The Chemistry of Pseudomonic Acid.† Part 7.[1] Stereochemical Control in the Preparation of C-2-substituted Monic Acid Esters *via* the Peterson Olefination

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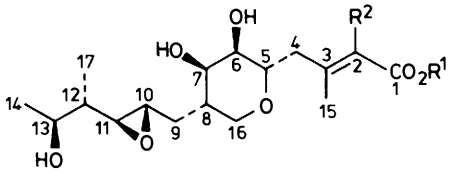
The preparation of 2-substituted monic acid esters (**1**; R ≠ H) by means of olefination reactions with the ketone (**3b**) and anions of the appropriate reagent (**6**) are described. Anions derived from 2-substituted phosphonoacetates generally did not react except for (**6d**) which afforded good yields of ethyl 2-fluoromonate (**1g**) and its isomer (**5c**). However, anions of α-substituted-α-silylesters reacted efficiently with (**3b**) but stereoselectivity was highly in favour of the biologically inactive isomonate esters (**5**). Only 2-fluoro- and 2-methyl-monate esters possessed antimicrobial activity.

As part of a continuing programme of semi-synthetic modification of the antibiotic pseudomonic acid (**1a**), substitution at C-2‡ of the nucleus by halogen, alkyl, and a variety of substituents has been studied. In animals and humans pseudomonic acid and esters of the nucleus, monic acid (**1b**), are rapidly metabolised to the biologically inactive monic acid, which is excreted as the major metabolite. The purpose of this study was, therefore, to replace the proton at C-2 with functionalities which may reduce the rate of metabolic cleavage of the α,β-unsaturated ester moiety.



(**1**)

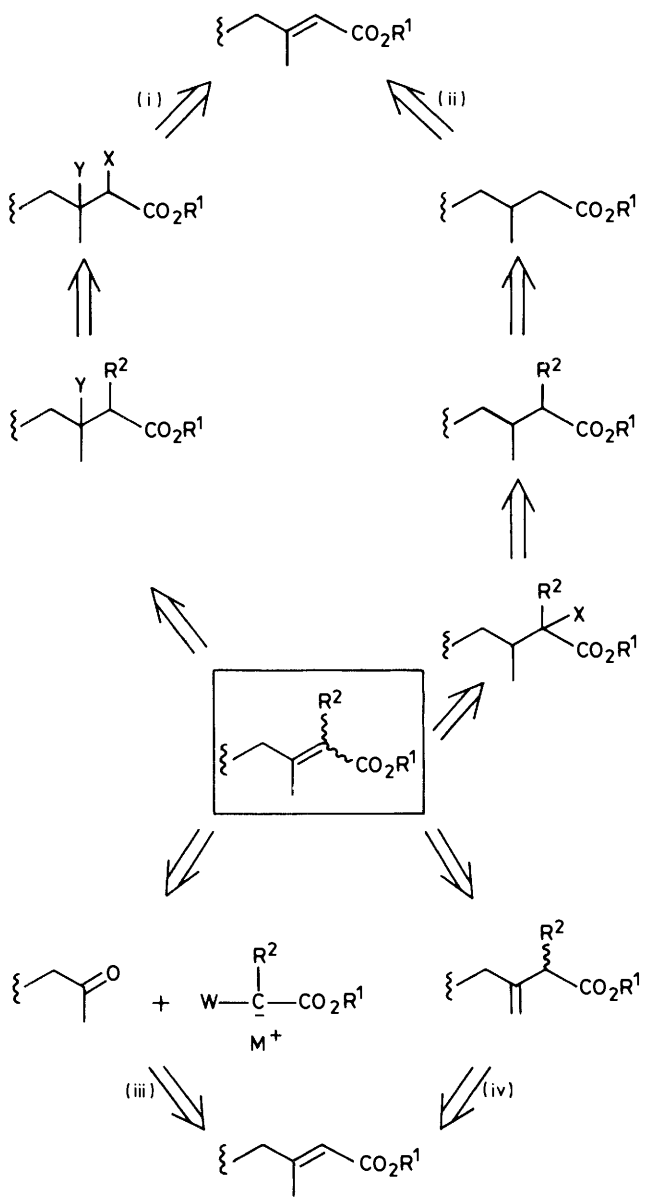
	R^1	R^2
a;	$[CH_2]_8CO_2H$	H
b;	H	H
c;	Me	H
d;	Me	Me
e;	$[CH_2]_8CO_2Me$	H
f;	Et	H
g;	Et	F
h;	Bu^t	H
i;	Bu^t	Me
j;	Et	Me
k;	Bu^t	Cl
l;	Me_3Si	Me
m;	H	Me

Results and Discussion

A number of methods for introducing substituents at C-2 have been studied. Four main approaches are depicted in Scheme 1.

(i) *The addition of X–Y to an α,β-unsaturated ester, displacement of X, followed by elimination of H–Y:* The lack of success in this approach is illustrated by the failure of bromine to add to monic acid (**1b**) or methyl monate (**1c**) and also the very slow regioselective addition of benzeneselenenyl bromide [2,3] to methyl monate (**1c**). The regiochemistry of the addition product was not clear but failure to eliminate with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) suggested structure (**2a**).

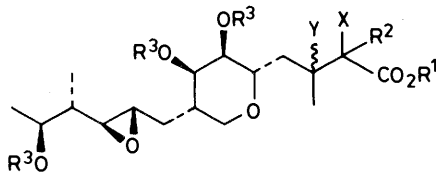
(ii) *Hydrogenation, alkylation, and electrophilic substitution*



Scheme 1.

† The approved generic name for pseudomonic acid is Mupirocin.
‡ For numbering system see structure (**1**).

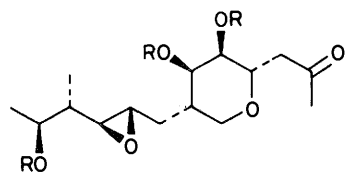
with X^+, followed by elimination of HX: Catalytic hydrogenation of methyl monate (**1c**) affords compound (**2b**) in quantitative yield. Protection of the hydroxy groups, followed by reaction of the lithium enolate of (**2c**), prepared with lithium di-isopropylamide (LDA), with methyl iodide gave the ester (**2d**). Attempts to introduce a second electrophile, benzeneselenenyl bromide, *via* the lithium enolate, failed to yield the precursor (**2e**) which could subsequently be subjected to elimination of PhSeOH to afford the desired compound (**1d**) and its *Z*-isomer after oxidation to selenoxide. Reversing the steps in this sequence produced initially the selenide (**2f**), but introduction of the methyl substituent failed to give (**2e**) possibly due to steric hindrance to formation of this crowded C-2 tertiary centre.



