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BASE-INDUCED CYCLIZATION OF (2R,3R)- AND (2S,3R)-N-2,4-DIMETHOXYBENZYL-N-BIS(ETHOXYCARBONYL)METHYL-2-BROMO-3-HYDROXYBUTYLAMIDE

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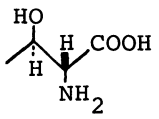
Reaction of (2R,3R)-N-2,4-dimethoxybenzyl-N-bis(ethoxycarbonyl)-methyl-2-bromo-3-hydroxybutylamide (6) with DBU yielded bicyclic β-lactam 7 by a direct cyclization, and its diastereomer 8 and unexpected γ-lactam 9 by another non-direct cyclization. Also (2S,3R)-isomer 19 gave 8 as a sole product. On the other hand, reactions of 6 and 19 with NaH advanced to afford azetidin-2-one derivatives via the corresponding epoxides.

We have proved that both L-threonine and D-allo-threonine are very important chiral synthons for the stereocontrolled synthesis of thienamycin.[1] In this synthetic route the key step is the formation of the azetidin-2-one ring system by cyclization of 2-bromo-3-hydroxybutylamide derivatives. Since we were interested in this type of ring closure and formation of other stereoisomers, we synthesized (2R,3R)- and (2S,3R)-N-2,4-dimethoxybenzyl-N-bis(ethoxycarbonyl)methyl-2-bromo-3-hydroxybutylamide (6 and 19) and investigated the ring closure aptitude of these compounds by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and sodium hydride.

The starting 6 was synthesized as follows. (2R,3R)-2-Bromo-3-hydroxylic acid (2) obtained from (2R,3R)-threonine (D-allo-threonine, 1) was converted to the corresponding tert-butyldimethylsilyl ether (3), which was further treated with oxalyl chloride in THF at 20°C for 16 h to give an acid chloride (4). Treatment of 4 with diethyl N-dimethoxybenzylaminomalonate[2] in THF in the presence of Et_3N gave a tert-butyldimethylsilyl ether (5), quantitatively, mp 90-91°, $[\alpha]_D^{25}$ -18.45° (c=2.0, $CHCl_3$), which was desilylated with EtOH-H_2O-HCl (9:2:1) to give 6 in quantitative yield, mp 74.5-75.5°C, $[\alpha]_D^{24}$ -18.0° (c=2.0, $CHCl_3$).

Treatment of 6 with 2 equiv of DBU in THF at 25°C for 4 h gave three products, bicyclic lactoneazetidinone (7, 74.9%), epimeric bicyclic lactone-azetidinone (8, 12%), and hydroxy-γ-lactam (9, 6.9%). The structure of 7 was confirmed as follows: cyclization of 5 with DBU in THF gave an azetidinone (10, 93%), $[\alpha]_D^{25}$ +28.5° (c=2.55, $CHCl_3$), which was desilylated with EtOH-H_2O-conc HCl (9:2:1) at 25°C to afford 11 (92%), and further treatment of 11 with DBU in THF gave 7 (89%) which was identical in all respects with that obtained from 6. However treatment of 11 with NaH gave only many unknown degradation products. To determine the mechanism for the formation of 8 and 9, another experiment was carried out. Treatment of 6 with 2 equiv[3] of NaH in THF at 0°C for 30 min gave a trans-epoxide (12, 86%). However, a prolonged reaction gave an enone 13[4], $[\alpha]_D^{24}$ -2.7° (c=0.77, EtOH), only in 6.3% yield and many other unknown degradation products. Treatment of 12 with 1 equiv of DBU in THF at 25°C for 6 h afforded two products, 8[5] (59.5%) and 9 (29.8%).[6] It is obvious that the formation of 8 and 9



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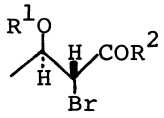
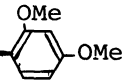
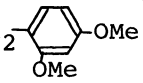


