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STEREOCONTROLLED SYNTHESES OF CHIRAL INTERMEDIATES OF THIENAMYCIN FROM THREONINES

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Summary: Both stereospecific and stereoselective syntheses of thienamycin intermediates which have the correct configurations at the three contiguous chiral centers are reported.

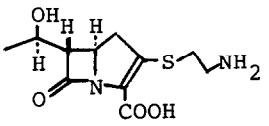
Thienamycin (1) isolated by Kahan et al[1] is a β-lactam antibiotic and exhibits broad antibiotic activity. A stereocontrolled total synthesis of (+)-thienamycin starting from L-aspartic acid has already been reported by the Merck research group.[2] We now report two other stereocontrolled syntheses of chiral thienamycin intermediates starting from D-allo- and L-threonine. Both routes are closely related to the content of our previous report[3] with regard to the β-lactam ring formation as a key reaction.

D-allo-threonine (2)[4] was converted to (2R,3R)-2-bromo-3-hydroxybutyric acid (3) with retention of the configuration[5] which was further transformed to (2R,3R)-2-bromo-3-acetoxybutyryl chloride (4).[3] Reaction of 4 with diethyl dimethoxybenzylaminomalonate (5)[6] in the presence of Et_3N in THF at 15°C gave the amide (6, 95% yield). Cyclization of 6 with DBU in benzene at 20°C for 15 h proceeded with inversion of the configuration at the carbon connected with bromine atom to give a β-lactam (7) as an oil, $[\alpha]_D^{24}$=+39.5° (c=2.03, EtOH), in 96% yield. Hydrolysis of 7 with 1 eq of 1N-aq NaOH-pyridine (2:1) afforded the monoacid (8)[7] as foam in 62% yield. Decarboxylation of 8 with 2,4,6-collidine at 160°C for 45 min, and following saponification of the ethyl ester and acetoxy group with 2.1 eq of 1N NaOH-pyridine (2:1) at 20°C for 15 h produced a mixture of two isomeric acids which was treated with catalitic amount of conc HCl in THF to give lactone (9, 62% yield), mp 87-89°C, $[\alpha]_D^{24}$=-65.9° (c=2.00, EtOH) from cis hydroxy carboxylic acid, stereoselectively, and carboxylic acid (10, 14% yield). Grignard reaction of 9 with 1.8 eq of MeMgBr in THF at -78°C for 30 min, and following silylation of an equilibrium mixture of hemiketal and keto-alcohol (3:1, from NMR in $CDCl_3$) with t-butyldimethylsilyl chloride and 4-dimethylaminopyridine in DMF gave the keto-silylether (cis-11, 80% yield), $[\alpha]_D^{24}$=-20.7° (c=1.96, EtOH). Dedimethoxybenzylation[8] of cis-11 with 9 eq of $K_2S_2O_8$ and 5 eq of K_2HPO_4 in CH_3CN-H_2O (1:1) under argon atmosphere at 65°C for 45 min afforded the N-deprotected azetidinone (cis-12, 72% yield). Baeyer-Villiger oxidation of the ketone (cis-12) with 5.2 eq of m-chloroperbenzoic acid in $CHCl_3$ at 25°C for 18 h gave an acetoxy azetidinone

(cis-13, quantitative yield), mp 52-53°C, $[\alpha]_D^{24}$=-119.1° (c=2.00, EtOH). Treatment of cis-13 with 2 eq of $PhSO_2Na$ in dioxane-H_2O (1:1) at 100°C for 45 min produced a sulfone (14, 63% yield), mp 166-167°C, $[\alpha]_D^{24}$=-12.4° (c=0.93, $CHCl_3$).

