Highly Stereocontrolled Construction of Tricyclo[6.2.2.0^{1,6}]dodecanes by Intramolecular Double Michael Reaction

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o-Anisaldehyde has been converted, *via* a [3,3]sigmatropic reaction and a Birch reduction, into the cyclohexenone (**10**) bearing an α,β-unsaturated group. Treatment of the latter with lithium hexamethyldisilazide induced an intramolecular double Michael reaction to give the tricyclo[6.2.2.0^{1,6}]dodecane derivative (**12**) (60%) as a single isomer. The annelation of (**20**) also yielded the corresponding tricyclic compound (**21**) (50%).

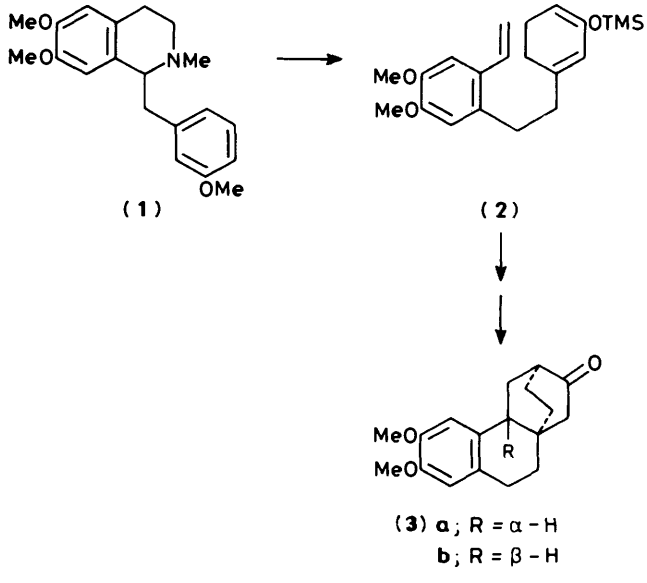
Bicyclo[2.2.2]octane is a partial structure for many natural products and it is believed that its derivatives are synthetic precursors of other skeletons. For example, diterpenoids such as atisirene and atisine are based on spiro-fused bicyclo[2.2.2]octanes. Furthermore, chasmanine,[1] aphidicolin,[2,3] maritimol,[3,4] and stemarin[5] have been synthesized *via* rearrangements from bicyclo[2.2.2]octanes. In view of this, it was felt that a general method for the stereocontrolled construction of spiro fused bicyclo[2.2.2]octanes would provide a versatile route to a number of natural products. To this end, we have studied intramolecular Diels–Alder reactions but only poor stereoselection was observed. Thus, the triene (**2**), derived from the tetrahydroisoquinoline (**1**), when heated in toluene at 200 °C in a sealed tube and then treated with acid gave a mixture of two stereoisomers (**3a**) and (**3b**) in a ratio of 5:2.[6] We then turned our attention to an intramolecular double Michael reaction. Although intermolecular double Michael reactions have been reported by several groups,[7] there has been no report of an intramolecular reaction. It was expected, however, that treatment of compounds possessing an enone and an α,β-unsaturated ester group at appropriate positions in the same molecule with metallic base would give rise to intramolecular tandem conjugate addition; diastereoselective control could then be achieved by cyclization *via* a metal chelated intermediate. We report a stereospecific synthesis of a tricyclo[6.2.2.0^{1,6}]dodecane system according to this methodology.[8]

The intramolecular double Michael reaction was first examined with the α,β-unsaturated ester (**10**), the latter having no hydrogen at the γ-position: it was prepared as follows. Reaction of *o*-anisaldehyde (**4**) with vinylmagnesium bromide in tetrahydrofuran followed by treatment with aqueous ammonium chloride gave the alcohol (**5**) (91%). Condensation of (**5**) with isobutyric acid was carried out in the presence of 1,3-dicyclohexylcarbodi-imide and 4-*N*,*N*-dimethylaminopyridine[9] to afford the ester (**6**) (85%). After treatment of (**6**) with lithium di-isopropylamide and hexamethylphosphoric triamide in tetrahydrofuran, the resulting mixture was treated with chlorotrimethylsilane at −78 °C and warmed to room temperature to give rise to a [3,3]sigmatropic rearrangement.[10] Acidic treatment of the product furnished the (*E*)-olefinic acid (**7**) (69%), which was reduced with lithium aluminium hydride in ether to the corresponding alcohol (**8**) (99%). The resulting alcohol (**8**) was subjected to Birch reduction using a large excess of lithium in liquid ammonia and tetrahydrofuran in the presence of propan-2-ol to yield the corresponding methyl enol ether; this was heated with a mixture of 10% hydrochloric acid and dichloromethane to afford the enone (**9**) (70%). Oxidation of (**9**) with pyridinium chlorochromate in dichloromethane, followed by treatment of the resulting product with Florisil gave the aldehyde; this was treated with Wadsworth-Emmons reagent[11] to provide, quantitatively, the α,β-unsaturated ester (**10**), the substrate of the double Michael reaction, as the (*E*)-isomer.

Table 1. Conditions and yield for the conversion of (**10**) into (**12**)

Entry	Base	Equiv.	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	NaH	1.5	THF	66	24	—
2	LHMDS	1.3	THF	−78—R.t.*	20	60
3	LHMDS	1.3	THF–HMPA	−78—R.t.	20	10
4	LDA	2.0	THF	−78	2	22
5	LDA	1.3	THF	−78	16	24
6	LDA	1.3	THF	−78 to −20	2	45

* R.t. = room temp.



Scheme 1.

