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THE CHEMISTRY OF PSEUDOMONIC ACID+. PART 9[1]. REDUCTION, INVERSION AND REPLACEMENT OF THE C-13 HYDROXYL GROUP

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Abstract - The preparations of methyl 13-deoxypseudomonate (2c) and methyl (13R)-monate (4f) via mesylate derivatives are described. Introduction of an amino function by nucleophilic displacement at the C-13 position was unsuccessful but the 13-amine (2f) was prepared via the o-methyloxime (7b) and lithium borohydride reduction.

The pseudomonic acids A (1a)[2], B (1b)[3], C (2a)[4,5] and D (1c)[6] are a group of novel antibiotics produced by fermentation of Pseudomonas fluorescens NCIB 10586. As part of our continuing programme studing the effect of chemical modification of these antibiotics this paper describes structural changes at C-13, namely deoxygenation, inversion of the hydroxyl and conversion to an amino group.

13-Deoxymonate

The acetonide (1d)[7] was quantitatively converted into the mesylate (1e) with mesyl chloride in pyridine. The mesylate (1e) was reduced under forcing conditions with sodium cyanoborohydride in hexamethylphosphoramide[8] at 75°C for 5 days to afford the 13-deoxy derivative (1f) in 36% yield. Previous work[9] has shown that the acetonide group could not be removed in the presence of the 10,11-epoxide and (1f) was reacted with potassium selenocyanate in refluxing 10% aqueous t-amyl alcohol[5] to afford the olefin (2b). Since saponification of the ester occurred during the reaction (2b) was re-esterified via its sodium salt with methyl iodide and treated with 80% acetic acid to give methyl 13-deoxypseudomonate C (2c). The use of other protecting groups such as the cyclic carbonate (1g) and the orthoformate (1h) failed to withstand the reaction conditions. A more direct route to (2c) was also studied. The acetonide of methyl pseudomonate C (2d) was converted into the mesylate (2e) in 87% yield and reduced with sodium cyanoborohydride to give a 64% yield of a mixture (ca 1:1) of 13-deoxy derivative (2f) and the dienes (3a). The components were separated by h.p.l.c. after hydrolysis of the acetonide groups with 80% glacial acetic acid to give (2c) and (3b).

(13R)-Monate derivatives

The nucleus of pseudomonic acid A contains eight chiral centres and we report here the inversion of one of these, namely at C-13. Our initial strategy was to use diethyl azodicarboxylate and triphenylphosphine activation of the alcohol (1j) and to invert by esterification using formic

+ The approved generic name for pseudomonic acid is mupirocin

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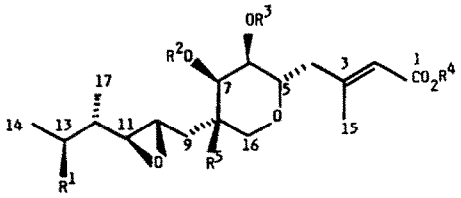
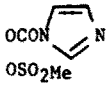
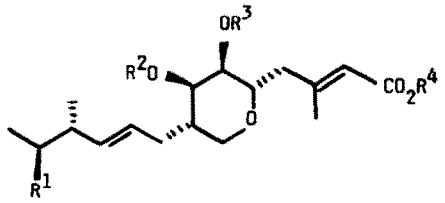
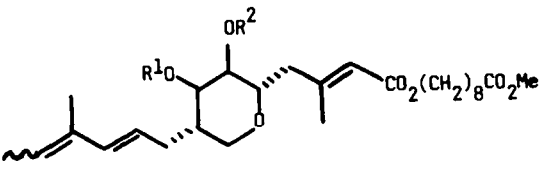


		R^1	R^2	R^3	R^4	R^5
(1)	a;	OH	H	H	$(CH_2)_8CO_2H$	H
	b;	OH	H	H	$(CH_2)_8CO_2H$	OH
	c;	OH	H	H	$(CH_2)_4C(H)=C(H)(CH_2)_2O_2H$	H
	d;	OH	$-C(Me)_2-$		$(CH_2)_8CO_2Me$	H
	e;	OSO_2Me	$-C(Me)_2-$		$(CH_2)_8CO_2Me$	H
	f;	H	$-C(Me)_2-$		$(CH_2)_8CO_2Me$	H
	g;	OH	$-C(=O)-$		$(CH_2)_8CO_2Me$	H
	h;	OH	$-CH(OMe)-$		$(CH_2)_8CO_2Me$	H
	i;	OH	H	H	Me	H
	j;	OH	$-C(=O)-$		Me	H
	k;	OH	$-CH(OMe)-$		Me	H
	l;	$OCH(OMe)_2$	$-CH(OMe)-$		Me	H
	m		$-C(=O)-$		Me	H
	n;	OSO_2Me	$-CH(OMe)-$		Me	H
	o;	Cl	H	H	Me	H
	p;	Cl	$-C(=O)-$		Me	H
	q;	$OSO_2C_6H_4Me_p$	$-CH(OMe)-$		Me	H
	r;	OSO_2CF_3	$-CH(OMe)-$		Me	H
	s;	I	$-C(=O)-$		Me	H

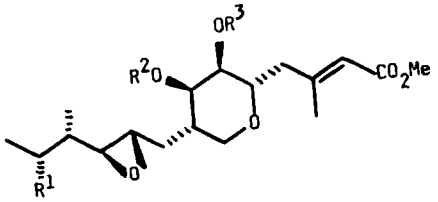


		R^1	R^2	R^3	R^4
(2)	a;	OH	H	H	$(CH_2)_8CO_2H$
	b;	H	$-C(Me)_2-$		$(CH_2)_8CO_2H$
	c;	H	H	H	$(CH_2)_8CO_2Me$
	d;	OH	$-C(Me)_2-$		$(CH_2)_8CO_2Me$
	e;	OSO_2Me	$-C(Me)_2-$		$(CH_2)_8CO_2Me$
	f;	H	$-C(Me)_2-$		$(CH_2)_8CO_2Me$
	g;	OH	H	H	H
	h;	OH	$-C(Me)_2-$		H
	i;	$\sim NH_2$	$-C(Me)_2-$		H
	j;	$\sim NH_3^+Cl^-$	H	H	Me
	k;	$\sim NHOMe$	H	H	Me



