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Enantioselective Synthesis of a Mealybug Pheromone with an Irregular Monoterpenoid Skeleton

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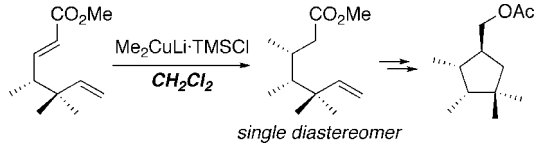
Received May 26, 2008



The first enantioselective synthesis of a mealybug sex pheromone with an unprecedented monoterpenoid skeleton has been accomplished by using a highly diastereoselective conjugate addition of an organocopper reagent to a γ-alkyl-α,β-unsaturated ester intermediate as the key step.

The obscure mealybug, *Pseudococcus viburni*, is an important agricultural pest of worldwide distribution that damages a broad range of economically important plants such as grapes, glasshouse crops, tee trees, and ornamental plants.[1] The flightless adult females release a potent sex pheromone to attract the short-lived, nonfeeding, winged adult males for reproduction. The sex pheromone was recently isolated by Millar and co-workers, and the structure was deduced, mainly from its mass and NMR spectra, to have a highly irregular monoterpenoid skeleton (**1**).[2] The relative stereochemistry of **1** was confirmed by a nonstereoselective synthesis of a mixture of its four possible diastereomers, followed by isolation of the natural diastereomer by preparative GC and NOE analysis of the isolated diastereomer.[2] They also achieved a diastereoselective synthesis of **1** as the racemate,[3] which, through enzymatic resolution of the synthetic racemate coupled with vibrational circular dichroism analysis of the isolated natural enantiomer, enabled them to determine the absolute configuration of the pheromone as depicted in Figure 1.[4] The highly irregular monoterpenoid structure of **1** bearing the unprecedented 2′−2 and 3′−4 linkages between two isoprene units as shown in Figure 1 and its potential use in insect pest management prompted our efforts for its synthesis.[5] In this paper, we describe the first enantioselective synthesis of **1**.

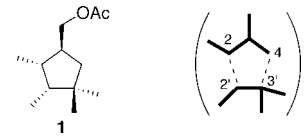
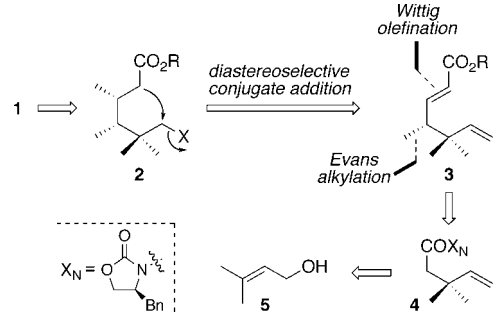


FIGURE 1. Sex pheromone of the obscure mealybug (**1**) with an unprecedented monoterpenoid skeleton.

Our retrosynthetic analysis of **1** is shown in Scheme 1. The cyclic monoterpene **1** would be obtainable by intramolecular alkylation of **2** followed by reduction of the ester functionality and subsequent acetylation of the resulting alcohol intermediate. To install the methyl substituent β to the ester group of **2**, we planned to utilize a distereoselective conjugate addition of a methyl anion species to γ-substituted α,β-unsaturated ester **3**, which in turn could be derived from chiral oxazolidinone derivative **4** via the Evans asymmetric alkylation and subsequent chain elongation by the Wittig reaction. The *N*-acyl oxazolidinone **4** should be readily prepared from **5** by the orthoester Claisen rearrangement with use of triethyl orthoacetate, followed by installation of the (*S*)-phenylalaninol-derived auxiliary (X_N).

