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SYNTHESIS OF AN *N*-(TETRAZOL-5-YL) AZETIDIN-2-ONE FROM L-TARTARIC ACID

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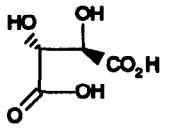
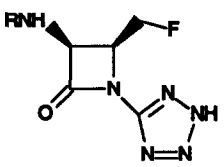
Abstract : L (+) tartaric acid was a useful starting synthon to obtain *N*-(tetrazol-5-yl) azetidin-2-ones.

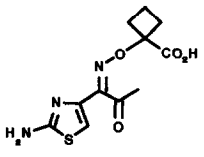
Analogues of monobactams in which the sulfonic group has been replaced by the isosteric tetrazole represent a new class of antibacterials.[1-4] In particular RU 44790 (1a) was shown to compare very favorably with aztreonam.[5] Our initial approach to the chiral (3*S*,4*S*) *N*-tetrazolyl-4-fluoromethyl azetidinone 1b relied on the introduction of the tetrazole substituent on the preformed β-lactam.[6,7] In the present letter, we report an alternate synthesis of this compound, starting with L-tartaric acid. This chiral synthon has been used previously by Gero *et al.*[8] to synthesize trans 3,4-disubstituted azetidin-2-ones.



L (+) tartaric acid



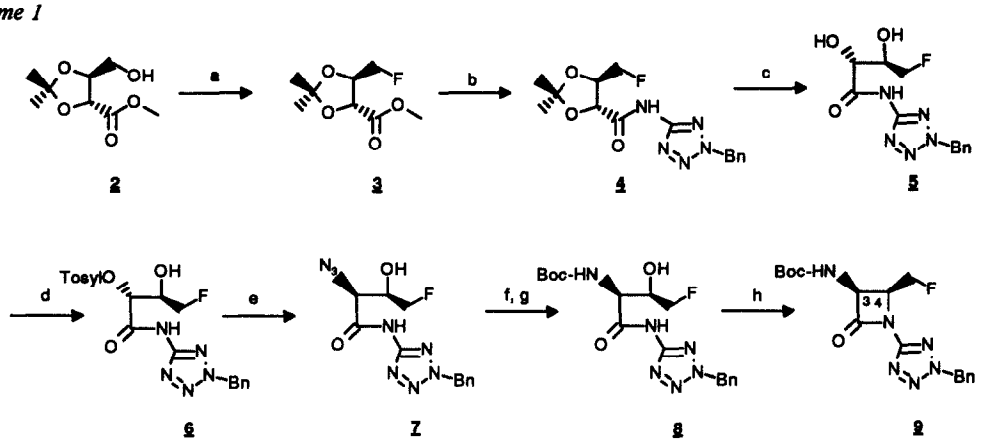
1a : (RU 44790) R =



1b : R = protective group

The alcohol 2 prepared from L-tartaric acid, according to the procedure of Rapoport *et al.*[9] was treated with trifluoromethane-sulfonic anhydride to provide the triflate which was converted *in-situ* to the fluoro compound 3. The ester function of 3 was transformed to the amide 4 by reaction with the potassium salt of 2-benzyl 5-amino tetrazole.[10] After deprotection of the ketal, the diol 5 was treated with tosyl chloride in pyridine to afford the monotosylate 6 in 36 % yield. Conversion of 6 to the azido-derivative 7 by warming in DMF with sodium azide, followed by hydrogenolysis and protection of the formed amine afforded the Boc protected compound 8. Finally, cyclisation of 8 by a classical Mitsunobu reaction[11,12] led to the pure cis β-lactam 9, as demonstrated by the coupling constant of 5.5 Hz[13] between H-3 and H-4 of the azetidine ring.[3]

Scheme 1



a) $(CF_3SO_2)_2O$, pyridine (1 eq.), CH_2Cl_2, -20 °C, 1/4 h then $Bu_4N^+F^-$, CH_3CN, 25 °C, 1 h, 51 % ; b) 2-benzyl 5-aminotetrazole, THF, MeOK, 25 °C, 1 h , 91 % ; c) HCl 2N, CH_3CN, 50 °C, 8 h, 79 % ; d) TSCl , pyridine, 0 °C, 2 h, 36 % ; e) N_3Na, DMF, 70 °C, 1/2 h, 48 % ; f) EtOAc, H_2, 5 % - Pd/C, 50 % ; g) diterbutyl dicarbonate, THF, reflux 1 h, 90 % ; h) DEAD, PPh_3, THF, 0 °C, 1/2 h, 58 %.

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13) Physical constants for **9** : mp . 158 °C ; IR ($CHCl_3$) : 3446, 1792, 1718, 1555, 1511 and 1370 cm^{-1} ; ^{1}HNMR ($CDCl_3$) : 1.47 (s, tBu), 4.54 (m, H_4, J_{H4F} = 29 Hz), 4.77 (dd, one H of CH_2F, J_{HF} = 45 Hz, Jgem = 11Hz), 5.24 (ddd, the second H of CH_2F, J_{HF} = 48 Hz, J_{HH3} = 1 Hz), 5.36 (d, NH, J = 10 Hz), 5.57 (d, H_3, J_{H3H4} = 5.5 Hz (after exchange with D_2O)), 5.72 (s, N-CH_2-ϕ), 7.38 (broad s, H Aromatic).