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The Use of π-Allyltricarbonyliron Lactone Complexes in the Synthesis of the β-Lactone Esterase Inhibitor (-)-Valilactone.

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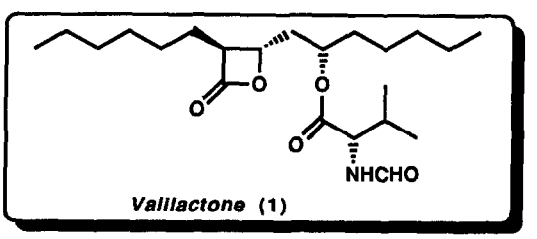
Abstract: A concise synthesis of the β-lactone esterase inhibitor valilactone (1) is reported. This synthesis employs the stereoselctive preparation of a π-allyltricarbonyliron lactone complex (7) that on oxidation with ceric ammonium nitrate, affords an appropriately substituted β-lactone (9) which was transformed to (1).

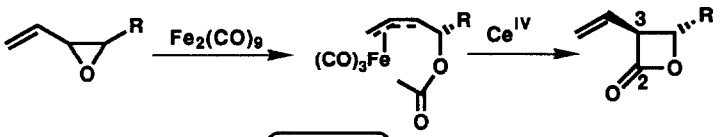
The β-lactone natural product valilactone (1) was recently isolated and characterised from a microbial MG 147-CF2 strain closely related to *Streptomyces albolongus*.[1] This compound is similar in structure to other biologically active β-lactones such as lipstatin,[2] esterastin,[3] the ebelactones A and B[4] and the antibiotic 1233A.[5,6] Upon screening for enzyme inhibitor activity against hog liver esterase and hog pancreatic lipase, (1) was found to be as potent as the ebelactones but showed no *N*-formylmethionine aminopeptidase activity and hence was similar to esterastin.



***Valilactone* (1)**

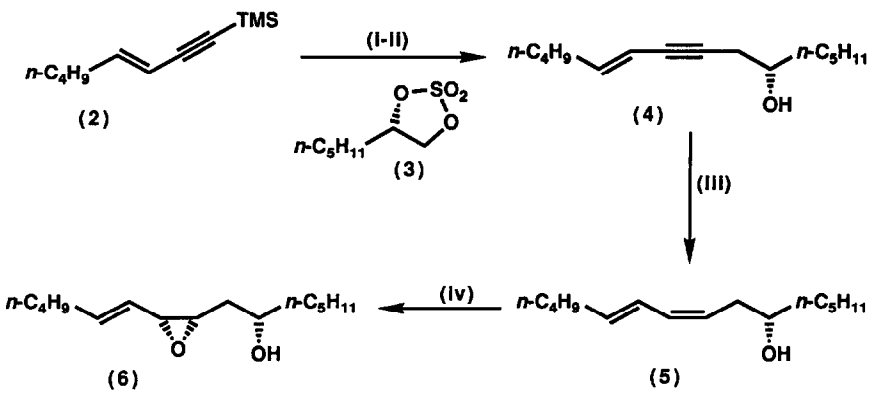
The syntheses of several β-lactones have been reported recently indicating that this is a developing area of interest.[7] The structural features in (1) make it an attractive target for synthesis using chemistry discovered in our group employing π-allyltricarbonyliron lactone complexes for the unusual construction of the 2,3-acyl to carbon

bond in β-lactones.[8,9] This methodology may be further extended to the preparation of other lactones[10] and lactams.[11] Here we report in full the synthesis of valilactone (1).[12] The key reactions of this synthesis are the conversion of alkenyl epoxides to π-allyltricarbonyliron complexes and the selective oxidation of these to give β-lactones with stereochemical control (scheme 1).



Scheme 1

For the synthesis of valilactone (1), we therefore required an efficient preparation of the hydroxyl substituted alkenyl epoxide (6), in an enantiomerically pure form, as the precursor for complex formation. In order to construct the necessary unsaturated carbon chain we envisaged initial coupling of the anion derived from the trimethylsilylacetylene (2) with the cyclic sulphate (3). Compound (2) was readily available in 85% yield by palladium catalysed cross-coupling of (*E*)-1-iodo-1-hexene[13] with trimethylsilylacetylene. The cyclic sulphate (3) was derived from the corresponding diol by sequential treatment with thionyl chloride followed by oxidation with ruthenium trichloride and sodium periodate.[14] In order to get this material in its correct configuration, we considered its preparation *via* asymmetric dihydroxylation of hept-1-ene.[15] However, as this method gave less than satisfactory optical yields (ee=91%[16]), we chose instead to proceed from enatiomerically pure precursors. Thus, coupling of the aldehyde derived from lead tetraacetate cleavage of 1,2:5,6-*di*-O-isopropilydene-D-mannitol, with butylidenetriphenylphosphorane, followed by hydrogenation, gave the required, optically pure, (*S*)-heptane-1,2-diol.[17] Treatment of the silylacetylene (2) with methyllithium gave the corresponding anion, which was then reacted with the cyclic sulphate (3) at 0°C in THF, gave the alcohol (4) in 63% yield (scheme 2).

