A Facile Synthesis of Methyl 2-Alkyl-2-alkenoates

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In the course of synthetic studies on highly oxygenated cyclohexane derivatives[1], we demonstrated the utility of the retro-Diels-Alder reaction in the synthesis of epoxycyclohexenones, quinone epoxides, and some natural products[2]. In this communication, we describe a facile synthesis of the title compounds starting from 6,6-dimethylfulvene and methyl acrylate; the synthesis involves a retro-Diels-Alder reaction. Other methods for the synthesis of methyl 2-alkyl-2-alkenoates are complicated multistep sequences[3,4].

The Diels-Alder adduct **1** is prepared from dimethylfulvene and methyl acrylate, deprotonated with lithium diisopropylamide in tetrahydrofuran at −70 to −20°, and alkylated with an alkyl halide. The alkylated product **2** is purified by chromatography on silica gel and subjected to the thermal retro-Diels-Alder reaction. In the case of **2b** ($R = C_2H_5$), the stereochemistry (i.e., the *exo* position of the ethyl group) was confirmed by hydrolysis of the ester group and conversion of the free acid **3**[6] to the phenylsulfenyllactone **4**[5].

For thermal cleavage, the alkylated products **2** are dissolved in diphenyl ether and the products **5** are distilled directly from this solution at 170–190° bath temperature. A small quantity of dimethylfulvene present in the distillate is removed by treatment with a small amount of maleic anhydride and redistillation to give the pure products **5**.

The present method provides a facile synthesis of methyl 2-alkyl-2-alkenoates (**5a–f**). It should be noted that compound **5e** has hitherto not been obtained by other methods[3]. The method might also be applicable to the synthesis of 2-alkylcrotonolactones which are useful intermediates for the preparation of some natural products[10].

The melting points are uncorrected. The I.R. spectra were measured on a Hitachi I.R. Spectrophotometer Model 285. The ^{1}H-N.M.R. spectra were recorded on a Hitachi 90 MHz High Resolution Spectrometer Model R-22. The microanalyses were performed by Faculty of Pharmaceutical Sciences, Hokkaido University.

Isopropylidene-2-methoxycarbonyl-bicyclo[2.2.1]hept-5-ene (1):
A solution of freshly distilled methyl acrylate (8 g) and dimethylfulvene (8 g) in benzene (20 ml) is heated at 60–70° for 18 h under nitrogen. The solvent is then evaporated and the residue is purified by column chromatography on silicic acid using hexane/ethyl acetate (19:1) as eluent; yield: 7.5 g (52%) of **1** as an oil.

^{1}H-N.M.R. (CCl_4): $\delta = 6.60$–6.30 (m, 2H, $=CH$); 3.60, 3.55 (each s, 3H, $-OCH_3$); 3.50, 3.35 (each m, 2H, $>CH-$); 2.20–2.80 (m, 1H, $-C\underline{H}-COOCH_3$); 1.60, 1.50 (each s, 6H, $=C-CH_3$); 1.20–2.00 ppm (m, 2H, $-CH_2-$). On the basis of these data, compound **1** is an *endo*/*exo* mixture.

7-Isopropylidene-2-*endo*-methoxycarbonyl-2-*exo*-methyl-bicyclo[2.2.1]hept-5-ene (2a); Typical Procedure:
In a three-neck flask fitted with stirrer, gas inlet, and dropping funnel, a 15% solution (13 ml) of butyllithium in hexane is added with stirring to a mixture of diisopropylamine (5 ml) and freshly distilled tetrahydrofuran (35 ml) at −70° under nitrogen. A solution of compound **1** (4.6 g, 24 mmol) in tetrahydrofuran (2 ml) is gradually added with stirring. After 5 min, methyl iodide (4 g, 28 mmol) is added and stirring is continued for additional 2 h while the temperature is allowed to slowly rise to −20°. The reaction mixture is then quenched with 1.2 normal hydrochloric acid (30 ml) and extracted with benzene. The organic extract is washed with saturated aqueous sodium chloride and dried with sodium sulfate. The solvent is evaporated and the residual product purified by column chromatography on silicic acid using hexane/ethyl acetate (9:1) as eluent; yield: 3.45 (70%) of **2a** as an oil.

