Tetrahedron Letters,Vol.24,No.10,pp 1037-1040,1983 0040-4039/83/101037-04$03.00/0
Printed in Great Britain

SYNTHESIS OF OPTICALLY ACTIVE AZETIDIN-2-ONES FROM L-THREONINE

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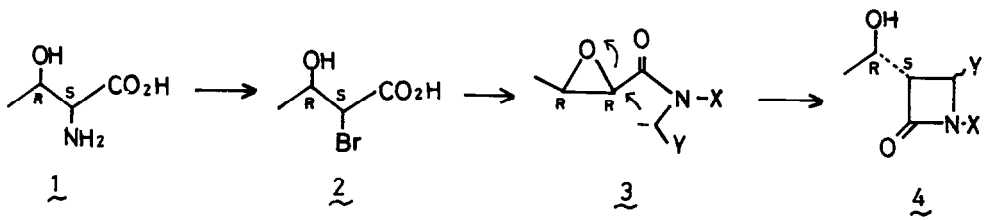
Summary: 3S-(1R-Hydroxyethyl)-4R-phenylsulfonylazetidin-2-one derivative was synthesized from L-threonine in an 8-step process including the novel transformation of the oxirane ring to the azetidin-2-one.

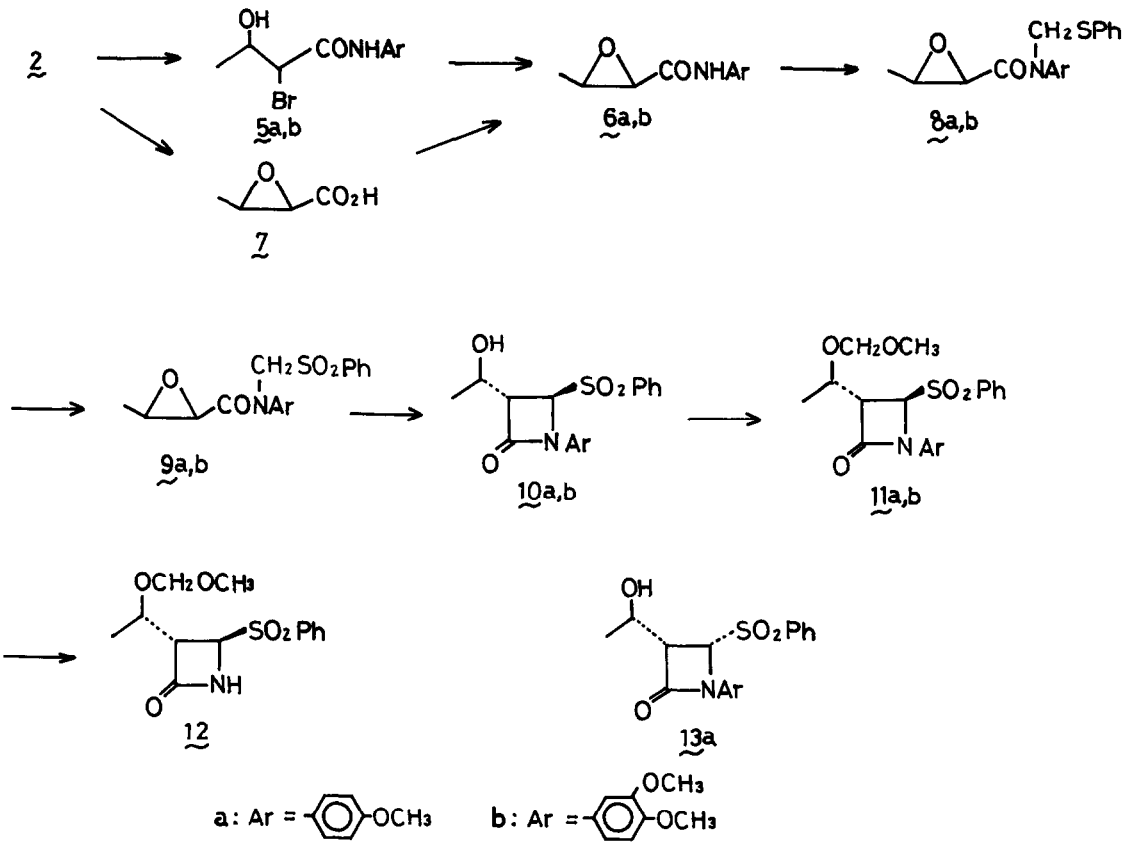
In a previous paper[1] we described the stereocontrolled synthesis of the 3S-(1R-hyroxyethyl)-4R-carboxyazetidin-2-one derivative, an important intermediate of the carbapenem antibiotics, from L-threonine. Our strategy was as follows: the negatively charged carbon in 3 prepared from L-threonine 1 via 2S-bromo-3R-hydroxybutyric acid 2[2] attacks the α-carbon on the α,β-epoxycarboxamide group to afford the azetidin-2-one 4 with inversion.



