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Synthesis of L-*epi*-Capreomycidine Derivatives via C–H Amination

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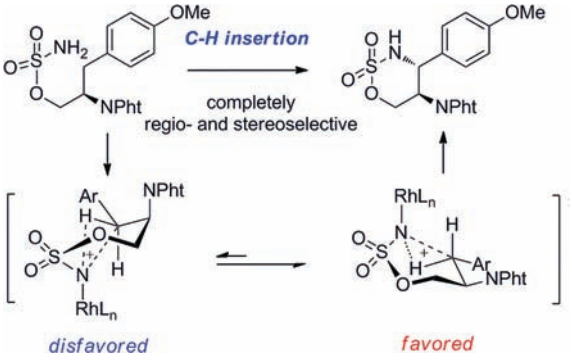
ABSTRACT



The L-*epi*-capreomycidine (Cpm) derivatives were efficiently and stereoselectively synthesized via nitrene C–H insertion starting from a readily available D-Tyr. Design of a substrate that takes into account hydrogen bonding is a critical feature in order to achieve high selectivity. Our synthetic strategy could be a new access to *epi*-Cpm and its derivatives, which are found in several biologically active natural products.

The muraymycins (MRYs) (Figure 1), isolated from a culture broth of *Streptomyces sp.*,[1] are members of a class of naturally occurring 6′-*N*-alkyl-5′-β-*O*-aminoribosyl-*C*-glycyluridine antibiotics.[2] The MRYs having a lipophilic side chain have been shown to exhibit excellent antimicrobial activity against Gram-positive bacteria. In particular, the efficacy of the MRYs in *S. aureus* infected mice represents a promising lead for the development of new antibacterial agents. The MRYs involve a cyclic guanidine amino acid, L-*epi*-capreomycidine (Cpm). Most of the previous syntheses of the Cpm class of amino acids were racemic.[3] Although an elegant asymmetric synthesis of L-Cpm has been reported by the Williams group,[4] only a few asymmetric and stereoselective syntheses of its epimer, L-*epi*-Cpm, have been reported.[5] Recently, we accomplished the first total synthesis of MRY D2 (**1**) and its epimer.[6] The L-*epi*-Cpm moiety was synthesized via the nitrene C–H insertion[7] of

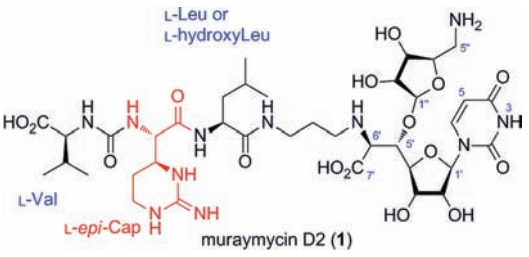


Figure 1. Structures of muraymycin D2.

(1) (a) McDonald, L. A.; Barbieri, L. R.; Carter, G. T.; Lenoy, E.; Lotvin, J.; Petersen, P. J.; Siegel, M. M.; Singh, G.; Williamson, R. T. *J. Am. Chem. Soc.* **2002**, *124*, 10260–10261. (b) Carter, G. T.; Lotvin, J. A.; McDonald, L. A. WO 2002085310 A2.

(2) (a) Ochi, K.; Ezaki, M.; Iwani, M.; Komori, T.; Kohsaka, M. EP-333177, 1989. (b) Yoshida, Y.; Yamanaka, H.; Sakane, K. JP H05–78385, 1993.

(3) (a) Bycroft, B. W.; Cameron, D.; Johson, A. W. *J. Chem. Soc.* **1971**, 3041–3049. (b) Bycroft, B. W.; Cameron, D.; Croft, L. R.; Johson, A. W. *Chem. Commun.* **1968**, 1301–1302. (c) Yamashita, A.; Norton, E. B.; Mansour, T. S. *Synth. Commun.* **2004**, *34*, 795–803.

(4) (a) DeMong, D. E.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 3529–3532. (b) DeMong, D. E.; Williams, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 8561–8565.

(5) Teshima, T.; Konishi, K.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 508–511.

(6) Tanino, T.; Ichikawa, S.; Shiro, M.; Matsuda, A. *J. Org. Chem.* **2010**, *75*, 1366–1377.

(7) For recent reviews, see: (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2903. (b) Davies, H. M. L.; Antoulinakis., E. G. *J. Organomet. Chem.* **2001**, *617–618*, 47–55.