		R^1	R^2
(3)	a;	-C(Me)$_2$-	
	b;	H	H

acid[10]. Treatment of methyl monate (1i) with three equivalents of phosgene in tetrahydrofuran (THF) with pyridine as base stereospecifically afforded the (13R)-chloride (4a) in high yield. The use of either one or two equivalents of phosgene gave a mixture of the desired alcohol (1j), the chloride (4a) and the unreacted triol (1i). Alternatively, methyl monate (1i) was converted into the orthoester (1k) by reaction with trimethyl orthoformate and p-toluenesulphonic acid. The transesterification product (1l) was also produced but unlike the corresponding derivatives of pseudomonic acid[9], (1k) and (1l) were stable and separated by silica gel chromatography. Treatment of the 13-hydroxyl (1k) with triphenyl phosphine in refluxing carbon tetrachloride[11] gave after removal of the protecting group the inverted chloride (4b) in 28% yeild. This was identical to the product from hydrolysis of the cyclic carbonate (4a) using 50% aqueous pyridine.



		R^1	R^2	R^3
(4)	a;	Cl	-C(=O)-	
	b;	Cl	H	H
	c;	OCHO	-CH(OMe)-	
	d;	OCHO	CHO	H
	e;	OCHO	H	CHO
	f;	OH	H	H
	g;	I	-C(=O)-	

Formation of the 13-chloride (4a) could be avoided using carbonyl diimidazole and thus reaction of methyl monate (1i) with three equivalents of the reagent gave the imidazolide (1m) which on hydrolysis with sulphuric acid in aqueous THF afforded the cyclic carbonate (1j) in 75% yield. However attempts to invert the 13-hydroxyl using diethyl azodicarboxylate, triphenylphosphine and formic acid failed and the inversion was achieved via the mesylate (1n). The mesylate (1n), quantitatively prepared from mesyl chloride and triethylamine, was reacted with sodium formate in N,N-dimethylformamide (DMF) at 80°C to give the (13R)-formate (4c). Brief acid treatment gave a mixture of diformates (4d) and (4e) which without isolation were hydrolysed under basic conditions to afford methyl (13R)-monate (4f) in 21% yield. Only minor differences were observed between the u.v., i.r. and 250 MHz ^{1}H-n.m.r. spectra of (4f) and methyl monate (1i). Significant differences in the ^{13}C-n.m.r. chemical shifts for C-10 to -13 and C-17 (see Table) in the two isomers were evident.

The (13R)-hydroxyl (4f) was also converted into the (13S)-chloride (1o) in 18% yield by reaction of the (13R)-hydroxyl of (4f) with phosgene and pyridine in methylene chloride followed by hydrolysis of the intermediate (1p) with 50% aqueous pyridine. The ^{13}C-n.m.r. specral differences between the

two epimenic chlorides (1o) and (4b) are summarised in the table.

Table $\delta_c(CDCl_3)$ of C-10 to -14 and C-17 for (4f), (1i), (4b) and (1o)

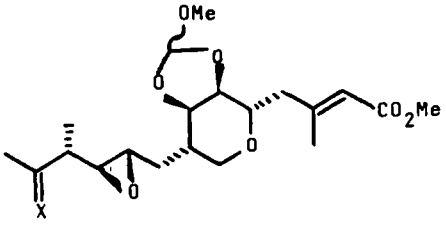
	$\delta_c(CDCL_3)$*			
Carbon	4f	1i	4b	1o
10	56.5	55.6	56.7	55.3
11	61.0	61.3	60.8	59.1
12	41.9	42.8	43.3	43.1
13	69.1	71.3	60.4	61.5
14	20.7	20.5	23.1	22.4
17	10.6	12.7	10.2	13.5

* ppm from $SiMe_4$

13-Aminomonate derivatives

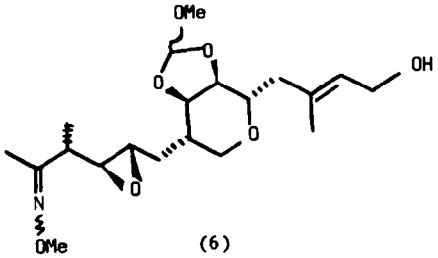
Attempts to prepare a 13-amino derivative by nucleophilic displacement from either the chloride (4a) or the sulphonates (1n), (1q) and (1r) with azide, hydrazine or phthalimide were unsuccessful. Routes to the 13-iodo derivatives (1s) and (4g) were also studied. The chloride (4a) was inert to halogen exchange with iodide and reaction of the alcohol (1j) with phosgene, pyridine and tetrabutylammonium iodide led to a complex mixture. Similarly iodide displacements of the sulphonates (1n), (1q) and (1r) gave mixtures. No reaction occurred when the imidazolide (1m) was treated with methyl iodide in an attempt to activate the imidazolide by quaternization for attack at C-13 by iodide. Direct methods for converting alcohols to iodides were also investigated[10,12] but did not produce the desired products.

However the 13-amino group was successfully introduced by reduction of an oxime. The cyclic orthoester (1k) was oxidised with pyridinium dichromate in DMF to the methyl ketone (5a) in 48% yield and was quantitatively converted into the O-methyloxime (5b) with O-methylhydroxylamine hydrochloride in 50% pyridine-ethanol. The oxime (5b) was isolated as a 3:1 mixture of geometrical



(5) a; X = O
b; X = N~OMe

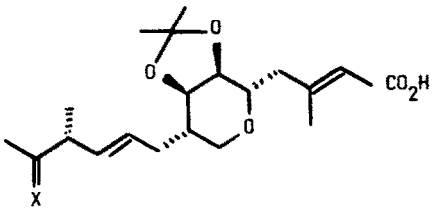
isomers from which the major E-isomer was obtained in 47% yield. No reduction of this oxime was observed with sodium borohydride alone or in the presence of trifluoroacetic acid[13], or by using either lithium triethylborohydride or diisobutylaluminium hydride in THF. The latter two reagents only produced the allylic alcohol (6). Neither diborane[14] nor zinc in ammoniacal solution[15] reduced the oxime. Limited success was obtained with lithium borohydride. When (5b) was treated



(6)

with lithium borohydride in THF reduction to the amine took place but the ester and epoxide functions were also reduced. The problems were avoided by carrying out the transformation in the pseudomonic acid C series.

