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The asymmetric synthesis of (2*S*,3*R*)-capreomycidine

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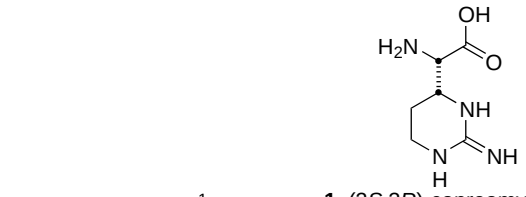
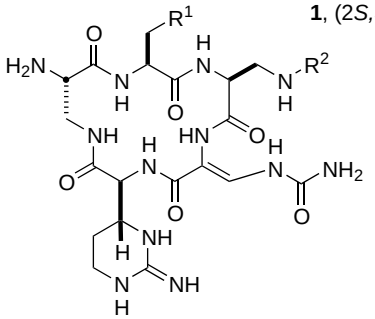
Abstract—An improved asymmetric synthesis of the guanidine-containing amino acid (2*S*,3*R*)-capreomycidine has been achieved in seven steps and 28% overall yield. The key synthetic step involved a Mannich-type reaction between a chiral glycine aluminum enolate and the benzyl-imine of 3-*tert*-butyldimethylsiloxy-propionaldehyde.

Capreomycidine **1** is a non-proteinogenic amino acid that is a constituent of the capreomycins **2a**–**d** and the tuberactinomycins **3a**–**b** (Fig. 1).[1,2] These cyclic pentapeptides are known for their unique tuberculostatic properties. First discovered by Herr et al.[3] in 1960, the capreomycins have recently attracted attention due to their demonstrated effectiveness against resistant strains of *Mycobacterium tuberculosis*.[4]

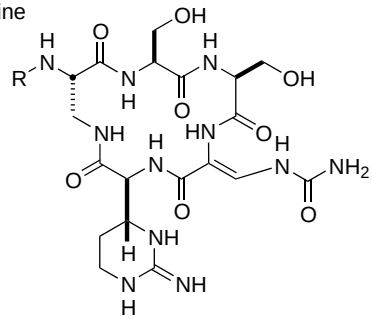
Various derivatives of both the capreomycins and tuberactinomycins have been made by synthetic modifications to the amino acid side chains and peptide backbone of the intact natural product.[5] This was done in order to determine the sectors of the molecule that are important for the expression of biological activity and also to perhaps discover more potent synthetic variants. Some of these derivatives have been shown to



1, (2*S*,3*R*)-capreomycidine



2a: capreomycin IA; R^1=OH, R^2=β-lysine
2b: capreomycin IB; R^1=H, R^2=β-lysine
2c: capreomycin IIA; R^1=OH, R^2=H
2d: capreomycin IIB; R^1=H, R^2=H



3a: tuberactinomycin N; R=γ-hydroxy-β-lysine
3b: tuberactinomycin O; R=β-lysine

Figure 1.

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be effective against other pathogens as well. The capreomycidne moiety contained in the macrocyclic portion of these substances has been shown to be essential for the expression of biological activity.[6]

