

# Synthesis and structure determination of diastereomeric carbapenems in the Ad<sub>N</sub>E-reaction of (±)-4,4-dimethyl-3-mercaptodihydrofuran-2(3H)-one with chiral carbapenem enol phosphate

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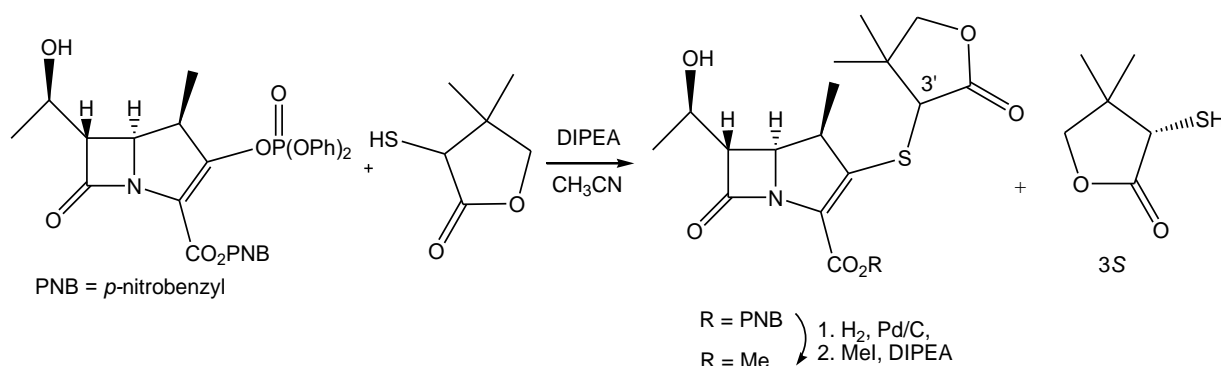
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## Abstract

Incorporation of a  $\gamma$ -lactone ring into the structure of carbapenems is considered as a potential “trap” for metallo- $\beta$ -lactamases that destructively act on carbapenems. New carbapenems containing a (±)-4,4-dimethyl-3-mercaptodihydrofuran-2(3H)-one fragment at C<sup>3</sup> have been synthesized. On chromatographing a mixture of the diastereomeric carbapenems on a column with silica gel deactivated with NEt<sub>3</sub>, a change of the ratio of isomers occurs. The remaining enantiomerically enriched (3S)-4,4-dimethyl-3-mercaptodihydrofuran-2(3H)-one with  $[\alpha]_D^{20}$  -34° was also isolated. The determining factor in the structural assignment of the diastereomeric carbapenems was the presence, in both diastereomers, of NOE interactions between the C<sup>3'</sup>-H proton of the lactone with the C<sup>4</sup>-H and C<sup>4</sup>-Me protons of the bicyclic carbapenems.

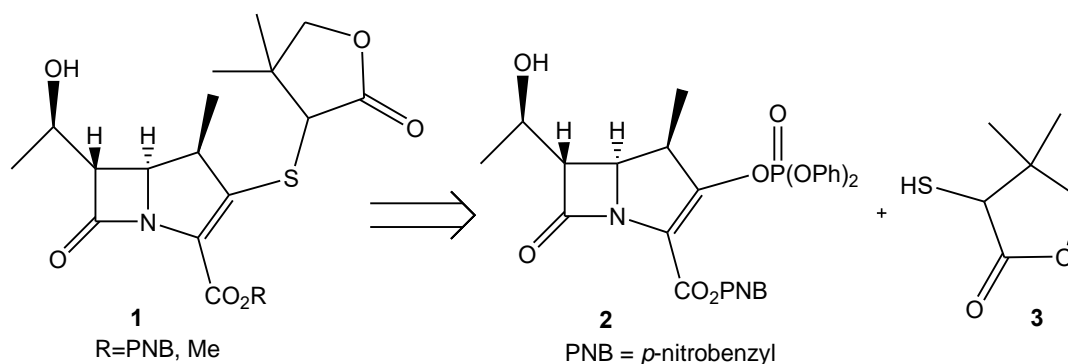


**Keywords:** 3-Deoxy-3-mercaptopantolactone, carbapenem enol phosphate, Ad<sub>N</sub>E-reaction, synthesis, diastereomeric carbapenems

## Introduction

Carbapenems are known as efficient broad-spectrum low-toxic antibiotics in the series of antimicrobial agents belonging to the  $\beta$ -lactam class.<sup>1-3</sup> A key problem in antibiotic therapy is that microbes develop new strains that are resistant to the drug, which eventually results in a decrease or complete loss of the drug activity.<sup>4-6</sup> Though carbapenems are resistant to the majority of lactamases (i.e. serine  $\beta$ -lactamases), however, Zn-dependent  $\beta$ -lactamases (NDM-1 and others) destroy the  $\beta$ -lactam ring by hydrolysis, thereby inactivating the antibiotic.<sup>7-9</sup> For this reason, the synthesis and introduction of new types of carbapenems with more stable structures are relevant in medicine in the fight against infectious diseases.