SCHEME 1. Retrosynthetic Analysis of 1



Known carboxylic acid **6**, prepared from **5** by the orthoester Claisen rearrangement and subsequent alkaline hydrolysis,[6] was converted into chiral oxazolidinone derivative **4** in a single operation by treatment of **6** with pivaloyl chloride and Et_3N in THF followed by exposure of the resulting mixed anhydride to (*S*)-4-benzyl-3-lithio-2-oxazolidinone (Scheme 2).[7] The asymmetric methylation at the considerably congested α-position of **4** proceeded uneventfully to give a 74% isolated yield of **7a** as a single stereoisomer, as judged by ^1H and ^{13}C NMR analyses.[8] The methylation product **7a** was reduced with $NaBH_4$ to furnish alcohol **7b**, which was then subjected to the Swern oxidation

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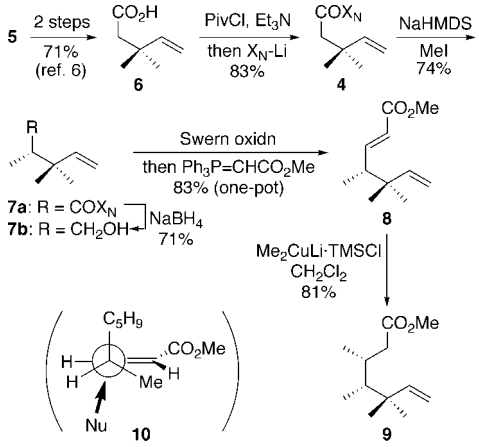
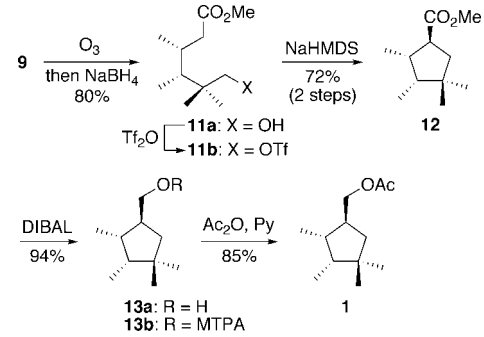
10.1021/jo801147c CCC: $40.75 © 2008 American Chemical Society
Published on Web 08/05/2008

SCHEME 2



conditions to afford an aldehyde intermediate. The resulting aldehyde was, however, so volatile that the isolated yield of the product was very poor. This problem was readily circumvented by conducting the two-step conversion of **7b** into **8** (Swern oxidation followed by Wittig olefination) in one pot without isolating the aldehyde intermediate.[9] The *E*-olefinic ester **8** was thus obtained in a satisfactory yield of 83% in geometrically pure form after chromatographic purification. For the diastereoselective introduction of a methyl group at the β-position of the enoate **8** to form **9** bearing *erythro* vicinal methyl groups, we examined the conjugate addition of organocopper reagents. In general, the conjugate addition of organocopper reagents to α,β-unsaturated esters is known to be sluggish as compared to the addition to α,β-unsaturated ketones, resulting in the recovery of starting enoates or the formation of desired products in low yields.[10] However, it has also been reported that some Lewis acidic additives such as $BF_3 \cdot OEt_2$ and TMSCl can activate the conjugate reaction,[10,11] and moreover, when the Lewis acid-promoted reactions are applied to (*E*)-γ-alkyl-α,β-unsaturated esters like **8**, the corresponding β,γ-*erythro* conjugate adducts like **9** predominate.[10,12] According to these precedents, we first attempted the following three reaction conditions for the conversion of **8** into **9**: (1) $Me_2CuLi \cdot LiI/BF_3 \cdot OEt_2$ in ether, (2) $Me_2CuLi \cdot LiBr \cdot Me_2S$/TMSCl in THF, and (3) $Me_2CuLi \cdot LiBr \cdot Me_2S$/TMSCl in THF/HMPA. Contrary to our expectation, none of these conditions were successful, resulting only in the recovery of the starting ester **8**. Faced with these disappointing outcomes, we next tried Yamamoto's method using Me_2CuLi/TMSCl in CH_2Cl_2, which was reported as the most powerful reagent system for the methylation of sterically congested α,β-enoates.[13] This method, which had never been applied to α,β-unsaturated esters bearing an asymmetric center at the γ-position, brought about dramatic success, furnishing the desired conjugate adduct **9** in 81% yield with complete diastereoselectivity; no diastereomer was detected by the ^1H and ^{13}C NMR analyses of the product. The selective formation of the diastereomer **9** would be rationalized by postulating a Felkin−Anh-type transition state model **10**.[10]