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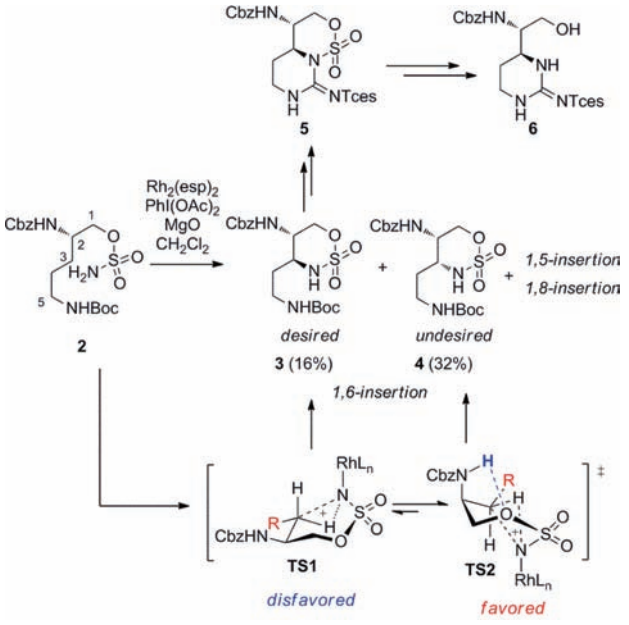
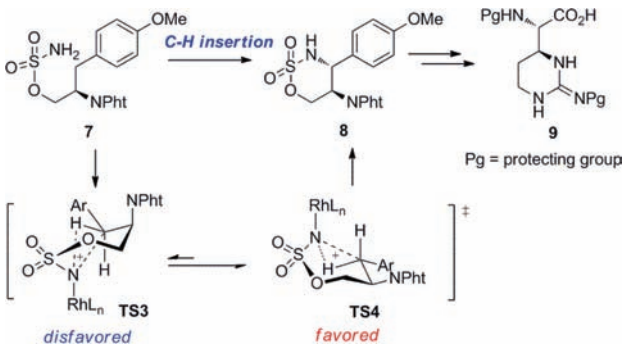
sulfamate **2** with the $Rh_2(esp)_2$ catalyst[8] to form **3**, construction of the cyclic guanidine skeleton **5**, desulfonylation upon acetolysis of the oxathiazinane ring, and hydrolysis of the acetate group providing **6** (Scheme 1). The key nitrene C−H insertion was largely dependent on the nature of the protecting group at both amino groups. Furthermore, the regio- and diastereoselectivity and the yield of the desired cyclic sulfamate **3** were very poor and needed to be improved. In particular, an unexpected reversal of diastereoselectivity was observed, and the undesired cyclic sulfamate **4** was obtained predominantly with the Cbz group as a protecting group for the amine at the 2-position. Thus, it was considered necessary to improve the synthetic route to the L-*epi*-Cpm for investigating further structure−activity relationships of MRYs. Here, we describe the improvement of the synthesis of suitably protected L-*epi*-Cpm derivatives **9**.

Scheme 1. Previous Synthetic Route



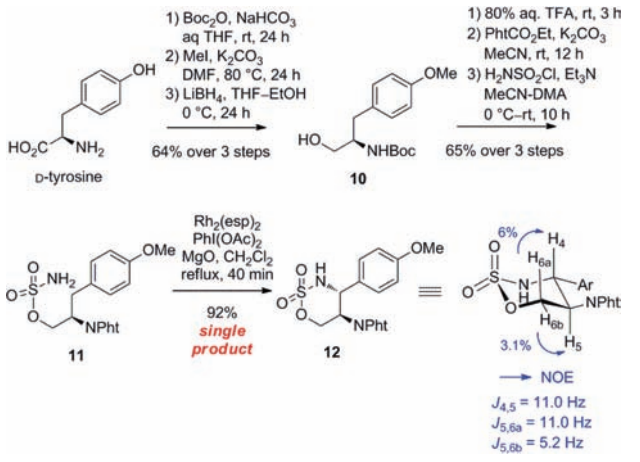
We hypothesized that the reverse stereoselectivity observed in the nitrene C−H insertion of **2** could be attributed to the existence of a free hydrogen atom attached to the nitrogen atom at the 2-position. Namely, the unwanted **TS2** would be expected to be more stable than the desired **TS1** due to formation of an intramolecular hydrogen bond with the oxygen atom attached to the sulfamate group, affording the undesired diastereomer. This being the case, upon removal of the intramolecular hydrogen bonding, the reaction would proceed via **TS2**. With this in mind, we designed an improved synthetic strategy that uses a nitrene C−H insertion as shown in Scheme 2. In order to control the regioselectivity of the nitrene insertion as well as its diastereoselectivity, the C−H moiety to be inserted by the

Scheme 2. Improved Synthetic Route



nitrene was changed to a benzylic position such as **7**, which is generally known to be suitable for C−H insertion. By doing so, the carboxylic acid could be masked as the stable phenyl ring during the synthesis. In the C−H insertion of **7** without the free hydrogen atom on the amino group, the **TS4** with all the substituents oriented in equatorial positions would be more stable vs the **TS3** that would provide the undesired diastereomer. The stereochemical course of this was suggested by Du Bois et al.[9] The synthesis of suitably protected L-*epi*-Cpm derivative **9** was initiated from readily available D-Tyr (Scheme 3).

