A New Approach to the Synthesis of Methyl (1*S*)-*cis*-3-(2-Acetoxyalkyl/2-Hydroxyalkyl/2-Oxoalkyl)-2,2-dimethylcyclopropanecarboxylates from (+)-3-Carene

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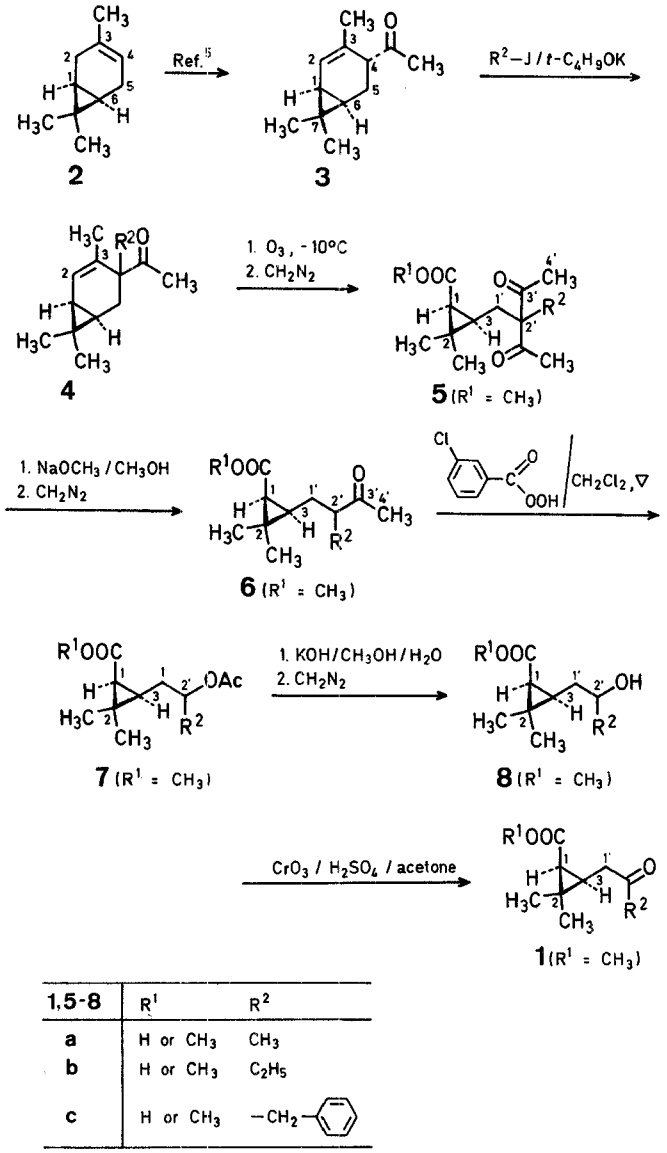
Methyl (1*S*)-*cis*-2,2-dimethyl-3-(2-oxopropyl)-cyclopropanecarboxylate (**1a**) is an important intermediate for the synthesis[1,2] of (–)-*cis*-chrysanthemic acid which can in turn be converted into (+)-(1*R*)-*trans*-chrysanthemic acid[3], a component of natural pyrethrins. Other related esters such as methyl (1*S*)-*cis*-3-(2-acetoxyalkyl/2-hydroxyalkyl/2-oxoalkyl)-2,2-dimethylcyclopropanecarboxylates are useful in the synthesis of (1*R*)-*trans*-pyrethroids[4].

