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Application of Radical Cyclisation/Iodine Atom Transfer to the Chiral Synthesis of (-)-Methylenolactocin

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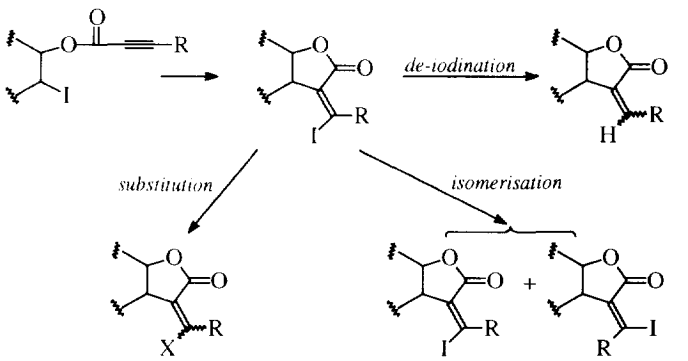
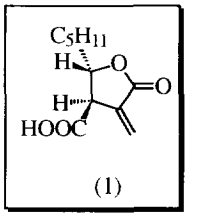
Abstract - Methylenolactocin, an antitumour antibiotic, has been synthesised through an efficient radical cyclisation process on a chiral iodo acetylenic ester. Chiral iodohydrins may be formed by regioselective opening of a chiral epoxy ester, prepared by Sharpless epoxidation. C-2 opening is achieved with TMSCl/NaI and C-3 attack with MgI_2. Subsequent esterification of the 2-iodo compound by reaction with substituted propynoyl triflates gives the key iodo acetylenic esters. This route is highly adaptable to the synthesis of analogues.

During of our work on the synthesis of alkylidene butyrolactones, we have looked to apply radical cyclisation/iodine atom transfer to the formation of natural products and structural analogues. For any general synthesis of alkylidene butyrolactones to be useful, it must be able to be widely adapted. In this respect, since the biological activity of α-methylene-γ-butyrolactones is thought to be associated with the propensity to undergo conjugate additions[1], the β-carbon is an important centre for derivatisation. The application of our optimised radical cyclisation/iodine atom transfer procedure[2] permits a number of variations at the β-carbon by using various acetylenic acids[3], geometric isomerisation[4], de-iodination[5] or substitution[6] (Scheme 1).



Scheme 1. Lactone modifications available *via* iodoalkylidene lactones

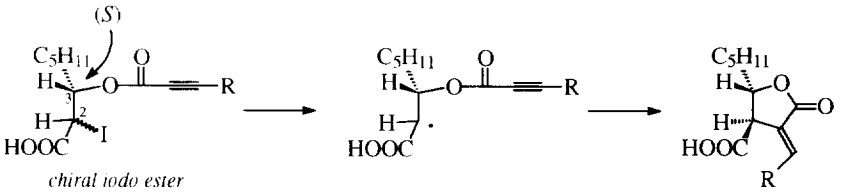
We now report the application of this strategy to a new enantioselective synthesis of (-)-methylenolactocin (**1**), an antitumour antibiotic from *Penicillium sp.*[7] Four previous enantioselective syntheses of methylenolactocin have now been published[8-11] with overall yields ranging up to 30 %. The first of these[8] employed an optically active cyclohexanol as a chiral auxiliary to achieve facial selectivity in an addition reaction, while the second[9] used a chiral lithium amide to obtain an



(1)

enantioselective deprotonation. In two very recent syntheses, Vaupel and Knochel[10] used a chiral amine to direct addition of a dialkylzinc to an aldehyde, while Zhu and Lu[11] employed Sharpless epoxidation methods[12,13] to attain the desired enantiomer. We also chose to introduce chirality by employing Sharpless epoxidation, but aimed to proceed to a chiral cyclisation precursor in a more direct fashion. In both of the two recent syntheses, the key cyclisation reaction involved formation of the 3,4-bond as in our lactone cyclisation reaction (Scheme 1). In one instance[10] this was achieved by a 5-*exo-trig* cyclisation of an acetal, while the other[11] involved a 5-*exo-dig* closure of the propargylic ester of an allylic alcohol. This latter route employed palladium (II) to achieve a similar alkylidene lactone synthesis to ours.

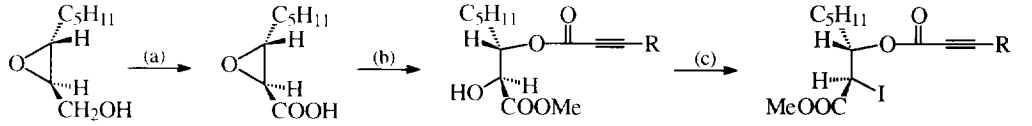
The route which we envisaged (Scheme 2) required the synthesis of a chiral iodo ester. Only the C-3 stereochemistry is important, as that at C-2 is lost through inversion at the radical centre[14]. The desired relative orientation of the alkyl side chain at C-3 and the ester functionality at C-2 would be thermodynamically controlled.



Scheme 2. Proposed route to (-)-methylenolactocin

REGIOSELECTIVE RING OPENING

Initial attempts involved the opening of a chiral epoxide by an acetylenic acid (Scheme 3). Sharpless oxidation of (*E*)-2-octene-1-ol generated the chiral epoxy alcohol (**2**) which was then oxidised with ruthenium chloride/periodic acid[15] to give epoxy acid (**3**). Regioselective ring opening of either (**2**) or (**3**) appeared to provide potential routes to a suitable chiral ester. Methods have been reported using $Ti(OPr^i)_4$[15,16] to catalyse the ring opening of an epoxy alcohol with nucleophiles such as benzoic acid in CH_2Cl_2, ammonium acetate in THF and 2,3-dimethylpropanoic acid in benzene in moderate to high yields[16]. Reaction of amines with epoxy acids has given 70-92% yields of ring opened products[15].



(2) (3) (4) R = TMS (5) R = Me (6) R = TMS (7) R = Me

(a) $RuCl_3/H_5IO_6$ (100%); (b) $Ti(OPr^i)_4$/R-C≡C-COOH (16-30%); (c) $(CF_3SO_2)_2O/Et_3N$, NaI (80-82%)

Scheme 3. Synthesis of (2*R*, 3*S*)-iodo acetylenic esters

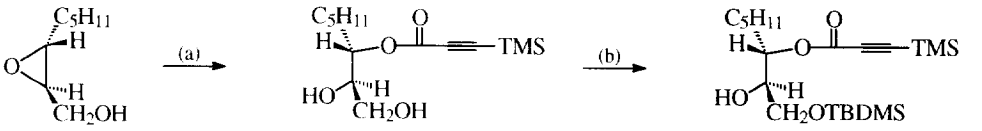
Opening the epoxy acid (**3**) with trimethylsilylpropynoic acid under various reaction conditions, using either CH_2Cl_2 or THF as solvent, led to complex product mixtures. Only low yields (16-22%) of the desired product (**4**) were obtained after esterification. Since we have previously shown that the acetylenic acids can act

as a nucleophiles in reactions with iodonium systems[3] or with cyclohexene oxide[17], the ability of the acid to act as a nucleophile in reactions of this type is not in question. Problems with competing nucleophiles may be the issue. Formation of the complex between epoxy acid and titanium isopropoxide which is crucial for the C-3 selectivity liberates one isopropoxide ligand. Complexation of trimethylsilylpropynoic acid to the titanium may also liberate further isopropoxide. In addition, if an appreciable proportion of epoxy acid becomes unbound, it too may act as a nucleophile. Furthermore, it is well documented that titanium (IV) can interact with the π-system of triple bonds[18]. This may tie up the acetylenic acid. In order to minimise these effects, various orders of addition were tested; either pre-forming the epoxy acid-titanium isopropoxide complex then adding the acetylenic acid, or pre-forming the acetylenic acid/titanium isopropoxide complex and then adding the epoxy acid. Although the latter method has been used successfully in the selective ring opening of epoxy-alcohols with various acids[19], these modifications gave no significant improvement. In some previous instances the acids have been silylated prior to reaction. This leads to silylation of the released isopropoxide ligands and reduces problems with competing nucleophiles. However, in our case the silylation of the acetylenic carboxylic acid, followed by addition to $Ti(OPr^i)_4$ and addition of epoxy acid (**3**), gave only a 17% isolated yield of ring opened alcohol (**4**) after esterification.

