TOTAL SYNTHESIS OF (+)-ALLIACOLIDE

Mark Ladlow and Gerald Pattenden*

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

<u>Summary</u>: A total synthesis of the unique epoxy-lactone alliacolide (3), featuring a novel, stereoselective intramolecular radical cyclisation onto an enolic double-bond, \underline{viz} (13) \rightarrow (14), as a key step, is described.

The alliacolides, e.g. alliacol A (1), alliacol B (2) and alliacolide (3), are a unique family of epoxy-lactones produced by the Basidiomycete <u>Marasmius</u> <u>alliaceus</u>.¹ The two unsaturated lactones (1) and (2), which have both been produced chemically from the saturated member (3), shows weak antibiotic properties in addition to displaying high cytotoxic activity. In this <u>Letter</u> we describe the first total synthesis of alliacolide (3)², which features a unique, stereoselective intramolecular radical cyclisation onto an enolic double bond, <u>viz</u> (13) + (14), to elaborate the tricycle.

Hydroboration followed by oxidation of the tetrahydropyranyl ether derived from 3-methyl-3-butenol first led to the carbinol (4), which was smoothly converted into the corresponding bromide (5) (CH_3SO_2CI , Et_3N , CH_2Cl_2 , $0-25^{\circ}C$; then LiBr-NaHCO₃, DMF-Me₂CO, reflux 20 h).³ Reaction between 3,3-dimethyl-4-penten-1-al⁴ and the Grignard reagent derived from (5) (THF, -10°C to 25°C) then produced the secondary alcohol (6; 87%) as a mixture of diastereoisomers. After oxidation of (6) to the unsaturated ketone (7) (PCC-alumina, C_6H_6 , 20°C, 18 h, 93%), cleavage of the double bond (OSO_4 -NaIO₄, Et_2O-H_2O , 36 h) led to the corresponding keto-aldehyde (8, 77%). When a solution of (8) in diethyl ether-tetrahydrofuran containing aqueous potassium hydroxide was heated under reflux for 36 h, work-up gave a high yield of the central cyclopentenone intermediate (9; 87%).⁵

Reaction between (9) and the anion derived from ethyl propynoate,⁶ followed by treatment of the resulting substituted propynoate, <u>in situ</u>, with methanolic sodium methoxide, led in one step (25% overall) to the methyl tetronate (10). Specific vinylic deprotonation of (10) (LDA, THF, -78°C, 1 h) followed by quenching with methyl iodide (-78°C to 25°C), then gave the correspondence C-methyl tetronate (11) in high yield (94%).⁷ Elaboration of

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(11) <u>via</u> the corresponding carbinol (H-15, MeOH, 42°C, 6 h) and mesylate $(CH_3SO_2Cl, Et_3N, \text{then NaI}, Me_2CO, reflux 0.5 h) finally gave [78% overall from (11)] the key iodo-lactone intermediate (12) as a mixture of diastereo-isomers which could be separated into <math>\alpha$ - and β - methyl epimers by straight-forward chromatography.⁸

Demethylation of (12) using trimethylsilyl iodide (25°C, 30 h) produced the polar tetronic acid (13; 76%) which, on treatment with tributytin hydride (0.02 M in C_6H_6 , AIBN, 85°C, 20 h) was smoothly converted in a stereoselective manner to deoxyalliacolide (14; 45%).^{9,10} The synthesis of (<u>+</u>)-alliacolide (3) was then completed by stereoselective epoxidation of (14) using <u>meta</u>chloroperbenzoic acid in the presence of sodium hypophosphate (0-5°C; 24 h). The synthetic alliacolide showed identical spectroscopic data to those of naturally derived material,¹¹ and the two samples did not separate from each other in mixed chromatography.