(**2**)

	R^1	R^2	R^3	X	Y
a;	Me	H	H	Br	SePh
b;	Me	H	H	H	H
c;	Me	H	Me_3Si	H	H
d;	Me	Me	Me_3Si	H	H
e;	Me	Me	Me_3Si	SePh	H
f;	Me	H	Me_3Si	SePh	H
g;	Et	H	Me_3Si	S^-	O^-
h;	Et	H	Me_3Si	S^-	OCO_2Et
i;	Et	Me	Me_3Si	Me_3Si	OH

(iii) *Olefination:* The ketone (**3**) which is readily available by ozonolysis of pseudomonic acid (**1a**) or its methyl ester (**1e**)[4] is a useful intermediate with which to approach the acrylic esters *via* either the Wittig reaction[5] or related olefination methods. Whilst formation of the tetrasubstituted double bond was found not to be possible using a variety of modified Wittig reaction conditions, the Peterson olefination procedure[6] proved to be an excellent alternative.



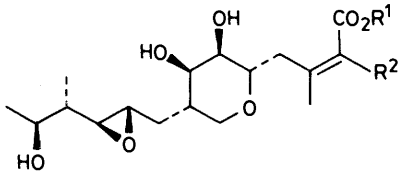
(**3**)

a; R = H
b; R = Me_3Si

(iv) *Electrophilic addition to dienolates:* Alkylation, with alkyl halides, of dienolate anions derived from α,β-unsaturated esters is reported[7,8] to occur exclusively at the α-position to give deconjugated products of structure (**4**). Reconjugation of the olefin under basic conditions results in formation of the desired C-2 substituted acrylic esters (**1**).

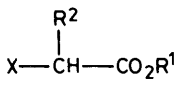
Only two of these routes were found to be of practical value, namely the olefination and the dienolate reactions. The alkylations involving dienolates are described in the following publication.[9]

Olefination.—Earlier work[5] had demonstrated that anions of the stabilised, Wadsworth–Emmons, phosphonoacetate derivatives react with the ketone (**3a**), or preferably (**3b**), to give esters of monic acid (**1b**) and isomonic acid (**5a**). For example, (**3b**) reacted smoothly with the sodium anion of (**6a**) to give ethyl esters (**1f**) and (**5b**) in a ratio of *ca.* 3:1. The ketone (**3b**) was found to be inert to reaction with the stabilised triphenyl-phosphonium-derived ylides.



(**5**)

	R^1	R^2
a;	H	H
b;	Et	H
c;	Et	F
d;	Bu^t	H
e;	Bu^t	Me
f;	Et	Me
g;	Bu^t	Cl
h;	Me_3Si	Me
i;	H	Me
j;	Me	H
k;	Me	Me



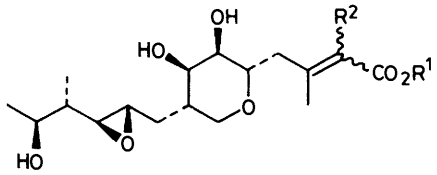
(**6**)

	X	R^1	R^2
a;	$(EtO)_2P(=O)$–	Et	H
b;	$(EtO)_2P(=O)$–	Et	Me
c;	$(EtO)_2P(=O)$–	Et	Br
d;	$(EtO)_2P(=O)$–	Et	F
e;	Me_3Si	Bu^t	H
f;	Me_3Si	Bu^t	Me
g;	Me_3Si	Et	Me
h;	Me_3Si	Bu^t	Cl
i;	Ph_2MeSi	Et	Me
j;	Me_3Si	Me_3Si	Me
k;	Me_3Si	H	H
l;	Me_3Si	H	Me

Anions derived from the *C*-substituted phosphonates (**6b**) and (**6c**) failed to react with ketone (**3b**) presumably due to steric or electronic factors, or both. In contrast, the anion derived from (**6d**)[10] and sodium hydride reacted with (**3b**) to give a mixture of the 2-fluoro-substituted esters (**1g**) and (**5c**) in 35 and 20% yield respectively. The stereochemistry of the isomers was assigned by analogy with the ^1H n.m.r. spectra of previous cases.[5] The 3-CH_3 group in (**1g**) and (**5c**) displayed doublets at δ_H 2.15 and 1.95 with the respective coupling constant J_{H-F} 4 and 5 Hz respectively.

Alternative olefination procedures for the preparation of

Table.



Compounds	R^1	R^2	*E*:*Z* Ratio of crude reaction product (h.p.l.c.)	Ratio of isolated yields (*E*:*Z*)	Total % yield isolated *E* and *Z* isomers
(1h) + **(5d)**	Bu^t	H	3.2:1	2.3:1	46
(1i) + **(5e)**	Bu^t	Me	NS	1:7.2	70
(1j) + **(5f)**	Et	Me	NS	1:3	77
(1j) + **(5f)**	Et	Me[a]	NS	. 1:1.6	43
(1k) + **(5g)**	Bu^t	Cl	8.1:1[b]	2.8:1[b]	58
(1l) + **(5h)**[c]	Me_3Si	Me	3:1	—	15[d]
(1b) + **(5a)**[c]	H	H	1:1.6	1:2.4	17
(1m) + **(5i)**[c]	H	Me	1:1.5	1:1.9	35

NS = Not separated in h.p.l.c. solvent system used. [a] Prepared with **(6i)**. [b] Note nomenclature for *E* and *Z* isomers. [c] Compounds were isolated and separated as their methyl esters (R^1 = Me). Isomer ratios and yields are for the methyl esters. [d] Only the *E*-isomer was isolated.

