Efficient synthesis of methyl (+)-(1*S*,3*R*)-3-(2,2-dimethoxycarbonylethyl)-2,2-dimethylcyclopropane-1-carboxylate from (+)-4α-acetyl-2-carene

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The title compound is synthesized from (+)-4α-acetyl-2-carene in four steps.

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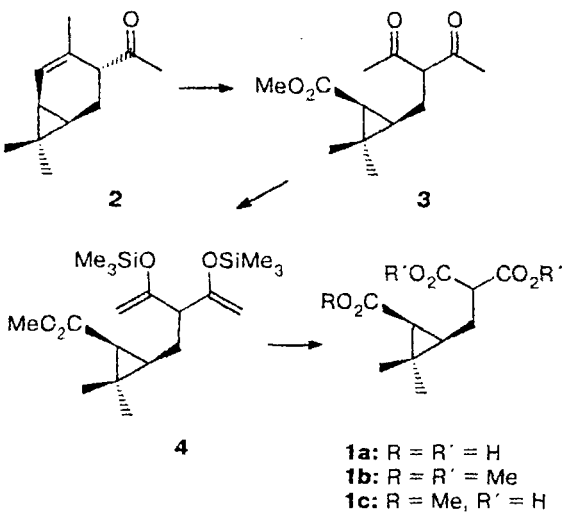
(+)-(1*S*,3*R*)-3-(2,2-Dicarboxyethyl)-2,2-dimethylcyclopropane-1-carboxylic acid (**1a**) was patented[1] as an acid component in the synthesis of a series of insecticides. However, the patented procedure for its synthesis is difficult to reproduce. We developed an efficient method of preparation of trimethyl ester **1b** from available[2] (+)-4α-acetyl-2-carene **2** (Scheme 1).

Scheme 1



Ozonolysis of compound **2** resulted in the known[3] ester **3**, which was silylated under the standard conditions of kinetic control[4] to give methyl (+)-(1*S*,3*R*)-3-[2,2-bis(1-trimethylsilyloxyvinyl)ethyl]-2,2-dimethylcyclopropane-1-carboxylate (**4**) in 85% yield. The structure of the latter was confirmed by a combination of spectroscopic data. Ozonolysis of ester **4** afforded compound **1c**, which was characterized in the form of trimethyl ester **1b**. Note that acid **1a** has been described earlier,[1] but its spectral parameters have not been reported.

Experimental

Specific rotation was measured on a Perkin—Elmer 141 polarimeter. IR spectra were recorded on Specord 74-1 and UR-20 instruments. ^{1}H NMR spectra were recorded on Tesla BS-487 and Tesla BS-567 spectrometers, and ^{13}C NMR spectra were recorded on a JEOL FX-90Q instrument (22.5 MHz) in $CDCl_3$ with Me_4Si as the internal standard. Chemical shifts are referenced to the δ scale. Mass spectra were obtained on an MKh-1320 spectrometer (direct inlet into the ion source, ionizing voltage 70 eV).

(+)-4α-Acetyl-2-carene (2) was prepared as described earlier.[2] n_D^{20} 1.4869, $[\alpha]_D^{20}$ +365.5° (neat) (*cf.* Ref. 2: n_D^{20} 1.4848, $[\alpha]_D^{20}$ +402°).

Methyl (+)-(1*S*,3*R*)-3-(2,2-diacetylethyl)-2,2-dimethylcyclopropane-1-carboxylate (3) was obtained according to the known procedure,[3] n_D^{20} 1.4681, $[\alpha]_D^{20}$ +19.7° (*c* 3.0, $CHCl_3$).