To test whether the trimethylsilyl protection of the acetylene was causing problems, the reaction was also performed using butynoic acid. This again gave low yields (20-30%) of ring opened adduct (**5**) (after esterification) despite numerous variations in reaction conditions. The ^1H NMR spectrum indicated the presence of isopropyl groups in the product mixtures, consistent with competitive epoxide opening by isopropoxide.

Despite the low yields of formation of (**4**) and (**5**), the subsequent step, conversion to the *(2R, 3S)*-iodo acetylenic esters (**6**) and (**7**) was readily achieved using a one pot treatment with trifluoromethanesulphonic anhydride and sodium iodide.

Further ring opening reactions were carried out on the epoxy alcohol (**2**) (Scheme 4). It was envisaged that (**2**) would bind more strongly to titanium than the acid (**3**) and hence would be less likely to act as a competing nucleophile. It was again proposed to open the ring selectively at C-3, then protect the primary alcohol prior to converting the secondary alcohol to an alkyl iodide.



(2) (8) (9)

(a) $Ti(OPr^i)_4$/TMS-C≡C-COOH (38%); (b) Et_3N/TBDMSCl (62%)

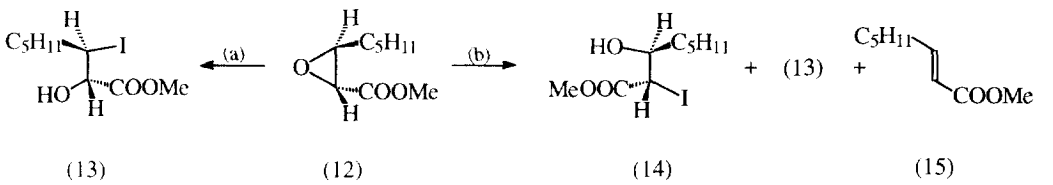
Scheme 4. Opening of epoxy alcohol (2)

Titanium isopropoxide catalysed ring opening of epoxy alcohol (**2**) with TMS-propynoic acid gave a 38% yield of (**8**), a higher yield of ring opened product than had been achieved with the corresponding acid. Protection of the primary alcohol as the TBDMS-ether (**9**) (62%) proved the viability of the method but the comparatively low yields gave no significant advantage over the former epoxy acid opening.

To improve overall yields, an alternative strategy to produce an iodo acetylenic ester was sought *via* a chiral iodohydrin formed by iodide attack on the epoxide ring. The *(2S,3S)*-epoxy alcohol (**10**) was now

required, as the C-3 stereochemistry would be retained, rather than being inverted as before. Alcohol (**10**) and the corresponding acid (**11**) were formed as described for the enantiomeric alcohol (**2**) and acid (**3**). However, a search of the literature for reliable method to selectively open epoxy acids or their derivatives with iodide at C-2 proved unfruitful. Many nucleophilic ring openings of epoxy acids have been reported and it is apparent that prediction of the conditions required to gain regioselectivity is not straightforward. Treatment of epoxy acids with amines or thiolates has been reported to produce C-2 opened adducts until $Ti(OPr^i)_4$ is added when C-3 adducts prevail[15]. Treatment of *trans* epoxy acids with Me_2CuLi gives a C-2 : C-3 ratio of 8 : 1, whereas the *cis* epoxy acid yields a 1 : 17 ratio[20]. With the corresponding methyl esters, ring opening of either the *cis* or the *trans* epoxide proceeds mainly through C-2 attack[21]. A C-3 selectivity of 2.8-3.0 : 1 has been reported for the opening of epoxy alcohols by ammonium chloride or bromide (71-84% yield)[16] in the presence of $Ti(OPr^i)_4$, with no reaction in the absence of the catalyst.

Treatment of the methylated *trans* epoxy acid (**12**), with either $LiI.H_2O/CH_2Cl_2$/HMPA or NaI/MeCN as sources of nucleophilic iodide both left the epoxide intact. However, reaction with magnesium iodide in diethyl ether provided the undesired C-3 adduct (**13**) quantitatively. In contrast, by the use of TMSCl/NaI in MeCN, the ring opening progressed rapidly to give predominantly the C-2 iodohydrin (**14**) in good yield (Scheme 5). Regioselectivity was 13 : 1 in favour of C-2 attack. The predominant side product, alkene (**15**), increased in proportion with increasing amounts of TMSCl/NaI, and the maximum yield of iodohydrin (**14**) (72%) was obtained when reaction was carried out to the point where a small amount of unreacted epoxide still remained.



(13) (12) (14) (15)

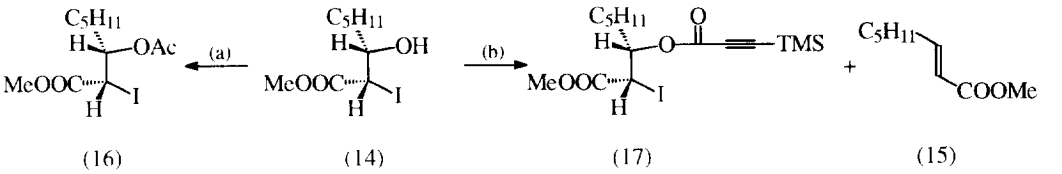
(a) MgI_2/Et_2O (94%); (b) NaI/TMSCl {72% of (**14**)}

Scheme 5. Regioselective iodohydrin formation

ESTERIFICATION OF THE IODOHYDRIN

Trial reactions on the esterification of the iodohydrin appeared encouraging. Although, basic conditions might be expected to induce ring closure to reform epoxide (**12**), treatment of alcohol (**14**) with acetyl chloride in the presence of triethylamine gave nearly quantitative formation of ester (**16**) with no evidence of ring closure (Scheme 6). However, reaction using trimethsilylpropynoyl chloride under identical conditions gave multiple products, predominantly the epoxide. Various combinations of temperature, reaction ratios and order of addition failed to cleanly esterify the alcohol.

Reaction of the acid with carbonyl diimidazole (CDI) to produce the activated carbonyl[22], followed by addition of alcohol (**14**), yielded only unreacted starting materials. Reaction of acid and alcohol in the presence of DCC/DMAP, which has been applied to similar propiolate ester syntheses[23], produced predominantly the N-acyl urea adduct. These adducts have been observed previously as side products in DCC coupling reactions where it has been found that acid catalysis by PTSA in pyridine[24] or by employing the hydrochloride salt of DMAP[25] suppressed their formation. Both these adaptations failed to assist.



(16) (14) (17) (15)

(a) AcCl/Et_3N (84%); (b) TMS-C≡C-COOTf {71% of (**17**)}

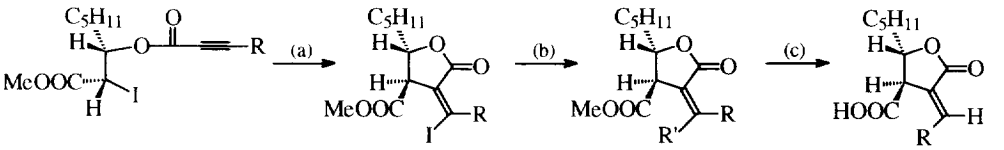
Scheme 6. Esterification of alcohol (14)

To increase the acylation power without the need for strongly basic conditions[26], the mixed anhydride, TMS-propynoyl triflate, was prepared. Triflate mixed anhydrides are aggressive reagents which can be used to acylate deactivated aromatics without the use of Friedel Crafts catalysts[27] and acylate amines and ethers[28]. The reagents can be prepared from the acid chloride and silver triflate[29] or by heating the sulphonic acid with the acid chloride or carboxylic anhydride[30]. As silver salts would not be compatible with the presence of alkyl iodides and to enable a one pot procedure, the simple addition of triflic anhydride to TMS-propynoic acid in CH_2Cl_2 was used to prepare the mixed anhydride. Subsequent addition of alcohol (**14**) lead to smooth esterification. This reaction was slow but gave good yields (>70%) of clean product, the *(2S,3S)*-iodo acetylenic ester (**17**). Once again, significant percentages of alkene (**15**).

