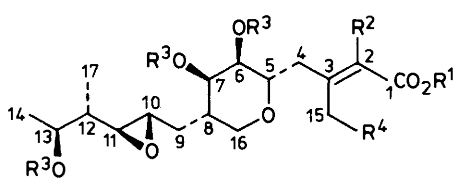
The Chemistry of Pseudomonic Acid.† Part 8.[1] Electrophilic Substitutions at C-2 and C-15 of the Pseudomonic Acid Nucleus by Means of Lithium Dienolates

Michael J. Crimmin, Peter J. O'Hanlon, and Norman H. Rogers *
Beecham Pharmaceuticals Research Division, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NT

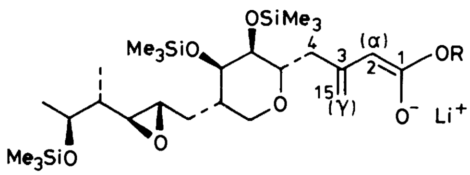
The regiochemistry of substitution at C-2 (α) and C-15 (γ) of lithium dienolates (**2**) derived from esters of monic acid (**1d**) depends on the nature of the electrophile. Substitution at C-2 affords diastereoisomeric mixtures of the deconjugated esters (**3**). The stereochemistry of reconjugation can be controlled. The ester (**3d**) when heated with hindered bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) favours formation of methyl 2-methylisomonate (**4f**) whilst, in contrast, use of potassium t-butoxide favours the biologically active methyl 2-methylmonate (**1m**).

The preparation of esters of 2-fluoromonic acid (**1a**) and 2-methylmonic acid (**1b**) by olefination reactions, particularly of the Peterson type, was described in the preceding publication.[1] As part of a continuing programme of chemical modification of the pseudomonic acid antibiotics a more direct method was explored for the introduction of a variety of substituents at C-2 and at C-15 of the nucleus of pseudomonic acid (**1c**). Dienolate anions (**2**) produced at low temperature were found to be useful and convenient intermediates for these reactions.



(**1**)

	R^1	R^2	R^3	R^4
a;	H	F	H	H
b;	H	Me	H	H
c;	$[CH_2]_8CO_2H$	H	H	H
d;	H	H	H	H
e;	Me	H	Me_3Si	H
f;	Me	H	H	H
g;	Et	H	H	H
h;	Et	H	Me_3Si	D
i;	Me	PhS	H	H
j;	Me	H	H	PhS
k;	Me	H	H	PhSe
l;	Me	Me	Me_3Si	$-CH(OH)C_6H_4Me$-*p*
m;	Me	Me	H	H
n;	Me	Et	H	H
o;	Me	$PhCH_2$	H	H
p;	Me	MeS	H	H
q;	Et	EtO_2C	H	H

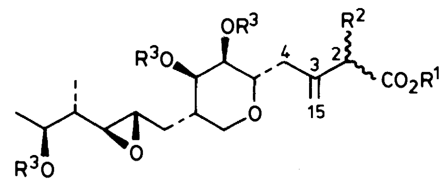


(**2**)

	R
a;	Me
b;	Et

Results and Discussion

The work described in this publication can be categorised into two main areas: the addition of electrophiles to the metal dienolates (**2**) at −78 °C and the reconjugation of the double bond in the products of α-addition (**3**).



(**3**)

	R^1	R^2	R^3
a;	Me	H	Me_3Si
b;	Me	H	H
c;	Et	D	Me_3Si
d;	Me	Me	Me_3Si
e;	Me	Me	H
f;	Me	Et	H
g;	Me	Pr^i	H
h;	Me	MeS	H
i;	Me	$PhCH_2$	H
j;	Me	PhS	H
k;	Me	Et	Me_3Si
l;	Me	$PhCH_2$	Me_3Si
m;	Me	MeS	Me_3Si
n;	Et	EtO_2C	Me_3Si

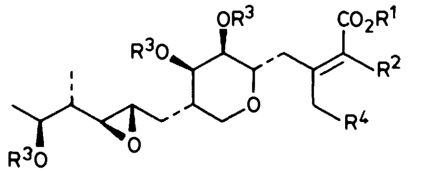
Reactions of Dienolates.—Electrophilic addition to lithium dienolates of the general structure (**2**) followed by stereoselective reconjugation of the double bond in the resulting products (**3**) offers an alternative and practical approach to the preparation of 2-substituted esters of monic acid (**1d**).

Before preparing lithium dienolates from esters of monic acid we protected the hydroxy groups as their trimethylsilyl ethers by reaction with trimethylsilyl chloride and triethylamine in tetrahydrofuran (THF) together with a catalytic quantity of 4-*NN*-dimethylaminopyridine (DMAP). The lithium dienolate (**2a**), for example, was prepared from the ester (**1e**) with lithium di-isopropylamide (LDA) in THF at −78 °C.

Electrophilic addition can occur at either the hard nucleophilic α-position (C-2) or the soft nucleophilic γ-position (C-15). The regiochemistry of addition is therefore dependent on the nature of the electrophile.[2] Addition to the α-position

† The approved generic name for pseudomonic acid is Mupirocin.

results in formation of the diastereoisomeric deconjugated esters (**3**) whilst addition to the γ-position affords mixtures of the conjugated esters (**1**) and (**4**) in varying ratios according to the electrophile.



(**4**)

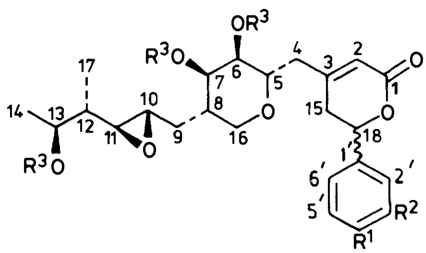
	R^1	R^2	R^3	R^4
a;	Me	H	H	H
b;	Me	H	Me_3Si	D
c;	Me	PhS	H	H
d;	Me	H	H	PhS
e;	Me	H	H	PhSe
f;	Me	Me	H	H
g;	Me	Et	H	H
h;	Me	$PhCH_2$	H	H
i;	Me	MeS	H	H

The regiochemistry of addition to the lithium dienolates (**2a** and **b**) prepared from methyl monate (**1f**) and ethyl monate (**1g**) has been exemplified with a variety of electrophilic reagents. When quenched with aqueous ammonium chloride, compound (**2a**) afforded a 3:1 mixture of the deconjugated product (**3a**) and (**1e**) which were separated by chromatography on silica gel. Removal of the trimethylsilyl ether protecting groups under mild acid conditions gave (**3b**) and methyl monate (**1f**). Formation of the isomeric methyl isomonate (**4a**) was not observed. The stereospecificity observed in the re-formation of the starting monate ester did not fortuitously result from incomplete formation of the dienolate (**2a**) since quenching with deuteriomethanol afforded α- and γ-deuteriated esters (**3c**) and (**1h**) in a similar 3:1 ratio, again without formation of the *Z*-isomer, (**4b**). After chromatographic separation, both esters (**3c**) and (**1h**) were shown by mass spectral analysis to have isotopic purities of >95%. Deuterium was not incorporated at C-4 thus confirming the selective formation of the dienolate (**2a**) with the C-3–C-15 *exo* double bond.[3] These results agree with the findings of Rathke and Sullivan[4] where deuteriation of the anion derived from ethyl crotonate gave an 87:13 mixture of ethyl 2-deuteriobut-3-enoate and ethyl 4-deuteriobut-2-enoate.

Addition of methyl iodide to the preformed lithium dienolate (**2a**) at −78 °C afforded almost exclusively the deconjugated product (**3d**), which after deprotection by mild acid hydrolysis gave the ester (**3e**) as a mixture of diastereoisomers in 43% overall yield. The C=O and C=C stretching frequencies of 1 725 and 1 640 cm^{-1} respectively are indicative of the non-conjugated enoate. In the ^1H n.m.r. spectrum the C-2 methyl protons appeared as two closely spaced doublets of equal intensity at δ 1.30, while the terminal olefinic methylene protons appeared as a multiplet at δ 5.05. The diastereoisomer ratio of approximately 1:1 was confirmed by the ^{13}C n.m.r. spectrum, in which doubling of the signals for carbons adjacent to C-2 was observed. Similarly the deconjugated esters (**3f**—**i**) were obtained in the respective yields of 29, 63, 70, and 33% using ethyl iodide, isopropyl iodide, methyl methanethiosulphonate,[5] and benzyl bromide.

