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SYNTHETIC CARBAPENEM ANTIBIOTICS II.[1]

STEREOISOMERS OF 7-HYDROXYETHYL-2,2,5-TRIMETHYL-3-OXA-1-AZABICYCLO[4.2.0]OCTAN-8-ONE

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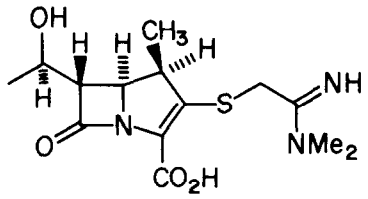
Summary: The titled compounds are key synthetic intermediates in the structure-activity relationship studies of novel 1-methyl carbapenem antibiotics. Preparation and structural determination of these stereoisomers by X-ray crystallography and proton NMR spectroscopy are reported.

1-Methyl substituted carbapenem carboxylic acids are a new class of synthetic β-lactam antibiotics. The noticeable gross improvements in biological and physical properties of carbapenem antibiotics resulting from the methyl substituent at C-1 position have recently been reported.[2,3] The compound which has been studied in detail is a 1β-methylcarbapenem carboxylic acid, (-)-(1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-1-methyl-2-(2-N,N-dimethylamino-2-iminoethylthio)-1-carbapen-2-em-3-carboxylic acid **1**.[3]



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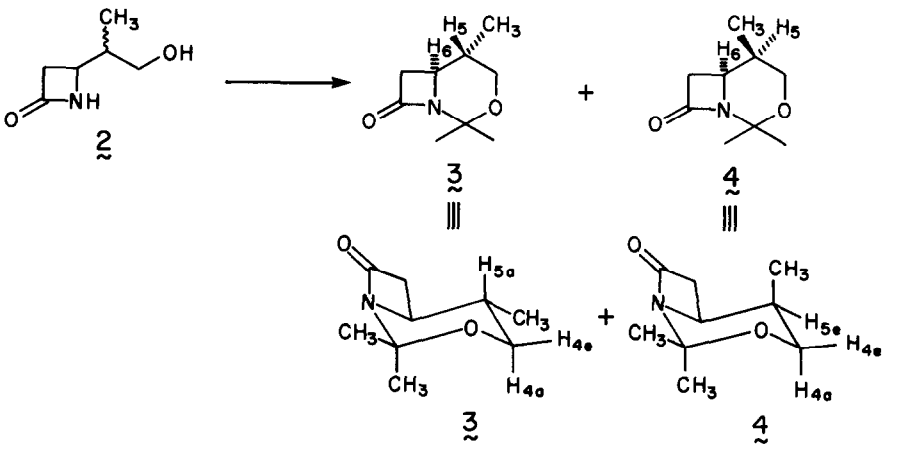
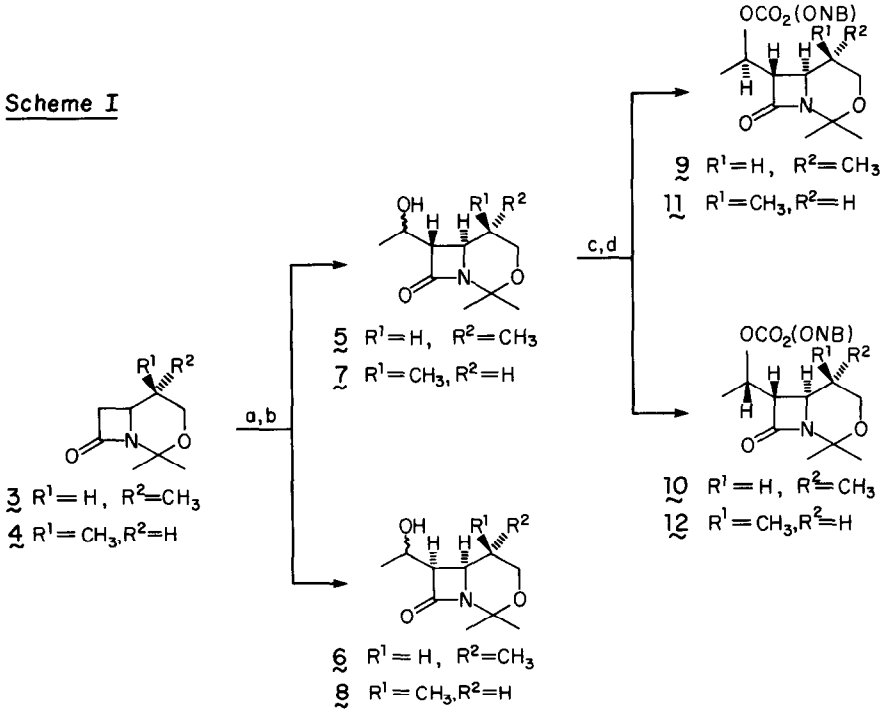
The structure-activity relationship (SAR) studies which led to the discovery of the 1β-methylcarbapenem nucleus as a new building block for synthetic carbapenem antibiotics have utilized the versatile synthetic intermediates, 5,7-substituted 2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-ones. The preparation and structural assignments of these compounds were essential in the SAR studies. We wish to report the synthetic scheme which provided all eight isomers of 5-methyl-7-hydroxyethyl substituted azabicyclooctanes **5** to **8**, and selective isomer isolation and structure determination of these compounds by X-ray crystallography and NMR spectroscopy.