RADICAL CYCLISATION AND DE-PROTECTION

Cyclisation of either the *(2R,3S)* or *(2S,3S)* iodo acetylenic esters (**6**) and (**17**) gave good yields of the TMS-iodo lactone (**18**). Initiation using $(Bu_3Sn)_2$ or $(Me_3Sn)_2$[31] in conjunction with AIBN produced a clean cyclised product which could be easily purified by chromatography, but on scale-up, the reaction times became significantly longer. Cyclisation using dibenzoyl peroxide also progressed smoothly and in high yields but purification of the iodolactone (**18**) was more difficult. De-silylation of the vinyl silane was achieved by treatment with KF/18-crown-6 in THF at RT[2] to give the iodomethylene lactone (**19**). Fluoride in THF is slightly basic[32] and does lead to some decomposition of the lactone due to the prolonged reaction time. Alternatively, dissolving the lactone in THF, adding acetone as a proton source, and treating with KF/18-crown-6 also effectively de-silylated the lactone, but in 10-15 min at 10°C. The optimum route to (**19**) is to prepare (**18**) by dibenzoyl peroxide initiated cyclisation and to de-silylate the crude mixture with KF/18-crown-6/THF/acetone. The iodo methylene lactone (**19**) is easily purified on silica. Photochemical de-iodination[5] by irradiation at 254 nm in THF gave smooth conversion to the *exo*-methylene lactone (**20**). The methyl ester was effectively hydrolysed by heating in butanone with 6M HCl to give the target natural product (**1**).

The reaction sequence was repeated using butynoic acid to form iodoester (**21**) which yielded the iodoethylidene lactone (**22**) and subsequently the (*E*)- and (*Z*)-ethylidene lactones (**23**) and (**24**). This demonstrates one of the many variables of this route. Acid hydrolysis leads to isomerisation of the alkylated double bond and both the (*E*)- and the (*Z*)-ethylidene lactone esters give the (*E*)-ethylidene lactonic acid (**25**).



(17) R = TMS
(21) R = Me

(18) R = TMS
(19) R = H
(22) R = Me

(20) R = R' = H
(23) R = Me; R' = H
(24) R = H; R' = Me

(1) R = H
(25) R = Me

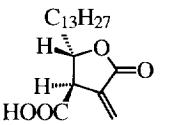
(a) Dibenzoyl peroxide (75-85%); (b) {For (18) KF/18-Crown-6 first}, hv/THF (85-94%); (c) 6M HCl/butanone (90%)

Scheme 7. Alkylidene lactone formation

SUMMARY

The overall yield of this synthesis of (-)-methylenolactocin is 26-29% over the 9 reaction steps from (*E*)-octen-2-ol. This is superior to three of the previously published methods[8,9,11], but less direct than that described by Vaupel and Knochel[10] who used a five step procedure to gain a 30% overall yield starting from (*E*)-3-trimethylsilylpropenal. The crucial steps in our synthesis are the C-2 selective ring opening of the epoxy methyl ester and the subsequent esterification of the iodohydrin under acidic conditions. The viability of this approach employing radical cyclisation techniques is born out by the trouble free cyclisations and subsequent de-silylation and de-iodination. The previously reported sensitivity of the products to base catalysed isomerisation created no problems.

One strength of our new synthesis is that chiral epoxides can be prepared cheaply in large quantities, and Sharpless epoxidation methods provide ready access to either enantiomer. Our synthesis is more direct and is higher yielding than the other synthesis which uses Sharpless methods[11]. Another other strong point of our approach is its potential versatility. The side chain could be altered by changing the allylic alcohol used in the epoxide preparation. A wide range of such compounds is readily accessible by hydrogenation of the corresponding acetylenic alcohols. Thus, other natural products of similar structure, such as protolichesterinic acid (**26**)[33], might be synthesised. Structural changes of this type might also be useful for changing the lipophilic nature of the compounds in structure activity studies. Modification of the active β-site can be attained either by the use of varied acetylenic acids, or by substitution reactions on the α-iodoalkylidene-γ-butyrolactone. The ability to open the epoxide selectively at C-3 using MgI_2, or at C-2 with TMSCl/NaI, gives access to chiral iodo derivatives which can be transformed subsequently into methylenolactocin analogues or into the as yet unknown regioisomers with carboxyl functionality and alkyl side chain positions reversed. We have therefore demonstrated a synthetic method for the synthesis of a naturally occurring antitumour antibiotic that has the potential to be widely manipulated.



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EXPERIMENTAL

General. IR spectra were recorded on Perkin Elmer 1600 series Fourier transform spectrophotometers. Low and high resolution MS were recorded using a Kratos MS80RFA (MACH3 processing) spectrometer by B. Clark, Chemistry Department, University of Canterbury, Private Bag, Christchurch, N.Z. Radial

Chromatography was performed using a 'Chromatotron' model 7924 (Harrison Research, Palo Alto, U.S.A.). NMR spectra were obtained on a Varian VXR-S 300 instrument operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Spectra were recorded as dilute $CDCl_3$ solutions and chemical shifts are quoted in ppm downfield from Me_4Si. Carbon types were determined by DEPT pulse sequences. Microanalyses were performed by Dr. R. G. Cunningham and associates in our Department.

Photolytic reactions were carried out in a Rayonet photochemical reactor at 254 nm using quartz vessels fitted with an argon inlet. In all irradiations, the solutions were degassed by passage of argon for 5 min and were continually purged throughout the irradiation. Sunlamp irradiations used a broad spectrum tungsten filament lamp (160 W).

(*E*)-octen-2-ol was prepared in high yield by a *trans* reduction of octyn-2-ol (using Red-Al®) prepared from propargyl alcohol and pentyl bromide[34,35]. Trimethylsilylpropynoic acid was prepared according to literature methods[36,37].

(2R,3R)-3-Pentyloxiranemethanol (2)[12]. To 1.2 g 4A powdered sieves in CH_2Cl_2 (150 ml) cooled to -20°C was added D-(-)-diethyl tartrate (6%, 0.483 g, 2.3 mmol) and $Ti(OPr^i)_4$ (5%, 0.551 g, 1.95 mmol, 0.577 ml), followed by *tert*-butyl hydroperoxide (2.8M, 28 ml, 78 mmol) over 5 min at -20°C. The reaction mixture was stirred for 20 min at -20°C, then a solution of (*E*)-2-octenol (5.0 g, 39 mmol) in CH_2Cl_2 (20 ml) was added at T = -15 to -20°C. After the resultant solution had been stirred at -20°C for 3.5 h, it was warmed to -10°C and a solution of $FeSO_4.7H_2O$ (13.01 g, 46.8 mmol) and tartaric acid (3.51 g, 23.4 mmol) in H_2O (40 ml) was added. The mixture was stirred for 0.5 h, separated and extracted with Et_2O (2 x 50 ml). The resultant solution was treated at 0°C with a cooled solution containing 30% NaOH (w/v) in saturated brine (3.9 ml, 29.25 mmol) and stirred at 0°C for 1 h. After separation, the organic phases were dried ($MgSO_4$) and evaporated. Recrystallisation from hexane gave (**2**) (5.62 g, 99%). A second recrystallisation gave (4.52 g, 80%). Enantiomeric excess was determined by mandelate ester formation to be > 98% (GC).