I.R. (film): $\nu_{max} = 1730\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 6.20$–6.35 (m, 2H, $C=CH$); 3.70 (s, 3H, $O-CH_3$); 3.30 (m, 2H, $>CH-$); 1.50–2.00 (m, 2H, $-CH_2-$); 1.65 [s, 6H, $=C(CH_3)_2$]; 1.35 ppm (s, 3H, 2-CH_3).

2-exo-*Ethyl Derivate* (**2b**); yield: 78%.

I.R. (film): $\nu_{max} = 1740\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 6.10$–6.30 (m, 2H, $=CH$); 3.65 (s, 3H, $-OCH_3$); 3.25 (m, 2H, $>CH-$); 1.25–1.95 (m, 4H, $-CH_2-$); 1.60 [2, 6H, $=C(CH_3)_2$]; 0.85 ppm (t, $J = 7$ Hz, 3H, $-CH_3$).

2-exo-*Allyl Derivative* (**2c**); yield: 80%.

I.R. (film): $\nu_{max} = 1740\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 6.10$–6.30 (m, 2H, $-HC=CH-$); 5.50, 5.90 (m, 1H, $=CH$); 4.95–5.05 (m, 2H, $=CH_2$); 3.65 (s, 3H, $-OCH_3$); 3.30 (m, 2H, $>CH-$); 2.56 (ABX, $J_{AB} = 14$ Hz, $J_{AX} = 7$ Hz, $J_{BX} = 7$ Hz, 2H, $-CH_2-$); 1.55 [s, 6H, $=C(-CH_3)_2$]; 1.90 (d, $J = 4$ Hz, 1H, 3-H); 1.50 ppm (dd, $J = 4$ Hz, 11 Hz, 1H, $HC-\underline{H}$).