The annelation of (**10**) was examined using several metallic bases. Treatment with sodium hydride or potassium hydride gave none of desired tricyclic compound, but with lithium hexamethyldisilazide (LHMDS) or lithium di-isopropylamide (LDA) the intramolecular double Michael reaction occurred to afford compound (**12**) as a single isomer. Some of the conditions tested and yields are listed in Table 1: the best result (60% yield)

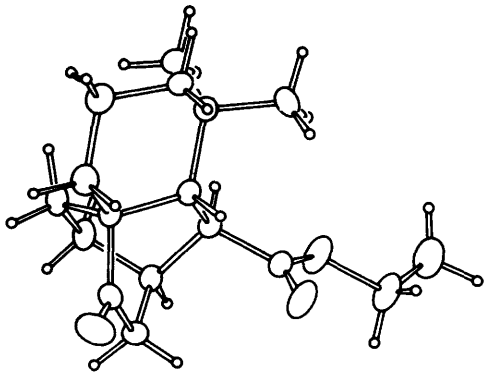
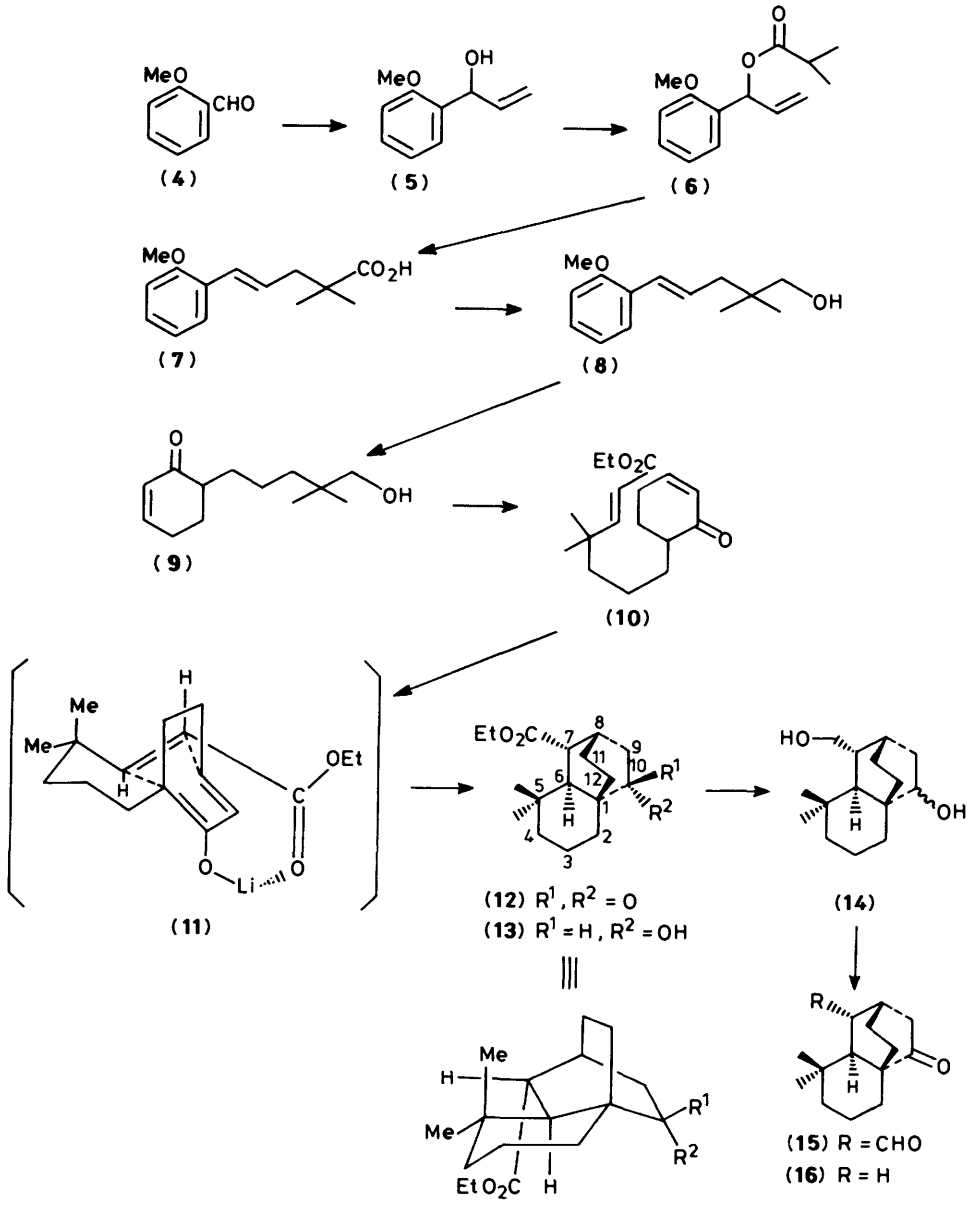


Figure 1. Molecular structure of (12).

was obtained with lithium hexamethyldisilazide (entry 2). The stereochemistry of (**12**), m.p. 97—98 °C, was inferred by spectroscopic analysis of the corresponding alcohol (**13**), the sole product (83%) of sodium borohydride reduction of (**12**). The i.r. spectrum of the alcohol (**13**) [$\nu_{max.}$($CHCl_3$) 3 450 (OH) and 1 700 cm^{-1} (C=O)], indicated the presence of hydroxy and ester groups, which are intramolecularly hydrogen-bonded. Furthermore, the chemical shifts of two methyl groups in ^1H n.m.r. spectrum were not significantly influenced by the reduction. These facts suggested that the hydrogen at the C-6 position and the ethano bridge having the carbonyl group of (**12**) are *cis*. This assignment was further confirmed by the *X*-ray analysis of (**12**). The crystal structure of (**12**) is shown in Figure 1 and the crystallographic numbering in Figure 2.

The stereospecific formation of (**12**), the stereochemical arrangement of which makes it suitable for the synthesis of atisirene-type diterpenoids, can be explained by the conjugate addition through the *endo* mode [see intermediate (**11**)] in which the two oxygens are held closely to the metal cation. The



Scheme 2.