Monic acid C (2g) was converted into the acetonide (2h) with 2,2-dimethoxypropane and p-toluenesulphonic acid followed by oxidation with pyridinium dichromate to the methyl ketone (7a) which was converted into a 3:1 isomeric mixture of oximes (7b) in 66% overall yield from (2g). Lithium borohydride reduction of (7b) in THF gave the amino acid (2i) which was subsequently reacted with diazomethane and deprotected with 80% acetic acid to afford the aminoester, which was isolated as its hydrochloride (2j) in 17% yeild. Also isolated was the partially reduced methoxyamine (2k) in 2% yield. Spectroscopic analysis showed both (2j) and (2k) to exist as equimolar epimeric mixtures.



(7) a; X = O

b; X = N∿∿OMe

The 13-deoxy compound (2c), methyl (13R)-monate (4f), and the 13-amino derivatives (2j) displayed little antimicrobial activity. The epimeric chlorides (1o) and (4b) were inactive.

EXPERIMENTAL

^{1}H N.m.r. data were recorded at either 60MHz on a Perkin-Elmer R24A or 250 MHz WM250 instrument and ^{13}C measurements were obtained using a Bruker WM250 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 70eV using a VG 70-70F instrument operating at 8eV. Column chromatography was carried out on Merck Kieselgel H (type 60). T.l.c. was performed on pre-coated Merck Kieselgel 60F$_{254}$ plates. High performance liquid chromatography (h.p.l.c.) unless otherwise stated was performed on a Waters Associates instrument using a C_{18} μ-Bondapak reverse-phase column with ammonium acetate buffer-methanol solutions as eluent. Both t.l.c. and h.p.l.c. were performed routinely on all compounds. DMF, THF, pyridine and triethylamine were dried over calcium hydride and distilled before use. Dichloromethane was distilled from phosphorus pentaoxide and toluene was dried over sodium wire.

Mesylate (1e) - Mesyl chloride (0.229g) was added to a solution of the acetonide[7] (1d) in pyridine (10ml) and the reaction stirred at room temperature for 16h. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic phase was washed with aqueous sodium hydrogen carbonate and brine then dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded the mesylate (1e) as an oil (0.63g, 100%); ν_{max} (film) 1740, 1715, 1650, 1355 and 1175 cm^{-1}; δH ($CDCl_3$) 1.04 (3H, d, J 6.5Hz, 17-H_3), 1.2-1.6 (21H, m, $(CH_2)_6$, CMe_2 and 14-H_3), 2.18 (3H, s, 15-H_3), 3.01 (3H, s, SO_2CH_3), 3.63 (3H, s, CO_2CH_3), 4.05 (2H, t, 9'-H_2), and 5.72 (1H,s,2-H).

13-Deoxymonte (1f) - A mixture of the mesylate (1e) (0.3g) and sodium cyanoborohydride (0.315g) in hexamethylphosphoramide (10ml) was heated at 75°C for 5 days. After cooling the reaction mixture was diluted with ethyl acetate (200ml) and washed with water (4x50ml), pH5 ammonium acetate buffer (50ml) and brine (50ml) then dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded the crude product which was chromatographed to afford (1f) as a colourless oil (0.09g, 36%); λ_{max} (EtOH) 218nm (ε 14,700); ν_{max} (film) 1740, 1715, and 1648 cm^{-1}; δH ($CDCl_3$) 0.96 (6H, t+d, 14-H_3 and 17-H_3), 1.2-1.6 (18H, m, $(CH_2)_6$ and CMe_2), 2.19 (3H, s, 15-H_3), 3.64 (3H, s, CO_2CH_3), 4.07 (2H,

t, 9'-H_2), and 5.75 (1H, s, 2-H); δ_C ($CDCl_3$) 11.2 (q, C-14), 15.4 (q, C-17), 19.1 (q, C-15), 24.9 (t, C-3'), 26.0 (t, C-7'), 26.3 and 28.3 (2q, $\underline{C}Me_2$), 27.2 (t, C-13), 28.8 (t, C-8'), 29.1 (t, C-4', -5' and -6'), 34.0 (t, C-9), 34.1 (t, C-2'), 35.2 (d, C-8), 37.2 (d, C-12), 44.1 (t, C-4), 51.3 (q, OMe), 55.7 (d, C-10), 63.4 (d, C-11), 63.7 (t, C-9'), 67.1 (t, C-16), 74.3 (d, C-6), 75.7 (d, C-7), 76.4 (d, C-5), 108.8 (s, $\underline{C}Me_2$), 117.8 (d, C-2), 156.1 (s, C-3), 166.6 (s, C-1), and 174.1 (s, C-1'); m/z 538 (M^+, 1%), 270 (40), 211 (100), and 141 (90) (Found: 538.3497. $C_{30}H_{50}O_8$ requires 538.3491).