SCHEME 3



Having secured the olefinic ester **9** in stereochemically homogeneous form, we moved on to the final stage of the synthesis (Scheme 3). Compound **9** was subjected to ozonolysis followed by reductive workup with $NaBH_4$ to afford alcohol **11a**, which was then transformed into the corresponding triflate **11b**. Intramolecular alkylation of **11b** to cyclic ester **12** proceeded smoothly despite our concern that the steric congestion around the electrophilic site of **11b** might interfere with the cyclization.[14] Fortunately, the cyclization product was obtained as a single stereoisomer, probably due to much greater thermodynamic stability of **12** as compared to the corresponding epimeric ester. When this cyclization was conducted with the corresponding mesylate (**11**, X = OMs) or iodide (**11**, X = I) as the cyclization precursor, only the formation of complex mixtures was observed. Finally, reduction of the ester **12** with DIBAL and acetylation of the resulting alcohol **13a** gave the target molecule **1**. The enantiomeric excess of **13a** was estimated to be ca. 98% by analyzing the ^1H NMR spectra of the (*R*)- and (*S*)-MTPA esters (**13b**) derived from **13a**.[15] The ^1H and ^{13}C NMR spectra of the synthetic product **1** were identical with those of the natural pheromone, and the specific rotation of **1** {$[\alpha]^{27}_D$ +15.1 (*c* 1.50, $CDCl_3$)} was equal in sign to that of an authentic sample of the natural pheromone {$[\alpha]_D$ +9.1 (*c* 0.4, $CDCl_3$)},[4] although the magnitude of the specific rotation of the synthetic sample **1** was considerably larger than the reported value for the authentic sample.

In conclusion, the first enantioselective synthesis of the sex pheromone of the obscure mealybug (**1**) was accomplished in 10 steps with an overall yield of 13% from known carboxylic acid **6**, using the Evans asymmetric alkylation of chiral oxazolidinone derivative **4**, the highly diastereoselective conjugate addition of lithium dimethylcuprate to γ-methyl-α,β-unsaturated ester **8**, and the intramolecular cyclization of triflate **11b** as the key steps.

Experimental Section

(*S*)-4-Benzyl-3-(2,3,3-trimethyl-4-pentenoyl)-2-oxazolidinone (7a). To a stirred solution of NaHMDS (1.07 M in THF, 45.8 mL, 49.0 mmol) in THF (220 mL) was added dropwise a solution of **4** (11.8 g, 41.0 mmol) in THF (100 mL) at −78 °C. After 1 h, MeI (5.1 mL, 82.0 mmol) was added, and the resulting mixture was gradually

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(15) The ^1H NMR signals for the two protons on the oxygen-bearing methylene carbon of the (*R*)-MTPA ester [δ 4.26 (1H, dd, J = 10.5, 6.8 Hz), 4.29 (1H, dd, J = 10.5, 5.9 Hz)] were clearly distinguishable from those of the (*S*)-MTPA ester [δ 4.19 (1H, dd, J = 10.5, 7.1 Hz), 4.34 (1H, dd, J = 10.5, 5.6 Hz)].