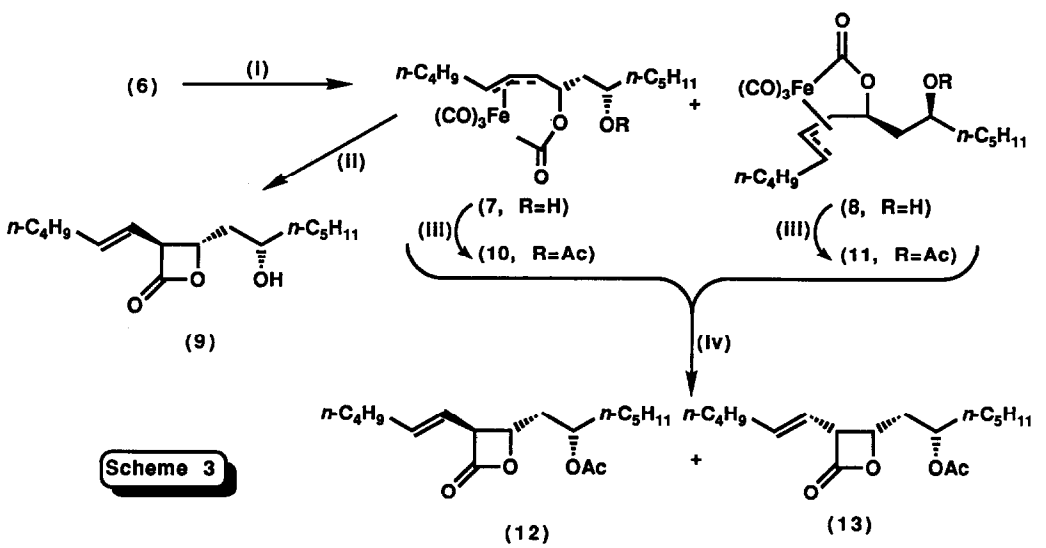


Scheme 2

Reagents: (I) MeLi, THF, 3h.; (3), 0°C to RT.; (II) 20% H_2SO_4, 63% overall; (III) Zn(Cu/Ag), MeOH-H_2O, 50°C. 90%; (Iv) $VO(acac)_2$, ^tBuOOH, CH_2Cl_2, 0°C to RT, 73%.

As stereoselective reduction of (4) to the *E,Z*-diene (6) using the Lindlar catalyst failed, we resorted to the use of Zn(Cu/Ag)[18] in methanol-water at 45-50°C. This method afforded (5) in excellent yield and with high stereoselectivity, ^{1}H nmr of the corresponding Mosher's ester showed only one isomer. Control of the *E,Z* geometry in (5) was necessary for later stereoselective complex formation. We next studied the hydroxyl directed formation of (6). As anticipated,[19] this reaction proceeded with a high stereoselectivity (>30:1)[20] to afford the required epoxide (6) using *t*-butylhydroperoxide and $VO(acac)_2$ at 0°C in CH_2Cl_2. Following the previously established procedure,[21] we found it unnecessary to protect the hydroxyl group in (6) prior to complexation. Hence, reaction of (6) with diiron nonacarbonyl in THF gave an 80% yield of the separable *exo* and *endo* complexes (7) and (8) in a ratio of 4:1 (scheme 3). Oxidation of (7) with ceric ammonium nitrate[11,12] in buffered ethanol, gave the required β-lactone (9) in a disappointing 26% yield. Attempts to improve this yield using other solvents, MeOH or MeCN, with or without added amine bases, Et_3N or pyridine) or by using alternative oxidants such as silver oxide, Me_3NO, $FeCl_3$, cupric triflate, ceric triflate or ceric ammonium nitrate on silica gel were unsuccessful.

