Tetrahedron Letters, Vol.32, No.23, pp 2651-2654, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF THE β-LACTONE ESTERASE INHIBITOR VALILACTONE USING π-ALLYLTRICARBONYLIRON LACTONE COMPLEXES.

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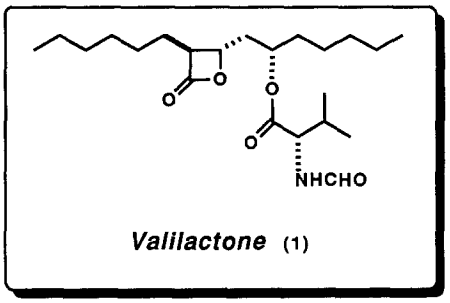
***Summary**: Synthesis of the esterase inhibitor valilactone (1) is reported employing the oxidation of π-allyltricarbonyliron lactone complexes with ceric ammonium nitrate to afford the inherent β-lactone ring.*

Currently there is considerable interest in biologically active β-lactone natural products. Synthesis of the HMG-CoA synthase inhibitor L-659,699[1] (formally ICI 1233A[2]), tetrahydrolipstatin[3-7] a pancreatic lipase inhibitor being developed as a lipid lowering agent, and studies on the immune response enhancing esterase inhibitor ebelactone A,[8,9] have been reported recently. Here we describe the first synthesis of valilactone (1), a β-lactone natural product isolated from *Streptomyces albolongus* and shown to be a potent esterase inhibitor.[10]



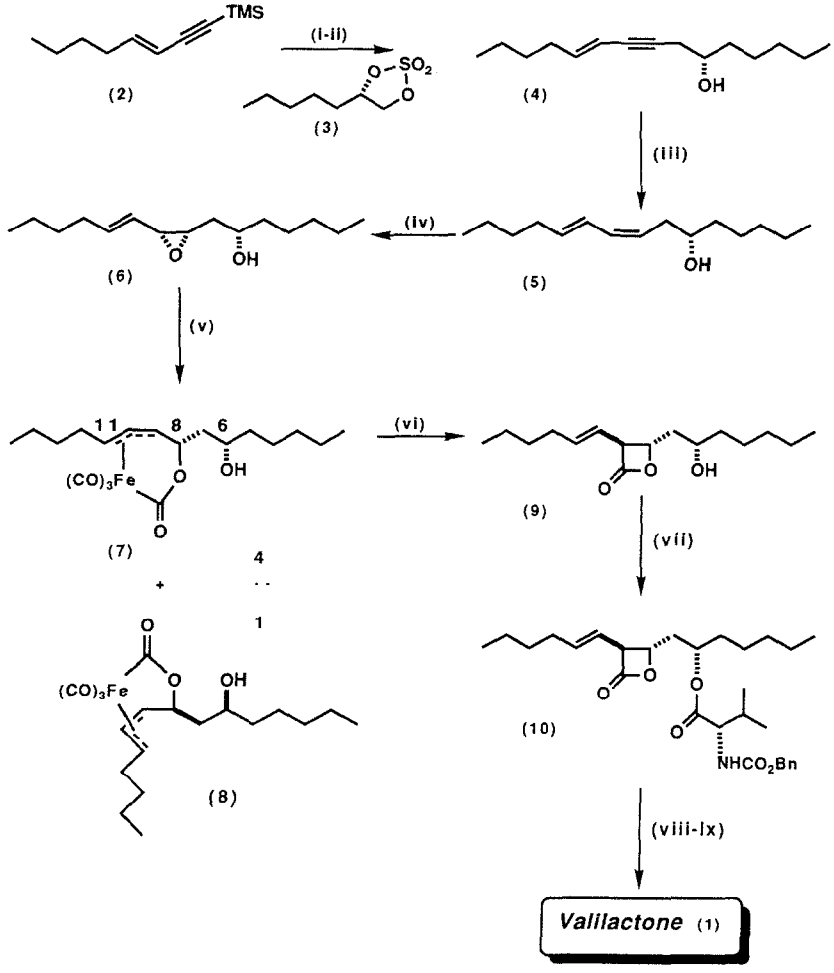
Valilactone (1)

The key step in this synthesis is the use of π-allyltricarbonyliron lactone complexes which on oxidation afford β-lactones.[11,12] These iron complexes are also useful for the preparation of β-lactams *via* intermediate π-allyltricarbonyliron lactam complexes.[13,14]

