Synthesis of (R)-Callosobruchus Acid from Methyl (R)-3-Carboxybutanoate†

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(\(\text{(R)}\)-Callosobruchus acid [(\(\text{E}\)-7,R)-3,7-dimethyl-2-octene-1,8-dioic acid (1)]) the pheromone component of azuki bean weevil (Callosobruchus chinensis), was synthesized from methyl (\(\text{R}\))-3-carboxybutanoate.

In 1981, callosobruchus acid [(\(\text{E}\)-3,7-dimethyl-2-octene-1,8-dioic acid (1))] was isolated and identified by Yamamoto et al. as the bioactive component of the copulation release pheromone of the azuki bean weevil, Callosobruchus chinensis.\(^1\) Since then, there have appeared two syntheses of \((\pm)-1\),\(^2,3\) a synthesis of both the enantiomers of \(1,4\) a synthesis of \((\text{S})-1,5\) and a synthesis of \((\text{R})-1.6\) Our syntheses of \((\text{R})\)- and \((\text{S})\)-1 revealed both of them to be bioactive.\(^5\) The absolute configuration of natural 1 still remains obscure.

In this paper, we report a new synthesis of \((\text{R})\)-1 by starting from methyl (\(\text{R}\))-3-carboxybutanoate (2). Half-ester 2 was prepared from enantiomerically pure (\(\text{R}\))-\((+)\)-methylsuccinic acid, which was obtained by the microbial transformation of squalene.\(^7\) Our synthetic scheme is shown in Fig. 1.

Starting half-ester 2, kindly provided by Mr. Tsukubokura of Nippon Oil Co., was reduced with borane-dimethyl sulfide complex to give alcohol 3a, which was converted to corresponding 3-butyldimethylsilyl (TBS) ether 3b. Reduction of ester 3b with diisobutylaluminum hydride afforded alcohol 4a. Corresponding tosylate 4b was treated with sodium iodide to give iodide 5. Chain-elongation of 5 by acetoacetic ester synthesis yielded methyl ketone 7 via 6. Ketone 7 was submitted to the Horner-Wittig condensation to give (\(\text{E}\))-ester 8a as the major product (\(\text{E}: \text{Z} = 3:1\)). Removal of the TBS protective group of 8a gave 8b, which was oxidized with chromic acid to give a carboxylic ester 8c. Finally, acid hydrolysis of this ester furnished (\(\text{R}\))-callosobruchus acid (1) as crystals, mp 91—92°C, [\(\alpha\]D]20

9.4° (CHCl₃). Its IR and 1H-NMR spectra were identical to those reported previously.\(^4\) The overall yield of \((\text{R})\)-1 from (\(\text{R}\))-2 was 2.8% in 11 steps.

In conclusion, methyl (\(\text{R}\))-3-carboxybutanoate (2) was shown to be a useful non-racemic chiral building block for enantioselective syntheses.

Experimental

All boiling point and melting point values are uncorrected. IR spectra were measured as films for oils or as KBr discs for solids with a JASCO IRA-102 spectrometer. 1H-NMR spectra were recorded with TMS as an internal standard at 90MHz on a Jeol JMN EX-90 spectrometer, or at 300MHz on a Bruker AC-300 spectrometer. 13C-NMR spectra were measured at 22.4MHz with a Jeol JMN EX-90 spectrometer, and optical rotation values were measured with a Jasco DIP-371 polarimeter. Merck Kieselgel 60 Art 7734 was used for column chromatography, and precoated plates of Merck Kieselgel 60 F₂₅₄ for TLC analysis.

Methyl (\(\text{R}\))-4-hydroxy-3-methylbutanoate (3a). A solution of borane-methyl sulfide complex (6.24ml, 10.0×w as BH₂, 62.4mmol) was added dropwise to a stirred and cooled solution of 2 (4.56g, 31.2mmol) in dry THF (80ml) at 0°C under argon. The temperature was gradually raised to room temperature, and stirring was continued for a further 4 h. The reaction was quenched by adding methanol (80ml × 3), and the mixture was concentrated in vacuo. The residual 3a was employed for the next step without further purification, n(CH₃)₂CO 1.4300; [\(\alpha\]D]20 +7.1° (c = 1.18, CHCl₃); IR νmax (film) cm⁻¹: 3400 (s, O–H), 1730 (s, C = O), 1170 (m, C–O), 1045 (m, C–O); 1H-NMR δ (90MHz, CDCl₃): 0.97 (3H, d, J = 6.4Hz), 1.64–2.60 (4H, m), 3.30–3.60 (2H, m), 3.69 (3H, s).