We believe the free hydroxyl group in (7) to be the source of the problem in these reactions. Many attempts to protect the alcohol prior to complexation were unsuccessful owing to the propensity of (6) to decompose *via* intramolecular ring opening of the epoxide. We therefore investigated the protection of the complex. Many methods such as benzylation or silylation surprisingly failed and led to decomposition. However, acetylation with acetic anhydride proceeded extremely well, and the acetates (10) and (11) derived from the mixture of *exo* and *endo* complexes (7) and (8) underwent oxidation with ceric ammonium nitrate on silica gel to give a 50% yield of the corresponding β-lactones (12) and (13) (scheme 3).

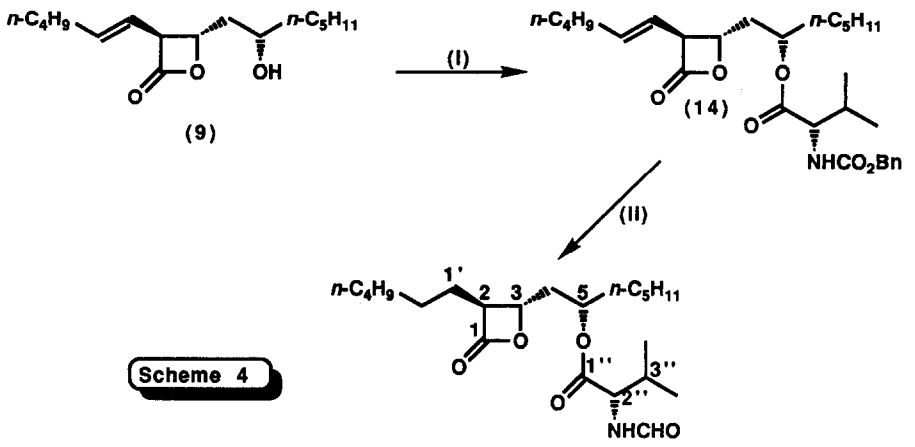


Reagents: (I) $Fe_2(CO)_9$, THF, 80%; (II) CAN, EtOH, RT, 26%; (II) Ac_2O, py, 95%; (IV) CAN/SiO_2, MeCN, 50%.

Nevertheless, in spite of these results we have been able to progress from the β-lactone (9) to the natural

product valilactone (1). To this end (9) was first coupled with carbobenzyloxy-L-valine (*N*-Cbz-L-valine) using dicyclohexyl carbodiimide in the presence of 4-*N*,*N*-dimethylaminopyridine in DMF to give (14).[4d]

For the final steps, (14) was treated with hydrogen and a palladium on carbon catalyst which had the effect of simultaneously reducing the unsaturated side chain and deprotecting the nitrogen substituent. The crude product was immediately formylated with acetic formic anhydride to give (1), identical in all respects to an authentic sample of valilactone,[22] in 62% overall yield (scheme 4).



Scheme 4

***Valilactone* (1)**

Reagents: (I) *N*-Cbz-L-valine, DCC, CH_2Cl_2, 0°C then DMF, DMAP, RT, 56%; (II) H_2/Pd/C, THF, then AcOCHO, CH_2Cl_2, 62%

The above synthesis constitutes a novel approach to these biologically active β-lactones and further exemplifies the use of π-allyltricarbonyliron lactone complexes in the synthesis of natural products.

Acknowledgemenents: *We thank the SERC and British Biotechnology, Oxford, for financial support ana we thank NATO and the Spanish Ministerio de Educación y Ciencia for a Fellowship (R.F.M.).*

Experimental:

^1H nmr spectra were recorded in $CDCl_3$ using a Bruker WM 250, Jeol GSX 270 or Bruker AM-500 nmr spectrometer. Infra-red spectra were recorded on a Perkin-Elmer 983G spectrometer. Mass spectra were recorded under EI conditions unless otherwise stated, using VG-7070B (Imperial College), VG 12-253 and VG ZAB-E instruments (SERC mass spectrometry service, Swansea); microanalyses were performed in the

Imperial College Chemistry Department microanalytical laboratory. Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured using an Optical activity AA-1000 polarimeter. Column chromatography were performed on Merck Kieselgel 60 (230-400 mesh) unless otherwise stated. Florisil refers to 200-300 U.S. mesh Florisil as supplied by BDH Ltd. Diethyl ether and tetrahydrofuran were distilled from sodium-benzophenone ketyl; dichloromethane from phosphorous pentoxide; toluene from sodium; and acetonitrile from calcium hydride. Petrol refers to petroleum ether (b.p. 40-60°C) which was distilled prior to use. Other solvents and reagents were purified by standard procedures as necessary. Analytical thin layer chromatography was performed using pre-coated aluminium sheets (Merck Kieselgel 60 F_{254}), and visualised by ultra-violet light, acidic ammonium molybdate (IV) or iodine as appropriate. Numbering for ^1H nmr assignments follows the systematic (IUPAC) nomenclature except for compounds (1), (9), (12) and (13), when the commonly used natural product numbering system is adopted.