Methyl 13-deoxypseudomonate C (2c) - (a) Methyl ester (1f) (0.08g) was dissolved in 10% aqueous t-amyl alcohol (10ml) and refluxed for 19 days with potassium selenocyanate (0.064g). After cooling, the solution was decanted and the residual solid washed several times with ethyl acetate. The solution and washings were evaporated under reduced pressure and the residue partitioned between ethyl acetate and brine. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil which was suspended in methanol (5ml) and water (5ml). Sodium hydrogen carbonate (0.016g) was added and the solution stirred at room temperature for 0.5h then the solvent removed under reduced pressure and the residue dried (P_2O_5). The residue was dissolved in DMF (10ml), treated with methyl iodide (1ml) and hexamethylphosphoramide (1 drop) and the reaction stirred at room temperature for 16h. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water and the organic phase separated, washed with brine and dried ($MgSO_4$). After removal of the solvent under reduced pressure the crude product (0.06g) was purified by preparative t.l.c. on silica (Merck type 60, 20x20x0.2 cm plate) eluting with 1% methanol in chloroform. The major band afforded the acetonide derivative (2f) as an oil (0.025g); δH ($CDCl_3$) 0.90 (6H, t+d, 14- and 17-H_3), 2.17 (3H, s, 15-H_3), 3.63 (3H, s, CO_2CH_3), 4.05 (2H, t, 9'-CH_2), 5.34 (2H, m, 10- and 11-H), and 5.72 (1H, s, 2-H). This oil was dissolved in 80% acetic acid (2ml) and stirred at room temperature for 16h. The solvent was removed under reduced pressure, the residue extracted with ethyl acetate which was then washed with sodium hydrogen carbonate, brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the crude product which was purified by preparative h.p.l.c. (Waters μ-porasil column, eluting with 6% acetonitrile, 20% dichloromethane, and 74% cyclohexane) to afford the title compound (2c) as an oil (0.013g, 18%); ν_{max} (CCl_4) 3475, 1742, 1718, and 1650 cm^{-1}; λ_{max} (EtOH) 219nm (εm 15,200); δH ($CDCl_3$) 0.91 (6H, t+d, 14- and 17-H_3), 1.25 (12H, m, -$(CH_2)_6$-), 2.21 (3H, s, 15-H_3), 3.65 (3H, s, CO_2CH_3), 4.06 (2H, t, 9'-H_2), 5.33 (2H, m, 10- and 11-H), and 5.75 (1H, s, 2-H); δ_C ($CDCl_3$) 11.8 (C-14), 19.2 (C-15), 20.3 (C-17), 24.9 (C-3'), 26.0 (C-7'), 28.7 (C-13), 29.1 (C-8'), 29.7 (C-4', -5', and -6'), 32.3 (C-9), 34.1 (C-2'), 38.4 (C-12), 42.2 (C-8), 43.2 (C-4), 51.4 (OCH_3), 63.8 (C-9'), 64.7 (C-16), 69.0 (C-6), 70.7 (C-7), 74.8 (C-5), 117.6 (C-2), 125.6 and 138.9 (C-10 and 11), 156.9 (C-3), 166.8 (C-1), and 174.3 (C-1'); m/z 482 (M^+, 3%), 464 (10), 446 (12), 295 (20), 270 (60), 195 (30), and 62 (100) (Found: 482.3223. $C_{27}H_{46}O_7$ requires 482.3205).

(b) Methyl 6,7-O-isopropylidenepseudomonate C (1.5g) was dissolved in dry pyridine (30ml) and the solution cooled to 0°C. Mesyl chloride (1.282g) was added slowly and the reaction mixture allowed to reach room temperature and stirring continued for 16h. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate. The organic layer was separated, washed with water and brine then dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was chromatographed on silica (50g) eluting with chloroform to afford pure mesylate (2e) as an oil (1.5g, 87%); ν_{max} (film) 1735, 1710, 1642, 1350, and 1172 cm^{-1}; δH ($CDCl_3$) 5.75 (1H, s, 2-H), 5.5 (2H, m, 10- and 11-H), 4.70 (1H, m, 13-H), 4.1 (3H, t, 9'-H_2), 3.64 (3H, s, CO_2CH_3), 3.96 (3H, s, SO_2CH_3), 2.19 (3H, s, 15-H_3), 1.2-1.5 (21H, m, $(CH_2)_6$, CMe_2, 14-H_3), and 1.07 (3H, d, 17-H_3); δ_C ($CDCl_3$) 16.0 (C-17), 18.3 (C-14), 19.0 (C-15), 24.9 (C-3'), 25.9 (C-7'), 26.3 and 28.7 ($\underline{C}Me_2$), 28.3 (C-8'), 29.0 (C-4',-5', and 6'), 33.9 (C-2'), 36.6 (C-8), 38.5 (C-9), 42.3 (C-4 and -12), 44.2 (SO_2Me), 51.2 ($CO_2\underline{Me}$), 63.6 (C-9'), 66.3 (C-16), 74.1 (C-6), 75.5 (C-7), 76.5 (C-5), 82.4 (C-13), 108.6 ($\underline{C}Me_2$), 117.7 (C-2), 129.8 and 132.7 (C-10 and -11), 156.1 (C-3), 166.5 (C-1), and 173.9 (C-1'). The mesylate (0.75g) was dissolved in hexamethylphosphoramide (13ml) and heated at 75°C for 5 days with sodium cyanoborohydride

(0.819g). After cooling the solution was diluted with ethyl acetate (250ml) and washed with water, ammonium acetate buffer (pH7), and saturated brine then dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded an oil which was chromatographed on silica (75g). Elution with chloroform yielded a colourless oil (0.407g, 64%) which was homogeneous on t.l.c. (1% MeOH-$CHCl_3$) and h.p.l.c. However spectroscopic data indicated a 1:1 mixture of (2f) and (3a), λ_{max} (EtOH) 224nm (εm 20,300); ν_{max} (film) 1742, 1718, and 1650 cm^{-1}; δH ($CDCl_3$) 0.8-1.2 (m), 2.19 (3H, s, 15-H_3), 3.64 (3H, s, CO_2CH_3), 4.06 (2H, t, 9'-H_2), 5.3-5.7 (2H, m, 10- and 11-H), 5.75 (1H, s, 2-H), 6.42 and 6.59 (1H, 2m, olefinic H's); m/z 522 [M^+ (2f), 2%] and 520 [M^+ (3a), 5]; m/z (C.I., NH_3) 540 [M (2f) NH_4^+, 80%], 523 [M (2f)H^+, 100], 538 [M (3a) NH_4^+, 65%], and 521 [M (3a) H^+, 65]. The mixture (0.2g) was hydrolysed by treatment with 80% aqueous acetic acid (20ml) at room temperature for 16h. The solvent was removed under reduced pressure and the product partitioned between ethyl acetate and aqueous sodium hydrogen carbonate. The organic layer was separated, washed with brine and dried ($MgSO_4$) then evaporated to dryness under reduced pressure. The residual oil was chromatographed on silica (10g) eluting with 2% methanol in chloroform to give (0.13g, 70%) which was homogeneous by t.l.c. but spectroscopic data indicated a mixture of (2c) and (3b), λ_{max} (EtOH) 226 nm (εm 21,260); ν_{max} (film) 3440, 1730, 1708, and 1640 cm^{-1}; δH ($CDCl_3$) 0.8-1.12 (m), 2.22 (3H, s, 15-H_3), 3.65 (3H, s, CO_2CH_3), 4.06 (2H, t, 9'-H_2), 5.2-5.6 (2H, m, 10- and 11-H), 6.40 and 6.58 (1H, 2m olefinic H's); δ_C ($CDCl_3$) showed diene signals at 137.0, 134.1, 132.3, 129.1, 128.8, 127.1, 123.8, and 123.5 [C-10 to -13 for (3b)]; m/z (C.I., NH_3) 500 [M (2c) NH_4^+, 60%], 483 [M (2c) H^+, 45), 498 [M (36) NH_4^+,100], and 481 [M (3b) H^+, 70]. A sample was separated into two components using a Waters μ-Poracil analytical column eluting with 10% acetonitrile, 20% dichloromethane, and 70% hexane to give (2c) retention time (Rt) 16.5 min and (3b) Rt 21 min; m/z 480 (M^+, 7%), 462 (2), 445 (3), 292 (33), 270 (38), 211 (15), and 192 (21).

