Tetrahedron Letters,Vol.27,No.11,pp 1305-1308,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

TOTAL SYNTHESIS OF (±)-ALLAMCIN. AN APPROACH TC ANTILEUKAEMIC IRIDOID LACTONES.

Kevin E.B. Parkes and Gerald Pattenden*

Department of Chemistry, The University, Nottingham, NG7 2RD.

Summary: A total synthesis of (±)-allamcin(1), which also constitutes formal syntheses of plumericin(2) and allamandin(3) found in Allamanda neriifolia, is described.

Allamcin(1) is a recently isolated member of the iridoid family of biologically active lactones found in Allamanda sp.[1] The lactone co-occurs with the structurally related plumericin(2) and allamandin(3), and also with the biogenetically significant metabolites plumieride(4) and gardenoside(5).[2] Plumericin(2) exhibits both antifungal and antibacterial activity, whereas allamandin(3) shows substantial in vivo activity against P-388 leukaemia in mouse and in vitro activity against cells derived from human carcinoma of the nasopharynx(KB).

The structure of allamcin(1), together with those of (2) and (3), features an interesting cyclic hemi-acetal ring portion, which also makes up part of a cyclic acetal, one 'ether' residue of which constitutes the β-oxygen of a spiro-fused E-α-ethylidene-β-oxy-γ-butyrolactone ring system. These structural features, densely packed together in a molecule accommodating six chiral centres combine to make allamcin(1), and related iridoids, a challenging target for synthesis.[3] In this Letter, we describe a total synthesis of (±)-allamcin which uses a strategy based on: (i) spiro-annulation of the β-oxy-γ-butyrolactone ring system on to the bicyclo[3.3.0] octenone(6) via the key acetoxy-aldehyde intermediate(9), (ii) specific oxidation of the more nucleophilic double bond in (12)(to 13), and (iii) in situ oxidative-cleavage and cyclisation from the 1,2-diol acetate(14b).

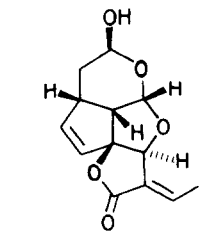
The bicyclo[3.3.0]octenone(6) is easily available, on large scale, starting from cycloocta-1,3-diene.[4] Conversion of (6) to the corresponding 2,4,6-triisopropylbenzenesulphonylhydrazone, followed by treatment with n-butyllithium(TMEDA -80°C, then 0°C) and quenching the resulting vinyl anion with dimethylformamide (at -80°C), fist led to the dienal(7; 90%).[5] The

dienal(7) was next converted into the corresponding enol acetate(8, 66%) by heating with isopropenyl acetate in the presence of p-toluenesulphonic acid. Treatment of (8) with peracetic acid in dichloromethane in the presence of sodium carbonate at -80°C, followed by chromatography then produced the acetoxy-aldehyde(9) whose structure and configuration followed conclusively from spectral data: δ_H 2.18(COMe), 2.23-2.36(m, HCH), 2.57-2.72(m, HCH), 3.52(m, CH), 4.01(m, CH), 5.35(m, CH_2CH:), 5.55(dd, J5.6 and 2.1, CCH:CH), 5.77(m, CHCH:), 6.06(dd, J5.5 and 2.2, CCH:), 9.5(CHO), δ_C20.5(q), 37.9(t), 47.7(d), 53.8(d), 96.4, 124.9(d), 128.0(d), 131.5(d), 143.1(d), 170.7, 195.7 p.p.m., nOe experiments and comparison with the C-2-epimer of (9), and the analogue(10).[6]

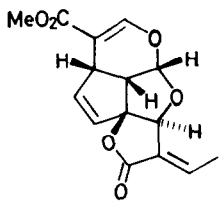
When a solution of (9) in tetrahydrofuran was added to a solution of the bis-anion(11) derived from 2-phenylthiobutanoic acid(LDA, 0°C) in tetrahydrofuran at -80°C, warming to 0°C and work-up produced four diastereoisomers of the spiro-lactone(12).[7,8] Treatment of this mixture with osmium tetraoxide (1 equiv., pH7, aq. phosphate buffer, THF, 72h) then led to a mixture of diastereoisomeric diols, from which the isomer (13, 24%) could be separated by chromatography; a mixture of isomeric diols(~20%) was also separated by chromatography.

The synthesis of allamcin(1) from (13) was achieved by several methods. Thus, saponification of (13)(K_2CO_3, MeOH, 25°C, 16h) followed by oxidation and elimination from the resulting sulphoxide, first produced the triol(14a) containing less than 10% of the corresponding Z-isomer. Oxidative cleavage of the 1,2-diol unit in (14a), with concomitant cyclisation ($NaIO_4$, then NaOAc) then produced (±)-allamcin m.p. 188-195°C decomp.(ether) which was identical (mixed t.l.c., p.m.r. and m.s.) with an authentic sample. Elimination of phenylsulphenic acid from (13), followed by treatment of the resulting acetate(14b) with $NaIO_4$-NaOAc also led to (±)-allamcin. Alternatively, methanolysis of (14b)(MeOH-K_2CO_3 25°C, 16h) led to the transposed methyl ether (15; 19%), which on treatment with periodic acid could be converted into (±)-allamcin. Since allamcin(1) has previously been converted into plumericin(2) and allamandin(3)[3], the present synthesis of (1) also constitutes formal syntheses of (±)-(2) and (±)-(3).

