SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NEW, NON-NATURAL 1β-METHYLCARBAPENEM BEARING A σ-SYMMETRIC BICYCLOPYRAZOLIUMTHIO GROUP AS THE PENDANT MOIETY

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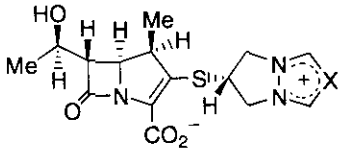
Abstract - Mercaptobicyclopyrazolium chloride (**3**) was successfully synthesized starting from pyrazole (**4**), and then exploited for the synthesis of new 1β-methylcarbapenem (**2**) which exhibits excellent antibacterial activities.

Since discovery of a non-natural 1β-methylcarbapenem antibiotic by a Merck Sharp & Dohme research group,[1] a number of new 1β-substituted carbapenem antibiotics have been synthesized because of their excellent biological and chemical behavior.[2,3] We disclosed a unique 1β-methylcarbapenem antibiotic, biapenem (**1**) bearing a σ-symmetric bicyclotriazoliumthio group as the pendant moiety.[2e] Biapenem (**1**) exhibited remarkable chemical stability and strong stability against human renal dehydropeptidase-I maintaining the superior antibacterial activities of a naturally occurring carbapenem antibiotic, (+)-thienamycin.[3] Here we describe synthesis of new, non-natural 1β-methylcarbapenem antibiotic (**2**) bearing a σ-symmetric bicyclopyrazoliumthio group at C2.



1 X = N
2 X = CH

In designing the pendant molecules of **1** and **2**, we adopted unique heterocycles, mercaptobicyclotriazolium and mercaptobicyclopyrazolium chloride (**3**) (X = N and CH) on the basis of

the following consideration. Namely, these particular heterocycles (**3**) can involve possible three kinds of structures, σ-symmetric one (σ-**3**) under electron delocalization and *R*- or *S*-**3** under electron localization as depicted in Figure 1.

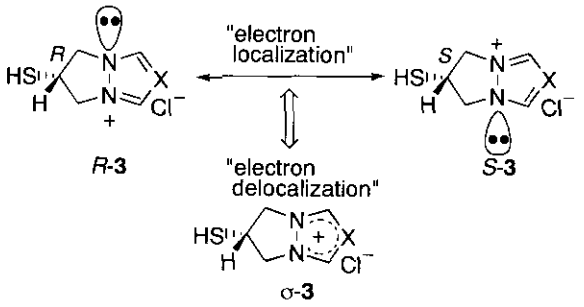
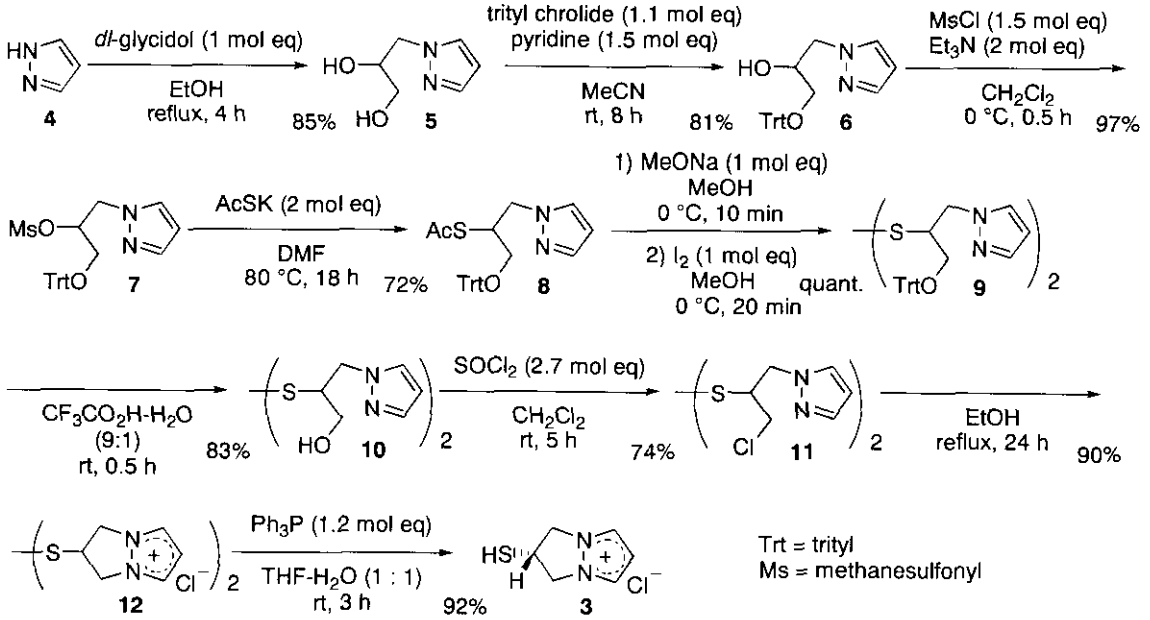


