004; accepted 20 October 2004
Available online 6 November 2004

Abstract—The chiral synthesis of maconelliol, [2,2-dimethyl-3-(1-methylethylidene)cyclobutyl] methanol, the alcohol moiety of the major sex pheromone component isolated from the pink hibiscus mealybug, *Maconellicoccus hirsutus*, is described. The compound was synthesized in six steps from alpha-pinene and the key step is dehydration of **5** to **7** through the intermediate **6**. The absolute configuration of the naturally occurring maconelliol was determined as *R*.

Recently, we identified maconelliyl 2-methylbutanoate **1**, [(*R*)-2,2-dimethyl-3-(1-methylethylidene)cyclobutyl]-methyl (*S*)-2-methylbutanoate, as a major sex pheromone component of pink hibiscus mealybug, *Maconellicoccus hirsutus*.[1] This novel cyclobutanoid monoterpene derivative and lavandulyl 2-methylbutanoate, (*R*)-2-isopropenyl-5-methylhex-4-enyl (*S*)-2-methylbutanoate, together constitute a blend, which proved to be a potent male attractant at a concentration as low as 0.1 μg per trap in field bioassays conducted in Florida, USA.[2] The terpene alcohol moiety of **1**, maconelliol **2**, contains a methylethylidene group that separates **2** from all cyclobutane derivatives previously discovered as semiochemicals, and underlines its novelty (Fig. 1). We undertook synthesis of **2** in order to confirm the maconelliol's structure, unambiguously determine the absolute configuration of pheromone component **1**, and provide material for field bioassays. Herein we report the conveniently chiral synthesis of maconelliol **2** in six steps from α-pinene.



1 **2**

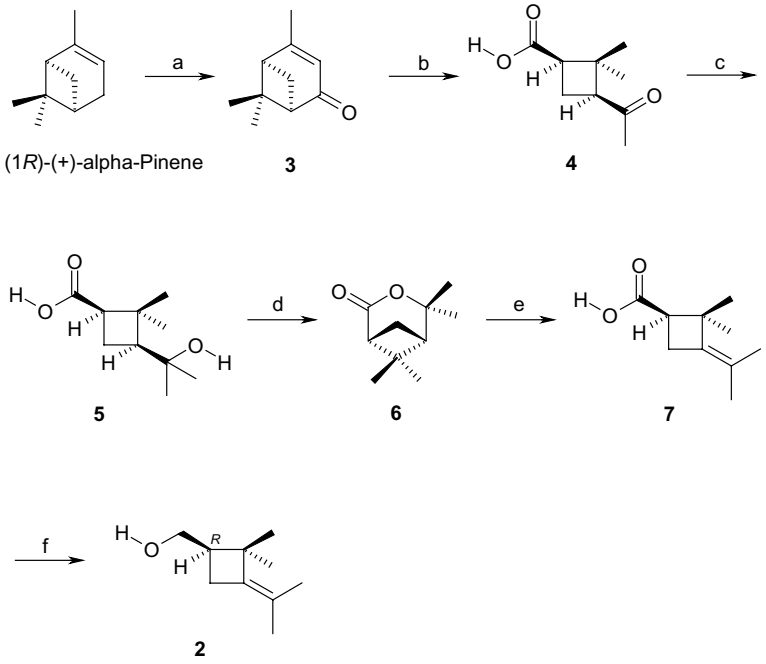
Figure 1. Structure of maconelliol **2** and major sex pheromone component **1**.

Our approach began with the preparation of the known (+)-(*cis*)-pinononic acid **4** from (1*R*)-(+)-α-pinene (91% ee) by allylic oxidation[3,4] and oxidative cleavage of resultant verbenone.[5] Treatment of **4** (91% ee) with three equivalent of CH_3MgCl in THF gave the tertiary hydroxy acid **5** as white crystals (67% yield, 80% ee). Partial loss of chirality is due to double epimerization during nucleophilic addition.[6]

To prevent possible decarboxylation during the dehydration, **5** was converted into the methyl ester using thionyl chloride in absolute methanol.[7] After examination of four dehydration reagents reacting with both methyl ester and free acid **5**, phosphorus oxychloride in pyridine[8] was found to be the most appropriate. The reaction of **5** with $POCl_3$ in pyridine at room temperature for 24 h yielded lactone **6**[9] (75%) exclusively, and no dehydrated isomer could be detected. The enantiomeric purity of resulting **6** was determined by chiral GC analysis[10] to be 80% ee (Scheme 1).