X= N-protecting group
Y= carbanion stabilizing group

In this communication we wish to report a convenient 8-step synthesis of the 3S-(1R-hydroxyethyl)-4R-phenylsulfonylazetidin-2-one derivative 12, the key intermediate of the carbapenem[3] and penem[4] antibiotics, from L-threonine .

Condensation of 2 with p-anisidine in CH_2Cl_2 at room temperature by use of N,N'-dicyclohexylcarbodiimide gave the amide 5a[5] in 90% yield. Treatment of 5a with 50% aqueous NaOH solution in CH_2Cl_2 in the presence of catalytic amount of benzyltriethylammonium iodide at room temperature for 30 min gave the epoxide 6a[6] quantitatively. The amide 6a was also prepared from 2 via 2R,3R-epoxybutyric acid 7[7] by epoxydation of 2 followed by condensation with p-anisidine in lower yield than the former process. N-Alkylation of 6a with phenylthiomethyl chloride (1.5 eq) and 50% aqueous NaOH soluiton in the presence of catalytic amount of benzyltriethylammonium iodide in CH_2Cl_2 at room temperature for 1 hr gave the N-phenylthiomethylamide 8a[8] in 87% yield which was subsequently treated with m-chloroperbenzoic acid (2 eq) in CH_2Cl_2 at room temperature for 16 hr to give the crystalline sulfone 9a[9] in 80% yield. The N-(3,4-dimethoxyphenyl)-amide 9b[10] was obtained from 2 and 3,4-dimethoxyaniline by the above-mentioned procedure in th similar yield.

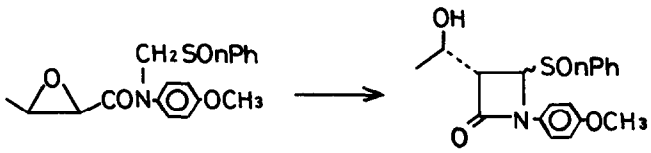


Ring transformations of 9a and 9b were conducted with n-butyllithium (2 eq) in hexamethylphosphoric triamide (HMPT)-tetrahydrofuran (1:6) at -50°C for 30 min under nitrogen atmosphere to give the crystalline azetidin-2-ones 10a[11] and 10b[12] in 82 and 71% yields, respectively. Diastereoisomers, other than 10a and 10b, were not isolated in this reaction conditions. When the reaction was carried out without HMPT, the ring transformation of 9a required room temperature and afforded 10a and its diastereoisomer 13a (10a/13a=3/1)[13]. Treatment of 10a and 10b with chloromethyl methyl ether and N,N-diethylaniline in dichloromethane at room temperature for 16 hr gave the O-protected azetidin-2-ones 11a[14] and 11b[15] in 95 and 94% yields, respectively. Removal [16] of the anisyl and 3,4-dimethoxyphenyl groups of 11a and 11b was achieved by ozonolysis in ethyl acetate under ice-salt cooling followed by decomposition of the ozonides with aqueous sodium thiosulfate solution at 50°C to give 3S-(1R-(methoxymethoxy)-ethyl)-4R-(phenylsulfonyl)-azetidin-2-one 12[17] in 57 and 71% yields, respectively.

This novel transformaiton of the oxirane ring to the azetidin-2-one was also observed in the epoxysulfide 8a and the epoxysulfoxide 14[18], prepared from 8a with m-chloroperbenzoic acid (1eq), in low yields.

Treatment of 8a with n-butyllithium in a similar manner to that of 9a gave the 4-phenylthioazetidin-2-one 15[19] in 7% yield of which NMR spectrum showed that 15 was a mixture of 4R and 4S diastereoisomers (4R/4S=1/2). Oxidation of 15 with m-choloroperbenzoic acid gave a mixture of 10a and its 4S-diastereoisomer 13a.

Treatment of 14 with n-butyllithium afforded a mixture of R and S-sulfoxides 16[20] in 17% yield which were separated by silica gel column chromatography. Both R and S-sulfoxides were oxidized by m-chloroperbenzoic acid to give the sulfone 10a.