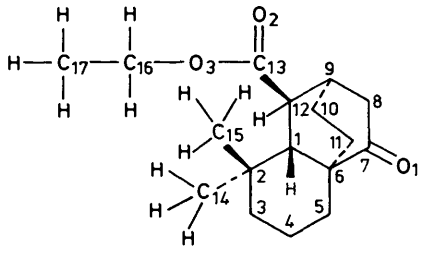


Figure 2. Crystallographic numbering for compound (**12**).

absence of cyclization using sodium or potassium cation and the reduced yield on the reaction carried out in the presence of hexamethylphosphoric triamide would support such a chelation effect.

Removal of the ethoxycarbonyl group of (**12**) was achieved by the following sequential reactions. Reduction of (**12**) using diisobutylaluminium hydride in ether gave the diol (**14**) (95%), oxidation of which the pyridinium dichromate in dimethylformamide afforded (**15**) (71%). A mixture of (**15**) and tris(triphenylphosphine)rhodium chloride [12] in refluxing xylene produced the ketone (**16**) (23%).

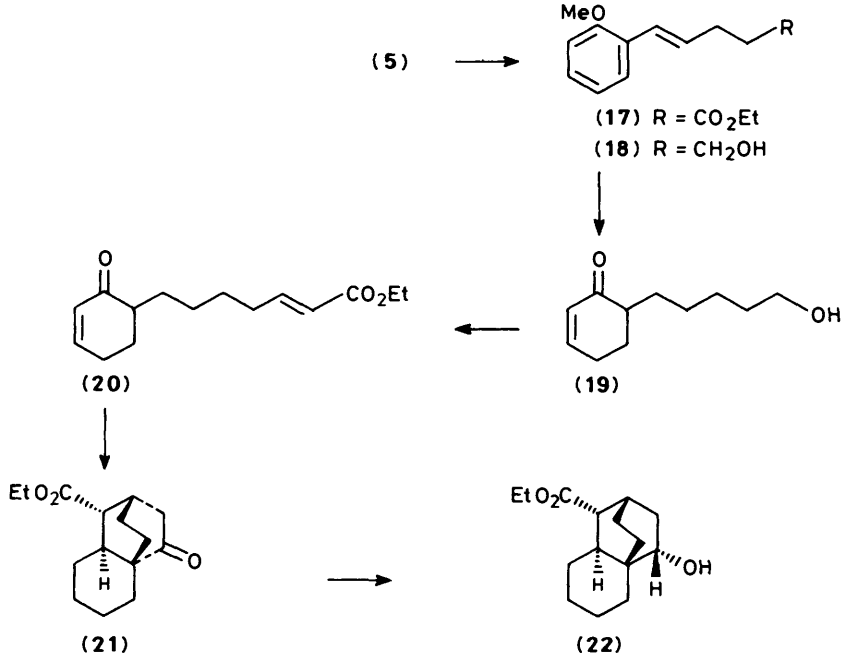
The intramolecular double Michael reaction of the α,β-unsaturated ester (**20**) possessing hydrogens at the γ position was investigated. The substrate was prepared from (**5**) through the orthoacetate Claisen rearrangement.[13] Thus, when heated a mixture of (**5**), triethyl orthoacetate, and trimethylacetic acid afforded the (*E*)-γ,δ-unsaturated ester (**17**) (81%). After reduction of (**17**) with lithium aluminium hydride, the resulting alcohol (**18**) (85%), was treated with lithium in liquid ammonia and tetrahydrofuran in the presence of propan-2-ol and the product was isomerized with hydrochloric acid to the enone (**19**) (50%). The α,β-unsaturated ester (**20**), derived from (**19**), was annelated using lithium hexamethyldisilazide under the same conditions as above to furnish the tricyclic compound (**21**) (13%). The yield was considerably increased (to 50%), when the reaction was carried out in hexane and quenched by the direct mixing of the reaction product with silica gel (see Experimental section). Structure (**21**) for the product was deduced on the basis of the spectral data. In the i.r. spectrum, the absorptions due to the α,β-unsaturated ester and enone disappeared and absorptions due to the saturated ester and six-membered ketone overlapped at 1 720 cm^{-1}. The n.m.r. spectrum showed no olefinic protons and indicated that an ethyl ester group was present. Furthermore, the ^{13}C n.m.r. data determined by INEPT technique were consistent with the proposed structure (**21**). The relative stereochemistry was determined on the assumption that the reaction proceeded *via* a similar intermediate to that above and by conversion into the alcohol (**22**). Reduction of (**21**) with sodium borohydride gave two epimers, while the reduction using L-selectride afforded a single product (**22**) produced by the selective attack of the hydride from the less hindered side. The i.r. spectrum of (**22**) showed absorptions due to the hydroxy and ester groups at 3 430 and 1 704 cm^{-1}, respectively, suggesting the presence of an intramolecular hydrogen bond as in (**13**).

Although the above highly stereocontrolled reaction could be regarded as a double Michael reaction, the anion-accelerated Diels–Alder mechanism could not be ruled out.[7] In spite of the ambiguity of the mechanism, it is obvious that the intramolecular double Michael reaction proceeds at low temperature with high regio- and stereo-selectivity.

Experimental

General Procedures.—I.r. spectra were measured with a Hitachi 260-10 spectrophotometer, and n.m.r. spectra with JEOL-PMX-60, JEOL-PS-100, and Varian XL-200 spectrometers. Ordinary mass spectra were taken with a Hitachi M-52G and accurate mass spectra with a JEOL-JMS-01SG-2 spectrometer. All new compounds described in the Experimental section were homogeneous on t.l.c.