The synthesis proceeds by reaction of the acetylide anion, generated from (2) by treatment with methyllithium, with the cyclic sulphate (3) to give the alcohol (4) on work-up with dilute sulphuric acid. The silylacetylene (2)[15] was prepared by the coupling of *trans*-1-iodohexene[16] with trimethylsilylacetylene in the presence of copper (I) iodide, tetrakis(triphenylphosphine) palladium (0) and n-butylamine. The cyclic sulphate (3)[17] was easily prepared from the known diol[18] by the literature procedure , using thionyl chloride in carbon

tetrachloride to form the sulphite, followed by oxidation with ruthenium trichloride trihydrate and sodium periodate in acetonitrile to give (3).

The coupled product (4)[19] was reduced stereoselectively to the *E,Z*-dienol (5) in excellent yield by reaction with Cu/Ag/Zn[20] in methanol and water at 45-50°C. The alcohol (5) then underwent highly stereoselective homoallylic hydroxyl group directed epoxidation[21] with $VO(acac)_2$ and *t*-butylhydroperoxide in dichloromethane to give (6).



Reagents: (i) MeLi, THF, 3h., then (3) at 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%; (v) $Fe_2(CO)_9$, THF. 80%; (vi) CAN, EtOH, RT. 26%; (vii) *N*-Cbz-L-valine, DCC, CH_2Cl_2, 0°C then DMF, DMAP, RT. 56%; (viii-ix) H_2/Pd/C, THF, then AcOCHO, CH_2Cl_2. 62%.

Following our previously established protocol (6) was reacted with diironnonacarbonyl in THF[22] to afford the separable iron complexes (7)[23] and (8) in a 4:1 ratio. On oxidation, with ceric ammonium nitrate in ethanol, the π-allyltricarbonyliron lactone complex (7) gave the required *trans*-β-lactone (9).[24] Attempts to improve the yield in this last step have so far proved unsuccessful even using various protecting systems for the hydroxyl group or using alternative oxidants and conditions. For the final steps of the synthesis the lactone (9) was coupled with carbobenzyloxy-L-valine (*N*-Cbz-L-valine), using dicyclohexylcarbodiimide (DCC), in the presence of 4-*N,N*-dimethylaminopyridine (DMAP), and dimethylformamide to give (10).[4]

Treatment of (10) with hydrogen and a palladium on carbon catalyst simultaneously removed the side chain double bond and effected deprotection of the nitrogen substituent, and the crude product on formylation with acetic formic anhydride gave the natural product valilactone (1) in 62% yield. (1) was identical in all respects (^{1}H nmr, IR, mp, mass spec. and $[\alpha]_D$) to an authentic sample of valilactone.[25]

The above synthesis describes a novel approach to these important biologically active molecules and illustrates further the application of π-allyltricarbonyliron lactone complexes in the preparation of natural products.[26,27]

Acknowledgements: *We thank the SERC and British Biotechnology, Oxford for financial support and we thank NATO for a Fellowship (R.F.M).*

References and Footnotes

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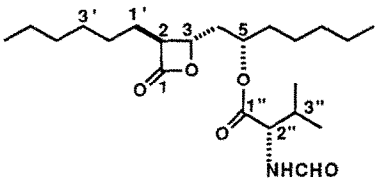
23. Data for compound (7): ν_{max}(film) 3423, 2956, 2930, 2856, 2076, 2010, 1662, 1513, 1460, 1377, 1325, 1188, 1130, 1033, 996, 885, 826, 729, 656, and 612 cm^{-1}; δ_H (270 MHz, $CDCl_3$): 4.74 (1H, dd, J 12.1 and 7.7 Hz, H-10), 4.45 (1H, d, J 7.7 Hz, H-9), 4.25 (1H, t, J 6.8 Hz, H-8), 3.98 (1H, m, 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), 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, calc. for $C_{16}FeH_{28}O_3$, 324.1387.
24. Data for compound (9), $[\alpha]_D^{20}$=-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, calc. for $C_{16}H_{28}O_3$, 268.2038.
25. We thank Dr. Kitahara, Kanegafuchi Chemicals Co., Osaka, Japan, for providing a small sample of the natural product for comparison purposes.
Data for compound (1), 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 above); 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 8.9, 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, calc. for $C_{22}H_{39}O_5N$, 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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(Received in UK 14 March 1991)