(2S,3R)-3-Pentyloxiranecarboxylic acid (3). H_5IO_6 (15.83 g, 69 mmol) and $RuCl_3$ (0.050 g, 0.26 mmol, 0.9%) were added to a solution of epoxy alcohol (**2**) (4.00 g, 27.78 mmol) in CCl_4/MeCN/H_2O (28/28/42 ml) and the suspension was stirred at RT for 3 h. The organic solvents were evaporated, the aqueous residue extracted with Et_2O (3 x 60 ml), dried ($MgSO_4$) and evaporated to give product (**3**) of sufficient purity to continue (4.38 g, 100%). Further purification of (**3**) from ruthenium residues could be achieved by chromatography on C-18 silica eluting with H_2O/MeOH 2 : 1).

Methyl (2S,3S)-2-hydroxy-3-(trimethylsilylpropynoyloxy)octanoate (4). $Ti(OPr^i)_4$ (2.08 g, 2.17 ml, 7.31 mmol) was added to a solution of epoxy acid (**3**) (1.100 g, 6.96 mmol) and trimethylsilylpropynoic acid (1.477 g, 10.4 mmol) in CH_2Cl_2 (20 ml) at -20°C. The reaction was allowed to warm slowly to RT and stirred for 18 h at RT before 5% H_2SO_4 was added. After stirring for 1 h, the product was extracted with Et_2O (3 x 50 ml), dried ($MgSO_4$) and the solvents evaporated. Methylation with CH_2N_2 followed by chromatography on silica using 30% EtOAc/hexanes gave (**4**) (0.480 g, 22%). IR, ν_{max} (film) 3500 (OH), 2175 (C≡C), 1722, 1713 (C=O) cm^{-1}; ^{1}H NMR, δ 0.24 (s, $(CH_3)_3Si$, 9H), 0.88 (br.s, H-8, 3H), 1.20-1.80 (m, H-4,5,6,7, 8H), 2.60 (br.s, OH, 1H), 3.83(s, OCH_3), 4.35 (d, *J* 4.0 Hz, H-2, 1H), 5.18 (dt, *J* 9.0, 4.0 Hz, H-3, 1H); ^{13}C NMR, δ -0.83 ($(CH_3)_3Si$), 14.0 (CH_3, C-8), 22.4 (CH_2, C-7), 24.9 (CH_2, C-6), 28.9 (CH_2, C-5), 31.4 (CH_2, C-4), 53.1 (OCH_3), 71.8 (CH,

C-2), 76.6 (CH, C-3), 94.19 (C, C-3'), 95.17 (C, C-2'), 152.8 (C, C-1'), 172.4 (C, C-1). HREIMS *m/z* Found (M^+-15) 299.1321 Calc. for $C_{14}H_{23}O_5Si$ 299.13147

Methyl (2S,3S)-2-hydroxy-3-(butynoyloxy)octanoate (5). A solution of butynoic acid (0.192 g, 2.28 mmol) in CH_2Cl_2 (2 ml) was added to a solution of epoxy acid (**3**) (0.241 g, 1.52 mmol) in CH_2Cl_2 (5 ml) cooled to -10°C. $Ti(OPr^i)_4$ (0.48 g, 0.50 ml, 1.68 mmol) was then added and the reaction mixture was stirred for 0.5 h at -10°C, then 12 h at RT. The reaction was quenched by the addition of 5% H_2SO_4 (10 ml) and stirred for 1 h. The CH_2Cl_2 was evaporated and the aqueous phase extracted with Et_2O (2 x 30 ml) to give crude product (0.338 g). Methylation using CH_2N_2 gave material that was used in a crude state for the preparation of the iodo compound (**7**), but could be purified on silica eluting with Et_2O/hexanes 3 : 2 to give pure alcohol (**5**) (0.117 g, 30%). IR, ν_{max} (film) 3480 (OH), 2242 (C≡C), 1725, 1712 (C=O) cm^{-1}; ^1H NMR, δ 0.87 (t, *J* 8.0 Hz, H-8, 3H), 1.20-1.70 (m, H-4,5,6,7, 8H), 1.99 (s, H-4', 3H), 3.00 (s, OH, 1H), 3.82 (s, OCH_3), 4.34 (d, *J* 5.5 Hz, H-2), 5.16 (ddd, *J* 14.0, 5.5, 5.5 Hz, H-3); ^{13}C NMR, δ 4.0 (CH_3, C-4'), 14.0 (CH_3, C-8), 22.5 (CH_2, C-7), 24.9 (CH_2, C-6), 29.1 (CH, C-5), 31.5 (CH_2, C-4), 53.1 (CH_3, OCH_3), 71.8 (CH, C-2), 76.4 (CH, C-3), 77.2 (C, C-3'), 86.7 (C, C-2'), 153.5 (C, C-1'), 172.5 (C, C-1). Anal. Found C, 60.8; H, 8.1%. $C_{13}H_{20}O_5$ requires C, 60.9; H, 7.9%.

Methyl (2R,3S)-2-iodo-3-(trimethylsilylpropynoyloxy)octanoate (6). A solution of alcohol (**4**) (0.250 g, 0.796 mmol) in CH_2Cl_2 (4 ml) at -50°C was treated with triethylamine (0.088 g, 0.875 mmol, 0.121 ml) followed by trifluoromethanesulphonic anhydride (0.247 g, 0.875 mmol, 0.147 ml). The reaction was stirred at -50°C for 0.75 h before a solution of NaI (0.179 g, 1.194 mmol) in MeCN (4 ml) was added. Stirring was continued at -40°C for 3 h then 4 h at RT. The product was diluted with CH_2Cl_2 (20 ml), washed with $Na_2S_2O_3$, dried ($MgSO_4$) and the solvents evaporated. The crude product was separated on silica eluting with 30% Et_2O/hexanes to give (**6**) (0.270 g, 80%). IR, ν_{max} (film) 2170 (C≡C), 1738, 1725 (C=O) cm^{-1}; ^1H NMR, δ 0.25 (s, $(CH_3)_3Si$, 9H); 0.89 (br.s, H-8, 3H), 1.20-1.70 (m, H-4,5,6,7, 8H); 3.76 (s, OCH_3, 3H), 4.48 (d, *J* 7.5 Hz, H-2, 1H), 5.17 (dt, *J* 7.5, 6.0 Hz, H-3, 1H); ^{13}C NMR, δ -0.8 (CH_3, $(CH_3)_3Si$), 14.0 (CH_3, C-8), 22.4 (CH_2, C-7), 22.8 (CH, C-2), 24.9 (CH_2, C-6), 31.3 (CH_2, C-5), 32.8 (CH_2, C-4), 53.3 (CH_3, OCH_3), 74.7 (CH, C-3), 94.1 (C, C-3'), 95.6 (C, C-2'), 152.1 (C, C-1'), 169.5 (C, C-1). HREIMS *m/z* Found (M^+) 424.0569. Calc. for $C_{15}H_{25}O_4SiI$ 424.05686.

Methyl (2R,3S)-2-iodo-3-(butynoyloxy)octanoate (7). A solution of alcohol (**5**) (0.137 g, 0.535 mmol) in CH_2Cl_2 (6 ml) at -65°C was treated with trifluoromethanesulphonic anhydride (0.166 g, 0.589 mmol, 0.98 ml) and triethylamine (0.059 g, 0.589 mmol, 0.82 ml) and the solution stirred at -65°C for 2 h. A solution of NaI (0.160 g, 1.07 mmol) in acetonitrile (6 ml) was added and the solution was stirred at -40°C for 1 h, then at RT for 2 h. The solution was diluted with CH_2Cl_2 (20 ml), washed with $Na_2S_2O_3$, dried ($MgSO_4$) and the solvents evaporated to give crude product (0.197 g). Purification on silica eluting with Et_2O/hexanes 1 : 3 gave (**7**) (0.161 g, 82%). IR, ν_{max} (film) 2241 (C≡C), 1740, 1710 (C=O) cm^{-1}; ^1H NMR, δ 0.89 (t, *J* 9.0 Hz, H-8, 3H), 1.20-1.80 (m, H-4,5,6,7, 8H), 2.03 (s, H-4', 3H), 3.77 (s, OCH_3), 4.49 (d, *J* 7.5 Hz, H-2), 5.15 (dt, *J* 7.5, 5.5 Hz, H-3); ^{13}C NMR, δ 4.1 (CH_3, C-4'), 14.0 (CH_3, C-8), 22.4 (CH_2, C-7), 23.1 (CH_2, C-6), 24.9 (CH, C-2), 31.3 (CH_2, C-5), 32.9 (CH_2, C-4), 53.3 (CH_3, OCH_3), 74.2 (CH, C-3), 77.3 (C, C-3'), 87.1 (C, C-2'), 152.7 (C, C-1'), 169.5 (C, C-1). HREIMS *m/z* Found (M^+) 366.0328. Calc. for $C_{13}H_{19}O_4I$ 366.03298.