(E)-1-(Trimethysilyl)-3-octen-1-yne **(2).** Anhydrous copper (I) iodide (0.7 g, 3.6 mmol) and tetrakis(triphenylphosphine)palladium (0) (1 g, 0.86 mmol) were added from a solid addition tube to a solution of *(E)*-1-iodo-1-hexene[13] (5.48 g, 26 mmol), trimethylsilyl acetylene (3.8 ml, 26 mmol), *n*-butylamine (4 ml, 40 mmol) in dry benzene (150 ml) under argon with exclusion of light. After stirring overnight, the mixture was poured into water and extracted with ether. The combined organic extracts were dried ($MgSO_4$). The solvent was evaporated and the residue was distilled in a Kugelrohr apparatus (100°C, 0.15 mm Hg) to give the *silylacetylene* (2) (4.0 g, 85%), as a colourless oil, ν_{max} (film) 2958, 2927, 2858 and 2137 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.23 (1H, dt, J 15.9 and 7 Hz, H-4); 5.50 (1H, dt, J 15.9 and 1.6 Hz, H-3); 2.10 (2H, m, allylic CH_2); 1.40-1.20 (4H, m, $CH_3CH_2CH_2$); 0.90 (3H, t, J 7 Hz, CH_2CH_3) and 0.18 (9H, s, $SiMe_3$); m/z 180 (M^+), 165, 73; Found: C, 73.16; H, 11.03. $C_{11}H_{20}Si$ requires: C, 73.33; H 11.11%.

4-Pentyl-1,3,2-dioxathiolane-2,2-dioxide **(3).** Lead tetraacetate (2.77 g, 6.26 mmol) was added portion wise from a solid addition tube to a suspension of 1,2:5,6-*di*-O-isopropylidene-D-mannitol (1.64 g, 6.26 mmol) in benzene (50 ml), dried over sodium. After stirring for twenty minutes, the white precipitate was removed by filtration through celite and was washed with ether. The filtrate was carefully concentrated, filtered again through celite and carefully concentrated. The residue was distilled (Kugelrohr, 80°C, water pump) to give the *(R)*-(+)-Glyceraldehyde, which was taken up in dry THF (3 ml) and added to a solution of butylidenetriphenylphosphorane [generated by adding *n*-butyllithium (5 ml of a 2.5M solution in hexane, 12.5 mmol) to a suspension of butyltriphenylphosphonium bromide (5 g, 12.5 mmol) in THF (40 ml) at 0°C under argon]. The mixture was stirred at room temperature for 6 h., then treated with a few drops of aqueous ammonium chloride and diluted with petrol (bp 30-40°C). The heterogeneous mixture was filtered through celite; the filtrate was evaporated and taken up in petrol (bp 30-40°C), filtered again through celite, concentrated and distilled (Kugelrohr, 100°C, water pump) to give a clear oil. This oil was taken up in methanol (5 ml) and added to a suspension of platinum oxide (20 mg, 0.09 mmol) in methanol (5 ml) under hydrogen (1 atm). The mixture was stirred overnight, flushed with argon and filtered through celite. Aqueous

hydrochloric acid (2 ml of a 3M solution) was added to the filtrate. The mixture was stirred for 3 h., poured into sodium bicarbonate solution, treated with brine and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and evaporated to give (*S*)-heptane-1,2-diol[17] (342mg, 21%) as an oil, $[\alpha]_D^{20}$= -16 (c 1.6, EtOH); ν_{max}(film) 3371, 2950, 2870 and 1070 cm^{-1}; δ_H ($CDCl_3$, 270 MHz) 3.7 (1H, m, H-2); 3.65 (1H, dd, J 11 and 3 Hz, H-1); 3.42 (1H, dd, J 11 and 7.5 Hz, H-1); 2.25 (2H, br s, OH); 1.5-1.2 (8H, m, 4 CH_2); 0.9 (3H, t, J 7 Hz, Me); m/z 132 (M^+); 131; 114; 101. Thionyl chloride (4.1 ml, 57 mmol) was added to a solution of the diol (5 g, 37 mmol) in dry carbon tetrachloride (40 ml). The solution was heated at reflux for 30 min. The mixture was cooled to 0°C, then treated cautiously and sequentially, with aqueous acetonitrile (40 ml in 60 ml of water), ruthenium trichloride trihydrate (50 mg, 0.19 mmol) and sodium periodate (17 g, 80 mmol). The black mixture was stirred gradually turning green, then yellow, when tlc indicated complete conversion of the sulphite to the sulphate. The mixture was poured into water and extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Evaporation of the solvent and distillation of the residue gave the *cyclic sulphate* (3) (6.2 g, 87%) as a colourless oil, bp 130 °C, 10 mm Hg, $[\alpha]_D^{20}$= -18.6 (neat); ν_{max} (film) 2933, 2866, 1465, 1390, 1210 and 849 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.79 (1H, t, J 8.5 Hz, H-2); 4.71 (1H, dd, J 8.5 and 6 Hz, H-1); 4.34 (1H, t, J 8.5 Hz, H-1); 1.95 (1H, m, H-3); 1.75 (1H, m, H-3); 1.6-1.3 (6H, m, 3 CH_2) and 0.9 (3H, t, J 7 Hz, Me); m/z 165 (M^+-C_2H_5), 137, 123, 96; Found: C, 43.60; H, 7.37. $C_7H_{14}O_4S$ requires: C, 43.28; H, 7.26%.