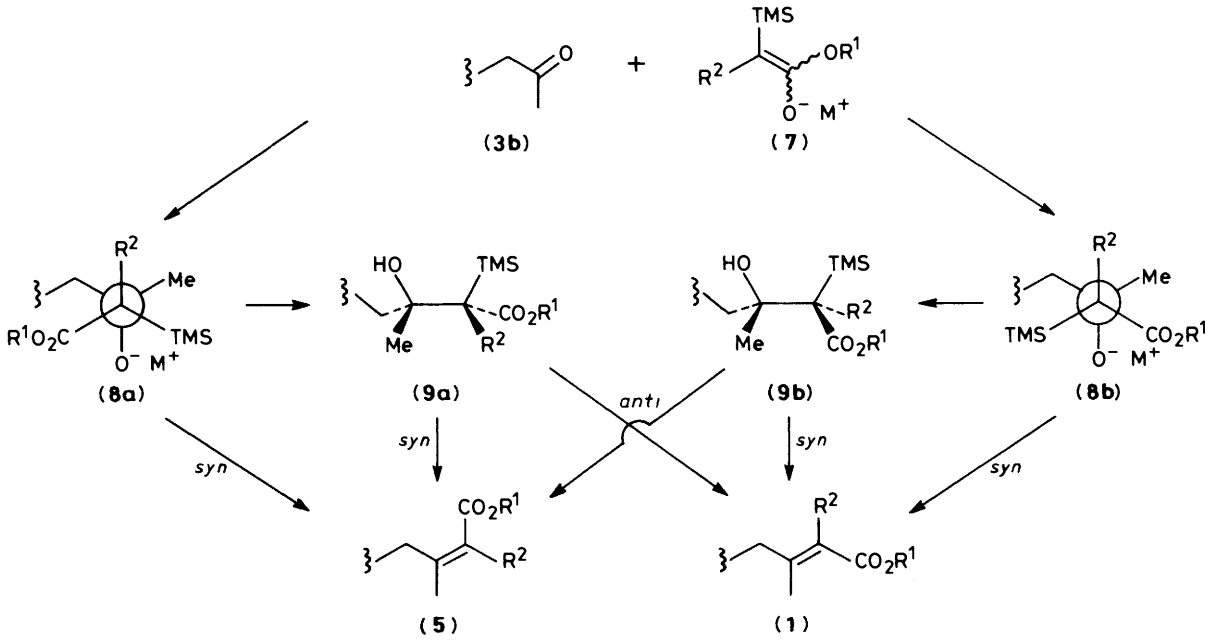
tetrasubstituted α,β-unsaturated esters were examined. Application of the method of Tanaka,[11] in which dianions of ethyl mercaptoacetate or ethyl mercaptopropionate prepared from the esters with LDA at −78 °C were treated with the ketone **(3b)**, met with limited success. The reaction initially involves formation of compound **(2g)** which, on reaction with ethyl chloroformate, affords, after work-up, a 1:4 mixture of esters **(1f)** and **(5b)** in 44% overall yield. The final stage of the reaction proceeds *via* spontaneous elimination of sulphur from a thiirane intermediate derived from **(2h)**. However, no reaction was observed with the dianion of ethyl 2-mercaptopropionate.

The Peterson method of olefination using anions of α-silyl esters[12] has, however, been used successfully for preparing 2-methyl- and 2-chloro-substituted esters of monic acid **(1b)** and isomonic acid **(5a)**. The silyl esters **(6e—j)** and acids **(6k** and **l)** were prepared by standard literature methods.[13-17] Anions of the α-silyl esters **(6e—j)** and dianions of the α-silyl acids **(6k** and **l)** were generated with the appropriate amount of LDA in tetrahydrofuran (THF) at −78 °C followed by addition of the ketone **(3b)** also in THF at the same temperature. In all cases, the reactions were very fast with completion of olefin formation as indicated by t.l.c. occurring in less than 15 minutes at −78 °C. After acid-catalysed removal of the *O*-trimethylsilyl ether protecting groups followed by chromatography on silica gel the pure *E* and *Z* enoic esters were obtained. In the reactions with the dianions derived from **(6k** and **l)**, the resulting mixture of enoic acids was converted into the methyl esters with diazomethane to facilitate isomer separation and isolation. The isolated yields and isomer ratios of the products of these reactions are summarised in the Table.

Assignments of the stereochemistry of the trisubstituted acrylates were made on the basis of ^1H and ^{13}C chemical shifts of the 3-CH_3 and 4-H_2 groups by analogy with the previously reported cases.[5] For example, in the *E*-isomer **(1f)** the signals for 3-CH_3 occur at δ_H 2.26 and δ_C 19.0 p.p.m. while those for 4-H_2 occur at δ_H 2.27 and 2.55 and δ_C 42.9 p.p.m. This pattern changes in the *Z*-isomer **(5b)** where 3-CH_3 resonates at δ_H 2.02 and δ_C 27.0 p.p.m. while 4-H_2 gives signals at δ_H 2.78 and 3.04 and δ_C 35.4 p.p.m. In the tetrasubstituted cases the changes in the ^1H n.m.r. spectra are analogous but the ^{13}C spectra are not indicative. For example in the *E*-isomer **(1j)** the 3-CH_3 resonates at δ_H 2.02 and 21.5 p.p.m., while 4-H_2 gives signals at δ_H 2.32 and 2.58 and δ_C 38.1 p.p.m.; and in the *Z*-isomer **(5f)** signals for 3-CH_3 occur at δ_H 1.80 and δ_H 21.5 p.p.m. while those for 4-H_2 occur at δ_H 2.63 and 2.75 and δ_C 38.6 p.p.m.

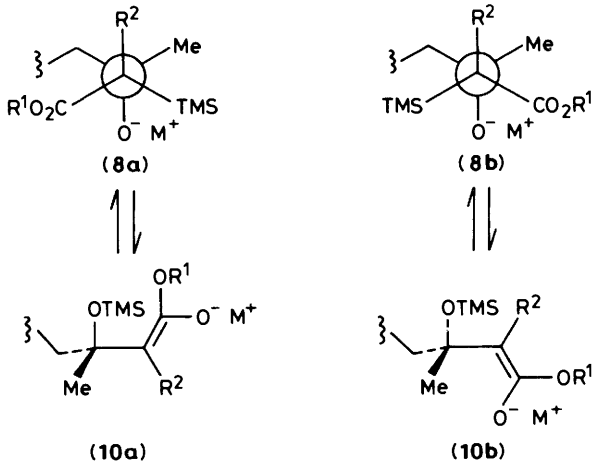
Although reasonable yields were generally observed, stereoselectivity in 2-substituted cases favoured the biologically less desirable *Z*-isomers [*E* in the case of **(5g)**]. The mechanism for the reaction is outlined in Scheme 2 and is believed to involve initial formation of the diastereoisomeric β-alkoxysilanes **(8a)** and **(8b)**, which undergo spontaneous *syn*-elimination even at low temperatures (−78 °C).[18] Therefore, if the intermediate β-hydroxysilanes **(9a)** and **(9b)** could be trapped, *anti*-elimination[19] under acid-catalysed conditions would reverse the stereoselectivity observed and thus, in the 2-substituted cases, afford a mixture of isomers favouring the more desirable *E*-isomers [*Z* in the case of **(1k)**]. Following the work of Larchevêque and Debal[18] and in view of our failure to trap compounds **(9a)** and **(9b)** at low temperature by either protonation or mesylation, attempts were made to change the counter-ion (M^+) from lithium to magnesium. In contrast to Larchevêque's[18] findings, use of the magnesium enolate **(7)** derived from **(6g)** followed by addition of the ketone **(3b)** did not allow isolation of β-hydroxysilanes **(9a)** and **(9b)**, corresponding to **(2i)**. However, stereoselectivity was reversed in favour of the *E*-isomer with a ratio of **(1j)** to **(5f)** of 2.5:1. This isomer ratio was not influenced by addition of hexamethylphosphoric triamide.[20] The instability of the tetrasubstituted hydroxysilanes **(2i)** may well be due to steric factors with subsequent release of strain to give the tetrasubstituted α,β-unsaturated ester, compared with the more stable disubstituted hydroxysilanes studied by Larchevêque.[18]