1-(2-*Methoxyphenyl*)*prop*-2-*en*-1-*ol* (**5**).—A solution of Grignard reagent [prepared from vinyl bromide (5.90 g, 55.1 mmol) and magnesium (1.24 g, 51.7 mmol)] in dry tetrahydrofuran (50 ml) was added dropwise to a stirred solution of *o*-anisaldehyde (**4**) (5.0 g, 36.8 mmol) in dry tetrahydrofuran (30



Scheme 3.

ml) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and then warmed to room temperature over 0.5 h. The reaction was quenched upon being slowly poured into saturated aqueous ammonium chloride. The mixture was extracted with ether, and the ethereal layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ether (20:1, v/v) gave the *allyl alcohol* (**5**) (5.5 g, 91%) as an oil (Found: C, 72.8; H, 7.25. $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.35%); $\nu_{max.}(CHCl_3)$ 3 550 cm^{-1} (OH); $\delta_H(CCl_4)$ 2.70 (1 H, d, 6 Hz, C*H*OH), 3.73 (3 H, s, OMe), 4.85—5.47 (2 H, m, CH=CH_2), 5.98 (1 H, ddd, *J* 5, 10 and 17 Hz, C*H*=CH_2), and 6.60—7.37 (4 H, m, ArH); *m/z* 164 (M^+).

1-(2-*Methoxyphenyl*)*prop*-2-*enyl Isobutanoate* (**6**).—To a stirred solution of the allylic alcohol (**5**) (2.0 g, 12.2 mmol), isobutyric acid (1.08 g, 12.2 mmol) and dimethylaminopyridine (300 mg, 2.4 mmol) in dichloromethane (60 ml) was added a solution of 1,3-dicyclohexylcarbodi-imide (2.76 g, 13.4 mmol) in dichloromethane (40 ml) at 0 °C. The resulting mixture was stirred at room temperature for 10 h. After separation of the precipitate by filtration, the filtrate was washed with brine, dried ($MgSO_4$), and concentrated to give an oil, which was chromatographed on silica gel. Elution with hexane–ether (10:1, v/v) gave the *ester* (**6**) (2.42 g, 85%) as an oil (Found: C, 71.65; H, 7.65. $C_{14}H_{18}O_3$ requires C, 71.75; H, 7.75); $\nu_{max.}(CHCl_3)$ 1 735 cm^{-1} (CO); $\delta_H(CCl_4)$ 1.15 (6 H, d, *J* 7 Hz, 2 × Me), 2.20—2.80 (1 H, m, C*H*Me_2), 3.80 (3 H, s, OMe), 4.90—5.30 (2 H, m, CH=CH_2), 5.95 (1 H, ddd, *J* 5, 10 and 17 Hz, C*H*=CH_2), and 6.40—7.35 (4 H, m, ArH); *m/z* 234 (M^+).

5-(2-*Methoxyphenyl*)-2,2-*dimethylpent*-4-*enoic Acid* (**7**).—A stirred solution of dry di-isopropylamine (1.04 g, 10.2 mmol) in dry tetrahydrofuran (60 ml) was cooled to −78 °C and treated with butyl-lithium in hexane solution (0.66 g, 10.2 mmol) over several minutes. After the mixture had been stirred for an additional 20 min, a solution of the ester (**6**) (2.0 g, 8.6 mmol) in dry tetrahydrofuran (40 ml) and dry hexamethylphosphoric triamide (1.8 ml, 10.2 mmol) was added dropwise at −78 °C. After an additional 15 min, chlorotrimethylsilane (2.2 ml, 17 mmol) was added rapidly to the mixture and the cooling bath then removed. The reaction mixture was allowed to warm to room temperature after which it was stirred for 0.5 h at ambient temperature and then poured into 5% aqueous sodium hydroxide (100 ml). The aqueous solution was washed with ether (2 × 100 ml) and acidified with concentrated hydrochloric acid. The mixture was extracted with dichloromethane and the extract was dried (Na_2SO_4) and evaporated to give a residue which was purified by chromatography on silica gel, eluting with hexane–ether (10:3, v/v) to afford the *carboxylic acid* (**7**) (1.38 g, 69%) as an oil; $\nu_{max.}(CHCl_3)$ 1 700 cm^{-1} (CO); $\delta_H(CCl_4)$ 1.23 (6 H, s, 2 × Me), 2.45 (2 H, d, *J* 7 Hz, =CHCH_2), 3.77 (3 H, s, OMe), 6.03 (1 H, dt, *J* 7 and 17 Hz, =C*H*CH_2), 6.50—7.40 (5 H, m, ArH and ArC*H*=); *m/z* 234 (M^+) (Found: M^+, *m/z* 234.1254. $C_{14}H_{18}O_3$ requires *M*, 234.1251).

5-(2-*Methoxyphenyl*)-2,2-*dimethylpent*-4-*en*-1-*ol* (**8**).—A solution of the carboxylic acid (**7**) (1.5 g, 6.41 mmol) in dry ether (10 ml) was added dropwise at 0 °C to a vigorously stirred suspension of lithium aluminium hydride (260 mg, 6.41 mmol) in dry ether (10 ml). After 5 min, the cooling bath was removed and the mixture was allowed to warm to room temperature. After 2 h, the mixture was treated by successive dropwise addition of water (0.26 ml), 15% aqueous sodium hydroxide (0.26 ml), and water (0.78 ml). The resulting granular precipitate was filtered off through Celite. The concentrated filtrate was chromatographed on silica gel with hexane–ether (100:5, v/v) as eluant to give the *alcohol* (**8**) (1.41 g, 99%) as an oil (Found: C, 76.05; H, 9.15. $C_{14}H_{20}O_2$ requires C, 76.3; H, 9.15%); $\nu_{max.}(CHCl_3)$ 3 620 cm^{-1} (OH); $\delta_H(CCl_4)$ 0.92 (6 H, s, 2 × Me), 2.13 (2 H, d, *J* 7 Hz, =CHCH_2), 3.28 (2 H, s, CH_2OH), 3.80 (3 H, s, OMe), 6.10 (1 H, dt, *J* 7 and 17 Hz, =C*H*CH_2), and 6.43—7.47 (5 H, m, ArH and ArC*H*=); *m/z* 220 (M^+).

