A protecting group-free synthesis of the Colorado potato beetle pheromone
Wu, Zhongtao; Buter, Jeffrey; Minnaard, Adriaan J.; Jäger, Manuel; Dickschat, J.S.

Published in:
Beilstein Journal of Organic Chemistry

DOI:
10.3762/bjoc.9.273

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2013

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Supporting Information

for

A protecting group-free synthesis of the Colorado potato beetle pheromone

Zhongtao Wu, Manuel Jäger, Jeffrey Buter and Adriaan J. Minnaard*

Address: Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 7, 9747 AG, Groningen, The Netherlands.

E-mail: Adriaan J. Minnaard* - a.j.minnaard@rug.nl

* Corresponding author

Experimental and spectroscopic details for 1, 3 and 4, and determination of the ee of 3 and 4.

1. General remarks

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Varian AMX400 (400 and 100 MHz, respectively) with CDCl$_3$ as solvent. Chemical shifts were determined relative to the residual solvent peaks (CHCl$_3$, $\delta = 7.19$ ppm for $^1$H-NMR, $\delta = 77.0$ ppm for $^{13}$C NMR). The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Enantiomeric excesses were determined by chiral HPLC using a Shimadzu LC-20AD HPLC equipped with a Shimadzu SPD-M20A diode array detector and columns (Chiralpak AD-H and OD-H) provided by Daicel corporation, in comparison with the corresponding enantiomers.
and racemic mixtures. \(2S,3S\)-2,3-Epoxygeraniol was obtained by the same procedure as used for \(2R,3R\)-2,3-epoxygeraniol, but using L-\((+)\)-diethyl tartrate. \(2R,3S\)-2,3-Epoxynerol was obtained by the same procedure as used for \(2S,3R\)-2,3-epoxynerol, but using D-\((-)\)-diisopropyl tartrate (DIPT). Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell \((c\) given in g/100 mL) at approx. 20 °C. Thin-layer chromatography (TLC) was performed on Merck TLC Silica gel 60 Kieselguhr F\(254\). Flash chromatography was performed on silica gel Merck Type 9385 230–400 mesh. Geraniol, nerol, D-\((-)\)-diisopropyl tartrate (DIPT), L-\((+)\)-DIPT, titanium tetraisopropoxide and tert-butyl hydroperoxide solution (TBHP) \((5\sim6\text{ M in decane})\) were purchased from Aldrich. Geraniol, nerol, D-\((-)\)-DIPT, L-\((+)\)-DIPT and titanium tetraisopropoxide were purified by Kugelrohr distillation. The catalyst [(2,9-dimethyl-1,10-phenanthroline)-Pd(\(\mu\)-OAc)]\(_2\)(OTf)\(_2\) was made according to the literature procedure.\(^1\) 4 Å molecular sieves were dried at 130 °C for 2 d in an oven and heated by a heat gun under vacuum before use.

### 2. Experimental Section

\(2R,3R\)-2,3-Epoxygeraniol (4).\(^2\) To 20 mL of dry CH\(_2\)Cl\(_2\) containing 4 Å molecular sieves \((2.0\text{ g})\) were added D-\((-)\)-DIPT \((228\text{ mg, }0.97\text{ mmol})\) and titanium tetraisopropoxide \((184\text{ mg, }0.65\text{ mmol})\) successively at \(-10\text{ °C under nitrogen. After having added TBHP (3.5 mL, 5\sim6\text{ M in decane}) slowly, the resulted mixture was stirred for an additional 30 min. Then the mixture was cooled to \(-23\text{ °C by a Cryostat and freshly distilled geraniol (2.0 g, 13.0 mmol) was added over 0.5 h keeping the inner temperature below \(-20\text{ °C. The mixture was stirred at \(-23\text{ °C for an additional 2.5 h, and was then quenched by water (2 mL). The mixture was vigorously stirred for 30 min while allowing to warm to rt. After adding aq NaOH (1.2 mL, 3 M), the mixture was stirred for another 30 min at rt and then filtered over a Büchner funnel under suction. The filtrate was stirred vigorously with 10% aqueous citric acid (6 mL) for 1 h at rt. The organic layer was separated, and the aqueous layer was extracted\).}\)
with DCM. The combined organic layers were dried over MgSO$_4$, filtered and evaporated in vacuo. The residue was purified by Kugelrohr distillation (120–122 °C, 2 torr) to afford epoxide (2R,3R)-4 (2.05 g, 93%) as a colorless oil. $[^{20}\alpha] = +2.3$ (c 1.32, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.04-5.00 (m, 1 H), 3.76 (d, $J = 12.0$ Hz, 1 H), 3.61 (dd, $J = 12.0$, 6.4 Hz, 1 H), 2.91 (dd, $J = 6.8$, 4.4 Hz, 1 H), 2.02 (q, $J = 7.6$ Hz, 2 H), 1.84 (br s, 1 H), 1.65-1.54 (m, 1 H), 1.54 (s, 3 H), 1.44-1.37 (m, 1 H), 1.23 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 132.1, 123.3, 62.9, 61.4, 61.2, 38.5, 25.6, 23.7, 17.6, 16.7. The spectral data matched with those reported in the literature$^{2c}$.

