Tetrahedron Letters,Vol.25,No.15,pp 1561-1562,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

AN ENANTIOSELECTIVE SYNTHESIS OF A 4-FLUOROMETHYL-AZETIDINONE

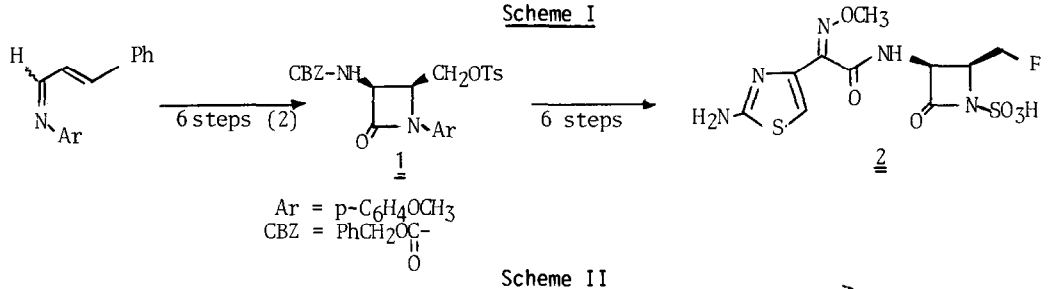
Georges Teutsch* and Alain Bonnet

Centre de Recherche Roussel Uclaf
93230 Romainville (France)

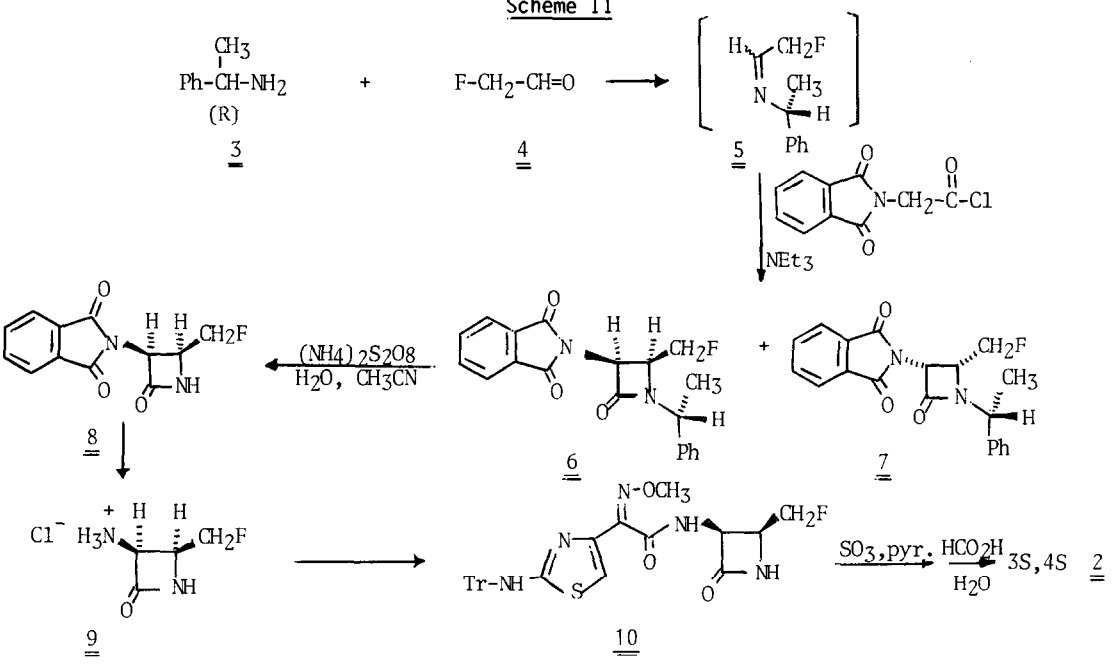
Abstract : (3S,4S) 3-amino-4-fluoromethyl-azetidinone 9 is obtained conveniently from (R) N-(2-fluoroethylidene)-α-methylbenzylamine via cycloaddition.

A recent report on the synthesis and in vitro antibacterial activity of racemic (cis)-3-[2-(2-aminothiazol-4yl)-(Z)-2-methoxyiminoacetamido]-4-fluoromethyl-2-oxo-1-azetidinesulfonic acid 2 (1) via tosylate 1 (scheme I) prompts us to disclose a more direct route to this compound in its optically active form. (Scheme II).

Scheme I



Scheme II



Our synthesis is based on the cycloaddition reaction of phthalimidoacetylchloride (3) with a chiral imine of fluoroacetaldehyde.

Addition of R(+) phenyl-ethylamine 3 to a titrated aqueous solution of fluoroacetaldehyde (4) at room temperature led to the rapid formation of an oil which was extracted into ethanol free chloroform (5) and stirred for 1 hour with magnesium sulfate. The resulting solution containing the labile fluoroethanimine 5 was cooled to -70°C and treated with equivalent amounts of phthalimidoacetylchloride and triethylamine (6), keeping the temperature below -50°C. The diastereoisomeric azetidinones 6 and 7 were obtained in 48% and 11% yields (6) respectively after chromatography on silica gel. Both possessed the cis configuration as shown by the 5Hz coupling constant of the H-3 proton in the NMR spectrum. No trans isomer could be detected.