warmed to 0 °C. The mixture was poured into aq NH_4Cl, acidified to pH 2.0 with 1 M aq sulfuric acid, and extracted with EtOAc. The extract was successively washed with saturated aq $NaHCO_3$, saturated aq $Na_2S_2O_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 10:1) to give 9.09 g (74%) of **7a** as a white solid, which was recrystallized from hexane/EtOAc to afford white needles; mp 77.8−78.0 °C; $[\alpha]^{24}_D$ +86.3 (*c* 1.30, $CHCl_3$); IR ν_{max} 3087 (w), 3028 (w), 1761 (s), 1696 (s), 1207 (m); ^{1}H NMR δ 1.10 (3H, s), 1.11 (3H, s), 1.17 (3H, d, *J* = 7.0 Hz), 2.75 (1H, dd, *J* = 13.7, 9.8 Hz), 3.26 (1H, dd, *J* = 13.7, 3.0 Hz), 4.00 (1H, q, *J* = 7.0 Hz), 4.11−4.16 (2H, m), 4.61−4.67 (1H, m), 4.98 (1H, d, *J* = 17.3 Hz), 4.99 (1H, d, *J* = 11.0 Hz), 5.95 (1H, dd, *J* = 17.3, 11.0 Hz), 7.22 (2H, d, *J* = 7.3 Hz), 7.27 (1H, t, *J* = 7.3 Hz), 7.33 (2H, t, *J* = 7.3 Hz); ^{13}C NMR δ 12.9, 23.5, 24.6, 37.8, 39.5, 44.1, 55.5, 65.7, 111.9, 127.3, 128.9 (2C), 129.4 (2C), 135.3, 145.9, 153.4, 175.9; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{24}NO_3$ ([M + H]$^+$) 302.1756, found 302.1754.

Methyl (*R*)-4,5,5-Trimethyl-2,6-heptadienoate (8). To a stirred solution of $(COCl)_2$ (0.510 mL, 5.98 mmol) in CH_2Cl_2 (13.6 mL) was added a solution of DMSO (0.85 mL, 12 mmol) in CH_2Cl_2 (21 mL) at −78 °C. After 15 min, a solution of **7b** (0.697 g, 5.43 mmol) in CH_2Cl_2 (10 mL) was added, and the resulting mixture was stirred for 1 h at −78 °C. To the mixture was added dropwise Et_3N (3.8 mL, 27 mmol), and the mixture was gradually warmed to −20 °C then stirred overnight. $Ph_3P{=}CHCO_2Me$ (9.1 g, 27.2 mmol) was then added, and the reaction mixture was gradually warmed to room temperature, then refluxed overnight. The mixture was washed with 0.1 M HCl (2×), saturated aq $NaHCO_3$, water, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 50:1) to give 0.831 g (84%) of **8** as a colorless oil; $[\alpha]^{22}_D$ +30.5 (*c* 1.10, $CHCl_3$); IR ν_{max} 1728 (vs), 1654 (m), 1270 (s); ^{1}H NMR δ 0.98 (3H, d, *J* = 4.9 Hz), 0.99 (6H, s), 2.14−2.21 (1H, m), 3.73 (3H, s), 4.96 (1H, dd, *J* = 17.5, 1.5 Hz), 5.01 (1H, dd, *J* = 11.0, 1.5 Hz), 5.77 (1 H, dd, *J* = 17.5, 11.0 Hz), 5.79 (1H, dd, *J* = 15.5, 1.0 Hz), 6.93 (1H, dd, *J* = 15.5, 9.3 Hz); ^{13}C NMR δ 14.6, 23.6, 25.2, 39.2, 46.1, 51.3, 112.1, 120.8, 146.0, 152.1, 167.0; HRMS (FAB) *m*/*z* calcd for $C_{11}H_{19}O_2$ ([M + H]$^+$) 183.1385, found 183.1390.