(6S,10E)-Pentadecen-8-yne-6-ol **(4).** Methyllithium (2.3 ml of a 1.4 M solution in ether, 3.22 mmol) was added to a solution of (2) (600 mg, 3.22 mmol) in THF (18 ml). The solution was stirred for 3.5 hours at room temperature, before the addition of the cyclic sulphate (3) (426 mg, 2.15 mmol in 9 ml of THF) at 0°C. The mixture was stirred at room temperature until tlc showed no remaining cyclic sulphate, then aqueous sulphuric acid was added (20%, 50 ml) and the mixture stirred overnight. The mixture was extracted with ether. The ethereal phases were washed with water, dried ($MgSO_4$) and evaporated to give a crude mixture, which after purification by flash chromatography afforded the *eneyne alcohol* (4) (300 mg, 63%) as a colourless oil, $[\alpha]_D^{20}$= 9.7 (c 0.7, $CHCl_3$); ν_{max}(film) 3376, 3019, 2955, 2927 and 956 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 6.09 (1H, dt, J 16.0 and 7.0 Hz, H-11); 5.40 (1H, dm, J 16.0 Hz, H-10); 3.70 (1H, m, H-6); 2.5 (1H, ddd, J 16.6, 4.7 and 2.0 Hz, H_A-7); 2.40 (1H, ddd, J 16.6, 6.8 and 2.0 Hz, H_B-7); 2.08 (2H, m, H-12); 1.90 (1H, d, J 4.9 Hz, OH); 1.66-1.20 (12 H, m, CH_2) and 0.85 (6H, m, Me-1 and Me-15); m/z 222 (M^+), 165, 122; observed: M^+, 222.1990. $C_{15}H_{26}O$ requires M^+, 222.1983; Found C, 80.82; H, 12.01, $C_{15}H_{26}O$ requires C, 81.08; H, 11.71%.

(6S,8Z,10E)-8,10 Pentadecadien-6-ol **(5).** Activated Zn(Cu/Ag)[18] was added to a solution of (4) (172 mg, 0.77 mmol) in MeOH (0.6 ml) and stirred at 45-50°C for 39 hr, until complete conversion of the alkyne (monitored by GC). The mixture was filtered, the solvent removed and the residue chromatographed on silica gel (20% ether-petrol) to yield *compound* (5) (156 mg, 90.4%) as a colourless oil $[\alpha]_D^{20}$= -2.2 (c 3.18,

$CHCl_3$); ν_{max}(film) 3353, 3019, 2926 and 1647 cm^{-1}; m/z 224 (M^+), 195, 185, 167, 153, 124; δ_H (270 MHz, $CDCl_3$) 6.30 (1H, dd, J 15.0 and 11.0 Hz, H-10); 6.10 (1H, t, J 11.0 Hz, H-9); 5.70 (1H, dt, J 15.0 and 7.0 Hz, H-11); 5.35 (1H, dt, J 11.0 and 8.0 Hz, H-8); 3.65 (1H, m, H-6); 2.35 (2H, m, H-7); 2.10 (2H, m, H-12); 1.65 (1H, OH); 1.50-1.20 (10H, m, 5 CH_2) and 0.98 (6H, m, Me-1 and Me-15); observed: M^+, 224.2140. $C_{15}H_{28}O$ requires M^+, 224.2139; Found: C, 80.40; H, 12.70. $C_{15}H_{28}O$ requires: C, 80.35; H, 12.50%.

