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THE EFFICIENT SYNTHESIS OF CHIRAL KEY INTERMEDIATES FOR MONOBACTAM ANTIBIOTICS

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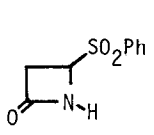
Summary: *Chemical asymmetric syntheses of the key intermediates (4,6,8) for the synthesis of monobactam antibiotics (SQ 26776 (azthreonam), sulfazecin, and SQ 26180) are accomplished from (±)-4-phenylsulfonyl-2-azetidinone.*

Recently much attention have been focused on the nonclassical β-lactam antibiotics, particularly carbapenem[1] and monobactam[2] antibiotics, because of their significant potency for the antibacterial activity. In the course of our synthetic studies on the β-lactam antibiotics, we have established the simple asymmetric synthesis of (+)-4-phenylthio-2-azetidinone ((+)-2) from (±)-4-phenylsulfonyl-2-azetidinone (1) as well as the formal total synthesis of (+)-thienamycin.[3] In this communication, we wish to report the simple and efficient synthesis of the chiral key intermediates (4,6,8) for the synthesis of monobactam antibiotics.

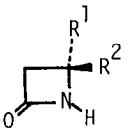
An introduction of the required functionalities at the C(3) position of a β-lactam ring would be carried out in a stereospecific trans manner by using the optically active 4-phenylthio--2-azetidinone (2). After functionalization at C(3), the phenylthio group at C(4) can be removed by reduction, and it also can serve as a suitable leaving group for stereospecific alkylation at C(4) by appling the chiral functionality at C(3). Thus, the phenylthio group of 2 is expected to work as an anchor in the transfer of the chirality. Firstly, the synthesis of the possible intermediate (4) for the synthesis of SQ 26776 (3), which is a synthetic monobactam antibiotic developed by Squibb group,[2b,2c,2d] was attempted.

Since the intermediate (4) has an amino group with β-configuration at C(3), it is required to use (4S)-4-phenylthio-2-azetidinone ((-)-2) as a starting material. (-)-2 was effectively synthesized from (±)-1 by the similar reaction used to the synthesis of (+)-2. Namely, treatment of (±)-1 with thiophenol (1.2 equiv) in the presence of cinchonine (1.2 equiv) in benzene (190 ml/g) at 33±2°C under an argon atmosphere for 150 hrs afforded (-)-2, $[\alpha]_D^{25}$-63.0° (c=1.03, $CHCl_3$), in 97% yield.[4] Repeated recrystallization from ether-n-hexane gave the essentially optically pure (-)-2, $[\alpha]_D^{25}$-134.6°(c=1.21, $CHCl_3$),[5] in ca. 30% yield from 1. With optically pure (-)-2 in hand, it was necessary to introduce the other functional groups. After the N-silyl protection of (-)-2, the lithium enolate of 9 was reacted with 2-naphthalenesulfonyl azide to give the stereochemically pure azide (10)[6,7] in 66% yield from 2, which was reduced to the amine (11) by exposure with hydrogen sulfide.[8] Because of its instability, 11 was directly acylated by treatment with benzyloxycarbonyl chloride to afford the protected product (12).[6] Then 12 was converted to the sulfone (13) by the desilylation, followed by mCPBA oxidation in 61% yield from 10. Finally, treatment of 13 with lithium dimethylcuprate gave the desired 4[6] stereospecifically in 92% yield. Thus, the conversion of (-)-2 to 4 in 7 steps was accomplished in 38% overall yield.

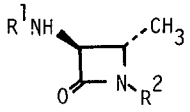
Scheme I

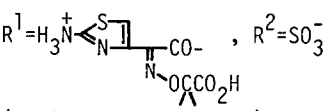


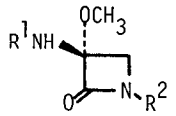
(±)-1



(+)-2: R^1=H, R^2=SPh (4R)
(-)-2: R^1=SPh, R^2=H (4S)

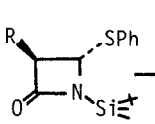
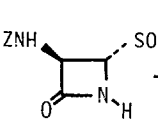