However, reaction of the dienolate (**2a**) with diphenyl disulphide did not give, after work-up, the expected deconjugated ester (**3j**), but a 1:1 mixture of the conjugated esters (**1i**) and (**4c**) in a combined yield of 33%. The ester (**3j**) was presumably formed initially and the lithium thiophenolate liberated in the reaction acted as a base for reconjugation of the double bond. The products of γ-addition to the dienolate, (**1j**) and (**4d**), were not observed. In contrast diphenyl diselenide reacted regiospecifically at the γ-position of the dienolate (**2a**) to give, after deprotection and chromatography, a 2:1 mixture of the conjugated esters (**1k**) and (**4e**) in 51% overall yield. Separation of the selenides was achieved with difficulty and assignment of stereochemistry was made from the ^1H n.m.r. spectrum. In the monate ester (**1k**) the 15-H_2 signal appears as an AB quartet centred at δ_H 4.24 and the 4-H_2 signal at δ_H 2.35 and 2.80. The expected changes in chemical shifts for the isomonate ester (**4e**)[1] were observed, the 15-H_2 signal moving upfield to *ca.* δ_H 3.8 and the signal for 4-H_2 moves downfield to δ_H 3.05 and 3.15.

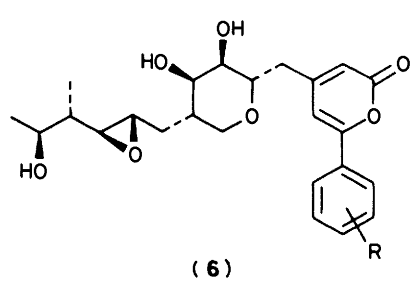
Carbonyl compounds are reported[6] to react at the γ-position of dienolates. Anisaldehyde was found to react smoothly and regiospecifically at C-15 of the dienolate (**2a**). However, the hydroxy ester (**1l**) was not isolated, but cyclised during the reaction to give the δ-lactone (**5a**). After deprotection and purification the lactone (**5b**) was obtained as a 1:1 mixture of diastereoisomers in 30% overall yield. Similarly benzaldehyde, *m*-nitrobenzaldehyde, *m*-cyanobenzaldehyde and thioanisaldehyde gave (**5c**—**f**) in yields of 55, 47, 37, and 68% respectively.



(**5**)

	R^1	R^2	R^3
a;	MeO	H	Me_3Si
b;	MeO	H	H
c;	H	H	H
d;	H	NO_2	H
e;	H	CN	H
f;	MeS	H	H

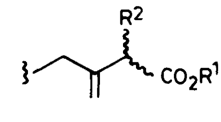
Attempts to prepare the corresponding pyrones (**6**) by either dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene or dioxane at reflux and also with 10% palladium–charcoal in diglyme at 160 °C failed. Condensation of the dienolate (**2a**) with methyl benzoate also failed to yield the pyrone (**6**; R = H).

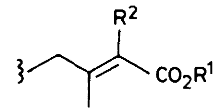
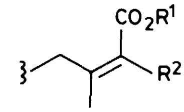


(**6**)

Reconjugation Studies.—Two methods for the reconjugation of the double bond in the trimethylsilyl-protected esters (**3d**, **k**—**m**) were studied. One involves the use of potassium t-butoxide in THF–t-butyl alcohol at 0 °C and tends to favour formation of the desired *E*-isomers. In contrast the use of the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in

Table.



Ratio[b]  : 

R^1	R^2	Compound	Reconjugation method[a]	Ratio[b]
Me	Me	**(3d)**	A	72 **(1m)**:28 **(4f)**
			B	21 **(1m)**:79 **(4f)**
Me	Et	**(3k)**	A	82 **(1n)**:14 **(4g)**
			B	23 **(1n)**:77 **(4g)**
Me	$PhCH_2$	**(3l)**	A	79 **(1o)**:21 **(4h)**
			B	55 **(1o)**:45 **(4h)**
Me	MeS	**(3m)**	B	55 **(1p)**:45 **(4i)**

[a] A = Bu'OH, 0 °C, THF–Bu'OH. B = DBU, THF (reflux), 24 h. [b] From h.p.l.c. peak heights before isolation.

THF under reflux with **(3d** and **k)** favours formation of the *Z*-isomers **(4f** and **g)** whilst with **(3l** and **m)** an approximately equimolar mixture of *E* and *Z* isomers was obtained. The ratio of isomeric products formed by the two methods is shown in the Table.

The assignment of *E* and *Z* stereochemistry of the trisubstituted acrylic esters methyl monate **(1f)** and methyl isomonate **(4a)** was assigned following the established procedure of the preceding paper.

The diester **(1q)** was prepared by reaction of the dienolate **(2b)** with ethyl chloroformate, followed by reconjugation of the initial product **(3n)** under comparatively mild conditions with DBU for 1 hour at room temperature, and then deprotection.

Only esters of 2-fluoromonic acid **(1a)** and 2-methylmonic acid **(1b)** possessed significant antibacterial and antimycoplasmal activity. Esters of 2-fluoromonic acid **(1a)** offered no advantages in metabolic stability. In contrast, esters of 2-methylmonic acid **(1b)** showed significant increases in stability in tissue homogenate and *in vivo* over analogous esters of monic acid **(1d)**. No antimicrobial activity was observed for either the deconjugated esters **(3)** or the dihydropyrones **(5)**.

Experimental

For general experimental conditions see the preceding paper.

General Method of Dienolate Formation for Compound **(2a)** *and Alkylation.*—To a solution of methyl monate **(1f)** (1.79 g, 5 mmol) and triethylamine (2.16 ml, 15.5 mmol) in THF was added trimethylsilyl chloride (1.97 ml, 15.5 mmol) and a catalytic amount of DMAP. 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 THF (10 ml) and refiltered ready for the next stage of the reaction.

A solution of LDA was prepared by reaction of butyl-lithium (4.84 ml; 1.55M in hexane) with di-isopropylamine (1.05 ml, 7.5 mmol) in THF (10 ml) at −78 °C for 15 min. The protected ester solution, *vide supra*, was added dropwise to the LDA solution and the mixture was stirred for 1 h at −78 °C before the addition of the electrophile (5.0 mmol). The solution was allowed to warm to room temperature in the cooling bath, then stirred overnight, quenched with aqueous ammonium chloride, extracted with ethyl acetate (3 × 50 ml), and the extract was dried ($MgSO_4$). Removal of solvent under reduced pressure gave the crude product which was used without purification in subsequent reactions.

General Method of Deprotection of Tris(trimethylsilyl) Ethers.—The protected material was taken up in THF–water (4:1; 10 mg ml^{-1}) and treated with conc. hydrochloric acid (1 drop/5 ml) for 5 min then finally 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 gel (10:1) using 0—3% dichloromethane–methanol as eluant.