Cyclization of 4-[2-hydroxy-1-methylethyl]-azetidin-2-one **2** (1:1 mixture of α/β isomers)[4] with 2,2-dimethoxypropane (BF_3·Et_2O/CH_2Cl_2, 80%) provided a 1:1 mixture of α- and β-methyl ketals **3** and **4** which were separable by HPLC (Prep-PAK 500/silica, 40% ethyl acetate/cyclohexane). The stereochemical assignments of **3** and **4** were based upon proton coupling constants. As expected, the α-methyl isomer **3** showed a large axial-axial coupling constant of 12 Hz ($J_{4a,5a}$) and a small axial-equatorial one of 4.8 Hz ($J_{4e,5a}$), while the β-methyl isomer **4** showed two small coupling constants of 3.2 Hz and 2.0 Hz which were attributable to $J_{4a,5e}$ and $J_{4e,5e}$, respectively.



Elaboration of α- and β-methyl azabicyclooctanes, **3** and **4**, respectively, to the 7-hydroxyethyl substituted bicyclic β-lactam via aldol condensation with acetaldehyde gave a total of eight stereoisomers. The syntheses and isomer separations of these bicyclic compounds are shown in Scheme I.

Scheme I



a) LDA/CH_3CHO/THF, -78°[5];
b) HPLC separation, Prep-PAK 500/silica, 40% EtOAc/cyclohexane.
c) o-nitrobenzyl chloroformate/4-dimethylaminopyridine, CH_2Cl_2, -20° to rt, 16h;
d) HPLC separation, Prep-PAK 500/silica, 40% EtOAc/cyclohexane.

Hydroxyethylation of α-methyl azabicyclooctane **3** gave an 80% yield of **5/6** (4:1 ratio) as a mixture of trans/cis geometric isomers. Each geometric isomer consisted of a pair of R/S epimers. A total of four epimers were obtained. Although fractional crystallization of the product mixture from diethyl ether did produce some pure trans isomer **5** as colorless crystals, most of pure **5** and **6**, respectively, were obtained by HPLC separation of the mother liquor. The R/S (2:3 ratio) epimer separation was not achieved at this stage. However, the separation became feasible when the hydroxy group was protected with an o-nitrobenzyloxycarbonyl (91%) or p-nitrobenzyloxycarbonyl group.

In contrast to the α-methyl azabicyclooctane **3**, hydroxyethylation of β-methyl isomer **4** proceeded in highly stereoselective manner to give almost exclusively trans-hydroxyethyl azabicyclooctane **7** (72%) (R/S ratio 1:4). Only a trace of cis isomer **8** was detected. Apparently, the β-methyl group of the azabicyclooctane effectively blocked the reaction from occurring on the β-face of the bicyclic β-lactam ring system. The significant implication of this "β-methyl effect" on biological and physical properties of the 1β-methylcarbapenem antibiotics will be discussed in a separate paper.