In this work, we report the synthesis of a new carbapenem **1** by coupling of the well-known carbapenem **2**<sup>10</sup> with thiol **3** which was obtained from pantolactone for the first time. During the reaction, a noticeable kinetic optical resolution of thiol **3** is also observed.

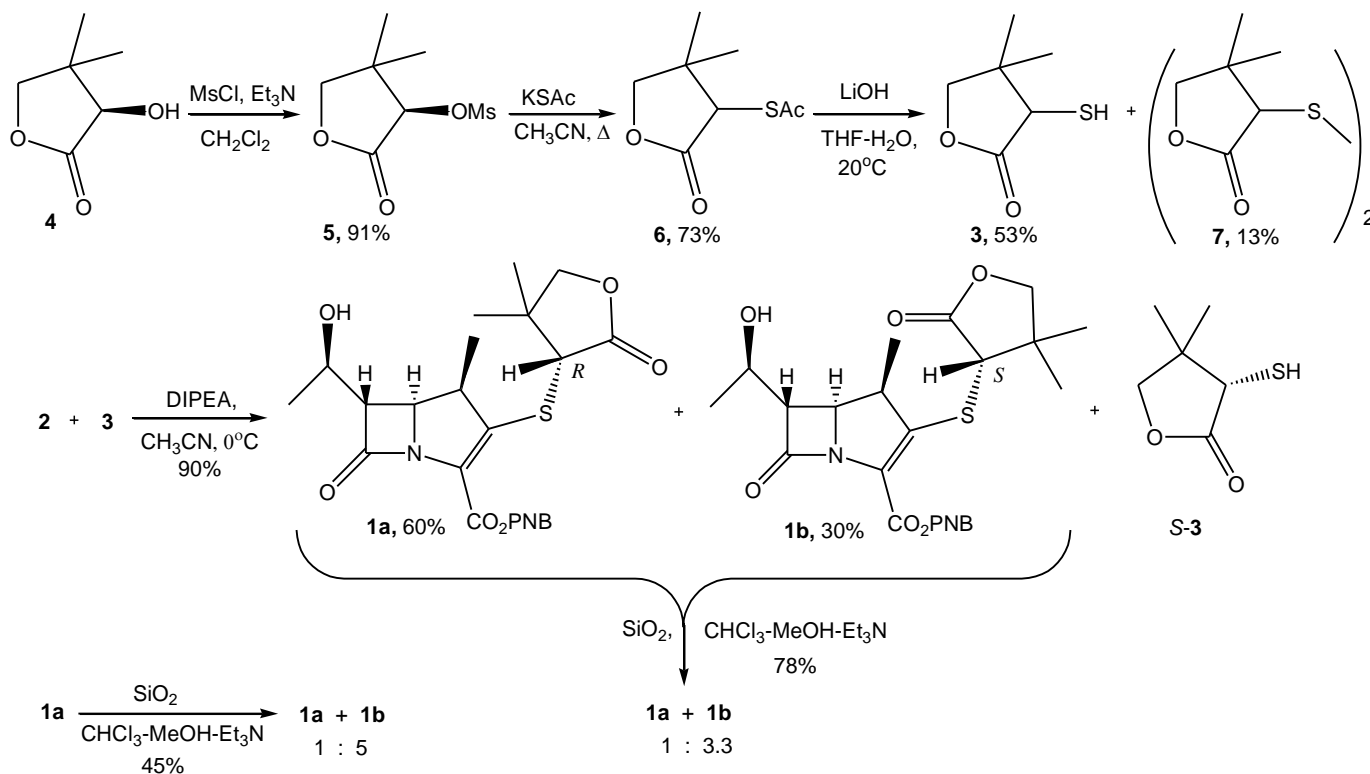


**Scheme 1.** Retrosynthesis of carbapenem **1**.

## Results and Discussion

Thiol **3** was prepared from (-)-pantolactone **4** (Scheme 2) by sequential mesylation,  $S_N2$ -substitution of mesylate **5** with potassium thioacetate and hydrolysis of thioacetate **6** by treatment with LiOH in THF-H<sub>2</sub>O. Unfortunately, the resulting thiol **3** was racemic. This may be due to the drastic conditions of the reactions in the sequence **5**  $\rightarrow$  **6**  $\rightarrow$  **3**, as well as the liability to epimerization at the C<sup>3</sup> center of pantolactone and its derivatives.<sup>11-13</sup> We also observed the formation of disulfide **7** in a number of experiments. Next, the racemic thiol **3** was used in the substitution reaction with enol phosphate **2** under the reported conditions.<sup>10</sup> As expected, the formation of two main diastereomers **1a** and **1b** was observed, where diastereomer **1a**, which is more polar on SiO<sub>2</sub>, was predominant (~2:1, by <sup>1</sup>H NMR). Rapid purification of the reaction mixture by flash chromatography allows one to isolate this mixture in a total yield of 90%. Surprisingly, the remaining thiol **3** was enantiomerically enriched ( $[\alpha]_D^{20}$  -34°, ee=89). The product of kinetic control **1a** predominates in the **1a+1b** mixture. This means that 3(*R*)-**3** reacted almost completely, while 3(*S*)-**3** reacted partially, so the residual thiol **3** has an *S*-configuration. Individual diastereomers **1a** and **1b** were isolated by repeated column chromatography of the **1a+1b** mixture (SiO<sub>2</sub>, eluent: CHCl<sub>3</sub>:MeOH, 150:1). However, during the separation of the diastereomers by column chromatography on silica gel deactivated with NEt<sub>3</sub>, we observed a significant change in the ratio of diastereomers with predomination of the less polar diastereomer **1b**. The yield of **1a+1b** is 78%. The ratio of diastereomeric carbapenems changes from **1a:1b** = 2:1 to **1a:1b** ~ 1:3.3 (by <sup>1</sup>H NMR). Assessment of the material

balance in the chromatography indicates that **1a** is consumed in two directions. The base-catalyzed isomerization **1a**→**1b** and adverse destruction of thermodynamically less stable **1a** (see below) occur in parallel. Similar chromatography of individual **1a** gives a mixture of **1a** + **1b** with a total yield of 45% and a ratio of 1:5.