Figure 1. Possible structures of mercaptobicyclotriazolium (or bicyclopyrazolium) chloride (**3**) (X = N or CH)

Thus, the bicyclotriazolium or bicyclopyrazolium moiety of **1** or **2** can provide not only quaternary ammonium nature but also *R*- or *S*- chirality of the fused heterocycle. Although synthetic attempts toward **3** (X = N) using 1, 2 ,4-triazole resulted in unsuccess, the synthesis of **3** (X = CH) starting from 1, 2-imidazole (pyrazole) (**4**) was successfully achieved as shown in Scheme 1.

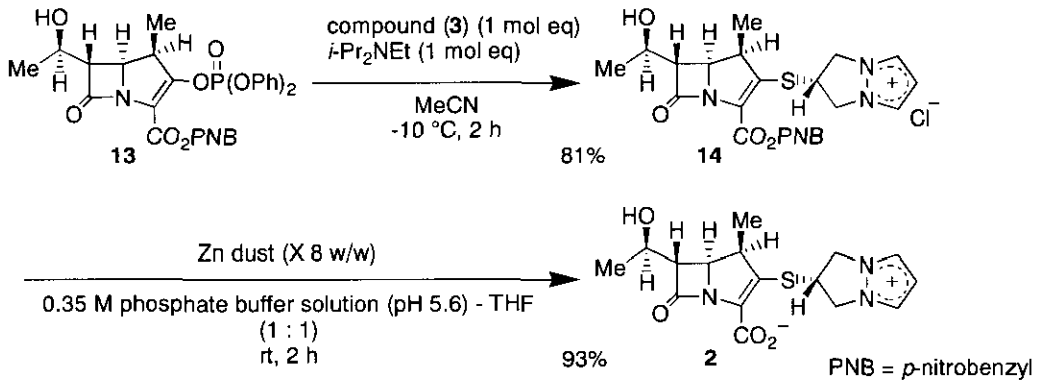


Scheme 1

Thus, pyrazole (**4**) was treated with *dl*-glycidol (1.1 mol eq) in EtOH under reflux for 4 h to give diol (**5**) (mp 32-33 °C from THF-hexane) in 85% yield. Selective protection of the primary OH group of **5** was carried out by reaction with trityl chloride (1.1 mol eq) in the presence of pyridine (1.5 mol eq) in MeCN at room temperature for 8 h to afford trityl ether (**6**) (mp 128-129 °C from AcOEt-hexane) in 81% yield

and a trace amount of di-trityl derivative of **5**. Mesylation of **6** with methanesulfonyl chloride (1.5 mol eq) and Et_3N (2 mol eq) in CH_2Cl_2 at 0 °C for 30 min followed by treatment of the mesylate (**7**) (mp 153-154 °C from AcOEt-hexane) with potassium thioacetate (2 mol eq) in DMF at 80 °C for 18 h gave acetylthiolate (**8**) (70% from **6**) as a pale yellow oil. Methanolysis of **8** with NaOMe (1 mol eq) in MeOH at 0 °C for 10 min followed by oxidation of the resultant thiol with iodine (1 mol eq) *in situ* furnished oily disulfide (**9**) quantitatively. Deprotection of trityl group of **9** in a solution of CF_3CO_2H and water (9 : 1) at room temperature for 30 min gave alcohol (**10**, 83%) as a pale yellow oil. After chlorination (74%) of **10** with $SOCl_2$ (2.7 mol eq) in CH_2Cl_2 at room temperature for 5 h, the resultant chloride (**11**) (colorless oil) was submitted to cyclization in EtOH under reflux for 24 h to give bis-bicyclopyrazolium disulfide·2Cl$^-$ (**12**) (colorless oil) in 90% yield. Reduction of **12** with Ph_3P in THF-water (1 : 1) at room temperature for 3 h afforded the desired mercaptobicyclopyrazolium chloride (**3**) ($C_6H_9N_2S$·Cl, colorless oil)[4] in 92% yield.