Methyl (E)-4-[(2S, 3R, 4R, 5S)-5-[(2S, 3S, 4S, 5R)-5-chloro-2,3-epoxy-4-methylhexyl]-3,4-dihydroxytetrahydropyran-2-yl]-3-methylbut-2-enoate (4b) - (a) Using phosgene and pyridine: Phosgene in toluene (12.5%, 75ml) was added to a solution of methyl monate (10.7g) in dichloromethane (250ml) and pyridine (20ml) at -20°C. The reaction mixture was stirred at room temperature for 18h then washed with 5M-hydrochloric acid, brine and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure the residual oil was chromatographed on silica (80g) eluting with 0 to 4% methanol in dichloromethane. Fractions containing pure product were combined and evaporated to yield the cyclic carbonate (4a) (6.8g, 57%); ν_{max} (KBr) 1810, 1718,and 1649 cm^{-1}; λ_{max} (EtOH) 220 nm (εm 12,494); δH ($CDCl_3$) 1.04 (3H, d, 17-H_3), 1.54 (3H, d, 14-H_3), 2.21 (3H, d, 15-H_3), 3.70 (3H, s, OCH_3), 4.32 (1H, dq, 13-H), 4.46 (1H, dd, 6-H), 4.73 (1H, dd, 7-H), and 5.75 (1H, d, 2-H); δ_C ($CDCl_3$) 10.1 (C-17), 19.0 (C-15), 23.0 (C-14), 33.0 (C-9), 34.2 (C-8), 43.0 (C-4), 43.6 (C-12), 50.7 (OCH_3), 55.6 (C-10), 60.6 and 60.8 (C-11 and -13), 66.3 (C-16), 74.3, 74.7, and 77.8 (C-5, -6, and -7), 118.3 (C-2), 153.8 and 154.4 (C-3 and OCO_2), and 166.4 (C-1); m/z (C.I., NH_3) 420 (MNH_4^+, 100%), 422 (MNH_4^++2, 49). The cyclic carbonate (4a) (0.404g) was refluxed in 50% aqueous pyridine for 2.5h. The reaction mixture was evaporated to dryness and the crude product chromatographed on silica (10g) eluting with 0 to 6% methanol in dichloromethane. Pure fractions were combined and evaporated to yield the title compound (0.28g, 74%) m.p. 87°C; ν_{max} (nujol) 3400 and 1719 cm^{-1}; λ_{max} (EtOH) 222nm (εm 13,322), δH ($CDCl_3$) 1.03 (3H, d, 17-H_3), 1.53 (3H, d, 14-H_3) 2.22 (3H, d, 15-H_3), 3.69 (3H, s, OCH_3), 4.32 (1H, dq, 13-H), and 5.77 (1H, br., 2-H); δ_C ($CDCl_3$) 10.2 (C-17), 19.2 (C-15), 23.1 (C-14), 31.6 (C-9), 39.8 (C-8), 42.8 (C-4), 42.2 (C-12), 50.8 (OCH_3), 56.8 (C-10), 60.4 (C-13), 60.7 (C-7), 65.3 (C-16), 69.1 (C-6), 70.6 (C-7), 75.1 (C-5), 117.2 (C-2), 157.2 (C-3), and 167.2 (C-1); m/z 376 (M^+, 1%), 277 (6), 245 (21), 141 (33), and 111 (100) (Found: 376.1633. $C_{18}H_{29}ClO_6$ requires 376.1614) (Found: C, 57.0; H, 7.9; Cl, 9.5. $C_{18}H_{29}ClO_6$ requires C, 57.3; H, 7.8; Cl, 9.4%).

(b) Using triphenylphosphine and carbon tetrachloride: The orthoester (1k) (0.8g) and triphenylphosphine (0.377g) were refluxed in carbon tetrachloride (10ml) for 24h. After cooling the reaction mixture was filtered and the filtrate evaporated to an oil which was chromatographed on silica (7g) eluting with dichloromethane. Pure fractions were combined and evaporated and the

resulting protected (13R)-chloride (0.37g, 42%) dissolved in methanol (20ml). Water was added until the solution went slightly clouded and then acidified to pH2. After 15 min. the pH was adjusted to 8 to 9 and the reaction mixture stirred for 3h. The reaction mixture was evaporated to dryness and the residue taken up in ethyl acetate–water. The organic phase was washed with brine then dried ($MgSO_4$) and evaporated under reduced pressure. The product was chromatographed on silica (10g) eluting with 0 to 6% methanol in dichloromethane. Pure fractions were combined and evaporated under reduced pressure to yield the (13R)-chloride (4b) (0.12g, 67%).

