Tetrahedron Letters, Vol.22, No.18, pp 1751 - 1754, 1981
Printed in Great Britain

0040-4039/81/181751-04$02.00/0

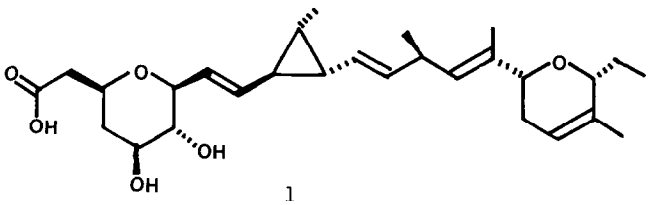
SYNTHETIC STUDIES ON AMBRUTICIN: DETERMINATION OF THE ABSOLUTE STEREOCHEMISTRY BY A CHIRAL SYNTHESIS OF THE CYCLOPROPANE RING

Nigel J. Barnes[a], Alan H. Davidson[a]*, Leslie R. Hughes[b], Garry Procter[c]*, and Veedianand Rajcoomar[c].

a Department of Chemistry, UWIST, Cardiff CF1 3NU
b ICI Pharmaceuticals, Alderley Park, Macclesfield SK10 4TG
c Department of Chemistry, University College, Cardiff CF1 1XL

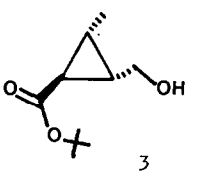
Abstract: *We report the highly stereoselective synthesis of the cyclopropane (3) and its conversion to a degradation product of ambruticin.*

Ambruticin (1) is an orally active antifungal agent which was isolated from the myxobacterium *Polyangium cellulosum fulvum*. The structure was determined by X-ray crystallography which gave the relative but not the absolute configuration of the molecule.[1,2,3] This additional information is critical for the correct choice of chiral precursors for our synthetic studies on ambruticin. Although it has been reported[1] that ozonolysis of ambruticin leads to complex mixtures, it appears possible that a derivative of the cyclopropane ring could be obtained by oxidative cleavage. Our initial efforts have therefore been directed towards a synthesis of the cyclopropane fragment (2) in which the two ends of the molecule are differentiated (X ≠ Y) allowing for further elaboration to ambruticin. In this communication we report a short highly stereoselective synthesis of both the racemic and optically active cyclopropane (3), and the determination of the absolute stereochemistry of ambruticin by correlation of optically active (3) with material obtained by degradation of the natural product.



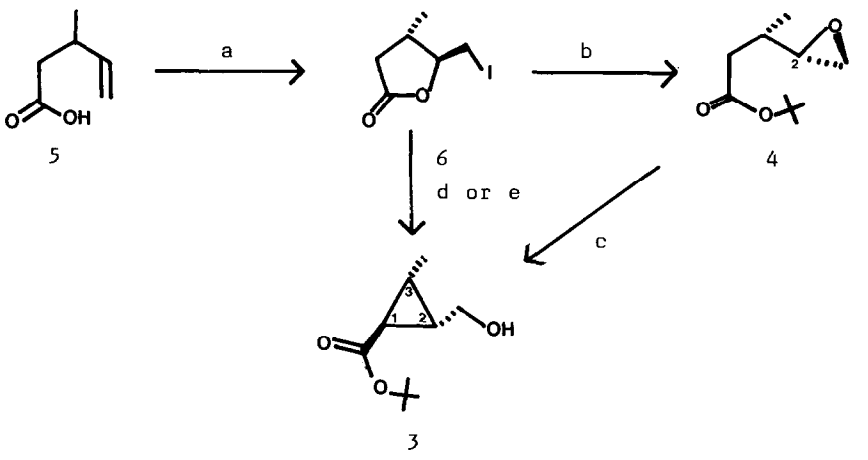
1

2



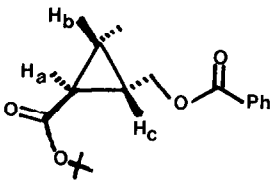
3

The essential requirements for the synthesis of (3) are that the stereochemistry of the cyclopropane ring should be carefully controlled and that the route should be readily applicable to the synthesis of optically active material. The key step in our route is the cyclisation of the epoxide (4) which proceeds with inversion of stereochemistry at C-2 to produce a *trans* arrangement of groups at C-1 and C-2.[4] The epoxide (4) is available by a highly stereoselective route[5] from the acid (5) both enantiomers of which are easily accessible.[6]