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REFERENCES

- I.W. Farrell, T.G. Halsall, V. Thaller, A.P.W. Bradshaw and J.R. Hanson, <u>J.Chem.Soc.</u>, <u>Perkin Trans.1</u>, 1981, 1790; A.P.W. Bradshaw, J.R. Hanson, D.S. Kirk and P.M. Scopes, <u>ibid</u>., 1981, 1794: A.P.W. Bradshaw, J.R. Hanson and I.H. Sadler, <u>ibid</u>., 1982, 2787; T. Anke, W.H. Watson, B.M. Giannetti and W. Steglich, <u>J.Antibiotics</u>, 1981, <u>34</u>, 1271.
- For a synthesis of (<u>+</u>)-8,9-deoxyalliacol B see: R.A. Raphael and S.J. Telfer, <u>Tetrahedron_Letters</u>, 1985, <u>26</u>, 489.
- 3. All new compounds showed satisfactory i.r., p.m.r. and c.m.r. data in addition to microanalytical or mass spectroscopic data. Yields refer to isolated, chromatographically homogeneous materials.
- 4. <u>cf</u>. R.K. Boeckman, Jnr. and S.S. Ko, <u>J.Am.Chem.Soc</u>., 1982, 104, 1033.
- 5. δ6.95 (d, <u>J</u>1, 1H), 4.48 (dd, <u>J</u>∿3.4, 1H), 3.64-3.72 (m, 2H), 3.24-3.33 (m,2H), 2.50 (m,1H), 2.2 (d, <u>J</u>1, 2H), 1.37-1.97 (m,8H), 1.13 (6H), 1.04 and 1.03 (d, <u>J</u>7, Me, diastereoisomers).
- 6. cf. K. Yamada, N. Miyaura, M. Itoh and A. Suzuki, Synthesis, 1977, 679,
- 7. N.G. Clemo and G. Pattenden, Tetrahedron Letters, 1982, 23, 581.

The tetronate (11) showed: $\delta 5.73(\text{br, 1H})$, 4.6(m, 1H), 4.16(OMe), 3.25-3.95(m, 4H), 2.06(:CMe), 2.18(d, <u>J</u> 14, 1H), 1.92(d, <u>J</u> 14, 1H), 1.3-1.9 (m, 9H), 1.2(Me), 1.15(Me), 1.05 and 1.0(d, <u>J</u> 7, Me diastereoisomers).

- δ(α-epimer) 1.04(d, <u>J</u> 7, CHMe), 5.69(:CH); δ(β-epimer) 0.98(d, <u>J</u> 7, CHMe), 5.63(:CH) p.p.m.
- 9. The stereochemistry assigned to (14) followed from inspection and comparison of n.m.r. shift data with those of natural alliacolide and its analogues; unpublished data.
- Intramolecular radical cyclisations onto enolic double bonds and their derivatives, have been found to be a generally useful synthetic operation; see: M. Ladlow, and G. Pattenden, <u>Tetrahedron Letters</u>, 1984, <u>25</u>, 4317, and unpublished work.

In separate studies, radical cyclisation of (12) using $Bu_3SnH-AIBN$ leads to the methyl ether corresponding to (14) in 95% isolated yield. Similarly, radical cyclisation of the nor-tetronate lacking the sidechain methyl group, gave the corresponding tricycle, δ 5.58(d, <u>J</u> 2, :C<u>H</u>) 3.37(OMe), 2.7(q, <u>J</u> 7, C<u>H</u>Me), 2.48(d, <u>J</u> 14, 1H), 2.35(dt, <u>J</u> 14 and 2, HC:C.C<u>H</u>H), 2.15(dt, <u>J</u> 14 and 2, HC:C.CH<u>H</u>), 2.04(m, 1H), 1.62(d, <u>J</u> 14, 1H), 1.29(d, <u>J</u> 7, CH<u>M</u>e), 1.4(Me), 1.11(Me); δ_{carbon} 176.9, 142.9, 134.8, 96.1, 80.2, 52.3, 45.4, 44.6, 42.3, 29.4, 28.8, 25.1, 24.1, 20.4, 10.0.

11. δ3.22(1H), 2.69(q, J 7.2, CHMe), 2.1(OH), 1.8-2.15(m, 1H), 1.96(d, J 13.8, 1H), 1.64(m, 1H), 1.29(d, J 13.8, 1H), 1.18(d, J 7.2, CHMe), 1.14(d, J 7.4, CHMe), 1.12(2 x Me) superimposable on that of naturally derived alliacolide. cf. 1-nor-alliacolide: δ3.32(1H), 2.73(q, J 7, CHMe), 2.4 (br, 1H), 2.14(m, 1H), 1.98(d, J 14, 1H), 1.74-1.9(m, 2H), 1.46-1.67 (m, 3H), 1.33(d, J 14, 1H), 1.17(d, J 7.2, 3H), 1.15(Me), 1.12(Me);
δ carbon 175.9, 90.2, 77.2, 70.5, 66.1, 46.8, 40.4, 38.1, 30.5, 24.3, 24.0, 23.9, 18.6, 6.8 p.p.m.

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