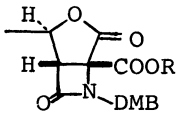
2. R^1=H, R^2=OH

3. R^1=SiBu^{t}Me$_2$, R^2=OH

4. R^1=SiBu^{t}Me$_2$, R^2=Cl

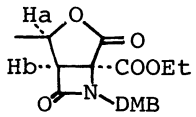
5. R^1=SiBu^{t}Me$_2$, R^2=NCH(COOEt)$_2$CH$_2$ 

6. R^1=H, R^2=NCH(COOEt)$_2$CH$_2$ 



7. R=Et

23. R=H



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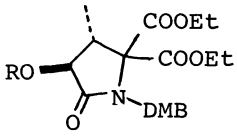
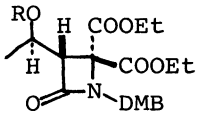


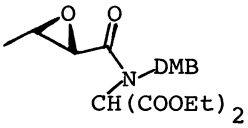
9. R=H

24. R=Ac



10. R=SiBu^{t}Me$_2$

11. R=H



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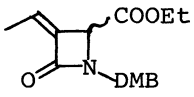

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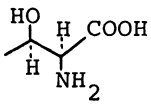

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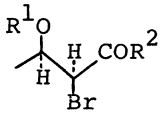
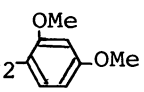
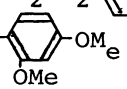


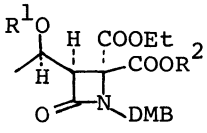
15. R^1=H, R^2=OH

16. R^1=SiBu^{t}Me$_2$, R^2=OH

17. R^1=SiBu^{t}Me$_2$, R^2=Cl

18. R^1=SiBu^{t}Me$_2$, R^2=NCH(COOEt)$_2$CH$_2$ 

19. R^1=H, R^2=NCH (COOEt)$_2$CH$_2$ 



20. R^1=SiBu^{t}Me$_2$, R^2=Et

21. R^1=H, R^2=Et

22. R^1=R^2=H

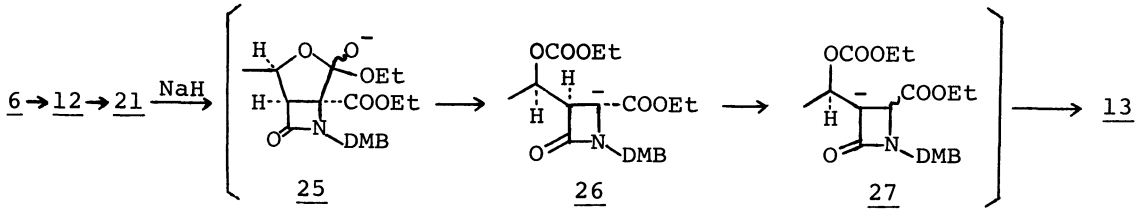
from 1 passes through the trans-epoxide 12. The production of 9 is against Baldwin's ring closure rules.[7]

The structure of 8 was confirmed as follows. (2S,3R)-Threonine (L-threonine, 14) was converted to 18 through 15, 16, and 17 according to the same procedure as (1 → 5). Treatment of 18 with DBU in THF gave an azetidinone (20, 86%). Desilylation of 20 with EtOH-H_2O-conc HCl (9:2:1) at room temperature for 3 h gave 21 (60%), mp 91-92°C, $[\alpha]_D^{24}$ -75.6° (c=0.44, $CHCl_3$). Treatment of 21 with DBU in THF at room temperature gave a lactone (8), which was identical to that obtained from 6. The structure of 8 was further confirmed by the spin-spin coupling constant of ^1H NMR. The dihedral angle between Ha on the lactone ring and bridge head Hb was approximately 5° when measured using a Dreiding molecular model for the lactone (8). The observed coupling constant (J_{HaHb}=7 Hz) supports the configuration of 8 as being correct.