Methyl 3-{[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]methyl}-2-methylbut-3-enoate **(3e)**.—The dienolate (1 mmol) was treated with methyl iodide (0.31 ml, 5 mmol) to yield the *title compound* as an oil (0.06 g, 43%); $\nu_{max.}$ (liquid film) 3 600—3 200, 2 960, 2 920, 1 725, 1 640, 1 450, 1 255, 1 120, 1 070, and 875 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.92 (3 H, d, *J* 7 Hz, 17-H_3), 1.22 (3 H, d, *J* 7 Hz, 14-H_3), 1.30 (3 H, 2 d, *J* 7 Hz, 2-CH_3), 1.36 (1 H, m, 12-H), 1.72 (2 H, m, 9-H_2), 2.00 (1 H, br m, 8-H), 2.24 (1 H, m, 4-H), 2.55 (1 H, m, 4-H), 2.74 (1 H, dd, *J* 7 and 1 Hz, 11-H), 2.82 (1 H, dt, *J* 1 and 7 Hz, 10-H), 3.25 (1 H, q, *J* 7 Hz, 2-H), and 5.05 (2 H, m, 15-H_2); δ_C($CDCl_3$) 12.6 (C-17), 16.2 and 16.5 (2-CH_3), 20.7 (C-14), 31.7 (C-9), 37.0 and 37.1 (C-4), 39.5 (C-8), 42.8 (C-12), 45.3 and 45.9 (C-2), 51.9 (OCH_3), 55.7 (C-10), 61.2 (C-11), 65.4 (C-16), 68.9 and 69.1 (C-6), 70.4 (C-7), 71.1 (C-13), 75.2 and 75.8 (C-5), 113.4 and 113.8 (C-15), 144.7 and 145.1 (C-3), and 175.3 (C-1); *m/z* (C.I., NH_3; rel. int.) 390 (MNH_4^+, 36%), 373 (MH^+, 100), 355 (72), and 337 (50).

Methyl 3-{[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]methyl}-2-isopropylbut-3-enoate **(3g)**.—The dienolate (1.5 mmol) was treated with isopropyl iodide (0.75 ml, 7.5 mmol) to give the crude product (2.24 g) as the tris(trimethylsilyl) ether. This material (1 g) was deprotected and chromatographed to yield the *title compound* as a mixture of diastereoisomers (0.409 g, 46%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 930, 2 880, 1 730, 1 645, 1 455, 1 435, 1 200, 1 160, 1 110, 1 045, and 905 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.89 and 0.93 (6 H, 2d, *J* 7 Hz, CH*Me*$_2$), 0.95 (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), 1.73 (2 H, t, *J* 7 Hz, 9-H_2), 2.00 (1 H, m, 8-H), 2.28 (1 H, dd, *J* 15 and 8 Hz, 4-H), 2.50 (1 H, m, 4-H), 2.72 (1 H, m, 11-H), 2.82 (1 H, dt, *J* 2 and 5 Hz, 10-H), 2.97 (2 H, br m, 2-H and OH), 3.67 and 3.68 (3 H, 2 s, CO_2CH_3), and 5.12 (2 H, m, 15-H_2); δ_C($CDCl_3$) 12.6 (C-17), 20.2 and 21.1 (CH*Me*$_2$), 20.7 (C-14), 29.5 and 30.1 (*C*HMe$_2$), 31.8 (C-9), 36.7 and 37.2 (C-4), 39.5 and 39.6 (C-8), 42.8 (C-12), 51.6 (CO_2CH_3), 55.7 (C-10), 60.3 (C-2), 61.3 (C-11), 65.3 (C-16), 69.0 and 69.4 (C-6), 70.5 (C-7), 71.1 (C-13), 75.4 and

75.5 (C-5), 115.4 and 115.5 (C-15), 142.8 (C-3), and 174.4 and 174.5 (C-1); *m/z* 400 (M^+, 0.6%), 227 (76), 153 (36), 141 (40), 111 (64), 97 (71), 95 (54), 83 (57), 81 (44), 71 (55), 69 (87), 67 (45), 57 (46), 55 (78), 45 (60), and 43 (100) (Found: M^+, 400.2481. $C_{21}H_{36}O_7$ requires *M*, 400.2458).

Methyl 3-{[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]methyl}-2-ethylbut-3-enoate (**3f**).—The dienolate (2 mmol) was treated with ethyl iodide (0.176 ml, 2.4 mmol) to give the crude product (1.1 g) as the tris(trimethylsilyl) ether. This material was deprotected (0.55 g) and chromatographed to yield the pure *title compound* as a mixture of diastereoisomers (0.112 g, 29%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 930, 2 880, 1 730, 1 645, 1 450, 1 430, 1 375, 1 240, 1 110, 1 040, and 900 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7 Hz, CH_2CH_3), 0.94 (3 H, d, *J* 7 Hz, 17-H_3), 1.23 (3 H, d, *J* 7 Hz, 14-H_3), 1.35 (1 H, q, *J* 7 Hz, 12-H), 1.55—1.95 (4 H, m, and t, *J* 6 Hz, CH_2CH_3 and 9-H_2), 2.00 (1 H, br, m, 8-H), 2.25 (1 H, dd, *J* 15 and 6 Hz, 4-H), 2.50 (1 H, dt, *J* 15 and 3 Hz, 4-H), 2.72 (1 H, dd, *J* 8 and 2 Hz, 11-H), 2.83 (1 H, dt, *J* 5 and 2 Hz, 10-H), 3.10 (1 H, m, 2-H), 3.70 (3 H, s, CO_2CH_3), and 5.09 (2 H, m, 15-H_2); δ_C($CDCl_3$) 12.2 (CH_2CH_3), 12.6 (C-17), 20.8 (C-14), 24.1 and 24.5 (CH_2CH_3), 31.8 (C-9), 37.0 and 37.1 (C-4), 39.5 (C-8), 42.8 (C-12), 51.8 (CO_2CH_3), 53.5 and 53.9 (C-2), 55.7 (C-10), 61.3 (C-11), 65.4 (C-16), 68.9 and 69.4 (C-6), 70.5 (C-7), 71.1 (C-13), 75.4 and 75.8 (C-5), 114.4 and 114.6 (C-15), 143.4 and 143.6 (C-3), and 174.7 (C-1); *m/z* 386 (M^+, 1%), 227 (70), 209 (19), 139 (67), 111 (54), 97 (71), 95 (62), 83 (63), 71 (64), 69 (93), 67 (64), 55 (99), and 41 (100) (Found: M^+, 386.2275. $C_{20}H_{34}O_7$ requires *M*, 386.2292).

Methyl 2-Benzyl-3-{[5-(2,3-epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]methyl}but-3-enoate (**3i**).—The dienolate (**2a**) (5 mmol) was treated with benzyl bromide (0.59 ml, 5 mmol) to give the crude product (2.31 g) as the tris(trimethylsilyl) ether. This material was deprotected (0.45 g) and chromatographed to yield the pure *title compound* as a mixture of diastereoisomers (0.145 g, 33%); ν_{max} (film) 3 600—3 200, 2 970, 2 930, 1 730, 1 645, 1 605, 1 495, 1 455, 1 435, 1 160, 1 110, 1 040, 910, and 700 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 7 Hz, 17-H_3), 1.21 (3 H, d, *J* 7 Hz, 14-H_3), 1.33 (1 H, q, *J* 7 Hz, 12-H), 1.71 (2 H, t, *J* 6 Hz, 9-H_2), 2.00 (1 H, m, 8-H), 2.28 (1 H, dd, *J* 15 and 7 Hz, 4-H), 2.50 (1 H, m, 4-H), 2.69 (1 H, dd, *J* 8 and 2 Hz, 11-H), 2.79 (1 H, dt, *J* 2 and 6 Hz, 10-H), 2.90 (1 H, m, C*H*HPh), 3.15 (1 H, m, CH*H*Ph), 5.14 (2 H, s, 15-H_2), and 7.15—7.30 (5 H, m, Ph); δ_C($CDCl_3$) 12.6 (C-17), 20.8 (C-14), 31.7 and 31.8 (C-9), 37.4, 37.5, and 37.6 (C-4 and CH_2Ph), 39.5 (C-8), 42.8 (C-12), 51.8 (CO_2CH_3), 53.4 and 53.7 (C-2), 55.7 (C-10), 61.3 (C-11), 65.4 (C-16), 68.9 and 69.1 (C-6), 70.5 (C-7), 71.2 (C-13), 75.3 and 75.8 (C-5), 114.8 and 115.0 (C-15), 126.3 (C-4′), 128.3 (C-3′), 128.9 (C-2′), 139.4 (C-1′), 143.3 and 143.6 (C-3), and 173.9 (C-1); *m/z* 448 (M^+, 0.5%), 357 (5), 227 (40), 129 (24), 91 (100), 69 (30), and 43 (30) (Found: M^+, 448.2471. $C_{25}H_{36}O_7$ requires *M*, 448.2461).