(2R,3R)-1-tert-Butyldiphenylsilyloxy-2,3-epoxy-3,7-dimethyl-6-octene (5). To a stirred solution of (2R,3R)-4 (87 mg, 0.51 mmol) in CH$_2$Cl$_2$ (2 mL) were added imidazole (43 mg, 0.63 mmol) and TBDPSCl (0.15 mL, 0.58 mmol) successively at rt. After 5 min, 5 mL of saturated aq NH$_4$Cl and 5 mL of CH$_2$Cl$_2$ were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (pentane/Et$_2$O = 50:1) to afford (2R,3R)-5 (188 mg, 90%) as a colorless oil. According to HPLC (Chiral OD-H column, heptane/iPrOH 99.9:0.1, 40 °C, 225 nm) the ee was 88%. Retention time: $t_{major} = 23.9$ and $t_{minor} = 20.4$ min. $[^{20}\alpha] = +9.7$ (c 1.17, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62-7.60 (m, 4 H), 7.36-7.29 (m, 6 H), 5.02 (t, $J = 7.2$ Hz, 1 H), 3.73 (dd, $J = 11.2$, 5.2 Hz, 1 H), 3.66 (dd, $J = 11.2$, 5.2 Hz, 1 H), 2.92 (t, $J = 5.2$ Hz, 1 H), 1.99 (q, $J = 7.6$ Hz, 2 H), 1.60-1.32 (m, 2 H), 1.60 (s, 3 H), 1.53 (s, 3 H), 1.06-0.99 (m, 12 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 135.6, 135.5, 133.5, 133.3, 132.0, 129.7, 127.8, 127.70, 127.69, 123.5, 62.90, 62.86, 60.5, 38.5, 26.8, 25.7, 23.8, 19.2, 17.6, 16.7; HRMS (C$_{26}$H$_{37}$O$_2$Si, APCI): calcd. 409.2557, found 409.2556.

(2R,3S)-3,7-Dimethyl-6-octene-1,2,3-triol (3). To a solution of (2R,3R)-4 (200 mg, 1.17 mmol) in THF (5.4 mL) was added dropwise a solution of HClO$_4$ (0.07 mL, 70%) in H$_2$O (1 mL) at rt. The resulting mixture was stirred for an additional 30 min at rt. Then ethyl acetate (10 mL) and water (3 mL) were added. The organic layer was
separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄, filtered and evaporated in vacuo. The crude product (2R,3S)-3 (206 mg, 94%) was obtained as a colorless oil, sufficiently pure for the next step. [α]²⁰_D = +5.7 (c 1.02, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.04-5.01 (m, 1 H), 3.70-3.61 (m, 5 H), 3.41 (dd, J = 6.4, 3.2 Hz, 1 H), 2.05-1.93 (m, 2 H), 1.61 (s, 3 H), 1.56-1.49 (m, 1 H), 1.54 (s, 3 H), 1.34-1.26 (m, 1 H), 1.14 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 131.9, 124.1, 76.9, 74.5, 63.1, 37.7, 25.6, 23.2, 22.1, 17.6.