6-(5-*Hydroxy*-4,4-*dimethylpentyl*)*cyclohex*-2-*enone* (**9**).—To a stirred solution of alcohol (**8**) (870 mg, 3.95 mmol) in a mixture of liquid ammonia (30 ml), dry tetrahydrofuran (10 ml), and propan-2-ol (10 ml) was added at −78 °C lithium metal (280 mg, 40 mmol) in a current of nitrogen. After the mixture had been stirred for 3 h, the solvent was evaporated to give a residue, which was extracted with ether. The ethereal layer was washed with saturated aqueous ammonium chloride, dried ($MgSO_4$), and evaporated to give the methyl enol ether, which was used directly in the following reaction. To the solution of the above product in dichloromethane (10 ml), 10% hydrochloric acid solution (5 ml) was added in small portions with stirring at ambient temperature. After being refluxed for 3.5 h, the mixture was extracted with dichloromethane. The extract was washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated to afford a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ether (5:3, v/v) gave the *enone* (**9**) (582 mg, 70%) as an oil (Found: C, 74.1; H, 10.4. $C_{13}H_{22}O_2$ requires C, 74.25; H, 10.55%); $\nu_{max.}(CHCl_3)$ 3 600 (OH), 1 660 cm^{-1} (CO); $\delta_H(CCl_4)$ 0.83 (6 H, s, 2 × Me), 1.15—2.50 (11 H, m, 5 × CH_2 and CH), 3.20 (2 H, s, CH_2OH) 5.85 (1 H, dt, *J* 1 and 10 Hz, COC*H*=), and 6.70—7.00 (1 H, m, =C*H*CH_2); *m/z* 210 (M^+).

6-(6-*Ethoxycarbonyl*-4,4-*dimethylhex*-5-*enyl*)*cyclohex*-2-*enone* (**10**).—A solution of the alcohol (**9**) (100 mg, 0.48 mmol) in dichloromethane (3 ml) was added to a stirred solution of pyridinium chlorochromate (206 mg, 0.96 mmol) in dichloromethane (5 ml). After 2 h, Florisil (206 mg) was added to the mixture with stirring. The supernatant was filtered through Celite and then the concentrated filtrate was purified by chromatography on silica gel. Elution with hexene–ether (20:1, v/v) afforded an aldehyde (89 mg, 90%); $\nu_{max.}(CHCl_3)$ 1 720 (CHO) and 1 670 cm^{-1} (=C–C=O); $\delta_H(CCl_4)$ 1.02 (6 H, s, 2 × Me), 1.10—2.55 (11 H, m, 5 × CH_2 and CH), 5.85 (1 H, dt, *J* 2 and 10 Hz, COCH=), 6.50—7.00 (1 H, m, =C*H*–CH_2), and 9.33 (1 H, s, CHO); *m/z* 208 (M^+). To a slurry of 60% sodium hydride (21 mg, 0.51 mmol) in dry 1,2-dimethoxyethane (3 ml) was added dropwise at room temperature with stirring triethyl phosphonoacetate (0.1 ml, 0.51 mmol). After the mixture had been stirred for 1 h a solution of the above aldehyde (89 mg, 0.43 mmol) in dry 1,2-dimethoxyethane (2 ml) was added dropwise. The mixture was stirred for 1 h after which it was diluted with a large amount of water. The mixture was extracted with ether and the ethereal extract was dried ($MgSO_4$), and evaporated to give a residue, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (100:3, v/v) afforded the *enone* (**10**) (119 mg, 100%) as an oil (Found: C, 73.15; H, 9.6. $C_{17}H_{26}O_3$ requires C, 73.35; H, 9.4%) $\nu_{max.}(CHCl_3)$ 1 700 and 1 660 cm^{-1} (CO); $\delta_H(CCl_4)$ 1.07 (6 H, s, 2 × Me), 1.27 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.10—2.50 (11 H, m, 5 × CH_2 and CH), 4.10 (2 H, q, *J* 7 Hz, CH_2CH_3), 5.57 (1 H, d, *J* 16 Hz, =C*H*CO_2Et), 5.80 (1 H, dt, *J* 2 and 10 Hz, COC*H*=CH), 6.50—6.90 (1 H, m, CO–CH=C*H*), and 6.73 (1 H, d, *J* 16 Hz, C*H*=CHCO_2Et); *m/z* 278 (M^+).

(±)-(1S*, 6R*, 7R*, 8S*)-7-*Ethoxycarbonyl*-5,5-*dimethyltricyclo*[6.2.2.$0^{1,6}$]*dodecan*-10-*one* (**12**).—To a stirred solution of lithium disilazide [prepared from 1,1,1,3,3,3-hexamethyldisilazane (191 mg, 1.19 mmol) and butyl-lithium (76 mg, 1.19 mmol)] in dry tetrahydrofuran (7 ml) was added a solution of the enone (**10**) (300 mg, 1.08 mmol) in dry tetrahydrofuran (3

ml) at −78 °C under an argon atmosphere. The mixture was allowed to warm to room temperature over 30 min. After the mixture had been stirred for 20 h at the same temperature, saturated aqueous ammonium chloride (10 ml) was added at 0 °C. The mixture was then extracted with ether. The extract was dried ($MgSO_4$) and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (20:1, v/v), afforded the ketone (**12**) (179 mg, 60%) as prisms, m.p. 97—98 °C (from hexane); $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1} (CO); δ_H(CCl_4) 0.77 and 1.06 (each 3 H, each s, 2 × Me), 1.25 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.20—2.55 (15 H, m, 6 × CH_2 and 3 × CH), 4.14 (2 H, q, *J* 7 Hz, CH_2CH_3); δ_C($CDCl_3$) 14.50, 18.14, 21.78, 24.01, 26.13, 29.34, 32.00, 32.17, 34.93, 39.28, 41.21, 43.92, 44.97, 45.15, 60.82, 175.19, and 214.00; *m/z* 278 (M^+).