[αS,2S,3R(E)]-3-Hex-1-enyl-α-pentyl-2-oxirane ethanol **(6)**. To a solution of vanadyl acetyl acetonate (2.6 mg, 0.01 mmol) in dry dichloromethane and 3M *tert*-butyl hydroperoxide (0.25 ml, 0.75 mmol) at 0°C was added (5) (110 mg, 0.5 mmol) in dry dichloromethane (0.1 M solution). The reaction was monitored by tlc. After 5 h the organic phase was washed with aqueous sodium bisulfite, dried ($MgSO_4$) and the solvent removed to give (5) (11 mg 10%) and (6) (86 mg, 73%), as a colourless oil, $[\alpha]_D^{20}$= -13.3 (c 3.0, $CHCl_3$); ν_{max}(film) 3418, 2927, 2857, 1663 and 967 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 5.90 (1H, dt, J 15.6 and 6.8 Hz, H-11); 5.3 (1H, ddt, J 15.6, 7.8 and 7.8 Hz, H-10); 3.88 (1H, m, H-6); 3.38 (1H, dd, J 7.8 and 4.4 Hz, H-9); 3.25 (1H, dt, J 7.8 and 4.6 Hz, H-8); 2.10-2.04 (3H, m, including OH and CH_2); 1.5-1.2 (12 H, m, 6 CH_2) and 0.88 (6 H, m, Me-1 and Me-15); m/z 240 (M^+), 222, 197, 187; observed: M^+, 240.2083. $C_{15}H_{28}O_2$ requires M^+, 240.2083.

(6S,8S,8-exo,11-exo)-6-hydroxy-9-11-η³-(8-Formyloxyhexadeca-9-en-9-ylato) tricarbonyliron **(7)**. Epoxide (6) (115 mg, 0.47 mmol) in THF (5 ml, 0.1M in epoxide) was added to $Fe_2(CO)_9$ (272 mg, 0.75 mmol) under argon. The reaction was monitored by tlc, and after two h was complete. The solvent was removed and the crude mixture was chromatographed on silica gel (50% petrol/ether) to give the *ferrilactones* (7) and (8) (153 mg, 80%) in a 4:1 ratio; compound (7) ν_{max}(film) 3423, 2956, 2930, 2856, 2076, 2010, 1662, 1513, 1460, 1377, 1325, 1188, 1130, 1033, 996, 885, 826, 729, 656, and 612 cm^{-1}; δ_H (270 MHz, $CDCl_3$): 4.74 (1H, dd, J 12.1 and 7.7 Hz, H-10), 4.45 (1H, d, J 7.7 Hz, H-9), 4.25 (1H, t, J 6.8 Hz, H-8), 3.98 (1H, m, H-11), 3.80 (1H, m, H-6), 2.25 (1H, m), 2.00 (1H, bs, OH), 1.75 (3H, m, including CH_2-7), 1.62 (2H, m), 1.54-1.25 (10H, m, 5 CH_2), 0.95 (3H, t, J 7.2 Hz, Me) and 0.88 (3H, t, J 6.8 Hz, Me); m/z 380 (M^+-CO), 352, 324, 296, 280, 168, 151, 140, 84, 28; observed M^+-3CO, 324.1387. $C_{16}H_{28}FeO_3$ requires M^+-3CO, 324.1387; Found: C, 56.01; H, 7.09. $C_{19}H_{28}FeO_3$ requires C, 55.90; H, 6.86%.

[3S(E),4S(S)]-3-Hex-1-enyl-4-(2-hydroxyheptyl)-2-oxetanone **(9)**. To a solution of (7) (350 mg, 0.77 mmol) in ethanol (16 ml), $(NH_4)_2Ce(NO_3)_6$ (2.96 g, 5.4 mmol) and buffer solution (pH=7, 6 drops) was added, and stirred for two hours, then the reaction was diluted with ether, washed with buffer solution (pH=7), dried ($MgSO_4$). The solvent was removed and the crude product was chromatographed on silica gel, first with 20% ether/petrol, then 50% ether/petrol to give (9) (46 mg 26%, based on recovered starting material, 112 mg); $[\alpha]_D^{20}$= -55.7 (c 0.37 ,$CHCl_3$), ν_{max} (film) 3453, 2928, 1821 and 1636 cm^{-1}; δ_H (270 MHz, $CDCl_3$, valilactone numbering): 5.80 (1H, dt, J 15.4 and 6.6 Hz, H-2'), 5.51 (1H, ddm, J 15.4

and 7.6 Hz, H-1'), 4.55 (1H, dt, J 6.6 and 4.4 Hz, H-3), 3.94 (1H, dd, J 7.6 and 4.4 Hz, H-2), 3.80 (1H, m, H-5), 2.10-1.96 (4H, m, 2 CH_2), 1.63-1.20 (13H, m,) and 0.91-0.87 (6H, m, 2 Me); m/z 268 (M^+), 250 (M^+-H_2O), 153, 124, 95, 83, 68, 55, 43, 29; observed M^+, 268.2033. $C_{16}H_{28}O_3$ requires MH^+, 268.2038.

