

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

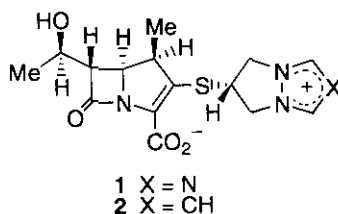
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Abstract - Mercaptobicyclopyrazolium chloride (**3**) was successfully synthesized starting from pyrazole (**4**), and then exploited for the synthesis of new 1 β -methylcarbapenem (**2**) which exhibits excellent antibacterial activities.

Since discovery of a non-natural 1 β -methylcarbapenem antibiotic by a Merck Sharp & Dohme research group,¹ a number of new 1 β -substituted carbapenem antibiotics have been synthesized because of their excellent biological and chemical behavior.^{2,3} We disclosed a unique 1 β -methylcarbapenem antibiotic, biapenem (**1**) bearing a σ -symmetric bicyclo[1.2.1]hexatriazoliumthio 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 1 β -methylcarbapenem antibiotic (**2**) bearing a σ -symmetric bicyclopyrazoliumthio group at C2.



In designing the pendant molecules of **1** and **2**, we adopted unique heterocycles, mercaptobicyclo[1.2.1]triazolium 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.

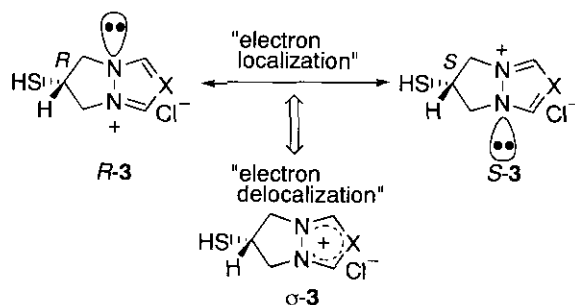
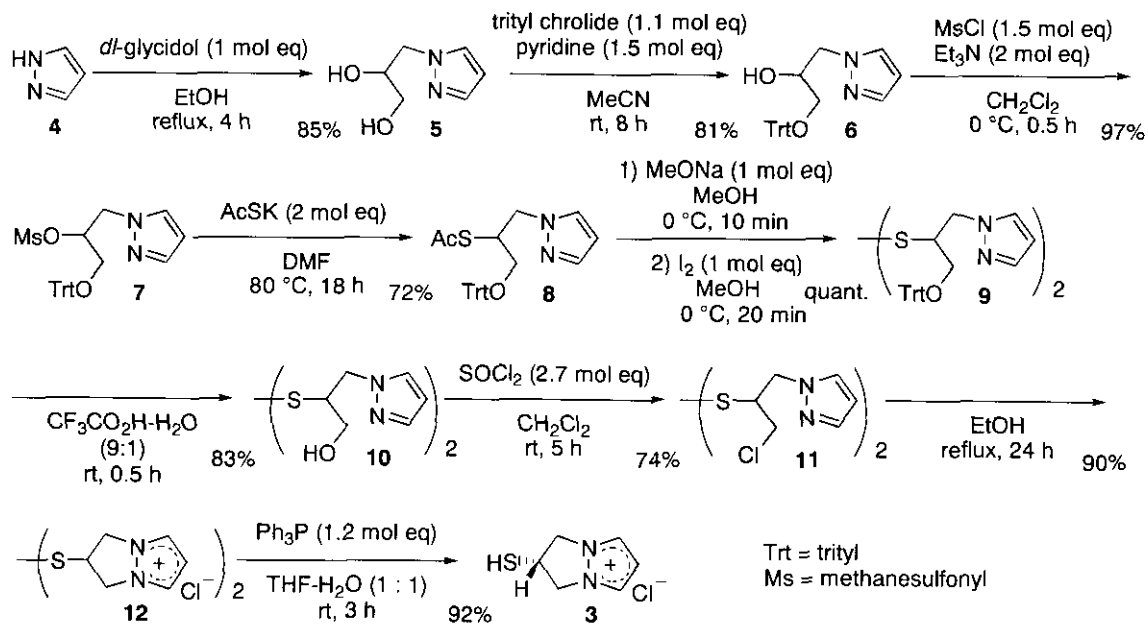


Figure 1. Possible structures of mercaptobicyclopentatriazolium (or bicyclopentopyrazolium) chloride (**3**) (X = N or CH)

Thus, the bicyclopentatriazolium or bicyclopentopyrazolium 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.