Fractional crystallization of **7** from diethyl ether produced pure S epimer of **7**, but HPLC isolation of pure R epimer from the mother liquor was difficult. The separation became attainable by HPLC when the mother liquor of **7** (R/S ratio 3:1) was converted to carbonates **11** and **12** (86%). The hydroxyethyl side chain stereochemical assignments by proton NMR spectra were found ambiguous.[5] The unequivocal structural assignments of these compounds were achieved by X-ray crystallography of **10** and **12**. The ORTEP view of **12** is shown in Figure 1.[6]

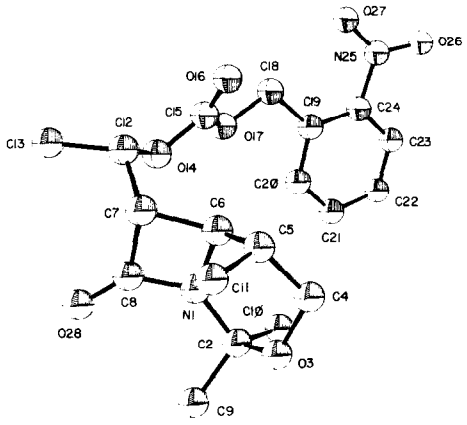
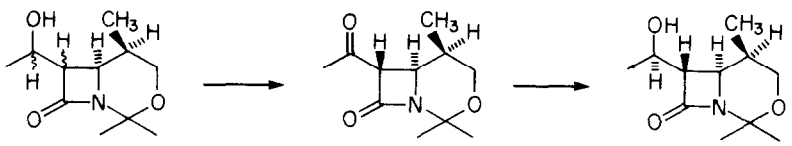


Fig. 1. ORTEP view of 1β-methyl bicyclic azetidinone **12.**

Since the trans R-hydroxyethyl side chain was the preferred C-6 substituent of carbapenem antibiotics, an effective stereocontrolled synthesis of **14** was devised. Similar to the unsubstituted azabicyclic ring system,[5] the mixture of aldol products **7/8** when oxidized with trifluoroacetic anhydride in DMSO at -20° gave a single isomer of acetonyl azabicyclooctane **13** which upon reduction with K-Selectride in 4:1 pentane/THF provided >90% pure trans R-hydroxyethyl isomer **14.** Crystallization from diethyl ethyl gave pure **14** as colorless crystals.



Utilization of these stereoisomers in the synthesis of novel 1-methyl substituted carbapenem antibiotics such as 1α- and 1β-methylthienamycin is reported in the subsequent paper.

Supplementary Material. Six tables containing bond lengths and bond angles for structure **10** and **12**. Ordering information is given on any current masthead page.

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4. Prepared from chlorosulfonylisocyanate with 1-acetoxy-2-methyl-1,3-butadiene, followed by reductive hydrolysis and catalytic hydrogenation.
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6. The single crystal structures of **10** and **12** gave the following unit cell parameters: **Structure 12**: a, 7.942(2)Å; b, 17.985(4)Å; c, 7.481(1)Å; α, 99.17(2)°; β, 111.50(2)°; γ, 91.19(2)°; V, 977.9(4)Å^3; Sp. gr., $P\bar{1}$; Z, 2. **Structure 10**: a, 9.706(5)Å; b, 13,360(8)Å; c, 10.901(5)Å; α, 51.42(2)°; β, 115.13(4)°; γ, 86.28(4)°; V, 997.5(8)Å^3; Sp. gr., $P\bar{1}$; Z, 2.
7. Proton NMR Chemical Shifts (in $CDCl_3$, TMS as internal standard) and coupling constants:

Cpd.	C_5-CH_3	C_2-CH_3	C_2-CH_3	C_9-CH_3	H_5	H_7	H_6	H_{4a}	H_{4e}	H_9	CH_2-(4-NO_2-Ph)	(4-NO_2-Ph)
3	0.88 (d) J = 6.3	1.38 (s)	1.75 (s)	-	1.72 (m)	2.59 (dd) $J_{7\beta,6}$ = 1.8 3.10 (dd) $J_{7\alpha,6}$ = 4.2 $J_{7\alpha,\beta}$ = 14.6	3.16 (ddd) $J_{6,7\alpha}$ = 4.2 $J_{6,7\beta}$ = 1.8 $J_{6,5}$ = 4.3	3.48 (t) $J_{4a,5a}$ = 12 $J_{4a,4e}$ = 12	3.73 (dd) $J_{4e,5a}$ = 4.8 $J_{4a,4e}$ = 12.0	-	-	-
4	1.10 (d) J = 7.2	1.38 (s)	1.67 (s)	-	1.90 (m)	2.80 (dd) $J_{7\alpha,\beta}$ = 14.6 $J_{7\alpha,6}$ = 2.2 2.88 (dd) $J_{7\beta,6}$ = 4.2 $J_{7\alpha,\beta}$ = 14.6	3.78 (m)	3.62 (dd) $J_{4a,5e}$ = 3.2 $J_{4a,4e}$ = 14.2	3.98 (dd) $J_{4e,5e}$ 2.0 $J_{4a,4e}$ = 14.2	-	-	-
9	0.86 (d) J 6.0	1.38 (s)	1.73 (s)	1.46 (d) J = 6.4	1.73 (m)	2.98 (dd) $J_{7,6}$ = 1.5 $J_{7,9}$ = 8.9	3.13 (dd) $J_{6,7}$ = 1.5 $J_{6,5}$ = 10.0	3.44 (t) $J_{4a,5a}$ = 11.8 $J_{4a,4e}$ = 11.8	3.71 (dd) $J_{4e,5a}$ = 4.8 $J_{4e,4e}$ = 11.8	5.10 (qq) $J_{9,7}$ = 8.9 $J_{9\text{-}CH_3}$ 6.4	5.58 (s)	7.54 (m) 7.66 (m) 8.16 (m)
10	0.90 (d) J = 6.0	1.40 (s)	1.75 (s)	1.42 (d) J = 6.5	1.80 (m)	3.06 (dd) $J_{7,6}$ = 1.8 $J_{7,9}$ = 10.0	3.16 (dd) $J_{6,7}$ = 1.8 $J_{6,5}$ = 6.0	3.46 (t) $J_{4a,5a}$ = 11.8 $J_{4a,4e}$ = 11.8	3.72 (dd) $J_{4e,5a}$ = 4.4 $J_{4e,4a}$ = 11.8	5.16 (dq) $J_{9,7}$ = 10.0 $J_{9\text{-}CH_3}$ = 6.5	5.56 (d) 5.62 (d) J = 12.6	7.53 (m) 7.70 (m) 8.18 (m)
11	1.12 (d) J = 6.1	1.40 (s)	1.73 (s)	1.46 (d) J = 6.1	1.95 (m)	3.20 (dd) $J_{7,6}$ = 1.5 $J_{7,9}$ = 8.5	3.74 (dd) $J_{6,7}$ = 1.5 $J_{6,5}$ = 5.0	3.60 (dd) $J_{4a,5e}$ = 3.0 $J_{4a,4e}$ = 12.0	3.90 (dd) $J_{4e,5e}$ = 2.1 $J_{4e,4a}$ = 12.0	5.07 (dq) $J_{9,7}$ = 8.5 $J_{9\text{-}CH_3}$ = 6.1	5.56 (d) 5.62 (d) J = 15.0	7.56 (t) 7.70 (m) 8.19 (d)
12	1.10 (d) J = 6.1	1.40 (s)	1.72 (s)	1.43 (d) J = 6.0	1.94 (m)	3.34 (dd) $J_{7,6}$ = 2.1 $J_{7,9}$ = 5.0	3.67 (dd) $J_{6,7}$ = 2.1 $J_{6,5}$ = 5.3	3.61 (dd) $J_{4a,5e}$ = 3.0 $J_{4a,4e}$ = 12.0	3.96 (dd) $J_{4e,5e}$ = 2.0 $J_{4e,4a}$ = 12.0	5.13 (dq) $J_{9,7}$ = 5.0 $J_{9\text{-}CH_3}$ = 6.0	5.58 (d) 5.64 (d) J = 16.8	7.53 (m) 7.68 (m) 8.17 (m)

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