Tetrahedron Letters,Vol.30,No.19,pp 2555-2558,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ASYMMETRIC HYDROLYSIS OF *dl* 3-(1-BENZOYLOXYETHYL)-AZETIDINONE DERIVATIVE AND CHEMICAL CONVERSION TO CARBAPENEM

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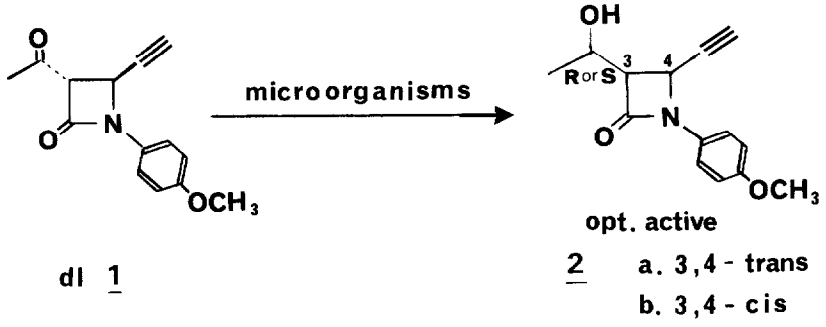
Summary: Asymmetric hydrolysis of *dl* R* benzoate (*dl* 3) was achieved effectively by *Bacillus subtilis* to give the optically-active R-hydroxyethyl azetidinone 8, and this product 8 was converted chemically into the known β-azetidinyl acetyl thioester derivative 12, which was further converted into carbapenem derivative 14.

In a previous communication[1] we reported the microbial transformation of *dl* 3-acetylazetidinone derivative 1, and obtained optically active R- or S-hydroxyethyl derivative 2 of 3,4-*trans* or -*cis* configuration, depending on the microorganisms employed. In the microorganisms so far examined, only *Saccharomyces rosei* was effective to produce the desired 3S,4S-(R)-hydroxyethyl azetidinone (2a), but the optical yield was disappointingly low. (Scheme 1).