The reaction mechanism for the formation of 13 was inferred on the fact that treatment of 21 with 1.4 equiv of NaH in THF at 20°C for 15 h gave 13 (Z-isomer, 13.9%), $[\alpha]_D^{24}$ -2.8° (c=0.47, EtOH), its geometrical E-isomer (7.5%), and several unknown degradation products. It is reasonable to consider that the 2-bromo-3-hydroxyamide (6) is first changed to 21 via the trans-epoxide (12), and then further converted to 13 through the intermediates 25, 26 and 27. The absolute configuration of 13 is not clear, but it is highly possible that with respect to most of the anion 26, the conversion process to 13 may proceed with retention of the configuration at the C_4 position of 26.

Next on our program, cyclization of (2S,3R)-isomer (19), obtained easily from 18 by desilylation with EtOH-H_2O-conc HCl (9:2:1), by either DBU or NaH was attempted. Treatment of 19 with 2 equiv of DBU in THF at 25°C for 3 h gave 8 as a single product (93.4%). However, treatment of 19 with 3.7 equiv of NaH in THF at room temperature for 16 h gave an acid (23, 75.6%)[8] as a crystalline solid, mp 180-184°C, $[\alpha]_D^{23}$ -77.9°(c=2.00, THF), via a cis-epoxide.

Thus, treatment of 6 with DBU incurs both direct azetidin-2-one formation to give 7 and epoxidation, and then successive ring closure of the resulting epoxide branches off two pathways to give 8 and 9. However, the same procedure of 19 incurs only the direct azetidin-2-one formation reaction, without passing through the epoxide, to give 8. On the other hand, the reaction of both 6 and 19 with NaH proceeds via the corresponding epoxides.



Thus we can obtain the required stereoisomers by use of the reaction of O-protected or nonprotected 2-bromo-3-hydroxybutylamide derivatives or their corresponding epoxides[9] with alkaline metal or tert-amine base.

References

1) M. Shiozaki, N. Ishida, T. Hiraoka and H. Yanagisawa, Tetrahedron Letters, 22, 5205 (1981).
2) M. Shiozaki, N. Ishida and T. Hiraoka, Tetrahedron, in press.
3) When this experiment was carried out with 1 equiv of NaH at 0°C for 30 min, the starting 6 was recovered.
4) Trace amount of E-isomer was detected.
5) A fair amount of 22 was detected, but 22 easily lactonized to 8 in an acidic medium.
6) ^{1}H NMR of the acetate (24) of 9; ($CDCl_3$) δ 1.05 (3H, t, J=7 Hz), 1.18 (3H, d, J=6.5 Hz), 1.20 (3H, t, J=7 Hz), 2.18 (3H, s), 2.99 (1H, dq, J=10, 6.5 Hz), 3.76 (6H, s), 4.04 (2H, q, J=7 Hz), 4.06 (2H, q, J=7 Hz), 4.43, 4.73 (2H, AB-q, J=16 Hz), 5.25 (1H, d, J=10 Hz), 6.31 (1H, d, J=2 Hz), 6.32 (1H, dd, J=2, 9.5 Hz), 6.90 (1H, d, J=9.5 Hz).
7) a) J. E. Baldwin, J. Chem. Soc., Chem. Commun., 734 (1976). b) J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R. C. Thomas, ibid, 736 (1976). c) J. E. Baldwin, ibid, 738 (1976). d) J. E. Baldwin and J. A. Reiss, ibid, 77 (1977). e) J. E. Baldwin and L. I. Kruse, ibid, 233 (1977). f) J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, J. Org. Chem. 42, 3846 (1977).
8) We guess that the production of the acid 23 is due to contamination by a fair amount of NaOH in the used NaH, or that of H_2O in the used solvent or atmospheric moisture.
9) cf) M. S. Manhas, B. B. Shankar, N. N. Bhongle, and A. K. Bose, 4th International Conference on Organic Synthesis (IUPAC), 1982 Tokyo, Japan; Abstracts for Poster Session, p 48.

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