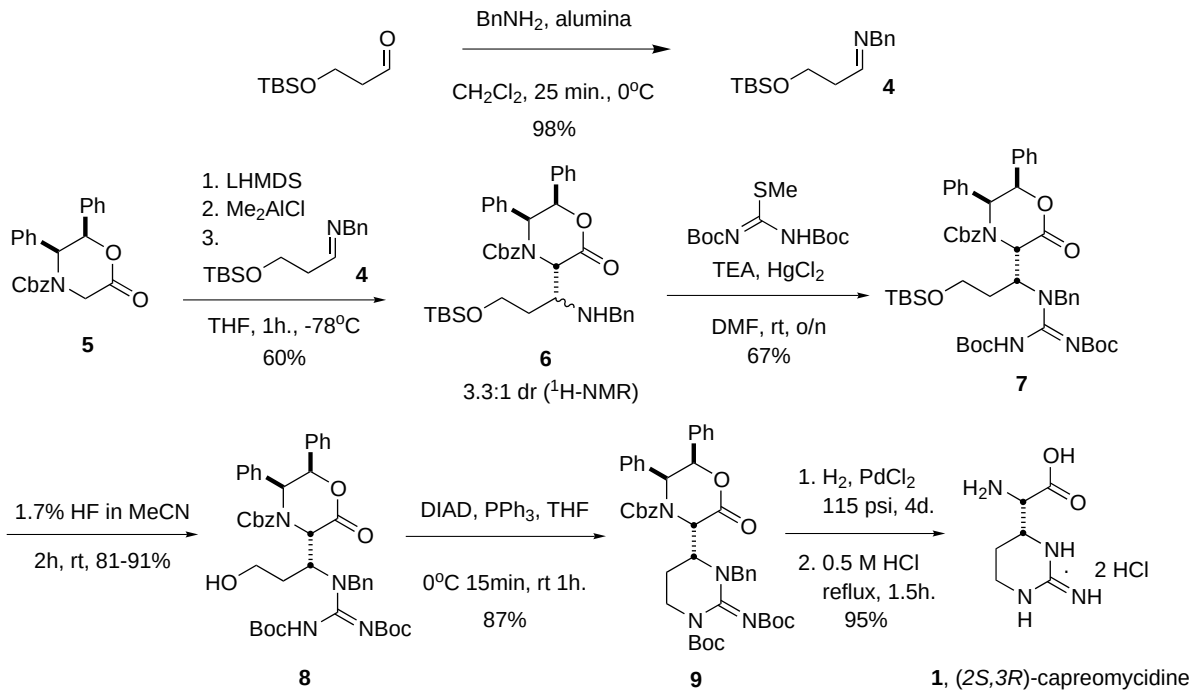
Total syntheses of the capreomycins as well as tuberactinomycin O have been reported by Shiba et al.[1,7] However, the capreomycidine moiety used in these syntheses was obtained not synthetically, but rather semi-synthetically by acid hydrolysis of the natural product.

Syntheses of capreomycidine and its epimer in both racemic and optically active form have previously been reported. Cameron and Bycroft were the first to report a racemic synthesis of both capreomycidine and *epi*-capreomycidine.[8] The desired product was obtained by elaboration of 2-aminopyrimid-4-ylacetate. Fractional recrystallization of picrate salts of the two diastereomers resulted in a tedious isolation of racemic capreomycidine and racemic *epi*-capreomycidine. Shiba and co-workers prepared racemic capreomycidine via a diastereoselective aldol reaction which produced a protected version of β-hydroxyornithine that was further elaborated to the final product.[9] Using a chloroacetylated intermediate in this same synthesis, Shiba enzymatically resolved two enantiomers with an acylase. This allowed for the synthesis of optically pure (2*S*,3*R*)-capreomycidine.[10] In a similar manner, the synthesis of *epi*-capreomycidine was also accomplished.[11]

In order to investigate a broader array of capreomycin derivatives for potential antituberculosis activity, it is desirable to have an effective means of obtaining significant quantities of a suitably protected form of (2*S*,3*R*)-capreomycidine via synthesis rather than by degradation of the natural product. Shiba's synthetic approach to (2*S*,3*R*)-capreomycidine was lengthy and proceeded in a low overall yield (~0.2%). With this as a backdrop, we sought to develop a more efficient synthesis of (2*S*,3*R*)-capreomycidine.

As shown in Scheme 1, treatment of 3-(*tert*-butyldimethylsiloxy)-propionaldehyde with benzylamine on alumina, gave the desired imine **4** in 98% yield.[12,13] Preparation of the lithium enolate of the chiral oxazinone **5** with lithium bis(trimethylsilyl)amide, followed by transmetallation with dimethylaluminum chloride, resulted in the formation of the corresponding aluminum enolate.[14,15] Addition of **4** to the enolate resulted in a 60% yield of the Mannich product **6** as an inseparable mixture of two diastereomers (3.3:1 *dr* by ^{1}H NMR) both arising from the approach of the imine to the face opposite that of the phenyls.