Methyl (\(\text{R}\))-4-(1-butyldimethylsilyloxy)-3-methylbutanoate (3b). TBSCl (9.41g, 62.4mmol) was added to a stirred solution of 3a (7.93g, 32.2 mmol) and imidazole (8.50g) in DMF (40ml), and the mixture was stirred for 15 h at room temperature. The reaction was quenched by adding ice-cooled water and stirring was continued for 2 h. The mixture was then extracted with ether. The ethereal solution was washed with brine, dried with magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel (150g), and elution with n-hexane-EtOAc (30:1) gave an oil, which was distilled to give 6.26g (82% from 2) of 3b, bp 88–90°C (10.5mmHg), ν(CH₃) 14349; [\(\alpha\]D]20 +6.8° (c = 1.08, CHCl₃); IR νmax (film) cm⁻¹: 1740 (s, C = O), 1250 (m), 1170 (m, C–O), 1091 (s, C–O), 835 (s); 1H-NMR δ (90MHz, CDCl₃): 0.03 (6H, s), 0.89 (9H, s), 0.94 (3H, d, J = 3.9Hz), 1.95–2.60 (3H, m), 3.38–3.54 (2H, m), 3.67 (3H, s). Anal. Found: C, 58.92; H, 10.73. Caled. for C₁₉H₃₅O₄Si: C, 58.49; H, 10.64%.

Fig. 1. Synthesis of Callosobruchus Acid (1).

Reagents: (a) BH₃–Me₃S·THF. (b) TBSCl, imidazole, DMF (82% from 2). (c) (iso-But₂)₂AlH, toluene (91%). (d) TiCl₄, CH₂N₂H₂ (92%). (e) Na, NaHCO₃, Me₂CO (87%). (f) MeCO₂H₂CO₂Et, NaOEt, EtOH (60%). (g) Ba(OH)₂, EtOH/H₂O (65%). (h) (MeO₂P)₂CH(CH₂)₂Me, n-BuLi, THF (38% of 8a and 12% of its (Z)-isomer). (i) AcO/THF/H₂O (90%). (j) CrO₃ (56%). (k) dil. HCl, heat (84%).

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Methyl (RE)-3-(butyl(dimethyl)silyloxy)-3,7-dimethyl-2-octenoate (8a). A mixture of n-Buli (1.62 mol in n-hexane, 0.69 ml, 1.12 mmol) was added to a stirred and cooled solution of trimethyl phosphonoacetate (205 mg, 1.13 mmol) in dry THF (4 ml) at 0°C under argon, and the mixture was stirred for 30 min at 0°C. To this was then added dropwise a solution of 7 (145 mg, 0.56 mmol) in dry THF (1 ml). Stirring was continued for 18 h at 0°C, and the mixture was poured into water (15 ml) and extracted with ether (25 ml x 3). The ethereal solution was washed with saturated brine, magnesium sulfate and concentrated in vacuo to give 180 mg of 8a as a mixture of E and Z isomers (3:1). The residue was purified by prep. TLC (developing with n-hexane–ether (10:1) on Merck silica gel (E, Rf = 0.45–0.69, Z, Rf = 0.69–0.73) to give 66 mg of 8a (38%), n<sub>D</sub> = 1.4550; [α]<sub>D</sub> +4.8° (c = 1.16, CHCl<sub>3</sub>); IR ν<sub>rnm</sub> (film) cm<sup>-1</sup> = 1730 (C = O), 1560 (C = C), 1230 (m), 1160 (s, C = O), 1100 (m, C = O), 845 (s); 1H-NMR δ<sub>H</sub> (90 MHz, CDCl<sub>3</sub>) = 0.03 (6H, s), 0.75–3.48 (12H, m), 1.75–1.86 (1H, m), 2.20–2.27 (2H, m), 2.16 (3H, s), 3.40 (2H, d, J = 5.9 Hz), 3.68 (3H, s), 5.67 (1H, br. s). Anal. Found: C = 64.95; H = 10.84. Calcd. for C<sub>21</sub>H<sub>33</sub>O<sub>5</sub>S: C = 64.92; H = 10.90.