(2R,3S)-1-tert-Butyldiphenylsilyloxy-3,7-dimethyl-6-octene-2,3-diol (6). To a stirred solution of (2R,3S)-3 (50 mg, 0.27 mmol) in CH₂Cl₂ (2 mL) were added imidazole (23 mg, 0.34 mmol) and TBDPSCl (0.08 mL, 0.31 mmol) successively at rt. After 5 min, 5 mL of saturated aq. NH₄Cl and 5 mL of CH₂Cl₂ were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (pentane/Et₂O = 3:1) to afford (2R,3S)-6 (92 mg, 80%) as a colorless oil. According to HPLC (Chiral AD-H column, heptane/iPrOH 99:1, 40 °C, 230 nm) the ee was 86%. Retention time: t_major = 31.5 and t_minor = 37.1 min. [α]²⁰_D = -1.8 (c 0.68, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.61-7.58 (m, 4 H), 7.38-7.29 (m, 6 H), 4.97 (t, J = 7.2 Hz, 1 H), 3.77-3.71 (m, 2 H), 3.43-3.40 (m, 1 H), 2.68 (br s, 2 H), 2.03-1.97 (m, 1 H), 1.90-1.83 (m, 1 H), 1.59 (s, 3 H), 1.51-1.45 (m, 1 H), 1.48 (s, 3 H), 1.30-1.24 (m, 1 H), 1.11 (s, 3 H), 0.99 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 135.55, 135.52, 132.7, 132.6, 131.7, 130.0, 127.873, 127.865, 124.3, 75.8, 73.9, 64.9, 38.1, 26.9, 25.7, 23.2, 22.1, 19.2, 17.6; HRMS (C₂₆H₃₈O₃SiNa, APCI): calcd. 449.2482, found 449.2477.

(S)-1,3-Dihydroxy-3,7-dimethyl-6-octene-2-one (1). To a suspension of 3 (200 mg, 1.06 mmol) and p-benzoquinone (346 mg, 3.20 mmol) in CH₃CN/H₂O (5 mL/0.5 mL) was added [(2,9-dimethyl-1,10-phenanthroline)-Pd(μ-OAc)]₂(OTf)₂ (5.6 mg, 0.0054 mmol). The resulting mixture was stirred overnight at rt and subsequently filtered over a silica pad. The pad was washed with ethyl acetate and the combined
filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (pentane/EtOAc = 3/1) to afford 1 (180 mg, 91%) as a colorless oil. \([\alpha]_{D}^{20} = +1.6 \, (c \ 0.50, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 4.97 (t, \(J = 7.2 \, \text{Hz}, \ 1 \, \text{H}\)), 4.42 (br t, \(J = 21.6 \, \text{Hz}, \ 2 \, \text{H}\)), 2.89 (br s, 2 H), 2.07-1.98 (m, 1 H), 1.88-1.78 (m, 1 H), 1.76-1.63 (m, 2 H), 1.60 (s, 3 H), 1.52 (s, 3 H), 1.30 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta \) 214.1, 133.3, 122.9, 78.5, 64.6, 39.9, 26.1, 25.6, 22.2, 17.7.

\((2S,3R)-2,3\text{-Epoxysterol (4)}.\) \((2S,3R)-4\) was prepared from nerol following a procedure similar to that for geraniol to \((2R,3R)-4\). \([\alpha]_{D}^{20} = -13.0 \, (c \ 1.03, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 5.02 (tt, \(J = 7.2, 1.2 \, \text{Hz}, \ 1 \, \text{H}\)), 3.74 (d, \(J = 12.0 \, \text{Hz}, \ 1 \, \text{H}\)), 3.60-3.55 (m, 1 H), 2.90 (dd, \(J = 7.2, 4.4 \, \text{Hz}, \ 1 \, \text{H}\)), 2.45 (br d, \(J = 32.0 \, \text{Hz}, \ 1 \, \text{H}\)), 2.08-1.99 (m, 2 H), 1.62 (s, 3 H), 1.62-1.57 (m, 1 H), 1.54 (s, 3 H), 1.45-1.37 (m, 1 H), 1.27 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta \) 132.4, 123.3, 64.4, 61.5, 61.2, 33.1, 25.6, 24.1, 22.1, 17.6. Spectral data matched with those reported in the literature.\(^5\)