The stereochemical outcome of the reaction is intriguing, but no satisfactory explanation can be offered. A direct analogy can be drawn with reactions of anions of the stabilised phosphonate reagents such as **(6a)** with ketones in which indirect equilibration of the intermediate betaines can occur. A preponderance of the more stable betaine results and, in the case of reactions with aldehydes, affords predominantly the *E*-isomer.[21] However, similar equilibration of the β-alkoxysilanes **(8)** at such low temperatures seems unlikely. Formation of the kinetically preferred β-alkoxysilane **(8a)** or **(8b)** followed by synchronous elimination to the olefin may offer an explanation for the stereochemical outcome of these reactions. Larson *et al.*[22] have also studied the reaction and suggest that the elimination is not totally synchronous but stepwise involving a β-silyloxy enolate



Scheme 2. TMS = Me_3Si, M = Li or Mg

(**10**) (Scheme 3). The stereochemistry of the product is thus dependent on the preponderance of the prepared conformer (**10a**) or (**10b**).



Scheme 3.

Experimental

^{1}H N.m.r. data were recorded at either 60 MHz on a Perkin-Elmer R24A or 250 MHz on a Bruker WM 250 instrument and ^{13}C measurements were obtained using a Bruker WM 250 spectrometer; all n.m.r. data were recorded at ambient temperatures with tetramethylsilane as internal standard. The numbering system used for assigning the chemical shifts is that shown in formula (**1**). Mass spectra were obtained at 70 eV using a VG 70-70F instrument operating at 8 eV. Column chromatography was carried out on Merck Kieselgel H (type 60). T.l.c. was performed on pre-coated Merck Kieselgel 60 F_{254} plates. High-performance liquid chromatography (h.p.l.c.) was performed on a Waters Associates instrument using a C_{18} μ-Bondapak reverse-phase column with ammonium acetate buffer–methanol solutions as eluant. Both t.l.c. and h.p.l.c. were performed routinely on all compounds. THF, triethylamine, and di-isopropylamine were dried over calcium hydride and distilled before use. Solutions of LDA in THF were prepared immediately before use from 1.6M butyl-lithium in hexane and di-isopropylamine.

Tris(trimethylsilyl) Ether (**3b**).—To a solution of {(2*S*,3*R*,-4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-(2,3-epoxy-5-hydroxy-4-methyl-hexyl)]-3,4-dihydroxytetrahydropyran-2-yl}acetone (**3a**) (9.06 g, 30 mmol) in THF (250 ml) at 0 °C was added triethylamine (13.0 ml, 93 mmol) followed by trimethylsilyl chloride (11.8 ml, 93 mmol) and a catalytic amount of 4-(*NN*-dimethylamino)pyridine. The cooling bath was removed and the solution was stirred at room temperature for a further 2.5 h. After this time t.l.c. (25% Et_2O–hexane) indicated the reaction to be complete. The solution was filtered, concentrated under reduced pressure, then dissolved in THF (100 ml) and filtered again to give a solution of the ketone (**3b**) (30 mmol).

Hydrolysis of Tris(trimethylsilyl) Ethers.—The tris(trimethylsilyl) ether (**3b**) was dissolved in THF–water (4:1; 0.01 g ml^{-1}) and treated with conc. hydrochloric acid (1 drop/5 ml) for 5 min then quenched with aqueous sodium hydrogen carbonate. Extraction with ethyl acetate, drying ($MgSO_4$), and removal of solvent under reduced pressure gave the triol which was further purified by column chromatography on silica (10:1) using 0—6% methanol–dichloromethane as eluant.

Ethyl 2-Fluoromonate (**1g**) *and Ethyl 2-Fluoroisomonate* (**5c**).—To a suspension of sodium hydride (50% in oil; 1.58 g, 33 mmol) in dry THF (50 ml) at 0 °C was slowly added a solution of ethyl *OO*-diethylphosphonofluoroacetate (7.97 g, 33 mmol) in dry THF (50 ml). When addition was complete (~20 min) the ice-bath was removed and the mixture was stirred at room temperature for 2 h. The resulting slightly cloudy, pale orange solution was cooled to 0 °C and the ketone (**3b**) (30 mmol) was added dropwise. During the addition the solution cleared and darkened in colour and a syrupy material was deposited on the flask. The mixture was then stirred at room temperature for 15

h, then aqueous ammonium chloride was added, and the mixture was extracted with ethyl acetate (3 × 100 ml). The organic phase was washed with brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a crude material (21.2 g). Hydrolysis of the trimethylsilyl ethers followed by chromatography as described yielded two major components, *ethyl 2-fluoroisomonate* (**5c**) (4.12 g, 35%), m.p. 71—72 °C; $\nu_{max.}$(film) 3 600—3 200, 2 980, 1 720, 1 660, 1 300, 1 150—1 050, and 755 cm^{-1}; $\lambda_{max.}$(EtOH) 227 nm (ε 10 300); δ_H (250 MHz; $CDCl_3$) 0.94 (3 H, d, *J* 6 Hz, 17-H_3), 1.21 (3 H, d, *J* 6 Hz, 14-H_3), 1.35 (3 H, t, *J* 7 Hz, OCH_2CH_3), 1.68 (2 H, t, *J* 6 Hz, 9-H_2), 1.95 (3 H, d, J_{H-F} 5 Hz, 15-H_3), 2.00 (1 H, m, 8-H), 2.70 (1 H, dd, *J* 7 and 1 Hz, 11-H), and 4.28 (2 H, q, *J* 7 Hz, $CO_2CH_2CH_3$); δ_C($CDCl_3$) 12.6 (C-17), 14.1 (OCH_2CH_3), 17.7 (d, *J* 9.8 Hz, C-15), 20.7 (C-14), 31.8 (C-9), 33.9 (C-4), 39.2 (C-8), 42.8 (C-12), 55.8 (C-10), 61.2 and 61.5 (C-11 and OCH_2), 65.6 (C-16), 68.4 (C-6), 70.2 (C-7), 71.1 (C-13), 76.4 (C-5), 132.2 (d, *J* 11.8 Hz, C-3), 144.6 (d, *J* 252 Hz, C-2), and 162.2 (d, *J* 33.5 Hz, C-1); *m/z* (C.I., NH_3; relative intensity) 408 (MNH_4^+, 35%), 391 (MH^+, 100), 373 (90), 355 (45), 227 (40), and 183 (53); and *ethyl 2-fluoromonate* (**1g**) (2.28 g, 19.5%), m.p. 68—69 °C; $\nu_{max.}$(film) 3 600—3 200, 2 980, 1 720, 1 660, 1 305, 1 150—1 050, and 755 cm^{-1}; $\lambda_{max.}$(EtOH) 228 nm (ε 10 100); δ_H (250 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 6 Hz, 17-H_3), 1.22 (3 H, d, *J* 6 Hz, 14-H_3), 1.34 (4 H, m and t, *J* 7 Hz, OCH_2CH_3), 1.71 (2 H, m, 9-H_2), 2.00 (1 H, m, 8-H), 2.15 (3 H, d, *J* 4 Hz, 15-H_3), 2.55 (2 H, m, 4-H_2), 2.73 (1 H, dd, *J* 6 and 1 Hz, 11-H), 2.82 (1 H, m, 10-H), and 4.26 (2 H, q, *J* 7 Hz, OCH_2CH_3); δ_C($CDCl_3$) 12.7 (C-17), 14.2 (OCH_2CH_3), 17.2 (C-15), 20.8 (C-14), 31.7 (C-9), 34.3 (d, *J* 7.9 Hz, C-4), 39.3 (C-8), 42.8 (C-12), 55.7 (C-10), 61.1 and 61.3 (OCH_2 and C-11), 65.5 (C-16), 69.4 (C-6), 70.4 (C-7), 71.3 (C-13), 75.3 (C-5), 130.7 (d, *J* 11.9 Hz, C-3), 145.2 (d, *J* 246 Hz, C-2), and 161.4 (d, *J* 35 Hz, C-1); *m/z* 390 (M^+, < 1%), 227 (46), 97 (53), 71 (60), 69 (90), 57 (49), 55 (64), 45 (90), 43 (100), and 41 (94) (Found: M^+, 390.2075. $C_{19}H_{31}FO_7$ requires *M*, 390.2051).