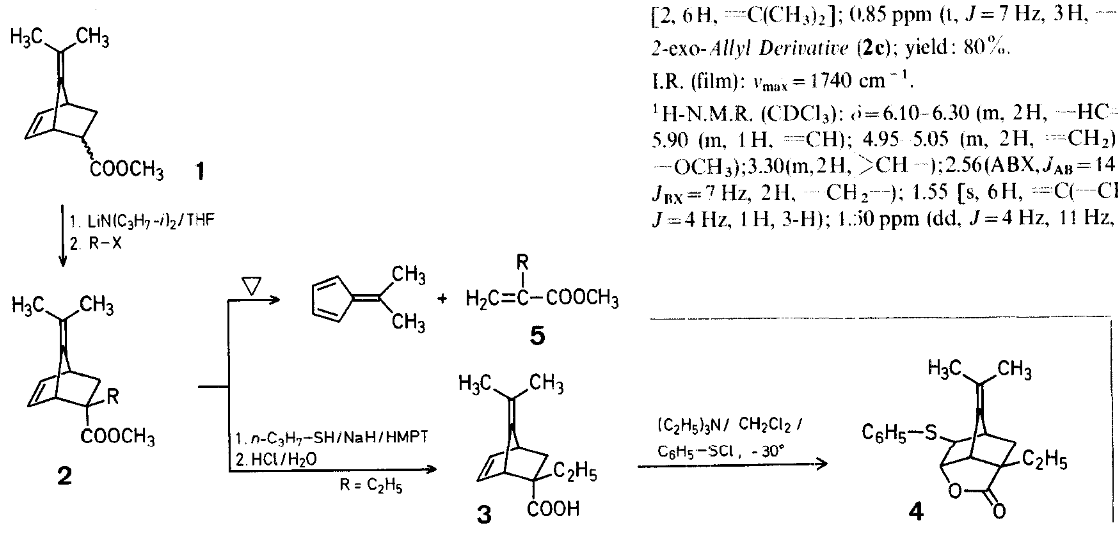

Table. Methyl α-Alkylacrylates (**5**) prepared

5	R—X used	Yield [%]	b.p./ambient pressure	I.R. (film) ν_{max} [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm]
a	$H_3C—J$	60	99–100° (Ref.[7], 100–101°)	1720, 1640	1.90 (3H)
b	$C_2H_5—Br$	58	124–125° (Ref.[8], 122–123°)	1720, 1630	1.10 (3H); 2.30 (2H)
c	$H_2C{=}CH—CH_2—Br$	31	150–151°[a]	1720, 1630	3.00 (2H); 4.95–5.10 (2H); 5.55–6.00 (1H)
d	$H_3C—CH{=}CH—CH_2—Br$	35	181–182°[b]	1720, 1630	1.65 (3H); 2.95 (2H); 5.30–5.50 (2H)
e	$C_6H_5—CH_2—Br$	83	oil[c]	1730, 1640, 1610	3.55 (2H); 7.10 (5H)
f	$C_2H_5OOC—CH_2—Br$	55	oil[c]	1730, 1640	1.25 (3H); 3.15 (2H); 4.10 (2H)

[a] Corresponding ethyl ester: b.p. 103°/140 torr[9].

[b] Corresponding ethyl ester: b.p. 104–106°/45 torr[7].

[c] Purified by chromatography on silica gel; see experimental part.

2-exo-*(2-Butenyl) Derivative* (**2d**); yield: 75%.

I.R. (film): $\nu_{max} = 1740$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 6.10–6.35 (m, 2H, $—CH{=}CH—$); 5.30–5.50 (m, 3H, $—CH{=}CH_2$); 3.65 (s, 3H, $—OCH_3$); 2.20–2.45 (m, 2H, $—CH_2—$); 1.45–2.00 (m, 2H, $—CH_2—$); 1.65 (d, $J = 6$ Hz, 3H, $=C—CH_3$); 1.60 ppm [s, 6H, $=C(CH_3)_2$].

2-exo-*Benzyl Derivative* (**2e**); yield: 38%.

I.R. (film): $\nu_{max} = 1740, 1610$ cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ = 6.80–7.10 (m, 5H, C_6H_5); 5.95, 6.15 (m, 2H, $=CH$); 3.40 (s, 3H, $—OCH_3$); 3.25 (m, 2H, $>CH—$); 2.65, 3.05 (ABq, $J = 15$ Hz, each 1H, $—C\underline{H}_2—C_6H_5$), 1.40–1.95 (m, 2H, $—CH_2—$); 1.60, 1.65 ppm (each s, each 3H, $=C(CH_3)_2$].

2-exo-*Ethoxycarbonylmethyl Derivate* (**2f**); yield: 38%.

I.R. (film): $\nu_{max} = 1740$ cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ = 5.95–6.22 (m, 2H, $=CH$); 4.05 (q, $J = 7$ Hz, 2H, $COOC\underline{H}_2—CH_3$); 3.55 (s, 3H, $—OCH_3$); 3.25 (m, 2H, $>CH—$); 2.30, 2.85 (ABq, $J = 15$ Hz, each 1H, $C\underline{H}_2—C_6H_5$); 1.50–2.00 (m, 2H, $—C\underline{H}_2—$); 1.60 [s, 6H, $=C(CH_3)_2$]; 1.25 ppm (t, $J = 7$ Hz, 3H, $—COOCH_2—C\underline{H}_3$).

Methyl Methacrylate (5a); Typical Procedure:

7-Isopropylidene-2-*endo*-methoxycarbonyl-2-*exo*-methylbicyclo-[2.2.1]hept-5-ene (**2a**; 1 g) is dissolved in diphenyl ether (2 ml). The mixture is heated at 170–190° (bath temperature) and the volatile products are distilled. The distillate contains ~10% dimethylfulvene. Maleic anhydride (60 mg) is added to the distillate; the mixture is allowed to stand for 24 h and then filtered. The filtrate is distilled to give pure **5a**; yield: 330 mg (70%); b.p. 99–100° (Ref.[7], b.p. 100–101°).

The same procedure is applicable to the synthesis of compounds **5b, c, d**.

4-Ethyl 1-Methyl 2-Methylenesuccinate (5f):

A solution of compound **2f** (100 mg) in toluene (10 ml) is heated at 170–180° in a sealed tube for 30 min. The solvent is evaporated and the residual product purified by column chromatography on silicic acid using hexane/ethyl acetate (9:1) as eluent; yield: 34 mg (55%).