\((2S,3R)-1\text{-tert-Butyldiphenylsilyloxy-2,3-epoxy-3,7-dimethyl-6-octene (5).}\) \((2S,3R)-5\) was prepared from \((2S,3R)-4\) following a procedure similar to that for \((2R,3R)-4\) to \((2R,3S)-5\). According to HPLC (Chiral OD-H column, heptane/iPrOH 99.9:0.1, 40 °C, 230 nm) the ee was 74%. Retention time: \(t_{\text{major}} = 31.4\) and \(t_{\text{minor}} = 24.7\) min. \([\alpha]_{D}^{20} = -7.4 \, (c \ 0.76, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 7.61-7.58 (m, 4 H), 7.37-7.32 (m, 6 H), 5.00-4.96 (m, 1 H), 3.81 (dd, \(J = 8.8, 2.4 \, \text{Hz}, \ 1 \, \text{H}\)), 3.74-3.67 (m, 2 H), 2.04 (q, \(J = 8.4 \, \text{Hz}, \ 2 \, \text{H}\)), 1.79-1.65 (m, 2 H), 1.60 (s, 3 H), 1.52 (s, 3 H), 1.40 (s, 3 H), 1.00 (s, 9 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta \) 135.5, 132.9, 132.8, 132.2, 129.92, 129.89, 127.8, 123.3, 77.4, 75.5, 64.3, 40.3, 26.8, 25.64, 25.56, 23.0, 19.2, 17.6. HRMS (C\(_{26}\)H\(_{36}\)O\(_2\)SiNa, APCI): calcd. 431.2377, found 431.2372.

\((2S,3S)-3,7\text{-Dimethyl-6-octene-1,2,3-triol (3).}\) \((2S,3S)-3\) was prepared from \((2S,3R)-4\) following a procedure similar to that for \((2R,3R)-4\) to \((2R,3S)-3\). \([\alpha]_{D}^{20} = -1.1 \, (c \ 1.09, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 5.06-5.02 (m, 1 H), 3.68-3.66 (m, 2 H), 3.46-3.44 (m, 1 H), 2.84 (br s, 3 H), 1.99 (apparent q, \(J = 8.0 \, \text{Hz}, \ 2 \, \text{H}\)), 1.61 (s, 3 H), 1.55 (s, 3 H), 1.52-1.50 (m, 1 H), 1.25-1.23 (m, 1 H), 1.10 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta \) 132.0, 124.1, 75.6, 74.5, 63.3, 39.1, 25.7, 22.2, 22.1, 17.6;
HRMS (C$_{10}$H$_{21}$O$_{3}$, APCI): calcd. 189.1485, found 189.1484.

(2S,3S)-1-tert-Butyldiphenylsilyloxy-3,7-dimethyl-6-octene-2,3-diol (6). (2S,3S)-6 was prepared from (2S,3S)-3 following a procedure similar to that for (2R,3S)-3 to (2R,3S)-6. According to HPLC (Chiral AD-H column, heptane/iPrOH 99:1, 40 °C, 230 nm) the ee was 68%. Retention time: $t_{\text{major}} = 26.7$ and $t_{\text{minor}} = 20.7$ min. $[\alpha]_{D}^{20} = -7.2$ (c 1.09, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61-7.59 (m, 4 H), 7.38-7.31 (m, 6 H), 5.03-5.00 (m 1 H), 3.76-3.68 (m, 2 H), 3.46-3.43 (m, 1 H), 1.94 (dd, $J$ = 17.2, 6.8 Hz, 2 H), 1.60 (s, 3 H), 1.52 (s, 3 H), 1.49-1.43 (m, 2 H), 1.02 (s, 3 H), 1.00 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 135.53, 135.50, 132.7, 132.6, 131.6, 130.0, 127.9, 127.8, 124.3, 75.0, 73.6, 65.0, 39.0, 26.8, 25.7, 22.21, 22.17, 19.2, 17.6; HRMS (C$_{26}$H$_{38}$O$_{3}$SiNa, APCI): calcd. 449.2482, found 449.2478.