Orthoester (1k) - p-Toluenesulphonic acid (0.1g) was added to a suspension of methyl monate (10.0g) in trimethyl orthoformate (100ml) and stirred at room temperature for 1h. The clear solution was washed with aqueous sodium hydrogen carbonate and brine then dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was chromatographed on silica (10g) eluting with 0 to 4% methanol in dichloromethane and the fractions containing pure product were combined and evaporated to yield the title compound as an oil (6.4g, 57%); λ_{max} (EtOH) 222nm (εm 11,670); ν_{max} (film) 3500, 1718, and 1648 cm^{-1}; δH ($CDCl_3$) 0.90 (3H, d, 17-H_3), 1.18 (3H, d, 14-H_3), 2.17 (3H, s, 15-H_3), 3.30 and 3.35 (3H, 2s, CHOCH_3), 3.65 (3H, s, CO_2CH_3), 4.0-4.3 (2H, m, 6- and 7-H), and 5.70 (2H, m, 2-H and CHOMe); δ_C ($CDCl_3$) 11.9 (C-17), 18.6 and 18.7 (C-15), 20.2 (C-14), 33.2 and 33.3 (C-8), 34.3 and 34.9 (C-8), 42.3 (C-12), 43.6 and 43.9 (C-4), 50.3 (CO_2CH_3), 51.6 and 52.4 (CHOCH_3), 54.7 (C-10), 60.5 (C-11), 66.3 (C-16), 70.1 (C-13), 73.2 and 73.8 (C-7), 74.4 and 75.0 (C-6), 75.3 and 77.1 (C-5), 115.0 and 116.6 (CHOMe), 117.2 (C-2), 155.5 and 155.7 (C-3), and 166.4 (C-1); m/z (C.I., NH_3) 418 (MNH_4^+, 61%) (Found: C, 60.3; H, 7.8. $C_{20}H_{32}O_8$ requires C,60.0; H, 8.0%).

Cyclic carbonate (1j) - Carbonyl diimidazole (6.8g) and methyl monate (5.0g) in toluene (50ml) were refluxed for 1h. The solution was evaporated under reduced pressure and the residual oil dissolved in ethyl acetate. After washing with M-hydrochloric acid, aqueous sodium hydrogen carbonate and brine the solution was dried ($MgSO_4$) and evaporated under reduced pressure to give the imidazolide (1m) as an oil (4.7g); ν_{max} (film) 1810, 1760, 1735, and 1718 cm^{-1}; δH ($CDCl_3$) 1.07 (3H, d, 17-H_3), 1.48 (3H, d, 14-H_3), 2.21 (3H, d, 15-H_3), 4.43 (1H, dd, 6-H), 4.70 (1H, dd, 7-H), 5.18 (1H, m, 13-H), 5.77 (1H, d, 2-H), 7.09 (1H, m, 4'-H), 7.45 (1H, m, 5'-H), and 8.15 (1H, m, 2'-H);δ_C ($CDCl_3$) 12.4 (C-17), 17.2 (C-14), 19.0 (C-15), 33.1 (C-9), 34.1 (C-8), 40.9 (C-12), 43.7 (C-4), 50.9 (OCH_3), 54.5 (C-10), 59.7 (C-11), 66.4 (C-16), 74.3, 74.7, 77.8 and 78.0 (C-5, -6, -7, and -13), 117.2, 130.5, and 137.1 (imidazole), 118.3 (C-2), 148.2 and 153.9 (OCO_2 and OCON), 154.4 (C-3) and 166.5 (C-1); m/z 478 (M^+, 0.2%), 447 (0.2), 419 (8), and 41 (100) (Found 478.1981, M^+, ($C_{23}H_{30}N_2O_9$ requires 478.2013). The imidazolide (4.7g) in THF (75ml) was treated with 0.5M sulphuric acid (150ml) and the reaction stirred overnight. The solution was extracted with ethyl acetate and the combined extracts washed with aqueous sodium hydrogen carbonate then dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was chromatographed on silica (25g) eluting with 0 to 6% methanol in dichloromethane and the pure fractions combined to yield after evaporation under reduced pressure the title compound as an oil (4.0g, 75%); λ_{max} (EtOH) 221 nm (εm 12,639); ν_{max} ($CHCl_3$) 3500, 1808, and 1712 cm^{-1}; δH ($CDCl_3$) 0.95 (3H, d, 17-H_3), 1.30 (3H, d, 14-H_3), 1.17 (3H, s, 15-H_3), 3.65 (3H, s, OCH_3), 4.5-5.0 (2H, m, 6- and 7-H), and 5.78 (1H, s, 2-H); δ_C ($CDCl_3$) 12.5 (C-17), 19.1 (C-15), 20.7 (C-14), 33.3 (C-9), 34.1 (C-8), 43.8 and 42.7 (C-4 and -12), 50.9 (OCH_3), 54.5 (C-10), 61.2 (C-11), 66.6 (C-16), 70.8 (C-13), 74.3, 74.9, and 77.9 (C-5, -6 and -7), 118.4 (C-2), 154.1 and 154.4 (C-3 and OCO_2), and 166.7 (C-1); m/z 384 (M^+, 1.1%), 352 (3), 267 (6), and 253 (4) (Found: 384.1823, M^+, $C_{19}H_{28}O_8$ requires 384.1862).

Methyl (13R)-monate (4f) - Mesyl chloride (0.21ml) was added to a solution of the orthoester (1k) (1.0g) in dichloromethane (25ml) and triethylamine (0.39ml) at -10°C. After stirring at room temperature for 1h, the solution was washed with aqueous sodium hydrogen carbonate, brine then dried ($MgSO_4$). The soluent was evaporated under reduced pressure and the mesylate (1n) was dissolved in DMF (25ml) and sodium formate (0.3g) added. The reaction mixture was heated at 80°C for 18h then evaporated to dryness under reduced pressure. The residue was extracted with ethyl

acetate–water and the organic phase washed with aqueous sodium hydrogen carbonate, brine then dried ($MgSO_4$) and evaporated to an oil under reduced pressure. The product was dissolved in 1,4-dioxan–water (4:1, 20ml) and treated with 10M-hydrochloric acid (10 drops). After 15 min saturated sodium hydrogen carbonate (5ml) was added and reaction mixture stirred for 3h. The product was extracted with ethyl acetate which was dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography of the residual oil on silica (10g) eluting with 0 to 6% methanol in dichloromethane. Pure fractions were combined and evaporated under reduced pressure to afford (4f) as an oil (0.19g, 21%); ν_{max} ($CHCl_3$) 3,400 (broad), 1720, and 1648 cm^{-1}; λ_{max} (EtOH) 221 nm (εm 12,713); δH ($CDCl_3$) 0.93 (3H, d, 17-H_3), 1.25 (3H, d, 14-H_3), 2.21 (3H, s, 15-H_3), 3.69 (3H, s, OCH_3), and 5.76 (1H, s, 2-H); δ_c ($CDCl_3$) 10.6 (C-17), 19.2 (C-15), 20.5 (C-14), 31.8 (C-9), 39.6 (C-8), 41.9 (C-12), 42.9 (C-4), 50.9 (OCH_3), 56.5 (C-10), 61.0 (C-11), 65.4 (C-16), 69.1 and 69.2 (C-6 and -13), 70.5 (C-7), 75.1 (C-5), 117.3 (C-2), 157.2 (C-3), and 167.3 (C-1); m/z 358 (M^+, 1%), 308 (5), 239 (12), 227 (52), and 111 (100) (Found: 358.1998, M^+, $C_{18}H_{30}O_7$ requires 358.2007).