Keywords: *Maconellicoccus hirsutus*; Cyclobutanoid terpene alcohol; Maconelliol; Sex pheromone; Chiral synthesis.
* Corresponding author. Tel.: +1 301 504 5223; fax: +1 301 504 6580; e-mail: zhanga@ba.ars.usda.gov

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.131



Scheme 1. Preparation of the optically active maconelliol **2**. Reagents and conditions: (a) O_2/Co(4-Me$C_5H_4N)_2Br_2$, rt, 7 d, steam dist.; (b) $NaIO_4$/$RuCl_3$/CCl_4/acetone/H_2O (2:2:3), rt, 24 h; (c) CH_3MgCl/THF, reflux, 2 h; (d) $POCl_3$/pyridine, rt, 24 h; (e) *p*-TsOH/C_6H_6, reflux, 2 d; (f) $LiAlH_4$/ether, rt, overnight.

The lactone **6** was then easily converted to **7**[11] (78%) by *p*-toluenesulfonic acid[12] in benzene without isomerization of the double bond. The resultant acid **7** was reduced with $LiAlH_4$ in ether[13,14] to furnish the (*R*)-(−)-maconelliol **2**[15] {88%, 78% ee, $[\alpha]_D^{24} - 31$ (*c* 0.1, MeOH)}. Similarly, (1*S*)-(−)-α-pinene (85% ee) was also converted into (*S*)-(+)-maconelliol **2** {70% ee, $[\alpha]_D^{24} + 23$ (*c* 0.1, MeOH)}. All spectral and chiral GC data of synthetic (*R*)-(−)-maconelliol **2** are in good accord with those of the naturally occurring product.[1]

In conclusion, the first chiral synthesis of (−)- and (+)-maconelliol **2** was accomplished starting from α-pinene. The key step was dehydration of **5** to **7**. It was successfully achieved through lactonization. All other attempts to dehydrate **5** or its methyl ester resulted in undesired isopropenyl isomer, which could not be efficiently separated from **7** by column chromatography. The absolute configuration of the naturally occurring maconelliol **2** was determined to be *R*. Therefore, the major sex pheromone component **1** from *M. hirsutus* has been assigned as (*R*)-maconelliyl (*S*)-2-methylbutanoate[1] after esterification of (*R*)-(−)-maconelliol **2** with (*S*)-(+)- and (*R*)-(−)-2-methylbutyric acids[16] individually.

Acknowledgements

We thank Dr. James Oliver of the Chemicals Affecting Insect Behavior Laboratory for assistance with syntheses, and Dr. Walter Schmidt and Ms. Ute Klingebiel, NMR Facility for help in NMR spectroscopy. Mention of trade names or commercial products is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the US Department of Agriculture.

References and notes

1. Zhang, A.; Amalin, D.; Shirali, S.; Serrano, M. S.; Franqui, R. A.; Oliver, J. E.; Klun, J. A.; Aldrich, J. R.; Meyerdirk, D. E.; Lapointe, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 9601–9606.
2. Zhang, A.; Amalin, D. *Environ. Entomol.*, in press.
3. Lajunen, M.; Koskinen, A. M. P. *Tetrahedron Lett.* **1994**, *35*, 4461–4464.
4. King, H. C. A.; Koros, E.; Nelson, S. M. *J. Chem. Soc.* **1963**, 5449–5457.
5. Moglioni, A. G.; Carcia-Exposito, E.; Aguado, G. P.; Parella, T.; Branchadell, V.; Moltrasio, G. Y.; Ortuno, R. M. *J. Org. Chem.* **2000**, *65*, 3934–3940.
6. Conversion of ketoacid **4** to hydroxyacid **5** without epimerization at both stereogenic centers was essential. We tried different conditions with purified (1*R*,3*S*) ketoacid **4** by crystallization (>96% ee) as precursor. Reaction of methylmagnesium chloride with (1*R*,3*S*) **4** formed an insoluble in THF intermediate bromomagnesium salt, the further reaction of which at the carbonyl group required either heating or sonication at rt. As a result, partial epimerization occurred at both centers. Methyllithium, on the other hand, gave with (1*R*,3*S*) **4** a THF-soluble carboxylate that reacted with an additional 1.2 equiv of MeLi at −20 °C, but still ~15% double epimerization took place. A solution has been found by reacting (1*R*,3*S*) **4** with 1.0 equiv MeLi at −20 °C, followed by the addition of 1.6 equiv of MeMgCl, from which (1*R*,3*S*) **5** was isolated in 89% yield and 96% ee with virtually no change of chirality. This methodology will be used to scale up (*R*)-(−)-maconelliol **2** synthesis in the future.