8a: n=0 15: n=0

14: n=1 16: n=1

References

1. M. Shiozaki, N. Ishida, T. Hiraoka and H. Yanagisawa, Tetrahedron Lett., 22, 5205 (1981).
2. Y. Shimohigashi, M. Waki and N. Izumiya, Bull. Chem. Soc. Japan, 52, 949 (1979).
3. (a) T. Kobayashi, N. Ishida and T. Hiraoka, J. Chem. Soc., Chem. Commun., 736 (1980). (b) A. Nishida, M. Shibasaki and S. Ikegami, Tetrahedron Lett., 22, 4819(1981).
4. (a) A. Yoshida, T. Hayashi, N. Takeda, S. Oida and E. Ohki, Chem. Pharm. Bull. 29, 2899 (1981). (b) A. Longo, P. Lombardi, C. Gandolfi and G. Franceschi, Tetrahedron Lett., 22, 355 (1981).
5. Mp 111-113°C (recryn. from benzene). IR (nujol; cm^{-1}): 3370, 3250, 1655, 1535 and 1510.
6. Mp 75°C. IR (nujol; cm^{-1}): 3250 and 1665.
7. H. Shimazaki, Nippon Kagaku Zasshi, 87, 459 (1966).
8. Syrup. IR ($CHCl_3$ soluiton ; cm^{-1}): 1670 and 1510.
9. Mp 158-159°C (recryn. from benzene). IR (nujol; cm^{-1}) 1700, 1510 and 1150. NMR ($CDCl_3$; δ) 1.19 (3H, d, J=5.5 Hz, 4-CH_3), 2.8-3.2 (2H, m, 2 and 3-CH), 3.81 (3H, s, OCH_3), 5.09 (2H, ABq, Δδ=0.53 ppm, J=13.5 Hz, N-CH_2-SO_2), 7.09 (4H, A_2B_2q, Δδ=0.37 ppm, J=9 Hz, phenyl protons of anisyl group) and 7.4-8.0 (5H, m, SO_2Ph).
10. 5b: Mp 162-163°C (recryn. from EtOAc): IR (nujol; cm^{-1}) 3550, 3270, 1660 and 1515. 6b: This compound has two mps 92-94°C and 106°C: IR (nujol; cm^{-1}) 3330, 1665 and 1605. 8b: syrup. IR (liq. film; cm^{-1}) 1680 and 1510. 9b: Mp 145.5-146.5°C (recryn. from benzene): IR(nujol; cm^{-1}) 1690, 1510, 1250 and 1140: MNR ($CDCl_3$:δ) 1.25 (3H, d, J=5.5 Hz, 4-CH_3), 3.00 (1H,dq, J=4.5 and 5.5 Hz, 3-H), 3.26 (1H, d, J=4.5 Hz, 2-H), 3.90 (6H, s, OCH_3), 5.13 (2H, ABq, Δδ=0.97 ppm, J=14 Hz, NCH_2SO_2), 6.93 (3H, br s, N-phenyl protons) and 7.5-8.1 (5H, m, SO_2Ph).
11. Mp 186-187°C (recryn. from ethanol). IR (nujol; cm^{-1}) 3540, 1780, 1510 and 1150. NMR (DMSO-d_6;δ) 0.86 (3H, d, J=6.5 Hz, C-CH_3), 3.45 (1H, dd, J=2 and 3 Hz, 3-H), 3.76 (3H, s, OCH_3), 4.00 (1H, m, CH_3-CH(OH)), 5.10 (1H, d, J=5 Hz, OH), 5.77 (1H, d, J=2 Hz, 4-H), 7.08

(4H, A_2B_2q, $\Delta\delta$=0.47 Hz, J=9 Hz, phenyl protons of anisyl group) and 7.5-8.0 (5H, m, SO_2Ph).