Methyl 3-{[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]methyl}-2-methylthiobut-3-enoate (**3h**).—The dienolate (1 mmol) was treated with methyl methanethiosulphonate (0.51 ml, 5 mmol) to give the crude product (2.61 g) as the tris(trimethylsilyl) ether. This material was deprotected (0.54 g) and chromatographed to yield the *title compound* (0.29 g, 70%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 920, 1 730, 1 640, 1 435, 1 270, 1 150, 1 110, 1 040, and 910 cm^{-1}; δ_H($CDCl_3$) 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), 1.73 (2 H, t, *J* 7 Hz, 9-H_2), 2.00 (1 H, m, 8-H), 2.07 and 2.08 (3 H, 2 s, SCH_3), 2.28 (1 H, dd, *J* 15 and 8 Hz, 4-H_2), 2.57 (1 H, dd, *J* 15 and 3 Hz, 4-H), 2.71 (1 H, dd, *J* 8 and 2 Hz, 11-H), 2.80 (1 H, dt, *J* 2 and 5 Hz, 10-H), 3.73 (3 H, s, CO_2CH_3), 4.05 and 4.09 (1 H, 2 s, 2-H), and 5.25 (2 H, s, 15-H_2); δ_C($CDCl_3$) 12.6 (C-17), 14.0 and 14.2 (SCH_3), 20.7 (C-14), 31.6 and 31.7 (C-9), 35.7 and 35.8 (C-4), 39.4 and 39.5 (C-8), 42.7 (C-12), 52.4 and 52.5 (CO_2CH_3), 53.4 and 54.0 (C-2), 55.7 (C-10), 61.2 (C-11), 65.4 (C-16), 68.5 and 68.9 (C-6), 70.3 (C-7), 71.1 (C-13), 75.6 and 75.9 (C-5), 117.0 and 117.2 (C-15), 139.0 and 139.4 (C-3), and 171.3 (C-1); *m/z* 404 (M^+, 1%), 386 (6), 339 (5), 256 (11), 227 (62), 97 (86), 69 (85), 55 (80), and 43 (100) (Found: M^+, 404.1845. $C_{19}H_{32}O_7S$ requires *M*, 404.1855).

Methyl 2-Phenylthiomonate (**1i**) *and Methyl 2-Phenylthioisomonate* (**4c**).—The dienolate (5 mmol) was treated with diphenyl disulphide (1.20 g, 5.5 mmol) to give the *title compounds* as a mixture of stereoisomers (0.83 g, 36%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 920, 1 710, 1 580, 1 480, 1 440, 1 260, 1 220, 1 100, 1 080, 1 050, 900, 690, and 660 cm^{-1}; $\lambda_{max.}$(EtOH) 211 nm (ε 12 400); δ_H (250 MHz; $CDCl_3$) 0.94 (3 H, 2 d, *J* 7 Hz, 17-H_3), 1.22 (3 H, d, *J* 7 Hz, 14-H_3), 1.31 (1 H, q, *J* 7 Hz, 12-H), 1.70 (2 H, m, 9-H_2), 2.00 (1 H, m, 8-H), 2.16 and 2.22 (3 H, 2 s, 15-H_3), 2.45 (1 H, br s, OH), and 7.1—7.4 (5 H, m, Ph); δ_C($CDCl_3$) 12.6 (C-17), 20.7 (C-14), 22.0 and 22.8 (C-15), 31.8 and 31.9 (C-9), 39.1, 39.3, and 39.4 (C-8 and C-4), 42.8 and 42.9 (C-12), 52.0 and 52.4 (CO_2CH_3), 55.6 and 55.8 (C-10), 61.2 (C-11), 65.4 and 65.6 (C-16), 68.9 and 69.7 (C-6), 70.5 and 70.6 (C-7), 71.1 (C-13), 75.8 and 76.0 (C-5), 122.8 and 123.0 (C-2), 126.4 (C-4′), 128.9 (C-2′, -3′, -5′, and -6′), 135.4 and 135.5 (C-1′), 152.7 and 154.0 (C-3), and 167.5 and 168.7 (C-1); *m/z* 466 (M^+, 10%), 285 (11), 227 (60), 111 (87), 97 (62), 95 (59), 69 (93), 55 (78), and 43 (100) (Found: M^+, 466.2023. $C_{24}H_{34}O_7S$ requires *M*, 466.2024).

Methyl 3-{[5-(2,3-Epoxy-5-hydroxy-4-methylhexyl)-3,4-dihydroxytetrahydropyran-2-yl]methyl}-4-phenylselenobut-2-enoates (**1k**) *and* (**4e**).—The dienolate (**2a**) (5 mmol) was treated with diphenyl diselenide (1.56 g, 5 mmol) to yield the two isomers of the title compound (total recovery 1.32 g, 51%); *monate isomer* (**1k**) (0.444 g, 17%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 1 715, 1 640, 1 580, 1 475, 1 435, 1 245, 1 160, 1 110, 1 040, 905, and 690 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.93 (3 H, d, *J* 7 Hz, 17-H_3), 1.21 (3 H, d, *J* 7 Hz, 14-H_3), 1.32 (1 H, q, *J* 7 Hz, 12-H), 1.70 (2 H, m, 9-H_2), 2.00 (1 H, m, 8-H), 2.35 (1 H, dd, *J* 8 and 14 Hz, 4-H), 2.70 (1 H, dd, *J* 8 and 1 Hz, 11-H), 2.80 (2 H, m, 10-H and 4-H), 4.14 (1 H, d, J_{AB} 10 Hz, C*H*HSePh), 4.34 (1 H, d, J_{AB} 10 Hz, CH*H*SePh), 5.70 (1 H, s, 2-H), 7.25 (3 H, m, SePh), and 7.4—7.6 (2 H, m, SePh); δ_C($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 29.0 (C-15), 31.7 (C-9), 39.4 (C-8), 39.7 (C-4), 42.9 (C-12), 50.9 (OCH_3), 55.6 (C-10), 61.3 (C-11), 65.4 (C-16), 69.0 (C-6), 70.4 (C-7), 71.2 (C-13), 75.7 (C-5), 118.3 (C-2), 127.6, 128.9, and 134.7 (SePh), 156.1 (C-3), and 166.4 (C-1); *m/z* 514 (M^+, 9%), 482 (18), 339 (10), 227 (28), 155 (28), 141 (44), 129 (45), 113 (42), 111 (48), 97 (48), 95 (58), 81 (59), 71 (58), 69 (79), 55 (83), 45 (73), 43 (100), and 41 (98) (Found: M^+, 514.1481. $C_{24}H_{34}O_7{}^{80}Se$ requires *M*, 514.1469); *isomonate isomer* (**4e**) (0.242 g, 9%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 1 710, 1 635, 1 580, 1 480, 1 440, 1 375, 1 200, 1 155, 1 110, 1 040, 905, and 690 cm^{-1}; 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), 1.5—1.8 (2 H, m, 9-H_2), 2.00 (1 H, m, 8-H), 2.65 (1 H, dd, *J* 8 and 1 Hz, 11-H), 2.77 (1 H, dt, *J* 1 and 4 Hz, 10-H), 3.0—3.2 (2 H, m, 4-H_2), 4.5 (1 H, br s, OH), 5.49 (1 H, s, 2-H), 7.25 (3 H, s, Ph), and 7.46 (2 H, m, Ph); δ_C($CDCl_3$) 12.6 (C-17), 20.7 (C-14), 31.8 (C-9), 32.3 (C-15), 37.2 (C-4), 39.1 (C-8), 42.8 (C-12), 51.5 (OCH_3), 55.8 (C-10), 61.2 (C-11), 65.5 (C-16), 68.0 (C-6), 70.2 (C-7), 71.0 (C-13), 76.7 (C-5), 118.2 (C-2), 127.8, 129.1, and 134.3 (SePh), 158.0 (C-3), and 167.9 (C-1); *m/z* 514 (M^+, 9%), 482 (28), 480 (15), 339 (15), 227 (41), 141 (60), 129 (51), 111 (65), 97 (55), 95 (81), 84 (66), 81 (67), 71 (65), 69 (85), 55 (84), 45 (70), 43 (92), and 41 (100) (Found: M^+, 514.1467. $C_{24}H_{34}O_7{}^{80}Se$ requires *M*, 514.1469).