a) I_2 (3 equivalents), CH_3CN, 24 h at 4°C, 75%; b) LiO^tBu (1.5 equivalents), THF, 3 h at 0°C, 70%; c) LDA (1.1 equivalents), THF, 1 h at -78°C and 2 h at -30°C, 90%; d) LiO^tBu (1.5 equivalents) THF 3 h 0°C then KO^tBu (2 equivalents) 1.5 h 20°C; e) KO^tBu (2 equivalents), THF, 0.5 h 0°C then 2 h at 20°C, 40%.

Treatment of the racemic acid (5)[7] with iodine in acetonitrile[5] gave predominantly the thermodynamically more stable *trans* iodolactone (6) (ratio *trans*:*cis*: 20:1) which was converted to the epoxide (4) with lithium *tert*-butoxide in THF. The cyclisation was carried out using lithium diisopropylamide[8,9] (-78° to -20°) to give only the *trans* cyclopropane (3) in 50% overall yield from the acid (5). The iodolactone (6) could also be converted directly to the cyclopropane (3) by treatment with lithium *tert*-butoxide followed by potassium *tert*-butoxide. The yield for this one-pot procedure was as high as 75% on a small scale (200 mg of iodolactone (6)) but lower yields (~50%) were obtained when the reaction was scaled up (1 g). Treatment of the iodolactone (6) with potassium *tert*-butoxide alone gave only a low yield (<40%) of the cyclopropane (3) together with products arising from the elimination of hydrogen iodide. The stereochemistry of the cyclopropane (3) was confirmed from the 300 MHz ^1H spectrum of the benzoate (7). The proton H_a is clearly visible as a triplet, coupling constant J = 4.5 Hz, indicating[10] it is *trans* to H_b and H_c.