$^1$H NMR data for (S)-1,3-Dihydroxy-3,7-dimethyl-6-octen-2-one (1)

<table>
<thead>
<tr>
<th>Assignments</th>
<th>(S)-1$^6$</th>
<th>(S)-1$^7$</th>
<th>Synthetic (S)-1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CDCl$_3$</td>
<td>CDCl$_3$</td>
<td>CDCl$_3$</td>
</tr>
<tr>
<td></td>
<td>500 MHz</td>
<td>500 MHz</td>
<td>400 MHz</td>
</tr>
<tr>
<td>$\delta_H$ (J)</td>
<td>$\delta_H$ (J)</td>
<td>$\delta_H$ (J)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4.50 (d, 4.9 Hz)</td>
<td>4.51 (d, 19.7 Hz)</td>
<td>4.42 (br t, 21.6 Hz)</td>
</tr>
<tr>
<td>2</td>
<td>4.48 (d, 4.9 Hz)</td>
<td>4.47 (d, 19.7 Hz)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3-Me</td>
<td>1.37 (s)</td>
<td>1.37 (s)</td>
<td>1.30 (s)</td>
</tr>
<tr>
<td>4</td>
<td>1.79 (br ddd, 14, 9.8, 6.1 Hz)</td>
<td>1.79 (br ddd, 14.1, 9.7, 6.0 Hz)</td>
<td>1.79-1.83 (m)</td>
</tr>
<tr>
<td></td>
<td>1.71 (br ddd, 14, 10, 5.8 Hz)</td>
<td>1.71 (br ddd, 14.1, 9.7, 6.0 Hz)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>2.09 (br dt, 14, 6.4 Hz)</td>
<td>2.08 (m)</td>
<td>2.07-1.98 (m)</td>
</tr>
<tr>
<td></td>
<td>1.90 (br dt, 14, 6.4 Hz)</td>
<td>1.89 (m)</td>
<td>1.88-1.78 (m)</td>
</tr>
<tr>
<td>6</td>
<td>5.04 (br t, 6.4 Hz)</td>
<td>5.04 (tm, 7.2, 1.4 Hz)</td>
<td>4.97 (t, 7.2 Hz)</td>
</tr>
<tr>
<td>7-Me</td>
<td>1.58 (s)</td>
<td>1.58 (br s)</td>
<td>1.52 (s)</td>
</tr>
<tr>
<td>7-Me</td>
<td>1.67 (s)</td>
<td>1.66 (m)</td>
<td>1.60 (s)</td>
</tr>
<tr>
<td>-OH</td>
<td>2.90-2.95 (m)</td>
<td>2.94 (br s)</td>
<td>2.89 (br s)</td>
</tr>
</tbody>
</table>

In our studies, the chemical shift of residual CHCl$_3$ was set to 7.19 ppm whereas in the literature this was 7.26 ppm. Therefore the values of synthetic 1 are consistently 0.07 ppm lower.
3. References


4. $^1$H NMR, $^{13}$C NMR Spectra and HPLC chromatograms

(2R,3R)-2,3-Epoxygeraniol (4).
(2R,3R)-1-tert-Butyldiphenylsilyloxy-2,3-epoxy-3,7-dimethyl-6-octene (5).
Mixture of (2R,3R)-5 and (2S,3S)-5
(2R,3S)-3,7-Dimethyl-6-octene-1,2,3-triol (3).
(2R,3S)-1-\textit{tert}-Butyldiphenylsilyloxy-3,7-dimethyl-6-octene-2,3-diol (6).
Mixture of (2R,3S)-6 and (2S,3R)-6
(S)-1,3-Dihydroxy-3,7-dimethyl-6-octen-2-one (1).
(2S,3R)-2,3-Epoxynerol (4).
(2S,3R)-1-tert-Butyldiphenylsilyloxy-2,3-epoxy-3,7-dimethyl-6-octene (5).
Mixture of (2S,3R)-5 and (2R,3S)-5
(2S,3S)-3,7-Dimethyl-6-octene-1,2,3-triol (3).
(2S,3S)-1-tert-Butyldiphenylsilyloxy-3,7-dimethyl-6-octene-2,3-diol (6).
Mixture of (2S,3S)-6 and (2R,3R)-6