Introduction of thiol (**3**) into the 1β-methylcarbapenem skeleton was carried out as follows (Scheme 2).



Scheme 2

The compound (**13**), prepared by our asymmetric synthesis procedure,[2e] was allowed to react with **3** (1 mol eq) in the presence of *i*-Pr_2NEt (1 mol eq) in MeCN at -10 °C for 2 h to give thioether (**14**)

Table 1. Antibacterial activity of **2**

Organism	MIC (μg/mL)[a]	Organism	MIC (μg/mL)[a]
S. aureus Terajima	0.025	*S. marcescens* IAM 1184	0.1
E. coli NIHJ JC-2	0.1	*P. vulgaris* OX-19	1.56
K. pneumoniae PCI-602	0.1	*P. aeruginosa* NCTT 10490	0.78

[a] Tested by the agar dilution method (inoculum size: 10^6 cells / mL)

[$C_{23}H_{25}N_4O_6S$·Cl, FAB-MS *m/z* 485 $(M\text{-}Cl)^+$, $[\alpha]_D^{25}$ +52.3 ° (*c* 0.5, H_2O)] as a pale yellow oil in 81% yield. Deprotection of *p*-nitrobenzyl group of **14** was efficiently carried out by exploiting our method[5]

with Zn dust. Treatment of **14** with excess Zn dust in a mixture of 0.35 M phosphate buffer solution (pH 5.6) and THF (1 : 1) at room temperature for 2 h followed by the usual work-up[2e,5] of the reaction mixture readily afforded the desired 1β-methylcarbapenem (**2**) [$C_{16}H_{19}N_3O_4S$, colorless needles (H_2O-EtOH), mp 225-230 °C (decomp); $[\alpha]_D^{25}$ -30.9 ° (*c* 0.5, H_2O)][4] in 93% yield. This new 1β-methylcarbapenem (**2**) exhibited excellent antibacterial activities against several bacterias as shown in Table 1.[3]

REFERENCES AND NOTES

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4. Selected analytical data. **2**: Colorless needles; mp 225-230 °C (decomp) (H_2O-EtOH); IR ν_{max}(KBr) 1750, 1600 cm^{-1}; ^1H NMR (270 MHz, D_2O) δ 1.27 (d, 3H, *J* = 7.3 Hz), 1.31 (d, 3H, *J* = 6.4 Hz), 3.40-3.47 (m, 1H), 3.53 (dd, 1H, *J* = 3.0, 5.9 Hz), 4.20-4.40 (m, 2H), 4.63 (dd, 2H, *J* = 3.5, 12.3 Hz), 4.80-4.90 (m, 1H), 4.90-5.05 (m, 2H), 6.89 (t, 1H, *J* = 3.0 Hz), 8.21 (d, 1H, *J* = 3.0 Hz), 8.24 (d, 1H, *J* = 3.0 Hz); Anal. Calcd for $C_{16}H_{19}N_3O_4S$: C, 55.00; H, .5.48; N, 12.03. Found: C, 54.78; H, 5.45; N, 12.09. **3**: Colorless oil; ^1H NMR (270 MHz, D_2O) δ 4.30-4.50 (m, 3H), 4.80-5.00 (m, 2H), 6.78 (t, 1H, *J* = 2.6 Hz), 8.10 (d, 2H, *J* = 2.6 Hz); FAB HRMS calcd for $C_6H_9N_2SCl$ MW-Cl 141.0486, found *m/z* 141.0488 [$(M-Cl)^+$].
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