Reaction of Methyl Monate (**1c**) *with Benzeneselenenyl Bromide*.—To a solution of methyl monate (**1c**) (358 mg, 1.00 mmol) and triethylamine (0.43 ml, 3.10 mmol) in THF (20 ml) was added trimethylsilyl chloride (0.39 ml, 3.10 mmol) and a catalytic amount of 4-(*NN*-dimethylamino) pyridine. After the mixture had been stirred at room temperature for 2 h the triethylamine hydrochloride was filtered off and the solution was concentrated under reduced pressure. The resultant oil was taken up in ethyl acetate, washed successively with water and brine, then dried ($MgSO_4$). Removal of solvent under reduced pressure gave the tris(trimethylsilyl) ether which was taken up in dichloromethane (2 ml) and treated with benzeneselenenyl bromide (708 mg, 3.0 mmol) and pyridine (0.24 ml, 3.00 mmol) at 37 °C for 5 days. The mixture was poured into water then extracted with ethyl acetate and the extract was dried ($MgSO_4$). Removal of solvent under reduced pressure gave the crude tris(trimethylsilyl) ether as an oil which was hydrolysed and chromatographed as described to give a material (64 mg, 0.11 mmol) with the following characteristics; $\nu_{max.}$(film) 3 600—3 200, 2 970, 1 730, 1 435, 1 125, 1 110, and 730 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 0.92 (3 H, d, *J* 7 Hz, 17-H_3), 1.20 (3 H, d, *J* 7 Hz, 14-H_3), 1.50 (3 H, s, 15-H_3), 3.65 (3 H, s, CO_2CH_3) and 7.2—7.9 (5 H, m, Ph).

Ethyl Monate (**1f**) *and Ethyl Isomonate* (**5b**).—*From the ketone* (**3b**) *and the dienolate of ethyl 2-mercaptoacetate*. Tetramethylenediamine (0.66 ml, 4.4 mmol) was added to a solution of LDA (4.4 mmol) in THF (10 ml at −78 °C). A solution of ethyl 2-mercaptoacetate (0.24 g, 2 mmol) in THF (5 ml) was then added and the reaction mixture was stirred for 1 h at −78 °C to form the dianion. A solution of the protected ketone (**3b**) (2 mmol) in THF was added dropwise and the solution was stirred at −78 °C for 2 h before being quenched with ethyl chloroformate (0.16 ml, 2 mmol). After a further 0.5 h at −78 °C the solution was warmed to room temperature and finally quenched with aqueous ammonium chloride. Extraction with ethyl acetate, drying of the extract ($MgSO_4$), and removal of solvent under reduced pressure gave an oil. The tris(trimethylsilyl) ether was hydrolysed and chromatographed as described to yield two major components, ethyl isomonate[5] (**5b**) (0.204 g, 27%) and ethyl monate[5] (**1f**) (0.05 g, 7%).

t-Butyl 2-(Trimethylsilyl)propionate (**6f**).—t-Butyl trimethylsilylacetate (9.40 g, 50 mmol) in THF (10 ml) was added dropwise to a cooled (−78 °C) solution of LDA (55 mmol) in THF (50 ml) and stirred for 1 h. Methyl iodide (3.1 ml, 50 mmol) was then added, and the solution was stirred for a further 1 h at −78 °C, then at room temperature for 1 h before being quenched with aqueous ammonium chloride. The mixture was extracted with ether, the extract was dried ($MgSO_4$), the solvent removed at atmospheric pressure, and the residue vacuum-distilled to give the title compound (6.96 g, 69%), b.p. 68 °C at 10 mmHg; $\nu_{max.}$(film) 2 980, 1 710, 1 455, 1 390, 1 365, 1 320, 1 250, 1 210, 1 150, 1 050, 1 025, 980, 900, 840, and 750 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 0.05 (9 H, s, $SiMe_3$), 1.10 (3 H, d, *J* 7 Hz, CH_3), 1.40 (9 H, s, CO_2CMe_3), and 1.90 (1 H, q, *J* 7 Hz, CH); *m/z* (C.I., NH_3) 219 (MNH_4^+, 7%), 203 (MH^+, 9), 164 (73), 147 (22), 131 (16), 90 (100), and 74 (15).

2-(*Trimethylsilyl*)*propionic acid* (**6l**).—A solution of trimethylsilylacetic acid (5.00 g, 37.9 mmol) in THF (10 ml) was added to a solution of LDA (83.4 mmol) in THF (50 ml) at 0 °C and the mixture was stirred for 1 h. Methyl iodide (2.64 ml, 41.7 mmol) was then added and the solution was stirred for 1 h at 0 °C and for a further 1 h at room temperature. The mixture was quenched to pH 2 with 1M hydrochloric acid then extracted with ether and the extract was dried ($MgSO_4$). Removal of solvent gave a crude material which was recrystallised from hexane at low temperature (3.53 g, 64%), m.p. 57—58 °C; $\nu_{max.}$(KBr) 3 500—2 500, 2 960, 1 685, 1 410, 1 320, 1 250, 1 140, 1 080, 1 030, and 850 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 0.1 (9 H, s, $SiMe_3$), 1.10 (3 H, d, *J* 7 Hz, CH_3), 2.0 (1 H, q, *J* 7 Hz, CH), and 11.3 (1 H, s, CO_2H); *m/z* 131 ($M^+ - CH_3$, 8%), 86 (11), 75 (100), 73 (69), 56 (52), 45 (56), and 43 (45).