2-Hydroxy-3-(trimethylsilylpropynoyloxy)octan-1-ol (8). To a solution of epoxy alcohol (**2**) (0.400 g, 2.78 mmol) in THF (20 ml) was added $Ti(OPr^i)_4$ (0.947 g, 0.991 ml, 3.34 mmol) followed by trimethylsilylpropynoic acid (0.434 g, 3.06 mmol). The reaction was stirred for 1.5 h Ether (60 ml) and 5% H_2SO_4 (25 ml) were added and the mixture was stirred for 1 h. The solvents were evaporated and the aqueous phase extracted with Et_2O. The crude product (1.025 g) was chromatographed on silica eluting with Et_2O/hexanes 3 : 2 to give (**8**) (0.300 g, 38%). IR, ν_{max} (film) 3410 (OH), 2235 (C≡C), 1713 (C=O), 1228 (ester) cm^{-1}; ^1H NMR, δ 0.25 (s, $(CH_3)_3Si$, 9H), 0.89 (t, *J* 7.0 Hz, H-8, 3H), 1.20-1.40 (m, H-5,6,7, 6H), 1.65-1.78 (m, H-4, 2H), 2.62 (s, OH, 2H), 3.54-3.74 (m, H-1,2, 3H), 4.94 (ddd, *J* 7.5, 7.5, 6.0 Hz, 1H); ^{13}C NMR, δ -0.8 (CH_3, $(CH_3)_3Si$), 14.0 (CH_3, C-8), 22.5 (CH_2, C-7), 25.0 (CH_2, C-6), 30.2 (CH_2, C-5), 31.6 (CH_2, C-4), 62.6 (CH_2, C-1), 72.7 (CH, C-2), 76.4 (CH, C-3), 94.2 (C, C-3'), 95.4 (C, C-2'), 153.4 (C, C-1'). Anal. Found C,58.4; H,9.1%. $C_{14}H_{26}O_4Si$ requires C,58.7; H,9.2%.

1-(tert-Butyldimethylsilyloxy)-3-(trimethylsilylpropynoyloxy)octan-2-ol (9). To a solution of diol (**8**) (0.220 g, 0.77 mmol) in CH_2Cl_2 (6 ml) at 25°C was added triethylamine (0.070 g, 0.85 mmol, 0.97 ml) and *tert*-butyldimethylsilyl chloride (0.115 g, 0.85 mmol), and the solution was stirred at 25°C for 18 h. The reaction mixture was diluted with CH_2Cl_2 (20 ml) and washed with H_2O (2 x 20 ml). The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified on silica (ice cold EtOAc/hexanes 1 : 4) to give (**9**) (0.191 g, 62%). IR, ν_{max} (film) 2150 (C≡C), 1715 (C=O), 1227 (ester) cm^{-1}; ^1H NMR, δ 0.08 (s, $(CH_3)_3C(C\mathbf{H}_3)_2Si$-, 6H), 0.25 (s, $(CH_3)_3Si$, 9H), 0.90 (br.s, $(C\mathbf{H}_3)_3C(CH_3)_3Si$-, H-8, 12H), 1.20-1.40 (m, H-5,6,7, 6H), 1.72 (m, $W_{h/2}$ 12 Hz, H-4, 2H), 3.50-3.70 (m, H-1,2, 3H), 5.02 (ddd, *J* 6.0, 6.0, 5.5 Hz, H-3, 1H); ^{13}C NMR, δ -5.4 ($(CH_3)_3C(\mathbf{C}H_3)_2Si$, 2 x C), -0.8 ($(CH_3)_3Si$, 3 x C), 14.1 ($CH_3$,C-8), 22.5 ($CH_2$, C-7), 24.8 ($CH_2$, C-6), 25.9 ($CH_3$, $(\mathbf{C}H_3)_3C$, 3 x C), 30.1 (CH_2, C-5), 31.6 (CH_2, C-4), 63.3 (CH_2, C-1), 72.2 (CH, C-2), 76.1 (CH, C-3), 94.4 (C, C-3'), 94.5 (C, C-2'), 152.8 (C, C-1'); Anal. Found C,60.0; H,10.1% $C_{20}H_{40}O_4Si_2$ requires C,60.4; H,10.1%.

(2S,3S)-3-Pentyloxiranemethanol (10)[12]. Prepared as for the (*2R,3R*)-isomer (**2**) but using 4.67 g (*E*)-2-octen-1-ol and L-(+)-diethyl tartrate to give (**10**) (5.20 g, 99%), second recrystallisation (4.75 g, 90%).

(2R,3S)-3-Pentyloxiranecarboxylic acid (11). H_5IO_6 (23.75 g, 104.18 mmol) and $RuCl_3$ (0.075 g, 0.39 mmol, 0.9%) were added to a solution of epoxy alcohol (**10**) (6.00 g, 41.67 mmol) in CCl_4/MeCN/H_2O (42/42/63 ml) and the suspension was stirred at RT for 3 h. The organic solvents were evaporated, the aqueous residue extracted with Et_2O (3 x 100 ml), dried ($MgSO_4$) and evaporated to give product (**11**) of sufficient purity to continue (6.44 g, 95%). Further purification of (**11**) from ruthenium residues could be achieved by chromatography on C-18 silica eluting with H_2O/MeOH 2 : 1).

Methyl (2R,3S)-3-Propyloxiranecarboxylate (12). A solution of CH_2N_2 in Et_2O (0.139M, 30 mmol, 215 ml) was added to a solution of acid (**11**) (4.50 g, 28.48 mmol) in Et_2O (30 ml). The solution was stirred at RT for 5 min before the solvents were evaporated *in vacuo*. The product was filtered through silica using Et_2O/hexanes 1 : 1 as eluent to give (**12**) (4.80 g, 98%).

Methyl (2S,3R)-2-hydroxy-3-iodooctanoate (13). A solution of MgI_2 [made from I_2 (3.68 g, 14.48 mmol) and magnesium (0.5 g, 20.58 mmol)] in Et_2O (50 ml) was added to a solution of epoxide (**12**) (0.50 g, 2.91 mmol)

in Et_2O (100 ml), and the solution was stirred at RT for 5 min. The reaction mixture was poured into HCl (5%, 50 ml), separated, the organic phase was washed with $Na_2S_2O_3$ (5%, 50 ml), H_2O (20 ml), then dried ($MgSO_4$) and the solvents were evaporated to give (**13**) (0.822 g, 94%) as a colourless oil. IR, ν_{max} (film) 3475 (OH), 1740 (C=O), 1220 (ester) cm^{-1}; ^1H NMR 0.90 (t, *J* 13.0 Hz, H-8, 3H), 1.21-1.60 (m, H-7,6,5,4, 7H), 1.92 (m, $W_{h/2}$ 24 Hz, H-4, 1H), 3.23 (d, *J* 6.0 Hz, OH, 1H), 3.82 (s, OCH_3, 3H), 4.24 (br.d, *J* 3.0 Hz, H-2, 1H), 4.29 (q, *J* 3.5, 3.5, 3.5 Hz, H-3, 1H); ^{13}C NMR 14.0 (CH_3, C-8), 22.4 (CH_2, C-7), 29.4 (CH_2, C-6), 30.8 (CH_2, C-5), 35.1 (CH_2, C-4), 37.3 (CH, C-3), 53.0 (CH_3, OCH_3), 75.5 (CH, C-2), 171.8 (C, C-1). Anal. Found C, 36.1, H, 5.6%. $C_9H_{17}O_3I$ requires C, 36.0, H, 5.7%.

