SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NEW, NON-NATURAL 1β-METHYL CARBAPENEM 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 bicyclop yrazoliumthio group at C2.

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, \( \sigma \)-symmetric one (\( \sigma - 3 \)) 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)](image)

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](image)

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$_3$N (2 mol eq) in CH$_2$Cl$_2$ 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 acetyltiolate (8) (70% from 6) as a pale yellow oil. Methanalysis 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$_3$CO$_2$H 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$_2$Cl$_2$ 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$_3$P in THF-water (1 : 1) at room temperature for 3 h afforded the desired mercaptobicyclopyrazolium chloride (3) (C$_6$H$_5$N$_2$S-Cl, colorless oil) in 92% yield.

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

\[
\begin{align*}
\text{HO} & \quad \text{Me} \\
\text{N} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{H} & \quad \text{H} \\
\text{CO}_2\text{PNB} & \quad \text{OP(Ph)}_2
\end{align*}
\]

**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-Pr$_2$NEt (1 mol eq) in MeCN at -10 °C for 2 h to give thioether (14)

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (µg/mL)$^a$</th>
<th>Organism</th>
<th>MIC (µg/mL)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus Terajima</td>
<td>0.025</td>
<td>S. marcescens IAM 1184</td>
<td>0.1</td>
</tr>
<tr>
<td>E. coli NlHJ JC-2</td>
<td>0.1</td>
<td>P. vulgaris OX-19</td>
<td>1.56</td>
</tr>
<tr>
<td>K. pneumoniae PCI-602</td>
<td>0.1</td>
<td>P. aeruginosa NCTT 10490</td>
<td>0.78</td>
</tr>
</tbody>
</table>

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

[C$_{23}$H$_{25}$N$_4$O$_6$S-Cl, FAB-MS m/z 485 (M-Cl)$^+$, [α]$^2_D$ +52.3 ° (c 0.5, H$_2$O)] 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\textsuperscript{2e,5} of the reaction mixture readily afforded the desired 1β-methylcarbapenem (2) [C\textsubscript{16}H\textsubscript{19}N\textsubscript{2}O\textsubscript{8}S, colorless needles (H\textsubscript{2}O-EtOH), mp 225-230 °C (decomp); [\alpha]\textsubscript{D}\textsuperscript{25} = -30.9 ° (c 0.5, H\textsubscript{2}O)]\textsuperscript{4} in 93% yield. This new 1β-methylcarbapenem (2) exhibited excellent antibacterial activities against several bacteria as shown in Table 1.\textsuperscript{3}

REFERENCES AND NOTES


4. Selected analytical data. 2: Colorless needles; mp 225-230 °C (decomp) (H\textsubscript{2}O-EtOH); IR ν\textsubscript{max}(KBr) 1750, 1600 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (270 MHz, D\textsubscript{2}O) 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\textsubscript{16}H\textsubscript{19}N\textsubscript{2}O\textsubscript{8}S: C, 55.00; H, 5.48; N, 12.03. Found: C, 54.78; H, 5.45; N, 12.09. 3: Colorless oil; \textsuperscript{1}H NMR (270 MHz, D\textsubscript{2}O) 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\textsubscript{6}H\textsubscript{9}N\textsubscript{2}SCl MW-Cl 141.0486, found m/z 141.0488 [(M-Cl)+].


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