General Procedure for the Peterson Olefination Reaction.—To a solution of LDA (2.64 mmol) in THF (10 ml) at −78 °C was added a solution of a trimethylsilyl-substituted carboxylate (**6e—j**) (2.40 mmol) in THF (5 ml). After 1 h at −78 °C a solution of the ketone (**3b**) (2 mmol) in THF was added and the mixture was stirred for 1 h at −78 °C, then for a further 1 h at room temperature. The reaction mixture was quenched with aqueous ammonium chloride then extracted with ethyl acetate and the extract was dried ($MgSO_4$). The solvent was removed under reduced pressure and the resultant tris(trimethylsilyl) ethers were hydrolysed and chromatographed as described.

t-Butyl Monate (**1h**) *and t-Butyl Isomonate* (**5d**).—The anion of t-butyl trimethylsilylacetate was formed and treated with the ketone (**3b**) as described in the general methods to give *t-butyl isomonate* (**5d**) (112.3 mg, 14%); $\nu_{max.}$(film) 3 600—3 200, 2 980, 2 930, 1 680, 1 640, 1 450, 1 370, 1 250, 1 150, 1 050, 910, 860, and 730 cm^{-1}; $\lambda_{max.}$(EtOH) 224 nm (ε 12,380); δ_H (250 MHz, $CDCl_3$) 0.94 (3 H, d, *J* 7 Hz, 17-H_3), 1.21 (3 H, d, *J* 7 Hz, 14-H_3), 1.30 (1 H, q, *J* 7 Hz, 12-H), 1.47 (9 H, s, CO_2CMe_3), 1.50—1.85 (2 H, m, 9-H_2), 2.00 (4 H, s and m, 15-H_3 and 8-H), 2.40 (1 H, br s, OH), 3.06 (1 H, dd, *J* 11 and 4 Hz, 4-H), 5.10 (1 H, br s, OH), and 5.76 (1 H, br s, 2-H); δ_C($CDCl_3$) 12.6 (C-17), 20.7 (C-14), 26.9 (C-15), 28.2 (CO_2CMe), 31.9 (C-9), 35.3 (C-4), 39.0 (C-8), 42.9 (C-12), 55.9 (C-10), 61.3 (C-11), 65.6 (C-16), 67.6 (C-6), 70.2 (C-7), 71.1 (C-13),

76.4 (C-5), 80.9 (CO_2CMe_3), 119.6 (C-2), 157.1 (C-3), and 167.9 (C-1); *m/z* (C.I., NH_3) 418 (MNH_4^+, 4%), 401 (MH^+, 15), 345 (50), 327 (100), 309 (25), and 227 (16); and *t-butyl monate* (**1h**) (251 mg, 32%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 920, 1 705, 1 645, 1 450, 1 390, 1 365, 1 240, 1 140, 1 050, 905, and 830 cm^{-1}; $\lambda_{max.}$(EtOH) 224 nm (ε 15 740); δ_H (250 MHz; $CDCl_3$) 0.94 (3 H, d, *J* 7 Hz, 17-H_3), 1.22 (3 H, d, *J* 7 Hz, 14-H_3), 1.35 (1 H, q, *J* 7 Hz, 12-H), 1.47 (9 H, s, CO_2CMe_3), 1.73 (2 H, m, 9-H_2), 2.00 (1 H, m, 8-H), 2.16 (3 H, s, 15-H_3), 2.27 (1 H, dd, *J* 8 and 13 Hz, 4-H), 2.55 (3 H, m, 2 OH and 4-H), 2.70 (2 H, m, 11-H and OH), 2.81 (1 H, dt, *J* 2 and 5 Hz, 10-H), and 5.68 (1 H, s, 2-H); δ_C($CDCl_3$) 12.7 (C-17), 18.8 (C-15), 20.8 (C-14), 28.3 (CO_2CMe_3), 31.7 (C-9), 39.5 (C-8), 42.8 (C-12 and C-4), 55.6 (C-10), 61.3 (C-11), 65.4 (C-16), 69.1 (C-6), 70.4 (C-7), 71.3 (C-13), 75.0 (C-5), 79.8 (CO_2CMe_3), 119.5 (C-2), 154.9 (C-3), and 166.4 (C-1); *m/z* 344 ($M^+ - C_4H_8$, < 1%), 227 (30), 111 (53), 95 (38), 71 (40), 69 (58), 57 (100), 55 (50), 43 (73), and 41 (97).

t-Butyl 2-Methylmonate (**1i**) *and t-Butyl 2-Methylisomonate* (**5e**).—The anion of t-butyl 2-(trimethylsilyl)propionate was prepared and treated with the ketone (**3b**) as described in the general method to give *t-butyl 2-methylisomonate* (**5e**) (0.502 g, 61%); $\nu_{max.}$(film) 3 600—3 200, 2 980, 2 930, 1 690, 1 450, 1 370, 1 290, 1 250, 1 165, 1 100, 910, 850, and 730 cm^{-1}; $\lambda_{max.}$(EtOH) 225 nm (ε 7 760); δ_H (250 MHz; $CDCl_3$) 0.95 (3 H, d, *J* 7 Hz, 17-H_3), 1.21 (3 H, d, *J* 7 Hz, 14-H_3), 1.30 (1 H, q, *J* 7 Hz, 12-H), 1.50 (9 H, s, CO_2CMe_3), 1.70 (2 H, m, 9-H_2), 1.83 (3 H, s, 2-CH_3), 1.87 (3 H, s, 15-H_3), 2.00 (1 H, m, 8-H), 2.40 (1 H, br s, OH), 2.65 (2 H, m, 11-H and 4-H), 2.77 (2 H, m, 10-H and 4-H), and 5.38 (1 H, d, OH); δ_C($CDCl_3$) 12.6 (C-17), 16.0 (C-15), 20.7 (C-14, 2-CH_3), 28.2 (CO_2CMe_3), 31.9 (C-9), 38.7 (C-4), 39.1 (C-8), 42.9 (C-12), 55.9 (C-10), 61.2 (C-11), 65.7 (C-16), 68.4 (C-6), 70.5 (C-7), 71.1 (C-13), 76.1 (C-5), 81.5 (CO_2CMe_3), 126.3 (C-2), 142.6 (C-3), and 171.1 (C-1); *m/z* (C.I., NH_3) 415 (MH^+, 5%), 359 (22), 342 (21), 341 (100), 227 (14), 125 (35), 111 (22), 97 (25), 72 (30), 58 (61), and 44 (51); and *t-butyl 2-methylmonate* (**1i**) (0.069 g, 8.5%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 930, 1 700, 1 450, 1 370, 1 290, 1 250, 1 170, 1 110, 910, 850, and 730 cm^{-1}; $\lambda_{max.}$(EtOH) 225 nm (ε 8 720); δ_H (250 MHz; $CDCl_3$) 0.95 (3 H, d, *J* 7 Hz, 17-H_3), 1.22 (3 H, d, *J* 7 Hz, 14-H_3), 1.30 (1 H, m, 12-H), 1.50 (9 H, s, CO_2CMe_3), 1.74 (2 H, m, 9-H_2), 1.86 (3 H, s, 2-CH_3), 1.97 (3 H, br s, 15-H_3), 2.00 (1 H, m, 8-H), 2.33 (1 H, m, 4-H), 2.54 (1 H, m, 4-H), 2.70 (1 H, dd, *J* 9 and 2 Hz, 11-H), and 2.82 (1 H, dt, *J* 2 and 7 Hz, 10-H); δ_C($CDCl_3$) 12.7 (C-17), 15.9 (C-15), 20.8 (C-14), 21.1 (2-CH_3), 28.3 (CO_2CMe_3), 31.8 (C-9), 37.7 (C-4), 39.5 (C-8), 42.9 (C-12), 55.7 (C-10), 61.4 (C-11), 65.4 (C-16), 69.6 (C-6), 70.6 (C-7), 71.3 (C-13), 76.1 (C-5), 80.5 (CO_2CMe_3), 126.5 (C-2), 139.8 (C-3), and 170.1 (C-1); *m/z* (C.I., NH_3) 432 (MNH_4^+, 9%), 415 (MH^+, 8), 376 (14), 359 (32), 358 (27), 341 (100), 323 (11), 227 (17), 155 (14), 125 (15), and 58 (35).