Methyl (2S,3S)-2-iodo-3-hydroxyoctanoate (***14***). A mixture of epoxide (**12**) (1.850 g, 10.75 mmol) and NaI (1.694 g, 11.29 mmol) in acetonitrile (40 ml) was stirred until the NaI dissolved. The solution was then cooled to -20°C and trimethylsilyl chloride (1.220 g, 11.29 mmol) was added dropwise over 10 min. The solution was stirred for 1 h at -20°C, then warmed to RT. H_2O (50 ml) was added and the majority of the acetonitrile evaporated. The product was extracted with Et_2O (3 x 50 ml), separated, and the solvents dried ($MgSO_4$) and evaporated to give crude product (3.00 g), containing 78% *methyl (2S,3S)-2-iodo-3-hydroxyoctanoate* (**14**), 6% *methyl (2S,3R)-2-hydroxy-3-iodooctanoate* (**13**), 7% methyl (*E*)-oct-2-enoate (**15**) and 9% unreacted epoxide (**12**) by ^1H NMR. Purification by recrystallisation from pentane at -10°C gave (**14**) as a pale yellow crystalline solid (2.322 g, 72%). MP (from pentane) 54-55°C; IR, ν_{max} (KBr) 3468 (OH), 1731 (C=O) cm^{-1}; ^1H NMR, δ 0.90 (t, *J* 13.0 Hz, H-8, 3H), 1.20-1.65 (m, H-4_A,5,6,7, 7H), 1.82-1.97 (m, H-4_B, 1H), 2.86 (d, *J* 6.5 Hz, OH, 1H), 3.78 (s, OCH_3, 3H), 3.95 (m, $W_{h/2}$ 7.0 Hz, H-3, 1H), 4.31 (d, *J* 7.5 Hz, H-2, 1H); ^{13}C NMR, δ 14.0 (CH_3, C-8), 22.5 (CH_2, C-7), 24.6 (CH, C-2), 25.1 (CH_2, C-6), 31.5 (CH_2, C-5), 34.2 (CH_2, C-4), 52.9 (CH_3, OCH_3), 73.1 (CH, C-3), 171.8 (C, C-1). Anal. Found C, 36.2; H, 6.0% $C_9H_{17}O_3I$ requires C, 36.0, H, 5.7%.

Methyl (2S,3S)-2-iodo-3-acetoxyoctanoate (***16***). To a solution of alcohol (**14**) (0.020 g, 0.067 mmol) in CH_2Cl_2 (1 ml) at 0°C was added acetyl chloride (0.006 g, 7 ml, 0.100 mmol)), DMAP (0.008 g, 0.067 mmol) and triethylamine (0.010 g, 14 ml, 0.100 mmol), and the reaction was stirred at RT for 16 h. Filtration of the product through a silica plug (CH_2Cl_2) gave (**16**) (0.020 g, 84%). ^1H NMR, δ 0.89 (t, *J* 10.0 Hz, H-8, 3H), 1.20-1.40 (m, H-5,6,7, 6H), 1.60-1.80 (m, H-4, 2H), 2.06 (s, CH_3CO, 3H), 3.74 (s, OCH_3,3H), 4.48 (d, *J* 8.0 Hz, H-2, 1H), 5.08 (ddd, *J* 8.0, 8.0, 3.0 Hz, H-3, 1H).

Methyl (2S,3S)-2-iodo-3-(trimethylsilylpropynoyloxy)octanoate (***17***). A solution of trimethylsilylpropynoic acid (0.155 g, 1.10 mmol) in CH_2Cl_2 (1 ml) was added to a solution of trifluoromethanesulphonic anhydride (0.309 g, 1.10 mmol, 0.185 ml) in CH_2Cl_2 (4 ml) at -20°C and the solution was stirred for 1h at RT before being again cooled to -20°C. Alcohol (**14**) (0.300 g, 1.0 mmol) was added and the solution was allowed to warm to RT and stirred for 10 h (monitored by GC). H_2O was added and the product separated, washed with $Na_2S_2O_3$, dried ($MgSO_4$) and the solvents evaporated to give crude product (0.339 g). Purification on silica (CH_2Cl_2) gave methyl (*E*)-oct-2-enoate (**15**) (0.030 g, 25%) and iodoester (**17**) (0.300 g, 71%). IR, ν_{max} (film) 2100 (C≡C), 1745, 1720 (C=O), 1213 (ester) cm^{-1}; ^1H NMR, δ 0.24 (s, $(CH_3)_3Si$, 9H); 0.90 (t, *J* 9.0 Hz, 3H), 1.20-1.90 (m, H-4,5,6,7, 8H), 3.75 (s, OCH_3), 4.47 (d, *J* 8.5 Hz, H-2, 1H), 5.23 (ddd, *J* 9.0, 8.5, 3.0 Hz, H-3, 1H); ^{13}C NMR, δ -0.8 (CH_3, $(CH_3)_3Si$), 14.0 (CH_3, C-8), 21.3 (CH, C-2), 22.4 (CH_2, C-7), 24.1 (CH_2, C-6),

31.4 (CH_2, C-5), 32.5 (CH_2, C-4), 53.1 (CH_3, OCH_3), 75.3 (CH, C-3), 93.7 (C, C-3'), 95.3 (C, C-2'), 151.5 (C, C-1'), 169.5 (C, C-1). Anal. Found C, 42.8; H, 6.3% $C_{15}H_{25}O_4SiI$ requires C,42.5; H, 5.9%.

*Methyl (4E,2S-trans)-tetrahydro-4-[iodo(trimethylsilyl)methylene]-5-oxo-2-pentyl-3-furancarboxylic acid (**18**).* (i) A solution of iodo ester (**17**) (0.054 g, 0.127 mmol), $(Bu_3Sn)_2$ (0.007 g, 0.006 ml, 0.012 mmol) and AIBN (2 mg) in benzene (0.5 ml) was heated with a heat lamp (250 W) for 3 h. The solvent was evaporated, and the product was re-dissolved in Et_2O (3 ml). A solution of iodine in Et_2O was added until the iodine colour persisted. The solution was washed with a saturated aqueous solution of KF (2 x 10 ml), dried ($MgSO_4$) and evaporated to give crude product (0.055 g). Purification on silica eluting with EtOAc/hexanes 1 : 4 gave pure (**18**) (0.047 g, 85%). $[\alpha]_D$ = +41.1° (c=1.20, $CHCl_3$); IR, ν_{max} (film) 1753 (C=O), 1212 (ester) cm^{-1}; ^1H NMR, δ 0.37 (s, $(CH_3)_3Si$, 9H); 0.90 (br.t, H-5", 3H); 1.10-1.80 (m, H-1",2",3",4", 8H); 3.63 (d, *J* 3.0 Hz, H-4, 1H); 3.77 (s, OCH_3), 4.56 (ddd, *J* 6.5, 6.5, 3.0 Hz, H-5, 1H); ^{13}C NMR, δ -1.3 (CH_3, $(CH_3)_3Si$), 14.0 (CH_3, C-5"), 22.5 (CH_2, C-4"), 24.2 (CH_2, C-3"), 31.3 (CH_2, C-2"), 36.4 (CH_2, C-1"), 53.0 (CH_3, OCH_3), 61.3 (CH, C-3), 78.6 (CH, C-2), 136.7 (C, C-4'), 143.6 (C, C-4), 163.2 (C, C-5), 169.6 (C, C-3'); Anal. Found C, 42.9; H,6.2%. $C_{15}H_{25}O_4SiI$ requires C,42.5; H,5.9%.

