Synthesis and Antibacterial Activity of New 1β-Methylcarbapenems Having the Potential for Intramolecular Nonbonded S···O Interactions

Yoshimitsu NAGAO,*[,a] Hitoshi IIMORI,[a] Ki Hong NAM,[a,1)] Shigeki SANO,[a] and Motoo SHIRO[b]

Faculty of Pharmaceutical Sciences, The University of Tokushima,[a] Sho-machi, Tokushima 770–8505, Japan and Rigaku Corporation,[b] 3–9–12 Matsubara-cho, Akishima, Tokyo 196–8666, Japan.
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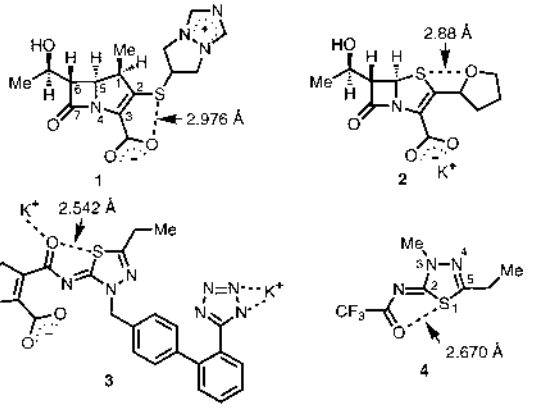
Mercaptoacetyliminothiadiazoline derivatives (19, 20) useful for the pendant moiety of 1β-methylcarbapenem antibiotics were efficiently synthesized. Acetyl derivative (18) of 20 was submitted to X-ray analysis, and a significant nonbonded S···O close contact was recognized in the crystallographic structure. New 1β-methylcarbapenems (5, 6) were synthesized by exploiting 19 and 20, and exhibited considerable antibacterial activities *in vitro*.

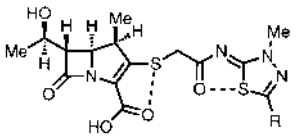
Key words carbapenem antibiotic; thiadiazoline; X-ray analysis; crystallographic structure; close contact

Since discovery of a non-natural 1β-methylcarbapenem antibiotic by a Merck Sharp & Dohme research group,[2)] we have been extensively studying the development of new 1β-substituted carbapenems and useful new methods for synthesizing them.[3)] Nagao and Wyeth Lederle groups disclosed a unique 1β-methylcarbapenem antibiotic, biapenem (**1**), bearing a σ-symmetric bicyclotriazoliumthio group as the pendant moiety.[3h,k)] Interestingly, an intramolucular nonbonded S···O interaction ("close contact") was recognized in the crystal structure of **1**.[3k)] Ishiguro *et al*. reported a significant relationship between an intramolecular nonbonded S···O interaction in the molecule of penem antibiotic (**2**) and its antibacterial activities.[4)] The intramolecular nonbonded interactions such as S···O, S···S, S···N have been observed in a large amount of organosulfur compounds.[5)] We also reported the fascinating intramolecular nonbonded S···O interactions in the molecules of 2-acylimino-1,3,4-thiadiazolines (*e.g.*, **3**), which exhibited strong angiotensin II receptor antagonistic activity, and the structural stability of their model compounds (*e.g.*, **4**) involving such a nonbonded interaction on the basis of the *ab initio* MO calculations.[6)] With background described above, we now report the synthesis and antibacterial activities of new 1β-methylcarbapenems (**5**, **6**) having the potential for intramolecular nonbonded interactions in their molecules, as shown in Chart 1.



Commercially available 2-amino-1,3,4-thiadiazole (**7**) and its 5-methyl derivative (**8**) were treated with trifluoroacetic anhydride in toluene at 0 °C and then room temperature to afford the corresponding 2-trifluoroacetylamino derivatives (**9**, **10**) in 70 and 80% yields. Regioselective methylation of **9** and **10** with MeI and K_2CO_3 in *N*,*N*-dimethylformamide (DMF) gave their 3-methylthiadiazoline derivatives (**11**, **12**) as colorless prisms in 78 and 97% yields, respectively. After hydrolysis of **11** and **12** with 5% aqueous NaOH in tetrahydrofuran (THF), the resultant 2-iminothiadiazolines (**13**, **14**) were allowed to react with bromoacetyl chloride in the presence of pyridine in CH_2Cl_2 to obtain the corresponding 2-bromoacetylimino-3-methylthiadiazolines (**15**, **16**) as pale yellow prisms in 83% and quatitative yields, as shown in Chart 2. Treatment of **15** and **16** with potassium thioacetate in acetone furnished crystalline 2-acetylthioacetylimino derivatives (**17**, **18**),[7)] which were submitted to alkaline hydrolysis with 4 N NaOH in MeOH to afford the desired thiols (**19**, **20**) in excellent yields, respectively (Chart 2).