***(6S,8S,8-exo,11-exo)-6-Acetoxy-9-11-η^3-(8-formyloxyhexadeca-9-en-9-ylato) tricarbonyliron* (10).** Pyridine (100 μl) was added to a mixture of ferrilactones (7) and (8) (46 mg, 0.11 mmol) and then acetic anhydride (20 μl) at room temperature and the mixture was left overnight. The reaction was quenched by addition of ice/water, extracted with ether and, the ether extracts washed with 1N HCl (aq), $NaHCO_3$ (aq) and water, dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash chromatography on silica gel gave the acetates (10) and (11) (49 mg, 98%). Compound (10): ν_{max} (film): 2955, 2930, 2859, 2006, 1732, 1663, 1459, 1372, 1242, 1127, 1024, 984, 653 and 611 cm^{-1}; δ_H (270 MHz, $CDCl_3$): 5.06 (1H, m, H-6); 4.71 (1H, dd, J 12.2 and 7.8 Hz, H-10); 4.45 (1H, d, J 7.8 Hz, H-9); 4.06 (1H, t, J 7 Hz, H8); 3.97 (1H, m, H-11); 2.23 (1H, m, H-7); 2.05 (3H, s, $COCH_3$); 1.90-1.61 (3H, m); 1.59-1.24 (12H, m); 0.93 (3H, m, Me) and 0.87 (3H, m, Me); m/z: 394 (M^+-2 CO), 251, 238, 222, 206, 149, 43, 28; observed (M^+-3 CO-CO_2) 322.1601. $C_{17}H_{30}FeO_2$ requires (M^+-3 CO-CO_2), 322.1595.

***[3S(E),4S(S)]-3-Hex-1-enyl-4-(2-acetoxyheptyl)-2-oxetanone* (12)** and ***[3R(E),4S(S)]-3-Hex-1-enyl-4-(2-acetoxyheptyl)-2-oxetanone* (13)**. To the mixture of exo/endo ferrilactones (10) and (11) (in a ratio 2:1) (20 mg, 0.044 mmole) in acetonitrile (3ml) was added Cerium (IV)/SiO_2 reagent (ceric ammonium nitrate coated on silica, containing 20% of ceric ammonium nitrate)[23], and the mixture stirred at room temperature until no starting material was observed by tlc (48 h). The reaction was diluted with ether and filtered through celite and evaporated *in vacuo*. The crude mixture was chromatographed on silica gel eluting with ether-petrol 10% to give the *trans*-β-lactone (12), 3.7 mg (42%, with respect to the exo ferrilactone) and the *cis*-β-lactone (13), 2.5 mg (58%, with respect to the endo ferrilactone).

Compound (12): ν_{max}(film): 2955, 2926, 2857, 1825, 1736, 1634, 1459, 1372, 1119, 1024, 970 and 879 cm^{-1}; δ_H (270 MHz, $CDCl_3$): 5.74 (1H, dt, J 15.4 and 6.8 Hz, H-2'); 5.48 (1H, dd, 15.4 and 7.4, H-1'); 5.02 (1H, m, H-5); 4.41 (1H, m, H-3); 3.81 (11H, dd J 7.4 and 4.3 Hz, H-2); 2.09 (1H, m); 2.04 (3H, s, $COCH_3$); 1.66-1.23 (15H, m); 0.88 (6H, m, 2 Me); m/z: 206 (M^+-C_2O_4H), 163, 149, 135, 121, 107, 933, 79, 65, 57, 51 and 43; observed MH^+ 311.2222. $C_{18}H_{31}O_4$ requires MH^+, 311.2222.