Methyl (+)-(1*S*,3*R*)-3-[2,2-bis(1-trimethylsilyloxyvinyl)-ethyl]-2,2-dimethylcyclopropane-1-carboxylate (4). Pr^i_2NH (5 g, 0.049 mol) and a 2.45 *M* solution of Bu^nLi (20.6 mL) in hexane were added with cooling (−18 °C) to 100 mL of anhydrous THF in an atmosphere of argon. The reaction mixture was stirred for 10 min and then cooled to −78 °C. A solution of dioxo ester **3** (6.48 g, 0.027 mol) in 20 mL of THF was added dropwise, and stirring was continued for 20 min. After addition of Me_3SiCl (12 mL, 0.094 mol) and 1-h stirring, the reaction mixture was warmed to ~20 °C, stirred for 2 h, and poured into dry pentane (150 mL). The precipitate that formed was filtered off, and the filtrate was concentrated to give ester **4** (8.95 g, 85%) as a yellow liquid, b.p. 120—125 °C (1 Torr), $[\alpha]_D^{20}$ +1.65° (*c* 3, pentane). IR (CCl_4), ν/cm^{-1}: 1020, 1265 (C—O—$SiMe_3$); 1375, 1380 (C—Me_2); 1665 (C=CH_2); 1715 (CO_2). ^{1}H NMR (60 MHz, CCl_4), δ: 0.03—0.23 (m, 18 H, $(SiMe_3)_2$); 1.1, 1.18 (both s, 6 H, C—Me_2); 1.35—1.44 (m, 1 H, HC(3)); 1.76—2.35 (m, 3 H, CH_2, HC(1)); 3.59 (s, 3 H, CO_2Me); 3.55—3.65 (m, 1 H, =C—CH); 4.06—4.31 (m, 4 H, $(C=CH_2)_2$). MS, *m/z*: 384 $[M]^+$, 369 $[M - Me]^+$, 325 $[M - CO_2Me]^+$, 73 $[SiMe]^+$ (100%).

Methyl (+)-(1*S*,3*R*)-3-(2,2-dimethoxycarbonylethyl)-2,2-dimethylcyclopropane-1-carboxylate (1b). Compound **4** (8.0 g, 0.02 mol) was dissolved in a mixture of anhydrous MeOH (75 mL) and CH_2Cl_2 (30 mL). The solution was cooled to −78 °C, and an ozone—oxygen mixture was passed through until blue coloration. The reaction mixture was purged with nitrogen, stirred at the same temperature for 2 h following

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addition of Me_2S (12 mL), and left at ~20 °C for 16 h. Then it was diluted with 200 mL of ether and washed with brine (100 mL) and 10% KOH (3×50 mL). The combined aqueous layer was acidified with cooling (3—5 °C) with 10% H_2SO_4 to pH 4, and the products were extracted with ether (3×50 mL). The ethereal extract was washed with brine (3×30 mL) and dried with anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. The yellow oil that formed (5.6 g) was identified as monoester **1c**. IR (CCl_4), ν/cm^{-1}: 1380, 1383 (C—Me_2); 1725 (CO_2Me); 1710, 2560—3000 (CO_2H). A solution of **1c** in 50 mL of ether was treated with an ethereal solution of CH_2N_2 at ~20 °C, the solvent was removed, and the residue (5.9 g) was chromatographed on SiO_2 (L 40/100, 80 g) in a hexane—ethyl acetate (4 : 1) system to give ester **1b** as a colorless oil that turns yellow with time. Yield 4.24 g (80%), $[\alpha]_D^{20}$ +5.66° (*c* 2.12, $CHCl_3$). Found (%): C, 57.23; H, 7.38. $C_{13}H_{20}O_6$. Calculated (%): C, 57.35; H, 7.40. IR (CCl_4), ν/cm^{-1}: 1380, 1385 (C—Me_2); 1720, 1730 (CO_2Me). ^1H NMR (100 MHz, $CDCl_3$), δ: 1.15, 1.21 (both s, 6 H, Me_2); 1.43—1.55 (m, 2 H, HC(1), HC(3)); 2.0—2.4 (m, 2 H, CH_2); 3.2—3.4 (m, 1 H, $\underline{C}H(CO_2Me)_2$); 3.65, 3.67, 3.74 (all s, 9 H, CO_2Me). ^{13}C NMR, δ: 171.86, 169.83, 169.63, 52.45, 51.58, 51.20, 41.72, 30.45, 28.77, 28.44, 25.57, 23.14, 14.14. MS, *m/z*: 272 $[M]^+$, 257 $[M - Me]^+$, 241 $[M - COMe]^+$, 240 $[M - MeOH]^+$, 213 $[M - CO_2Me]^+$, 208 $[M - 2\ MeOH]^+$, 199 $[M - CH_2CO_2Me]^+$.

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