4-{[5-(2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*)-3,4-*dihydroxytetrahydropyran*-2-*yl*]*methyl*}-6-(4-*methoxyphenyl*)-5,6-*dihydro*-2-*pyrone* (**5b**).—The dienolate (1 mmol) was treated with *p*-anisaldehyde (0.085 ml, 0.7 mmol) to give the crude product (0.238 g) as the tris(trimethylsilyl) ether. This material was deprotected and chromatographed to yield the *title compound* (0.135 g, 30%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 930, 1 700, 1 640, 1 615, 1 585, 1 515, 1 380, 1 250, 1 175, 1 110, 1 035, 910, and 830 cm^{-1}; $\lambda_{max.}$(EtOH) 226 nm (ε 16 900); δ_H (250 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 7 Hz, 17-H_3), 1.21 (3 H, d, *J* 7 Hz, 14-H_3), 1.33 (1 H, q, *J* 7 Hz, 12-H), 1.69 (2 H, m, 9-H_2), 2.00 (1 H, m, 8-H), 2.40 (1 H, dd, *J* 12 and 8 Hz, 4-H), 5.33 [1 H, m, OC*H*(Ar)CH_2], 5.80 (1 H, s, 2-H), 6.91 (2 H, d, J_{AB} 8 Hz, 2′- and 6′-H), and 7.32 (2 H, d, J_{AB} 8 Hz, 3′-and 5′-H); δ_C($CDCl_3$) 12.6 (C-17), 20.8 (C-14), 31.7 (C-9), 35.9 and 36.0 (C-15), 38.8 and 39.0 (C-4), 39.8 (C-8), 42.7 (C-12), 55.4 (OCH_3), 55.6 (C-10), 61.1 (C-11), 65.5 (C-16), 68.5 (C-6), 70.3 (C-7), 71.1 (C-13), 74.4 and 74.9 (C-5), 78.9 and 79.0 [*C*H(Ar)O], 114.1 (C-3′ and -5′), 117.1 and 117.4 (C-1′), 127.7 (C-2′ and C-6′), 130.7 (C-4′), 159.5 and 159.8 (C-3), and 165.8 (C-1); *m/z* 462 (M^+, 2%), 216 (12), 174 (14), 159 (18), 135 (28), 121 (100), 111 (19), 95 (23), 83(24), 71 (30), 69 (39), 55 (37), and 43 (47) (Found: M^+ 462.2253. $C_{25}H_{34}O_8$ requires *M*, 462.2253).

4-{[5-(2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*)-3,4-*dihydroxytetrahydropyran*-2-*yl*]*methyl*}-6-*phenyl*-5,6-*dihydro*-2-*pyrone* (**5c**).—The dienolate (2 mmol) was treated with benzaldehyde (0.203 ml, 2 mmol) to give the *title compound* (0.478 g, 55%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 900, 1 700, 1 640, 1 450, 1 380, 1 270, 1 255, 1 110, 1 050, 925, 750, and 700 cm^{-1}; $\lambda_{max.}$(EtOH) 208 nm (ε 14 520); δ_H (250 MHz; $CDCl_3$) 0.92 (3 H, d, *J* 7 Hz, 17-H_3), 1.22 (3 H, d, *J* 7 Hz, 14-H_3), 1.33 (1 H, q, *J* 7 Hz, 12-H), 1.68 (2 H, m, 9-H_2), 2.00 (1 H, m, 8-H), 2.10 (1 H, br s, OH), 2.42 (1 H, dd, *J* 15 and 10 Hz, 4-H), 5.40 (1 H, m, 18-H), 5.99 (1 H, s, 2-H), and 7.40 (5 H, s, Ph); δ_C($CDCl_3$) 12.5 (C-17), 20.7 (C-14), 31.7 (C-9), 35.9 and 36.0 (C-15), 38.8 and 39.0 (C-4), 39.8 (C-8), 42.7 (C-12), 55.6 (C-10), 61.0 (C-11), 65.5 (C-16), 68.4 (C-6), 70.2 (C-7), 71.0 (C-13), 74.3 and 74.9 (C-5), 79.0 and 79.1 (C-18), 117.1 and 117.3 (C-2), 126.1 and 128.7 (C-2′ to -6′), 138.5 (C-1′), 159.5 and 159.6 (C-3), and 165.7 (C-1); *m/z* 432 (M^+, 2%), 188 (35), 143 (79), 141 (52), 129 (58), 91 (57), 71 (65), 69 (80), 45 (79), 43 (98), and 41 (100) (Found: M^+, 432.2158. $C_{24}H_{32}O_7$ requires *M*, 432.2146).

4-{[5-(2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*)-3,4-*dihydroxytetrahydropyran*-2-*yl*]*methyl*}-6-(3-*nitrophenyl*)-5,6-*dihydro*-2-*pyrone* (**5d**).—The dienolate (2 mmol) was treated with *m*-nitrobenzaldehyde (0.302 g, 2.00 mmol) to give the title compound (0.445 g, 47%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 920, 1 705, 1 640, 1 530, 1 350, 1 250, 1 110—1 040, and 905 cm^{-1}; $\lambda_{max.}$(EtOH) 219 nm (ε 17 180); δ_H (250 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 7 Hz, 17-H_3), 1.22 (3 H, d, *J* 7 Hz, 14-H_3), 1.34 (1 H, q, *J* 7 Hz, 12-H), 1.72 (2 H, m, 9-H_2), 2.00 (1 H, m, 8-H), 3.05 (1 H, br s, OH), 5.53 (1 H, m, 18-H), 6.02 (1 H, s, 2-H), 7.60 (1 H, t, *J* 7 Hz, 5′-H), 7.80 (1 H, d, *J* 7 Hz, 6′-H), 8.22 (1 H, d, *J* 7 Hz, 4′-H), and 8.28 (1 H, s, 2′-H); δ_C($CDCl_3$) 12.6 (C-17), 20.8 (C-14), 31.7 (C-9), 35.7 and 36.0 (C-15), 38.8 and 39.0 (C-4), 39.9 (C-8), 42.8 (C-12), 55.6 (C-10), 61.1 (C-11), 65.5 (C-16), 68.5 (C-6), 70.3 (C-7), 71.1 (C-13), 74.4 and 75.1 (C-5), 77.6 (C-18), 117.2 and 117.4 (C-2), 121.1 (C-2′), 123.5 (C-4′), 130.0 (C-5′), 132.3 (C-6′), 142.9 (C-1′), 148.4 (C-3′), 159.3 and 159.4 (C-3), and 164.8 (C-1).

6-(3-*Cyanophenyl*)-4-{[5-(2,3-*epoxy*-5-*hydroxy*-4-*methylhexyl*)-3,4-*dihydroxytetrahydropyran*-2-*yl*]*methyl*}-5,6-*dihydro*-2-*pyrone* (**5e**).—The dienolate (2 mmol) was treated with *m*-cyanobenzaldehyde (0.262 g, 2 mmol) to give the *title compound* (0.342 g, 37%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 930, 2 230, 1 710, 1 640, 1 380, 1 250, 1 110, 1 045, and 905 cm^{-1}; $\lambda_{max.}$(EtOH) 226 nm (ε 19 375); δ_H (250 MHz; $CDCl_3$) 0.93 (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), 1.71 (2 H, m, 9-H_2), 2.01 (1 H, m, 8-H), 2.45 (1 H, dd, *J* 14 and 10 Hz, 4-H), 5.46 (1 H, m, 18-H), 6.01 (1 H, s, 2-H), 7.53 (1 H, t, *J* 8 Hz, 5′-H), 7.65 (2 H, m, 4′- and 6′-H), and 7.75 (1 H, s, 2′-H); δ_C($CDCl_3$) 12.6 (C-17), 20.8 (C-14), 31.6 (C-9), 35.6 and 35.9 (C-15), 38.7 and 39.0 (C-4), 39.9 (C-8), 42.7 (C-12), 55.6 (C-10), 60.9 and 61.0 (C-11), 65.5 (C-16), 68.5 (C-6), 70.2 (C-7), 71.0 (C-13), 74.4 and 75.1 (C-5), 77.7 (C-18), 112.7 (C-3′), 117.3 and 117.4 (C-2), 118.4 (CN), 129.7, 130.6, and 132.1 (C-2′, -4′, -5′, and -6′), 140.3 (C-1′), 159.2 and 159.3 (C-3), and 164.7 (C-1); *m/z* (C.I., NH_3), 458 (M^+, 23%), 440 (20), 414 (22), 396 (36), 229 (39), 227 (100), 185 (39), 166 (45), and 155 (63).