(ii) A solution of iodo ester (**17**) (0.757 g, 1.78 mmol), $(Me_3Sn)_2$ (0.058 g, 0.89 mmol) and AIBN (2 mg) in benzene (6.0 ml) was heated with a sunlamp for 36 h with periodic addition of $(Me_3Sn)_2$ (3 x 0.020 g) . The solvent was evaporated, and the product was re-dissolved in Et_2O (20 ml). A solution of iodine in Et_2O was added until the iodine colour persisted. The solution was washed with a saturated aqueous solution of KF (2 x 30 ml), dried ($MgSO_4$) and evaporated to give multiple products. Purification on silica eluting with EtOAc/hexanes 1 : 3 gave pure (**18**) (0.378 g, 50%), identical to the product obtained above.

(iii) A solution of iodoester (**17**) (0.650 g, 1.54 mmol) and dibenzoyl peroxide (0.018 g, 0.07 mmol) in benzene (15 ml) was heated under reflux for 2 h. An additional portion of dibenzoyl peroxide (0.018 g, 0.07 mmol) was added followed by heating for a further 3 h. The solvent was evaporated and the crude product purified by radial chromatography on silica, eluting with Et_2O/hexanes 1 : 9 to give (**18**) (0.533 g, 82%), identical to the product obtained above.

*Methyl (4E,2S-trans)-tetrahydro-4-(iodomethylene)-5-oxo-2-pentyl-3-furancarboxylic acid (**19**).*

(i) A mixture of TMS-lactone (**18**) (0.100 g, 0.236 mmol), KF (0.055 g, 0.95 mmol) and 18-crown-6 (5 mg) in THF (2 ml) was stirred at RT for 24 h. Evaporation, followed by chromatography on silica using Et_2O/hexanes 1 : 1 as eluent gave (**19**) (0.074 g, 89%). $[\alpha]_D$ = +75.8° (c=1.00, $CHCl_3$); IR, ν_{max} (film) 1760 (C=O), 1266, 1173 (ester) cm^{-1}; ^1H NMR, δ 0.90 (br.s, H-5", 3H), 1.10-1.80 (m, H-1", 2", 3", 4", 8H), 3.48 (dd, *J* 3.5, 2.5 Hz, H-3, 1H), 3.79 (s, OCH_3), 4.66 (ddd, *J* 6.5, 6.5, 3.5 Hz, H-2, 1H); 8.09 (d, *J* 2.5 Hz, H-4', 1H); ^{13}C NMR, δ 13.9 (CH_3, C-5"), 22.4 (CH_2, C-4"), 24.2 (CH_2, C-3"), 31.3 (CH_2, C-2"), 36.6 (CH_2, C-1"), 53.0 (CH_3, OCH_3), 54.1 (CH, C-3), 79.5 (CH, C-2), 98.2 (CH, C-4'), 137.9 (C, C-4), 164.7 (C, C-5), 168.8 (C, C-3'); HREIMS (M^+) *m/z* 352.01744. Calc for $C_{12}H_{17}IO_4$ 352.01716.

(ii) A mixture of TMS-lactone (**18**) (0.560 g, 1.32 mmol), KF (0.153 g, 2.6 mmol) and 18-crown-6 (25 mg) in THF (35 ml) and dry acetone (0.5 ml) was stirred at 10°C for 2 h. Evaporation, followed by chromatography on silica using Et_2O/hexanes 1 : 1 as eluent gave (**19**) (0.475 g, 85%), identical to the product obtained above.

*Methyl (2S-trans)-tetrahydro-4-methylene-5-oxo-2-pentyl-3-furancarboxylic acid (**20**).* A solution of iodo lactone (**19**) (0.074 g, 0.21 mmol) in THF (2 ml) in a quartz tube was irradiated for 45 min at 254 nm.

Evaporation of the solvent and filtration through silica (Et_2O) gave (**20**) (0.040 g, 85%). $[\alpha]_D$ = -5.3° (c=0.956,$CHCl_3$); IR, ν_{max} (film) 1770, 1742 (C=O), 1263 (ester) cm^{-1}; ^1H NMR, δ 0.90 (t, *J* 7.0 Hz, H-5", 3H), 1.20-1.55 (m, H-2", 3", 4", 6H), 1.70 (m, $W_{h/2}$ 13.0 Hz, 2H), 3.60 (ddd, *J* 7.0, 3.0, 3.0 Hz, H-3, 1H), 3.80 (s, OCH_3, 3H), 4.82 (ddd, *J* 7.0, 6.0, 6.0 Hz, H-2, 1H), 5.94 (d, *J* 2.5 Hz, H-4'$_A$, 1H), 6.42 (d, *J* 2.5 Hz, H-4'$_B$); ^{13}C NMR, δ 14.0 (CH_3, C-5"), 22.5 (CH_2, C-4"), 24.5 (CH_2, C-3"), 31.4 (CH_2, C-2"), 35.7 (CH_2, C-1"), 49.8 (CH, C-3), 53.0 (CH_3, OCH_3), 79.1 (CH, C-2), 125.3 (CH_2, C-4'), 133.1 (C, C-4), 168.4 (C, C-5), 169.8 (C, C-3'). Analysis C, 63.2; H,8.3% $C_{12}H_{18}O_4$ requires C, 63.7; H, 8.0%. HREIMS (M^+) *m/z* Found 226.12024. Calc. for $C_{12}H_{18}O_4$ 226.12051

*(2S-trans)-Tetrahydro-4-methylene-5-oxo-2-pentyl-3-furancarboxylic acid (**1**).* A solution of methyl ester (**20**) (0.038 g, 0.17 mmol) in butanone (2 ml) containing HCl (6M, 6 drops) was heated under reflux for 2 h. H_2O (5 ml) was added and the organic solvent was removed. The aqueous residue was extracted with CH_2Cl_2 (3 x 10 ml) and the solvents were evaporated. The crude product was dissolved in toluene (20 ml) and extracted with 5% $NaHCO_3$ (3 x 20 ml). The basic extract was then acidified to pH 2 with HCl, extracted with CH_2Cl_2 (3 x 10 ml), dried ($MgSO_4$) and the solvents evaporated to give (**1**) (0.032 g, 90%). The product was recrystallised from EtOAc/hexanes to give a white crystalline solid; mp 82-83°C; $[\alpha]_D$ = -12.4° (c=0.5, CH_3OH); (Lit[7] mp 82.5-83.5, $[\alpha]_D$ = -2.37° (c=3.0, CH_3OH)[7], -6.7° c=0.5, CH_3OH)[8]). ^1H and ^{13}C NMR identical to published data[7].

*Methyl (2S,3S)-2-iodo-3-(butynoyloxy)octanoate (**21**).* A solution of butynoic acid (0.103 g, 1.23 mmol) in CH_2Cl_2 (1 ml) was added to a solution of trifluoromethanesulphonic anhydride (0.345 g, 1.23 mmol, 0.206 ml) in CH_2Cl_2 (8 ml) at -20°C and the solution was stirred for 1 h at RT before being again cooled to -20°C. Alcohol (**14**) (0.300 g, 1.0 mmol) was added the solution was allowed to warm to RT and stirred for 10 h (monitored by GC). H_2O was added and the product separated, washed with $Na_2S_2O_3$, dried ($MgSO_4$) and the solvents evaporated. Purification on silica (20% EtOAc/hexanes) gave iodoester (**21**) (0.274 g, 75%). IR, ν_{max} (film) 2240 (C≡C), 1740, 1730 (C=O), 1248 (ester) cm^{-1}; ^1H NMR, δ 0.88 (t, *J* 6.0 Hz, 3H), 1.30 (m, $W_{h/2}$ 18 Hz, 6H), 1.74 (m, $W_{h/2}$ 24.0 Hz, 1H), 1.98 (s, H-4", 3H), 2.00 (m, $W_{h/2}$ 9.0 Hz, 1H), 3.74 (s, OCH_3, 3H), 4.46 (d, *J* 9.0 Hz, H-2, 1H), 5.19 (ddd, *J* 8.5, 8.5, 3.0 Hz, H-3, 1H); ^{13}C NMR, δ 3.93 (CH_3, C-4"), 13.97 (CH_3, C-8), 21.58 (CH, C-2), 22.42, 24.05, 31.37, 32.54 (4 x CH_2, C-4,5,6,7), 53.09 (CH_3, OCH_3), 71.79 (C, C-3'), 74.90 (CH, C-3), 86.81 (C, C-2'), 152.19 (C, C-1'), 169.47 (C, C-1). Anal. Found C, 42.8; H, 5.3%. $C_{13}H_{19}IO_4$ requires C, 42.6; H, 5.2%.