Scheme 1



dl 1

opt. active

2 a. 3,4 - trans

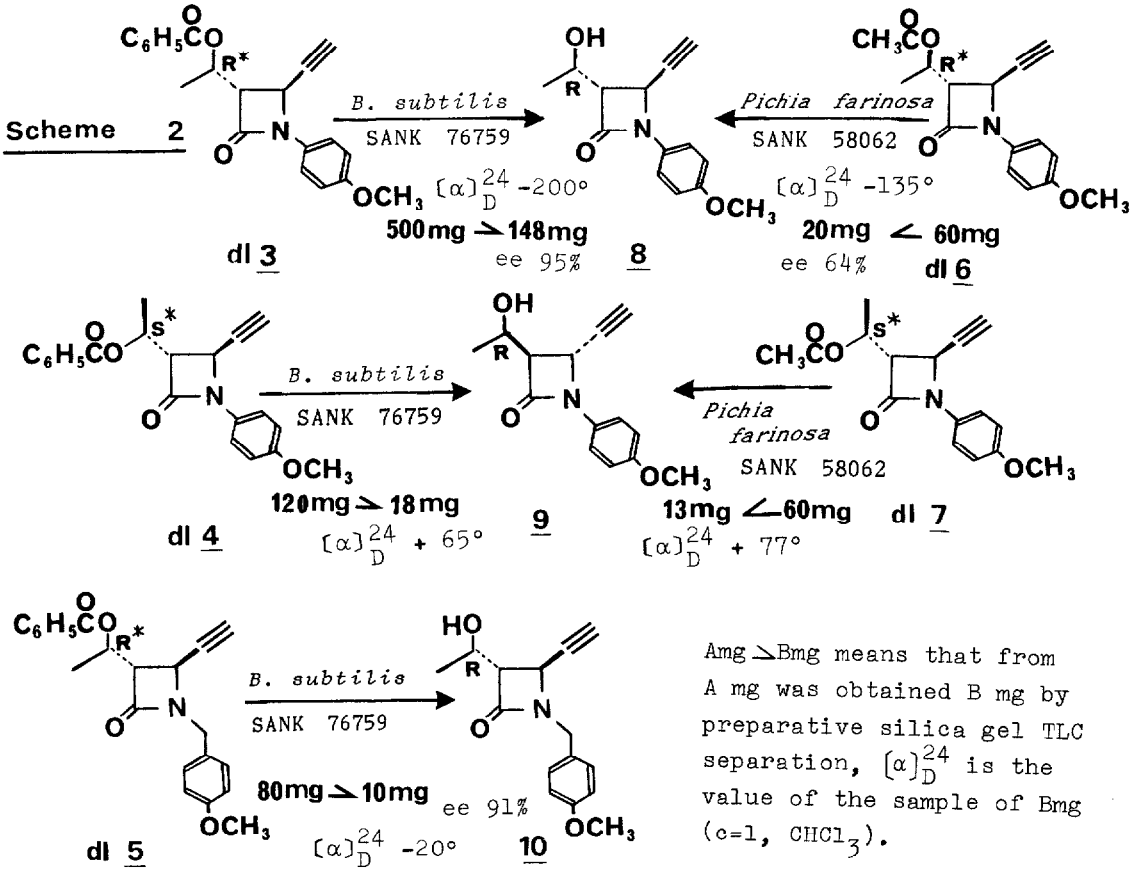
b. 3,4 - cis

Here we wish to report the microbial asymmetric hydrolysis of esters in *dl* monocyclic β-lactams. The procedure is as follows : after feeding 500 mg of *dl* R*-benzoate (*dl* 3)[2] in 1 l of culture medium of *Bacillus subtilis* at an exponential phase, followed by incubation at 37°C for 24 hr, the products were extracted with ethylacetate. Evaporation of the solvent gave the crude products (520 mg), which were separated on silica gel preparative TLC(2mm),c-Hex.: EtOAc = 1:1, to afford 148 mg of the optically-

active R-hydroxyethyl derivative 8 (mp 133°C, $[\alpha]_D^{24}$ -200°(c=1, $CHCl_3$), *ee* 95%. For S*-benzoate (*dl* 4) the product was R-hydroxyethyl derivative 9, but the optical and conversion yields were low.

For acetates (*dl* 6 and *dl* 7) *Pichia farinosa* was more effective than *Bacillus subtilis*, but the optical yields were not satisfactory.(Scheme 2). N-*p*-anisyl- R* - Benzoate (*dl* 5) gave R-hydroxyethyl derivative 10, $[\alpha]_D^{24}$ -20°, *ee* 91% (*cf.*standard 10 derived from 6-APA, $[\alpha]_D^{24}$ -22°), Rf=0.22 (c-Hex:AcOEt=1:1). NMR($CDCl_3$,60 MHz) δ: 1.24(3H,d,J=6Hz), 2.39(1H,d,J=2Hz), 3.22(1H,dd,J=5 and 2Hz),3.70(3H,s), 3.9-4.4(1H,m), 3.97(1H,d,J=15Hz), 4.59(1H,d,J=15Hz), 6.7-7.3(4H,A_2B_2).[2]. It is noteworthy to point out here that in both *Bacillus subtilis* and *Pichia farinosa* , all of the hydrolyzed products have a hydroxyethyl group of R-configuration. (Scheme 2).

Scheme 2

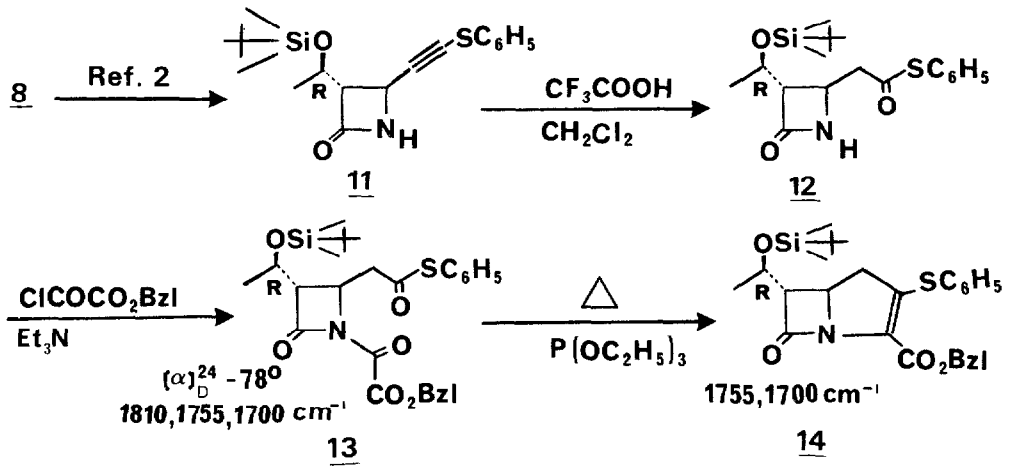


Amg ⟶ Bmg means that from A mg was obtained B mg by preparative silica gel TLC separation, $[\alpha]_D^{24}$ is the value of the sample of Bmg (c=1, $CHCl_3$).