7. Zhang, A.; Robbins, P. S.; Leal, W. S.; Linn, C. E., Jr.; Villani, M. G.; Roelofs, W. L. *J. Chem. Ecol.* **1997**, *23*, 231–245.
8. Tomas, A. F.; Vial, C.; Ozainne, M.; Ohloff, G. *Helv. Chim. Acta* **1973**, *56*, 238–239.
9. Properties of synthetic **6**: colorless oil; optical purity: 80% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (3H, s, C_6–$CH_{3\text{-}ax}$), 1.37 (3H, s, C_4–CH_3), 1.38 (3H, s, C_4–CH_3), 1.49 (3H, s, C_6–$CH_{3\text{-}eq}$), 1.81 (1H, d, J = 10.59 Hz, $H_{7\text{-}ax}$), 2.10 (1H, dd, J = 6.05, 5.67 Hz, H_5), 2.48 (1H, ddd, J = 10.59, 5.67, 5.30 Hz, $H_{7\text{-}eq}$), 2.63 (1H, dd, J = 6.05, 5.30 Hz, H_1); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.04 (C_2), 82.44 (C_4), 50.34 (C_1), 50.01 (C_5), 40.91 (C_6), 29.11 (CH_3), 26.11 (CH_3), 25.81 (CH_3), 25.27 (C_7), 25.25 (CH_3); 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 (M^+–CH_3): obsd. 153.0911, calcd. for $C_9H_{13}O_2$ 153.0916.
10. Chiral GC analysis was carried on a Hewlett Packard 6890 GC equipped with a 30 m × 0.25 mm ID, 0.25 μm film-thickness β-DEX 120 capillary column (Supeco, Inc., Bellefonte, PA) in the split mode (100:1) with hydrogen as carrier (55 cm/s, either 90 or 100 °C isothermal).
11. Properties of synthetic **7**: colorless oil; optical purity: 80% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, s, C_2–CH_3), 1.37 (3H, s, C_2–CH_3), 1.48 (3H, br s, =C–CH_3), 1.58 (3H, br s, =C–CH_3), 2.55 (1H, m, $H_{4\text{-}cis}$), 2.81 (2H, m, H_1 and $H_{4\text{-}trans}$), 10.50 (1H, s, COOH); ^{13}C NMR (75 MHz, C_6D_6): δ 179.78 (C=O), 135.57 (C_3), 123.27 (=C), 47.47 (C_2), 45.09 (C_1), 28.15 (C_2–$CH_{3\text{-}trans}$), 25.94 (C_4), 22.09 (C_2–$CH_{3\text{-}cis}$), 19.51 (=C–CH_3), 18.52 (=C–CH_3); 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 $C_{10}H_{16}O_2$ 168.1150.
12. Screttas, C. G.; Smonou, I. C. *J. Org. Chem.* **1988**, *53*, 893–894.
13. Nie, J.; Shi, D.; Daly, J. W.; Daly; Kirk, K. L. *Med. Chem. Res.* **1996**, 318–331.
14. Moffett, R. B. *Org. Synth. Coll.* **1963**, *IV*, 834–835.
15. Properties of synthetic **2**: colorless oil; optical purity: 78% ee; $[\alpha]_D^{24}$ −31 (*c* 0.1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (3H, s, C_2–$CH_{3\text{-}cis}$), 1.25 (3H, s, C_2–$CH_{3\text{-}trans}$), 1.38 (1H, br, OH), 1.44 (3H, br s, =C–CH_3), 1.57 (3H, br s, =C–CH_3), 2.08 (2H, m, H_1 and H_4), 2.58 (1H, bm, H_4), 3.62 (1H, dd, J = 17.00, 11.40 Hz, O–CH), 3.75 (1H, dd, J = 17.00, 11.30 Hz, O–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.42 (C_3), 122.43 (C=), 64.36 (C–OH), 44.11 (C_2), 42.74 (C_1), 28.69 (C_2–CH_3), 27.71 (C_4), 20.91 (C_2–CH_3), 19.53 (=C–CH_3), 18.48 (=C–CH_3); 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 $C_{10}H_{18}O$ 154.1358.
16. Shirali, S.; Zhang, A. *Synth. Commun.* **2004**, *34*, 3435–3441.