The guanidinylation of Mannich product **6** proved to be a far more challenging step than expected. Treatment of **6** with *N*,*N*′-di-*tert*-butoxycarbonyl-*S*-methylisothiourea and triethylamine in DMF as well as treatment of **6** with Goodman's benzyloxycarbonyl protected triflylguanidine reagent resulted in no reaction.[16,17] Subjecting **6** to a combination of *N*,*N*′-di-*tert*-butoxycarbonylthiourea, mercuric chloride and triethylamine in DMF according to the protocol described by Kim et al., the desired product **7** was obtained in a modest yield of 50% as a single diastereomer (determined by ^{13}C NMR).[18] It was then decided to determine what effect switching from *N*,*N*′-di-*tert*-butoxycarbonylthiourea to the corresponding *N*,*N*′-di-*tert*-butoxycarbonyl-*S*-methylisothiourea might have on the guanidinylation yield. This approach, also recently reported by Cammidge and co-workers, resulted in an improved 67% yield of the desired



Scheme 1.

guanidine **7**.[19] Judging from the analysis of recovered starting material, the guanidinylation only occurs with the major diastereomer of Mannich product **6**, therefore explaining the moderate yield and single product from this reaction.

Removal of the *tert*-butyldimethylsilyl protecting group from **7** with 1.7% aqueous HF in acetonitrile provided the primary alcohol **8** in 81–91% yield. Unfortunately, this cyclization precursor proved unstable to both acid and base. Rapid silica gel purification using Whatman brand silica gel gave satisfactory results. Attempted removal of the TBS group by other means proved unsuccessful.

Using the method described by Dodd and Kozikowski, the cyclic guanidine **9** was formed by treatment of **8** under Mitsunobu conditions in 87% yield.[20] The bicyclic compound **9** was then subjected to hydrogenolysis in 3:1 THF:EtOH using $PdCl_2$ and 115 psi hydrogen gas for 4 days at room temperature. Upon removal of the catalyst by filtration through Celite, and evaporation, the residue was triturated twice with ether. The hydrogenation product was refluxed in 0.5 M aqueous HCl to remove the remaining Boc group and lyophilized to provide the di-hydrochloride salt of capreomycidine **1** in 95% yield from **9**. Neutralization with ammonium hydroxide, followed by desalting via Dowex 50WX2-100 cationic exchange resin (product eluted with 1.5% NH_4OH) provided the free amino acid. Spiking of this free amino acid with ammonium acetate provided our synthetic capreomycidine in a form that was identical to the form of the natural capreomycidine obtained from Oregon State University and resulted in proton and carbon spectra that matched the natural sample. Upon synthesis of the enantiomer of natural capreomycidine in similar yield from the antipode of **5**, the α-amines of both (2*S*,3*R*)- and (2*R*,3*S*)-capreomycidine were protected as the corresponding benzyl carbamates. Chiral HPLC analysis of these enantiomeric carbamates showed that our synthetic capreomycidine possessed an *er* of 99.2:0.8 (>99% ee).[21] The optical rotations of the synthetic and natural mono-HCl salts of capreomycidine were also agreeable (synthetic: $[M]_D^{20} = +28.2$ ($c = 0.75$, H_2O); natural: $[M]_D^{20} = +32.5$ ($c \sim 0.75$, H_2O)).[22,23]

Since the desired (2*S*,3*R*)-capreomycidine was obtained from the major diastereomer of **6**, one can infer that the major diastereomer of **6** was of the (2*S*,3*R*)-configuration. This can be explained by a Zimmerman–Traxler 'chair' transition state between the *E*-enolate and the *E*-imine.

In summary, we have employed a novel and moderately diastereoselective Mannich-type reaction with the chiral glycine template **5** as a key step in the asymmetric synthesis of (2*S*,3*R*)-capreomycidine. The synthesis recorded here proceeds in six steps with an overall yield of 28%. Application of this methodology to the total synthesis of capreomycin and derivatives is currently under study in these laboratories.