I.R. (film): $\nu_{max} = 1730, 1640$ cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ = 6.20 (br. s, 1H, $=CH$); 5.10 (dd, $J = 2$ Hz, 3 Hz, 1H, $=CH$); 4.10 (q, $J = 7$ Hz, 2H, $COOC\underline{H}_2—CH_3$); 3.70 (s, 3H, $—OCH_3$); 3.15 (br.s, 2H, $C\underline{H}_2—COOC_2H_5$); 1.25 ppm (t, $J = 7$ Hz, 3H, $—CH_3$).

Methyl 2-Benzylpropenoate (5e):

Prepared analogous to **5f**; yield: 83%.

I.R. (film): $\nu_{max} = 1730, 1640, 1610$ cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ = 7.10 (m, 5H, C_6H_5); 6.10 (br. s, 1H, $=CH$); 5.30 (dd, $J = 3$ Hz, 2 Hz, 1H, $=CH$); 3.70 (s, 3H, $—OCH_3$); 3.55 ppm (br. s, 2H, $C\underline{H}_2—C_6H_5$).

2-*exo*-Ethyl-7-isopropylidenebicyclo[2.2.1]hept-5-ene-
2-*endo*-carboxylic Acid (3):

Freshly distilled propylmercaptan (0.5 ml) is added to a suspension of finely ground lithium hydride (0.15 g) in dry hexamethylphosphoric triamide (HMPT; 5 ml) under nitrogen with stirring at 25°. After 1 h, a solution of **2b** (0.2 g) in HMPT (0.5 ml) is added and stirring is continued for an additional 10 h. The reaction mixture is filtered and the filtrate acidified with 3 normal hydrochloric acid. The mixture is extracted with ether, the extract is dried with sodium sulfate, and the ether evaporated. The residual product (141 mg) is recrystallized from ethanol/water to give colorless crystals; m.p. 107–109°.

$C_{13}H_{18}O_2$	calc.	C 75.69	H 8.80
(206.3)	found	75.19	8.87

I.R. (KBr) $\nu_{max} = 3100, 1700$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 8.10 (br.s, 1H, $—OH$); 6.15–6.45 (m, 2H, $=CH$); 3.30 (m, 2H, $>CH—$); 1.30–2.00 (m, 4H, $—CH_2—$) 1.60, 1.62 [each s, each 3H, $=C(CH_3)_2$]; 0.95 ppm (t, $J = 7$ Hz 3H, $CH_2—C\underline{H}_3$).

7,7-Dimethyl-2-*exo*-ethyl-4-*endo*-hydroxy-5-phenylsulfenyl-bicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid Lactone (4):

A solution of the carboxylic acid **3** (80 mg) in dichloromethane (0.7 ml) is added to a stirred mixture of triethylamine (0.12 ml) and phenylsulfenyl chloride[11] (0.1 ml) at −30°. After 30 min, the mixture is extracted with benzene and the extract dried with sodium sulfate. The solvent is evaporated and the residual product purified by column chromatography on silicic acid using benzene as eluent to give crystalline **4** (36 mg). The product is recrystallized from hexane/ether to give colorless crystals; m.p. 101.4–102.1°.

$C_{19}H_{22}O_2S$	calc.	C 72.59	H 7.05	S 10.18
(314.4)	found	72.41	7.00	9.98

I.R. (KBr) $\nu_{max} = 1780$ cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ = 7.15 (m, 5H, $S—C_6H_5$); 4.45 (d, $J = 5$ Hz, 1H, $O—CH—$); 3.32 (d, $J = 5$ Hz, 1H, $—CH—$), 3.15 (s, 1H, S—CH—); 2.80 (m, 1 H, —CH—); 1.70 (s, 6 H, $=C(CH_3)_2$]; 1.10–2.10 (m, 4 H, $-CH_2-$); 0.90 ppm (t, $J = 7$ Hz, 3 H, $CH_2-\underline{C}\underline{H}_3$).

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