We report here a facile five-step synthesis of compound **1a** and other related ketoesters (**1b, c**) from (+)-3-carene (**2**) via (+)-4α-acetyl-2-carene (**3**)[5]. Base-catalyzed methylation of compound **3** with methyl iodide/potassium *t*-butoxide affords 4-acetyl-4-methyl-2-carene (**4a**) which on ozonolysis followed by oxidative work-up is converted into (1*S*)-*cis*-3-(2,2-diacetylpropyl)-2,2-dimethylcyclopropanecarboxylic acid (**5a**, $R^1 = H$). This acid is esterified with diazomethane to ester **5a** ($R^1 = CH_3$) and characterized as such. Ester **5a** ($R^1 = CH_3$) which possesses a β-diketone moiety undergoes *C*–*C* and ester cleavage; subsequent esterification with diazomethane affords methyl(1*S*)-*cis*-2,2-dimethyl-3-(2-methyl-3-oxobutyl)-cyclopropanecarboxylate (**6a**, $R^1 = CH_3$). Baeyer-Villiger oxidation of **6a** ($R^1 = CH_3$) yields (1*S*)-*cis*-3-(2-acetoxypropyl)-2,2-dimethylcyclopropanecarboxylate (**7a**, $R^1 = CH_3$). Hydrolysis of **7a** at room temperature, followed by esterification with diazomethane gives methyl (1*S*)-*cis*-3-(2-hydroxypropyl)-2,2-dimethylcyclopropanecarboxylate (**8a**, $R^1 = CH_3$) which is converted into the title compound **1a** by Jones' oxidation. Analogous sequences afford the ketoesters **1b** and **1c**.



1,5-8	R^1	R^2
a	H or CH_3	CH_3
b	H or CH_3	C_2H_5
c	H or CH_3	$-CH_2-C_6H_5$

(+)-4-Acetyl-4-methyl-2-carene (4a); Typical Procedure:

To an ice-cooled and stirred solution of potassium *t*-butoxide (8.4 g, 75 mmol) and (+)-4α-acetyl-2-carene[5] (**3**; 8.9 g, 50 mmol) in *t*-butanol (100 ml), methyl iodide (10.65 g, 75 mmol) is added in one portion and the mixture stirred at 0 °C for 2 h and at room temperature for 24 h. The mixture is then filtered, *t*-butanol removed by distillation under reduced pressure, and the residue diluted with water (100 ml), extracted with ether (4 × 50 ml), and evaporated. The product is column-chromatographed on silica gel (elution with benzene/petroleum ether 1/4 and benzene/petroleum ether 1/1, successively) to give **4a**; yield: 6.3 g (65%); b.p. 102–107 °C/0.1 torr (see table); $[\alpha]_D^{28}$: + 133.5° (c = 2.9, chloroform).

^{1}H-N.M.R. (CCl_4/TMS_{int}): δ = 1.00, 1.16 (s, 9H, 4-CH_3 and 7,7-di-CH_3); 1.56 (s, 3H, 3-CH_3); 2.03 (s, 3H, CO-CH_3); 5.5 ppm (m, 1H, 2-H).

Methyl (1*S*)-*cis*-3-(2-Acetyl-2-methyl-3-oxobutyl)-2,2-dimethylcyclopropanecarboxylate (5a); Typical Procedure:

A stream of ozonised oxygen is passed through a cooled (–10 °C) solution of (+)-4-acetyl-4-methyl-2-carene (**4a**; 4.8 g, 25 mmol) in ethyl acetate (100 ml) until absorption is completed. To the ozonide solution thus obtained, a solution of chromium(VI) oxide (2.6 g, 26 mmol) in conc. sulfuric acid (2.2 ml) is added dropwise and the mixture is stirred for 2 h at 0 °C. It is then washed with water (50 ml) and the organic layer is separated and extracted with aqueous 10% sodium carbonate (50 ml). The aqueous extract is acidified with dilute hydrochloric acid and extracted with ether (2 × 75 ml). The ether extract is washed with water (2 × 20 ml) and a 0.5 molar solution of diazomethane in ether (80 ml) is added for esterification.