Scheme 3. C−H Insertion Sulfamate Protected with Phthaloyl Group

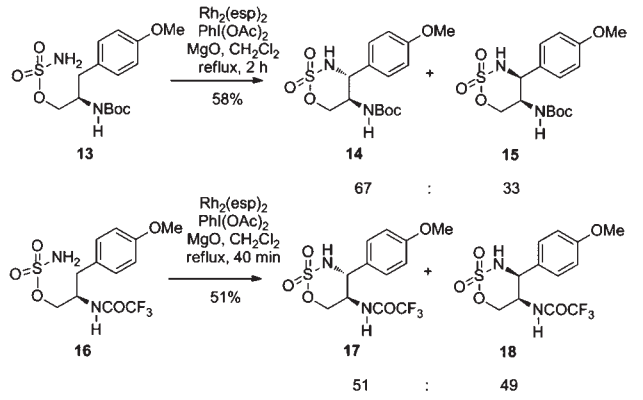


Sequential protection with the Boc and methyl groups followed by reduction with $LiBH_4$ gave **10** in 64% over three steps. After the Boc group was changed to the phthaloyl (Pht) group, the sulfamoyl group was installed to give the sulfamate **11**, the precursor for the nitrene C−H insertion, in 65% yield over three steps. The precursor **11** was treated with 10 mol % of $Rh_2(esp)_2$ in the presence of $PhI(OAc)_2$ and MgO in CH_2Cl_2 at reflux for 40 min, and the desired dioxo-oxathiazinane derivative **12** was obtained

(8) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378–15379.

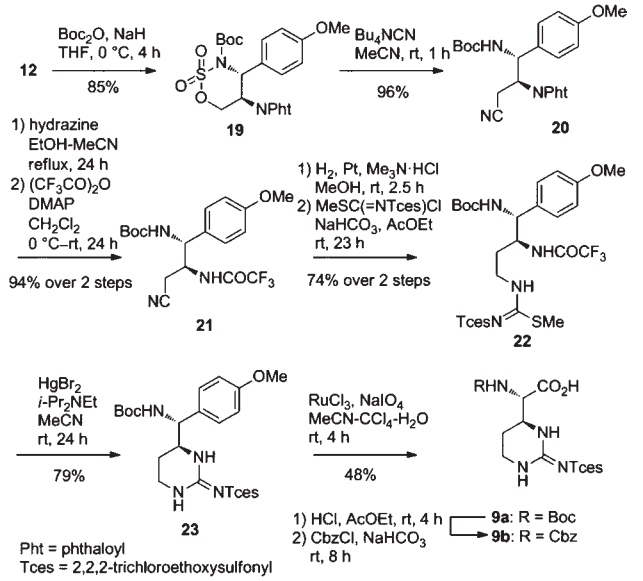
(9) When, P. M.; Lee, J.; Du Bois, J. D. *Org. Lett.* **2003**, *5*, 4823–4826.