3: R^1=  , R^2=SO_3^-
(SQ 26776, Azthreonam)
4: R^1=Z, R^2=H



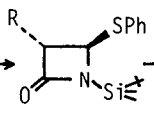
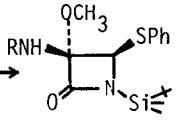
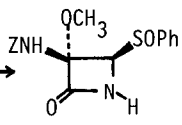
5: R^1=γ-D-Glu-D-Ala, R^2=SO_3H (Sulfazecin)
6: R^1=Z, R^2=H
7: R^1=CH_3CO-, R^2=SO_3H (SQ 26180)
8: R^1=CH_3CO-, R^2=$Si(Me)_2{}^tBu$

Z=-$\overset{O}{\overset{\|}{C}}OCH_2Ph$

(-)-2 —a,b,c,d→  —e,f→  —g→ 4

9: R=H
10: R=N_3
11: R=NH_2
12: R=NHZ

13

(+)-2 —a,b,c,d or h→  —i→  —e,j→ 

14: R=H
15: R=NHZ
16: R=$NHCOCH_3$

17: R=Z
18: R=CH_3CO-

↓l

8

19

↓k

6

a) ^{t}Bu$(Me)_2$SiCl, DMF, Et_3N. b) LDA, 2-naphthalenesulfonyl azide, $(Me)_3$SiCl. c) H_2S, Et_3N, CH_2Cl_2, 0°C. d) $PhCH_2OCOCl$, $NaHCO_3$. e) 10% HCl, MeOH. f) m-CPBA (3 equiv). g) Me_2CuLi (2.4 equiv), THF, -73°C for 15 min, then 0°C for 2.7 hrs. h) Ac_2O, $NaHCO_3$. i) 1) LiOMe (1.3 equiv), MeOH-THF, 2) ^{t}BuOCl (1.5 equiv), 3) LiOMe (1.3 equiv) in MeOH-THF at -73°C. j) m-CPBA (1.5 equiv), CH_2Cl_2, -73°C. k) n-Bu_3SnH (9 equiv), AIBN (azobis-(isobutyronitrile)), PhH, reflux for 5 min. l) Raney-Ni, EtOH, reflux for 9 min.

Then we turned our attention to the synthesis of the methoxylated monobactams (5 and 7). Similarly, in this synthesis amination and successive methoxylation to the C(3) position of (+)-2 are required in a stereospecific trans manner. The optically pure (+)-2, $[\alpha]_D^{25}$+134.2° (c=0.95, $CHCl_3$),[5] was converted to 15 according to the same method as used for the synthesis of 12. Then 15 was subjected to the methoxylation reaction. The careful addition of a small excess of reagents to a THF solution of 15 at -73°C under the conditions as shown in Scheme I provided the methoxlated derivative (17)[6] in 92% yield.[9] The addition of a large excess of base or the reaction at elevated temperature resulted in the decrease of the yield. Attempts to remove the phenylthio group of 17 by using Raney nickel caused the reductive cleavage of a benzyloxycarbonyl group and no desired product was obtained. Consequently, the desired compound (6)[6] could be obtained by reduction of the sulfoxide (19) derived from 17 with n-Bu_3SnH in 53% yield from 17. The structural identity of 6 was confirmed by comparison with the reported spectral data (IR, NMR, and $[\alpha]_D$).[2f]

Likewise, the key intermediate (8) for the synthesis of SQ 26180 (7)[3] was synthesized too. Namely, (+)-2 was converted to 16[6] as described above in 56% yield from 2. The methoxylation of 16 (66% yield) and following desulfurization with Raney nickel (48% yield) gave 8,[6] which can be convertible to SQ 26180 by the desilylation followed by sulfonation.[2i]

Thus, we could accomplish the synthesis of the intermediates (4,6,8) by employing chemical asymmetric reaction. Since the transformations of these synthetic intermediates to monobactam antibiotics such as SQ 26776 (azthreonam),[2b] sulfazecin,[2f] and SQ 26180[2c] can be highly possible, the new routes for the total syntheses of these monobactam in chiral form could be developed efficiently. In addition, it should be noteworthy that both enantiomers ((+)-2 and (-)-2) are especially useful as chiral synthon for the synthesis of β-lactam antibiotics.