(±)-(1S*, 6R*, 7R*, 8S*, 10S*)-7-*Ethoxycarbonyl*-5,5-*dimethyltricyclo*[6.2.2.$0^{1,6}$]*dodecan*-10-*ol* (**13**).—Sodium borohydride (1 mg, 0.03 mmol) was added to a solution of the ketone (**12**) (6 mg, 0.02 mmol) in ethanol (1 ml) at room temperature. After the mixture had been stirred at the same temperature for 0.5 h, the solvent was evaporated to give a residue, which was extracted with dichloromethane. The extract was washed with saturated brine, dried ($MgSO_4$), and evaporated to give a residue, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (20:1, v/v) afforded the *alcohol* (**13**) (5 mg, 83%) as an oil; $\nu_{max.}$($CHCl_3$) 3 450 (OH), 1 700 cm^{-1} (CO); δ_H($CDCl_3$) 0.76 and 0.97 (each 3 H, each s, 2 × Me), 1.27 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.20—2.50 (15 H, m, 6 × CH_2 and 3 × CH), 3.10—3.25 (2 H, m, CHOH, 1 H disappeared with D_2O), and 4.16 (2 H, q, *J* 7 Hz, CH_2CH_3); *m/z* 280 (M^+) (Found: M^+, *m/z* 280.2037. $C_{17}H_{28}O_3$ requires *M*, 280.2019).

(±)-(1S*, 6R*, 8S*)-5,5-*Dimethyltricyclo*[6.2.2.$0^{1,6}$]*dodecan*-10-*one* (**16**).—Di-isobutylaluminium hydride (84 mg, 0.6 mmol) was added dropwise at −78 °C to a solution of (**12**) (50 mg, 0.18 mmol) in dry ether (3 ml). The mixture was allowed to warm to room temperature over a 30 min period after which it was stirred for 2 h at room temperature: it was then quenched with water (0.68 ml) with stirring. The resulting granular precipitate was filtered off through Celite. The concentrated filtrate was chromatographed on silica gel eluting with hexane–ethyl acetate (1:2, v/v) to give the diol (**14**) (40 mg, 95%) as a powder; δ_H[$(CD_3)_2CO$–CCl_4] 0.85 and 0.97 (each 3 H, each s, 2 × Me), 1.10—2.10 (15 H, m, 6 × CH_2 and 3 × CH), 3.27—3.76 (3 H, m, CHOH and CH_2OH); *m/z* 220 (M^+ − 18).

A solution of the diol (**14**) (20 mg, 0.084 mmol) in dimethylformamide (1 ml) was added to a stirred solution of pyridinium dichromate (126 mg, 0.34 mmol) in dimethylformamide (2 ml). The reaction mixture was stirred for 3 h before it was diluted with water (30 ml) and extracted with ether. The ethereal layer was washed with saturated brine, dried ($MgSO_4$), and evaporated to give a residue. This crude product was purified by chromatography on silica gel eluting with hexane–ethyl acetate (10:3, v/v) to afford the aldehyde (**15**) (14 mg, 71%) as a powder; $\nu_{max.}$($CHCl_3$) 1 710 cm^{-1} (CO); δ_H(CCl_4) 0.77 and 1.07 (each 3 H, each s, 2 × Me), 1.00—2.60 (15 H, m, 6 × CH_2 and 3 × CH), and 9.67 (1 H, br s, CHO); *m/z* 234 (M^+).

A solution of the aldehyde (**15**) (10 mg, 0.043 mmol) and tris(triphenylphosphine)rhodium chloride (47 mg, 0.051 mmol) in xylene (2 ml) was heated under reflux for 1 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel and eluted with hexane–ethyl acetate (100:3, v/v) to give the *ketone* (**16**) (2 mg, 23%) as an oil; $\nu_{max.}$($CHCl_3$) 1 710 cm^{-1} (CO); δ_H(CCl_4) 0.83 and 1.03 (each 3 H, each s, 2 × Me), 0.97—2.20 (16 H, m, 7 × CH_2 and 2 × CH); *m/z* 206 (M^+) (Found: M^+, *m/z* 206.1671. $C_{14}H_{22}O$ requires *M*, 206.1678).

1-*Ethoxycarbonyl*-4-(2-*methoxyphenyl*)*but*-3-*ene* (**17**).—A mixture of (**5**) (17.5 g, 0.11 mol), triethyl orthoacetate (39.1 g, 0.21 mol), and trimethylacetic acid (3.1 g, 30.6 mmol) was heated under reflux for 8 h. After evaporation of reagents, the residue was purified by distillation to give the *ester* (**17**) (20.5 g, 81%), b.p. 176—180 °C (6 mmHg) (Found C: 71.9; H, 7.95. $C_{14}H_{18}O_3$ requires C, 71.75; H, 7.75%); $\nu_{max.}$($CHCl_3$) 1 730 cm^{-1} (CO); δ_H(CCl_4) 1.23 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.37—2.62 (4 H, m, $=CHCH_2CH_2$), 3.77 (3 H, s, OMe), 4.05 (2 H, q, *J* 7 Hz, CH_2CH_3), 6.08 (1 H, dt, *J* 7 and 16 Hz, $=CHCH_2$), and 6.43—7.33 (5 H, m, ArH and ArC*H*=); *m/z* 234 (M^+).