Table. Compounds **1** and **4–8** prepared

Educt	Product	Yield[a] [%]	b.p./torr[b] [°C]	$[\alpha]_D^{28}$[c] (c)	Molecular Formula[d]	M.S. *m/e* (M^+)
3[5]	**4a**	65	102–107°/ 0.2	+133.5° (2.9)	$C_{13}H_{20}O$ (192.2)	192
3	**4b**	69	110–115°/ 0.35	+106.3° (4.5)	$C_{14}H_{22}O$ (206.3)	206
3	**4c**	70	145–150°/ 0.3	+140.4° (2.4)	$C_{19}H_{24}O$ (268.3)	268
4a	**5a**	52	118–120°/ 0.3	−0.4° (1.55)	$C_{14}H_{22}O_4$ (254.3)	254
4b	**5b**	50	127–132°/ 0.2	+7.2° (2.4)	$C_{15}H_{24}O_4$ (268.3)	268
4c	**5c**	47	175–180°/ 0.2	+4.8° (1.86)	$C_{20}H_{26}O_4$ (330.4)	330
5a	**6a**	75	100–105°/ 0.13	+28.5° (1.81)	$C_{12}H_{20}O_3$ (212.2)	212
5b	**6b**	78	115–120°/ 0.2	+22.3° (1.09)	$C_{13}H_{22}O_3$ (226.3)	226
5c	**6c**	77	150–155°/ 0.13	+15.8° (1.14)	$C_{18}H_{24}O_3$ (288.3)	288
6a[1]	**7a**	65	105–110°/ 0.2	+21.1° (1.45)	$C_{12}H_{20}O_4$ (228.2)	228
6b	**7b**	64	110–115°/ 0.15	+19.2° (1.35)	$C_{13}H_{22}O_4$ (242.3)	242
6c	**7c**	59	150–155°/ 0.13	+0.5° (1.08)	$C_{18}H_{24}O_4$ (304.3)	304
7a[1]	**8a**	67	115–120°/ 0.2	+5.2° (1.2)	$C_{10}H_{18}O_3$ (186.2)	186
7b	**8b**	65	110–115°/ 0.15	+3.8° (1.10)	$C_{11}H_{20}O_3$ (200.2)	200
7c	**8c**	62	160–165°/ 0.13	+4.6° (1.4)	$C_{16}H_{22}O_3$ (262.3)	262
8a[1]	**1a**[1,2]	63	90–95°/ 0.15	+35.0° (2.32)	$C_{10}H_{16}O_3$ (184.2)	184
8b	**1b**	65	100–105°/ 0.15	+33.6° (3.8)	$C_{11}H_{18}O_3$ (198.2)	198
8c	**1c**	61	140–145°/ 0.15	+9.0 (1.54)	$C_{16}H_{20}O_3$ (260.3)	260

[a] Yield of pure isolated product.
[b] Bath temperature.
[c] In chloroform.
[d] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.38; H, ±0.37. Exception: **3**; C, ±0.49.

The excess diazomethane is destroyed with acetic acid (0.72 g) in ether (5 ml) and the solvent is evaporated. The crude product is column-chromatographed on silica gel using benzene as eluent to give pure **5a**; yield: 3.3 g (52%); b.p. 118–120°C/0.3 torr; $[\alpha]_D^{28}$: −0.4 (*c* = 1.55, chloroform).

^{1}H-N.M.R. (CCl_4/TMS_{int}): δ = 0.83 (m, 1H, 3-H); 1.16 (s, 6H, 2,2-di-CH_3); 1.25 (s, 3H, 2′-CH_3); 1.40 (d, 1H, *J* = 8Hz, 1-H); 2.05 (s, 6H, 2 CO-CH_3); 2.16 (m, 2H, 1′,1′-H_2); 3.60 ppm (s, 3H, OCH_3).

Methyl (1*S*)-*cis*-2,2-Dimethyl-3-(2-methyl-3-oxobutyl)-cyclopropanecarboxylate (6a); Typical Procedure:

A solution of compound **5a** (2.5 g, 10 mmol) in methanol (50 ml) containing sodium methoxide (1.6 g, 30 mmol) is refluxed for 6 h, methanol removed under reduced pressure, and the residue diluted with water (25 ml), acidified with dilute hydrochloric acid, and extracted with ether (4 × 25 ml). The ether layer is washed with water (2 × 20 ml) and the product esterified by adding, at 0°C, a 0.5 molar solution of diazomethane in ether (30 ml, 15 mmol). The solvent is evaporated and the product column-chromatographed on silica gel using petroleum ether/benzene (1/1) as eluent to give **6a**; yield: 1.6 g (75%); b.p. 100–105°C/0.13 torr; $[\alpha]_D^{28}$: +28.5° (*c* = 1.81, chloroform).

^{1}H-N.M.R. (CCl_4/TMS_{int}): δ = 1.03 (d, 3H, *J* = 7Hz, 2′-CH_3); 1.12, 1.14 (s, 6H, 2,2-di-CH_3); 1.33 (d, 1H, *J* = 8Hz, 1-H); 2.00 (s, 3H, CO-CH_3); 2.16–2.43 (m, 1H, 2′-H); 3.48 ppm (s, 3H, OCH_3).