Acknowledgements

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References

1. Nomoto, S.; Teshima, T.; Wakamiya, T.; Shiba, T. *Tetrahedron* **1978**, *34*, 921.
2. Yoshioka, H.; Aoki, T.; Goko, H.; Nakatsu, K.; Noda, T.; Sakakibara, H.; Take, T.; Nagata, A.; Abe, J. *Tetrahedron Lett*. **1971**, *23*, 2043–2046.
3. Herr, Jr., E. B.; Haney, M. E.; Pittenger, G. E.; Higgens, C. E. *Proc. Ind. Acad. Sci*. **1960**, *69*, 134.
4. Rastogi, N.; Labrousse, V.; Goh, K. S. *Curr. Microbiol*. **1996**, *33*, 167.
5. (a) Dirlam, J. P.; Belton, A. M.; Birsner, N. C.; Brooks, R. R.; Chang, S.-P. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 1139–1144; (b) Linde, II, R. G.; Birsner, N. C.; Chandrasekaran, R. Y.; Clancy, J.; Howe, R. J. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 1149–1152; (c) Wakamiya, T.; Teshima, T.; Sakakibara, H.; Kiyoshi, F.; Shiba, T. *Bull. Chem. Soc. Jpn*. **1977**, *50*, 1984–1989.
6. (a) Wank, H.; Rogers, J.; Davies, J.; Schroeder, R. *J. Mol. Biol*. **1994**, *236*, 1001; (b) Yarus, M. *Science* **1988**, *240*, 1751; (c) von Ahsen, U.; Schroeder, R. *Nucl. Acids Res*. **1991**, *19*, 2261.
7. Teshima, T.; Nomoto, S.; Wakamiya, T.; Shiba, T. *Tetrahedron Lett*. **1976**, 2343–2346.
8. Bycroft, B. W.; Cameron, D.; Johnson, A. W. *J. Chem. Soc. (C)* **1971**, 3040.
9. Wakamiya, T.; Katsutoshi, M.; Tatsuzo, U.; Teshima, T.; Shiba, T. *Bull. Chem. Soc. Jpn*. **1978**, *51*, 850–854.
10. Shiba, T.; Ukita, T.; Mizuno, K.; Teshima, T.; Wakamiya, T. *Tetrahedron Lett*. **1977**, 2681–2684.
11. Teshima, T.; Konishi, K.; Shiba, T. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 508–511.
12. (a) Kozikowski, A. P.; Stein, P. D. *J. Org. Chem*. **1984**, *49*, 2301–2309; (b) Pirrung, M. C.; Webster, N. J. G. *J. Org. Chem*. **1987**, *52*, 3603–3613.
13. Texier-Boullet, F. *Synthesis* **1985**, 679–681.
14. Lactones **5** are commercially available from Aldrich Chemical Co.: **5**: catalog #33187-2 (CAS Registry #100516-54-9); the antipode of **5**: catalog #33185-6 (CAS Registry #105228-46-4).
15. (a) Wada, M.; Aiura, H.; Akiba, K. *Tetrahedron Lett*. **1987**, *28*, 3377–3380; (b) Iwasaki, G.; Shibasaki, M. *Tetrahedron Lett*. **1987**, *28*, 3257–3260.
16. (a) Yuan, C.; Williams, R. M. *Tetrahedron Lett*. **1996**, *37*, 1945–1948; (b) Tian, Z.; Edwards, P.; Roeske, R. W. *Int. J. Peptide Protein Res*. **1992**, *40*, 119–126.
17. Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem*. **1998**, *63*, 3804–3805.
18. (a) Kim, K. S.; Qian, L. *Tetrahedron Lett*. **1993**, *34*, 7677–7680; (b) Iwanowicz, E. J.; Poss, M. A.; Lin, J. *Synth. Commun*. **1993**, *23*, 1443–1445.
19. Guo, Z.-X.; Cammidge, A. N.; Horwell, D. C. *Synth. Commun*. **2000**, *30*, 2933–2943.

20. Dodd, D. S.; Kozikowski, A. P. *Tetrahedron Lett*. **1994**, *35*, 977–980.
21. Enantiomeric ratios were determined using a Daicel Crownpak CR chiral HPLC column (pH 2 aqueous perchloric acid, 1.6 mL/min, UV detection at 205 nm). Retention times: (2*S*,3*R*)-capreomycidine: 21.22 min; (2*R*,3*S*)-capreomycidine: 31.95 min.
22. The mono-HCl salt of capreomycidine was prepared by recrystallization of the di-HCl salt from methanol/pyridine/ethanol (1st crop: 50%).
23. (a) Tatsuta, K.; Mikami, N.; Fujimoto, K.; Umezawa, S. *J. Antibiot*. **1973**, *26*, 625–646; (b) In this report, the optical rotation was reported as a molar optical rotation; the molar optical rotation is defined as: $[M]_D^{20} = [\alpha]_D^{20} \times MW/100$.