4-{[5-(2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*)-3,4-*dihydroxytetrahydropyran*-2-*yl*]*methyl*}-6-(4-*methylthiophenyl*)-5,6-*dihydropyrone* (**5f**).—The dienolate (2 mmol) was treated with thioanisaldehyde (0.266 ml, 2 mmol) to give the *title compound* (0.65 g, 68%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 920, 1 700, 1 640, 1 600, 1 495, 1 380, 1 250, 1 110—1 040, 920, and 810 cm^{-1}; $\lambda_{max.}$(EtOH) 220 (ε 18 350) and 260 nm (13 710); δ_H (250 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 7 Hz, 17-H_3), 1.21 (3 H, d, *J* 7 Hz, 14-H_3), 1.33 (1 H, q, *J* 7 Hz, 12-H), 1.69 (2 H, m, 9-H_2), 2.00 (1 H, m, 8-H), 2.49 (3 H, s, SCH_3), 2.92 (1 H, br s, OH), 5.35 (1 H, m, 18-H), and 7.30 (4 H, m, ArH); δ_C($CDCl_3$) 12.5 (C-17), 15.6 (SCH_3), 20.8 (C-14), 31.6 (C-9), 35.7 and 35.9 (C-15), 38.7 and 38.9 (C-4), 39.8 (C-8), 42.7 (C-12), 55.6 (C-10), 60.9 (C-11), 65.4 (C-16), 68.4 (C-6), 70.2 (C-7), 70.9 (C-13), 74.3 and 74.9 (C-5), 78.7 and 78.8 (C-18), 117.0 and 117.3 (C-2), 126.5 and 126.7 (C-2′ and -6′, and C-3′ and -5′), 135.2 (C-4′), 139.3 (C-1′), 159.5 and 159.6 (C-3), and 165.6 (C-1); *m/z* 478 (M^+, 9%), 434 (9), 232 (17), 190 (72), 137 (100), 69 (36), 55 (32), 43 (48), and 41 (43) (Found: M^+, 478.1985. $C_{25}H_{34}O_7S$ requires *M*, 478.2023).

Deuteriation of the Dienolate (**2b**). *Preparation of Labelled Compounds* (**3c**) *and* (**1h**).—The dienolate (**2b**) (2 mmol) was treated with methan[^{2}H]ol (CH_3OD) (1.0 ml) to give the crude product (1.06 g) as the tris(trimethylsilyl) ether. This material was chromatographed on silica gel using 8% ether–hexane as eluant to give two pure fractions. *Ethyl* (E)-3-{[5-(2,3-*Epoxy*-4-*methyl*-5-*trimethylsilyloxyhexyl*)-3,4-*bis*(*trimethylsilyloxy*)*tetrahydropyran*-2-*yl*]*methyl*}[4-^{2}H]*but*-2-*enoate* (**1h**) 0.062 g, 5%); $\nu_{max.}$(film) 2 960, 2 900, 1 715, 1 650, 1 450, 1 375, 1 250, 1 120, 1 060, 865, and 840 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.13 (9 H, Me_3Si), 0.16 (18 H, $2Me_3Si$), 0.90 (3 H, d, *J* 7 Hz, 17-H_3), 1.20 (3 H, d, *J* 7 Hz, 14-H_3), 1.28 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.39 (1 H, m, 12-H), 1.55 (1 H, m, 8-H), 1.71 (2 H, m, 9-H_2), 2.04 (1 H, dd, *J* 14 and 11 Hz, 4-H), 2.19 (2 H, m, 15-H_2D), 2.54 (1 H, br d, *J* 14 Hz, 4-H), 2.68 (2 H, m, 10- and 11-H), 4.13 (2 H, q, *J* 7 Hz, CH_2CH_3), and 5.74 (1 H, s, 2-H); *m/z* (C.I., NH_3) 607 (MNH_4^+, 11%), 590 (MH^+, 21), 117 (27), 90 (100), and 73 (35). *Ethyl* 3-{[5-(2,3-*epoxy*-4-*methyl*-5-*trimethylsilyloxyhexyl*)-3,4-*bis*(*trimethylsilyloxy*)*tetrahydropyran*-2-*yl*]*methyl*}[2-^{2}H]-*but*-3-*enoate* (**3c**) 0.194 g, 16%); $\nu_{max.}$(film) 2 960, 2 900, 1 740, 1 650, 1 450, 1 370, 1 250, 1 125, 1 080, 960, and 830 cm^{-1}; δ_H($CDCl_3$) 0.11 (9 H, s, Me_3Si), 0.14 (18 H, s, $2Me_3Si$), 0.88 (3 H, d, *J* 7 Hz, 17-H_3), 1.20 (3 H, d, *J* 7 Hz, 14-H_3), 1.25 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.38 (1 H, m, 12-H), 1.55 (1 H, m, 8-H), 1.80 (2 H, m, 9-H_2), 2.03 (1 H, dd, *J* 12 and 10 Hz, 4-H), 2.55 (1 H, d, *J* 12 Hz, 4-H), 2.68 (2 H, m, 10- and 11-H), 3.10 (1 H, m, 2-HD), 4.13 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.99 (1 H, s, 15-H), and 5.03 (1 H, s, 15-H); *m/z* 607 (MNH_4^+, 7%), 590 (MH^+, 24), 296 (11), 243 (12), 169 (17), 117 (38), 90 (100), and 73 (45).

Ethyl 2-Ethoxycarbonylmonate (**1q**).—To a solution of ethyl monate (**1g**) (0.744 g, 2 mmol) and triethylamine (0.87 ml, 6.2 mmol) in THF (20 ml) was added trimethylsilyl chloride (0.79 ml, 6.2 mmol) and a catalytic amount of DMAP. 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 THF (10 ml) and refiltered ready for the next stage of the reaction.

A solution of LDA was prepared by reaction of butyl-lithium (1.5 ml of a 1.6M hexane solution) with di-isopropylamine (0.34 ml, 2.4 mmol) in THF (10 ml) at −78 °C for 15 min. The solution of the protected ester, *vide supra*, was added dropwise to the LDA solution and the mixture was stirred for 1 h at −78 °C before the addition of ethyl chloroformate (0.21 ml, 2.2 mmol). The solution was allowed to warm to room temperature in the cooling bath, then stirred overnight, quenched with aqueous ammonium chloride, extracted with ethyl acetate (3 × 50 ml), and the extract was dried ($MgSO_4$). Removal of solvent under reduced pressure gave the crude product (1.15 g) which was purified by column chromatography on silica using 10% ether in hexane as eluant to give the desired deconjugated derivative (0.256 g) as the second major fraction. This material was taken up in dichloromethane (10 ml) and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.061 ml, 0.42 mmol) at room temperature for 1 h. The resulting solution was poured into brine, extracted with dichloromethane, the extract was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oil (0.176 g) which was dissolved in THF–water (4:1; 100 ml) and treated with a few drops of hydrochloric acid for 5 min then finally quenched with aqueous sodium hydrogen carbonate. Extraction with ethyl acetate, drying of the extract ($MgSO_4$), and removal of solvent under reduced pressure gave *ethyl 2-ethoxycarbonylmonate* (**1q**) (0.102 g, 11%); $\nu_{max.}$ (liquid film) 3 600—3 200, 2 980, 2 930, 1 715, 1 630, 1 510, 1 450, 1 370, 1 250, 1 060, and 910 cm^{-1}; $\lambda_{max.}$(EtOH) 223 nm (ε 9 800); δ_H (250 MHz; $CDCl_3$) 0.98 (3 H, d, *J* 7 Hz, 17-H_3), 1.23 (3 H, d, *J* 7 Hz, 14-H_3), 1.28—1.38 (6 H, 2 t, 2OCH_2CH_3), 2.05 (1 H, m, 8-H), 2.15 (3 H, s, 15-H_3), and 4.2—4.4 (4 H, 2 q, 2OCH_2CH_3); δ_C($CDCl_3$) 12.6 (C-17), 14.0 and 14.1 (OCH_2CH_3), 20.7 (C-14), 22.5 (C-15), 31.7 (C-9), 38.5 (C-4), 39.2 (C-8), 42.9 (C-12), 55.8 (C-10), 61.1, 61.3, and 61.6 (C-11 and OCH_2), 65.6 (C-16), 68.7 (C-6), 70.4 (C-7), 71.2 (C-13), 76.0 (C-5), 125.8 (C-3), 157.2 (C-2), and 165.8 and 166.5 (2CO); *m/z* 444 (M^+, 0.5%), 399 (9), 353 (15), 296 (22), 278 (15), 250 (28), 227 (100), 200 (48), 183 (60), 154 (78), and 137 (82) (Found: M^+, 444.2368. $C_{22}H_{36}O_9$ requires *M*, 444.2359).