Pig liver esterase (PLEase), which is very commonly used for the asymmetric hydrolysis of C_2-symmetric diesters[3], seemed to be very attractive to our β-lactam esters, but from 60 mg of R*-benzoate (*dl* 3) only 12.4 mg of the hydrolyzed product 8, ($[\alpha]_D^{24}$ -86°) was obtained, which means PLEase was not effective in this case.

As described above the best result so far obtained was from the application of the R*-benzoate (*dl* 3) to *Bacillus subtilis*, and we further transformed this optically-active R-hydroxyethyl derivative 8 into the carbapenem derivative 14 as shown in scheme 3. The R-hydroxyethyl derivative 8 hydrolyzed by *Bacillus subtilis* was transformed into phenylthio derivative 11 (mp 78°C, $[\alpha]_D^{24}$ +46°) by the same procedure described in *Ref*.2) in 42 % yield from 8. Hydration of the triple bond was smoothly achieved by treatment with 5 eq. of trifluoroacetic acid to afford the known β-azetidinyl-acetylthioester derivative 12[4] From this compound 12 by the reported procedure (benzyl oxalyl chloride/Et_3N, and then heating in xylene in the presence of triethyl phosphite) the carbapenem derivative 14 was obtained without any difficulties[5]. (Scheme 3).

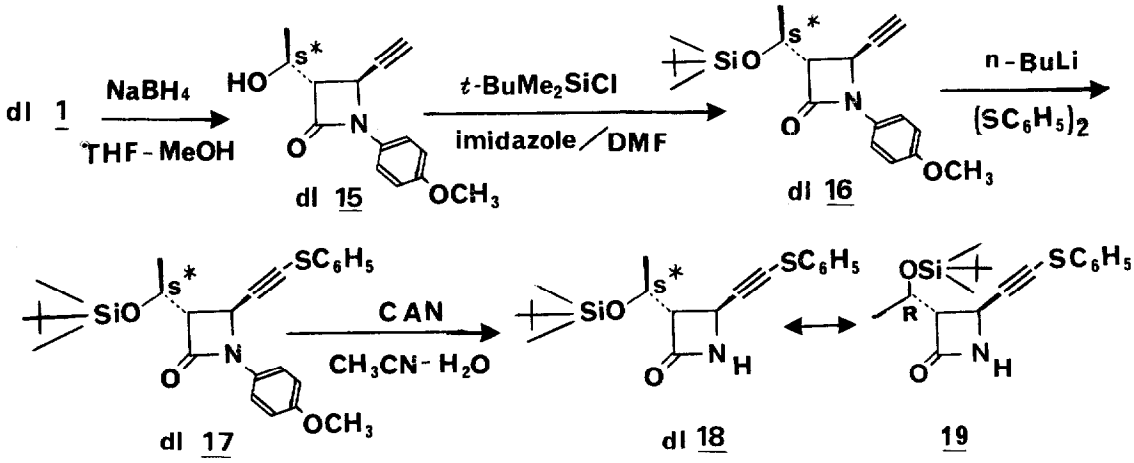
Scheme 3



Reference and Footnotes

1) K.Hirai and A.Naito, Tetrahedron Lett.,1989 in press.

2) The preparation of starting esters and their structure determination were performed as follows : Sodium borohydride reduction of *dl* 3-acetylazetidinone (1)[1] in THF and methanol gave the S*-alcohol 15 (mp 109°C) and R*-alcohol in a ratio of 3:2. The structure of the easily crystalizable S*-alcohol 15 was confirmed unequivocally by the comparison of its chemically converted derivative (*dl* 18,mp 93°C) with the standard compound 19 prepared from 6-APA by the reported procedure[4]. *dl* 15:NMR (60 MHz, $CDCl_3$) δ :1.37(3H,d,J=6Hz), 2.55(1H,d,J=2Hz), 2.67(1H,OH), 3.40(1H,dd,J=4 and 2Hz), 3.75(3H,s), 3.9-4.4(1H,m), 4.45(1H,t,J=2Hz), 6.75-7.60(4H,A_2B_2). IR(Nujol) cm^{-1}:3550,3220,2130,1732,1520. *dl* 16: 0.1(6H,s), 0.8(9H,s), 1.33(3H,d,J=6Hz), 2.46(1H,d,J=2Hz), 3.42(1H,1dd,J=3 and 4.5Hz), 3.75(3H,s), 4.0-4.4(1H), 4.38(1H,t,J=2Hz), 6.6-7.5(4H,A_2B_2). *dl* 17:0.08(6H,s), 0.81(9H,s), 1.38(3H,d,J=6Hz), 3.48(1H,dd,J=3 and 4Hz), 3.74(3H,s), 4.0-4.4(1H), 4.62(1H,d,J=3Hz), 7.28(5H,br s), 6.65-7.60(4H,A_2B_2), *dl* 18:0.08(6H,s), 0.88(9H,s), 1.33(3H,d,J=6Hz), 3.50(1H,br t,J=3Hz), 4.1-4.40(1H,m), 4.36 (1H,d,J=3Hz), 6.1(1H,br s), 7.25-7.55(5H). Mp 93°C.