5-(2-*Methoxyphenyl*)*pent*-4-*en*-1-*ol* (**18**).—A solution of the ester (**17**) (10.0 g, 42.7 mmol) in dry ether (10 ml) was added dropwise at 0 °C to a vigorously stirred suspension of lithium aluminium hydride (2.43 g, 63.9 mmol) in dry ether (100 ml). After 10 min, the cooling bath was removed and the mixture was allowed to warm to room temperature. After 3 h, the mixture was treated to successive dropwise addition of water (2.43 ml), 15% aqueous sodium hydroxide (2.43 ml), and water (7.29 ml). The resulting granular precipitate was filtered off through Celite. The concentrated filtrate was chromatographed on silica gel with hexane–ethyl acetate (4:1, v/v) as eluant, to give the *alcohol* (**18**) (6.97 g, 85%) as an oil; $\nu_{max.}$($CHCl_3$) 3 350 cm^{-1} (OH); δ_H($CDCl_3$) 1.70 (2 H, quint, *J* 7 Hz, CH_2CH_2OH), 2.28 (2 H, q, *J* 7 Hz, $=CHCH_2$), 3.64 (2 H, t, *J* 7 Hz, CH_2OH), 3.78 (3 H, s, OMe), 6.17 (1 H, dt, *J* 7 and 16 Hz, $=CHCH_2$), and 6.50—7.30 (5 H, m, ArH and ArC*H*=); *m/z* 192 (M^+) (Found: M^+, *m/z* 192.1149. $C_{12}H_{16}O_2$ requires *M*, 192.1111).

6-(5-*Hydroxypentyl*)*cyclohex*-2-*enone* (**19**).—To a stirred solution of the alcohol (**18**) (1.0 g, 5.2 mmol) in a mixture of liquid ammonia (30 ml), dry tetrahydrofuran (15 ml), and propan-2-ol (15 ml) was added at −78 °C lithium metal (370 mg, 52.9 mmol) in a current of nitrogen. After the mixture had been stirred for 2 h, the solvent was evaporated to give a residue, which was extracted with ether. The ethereal layer was washed with saturated aqueous ammonium chloride, dried ($MgSO_4$), and evaporated to give the methyl enol ether (1.02 g, 100%), which was used directly in the following reaction. To the solution of the above product (100 mg) in methanol (8.9 ml), 3M-hydrochloric acid (5.3 ml) was added in small portions with stirring at ambient temperature. The mixture was heated at 60 °C for 40 min after which the solvent was removed under reduced pressure. The resulting solution was neutralized with sodium hydrogen carbonate and the mixture extracted with ether. The ethereal layer was dried ($MgSO_4$) and evaporated to give the crude product, which was purified by m.p.l.c. with hexane–ethyl acetate (4:1, v/v) as the eluant, to afford the *enone* (**19**) (47 mg, 50%) as a viscous oil (Found: C, 72.7; H, 10.0. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%) $\nu_{max.}$($CHCl_3$) 3 450 (OH) and 1 670 cm^{-1} (CO); δ_H(CCl_4), 1.15—2.60 (13 H, m, 6 × CH_2 and CH), 3.56 (2 H, t, *J* 7 Hz, CH_2OH), 5.88 (1 H, dt, *J* 2 and 10 Hz, COCH=), and 6.83 (1 H, m, $=CHCH_2$); *m/z* 182 (M^+).

6-(6-*Ethoxycarbonylhex*-5-*enyl*)*cyclohex*-2-*enone* (**20**).—A solution of the alcohol (**19**) (100 mg, 0.55 mmol) in dichloromethane (2 ml) was added to a stirred solution of pyridinium chlorochromate (240 mg, 1.1 mmol) in dichloromethane (3 ml). After 45 min, Florisil (240 mg) was added to the mixture with stirring. The supernatant was filtered through Celite and the concentrated filtrate was purified by chromatography on silica gel. Elution with hexane–ethyl acetate (7:3, v/v) afforded the aldehyde (67 mg, 68%) as an oil; $\nu_{max.}$($CHCl_3$) 1 720 and 1 670 cm^{-1} (CO); δ_H(CCl_4) 1.22—2.60

(13 H, m, 6 × CH_2 and CH), 5.82 (1 H, br d, *J* 10 Hz, COCH=), 6.82 (1 H, m, =C*H*CH_2), and 9.63 (1 H, br s, CHO).

Triethyl phosphonoacetate (0.1 ml, 0.51 mmol) was added dropwise with stirring to a slurry of 60% sodium hydride (24 mg, 0.6 mmol) in dry 1,2-dimethoxyethane (1 ml) at room temperature. After being stirred for 1 h, the mixture was added dropwise to a solution of the above aldehyde (67 mg, 0.37 mmol) in dry 1,2-dimethoxyethane (2 ml). The mixture was stirred for 2 h and then diluted with a large volume of water. The resulting mixture was extracted with ether and the ethereal extract dried ($MgSO_4$) and evaporated to give a residue, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (17:3, v/v) afforded the *enone* (**20**) (89 mg, 96%) as an oil (Found: C, 71.65; H, 8.7. $C_{15}H_{22}O_3$ requires C, 71.95; H, 8.85%); $\nu_{max.}$($CHCl_3$) 1 705 and 1 670 cm^{-1} (CO); δ_H($CDCl_3$) 1.28 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.30—2.50 (13 H, m, 6 × CH_2 and CH), 4.17 (2 H, q, *J* 7 Hz, CH_2CH_3), 5.77 (1 H, dt, *J* 2 and 16 Hz, =C*H*CO_2Et), 5.94 (1 H, dt, *J* 2 and 10 Hz, =CHCO), 6.90 (1 H, dt, *J* 5 and 10 Hz, C*H*=CHCO), and 6.93 (1 H, dt, *J* 7 and 16 Hz, C*H*=CHCO_2Et); *m/z* 250 (M^+).