Methyl (3*R*,4*R*)-3,4,5,5-Tetramethyl-6-heptenoate (9). To a stirred suspension of CuI (13.5 g, 71.0 mmol) in ether (70 mL) was added MeLi (1.09 M in ether, 129 mL, 141 mmol) at 0 °C, and the resulting mixture was stirred for 1 h. The solvent was removed under reduced pressure at 0 °C, and CH_2Cl_2 (50 mL) was added to the residue. The mixture was stirred for 10 min at 0 °C, and then the solvent was removed again under reduced pressure at 0 °C. To the residue was added precooled CH_2Cl_2 (180 mL), and the mixture was cooled to −78 °C. To the mixture were successively added TMSCl (9.0 mL, 71.0 mmol) and a solution of **8** (1.29 g, 7.10 mmol) in CH_2Cl_2 (14 mL). The mixture was gradually warmed to 0 °C, then stirred for 5 days. The mixture was quenched with a mixture of saturated aq NH_4Cl and 28% aq NH_3 (1:1) and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 20:1) to give 1.13 g (81%) of **9** as a colorless oil; $[\alpha]^{23}_D$ −5.5 (*c* 1.20, $CHCl_3$); IR ν_{max} 3083 (w), 1740 (s), 1278 (m), 1171 (m); ^{1}H NMR δ 0.78 (3H, d, *J* = 7.0 Hz), 0.92 (3H, d, *J* = 7.0 Hz), 0.99 (3H, s), 1.03 (3H, s), 1.30 (1H, dq, *J* = 1.5, 7.0 Hz), 1.88 (1 H, dd, *J* = 11.5, 15.3 Hz), 2.29−2.37 (1H, m), 2.45 (1H, dd, *J* = 15.3, 2.5 Hz), 3.66 (3H, s), 4.95 (1H, dd, *J* = 17.5, 1.5 Hz), 4.96 (1H, dd, *J* = 11.0, 1.5 Hz), 5.83 (1H, dd, *J* = 17.5, 11.0 Hz); ^{13}C NMR δ 9.0, 21.5, 25.1, 25.6, 29.7, 37.1, 40.1, 47.1, 51.3, 111.2, 147.1, 174.4; HRMS (EI) *m*/*z* calcd for $C_{12}H_{22}O_2$ (M^+) 198.1620, found 198.1619.

Methyl (3*R*,4*R*)-6-Hydroxy-3,4,5,5-tetramethylhexanoate (11a). Olefin **9** (102 mg, 0.516 mmol) in MeOH/CH_2Cl_2 (5:1, 5.2 mL) was treated with ozone at −78 °C for 1 h. After removal of excess O_3 by a stream of O_2, $NaBH_4$ (58.6 mg, 1.55 mmol) was added at −78 °C, and the resulting mixture was gradually warmed to room temperature and stirred for 2 h. The mixture was quenched with saturated aq NH_4Cl and extracted with ether. The extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 10:1) to give 84.2 mg (80%) of **11a** as a colorless oil; $[\alpha]^{22}_D$ +4.7 (*c* 1.00, $CHCl_3$); IR ν_{max} 3457 (m), 1737 (s), 1279 (m), 1172 (m), 1040 (m); ^{1}H NMR δ 0.80 (3H, d, *J* = 7.5 Hz), 0.86 (3H, s), 0.94 (3H, s), 0.96 (3H, d, *J* = 7.0 Hz), 1.27−1.36 (1H, br s, OH), 1.47 (1H, dq, *J* = 1.0, 7.5 Hz), 1.97 (1 H, dd, *J* = 15.0, 11.5 Hz), 2.28−2.37 (1H, m), 2.45 (1H, dd, *J* = 15.0, 1.5 Hz), 3.39 (1H, d, *J* = 10.7 Hz), 3.43 (1H, d, *J* = 10.7 Hz), 3.67 (3H, s); ^{13}C NMR δ 8.8, 21.6, 22.1, 22.3, 29.3, 37.5, 38.4, 42.5, 51.4, 70.7, 174.5; HRMS (FAB) *m*/*z* calcd for $C_{11}H_{23}O_3$ ([M + H]$^+$) 203.1647, found 203.1650.