Introduction of the thiols (**19**, **20**) into the 1β-mehtylcarbapenem skeleton was performed as follows (Chart 3): Chiral compound **21**, prepared according to the asymmetric synthesis which was established by us,[3h)] was treated with **19** and **20** in the presence of *i*-Pr_2NEt in MeCN to give thioethers (**22**, **23**) in 79 and 85% yields. Deprotection of the



5 R = H, **6** R = Me
(Dotted line shows a possible nonbonded S···O interaction)

Chart 1. New 1β-Methylcarbapenems

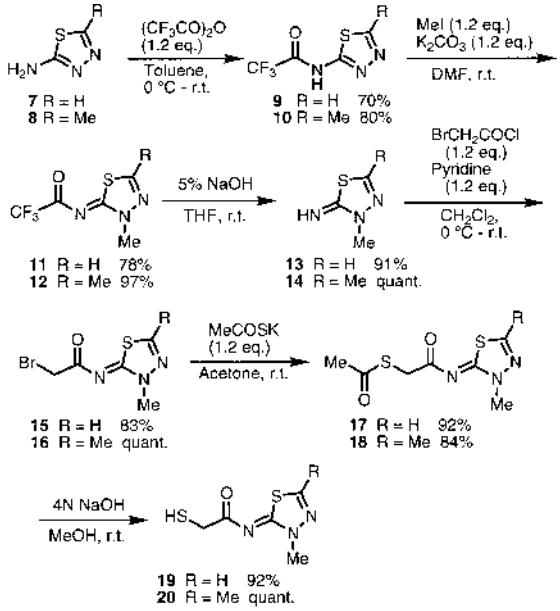


Chart 2. Synthesis of 2-Mercapotacetylimino-3-methyl-1,3,4-thiadiazoline Derivatives (**19**, **20**)

* To whom correspondence should be addressed. e-mail: ynagao@ph2.tokushima-u.ac.jp

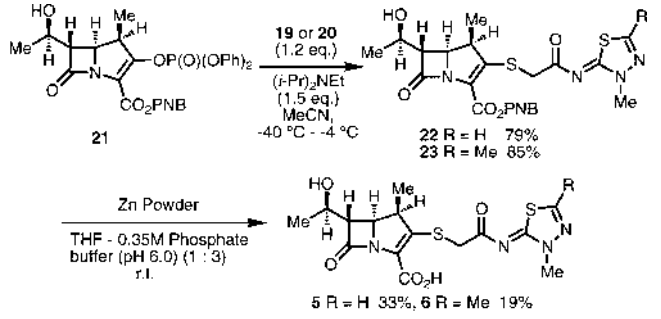


Chart 3. Synthesis of New 1β-Methylcarbapenems (**5**, **6**)

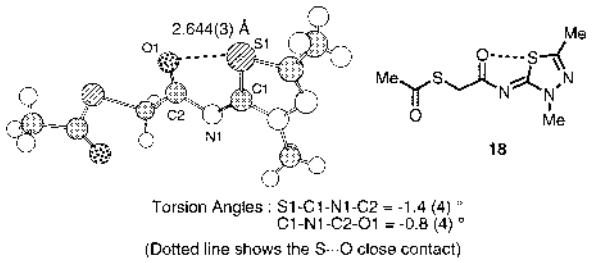


Chart 4. Computer-Generated Drawing Derived from the X-Ray Coordinates of Compound **18**