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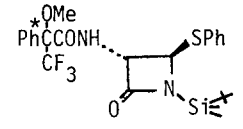
4) Chinchona alkaloid catalyzed asymmetric addition of aromatic thiols to cycloalkenones is reported. In this reaction, an opposite enantiomer is obtained by using chinchonine in spite of cinchonidine. See H.Hiemstra and H.Wynberg, J. Am. Chem. Soc., 103, 417 (1981).

5) In the previous paper,[3b] we reported $[\alpha]_D^{25}$+105.1° for the pure (+)-2. However, as a result of careful purification, we obtained $[\alpha]_D^{25}$+134.2° (c=0.98, $CHCl_3$). The purity of this enantiomer was confirmed by means of HPLC analysis for the N-acyl derivative (i). For this analysis, see J.A.Dale, D.A.Dull, and H.S.Mosher, J. Org. Chem., 34, 2543 (1969).



i

6) Selected physical data are as follows: 4; mp. 91-93°C, $[\alpha]_D^{25}$-18.8° (c=1.33, $CHCl_3$), IR($CHCl_3$) 1760, 1720 cm^{-1}, NMR($CDCl_3$) δ7.34 (s,5H), 6.28 (br s,1H), 5.77 (br d,1H,J=7.0 Hz), 5.13 (s,2H), 4.31 (dd,1H,J=7.0 and 2.0 Hz), 3.71 (dq,1H,J=2.0 and 6.0 Hz), 1.39 (d,3H,J=6.0 Hz). 6; $[\alpha]_D^{25}$+62.5° (c=0.48, CH_3OH), (Lit. 2f, $[\alpha]_D^{25}$+68.2° (c=1, CH_3OH)), IR($CHCl_3$) 1770, 1725 cm^{-1}, NMR($CDCl_3$) δ7.39 (s,5H), 6.03 (br s, 2H), 5.18 (s,2H), 3.78 (AB q, 2H,J=7.0 Hz), 3.52 (s,3H). 8; $[\alpha]_D^{25}$+95.3° (c=1.07, $CHCl_3$), IR($CHCl_3$) 1735, 1688 cm^{-1}, NMR($CDCl_3$) δ7.77 (br s,1H), 3.75 (AB q,2H,J=7.2 Hz), 3.48 (s,3H), 2.09 (s,3H), 0.97 (s,9H), 0.26 (s,6H). 10; $[\alpha]_D^{25}$+66.4° (c=1.40, $CHCl_3$), IR(neat) 2100, 1755 cm^{-1}, NMR($CDCl_3$) δ7.38 (m,5H), 4.72 (d,1H,J=2.0 Hz), 4.51 (d,1H,J=2.0 Hz), 1.00 (s,9H), 0.34 (s,6H). 12; IR($CHCl_3$) 1750, 1725 cm^{-1}, NMR($CDCl_3$) δ5.61 (d,1H,J=8.0 Hz), 5.11 (S,2H), 5.02 (br s,1H), 4.53 (dd,1H,J=8.0 and 2.5 Hz). 16; IR($CHCl_3$) 1750, 1680 cm^{-1}, NMR($CDCl_3$) δ6.70 (br d,1H,J=8.0 Hz), 5.17 (d,1H,J=2.3 Hz), 4.45 (dd,1H,J=8.0 and 2.3 Hz). 17; $[\alpha]_D^{25}$-148.5° (c=1.17, $CHCl_3$), IR($CHCl_3$) 1750, 1580 cm^{-1}, NMR($CDCl_3$) δ5.61 (br s,1H), 5.19 (s,2H), 4.95 (s,1H), 3.57 (s,3H). 18; $[\alpha]_D^{25}$-150.4° (c=0.61, $CHCl_3$), IR($CHCl_3$) 1759, 1680 cm^{-1}, NMR($CDCl_3$) δ6.54 (br s,1H), 4.99 (s,1H), 3.60 (s,3H), 2.15 (s,3H).

7) Azidation was carried out by employing the method reported by Kühlen and Jensen with slight modification (see K.Kühlen and H.Jensen, Liebigs Ann. Chem., 1974, 369). The addition of the enolate of 9 to a cooled THF solution of 2-naphthalenesulfonyl azide improved the yield significantly. For the synthesis of 2-naphthalenesulfonyl azide, see G.G.Hazen, L.M.Weinstock, R.Connell, and F.W.Bollinger, Synth. Commun., 11, 947 (1981).

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