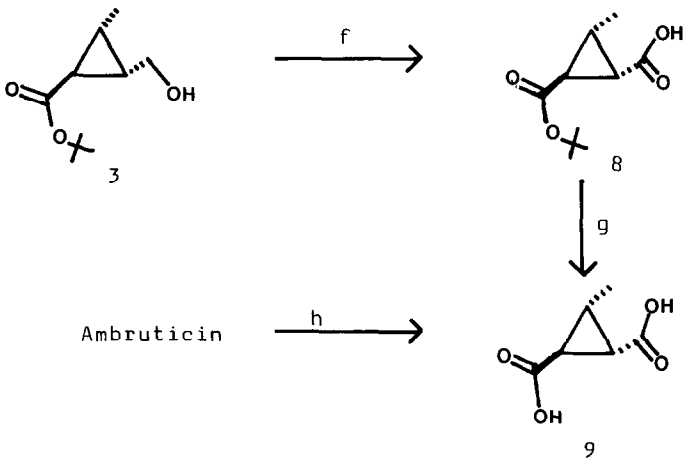
7

The absolute configuration of ambruticin was determined by preparing (1*S*,2*S*,3*R*) cyclopropane (3) from optically active (*S*) acid (5) (obtained from (*R*) citronellal by a modification of a literature procedure[6,11]). Oxidation using Jones reagent gave the (1*S*,2*S*,3*R*) *tert*-butyl ester-acid (8) (m.p. 108-109°C (racemic 112-116°C) $[\alpha]_D^{21}$ + 93° (*c* 0.004 g ml^{-1}, $CHCl_3$)) which was hydrolysed with TFA to the (1*S*,2*S*) dicarboxylic acid (9).[12] Ozonolysis of ambruticin followed by oxidative work up (excess Jones reagent, 3 days, room temperature) gave a yellow oil which was washed three times with 40-60° petroleum ether and the residue taken up in ether. The dicarboxylic acid (9) crystallised from the solution upon addition of petroleum ether and was recrystallised four times from ether-petroleum ether. Comparison by nmr, ir, and m.p. (m.p. and mixed m.p. 160.5-162.5°C) showed the degradation product to be identical to that produced by synthesis. Moreover, the CD spectra (synthetic (9) $\Delta\varepsilon_{212}$ - 18 dm^2 mol^{-1} (H_2O); (9) from natural material $\Delta\varepsilon_{212}$ - 16 dm^2 mol^{-1} (H_2O)) and optical rotations (synthetic (9) $[\alpha]_D^{21}$ + 98° (*c* 0.004 g ml^{-1}, EtOH); (9) from natural material $[\alpha]_D^{21}$ + 100° (*c* 0.001 g ml^{-1}, EtOH)) showed unambiguously that they also possessed the same absolute configuration, and hence the absolute stereochemistry of ambruticin is that shown in (1).

In summary, the absolute configuration of ambruticin has been determined by synthesis of the optically active cyclopropane (3) and comparison to a degradation product of the natural material. The cyclopropane (3) was prepared in a suitable form for incorporation into a convergent synthesis of optically active ambruticin and this work is continuing.

Acknowledgements

We thank the SRC and ICI Pharmaceuticals for a CASE award (N.J.B.), the Dyson Perrins Laboratory Oxford for the 300 MHz nmr spectra, and Dr.J.Moffat and Dr.J.P.Poyser, ICI Pharmaceuticals, for providing a sample of ambruticin.



f) excess Jones reagent 72 h at 20°C, 60%; g) TFA, 0.5 h 20°C, 90%; h) O_3, acetone, 1 h at -78°C then excess Jones reagent 72h at 20°C.

References

1. D.T.Connor, R.C.Greenough and M.Von Strandtmann, *J.Org.Chem.*, *42*, 3664, 1977.
2. S.M.Ringel, R.C.Greenough, S.Roemer, D.Connor, A.L.Gutt, B.Blair, G.Kanter and M.Von Strandtmann, *J.Antibiot.*, *30*, 371, 1977.
3. D.T.Connor and M.Von Strandtmann, *J.Org.Chem.*, *43*, 4606, 1978.
4. G.Stork and J.F.Cohen, *J.Amer.Chem.Soc.*, *96*, 5270, 1974.
5. P.A.Bartlett and J.Myerson, *J.Amer.Chem.Soc.*, *100*, 3950, 1978.
6. R.E.Ireland, G.J.McGarvey, R.C.Anderson, R.Badoud, B.Fitzsimmons and S.Thaisrivongs, *J.Amer.Chem.Soc.*, *102*, 6178, 1980.
7. H.J.Gunther and V.Jager, *Tetrahedron Letters*, 2543, 1977.
8. J.H.Babler and A.J.Tortorello, *J.Org.Chem.*, *41*, 885, 1976.
9. J.Ficini and J.D'Angelo, *Tetrahedron Letters*, 2411, 1976.
10. L.M.Jackman and S.Sternhell in "Applications of Nuclear Magnetic Resonance Spectroscopy", Pergamon, 1969, p.286.
11. D.B.Collum, J.H.McDonald and W.Clark Still, *J.Amer.Chem.Soc.*, *102*, 2118. 1980.
12. The racemic acid (9) was also prepared m.p. 130°C and 147-148°C; lit. m.p. 138°C and 150°C - see M.G.Ettlinger, S.H.Harper and F.Kennedy, *J.Chem.Soc.*, 922, 1957.

(Received in UK 16 February 1981)