Methyl Monate (**1c**) *and Methyl Isomonate* (**5j**).—The dianion of trimethylsilylacetic acid was prepared (2.2 equiv. of LDA at 0 °C) and treated with the ketone (**3b**) as in the general method. The crude material was treated with excess of diazomethane, then treatment as before gave methyl isomonate [5] (0.087 g, 12%) and methyl monate [5] (0.037 g, 5%).

Ethyl 2-Methylmonate (**1j**) *and Ethyl 2-Methylisomonate* (**5f**).—(a) Via (**6g**). The anion of ethyl 2-(trimethylsilyl)propionate was prepared and treated with the ketone (**3b**) as in the general method to give *ethyl 2-methylisomonate* (**5f**) (0.445 g, 58%); $\nu_{max.}$(film) 3 600—3 200, 2 980, 2 920, 1 690, 1 625, 1 450, 1 380, 1 275, 1 190, 1 090, 900, and 750 cm^{-1}; $\lambda_{max.}$(EtOH) 227 nm (ε 7 440); δ_H($CDCl_3$) 0.95 (3 H, d, *J* 7 Hz, 17-H_3), 1.25 (7 H, m, 14-H_3, 12-H, and OCH_2CH_3), 1.55 (2 H, m, 9-H_2), 1.80 (6 H, s, 15-H_3 and 2-CH_3), 1.95 (1 H, m, 8-H), and 4.15 (2 H, q, *J* 7 Hz, OCH_2CH_3); and *ethyl 2-methylmonate* (**1j**) (0.149 g, 19%) which crystallised from benzene to give fine white needles, m.p. 89—90 °C; $\nu_{max.}$ (liquid film) 3 600—3 200, 2 970, 2 930, 1 700, 1 635, 1 450, 1 370, 1 280, 1 215, 1 100, 1 050, and 905 cm^{-1}; $\lambda_{max.}$(EtOH) 225 nm (ε 9 390); δ_H (250 MHz; $CDCl_3$) 0.94 (3 H, d, *J* 7 Hz, 17-H_3) 1.22 (3 H, d, *J* 7 Hz, 14-H_3), 1.30 (3 H, t, *J* 7 Hz, OCH_2CH_3), 1.35 (1 H, m, 12-H), 1.73 (2 H, m, 9-H_2), 1.89 (3 H, m, 2-CH_3), 2.02 (4 H, m, 15-H_3 and 8-H), 2.32 (1 H, dd, *J* 9 and 15 Hz, 4-H), 2.58 (1 H, dd, *J* 4 and 15 Hz, 4-H), 2.72 (1 H, dd, *J* 7 and 1 Hz, 11-H), 2.82 (1 H, dt, *J* 1 and 7 Hz, 10-H), and 4.19 (2 H, q, *J* 7 Hz, OCH_2CH_3); δ_C($CDCl_3$) 12.6 (C-17), 14.3 (OCH_2CH_3), 15.8 (C-15), 20.8 (C-14), 21.4 (2-CH_3), 31.8 (C-9), 38.0 (C-4), 39.6 (C-8), 42.8 (C-12), 55.7 (C-10), 60.2 (OCH_2CH_3), 61.3 (C-11), 65.5 (C-16), 69.6 (C-6), 70.5 (C-7), 71.2 (C-13), 76.1 (C-5), 124.8 (C-3), 142.9 (C-2), and 170.3 (C-1); *m/z* 386 (M^+, 3%), 227 (69), 141 (56), 125 (66), 97 (75), 95 (63), 69 (100), 55 (64), and 43 (96) (Found: M^+, 386.2294. $C_{20}H_{34}O_7$ requires *M*, 386.2360).

(b) Via (**6i**). The anion of ethyl 2-(diphenylmethylsilyl)-propionate was prepared and treated with the ketone (**3b**) as in the general method to give ethyl 2-methylisomonate (**5f**) (0.202 g, 27%) and ethyl 2-methylmonate (**1j**) (0.117 g, 16%).

(c) Via *the magnesium enolate of* (**6g**). To a solution of LDA (2.64 mmol) in THF (10 ml) at −78 °C was added ethyl 2-(trimethylsilyl)propionate (0.418 g, 2.4 mmol) and the mixture was stirred for 0.5 h to form the enolate before being treated with a solution of magnesium bromide in THF [from magnesium (0.68 g, 2.4 mg-atom) and dibromoethane (0.21 ml, 2.4 mmol]. After 0.5 h at −78 °C the mixture was treated with a solution of the ketone (**3b**) in THF and stirred for 0.5 h at −78 °C, then for a further 0.5 h at room temperature. The reaction mixture was quenched with aqueous ammonium chloride then extracted with ethyl acetate and the extract was dried ($MgSO_4$). Removal of solvent under reduced pressure gave the tris(trimethylsilyl) ethers which were hydrolysed and chromatographed as described to give ethyl 2-methylisomonate (**5f**) (0.111 g, 15%) and ethyl 2-methylmonate (**1j**) (0.286 g, 37%).