Methyl (E)-4-{[(2S,3R,4R,5S)-5-(2S,3S,4S,5S)-5-chloro-2,3-epoxy-4-methylhexyl]-3,4-dihydroxytetrahydropyran-2-yl}-3-methylbut-2-enoate (1o) – Methyl (13R)-monate (4f) (0.13g) in methylene chloride (10ml) was treated with pyridine (0.5ml) and phosgene in toluene (12.5%, 2ml). The reaction was stirred overnight at room temperature then washed with 5M-hydrochloric acid, aqueous sodium hydrogen carbonate and brine then dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded an oil which was chromatographed on silica (5g) eluting with 0 to 2% methanol in dichloromethane. Pure fractions were combined and evaporated under reduced pressure to give (1p) (0.078g). The cyclic carbonate (0.078g) was refluxed in 50% aqueous pyridine for 2.5h, and then the reaction mixture evaporated under reduced pressure and the residue chromatographed on silica (2.0g) eluting with 0 to 2% methanol in dichloromethane. Pure fractions were combined and evaporated under reduced pressure to afford the title compound (0.026g, 18%) m.p. 111–2°C; ν_{max} (nujol) 1718 and 1650 cm^{-1}; δH ($CDCl_3$) 1.05 (3H, d, 17-H_3), 1.59 (3H, d, 14-H_3), 2.22 (3h, d, 15-H_3), 3.69 (3H, s, OCH_3), 4.17 (1H, dq, 13-H), and 5.77 (1H, d, 2-H); δ_c ($CDCl_3$) 13.5 (C-17), 19.2 (C-15), 22.4 (C-14), 31.6 (C-9), 39.8 (C-8), 42.9 (C-4), 43.1 (C-12), 50.9 (OCH_3), 55.3 (C-10), 59.1 (C-11), 61.5 (C-13), 65.3 (C-16), 69.1 (C-6), 70.6 (C-7), 74.9 (C-5), 117.3 (C-2), 157.0 (C-3), and 167.1 (C-1); m/z (C.I., NH_3) 394 (MNH_4^+, 19%), 396 (MNH_4^++2, 6), 377 (MH^+, 6), and 379 (MH^++2, 2) (Found: C, 57.5; H, 7.6. $C_{18}H_{29}ClO_6$ requires C, 57.3; H, 7.8%).

Oxime (5b) – Pyridinium dichromate (7.3g) was added to a solution of the alcohol (1k) (1.2g) in DMF (30ml) at 0°C and stirred at ambient temperature for 3h. The dark solution was poured into water (300ml) and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the residual oil chromatographed on silica (10g) eluting with 0 to 4% methanol in dichloromethane to afford the pure methyl ketone (5a) as an oil (0.55g, 48%); λ_{max} (EtOH) 222 nm (εm 11,320); ν_{max} ($CHCl_3$) 1715 and 1645 cm^{-1}, δH ($CDCl_3$) 1.11 (3h, d, 17-H_3), 2.20 (6H, s, 14- and 15-H_3), 3.32 (3H, s, $CHOCH_3$) 3.64 (3H, s, CO_2CH_3), and 5.71 (2H, m, 2-H and $CHOCH_3$); O-Methylhydroxylamine hydrochloride (0.72g) was added to a solution of the methyl ketone (5a) (0.72g) ethanol (0.7ml) and pyridine (0.7ml). The reaction mixture was stirred at room temperature for 3h then poured into ethyl acetate–water. The organic phase was separated, washed with brine and dried ($MgSO_4$) then evaporated under reduced pressure to give a 3:1 mixture (by h.p.l.c.) of E and Z oximes (5b). Chromatography on silica (10g) eluting with 0 to 4% methanol in dichloromethane enabled the major E-isomer to be separated (0.36g, 47%); λ_{max} (EtOH) 216 nm (εm 16,890); ν_{max} ($CHCl_3$) 1710 and 1645 cm^{-1}; δH ($CDCl_3$) 1.13 (3H, d, 17-H_3), 1.85 (3H, s, 14-H_3), 2.19 (3H, s, 15-H_3), 2.78 (1H, dd, 11-H), 2.88 (1H, m, 10-H), 3.36 (3H, s, $CHOCH_3$), 3.69 (3H, s, CO_2CH_3), 3.84 (3H, s, $NOCH_3$), 3.94 (1H, dd, 6-H), 4.27 (1H, dd, 7-H), and 5.77 (2H, m, 2-H and $CHOCH_3$); δ_c ($CDCl_3$) 12.6 (C-17), 13.9 (C-15), 33.6 and 34.7 (C-8 and -9), 41.7 (C-12), 44.1 (C-4), 50.8 (CO_2CH_3), 52.2 ($CHOCH_3$), 55.6 (C-10), 60.4 (C-11), 61.3 ($NOCH_3$), 66.7 (C-16), 74.3, 74.8 and 75.8 (C-5, -6, and -7), 115.5 ($CHOCH_3$), 117.6 (C-2), 156.0 (C-3), 157.6 (C-13) and 166.9 (C-1); m/z 396 (M^+–OCH_3, 8%), 364 (6), 336 (4), 314 (9), 279 (7), 254 (17), 149 (78), 55 (80) and 41 (100) (Found: 396.2016. $C_{20}H_{30}NO_7$ requires 396.2022); m/z (C.I.NH_3) 428 (MH^+, 7%).