[6 : MP 156°C, $(\alpha)_D$ -64° ± 2° in DMF, νcm^{-1} ($CHCl_3$) 1787, 1769, 1725, 1612, 1590, 1495, δppm ($CDCl_3$) 1.75 (d, J=7, CH_3) 3.8-4.8 (m, H-4 and CH_2F) 5.08 (q, J=7, $CH-CH_3$) 5.42 (d, J=5, H-3) 7.40 (s, phenyl) 7.8 (m, phthalimide); 7 : amorphous, $(\alpha)_D$ +50° ± 1.5° in $CHCl_3$, νcm^{-1} ($CHCl_3$) : as for 6, δppm ($CDCl_3$) 1.80 (d, J=7, CH_3) 4.2 (m, H-4) 4.0-4.6 (m, CH_2F) 5.0 (q, J=7, $CH-CH_3$) 5.46 (d, J=5, H-3) 7.39 (s, phenyl) 7.8 (m, phthalimide)].

Oxidative debenzylation using ammonium persulfate in aqueous acetonitrile (7) afforded compound 8 (40%) [MP 160-162°C, $(\alpha)_D$ +7° ± 1° in MeOH, CD(EtOH) Δεmax + 2.9 (243 nm)-0.99 (297 nm)] which was hydrazinolyzed (hydrazine hydrate in dioxane followed by acidification with normal aqueous HCl) (8) to the aminoazetidinone 9 (77%) [MP > 220°C (dec), $(\alpha)_D$ -36.5° ± 1° in H_2O, δppm (DMSO) 3.8-4.7 (m, H-4 and CH_2F) 5.26 (d, J=5, H-3) 8.9 (bs, NH-CO)]. Amidification with the trityl protected 2-(2-aminothiazol-4-yl)-(Z)-2-methoxyimino-acetic acid side chain in the described manner (9) afforded compound 10 (68%) [MP > 220°C (dec), $(\alpha)_D$ -5° ± 0.5° in DMSO, νcm^{-1} ($CHCl_3$) 3425, 2825, 1780, 1680, 1530, 1090, δppm ($CDCl_3$) 4.06 (s, OCH_3) 4.2 (m, H-4) 4.4-4.9 (m, CH_2F) 5.52 (dd, J=5, J=9, H-3) 6.68 (s, H-5 thiazol) 7.30 (s, phenyl), CD (EtOH) Δεmax -1.25 (264 nm)] which was sulfonated with SO_3, pyridine complex in DMF (10) and detritylated with 33% aqueous formic acid at 50°C for 30 min to the optically active product 2 (39% from 10). [MP > 220°C (dec), $(\alpha)_D$ -14.5° ± 2° in H_2O, νcm^{-1} (nujol) 1770, 1667, 1637, 1570, 1560, 1535, λmax (EtOH, HCl N/10) 266 nm (12400) δppm (DMSO) 3.85 (s, OCH_3) 4.2-4.9 (m, H-4 and CH_2F) 5.24 (dd, J=5, J=9, H-3) 6.72 (s, H-5 thiazol) 9.33 (d, J=9, NHCO)].

In an in vitro antibacterial screening on a number of Gram negative strains (11) this compound displayed Minimum Inhibitory Concentrations which were half of those of the corresponding racemic compound prepared according to the same scheme, but starting with racemic phenyl-ethylamine. These results suggest that (-) 2 has indeed the 3S, 4S configuration.

References and notes

1. J.S. Skotnicki, T.J. Commons, R.W. Rees and J.L. Speth; J. Antibiotics 36 1201 (1983)
2. D.R. Kronenthal, C.Y. Han and M.K. Taylor, J. Org. Chem. 47 2765 (1982)
3. J.C. Sheehan and V.S. Frank, J. Amer. Chem. Soc. 71 1856 (1949)
4. The aqueous fluoroacetaldehyde solution was obtained from N-methoxy-N-methyl fluoroacetamide by DIBAH reduction followed by aqueous HCl hydrolysis according to a process described by S. Nahm and S.M. Weinreb in Tetrahedron Lett. 22 3815 (1981)
5. The presence of ethanol decreases the yield of the subsequent cycloaddition by formation of ethyl-phthalimidoacetate.
6. Stoechiometry and yields are based on the starting phenyl-ethylamine.
7. J.G. Gleason and L.Wu, J. Amer. Chem. Soc. 99 2352 (1977)
8. J.C. Sheehan and P.A. Cruikshank, J. Amer. Chem. Soc. 78 3677 (1956)
9. R. Bucourt, R. Heymes, A. Lutz, L. Pênasse and J. Perronnet ; Tetrahedron 34 2233 (1978)
10. D.M. Floyd, A.W. Fritz, J. Pluscec, E.R. Weaver and C.M. Cimarusti, J. Org. Chem. 47 5160 (1982)

11. We thank Mr. J.F. Chantôt for performing the antibacterial screening.

(Received in France 8 February 1984)