Methyl 2-Methylmonate (**1d**) *and Methyl 2-Methylisomonate* (**5k**).— (a) *Reaction of the ketone* (**3b**) *with the anion of* (**6j**). The anion of (**6j**) was formed and treated with the ketone (**3b**) as described in the general methods to give, after esterification with excess of diazomethane, a mixture of *E* and *Z* isomers (**1d**) and (**5k**) in the ratio 3:1 (reverse-phase h.p.l.c.). Column chromatography allowed isolation of the E-*isomer* (**1d**) (0.115 g, 15%); $\nu_{max.}$(film) 3 600—3 200, 2 980, 2 930, 1 710, 1 640, 1 450, 1 380, 1 290, 1 220, 1 110, 1 060, 930, and 900 cm^{-1}; $\lambda_{max.}$(EtOH) 226 nm (ε 6 880); δ_H (250 MHz; $CDCl_3$) 0.94 (3 H, d, *J* 7 Hz, 17-H_3), 1.21 (3 H, d, *J* 7 Hz, 14-H_3), 1.34 (1 H, q, *J* 7 Hz, 12-H), 1.73 (2 H, m, 9-H_2), 1.89 (3 H, d, *J* 2 Hz, 2-CH_3), 2.00 (1 H, m, 8-H), 2.02 (3 H, d, *J* 2 Hz, 15-H_3), 2.32 (1 H, dd, *J* 15 and 9 Hz, 4-H), 2.58 (1 H, dd, *J* 15 and 3 Hz, 4-H), 2.72 (1 H, dd, *J* 8 and 2 Hz, 11-H), 2.82 (1 H, dt, *J* 2 and 5 Hz, 10-H), and 3.62 (3 H, s, CO_2CH_3); δ_C($CDCl_3$) 12.6 (C-17), 15.8 (2-CH_3), 20.8 (C-14), 21.5 (C-15), 31.8 (C-9), 38.1 (C-4), 39.6 (C-8), 42.8 (C-12), 51.3 (CO_2CH_3), 55.7 (C-10), 61.3 (C-11), 65.5 (C-16), 69.6 (C-6), 70.5 (C-7), 71.1 (C-13), 76.2 (C-5), 124.2 (C-2), 143.7 (C-3), and 170.6 (C-1); *m/z* 372 (M^+, 2%), 227 (65), 209 (23), 141 (47), 125 (57), 111 (53), 97 (62), 95 (57), 69 (95), 55 (62), and 43 (100) (Found: M^+, 372.2124. $C_{19}H_{32}O_7$ requires *M*, 372.2102).

(b) *Reaction of the ketone* (**3b**) *with the dianion of* (**6l**). The dianion of (**6l**) was prepared (2.2 equiv. of LDA at 0 °C) and treated with the ketone (**3b**) as described in the general methods. The crude material was treated with excess of diazomethane, then the tris(trimethylsilyl) ethers were hydrolysed and chromatographed as described to give *methyl 2-methylisomonate* (**5k**) (0.172 g, 23%), m.p. 83.5—84.0 °C; $\nu_{max.}$(film) 3 600 3 200, 2 970, 2 920, 1 700, 1 630, 1 435, 1 380, 1 280, 1 195, 1 110, 1 050, and 900 cm^{-1}; δ_H($CDCl_3$) 0.95 (3 H, d, *J* 7 Hz, 17-H_3), 1.21 (3 H, d, *J* 7 Hz, 14-H_3), 1.30 (1 H, q, *J* 7 Hz, 12-H), 1.55—1.85 (2 H, m,

9-H_2), 1.89 (3 H, br s, 2-CH_3), 1.92 (3 H, s, 15-H_3), 2.00 (1 H, m, 8-H), 2.63 and 2.75 (2 H, m, 4-H_2), 2.67 (1 H, dd, *J* 8 and 2 Hz, 11-H), 2.79 (1 H, dt, *J* 2 and 5 Hz, 10-H), and 3.73 (3 H, s, CO_2CH_3); δ_C($CDCl_3$) 12.5 (C-17), 15.8 (2-CH_3), 20.7 (C-14), 21.5 (C-15), 32.0 (C-9), 38.6 (C-4), 39.2 (C-8), 42.9 (C-12), 51.8 (OCH_3), 55.8 (C-10), 61.2 (C-11), 65.6 (C-16), 68.7 (C-6), 70.4, (C-7), 71.0 (C-13), 76.6 (C-5), 124.2 (C-2), 146.5 (C-3), and 171.0 (C-1); *m/z* 372 (M^+, 0.5%), 227 (74), 125 (96), 111 (50), 97 (79), 96 (54), 95 (54), 69 (94), 55 (62), and 43 (100) (Found: M^+, 372.2163. $C_{19}H_{32}O_7$ requires *M*, 372.2178); and methyl 2-methylmonate (**1d**) (0.091 g, 12%).

t-Butyl 2-Chloromonate (**1k**) *and t-Butyl 2-Chloroisomonate* (**5g**).—The anion of t-butyl trimethylsilyl-α-chloroacetate was prepared and treated with the ketone (**3b**) as in the general method to give *t-butyl 2-chloroisomonate* (**5g**) (0.483 g, 56%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 930, 1 710, 1 450, 1 370, 1 280, 1 255, 1 160, 1 050, 1 000, 900, 840, 810, and 735 cm^{-1}; $\lambda_{max.}$(EtOH) 231 nm (ε 5 990); δ_H (250 MHz; $CDCl_3$) 0.94 (3 H, d, *J* 7 Hz, 17-H_3), 1.21 (3 H, d, *J* 7 Hz, 14-H_3), 1.30 (1 H, q, *J* 7 Hz, 12-H), 1.53 (9 H, s, CO_2CMe_3), 1.55—1.80 (2 H, m, 9-H_2), 2.03 (1 H, m, 8-H), 2.07 (3 H, s, 15-H_3), 2.39 (1 H, br s, OH), and 4.60 (1 H, br d, OH); δ_C($CDCl_3$) 12.7 (C-17), 20.7 (C-14), 22.8 (C-15), 28.0 (CO_2CMe_3), 31.9 (C-9), 38.0 (C-4), 39.1 (C-8), 43.0 (C-12), 55.9 (C-10), 61.3 (C-11), 65.7 (C-16), 68.2 (C-6), 70.4 (C-7), 71.3 (C-13), 76.0 (C-5), 83.7 (CO_2CMe_3), 121.1 (C-2), 145.6 (C-3), and 164.6 (C-1); *m/z* (C.I., NH_3) 454 (MNH_4^+, 4%), 452 (MNH_4^+, 12), 396 (27), 381 (36), 379 (100), 363 (35), 361 (97), 343 (25), 227 (75), and 209 (34); and an impure sample of t-butyl 2-chloromonate (**1k**) (0.016 g, 2%).

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