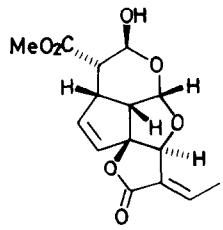
We thank Professor T. Yamanchi for a sample of natural(+)-allamcin, and one of us (K.E.B.P.) thanks the SERC for a Fellowship.



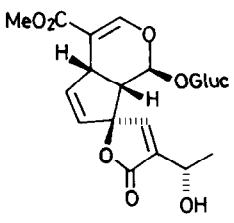
(1)



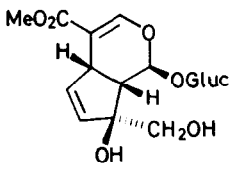
(2)



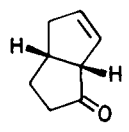
(3)



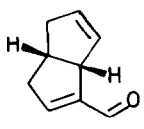
(4)



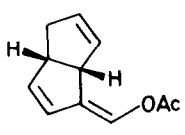
(5)



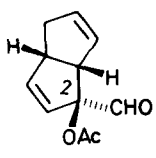
(6)



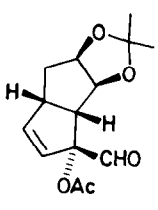
(7)



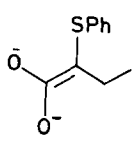
(8)



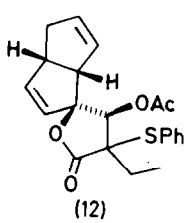
(9)



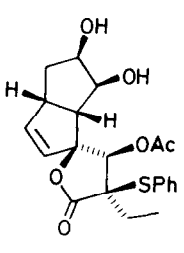
(10)



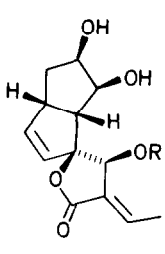
(11)



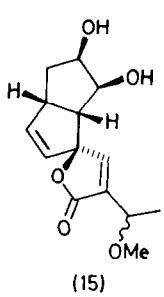
(12)



(13)



(14)



(15)

a, R = H
b, R = COMe

(1)

REFERENCES

1. F. Abe, T. Mori and T. Yamanchi, Chem.Pharm.Bull., 1984, 32, 2947.
2. H. Schmid, H. Bickel and T.M. Meijer, Helv.Chim.Acta, 1952, 35, 415; 1958, 41, 1109; s.m. Kupchan, A.L. Dessertine, B.T. Blaylock and R.F. Bryan, J.Org.Chem., 1974, 39, 2477.
3. For previous syntheses see: B.M. Trost, J.M. Balkovec and M. K-T. Mao, J.Am.Chem.Soc., 1983, 105, 6755 (plumericin); B.M. Trost and J.M. Balkovec, Tetrahedron Lett., 1985, 26, 1807 (allamandin).
4. J.K. Crandall and L-H. Chang, J.Org.Chem., 1967, 32, 532.
5. Satisfactory spectroscopic data together with microanalytical and/or mass spectroscopic data were obtained for all new compounds.
6. The C-2 epimer of (9) which was produced concurrently (ca 20%) showed: δ_H2.12(COMe), 2.23-2.36(m, HCH), 2.57-2.72(m, HCH), 3.63(m, 2xCH), 5.52(m, CH_2CH:), 5.74(m, CHCH:), 5.85(dd, J5.6 and 1.8, CCH:CH), 6.20 (brd, J5.6, CCH:). 9.57(CHO); δ_C20.8(q), 36.2(t), 47.2(d), 58.7(d), 96.0, 126.2(d), 127.1(d), 131.5(d), 145.7(d), 170.5, 197.3.
   Use of meta-chloroperbenzoic acid instead of peracetic acid in the oxidation of (8) led to largely the C-2-epimer of (9) (ratio 2:1).
   Furthermore, the C-2-epimer of (9) was produced almost exclusively (ratio 6:1) when (8) was treated with molybdenum pentoxide HMPA complex. These results indicate that the rearrangement of the presumed epoxy-acetate intermediate produced in the oxidations of (8) occurs with inversion at C-2.
   The p.m.r. spectrum of (10) showed δ1.23(Me), 1.42(Me), 1.50-2.24(m, CH_2), 2.04(COMe), 2.97(dd, J8 and 1, CHCHO), 3.33-3.60(m, :CHCH), 4.45-4.75(m, 2xCHO), 5.83(dd, J6 and 2, HC:CHCH), 6.19(dd, J6 and 3, HC:CHCH), 9.50(CHO) p.p.m.
7. For a related spiro-annulation methodology, using the carbanion from methyl 2-phenylthiopropanoate see: P. Barbier and C. Benezra, J.Org.Chem., 1983, 48, 2705.
8. We thank Anthony G. Smith for some preliminary studies on this approach to α-ethylidene-β-oxy-γ-butyrolactones.

(Received in UK 27 January 1986)