Methyl (1*S*)-*cis*-3-(2-Acetoxypropyl)-2,2-dimethylcyclopropanecarboxylate (7a); Typical Procedure:

To a solution of compound **6a** (1.5 g, 7.0 mmol) in dry dichloromethane (25 ml), 3-chlorobenzoperoxoic acid, (1.8 g, 10.3 mmol) is added and the mixture is refluxed for 6 h, then cooled, and filtered. The filtrate is washed with 10% aqueous sodium carbonate (10 ml) and water (2 × 10 ml), and evaporated. The product is chromatographed on alumina (activity II) and eluted with petroleum ether/benzene (4/1) to give **7a**; yield: 1.0 g (65 %); b.p. 105–110°C/0.2 torr; $[\alpha]_D^{28}$ + 21.1° (*c* = 1.45, chloroform).

^{1}H-N.M.R. (CCl_4/TMS_{int}): δ = 0.96–1.20 (m, 9H, 2,2-di-CH_3 and 2′-CH_3); 1.35 (d, 1H, *J* = 8Hz, 1-H); 1.78 (t, 2H, *J* = 6Hz, 1′,1′-H_2); 1.90 (s, 3H, O-CO-CH_3); 3.46 (s, 3H, OCH_3); 4.43–4.85 ppm (m, 1H, 2′-H).

Methyl (1*S*)-*cis*-3-(2-Hydroxypropyl)-2,2-dimethylcyclopropanecarboxylate (8a); Typical Procedure:

A solution of potassium hydroxide (0.6 g, 10.7 mmol) in water (2 ml) is added to a solution of compound **7a** (0.82 g, 3.6 mmol) in methanol (10 ml) and the mixture is stirred for 24 h at room temperature. Methanol is then distilled off, the residue is diluted with water (10 ml), and the solution acidified with dilute hydrochloric acid and extracted with ether (3 × 25 ml). The ether extract is washed with water (2 × 25 ml) and evaporated. The residual product is esterified by the addition at 0°C of a 0.5 molar solution of diazomethane in ether (12 ml, 5.4 mmol). The solvent is evaporated and the product distilled in vacuo; yield: 0.45 g (67%); b.p. 115–120°C/0.2 torr; $[\alpha]_D^{28}$: +5.2° (*c* = 1.2, chloroform).

^{1}H-N.M.R. (CCl_4/TMS_{int}): δ = 1.11 (d, 3H, *J* = 5Hz, 2′-CH_3); 1.16 (s, 6H, 2,2-di-CH_3); 1.71 (t, 2H, *J* = 6Hz, 1′,1′-H_2); 2.06 (s, 1H, OH); 3.55 ppm (s, 3H, OCH_3).

Methyl (1*S*)-*cis*-2,2-Dimethyl-3-(2-oxopropyl)-cyclopropanecarboxylate (1a); Typical Procedure:

A solution of chromium(VI) oxide (0.5 g, 5.0 mmol) in conc. sulfuric acid (0.5 ml) is added dropwise to a stirred solution of compound **8a** (0.75 g, 4.02 mmol) in acetone (5 ml) until a pale orange colour persists. The mixture is stirred for 3 h at 0°C, then diluted with water (20 ml), and extracted with ether (3 × 25 ml). The ether layer is separated, washed with water (2 × 15 ml), and evaporated. The residual product is column-chromatographed on silica gel using petroleum ether/benzene (1/1) as eluent to give **1a**; yield: 0.46 g (63 %); b.p. 90–95°C/0.15 torr; $[\alpha]_D^{28}$ + 35° (*c* = 2.32, chloroform).

^{1}H-N.M.R. (CCl_4/TMS_{int}): δ = 1.13, 1.24 (s, 6H, 2,2-di-CH_3); 1.45 (m, 2H, 1-H and 3-H); 2.10 (s, 3H, CO-CH_3); 2.80 (d, 2H, *J* = 6Hz, 1′,1′-H_2); 3.60 ppm (s, 3H, OCH_3).

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