Similarly, the trans carboxylic acid (10) was transformed to 14. After the treatment of 10 with t-butyldimethylsilyl chloride and 4-dimethylaminopyridine in DMF, the acid obtained was converted to the corresponding acid chloride (24) by treatment with $(COCl)_2$ in THF at 25°C for 2 h. The acid chloride was further treated with Me_2Cd in THF at 0°C for 2 h to give the keto-silylether (trans-11, 45% from 10) as an oil. By the same procedure described above, trans-11 was changed to trans-12, mp 72-73°C, in 82% yield, which was also converted to trans-13 (84% yield), mp 101-103°C, $[\alpha]_D^{24}$=+47.9° (c=1.00, $CHCl_3$). Treatment of trans-13 with $PhSO_2Na$ gave 14 in 84% yield. These compounds, cis-13, trans-13 and 14, are useful as intermediates for the syntheses of the penems[9] and the carbapenems.[10] However, D-allo-threonine is more expensive than L-threonine, and this synthetic route cannot avoid passing through the step of decarboxylation, in which a fair amount of trans isomer is produced, resulting in loss of stereospecificity.

We devised an alternative method from L-threonine, in which the construction of the correct configurations at three contiguous chiral centers proceeded stereospecifically. L-threonine (15) was converted to (2S,3R)-2-bromo-3-hydroxybutyric acid (16)[5] with retention of the configuration. Reaction of 16 with t- butyl N-2,4-dimethoxybenzylglycinate in THF at 20°C for 15 min by use of DCC as the condensing agent gave the amide (17, 86% yield). Treatment of 17 with 1 eq of $LiN(SiMe_3)_2$ in THF at 0°C for 15 min yielded the epoxide (18) in the reaction mixture, and without isolation of 18,[11] another 1 eq of $LiN(SiMe_3)_2$ in THF was added at 20°C to give an azetidinone (19, 61% yield) stereospecifically. This reaction (17→18→19) proceeded with double inversion of the configuration at the carbon attached bromine atom. Treatment of 19 with CF_3COOH in CH_2Cl_2 at 25°C for 2 h gave 10 in 77% yield. Protection of the alcohol (19) with t-butyldimethylsilyl chloride and 4-dimethylaminopyridine in DMF at 25°C for 15 h gave the silylether (20, 96% yield) which was reduced with excess $NaBH_4$ in EtOH-H_2O (10:1) at 70°C for 10 h or $LiAlH_4$ in THF at 0°C for 45 min to afford the alcohol (21, 52% and 50% yield, respectively),[12] mp 70.5-71.5°C, $[\alpha]_D^{24}$=-10.0° (c=1.00, $CHCl_3$). Dedimethoxybenzylation of 21 with $K_2S_2O_8$ and K_2HPO_4 at 63°C for 1.5 h gave the N-free azetidinone (22, 60% yield), mp 89-90°C, $[\alpha]_D^{24}$=-14.1° (c=0.625, $CHCl_3$). It should be possible to change 22 to thienamycin by the same procedure as that of the Merck research group.[2] On the other hand, there is another route for thienamycin from 20. Saponification of 20 with 1.1 eq of 1N NaOH-EtOH (1:2) at 50°C for 16 h gave a carboxylic acid (23, 92% yield), and following treatment of 23 with $(COCl)_2$ in THF at 25°C for 2.5 h yielded the acid chloride (24), and successive treatment of 24 with excess ethereal CH_2N_2 gave the diazomethylketone (25, 73% yield). Wolff rearrangement of 25 in $PhCH_2OH$ by irradiation with light



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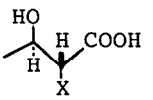

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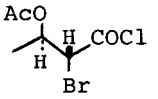
3. X=Br



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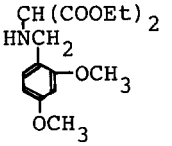

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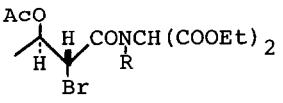

R=2,4-dimethoxybenzyl

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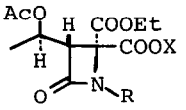
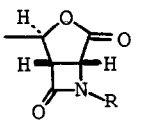