Methyl (RE)-8-hydroxy-3,7-dimethyl-2-octenoate (8b). A mixture of 8a (66.2 mg, 0.21 mmol) in acetic acid (1 ml), THF (1 ml) and water (1 ml) was stirred for 2h at 40°C. It was then neutralized by adding a sat. sodium hydrogen carbonate solution (10 ml) and extracted with ether. The ethereal solution was washed with brine, dried with magnesium sulfate and concentrated in vacuo to give 38 mg of 8b [n<sub>D</sub> = 1.4730; [α]<sub>D</sub> +11.3° (c = 0.65, CHCl<sub>3</sub>); IR ν<sub>rnm</sub> (film) cm<sup>-1</sup> = 3400 (s, O–H), 1715 (s, C = O), 1640 (m, C = C), 1220 (m), 1150 (m, C = O); 1H-NMR δ<sub>H</sub> (90 MHz, CDCl<sub>3</sub>) = 0.92 (3H, d, J = 6.6 Hz), 1.05–1.80 (6H, m), 2.03–2.28 (2H, m), 2.16 (3H, s), 3.47 (2H, d, J = 6.0 Hz), 3.60 (3H, s), 5.67 (1H, br. s). Anal. Found: C = 65.77; H = 10.10. Calcd. for C<sub>15</sub>H<sub>20</sub>O<sub>5</sub>S: C = 65.79; H = 10.07.

(R,E)-7-Methoxy-carboxyl-2,5-dimethyl-6-heptenoic acid (8c). A chronic acid solution was prepared from sodium dichromate (20.0 g, 67.1 mmol) which was mixed with 95% sulfuric acid (27.7 g, 268 mmol) and diluted with water to make up 100 ml in total volume. To a stirred and cooled solution of 8b (25 mg, 0.13 mmol) in ether (2 ml) was added the neutral chronic acid solution (0.71 ml) with ice-cooling. After stirring for 5 min the reaction was quenched by adding 2-propanol. The mixture was poured into brine (10 ml) and extracted with ether. The ethereal solution was dried with magnesium sulfate and concentrated in vacuo. The residue was further purified by prep. TLC (developing with n-hexane–ether (1:1) on Merck silica gel; R<sub>f</sub> = 0.41–0.53 to give 38 mg of 8c [n<sub>D</sub> = 1.4732; [α]<sub>D</sub> +11.6° (c = 0.75, CHCl<sub>3</sub>); IR ν<sub>rnm</sub> (film) cm<sup>-1</sup> = 3700–2300 (s, br. O–H), 1720–1690 (s, br. C = O), 1640 (m, C = C), 1220 (m), 1150 (m, C = O); 1H-NMR δ<sub>H</sub> (90 MHz, CDCl<sub>3</sub>) = 1.20 (3H, d, J = 7.0 Hz), 1.35–1.83 (4H, m), 2.00–2.28 (2H, m), 2.16 (3H, s), 3.69 (3H, s), 5.65 (1H, br. s). Anal. Found: C = 61.15; H = 8.48. Calcd. for C<sub>16</sub>H<sub>18</sub>O<sub>5</sub>S: C = 61.66; H = 8.47.

(R,E)-3,7-Dimethyl-2-octene-1,8-dioic acid (1). A mixture of ester 8e (23 mg, 0.11 mmol) and 1n HCl (1 ml) was stirred and heated under reflux for 2h. After cooling, the mixture was extracted with ether. The ether solution was extracted with 1.5% NaOH (5 ml x 3). This basic ag. solution was acidified with 6n HCl to pH 4 and then extracted with ether. The ethereal solution was washed with brine, dried with magnesium sulfate and concentrated in vacuo to give 23 mg of crude 1. This was further purified by prep. TLC (developing with n-hexane–ether (1:1) on Merck silica gel; R<sub>f</sub> = 0.29–0.45 to give 18 mg (84%) of 1. Further recrystallization from n-hexane–ether yielded 8 mg of pure 1, mp 91–92°C (lit. mp 91–92°C), [α]<sub>D</sub> = -9.4° (c = 0.25, CHCl<sub>3</sub>); [α]<sub>D</sub> = -11.75° (c = 1.105, CHCl<sub>3</sub>); IR ν<sub>rnm</sub> (BrCN) cm<sup>-1</sup> = 3300–2200 (br. s, Br – O, H), 1690 (m, C = O), 1635 (m, C = C), 1420 (m), 1295 (m), 1240 (m), 960 (m); 1H-NMR δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) = 1.20 (3H, d, J = 7.0 Hz), 1.41–1.61 (3H, m), 1.65–1.72 (1H, m), 2.16 (3H, s), 2.10–2.21 (2H, d, J = 7.2 Hz), 2.42–2.52 (1H, s), 3.03–3.48 (4H, m), 17.3–19.2, 21.5, 33.2, 39.5, 41.0, 115.4, 162.9, 172.3, 183.0. Anal. Found: C = 69.42; H = 8.07. Calcd. for C<sub>16</sub>H<sub>18</sub>O<sub>4</sub>S: C = 69.58; H = 8.05.

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