Compound (13): ν_{max}(film): 2926, 2855, 1824, 1735, 1634, 1459, 1370, 1125, 1025; δ_H (270 MHz, $CDCl_3$): 5.83 (1H, dt, J 15.4 and 6.8 Hz, H-2'); 5.42 (1H, dd, J 15.4 and 7.8, H-1'); 5.00 (1H, m, H-5); 4.66 (1H, dt, J 7.4 and 6.4, H-3); 4.34 (1H, m, H-2); 2.08 (1H, m); 2.05 (3H, s, $COCH_3$); 2.04-1.89 (2H, m); 1.64-1.20 (13H, m) and 0.89 (6H, m. 2 Me); m/z: 206 (M^+-C_2O_4H), 163, 149, 135, 121, 107, 93, 79, 65, 57, 51, 43 and 28;observed MH^+ 311.2222. $C_{18}H_{31}O_4$ requires MH^+, 311.2222.

[1S[1S[3S(E),4S]]]-Benzyl 1-[1-[(3-hex-1-enyl-1-2-oxo-4-oxetanyl),ethyl hexyl

***oxycarbonyl]-2-methylpropylcarbamate* (14).** DCC (51.5 mg, 0.25 mmol) was added to a solution of N-Cbz-L-valine (83 mg, 0.3 mmol) in dichloromethane (3 ml) at 0°C and after stirring for 15 min the white crystals were filtered off. The filtrate was added at r.t. to a mixture of the alcohol (9) (45 mg, 0.17 mmol) and DMAP (2.5 mg, 0.02 mmol) in DMF (0.68 ml). After four hours the reaction was, poured into ice-water (25 ml) and extracted with ether, dried ($MgSO_4$) and evaporated to give a crude mixture, which was chromatographed on silica gel with 10% ether/petrol to give (14) (49 mg, 56%) as white crystals; mp 58-60°C, $[\alpha]_D^{20}$= -38 (c 1.1, $CHCl_3$); ν_{max} ($CHCl_3$) 3369, 2956, 2927, 1824 and 1723 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.35 (5H, m, 5 arom H); 5.75 (1H, dt, J 15.3 and 6.8 Hz, H-2'); 5.45 (1H, dd, J 15.3 and 7.6 Hz, H-1'); 5.20 (1H, d, J 9.1 Hz, NH); 5.11 (2H, s, OCH_2Ph); 5.00 (1H, m, H-5); 4.39 (1H, m, H-3); 4.27 (1H, m, *CH*NH); 3.82 (1H, m, H-2); 2.21 (2H, m); 2.04 (3H, m); 1.58 (2H, m); 1.32 (10H, m); 0.99 (3H, d, J 6.8 Hz, Me) and 0.88 (9H, m, 3 Me); m/z 501 (M^+), 366, 251, 234, 206, 162, 149, 135, 91, 79, 71, 57; observed M^+, 501.3087. $C_{29}H_{43}NO_6$ requires M^+, 501.3090.

***[1S[1S[3S(E),1,S]]]-N-[1-[1-[(3-Hexyl-2-oxo-4-oxetanyl)methyl]hexyloxycarbonyl]-2-methylpropyl] formamide, valilactone* (1).** The β-lactone (14) (32 mg, 0.061 mmol) in THF (3 ml), was hydrogenated in the presence of 10% Pd/C (5 mg). After 28 hours the catalyst was filtered off, the solvent removed and the crude product was treated dropwise with formic acetic anhydride (10 μl). The mixture was diluted with ether, washed with $NaHCO_3$, then with water, dried ($MgSO_4$), filtered and the solvent was removed to yield *valilactone* (1) (15.5 mg, 62%); mp 55-56°C, $[\alpha]_D^{23}$= -32 (c 0.3, $CHCl_3$),($[\alpha]_D^{23}$= -33.6 (c 0.7, $CHCl_3$) for the natural product as supplied)); ν_{max}($CHCl_3$) 3324, 1820, 1735, 1684 and 1515 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.27 (1H, s, CHO), 6.02 (1H, d, J 8.6 Hz, NH), 5.03 (1H, m, H-5), 4.63 (1H, ddd, J 8.8, 4.7 and 0.6 Hz, H-2"), 4.29 (1H, m, H-3), 3.22 (1H, dt, J 8.0 and 4.1 Hz, H-2), 2.2 (2H, m, CH_2), 2.02 (1H, m), 1.8-1.5 (4H, m, 2 CH_2), 1.3 (14H, m, 7 CH_2), 0.99 (3H, d, J 6.9 Hz, C3"-Me), 0.92 (3H, d, J 6.9 Hz, C3"-Me) and 0.85 (6H, m, 2 Me); m/z 397 (M^+), 355, 253, 200, 128, 100; observed M^+, 397.2830. $C_{22}H_{39}NO_5$ M^+, 397.2828; Found: C, 66.21; H, 9.92; N, 3.33. $C_{22}H_{39}NO_5$ requires C, 66.47; H, 9.89; N, 3.52%.

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