7. X=Et
8. X=H



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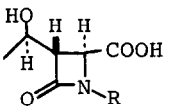

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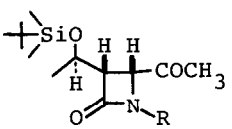
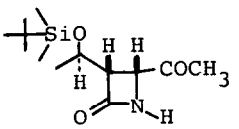
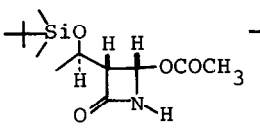


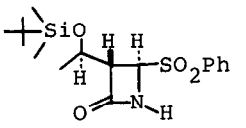
cis-11



cis-12



cis-13



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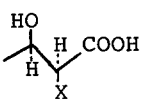
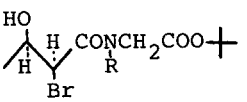
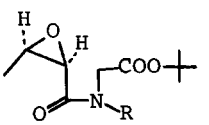


15. X=NH_2
16. X=Br



R=2,4-dimethoxybenzyl

17



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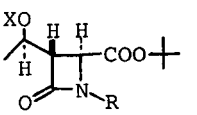
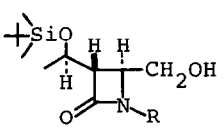


19. X=H
20. X=Si



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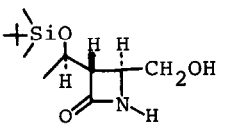

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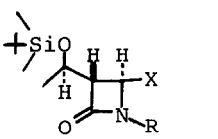
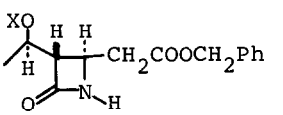


23. X=COOH
24. X=COCl
25. X=$COCHN_2$
26. X=CH_2COOCH_2Ph



27. X=Si
28. X=H

(a high pressure Hg lamp through a pyrex filter) gave the homologated benzylester (26, 46% yield).[13] Treatment of 26 with 10 eq of $K_2S_2O_8$ and 5 eq of K_2HPO_4 in CH_3CN-H_2O (1:1) at 64°C for 1 h effected removal of the N-protecting group to give 27 (51% yield). 27 was further treated with methanolic HCl to afford the O-desilylated 28 (75% yield) which had already been correlated with thienamycin.[2,14]

In the same way, the use of D-threonine and L-allo-threonine as starting materials might make it possible for the enantiomers of these intermediates to be produced. Moreover, considering the utilization of the cis-isomer of 21 obtained from 9 by $NaBH_4$ reduction and that of the epimer of 7 obtained from L- or D-threonine, it should be possible to synthesize all the stereoisomers (8 isomers) of thienamycin in a stereocontrolled manner.

References

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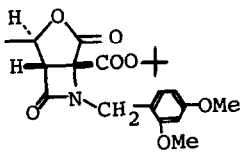
6. 5 was prepared from 2,4-dimethoxybenzaldehyde and diethyl aminomalonate by $NaBH_3CN$ reduction in EtOH.
7. The configuration of 8 was confirmed as follows: t-butyl esterification of the acid part of 8, saponification of both acetoxy and ethyl ester groups, and acidification gave a lactone (i).



(i)

8. W.F. Huffman, K.G. Holden, T.F. Buckley, III, J.G. Gleason, and L. Wu, J. Am. Chem. Soc., 99, 2352 (1977).
9. S. Oida, in 'Recent Advances in the Chemistry of β-Lactam Antibiotics', (2nd International Symposium), ed. G.I. Gregory, Special Publication, The Royal Society of Chemistry, p 330.
10. T. Kobayashi, N. Ishida, and T. Hiraoka, J.C.S. Chem. Comm., 736 (1980).
11. 18 can be easily isolated from the reaction mixture in usual work-up.
12. Reduction of methyl ester, which was obtained from 23, instead of t-butyl ester of 20 gave 21 quantitatively.
13. Irradiation of 25 in MeOH gave a homologated methyl ester in 67% yield.
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