The starting esters (*dl* 3- *dl* 7): the S*-alcohol (*dl* 15) was benzoylated (C_6H_5COCl/Et_3N) to *dl* 4 and was also converted into the R*-benzoate (*dl* 3), mp 101°C by Mitsunobu reaction ($C_6H_5CO_2H$, $(=NCO_2Et)_2$, $P(C_6H_5)_3$). In the case of N-*p*-anisyl derivative the R*-benzoate (*dl* 5), M^+ 363 was prepared by the same reaction sequence for the preparation of *dl* R*-benzoate 3. The acetates (*dl* 6 and *dl* 7) were prepared analogously. *dl* 3 : mp 101°C, Rf=0.5(CH_2Cl_2). IR (Nujol) cm^{-1}:3280, 2140, 1745, 1720, 1608, 1590. NMR(60 MHz, $CDCl_3$) δ: 1.55(3H,d,J=6.5Hz), 2.55(1H,d,J=2.5Hz), 3.60(1H,dd,J=2.5 and 6.5Hz), 3.70(3H,s), 4.60(1H,t,J=2.5Hz), 5.46(1H,q,J=6.5Hz), 6.7-7.6(7H), 7.8-8.0(2H). *dl* 4:Rf=0.61(CH_2Cl_2), NMR:1.59(3H,d, J=6.5Hz), 2.55(1H,d,J=2.5Hz), 3.70(3H,s), 4.38(1H,t,J=2.5Hz), 3.6-3.73(1H), 5.53(1H,dq,J=6.5 and 3Hz), 6.74-7.9(9H). *dl* 5: Rf=0.25(c-Hex:AcOEt=2:1), NMR :1.43(3H,d,J=6Hz), 2.51(1H,d,J=2Hz), 3.49(1H,dd,J=6 and 2Hz), 3.73(3H, s), 4.0(1H,d,J=15Hz) and 4.70(1H,d,J=15Hz), 5.40(1H,q,J=6 Hz), 6.6-6.7 (7H), 7.6-7.9(2H). *dl* 6: Rf=0.26(CH_2Cl_2), NMR δ:1.40(1H,d,J=6.5Hz), 2.00 (3H,s), 2.55(1H,d,J=2Hz), 3.45(1H,dd,J=6.5 and 2Hz), 3.76(3H,s), 4.50(1H, t,J=2Hz), 5.27(1H,q,J=6.5Hz), 6.7-7.6(4H,A_2B_2). *dl* 7:Rf=0.34(CH_2Cl_2), NMR δ :1.42(3H,d,J=6.5Hz), 2.0(3H,s), 2.55(1H,d,J=2Hz), 3.76(3H,s), 3.57 (1H,dd,J=5 and 2.5Hz), 4.31(1H,t,J=2.5Hz), 5.30(1H,dq,J=6.5 and 5Hz), 6.7-7.6(4H,A_2B_2). (-)8: NMR δ:1.27(3H,d,J=6Hz), 2.55(1H,d,J=2Hz), 3.38(1H, dd,J=4 and 2Hz), 3.75(3H,s), 4.1-4.5(1H), 4.60(1H,t,J=2Hz), 6.7-7.6 (4H,A_2B_2).

3) M.Ohno, Organic Synthesis an interdisciplinary challenge, 5th IUPAC Symp. on Org. Synth. (Freiburg, Aug. 1984).

4) H.Maruyama and T.Hiraoka, J. Org. Chem.,51, 399 (1986).

5) A.Yoshida, Y.Tajima, N.Takeda and S.Oida, Tetrahedron Lett.25,1793(1984).

(Received in Japan 15 October 1988; accepted 27 February 1989)