Scheme 4. C−H Insertion of Sulfamate with Donor Hydrogen



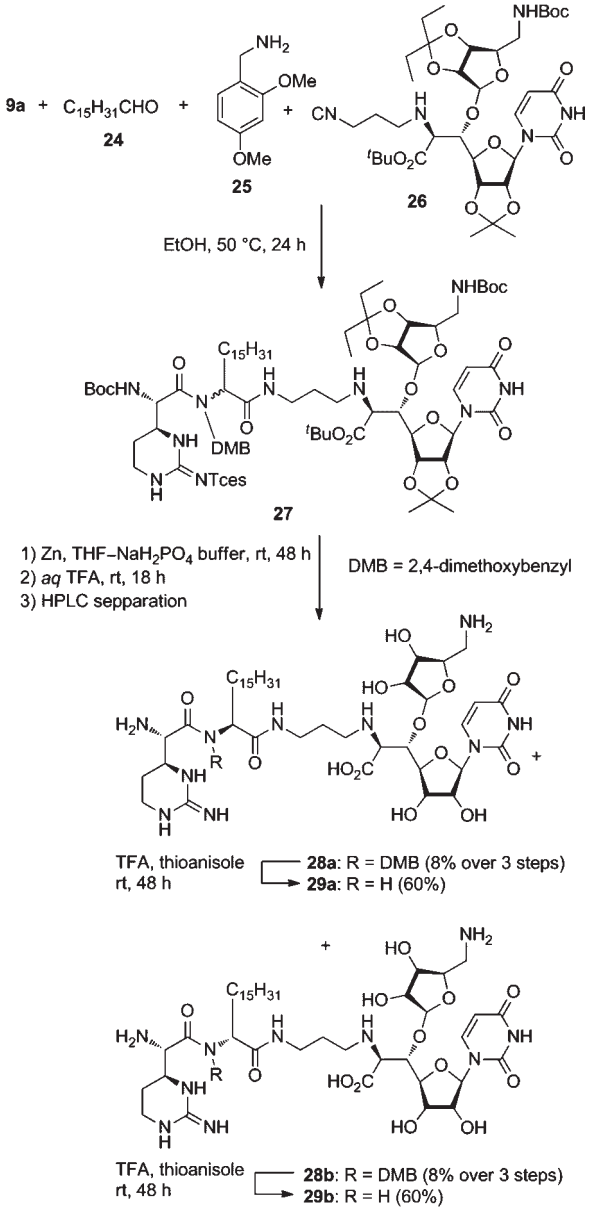
in an excellent yield of 92% as the sole product. Neither the diastereomer of **12** nor the 1,5- or 1,8-insertion product was detected. The structure of **12** was confirmed by several NMR measurements, including COSY and NOE. As expected, complete regio- and diastereoselectivity was achieved. To address the issue of intramolecular hydrogen bonding on the diastereoselectivity, the insertion reaction of the sulfamates protected with the Boc group **13** and the trifluoroacetyl group **16**, which possess a free hydrogen atom, was also investigated (Scheme 4). The C−H insertion of **13** resulted in a significant decrease in diastereoselectivity (**14**:**15** = 67:33). Furthermore, complete loss of selectivity was observed in the reaction of **16** with the more acidic hydrogen atom on the amino group (**17**:**18** = 51:49). These results clearly indicate that intramolecular hydrogen bonding in the transition state affects the diastereoselectivity, as suggested by our previous study. Therefore, the design of a substrate that takes into account hydrogen bonding is a critical feature in order to achieve high selectivity in this particular case of nitrene C−H insertion.

Scheme 5. Synthesis of Protected L-*epi*-Capreomycidines



The nitrogen atom of the dioxo-oxathiazinane ring of **12** was protected with the Boc group to give **19** (Boc_2O, NaH, THF, 85%), which was homologated by Bu_4NCN in MeCN, upon ring-opening of the dioxo-oxathiazinane and desufonylation; it gave **20** in 96% yield (Scheme 5). After protecting group manipulation in **20** (hydrazine, EtOH−MeCN, then $(CF_3CO)_2O$, DMAP, CH_2Cl_2, 94% over two steps), the cyano group of **21** was reduced to the primary amine, and this was converted to the *S*-methylisothiourea **22**, which was protected with the *N*-2,2,2-trichloroethoxysulfonyl (Tces)[10] group in 74% yield over two steps. Treatment of **22** with $HgBr_2$ in the presence of *i*-Pr_2NEt afforded the cyclic guanidine **23**, and the trifluoroacetyl group was also removed in the same step. Finally,

Scheme 6. Synthesis of Truncated Muraymycin Analogues



the methoxyphenyl group of **23** was oxidized to give the carboxylic acid **9a** in 48% yield ($RuCl_3$, $NaIO_4$, $MeCN-CCl_4-H_2O$). The Cbz-protected derivative **3e** was also prepared from **9b**.

Finally, truncated MRY analogues lacking the L-Val residue were synthesized by an Ugi four component assemblage (Scheme 6). Thus, **9a**, hexadecanal **24**, 2,4-dimethoxybenzylamine **25**, and the isonitrile of aminoribosyluridine derivative **26**[6,11] were reacted in EtOH, and fullly protected analogues **27** were obtained as a 1:1 mixture of diastereomers. Treatment of **27** with Zn followed by aq TFA gave **28a** and **28b** in 8% yield over three steps from **9a**, respectively, after HPLC separation. Final deprotection of the 2,4-dimethoxybenzyl (DMB) group was achieved by TFA in the presence of thioanisole to afford the truncated analogue **29a** and its diastereomer **29b** in 60% yield, respectively. The analogues **29a** and **29b** showed potent antibacterial activity against drug-resistant bacteria *S. aureus* SR3637 (MRSA) and *E. faecalis* SR7914 (VRE) with the MICs ranging 4−8 μg/mL.

In conclusion, the L-*epi*-Cpm derivatives were efficiently and stereoselectively synthesized via the nitrene C−H insertion starting from readily available D-Tyr. Our synthetic strategy could be a new access to *epi*-Cpm and its derivatives, which are found in several biologically active natural products.[12−14] Synthesis of MRY derivatives and their biological evaluation are currently underway and will be described.

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Supporting Information Available. Experimental procedures and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) DeMong, D. E.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 3529–3532. (b) DeMong, D. E.; Williams, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 8561–8565.

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