General Methods of Reconjugation.—*Method A.* A solution of the tris(trimethylsilyloxy)-protected deconjugated ester (1 mmol) and DBU (1.5 ml, 10 mmol) in THF (10 ml) was refluxed for 24 h, cooled, then quenched with excess of aqueous ammonium chloride. The resultant solution was extracted with ethyl acetate (2 × 50 ml) and the extract was dried ($MgSO_4$). Removal of solvent under reduced pressure gave the crude product as an oil which was deprotected and purified as before.

Method B. A solution of potassium t-butoxide (1 mmol) in THF (10 ml) was slowly added to a cooled (−20 to −30 °C) solution of the protected deconjugated ester (1 mmol) in THF. The mixture was stirred at that temperature for 30 min before being quenched with aqueous ammonium chloride and warmed to room temperature. The resultant solution was extracted with ethyl acetate (2 × 50 ml) and the extract was dried ($MgSO_4$). Removal of solvent under reduced pressure gave the crude product as an oil which was deprotected and purified as before.

Methyl 2-Methylmonate (**1m**).—The crude deconjugated protected ester (**3d**) (0.602 g, 1.02 mmol) was treated as described in method B to give, after acid hydrolysis, the crude product (0.42 g) as a 71:29 mixture of *E* and *Z* isomers. Purification of the major isomer by chromatography gave the title compound (0.118 g, 31%; total yield 0.247 g, 65%); the spectroscopic data were identical with those reported earlier for the same compound.[1]

Methyl 2-Methylisomonate (**4f**).—The protected deconjugated ester (**3d**) (1.08 g, 1.79 mmol) was treated as described in method A to give, after acid hydrolysis, the crude product (0.658 g) as a 21:79 mixture of the *E* and *Z* isomers. Purification of the major isomer by chromatography gave the title compounds (0.312 g, 47%) which slowly crystallised from ether, m.p. 83.5—84.0 °C.[1]

Methyl 2-Ethylmonate (**1n**).—The protected deconjugated ester (**3f**) (1 mmol) was treated as described in method B to give, after acid hydrolysis, the crude product as a 82:18 mixture of the *E* and *Z* isomers. Purification of the major isomer by chromatography gave the *title compound* (0.054 g, 14%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 930, 2 880, 1 710, 1 450, 1 430, 1 380, 1 300, 1 250, 1 215, 1 110, 1 055, and 905 cm^{-1}; $\lambda_{max.}$(EtOH) 225 nm (ε 6 500); δ_H (250 MHz; $CDCl_3$) 0.94 (3 H, d, *J* 7 Hz, 17-H_3), 0.99 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.22 (3 H, d, *J* 7 Hz, 14-H_3), 1.34 (1 H, q, *J* 7 Hz, 12-H), 1.74 (2 H, m, 9-H_2), 1.98 (3 H, s, 15-H_3), 2.00 (1 H, m, 8-H), 2.35 (3 H, m, 4-H and CH_2CH_3), 2.55 (1 H, dd, *J* 12 and 3 Hz, 4-H), 2.72 (1 H, dd, *J* 9 and 2 Hz, 11-H), 2.81 (1 H, dt, *J* 2 and 5 Hz, 10-H), and 3.73 (3 H, s, CO_2CH_3); δ_C($CDCl_3$) 12.7 (C-17), 13.5 (CH_2CH_3), 20.9 (C-14), 21.3 (C-15), 23.1 (CH_2CH_3), 31.8 (C-9), 37.3 (C-4), 39.7 (C-8), 42.9 (C-12), 51.2 (CO_2CH_3), 55.6 (C-10), 61.4 (C-11), 65.5 (C-16), 69.7 (C-6), 70.6 (C-7), 71.3 (C-13), 76.1 (C-5), 131.7 (C-2), 140.7 (C-3), and 170.7 (C-1); *m/z* 386 (M^+, 1%), 227 (37), 139 (63), 111 (52), 95 (64), 83 (56), 81 (48), 71 (57), 69 (92), 67 (62), 55 (89), and 43 (100) (Found: M^+, 386.2321. $C_{20}H_{34}O_7$ requires *M*, 386.2392).

Methyl 2-Ethylisomonate (**4g**).—The protected deconjugated ester (**3f**) (2 mmol) was treated as described in method A to give, after acid hydrolysis, the crude product (0.712 g) as a 27:73 mixture of *E* and *Z* isomers. Purification of the major isomer by chromatography gave the *title compound* (0.243 g, 31% total yield 0.463 g, 60%); $\nu_{max.}$(film) 3 600—3 200, 2 960, 2 930, 1 700, 1 640, 1 450, 1 375, 1 290, 1 240, 1 195, 1 105, 1 040, and 900 cm^{-1}; $\lambda_{max.}$(EtOH) 225 nm (ε 7 360); δ_H (250 MHz; $CDCl_3$) 0.94 (3 H, d, *J* 7 Hz, 17-H_3), 1.00 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.21 (3 H, d, *J* 7 Hz, 14-H_3), 1.32 (1 H, q, *J* 7 Hz, 12-H), 1.55—1.85 (2 H, m, 9-H_2), 1.92 (3 H, s, 15-H_3), 2.01 (1 H, m, 8-H), 2.32 (2 H, q, *J* 7 Hz, CH_2CH_3), 2.56 (1 H, dd, *J* 12 and 4 Hz, 4-H), 2.68 (1 H, dd, *J* 8 and 2 Hz, 11-H), 2.70 (1 H, dd, *J* 12 and 4 Hz, 4-H), 2.80 (1 H, dt, *J* 2 and 8 Hz, 10-H), and 3.75 (3 H, s, CO_2Me); δ_C($CDCl_3$) 12.5 (C-17), 13.2 (CH_2CH_3), 20.4 and 20.6 (C-14 and -15), 23.2 (CH_2CH_3), 32.0 (C-9), 38.8 and 39.2 (C-4 and C-8), 42.9 (C-12), 51.7 (OCH_3), 55.8 (C-10), 61.2 (C-11), 65.6 (C-16), 68.1 (C-6), 70.4 (C-7), 70.9 (C-13), 76.5 (C-5), 131.1 (C-2), 144.4 (C-3), and 171.3 (C-1); *m/z* 386 (M^+, 1%), 227 (74), 139 (89), 111 (56), 97 (52), 95 (64), 83 (58), 69 (88), 55 (77), and 43 (100) (Found: M^+, 386.2292. $C_{20}H_{34}O_7$ requires *M*, 386.2292).