Table 1. Antibacterial Activity of Compounds **5** and **6**

Organism	MIC (μg/ml)[a]	
	5	**6**
S. aureus TERAJIMA	0.25	0.125
S. pyogenes Cook	0.5	0.25
S. subtilis ATCC 6633	0.5	0.25
M. luteus ATCC 9341	0.5	0.125
E. coli NIHJ JC-2	32	32
K. pneumoniae PCI-602	0.25	0.125
S. enteritidis G14	1.5	0.5
S. marcescens IMA 1184	128	64
P. rettgeri IFO 3850	8	8
P. aeruginosa IFO 3445	>128	>128

a) Tested by the agar dilution method (inoculum size : 10^6 cell/ml).

p-nitrobenzyl group of **22** and **23** was done by means of treatment using excess Zn powder in THF–0.35 M phosphate buffer (1 : 3) at room temperature,[3i] and then the usual work-up[3i,k] of the reaction mixture afforded the desired compounds **5** (33% yield) and **6** (19% yield), respectively.[8]

Because both compounds **5** and **6** were amorphous powder, we attempted recrystallization of crystalline compounds **17** and **18** in a solution of THF and *n*-hexane. Fortunately, compound **18** was obtained as an excellent single crystal, which was submitted to X-ray crystallographic analysis.[9] The computer-generated drawing of the crystal structure of **18** is depicted in Chart 4. In the represented structure of **18**, significant close contact [2.644(3) Å] between S1 and O1 atoms and planarity of the S1–C1–N1–C2–O1 moiety (torsion angles shown in Chart 3) were recognized. The nonbonded S1···O1 atoms' distance [2.644(3) Å] is considerably lesser than the sum (3.32 Å) of the van der Waals radii (S and O). Thus, it can be suggested from the viewpoints of the structural data[3k] of **18** and **1** and the *ab initio* MO calculation[6] of **4** that intramolecular nonbonded S···O interactions in the molecules of **5** and **6** must be possible (Chart 1).

Finally, *in vitro* screening of new 1β-methylcarbapenem antibiotics (**5**, **6**) against several bacteria was performed. The data are summarized in Table 1. Although these new antibiotics did not exhibit remarkable antibacterial activities, this new synthetic approach based on the intramolecular nonbonded interaction concept seemes to be an attractive gateway toward the development of a new class of 1β-methylcarbapenem antibiotics.