Oxime (7b) - Monic acid C (1.05g) in THF (20ml) was treated with 2,2-dimethoxypropane (10ml) and p-toluenesulphonic acid (few crystals). After stirring at room temperature for 1h, 1M sodium hydroxide (25ml) was added and the mixture extracted with ethyl acetate (dicarded). The aqueous phase was separated, acidified to pH2 and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give an oil which was dissolved in DMF (30ml) and treated with pyridinium dichromate (7.3g) at room temperature. After stirring for 18h the dark solution was poured into water and the product extracted with ether (5x50ml). The combined extracts were washed with brine then dried ($MgSO_4$) and evaporation of the solvent under reduced pressure to yield the methyl ketone (7a) as an oil; ν_{max} (film) 2500-3500, 1730, 1715 and 1643 cm^{-1}, δH ($CDCl_3$) 1.15 (3H, d, 17-H_3), 1.34 and 1.47 (6h, 2s, $CHMe_2$), 2.11 (3H, s, 14-H_3), 2.14 (3H, m, 15-H_3), 4.1 (2H, m, 6- and 7-H), 5.55 (2H, m, 10- and 11-H), and 5.77 (1H, m, 2-H). The methyl ketone (7a) was dissolved in ethanol (10ml) and pyridine (10ml) and O-methylhydroxylamine hydrochloride (1g) added. The reaction mixture was stirred overnight then evaporated to dryness under reduced pressure and the residue dissolved in ethyl acetate (25ml) and water (25ml). The aqueous phase was adjusted to pH3 and the organic phase separated, washed with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded an oil which was chromatographed on silica (10g) eluting with 0 to 6% methanol in dichloromethane. Pure fractions were combined and evaporated to yeild a 3:1 mixture (by h.p.l.c.) of oximes (7b) as an oil (0.83g, 66%); ν_{max} ($CHCl_3$) 1705 and 1645 cm^{-1}; δH ($CDCl_3$) 1.15 (3H, d, 17-H_3), 1.34 and 1.48 (6H, 2s, CMe_2), 1.73 (3h, s, 14-H_3), 2.18 (3H, s, 15-H_3), 3.80 (3H, s, $NOCH_3$), 5.40 (2h, m, 10- and 11-H), and 5.76 (1H, m, 2-H).

Methyl 4-{(2S, 3R, 4R, 5S)-5-[(4R,5RS)-5-amino-4-methylhex-2(E)-enyl]-3,4-dihydroxytetrahydropyran-2-yl}-3-methylbut-2(E)-enoate hydrochloride (2j) - Lithium borohydride (0.226g) was added under nitrogen to the O-methyloxime (7b) (0.646g) in THF (30ml) and the reaction stirred at room temperature for 9 days then quenched with water. The THF was removed under reduced pressure and the resulting aqueous solution adjusted to pH 1.5 under a layer of ethyl acetate. The organic phase was separated and dried ($MgSO_4$) then evaporated to an oil which was dissolved in ethyl acetate and treated with excess ethereal diazomethane. The reagent and solvents were removed by blowing nitrogen on the surface and the residue partitioned between ethyl acetate and water. The pH of the aqueous phase was adjusted to 12 and the organic phase separated, washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was chromatographed on silica (5g) eluting with 0 to 6% methanol in dichloromethane. Fractions containing pure acetonide were combined and evaporated under reduced pressure to an oil which was dissolved in 80% acetic acid and left overnight. The solution was evaporated to dryness under reduced pressure and the residue partitioned between ethyl acetate and water. The pH of the aqueous phase was adjusted to 12 and the organic phase separated, dried ($MgSO_4$) and evaporated under reduced pressure to an oil which was chromatographed on silica (4g) eluting with 0 to 10% methanol in dichloromethane. Pure fractions were combined and evaporated under reduced pressure, redissolved in ethyl acetate and extracted with M-hydrochloric acid. The aqueous solution was evaporated under reduced pressure and the hydrochloride (2j) dried to yield (0.106g, 17%); λ_{max} (EtOH) 220 nm (εm 10,441); ν_{max} (KBr) 3400, 2940, 1705 and 1642 cm^{-1}; δH (CD_3OD) 1.09 and 1.11 (3H, 2d, 17-H_3), 1.24 and 1.26 (3H, 2d, 14-H_3), 2.19 (3H, m, 15-H_3), 3.68 (3H, s, OCH_3), 5.45 (1H, m, 10-H), 5.62 (1H, m, 11-H), and 5.75 (1H, s, 2-H); δ_C (CD_3OD) 15.6 and 16.2 (C-17), 16.6 and 17.4 (C-14), 19.3 (C-15), 33.3 and 33.6 (C-9), 41.6 and 42.2 (C-12), 43.1 and 43.3 (C-8), 43.9 (C-4), 51.2 (OCH_3), 53.0 (C-13), 65.7 (C-16), 70.0 (C-6), 71.3 (C-7), 76.2 (C-5), 117.8 (C-2), 132.0, 133.0, 133.1, and 133.2 (C-10 and -11), 159.0 (C-3), and 168.6 (C-1); m/z 342 (MH^+, 68%), 310 (13), 266 (5), 228 (5), and 210 (5); m/z (C.I., NH_3) 342 (M^+-Cl, 97%) and 44 (100) (Found: C, 57.0; H, 8.7. $C_{18}H_{32}ClNO_5$ requires C, 57.2; H, 8.5%). The methoxyamine (2k) was also isolated (0.022g, 3%); λ_{max} (EtOH) 219 nm (εm 9,982); ν_{max} ($CHCl_3$) 3400, 1710, and 1643 cm^{-1}; δH ($CDCl_3$) 1.9-2.1 (6H, m, 14- and 17-H_3), 2.22 (3H, d, 15-H_3), 2.81 and 2.93 (1H, 2m, 13-H), 3.52 (3H, s, $NHOCH_3$), 3.69 (3H, s, OCH_3), 5.44 (2H, m, 10- and 11-H), and 5.78 (1H, s, 2-H); m/z 372 (MH^+, 4%), 338 (4), 298 (4), 266 (25), and 74 (100) (Found: 372.2378. $C_{19}H_{34}NO_6$ requires 372.2386).

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