Methyl (1*S*,2*S*,3*R*)-2,3,4,4-Tetramethylcyclopentanecarboxylate (12). To a stirred solution of **11a** (0.338 g, 1.67 mmol) in CH_2Cl_2 (17 mL) was added 2,6-lutidine (0.21 mL, 1.84 mmol) at −50 °C. After 15 min, Tf_2O (0.31 mL, 1.84 mmol) was added, and the resulting mixture was gradually warmed to 0 °C. The reaction mixture was washed quickly with 0.1 M aq HCl, dried ($MgSO_4$), and concentrated in vacuo to give crude **11b**, which was then taken up in THF (17 mL). To the solution was added dropwise a solution of NaHMDS (1.07 M in THF, 1.87 mL, 2.00 mmol) at −78 °C. The reaction mixture was gradually warmed to 0 °C and then poured into saturated aq NH_4Cl. The mixture was extracted with ether, and the extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel chromatography (pentane/ether = 200:1) to give 0.221 g (72%) of **12** as a colorless oil; $[\alpha]^{21}_D$ +32.6 (*c* 1.30, $CHCl_3$); IR ν_{max} 1736 (s), 1260 (m), 1193 (m), 1171 (m), 1023 (m); ^{1}H NMR δ 0.78 (3H, d, *J* = 7.8 Hz), 0.86 (3H, s), 0.99 (3H, d, *J* = 6.8 Hz), 1.02 (3H, s), 1.64−1.69 (1H, m), 1.69−1.79 (2 H, m), 2.43−2.52 (2H, m), 3.68 (3H, s); ^{13}C NMR δ 10.2, 17.0, 23.7, 29.4, 40.2, 41.8, 43.9, 46.2, 50.0, 51.5, 177.3; HRMS (EI) *m*/*z* calcd for $C_{11}H_{20}O_2$ (M^+) 184.1463, found 184.1460.

[(1*S*,2*S*,3*R*)-2,3,4,4-Tetramethylcyclopentyl]methyl Acetate (1). To a stirred solution of **13a** (31.3 mg, 0.200 mmol) in pyridine (0.4 mL) was added dropwise Ac_2O (0.030 mL, 0.317 mmol) at 0 °C. The mixture was gradually warmed to room temperature and stirred overnight. The mixture was poured into saturated aq NH_4Cl and extracted with pentane. The organic layer was successively washed with 0.5 M HCl (2×), water, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel chromatography (pentane/ether = 100:1) to give 33.9 mg (85%) of **1** as a colorless oil; $[\alpha]^{27}_D$ +15.1 (*c* 1.50, $CDCl_3$); IR ν_{max} 1743 (vs), 1242 (s), 1043 (m); ^{1}H NMR δ 0.78 (3H, d, *J* = 7.3 Hz), 0.85 (3H, s), 0.95 (3H, d, *J* = 6.8 Hz), 0.97 (3H, s), 1.15 (1H, dd, *J* = 12.7, 9.3 Hz), 1.65 (1H, qui, *J* = 7.3 Hz), 1.67 (1H, dd, *J* = 12.7, 7.3 Hz), 1.87−1.96 (2H, m), 2.05 (3H, s), 3.99 (1H, dd, *J* = 10.7, 6.3 Hz), 4.06 (1H, dd, *J* = 10.7, 5.4 Hz); ^{13}C NMR δ 10.2, 17.1, 21.0, 23.8, 29.7, 39.1, 41.2, 44.4, 44.5, 46.2, 68.7, 171.4; HRMS (EI) *m*/*z* calcd for $C_{12}H_{22}O_2$ (M^+) 198.1620, found 198.1629.

Acknowledgment. We are grateful to Prof. Millar (University of California, Riverside) for providing the NMR spectra of the mealybug pheromone. This work was financially supported, in part, by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 19380065).

Supporting Information Available: Experimental procedures and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801147C