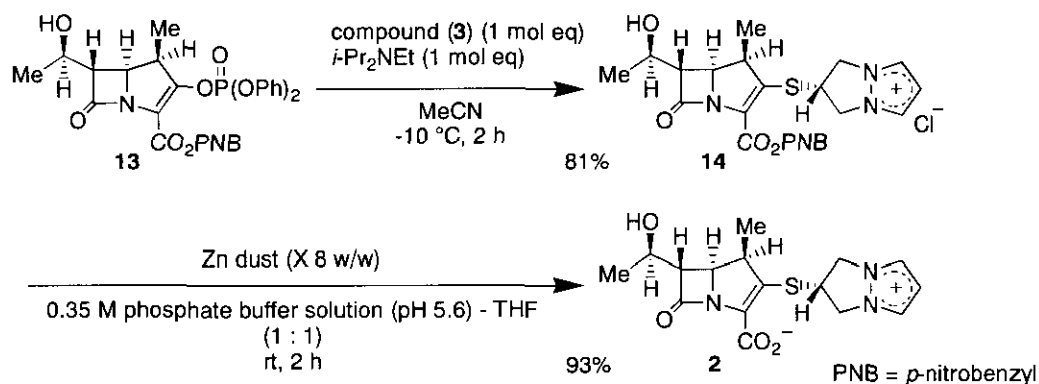


Scheme 1

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 Et₃N (2 mol eq) in CH₂Cl₂ 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 CF₃CO₂H 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 SOCl₂ (2.7 mol eq) in CH₂Cl₂ 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-bicyclopiazolium disulfide·2Cl⁻ (**12**) (colorless oil) in 90% yield. Reduction of **12** with Ph₃P in THF-water (1 : 1) at room temperature for 3 h afforded the desired mercaptobicyclopiazolium chloride (**3**) (C₆H₉N₂S·Cl, colorless oil)⁴ in 92% yield.

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



The compound (**13**), prepared by our asymmetric synthesis procedure,^{2c} was allowed to react with **3** (1 mol eq) in the presence of *i*-Pr₂NEt (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 |
|------------------------------|--------------------------|---------------------------------|--------------------------|
| <i>S. aureus</i> Terajima | 0.025 | <i>S. marcescens</i> IAM 1184 | 0.1 |
| <i>E. coli</i> NIHJ JC-2 | 0.1 | <i>P. vulgaris</i> OX-19 | 1.56 |
| <i>K. pneumoniae</i> PCI-602 | 0.1 | <i>P. aeruginosa</i> NCTT 10490 | 0.78 |

^a Tested by the agar dilution method (inoculum size: 10⁶ cells / mL)

[C₂₃H₂₅N₄O₆S·Cl, FAB-MS *m/z* 485 (M-Cl)⁺, [α]_D²⁵ +52.3 ° (c 0.5, H₂O)] as a pale yellow oil in 81% yield. Deprotection of *p*-nitrobenzyl group of **14** was efficiently carried out by exploiting our method⁵

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 1 β -methylcarbapenem (**2**) [C₁₆H₁₉N₃O₄S, colorless needles (H₂O-EtOH), mp 225-230 °C (decomp); [α]_D²⁵ -30.9 ° (c 0.5, H₂O)]⁴ in 93% yield. This new 1 β -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) (H₂O-EtOH); IR ν_{\max} (KBr) 1750, 1600 cm⁻¹; ¹H NMR (270 MHz, D₂O) 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 C₁₆H₁₉N₃O₄S: C, 55.00; H, .548; N, 12.03. Found: C, 54.78; H, 5.45; N, 12.09. **3**: Colorless oil; ¹H NMR (270 MHz, D₂O) 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 C₆H₉N₂SCI MW-Cl 141.0486, found *m/z* 141.0488 [(M-Cl)⁺].
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