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References and Notes

1) Present address: *Central Research Institute, Dong Kook Pharmaceutical Co., LTD., # 150–3, Hoijuk-Ri, Kwanghyewon-Myun, Jincheon-Gun, Choongcheongbook-Do, Korea*.
2) Shih D. H., Baker F., Cama L., Christensen B. G., *Heterocycles*, **21**, 29—40 (1984).
3) *a*) Nagao Y., Kumagai T., Takao S., Abe T., Ochiai M., Inoue Y., Taga T., Fujita E., *J. Am. Chem. Soc*., **108**, 4673—4675 (1986); *b*) Nagao Y., Kumagai T., Abe T., Ochiai M., Taga T., Machida K., Inoue Y., *J. Chem. Soc., Chem. Commun*., **1987**, 602—603; *c*) Nagao Y., " Perspectives in the Organic Chemistry of Sulfur," ed. by Zwanenburg B., Klunder A. J. H., Elsevier, Amsterdam, 1987, pp. 57—73; *d*) Nagao Y., Abe T., Shimizu H., Kumagai T., Inoue Y., *J. Chem. Soc., Chem. Commun*., **1989**, 821—822; *e*) *Idem*, *Heterocycles*, **33**, 523—528 (1992); *f*) Nagao Y., Kumagai T., Nagase Y., Tamai S., Inoue Y., Shiro M., *J. Org. Chem*., **57**, 4232—4237 (1992); *g*) Nagao Y., Nagase Y., Kumagai T., Kuramoto Y., Kobayashi S., Inoue Y., Taga T., Ikeda H., *ibid*., **57**, 4238—4242 (1992); *h*) Nagao Y., Nagase Y., Kumagai T., Matsunaga H., Abe T., Shimada O., Hayashi T., Inoue Y., *ibid*., **57**, 4243—4249 (1992); *i*) Kumagai T., Abe T., Fujimoto Y., Hayashi T., Inoue Y., Nagao Y., *Heterocycles*, **36**, 1729—1734 (1993); *j*) Kumagai T., Tamai S., Abe T., Nagase Y., Inoue Y., Nagao Y., *ibid.*, **37**, 1521—1527 (1994); *k*) Kumagai T., Tamai S., Abe T., Matsunaga H., Hayashi K., Kishi I., Shiro M., Nagao Y., *J. Org. Chem*., **63**, 8145—8149 (1998); *l*) Nagao Y., Tamai S., Tanigawa N., Sano S., Kumagai T., Kishi I., *Heterocycles*, **48**, 617—620 (1998).
4) Tanaka R., Oyama Y., Imajo S., Matsuki S., Ishiguro M., *Bioorg. Med. Chem*., **5**, 1389—1399 (1997).
5) Kucsman A., Kapovits I., "Organic Sulfur Chemistry: Theoretical and Experimental Advances," ed. by Bernardi F., Csizmadia I. G., Mangini A., Elsevier, Amsterdam, 1985, pp. 191—245 and references cited therein.
6) Nagao Y., Hirata T., Goto S., Sano S., Kakehi A., Iizuka K., Shiro M., *J. Am. Chem. Soc*., **120**, 3104—3110 (1998).
7) **17**: mp 78—78.5 °C ($CHCl_3$–*n*-hexane). ^{1}H -NMR (200 MHz, $CDCl_3$) δ: 2.40 (3H, s), 3.99 (3H, s), 4.01 (2H, s), 8.35 (1H, s). IR (KBr) cm^{-1}: 1656, 1736. Electron impact-mass spectra (EI-MS) *m/z*: 231.0147 (Calcd for $C_7H_9N_3O_2S_2$: 231.0136). *Anal*. Calcd for $C_7H_9N_3O_2S_2$: C, 36.35; H, 3.92; N, 18.17. Found: C, 36.27; H, 3.88; N, 18.01. **18**: mp 84—85 °C (THF–*n*-hexane). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.39 (3H, s), 2.52 (3H, s), 3.90 (3H, s), 3.99 (2H, s). IR (KBr) cm^{-1}: 1655, 1736. EI-MS *m/z*: 245.0312 (Calcd for $C_8H_{11}N_3O_2S_2$: 245.0293). *Anal*. Calcd for $C_8H_{11}N_3O_2S_2$: C, 39.17; H, 4.52; N, 17.13. Found: C, 38.92; H, 4.53; N, 17.05.
8) **5**: Colorless amorphous powder. ^{1}H-NMR (200 MHz, D_2O) δ: 1.19 (3H, d, J=7.1 Hz), 1.28 (3H, d, J=6.3 Hz), 3.43 (1H, dd, J=6.1, 2.0 Hz), 3.51—3.63 (1H, m), 3.79 (1H, d, J=15.6 Hz), 3.99 (3H, s), 4.01 (1H, d, J=15.2 Hz), 4.16—4.29 (2H, m), 8.82 (1H, s). IR (KBr) cm^{-1}: 1607, 1757. FAB-MS *m/z*: 421.0584 (Calcd for $C_{15}H_{18}N_4O_5S_2$+Na$^+$: 421.0616). $[\alpha]_D^{29}$ +18.1° (c=1.0, H_2O). **6**: Colorless amorphous powder. ^{1}H-NMR (200 MHz, D_2O) δ : 1.19 (3H, d, J=7.3 Hz), 1.30 (3H, d, J=6.4 Hz), 2.58 (3H, s), 3.41—3.56 (2H, m), 3.71 (1H, d, J=15.1 Hz), 3.90 (1H, d, J=14.9 Hz), 3.93 (3H, s), 4.14—4.27 (2H, m). IR (KBr) cm^{-1}: 1549, 1747. FAB-MS *m/z*: 435.0750 (Calcd for $C_{16}H_{20}N_4O_5S_2$+Na$^+$: 435.0773). $[\alpha]_D^{29}$ −189.4° (c=1.0, H_2O).
9) The crystal data of compound **18**: Monoclinic, $C2/c$(#15), a=17.609(2) Å, b=13.318(2) Å, c=12.851(2) Å, β=130.001(6)°, V=2308.6(6) Å^3, z=8, D_{calc}=1.412 g/cm^3, R=0.047, R_w=0.075.