*Methyl (4E 2S-trans)-tetrahydro-4-(iodoethylidene)-5-oxo-2-pentyl-3-furancarboxylic acid (**22**).* A solution of iodo ester (**21**) (0.200 g, 0.55 mmol) and dibenzoyl peroxide (0.013 g, 0.05 mmol) in benzene (5 ml) was heated under reflux for 60 min. Evaporation of the solvent and purification on silica eluting with Et_2O/hexanes 1 : 4 gave pure (**22**) (0.150 g, 75%). $[\alpha]_D$ = +32.7° (c=1.00, $CHCl_3$); IR, ν_{max} (film) 1754 (C=O), 1638 (C=C), 1214 (ester) cm^{-1}; ^1H NMR, δ 0.88 (t, *J* 6.5 Hz, H-5", 3H), 1.26-1.46 (m, 6H), 1.67 (m, $W_{h/2}$ 15 Hz, 2H), 3.17 (d, *J* 1.5 Hz, H-5', 3H), 3.53 (dq, *J* 3.0, 1.5 Hz, H-3, 1H), 3.76 (s, OCH_3, 3H), 4,50 (ddd, *J* 7.0, 6.0, 2.5 Hz, H-2, 1H); ^{13}C NMR, δ 13.94 (CH_3, C-5"), 22.42 (CH_2), 24.18 (CH_2), 30.87 (CH_3, C-5'), 31.24 (CH_2), 36.48 (CH_2), 52.85 (OCH_3), 58.85 (CH, C-3), 78.02 (CH, C-2), 123.3 (C, C-4'), 130.59 (C, C-4), 162.98 (C, C-5),

169.93 (C, C-3'); Anal. Found C 42.9, H 5.6%. $C_{13}H_{19}IO_4$ requires C, 42.6, H, 5.2%; HREIMS *m/z* (M^+) Found 366.03275. Calc. for $C_{13}H_{19}IO_4$ 366.03281.

*Methyl (4E,2S-trans) and (4Z, 2S-trans)-tetrahydro-4-ethylidene-5-oxo-2-pentyl-3-furancarboxylic acids (**23**) and (**24**).* A solution of iodo lactone (**22**) (0.050 g, 0.14 mmol) in THF (2 ml) in a quartz tube was irradiated for 45 min at 254 nm in a Rayonet. Evaporation of the solvent and purification by radial chromatography, eluting with Et_2O/hexanes 1 : 1 gave the (*E*)-isomer (**23**) (0.015 g, 47%); $[\alpha]_D$ = -5.3° (c=0.90, $CHCl_3$); IR, ν_{max} (film) 1755, 1740 (C=O), 1313 (ester) cm^{-1}; ^1H NMR, δ 0.89 (t, H-5", *J* 7.0 Hz, 3H), 1.26-1.72 (m, H-1", 2", 3", 4", 8H), 2.24 (dd, *J* 7.0, 2.5 Hz, H-5', 3H), 3.51 (ddq, *J* 5.0, 2.5, 2.5 Hz, H-3, 1H), 3.78 (s, OCH_3, 3H), 4.73 (ddd, *J* 8.0, 5.0, 5.0 Hz, H-2, 1H), 6.54 (qd, *J* 7.5, 2.5 Hz, H-4', 1H); ^{13}C NMR, δ 14.0 (CH_3, C-5"), 14.3 (CH_3, C-5'), 22.5 , 24.5, 31.5, 35.8 (CH_2, C-1",2",3",4"), 51.1 (CH, C-3), 52.8 (CH_3, OCH_3), 78.7 (CH, C-2), 124.2 (C, C-4), 142.3 (CH, C-4'), 167.5 (C, C-5), 170.8 (C, C-3'); HREIMS Found 240.13626. Calc. for $C_{13}H_{20}O_4$ 240.13616; and the (*Z*)-isomer (**24**); $[\alpha]_D$ = +15.2° (c = 0.41,$CHCl_3$) IR, ν_{max} (film) 1762, 1740 (C=O), 1214 (ester) cm^{-1}; ^1H NMR, δ 0.89 (t, *J* 7.0 Hz), 1.26-1.70 (m, H-1", 2", 3", 4", 5", 8H), 1.90 (dd, *J* 7.5, 1.5 Hz, H-5', 3H), 3.58 (ddq, *J* 4.0, 2.0, 2.0 Hz, H-3, 1H), 3.75 (s, OCH_3), 3H), 4.72 (ddd, *J* 7.5, 6.0, 3.5 Hz, H-2, 1H), 6.99 (qd, *J* 7.5, 2.5 Hz, H-5', 1H); ^{13}C NMR, δ 14.0 (CH_3, C-5"), 15.7 (CH_3, C-5'), 22.5 , 24.4, 31.4, 36.2 (CH_2, C-1",2",3",4"), 48.6 (CH, C-3), 52.8 (CH_3, OCH_3), 79.6 (CH, C-2), 125.9 (C, C-4), 140.3 (CH, C-4'), 168.2 (C, C-5), 170.8 (C, C-3'); HREIMS Found 240.13593. Calc. for $C_{13}H_{20}O_4$ 240.13616.

*(4E,2S-trans)-tetrahydro-4-ethylidene-5-oxo-2-pentyl-3-furancarboxylic acid (**25**).* A solution of methyl ester (**23**) or (**24**) (0.010 g, 0.042 mmol) in butanone (1 ml) containing HCl (6M, 3 drops) was heated under reflux for 2 h. H_2O (5 ml) was added and the organic solvent was removed. The aqueous residue was extracted with CH_2Cl_2 (3 x 10 ml) and solvents were evaporated. The crude product was dissolved in toluene (20 ml) and extracted with 5% $NaHCO_3$ (3 x 20 ml) The basic extract was then acidified to pH 2 with HCl, extracted with CH_2Cl_2 (3 x 10 ml), dried ($MgSO_4$) and the solvents evaporated to give (**25**) (0.007 g, 75%); $[\alpha]_D$= +18° (c=0.34, $CHCl_3$); IR, ν_{max} (film) 3400 (br., COOH), 1745 (C=O), 1216 (ester) cm^{-1}; ^1H NMR, δ 0.90 (t, *J* 7.0 Hz, H-5", 3H), 1.30-1.52 (m, 6H), 1.69 (m, $W_{h/2}$ 21 Hz, 2H), 1.97 (dd, *J* 7.0, 1.5 Hz, H-5', 1H), 3.62 (m, $W_{h/2}$ 6.5 Hz, H-3, 1H), 4.78 (ddd, *J* 7.5, 6.5, 3.0 Hz, H-2, 1H), 7.06 (qd, *J* 7.0, 2.5 Hz, H-4', 1H); ^{13}C NMR, δ 14.0 (CH_3, C-5"), 16.0 (CH_3, C-5'), 22.5, 24.4, 31.4, 36.2 (4 x CH_2, C-4", 3", 2", 1"), 48.1 (CH, C-3), 79.5 (CH, C-2), 125.3 (C, C-4), 141.2 (CH, C-4'), 169.0 (C, C-5), 174.7 (C, C-3'). Methylation with CH_2N_2 gave a methyl ester identical to (**23**).

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