12. Mp 114°C (recryn. from ethanol). IR (nujol; cm^{-1}) 3520, 1770, 1515, 1250 and 1150. NMR ($CDCl_3$;δ) 1.17 (3H, d, J=6.5 Hz, C-CH_3), 2.94 (1H, br d, J=4 Hz, OH), 3.43 (1H, dd, J=2 and 3.5 Hz, 3-H), 3.73 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.22 (1H, m, CH_3-C<u>H</u>(OH)), 5.31 (1H, d, J=2 Hz, 4-H), 6.55-6.90 (3H, m, N-phenyl protons) and 7.25-7.85 (5H, m, SO_2Ph).
13. Amorphous powder. IR (KBr; cm^{-1}) 3360, 1770, 1520 and 1250. NMR ($CDCl_3$;δ) 1.51 (3H, d, J=6.5 Hz, C-CH_3), 2.50 (1H, br s, OH), 3.74 (3H, s, OCH_3), 3.81 (1H, dd, J=4 and 6 Hz, 3-H), 4.82 (1H, m, CH_3-C<u>H</u>(OH)), 5.32 (1H, d, J=6 Hz, 4-H) and 6.45-7.9 (9H, m, phenyl protons).
14. Mp 85-86°C (recryn. from ethanol). IR (nujol; cm^{-1}) 1775, 1510, 1250 and 1150.
15. Syrup. IR (liq. film; cm^{-1}) 1775, 1520 and 1250.
16. Recently, N-deanisylaiton of azetidin-2-ones by ceric ammonium nitrate (CAN) was reported by D. R. Kronenthal, C. Y. Han and M. K. Taylor, J. Org. Chem., <u>47</u>, 2765 (1982). In our case CAN did not work as deprotection reagent on <u>11a</u>.
17. Syrup. IR (liq. film; cm^{-1}) 3280, 1785, 1320, 1305 and 1150. $(\alpha)_D^{25}$-15.8° ($CHCl_3$, c6.5). NMR ($CDCl_3$;δ) 1.15 (3H, d, J=6.5 Hz, C-CH_3), 3.28 (3H, s, $OCH_2O\underline{CH_3}$), 3.50 (1H, dd, J=2 and 3 Hz, 3-H), 4.12 (1H, dq, J=3 and 6.5 Hz, CH_3-C<u>H</u>(OCH_2OCH_3)), 4,57 (2H, s, $O\underline{CH_2}OCH_3$), 4.78 (1H, d, J=2 Hz, 4-H), 7.05 (1H, br s, NH) and 7.5-8.1 (5H, m, SO_2Ph).
18. Powder. IR (KBr; cm^{-1}) 1690, 1510 and 1250. NMR showed a mixture of the sulfoxide diastereoisomers. NMR ($CDCl_3$;δ) main isomer; 1.45 (3H, d, J=5.5 Hz, 4-CH_3), 3.07 (1H, dq, J=4.5 and 5.5 Hz, 3-CH), 3.34 (1H, d, J=4.5 Hz, 2-CH), 3.83 (3H, s, OCH_3). 4.73 (2H, ABq, $\Delta\delta$=0.9 ppm, J=12 Hz, NCH_2SO_2) and 6.8-8.0 (9H, m, phenyl protons): minor isomer: 1.39 (3H, d, J=5.5 Hz, 4-CH_3).
19. Syrup. IR (liq. film; cm^{-1}) 3400, 1745, 1515 and 1250. NMR ($CDCl_3$; δ) 4R isomer; 1.35 (3H, d, J=6.5 Hz, C-CH_3), 2.50 (1H, br s, OH), 3.07 (1H, dd, J=2 and 5 Hz, 3-H), 3.82 (3H, s, OCH_3), 4.0-4.5 (1H, m, CH_3-C<u>H</u>(OH)), 5.07 (1H, d, J=2 Hz, 4-H) and 6.6-7.6 (9H, m, phenyl protons): 4S isomer ; 1.51 (3H, d, J=6.5 Hz, C-CH_3), 2.50 (1H, br s, OH), 3.62 (1H, dd, J=5 and 5 Hz, 3-H), 3.80 (3H, s, OCH_3), 4.0-4.5 (1H, m, CH_3-C<u>H</u>(OH)), 5.38 (1H, d, J=5 Hz, 4-H) and 6.6-7.5 (9H, m, phenyl protons).
20. Less polar isomer: mp 182°C; IR (KBr; cm^{-1}) 3360, 1770, 1520 and 1250. NMR (DMSO-d_6; δ) 0.15 (3H, d, J=6.5 Hz, C-CH_3), 3.40 (1H, dd, J=2 and 2.5 Hz, 3-H), 3.78 (3H, s, OCH_3), 3.96 (1H, m,CH_3C<u>H</u>(OH)), 4.95 (1H, d, J=4.5 Hz, OH), 5.33 (1H, d, J=2 Hz, 4-H) and 7.2-8.0 (9H, m, phenyl protons). More polar isomer: powder; IR (KBr; cm^{-1}) 3360, 1770, 1520 and 1250: NMR (DMSO-d_6; δ) 0.70 (3H, d, J=6.5 Hz, C-CH_3) 3.27 (1H, dd, J=2 and 3.5 Hz, 3-H), 3.72 (3H, s, OCH_3), 3.95 (1H, m, CH_3C<u>H</u>(OH)), 5.00 (1H, d, J=5.5 Hz, OH), 5.38 (1H, d, J=2 Hz, 4-H) and 7.08-7.8 (9H, m, phenyl protons).

(Received in Japan 29 December 1982)