(±)-(1S*, 6R*, 7R*, 8S*)-7-*Ethoxycarbonyltricyclo*[6.2.2.0^{1,6}]*dodecan*-10-*one* (**21**).—To a stirred solution of lithium disilazide [prepared from 1,1,1,3,3,3-hexamethyldisilazane (88 mg, 0.55 mmol) and butyl-lithium (35 mg, 0.55 mmol)] was added a solution of the *enone* (**20**) (105 mg, 0.42 mmol) in dry hexane (3 ml) at −78 °C under a nitrogen atmosphere. After the mixture had been stirred for 2 h at the same temperature, it was allowed to warm to ambient temperature, during 20 min. The mixture was poured onto silica gel, filtered, and washed with ether. The filtrate was concentrated and the residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (10:1 v/v) gave the *ketone* (**21**) (52.2 mg, 50%) as an oil (Found: C, 71.7; H, 9.15. $C_{15}H_{22}O_3$ requires C, 71.95; H, 8.85); $\nu_{max.}$($CHCl_3$) 1 720 cm^{-1} (CO); δ_H($CDCl_3$) 1.25 (3 H, t, *J* 8 Hz, CH_2CH_3), 1.30—2.60 (17 H, m, 7 × CH_2 and 3 × CH), 4.17 (2 H, q, *J* 8 Hz, CH_2CH_3); δ_C($CDCl_3$) (INEPT) 14.26 (CH_3), 21.03 (CH_2), 21.63 (CH_2), 25.50 (CH_2), 26.17 (CH_2), 28.81 (CH_2), 29.84 (CH_2), 30.82 (CH), 36.96 (CH), 40.43 (CH_2), 44.98 (C), 49.77 (CH), 60.72 (CH_2), 174.54 (CO_2), and 216.38 (C=O); *m/z* 250 (M^+) (Found: M^+, *m/z* 250.1570. $C_{15}H_{22}O_3$ requires *M*, 250.1570).

(±)-(1S*, 6R*, 7R*, 8S*, 10S*)-7-*Ethoxycarbonyltricyclo*[6.2.2.0^{1,6}]*dodecan*-10-*ol* (**22**).—To a stirred solution of the ketone (**21**) (34 mg, 0.14 mmol) in dry tetrahydrofuran (1 ml) was added 1M-solution of L-selectride in tetrahydrofuran (0.2 ml, 0.2 mmol) at 0 °C under a nitrogen atmosphere. After the reaction mixture had been stirred for 5 min, ether and water were added to it. The aqueous layer was thoroughly extracted with ether and the combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a residue, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (9:1, v/v) afforded the *alcohol* (**22**) (20 mg, 58%) as an oil (Found: C, 71.2; H, 9.9. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6%); $\nu_{max.}$($CHCl_3$) 3 430(OH) and 1 704 cm^{-1} (CO); δ_H(CCl_4) 1.28 (3 H, t, *J* 8 Hz, CH_2CH_3), 1.38—2.20 (17 H, m, 7 × CH_2, and 3 × CH), 2.78 (1 H, br d, *J* 8 Hz), 3.28—3.44 (1 H, m, C*H*OH), and 4.18 (2 H, q, *J* 8 Hz, CH_2CH_3); *m/z* 252 (M^+).

X-*Ray Crystallographic Study of* (**12**).—Single crystals of (**12**), suitable for analysis were prepared by recrystallisation from hexane. They are triclinic, space group $P\bar{1}$, $C_{17}H_{26}O_3$, a = 13.852(4) Å, b = 8.492(2) Å, c = 7.163(2) Å, α = 109.87°(5), β = 95.37°(4), γ = 94.88°(4), V = 782.72 Å^3, Z = 2, D_c 1.18 g/cm^3. The intensity data were measured on a Phillips PW 1100 diffractometer using Cu-K_α (λ = 1.5418 Å) radiation. The intensities were corrected for Lorentz and polarization factors, but not for the absorption and solved by introducing some non-automatic input parameters in MULTAN 80 program. Hydrogen atoms were located from difference Fourier map and refined with isotropic temperature factors. The block-diagonal least squares refinement converged to give an R factor of 0.062 (R_w = 0.061) for a total of 2 786 independent reflections within θ = 78°. The atomic co-ordinates are given in Table 2. Bond lengths, bond angles, and the thermal parameters* are available as a supplementary publication [SUP. No. 56603 (7 pp.)]. The structure factors may be obtained on request from the Editorial Office.

Table 2. Atomic co-ordinates (× 10^4) for compound (**12**)

Atom	*x*	*y*	*z*
C(1)	7 622(1)	1 526(2)	11 730(2)
C(2)	7 271(1)	−406(2)	10 978(3)
C(3)	7 347(2)	−984(3)	12 786(4)
C(4)	8 372(2)	−562(3)	13 950(3)
C(5)	8 661(2)	1 332(3)	14 762(3)
C(6)	8 613(1)	2 118(2)	13 134(2)
C(7)	8 660(1)	4 022(2)	14 038(3)
C(8)	8 619(2)	4 873(3)	12 514(3)
C(9)	8 539(1)	3 547(3)	10 413(3)
C(10)	9 431(1)	2 589(3)	10 299(3)
C(11)	9 504(1)	1 844(2)	11 965(3)
C(12)	7 617(1)	2 271(2)	10 036(3)
C(13)	6 706(1)	3 101(3)	9 823(3)
C(14)	7 832(2)	−1 501(3)	9 364(3)
C(15)	6 196(2)	−675(3)	10 092(4)
C(16)	5 560(2)	3 655(4)	7 519(4)
C(17)	5 154(3)	2 828(5)	5 460(5)
O(1)	8 723(1)	4 799(2)	15 827(2)
O(2)	6 298(1)	3 903(2)	11 146(2)
O(3)	6 421(1)	2 853(2)	7 904(2)

Acknowledgements

We are grateful to Professor Y. Iitaka and Dr. A. Itai, Faculty of Pharmaceutical Sciences, University of Tokyo, for *X*-ray analysis and Dr. M. Koizumi, Chugai Pharmaceutical Co., for his kind help. We also thank Mr. K. Kawamura, Miss E. Kurosawa, Miss K. Mushiake, Miss K. Koike, and Miss J. Abe of our Institute for microanalysis, for spectral measurements and for preparation of the manuscript. We are indebted to Mr. K. Sasaki, Department of Chemistry, Tohoku University, for measurement of INEPT ^{13}C-n.m.r. spectroscopy. A part of this work was financially supported by Grant-in-Aid for Special Project No. 58210006 from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged.

* For details of the Supplementary Publications Scheme, see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1986, Issue 1.

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Received 17*th May* 1985; *Paper* 5/832