Methyl 2-Benzylmonate (**1o**).—The protected deconjugated ester (**3l**) (0.647 g, 0.97 mmol) was treated as described in method B to give, after acid hydrolysis, the crude product as an 80:20 mixture of the *E* and *Z* isomers. Purification of the major isomer by column chromatography gave the *title compound* (0.043 g, 10%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 930, 1 715, 1 645, 1 600, 1 495, 1 450, 1 435, 1 370, 1 080, 960, 910, 760, and 690 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 0.92 (3 H, d, *J* 7 Hz, 17-H_3), 1.22 (3 H, d, *J* 7 Hz, 14-H_3), 1.32 (1 H, m, 12-H), 1.69 (2 H, t, *J* 6 Hz, 9-H_2), 1.98 (1 H, m, 8-H), 2.10 (3 H, s, 15-H_3), 2.40 (1 H, dd, *J* 12 and 8 Hz, 4-H), 2.60 (1 H, dd, *J* 12 and 3 Hz, 4-H), 2.69 (1 H, dd, *J* 8 and 1 Hz, 11-H), 2.78 (1 H, dt, *J* 1 and 5 Hz, 10-H), and 7.1—7.3 (5 H, m, Ph); δ_C($CDCl_3$) 12.6 (C-17), 20.8 (C-14), 21.5 (C-15), 31.8 (C-9), 35.4 (CH_2Ph), 38.1 (C-4), 39.7 (C-8), 42.9 (C-12), 51.2

(OMe), 55.6 (C-10), 61.3 (C-11), 65.5 (C-16), 69.6 (C-6), 70.6 (C-7), 71.4 (C-13), 75.9 (C-5), 126.0 (C-2), 128.4 (C-2′, -3′, and -4′), 140.0 (C-1′), 144.5 (C-3), and 170 (C-1); *m/z* 448 (M^+, 0.5%), 227 (18), 201 (16), 172 (22), 143 (36), 129 (47), 91 (100), 69 (62), 55 (58), 45 (78), 43 (86), and 41 (94) (Found: M^+, 448.2484. $C_{25}H_{37}O_7$ requires *M*, 448.2461).

Methyl 2-Benzylisomonate (**4h**).—The protected deconjugated ester (**3l**) (1.22 g, 1.84 mmol) was treated as described in method A to give, after acid hydrolysis, the crude product as a 55:45 mixture of the *E* and *Z* isomers. The crude product was chromatographed to give the *title compound* (0.129 g, 16%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 930, 1 705, 1 640, 1 495, 1 450, 1 435, 1 380, 1 280, 1 215, 1 110, 1 080, 1 050, 900, 700, and 655 cm^{-1}; $\lambda_{max.}$(EtOH) 213 nm (ε 11 300); δ_H (250 MHz; CD_3OD) 0.94 (3 H, d, *J* 7 Hz, 17-H_3), 1.20 (3 H, d, *J* 7 Hz, 14-H_3), 1.40 (1 H, m, 12-H), 1.6—1.7 (2 H, m, 9-H_2), 1.92 (3 H, s, 15-H_3), 1.96 (1 H, m, 8-H), and 7.2—7.4 (5 H, m, Ph); δ_C(CD_3OD) 12.2 (C-17), 20.4 (C-14), 21.3 (C-15), 33.0 (C-9), 36.5 (CH_2Ph), 38.8 (C-4), 41.0 (C-8), 43.6 (C-12), 51.8 (OCH_3), 56.8 (C-10), 61.4 (C-11), 66.3 (C-16), 70.6 and 70.7 (C-6 and -7), 71.6 (C-13), 77.8 (C-5), 126.8 (C-2), 129.3—129.5 (C-2′, -3′, and -4′), 140.8 (C-1′), 146.8 (C-3), and 171.5 (C-1); *m/z* 448 (M^+, 1%), 416 (9), 398 (7), 227 (89), 201 (79), 172 (61), 143 (48), 129 (67), 91 (100), 69 (38), and 43 (33) (Found: M^+, 448.2493. $C_{25}H_{36}O_7$ requires *M*, 448.2461).

Methyl 2-Methylthiomonate (**1p**) *and Methyl 2-Methylthioisomonate* (**4i**).—The protected deconjugated ester (**3h**) (0.52 g, 1 mmol) was treated as described in method A to give, after acid hydrolysis, the crude product as a 50:50 mixture of the *E* and *Z* isomers. Column chromatography allowed isolation of both isomers; *methyl 2-methylthiomonate* (**1p**) (0.066 g, 16%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 920, 1 710, 1 615, 1 435, 1 175, 1 150, 1 110, 1 080, 1 050, and 905 cm^{-1}; $\lambda_{max.}$(EtOH) 211 nm (ε 5 300); 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), 1.31 (1 H, q, *J* 7 Hz, 12-H), 1.60—1.85 (2 H, m, 9-H_2), 2.02 (1 H, br m, 8-H), 2.12 (3 H, s, 15-H_3), 2.20 (3 H, s, SCH_3), 2.58 (2 H, m, 4-H_2), 2.67 (1 H, dd, *J* 2 and 10 Hz, 11-H), 2.79 (1 H, dt, *J* 2 and 8 Hz, 10-H), and 3.84 (3 H, s, CO_2CH_3); δ_C($CDCl_3$) 12.7 (C-17), 16.9 (SCH_3), 20.7 (C-14), 21.8 (C-15), 31.8 (C-9), 39.2 (C-4), 39.5 (C-8), 42.9 (C-12), 52.6 (CO_2CH_3), 55.8 (C-10), 61.3 (C-11), 65.6 (C-16), 68.6 (C-6), 70.5 (C-7), 71.2 (C-13), 75.7 (C-5), 125.1 (C-2), 147.9 (C-3), and 169.2 (C-1); *m/z* 404 (M^+, 4%), 386 (4), 258 (5), 227 (49), 128 (79), 85 (56), 69 (89), 55 (76), and 43 (100) (Found: M^+, 404.1892. $C_{19}H_{32}O_7S$ requires *M*, 404.1855. *Methyl 2-methylthioisomonate* (**4i**) (0.050 g, 12%); $\nu_{max.}$(film) 3 600—3 200, 2 970, 2 920, 1 720, 1 435, 1 380, 1 270, 1 220, 1 110, 1 050, and 905 cm^{-1}; $\lambda_{max.}$(EtOH) 220 nm (ε 7 500); 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), 1.33 (1 H, q, *J* 7 Hz, 12-H), 1.73 (2 H, m, 9-H_2), 2.00 (4 H, br m and s, 8-H and 15-H_3), 2.20 (3 H, s, SCH_3), and 3.83 (3 H, s, CO_2CH_3); δ_C($CDCl_3$) 12.7 (C-17), 17.1 (SCH_3), 20.8 (C-14), 21.9 (C-15), 31.8 (C-9), 38.0 (C-4), 39.1 (C-8), 42.9 (C-12), 52.1 (CO_2CH_3), 55.7 (C-10), 61.4 (C-11), 65.4 (C-16), 69.4 (C-6), 70.4 (C-7), 71.3 (C-13), 75.8 (C-5), 124.7 (C-2), 146.4 (C-3), and 167.8 (C-1); *m/z* 404 (M^+, 4%), 386 (10), 227 (51), 141 (44), 128 (62), 85 (57), 69 (92), 55 (84), 45 (84), and 43 (100) (Found: M^+, 404.1891. $C_{19}H_{32}O_7S$ requires *M*, 404.1855).

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References

1 M. J. Crimmin, P. J. O'Hanlon, and N. H. Rogers, preceding paper.
2 M. Majewski, G. B. Mpango, M. T. Thomas, A. Wu, and V. Snieckus, *J. Org. Chem.*, 1981, **46**, 2029 and references therein.
3 J. A. Katzenellenbogen and A. L. Crumrine, *J. Am. Chem. Soc.*, 1976, **98**, 4925; F. L. Harris and L. Weiler, *Tetrahedron Lett.*, 1984, **25**, 1333.
4 M. W. Rathke and D. Sullivan, *Tetrahedron Lett.*, 1972, 4249.
5 P. R. Ortiz de Moutellano and C. K. Hsu, *Tetrahedron Lett.*, 1976, 4215.
6 I. Casino and R. Mestres, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1651.

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