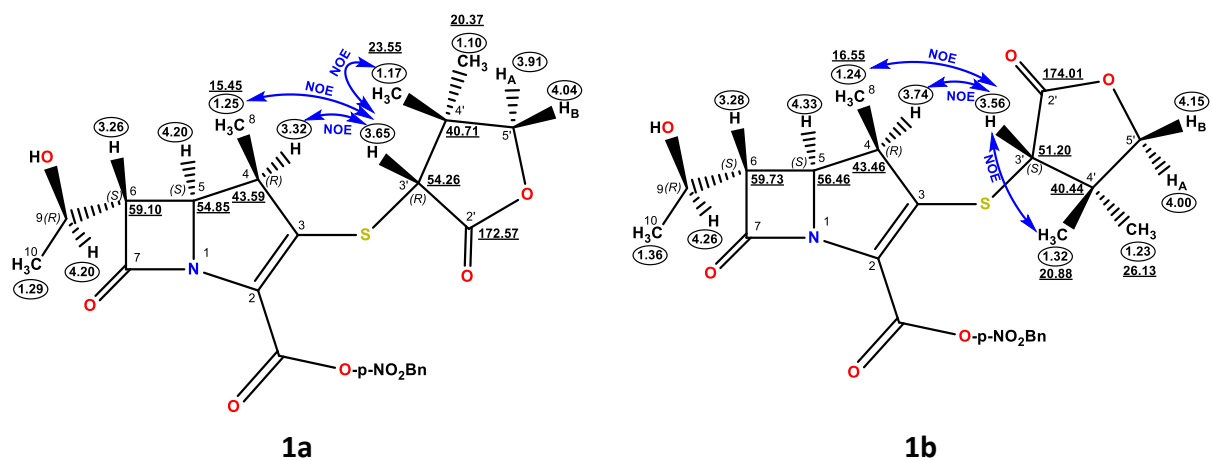
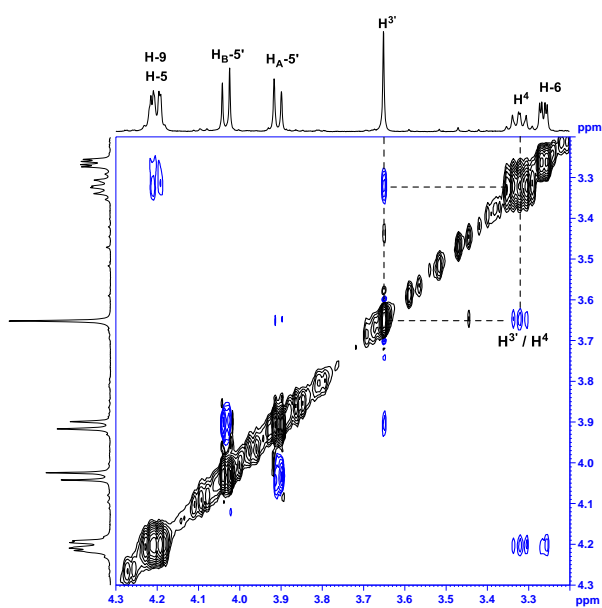
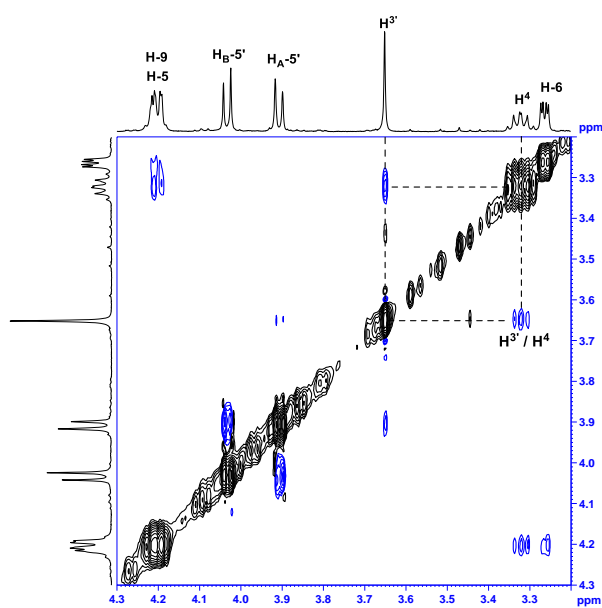
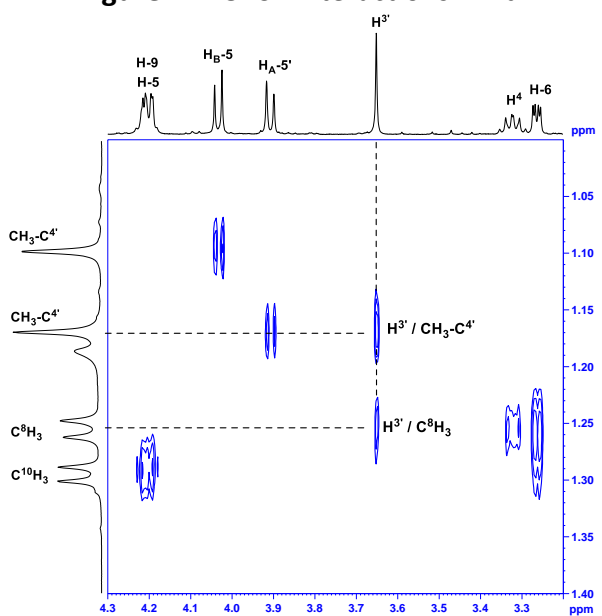
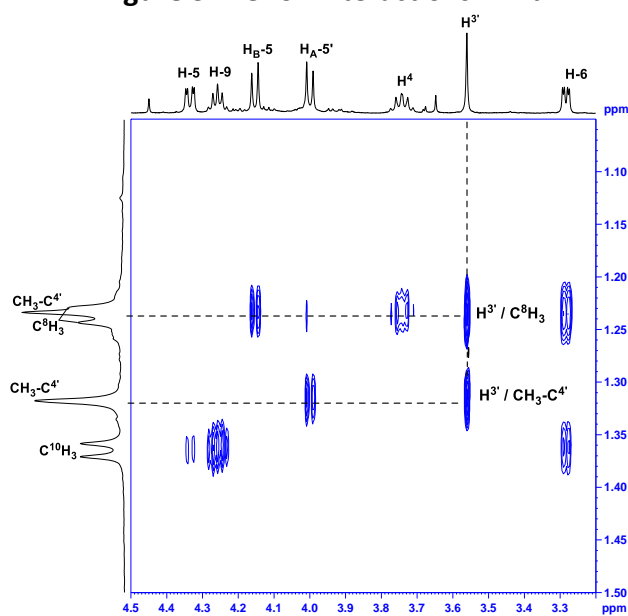


**Scheme 2.** Synthesis of thiol **3** and carbapenems **1a** and **1b**.

The chemical shifts of all protons and carbon atoms for the individual diastereomers **1a** and **1b** were assigned based on the  $^{13}\text{C}$  NMR spectra recorded with proton decoupling and in the DEPT-90 and DEPT-135 modes, as well as two-dimensional correlation spectra  $\{^1\text{H}, ^{13}\text{C}\}$  HSQC,  $\{^1\text{H}, ^{13}\text{C}\}$  HMBC,  $\{^1\text{H}, ^1\text{H}\}$  COSY and  $\{^1\text{H}, ^1\text{H}\}$  NOESY. The structure of the bicyclic part known to be  $4R, 5S, 6S$  is confirmed by the constants of spin-spin coupling between the protons at the  $C^4$ ,  $C^5$  and  $C^6$  carbon atoms. The connection of the five-membered lactone through the S atom to the bicycle gives two diastereomers differing in configuration at  $C^{3'}$  (*R* or *S*). Thus, the proton at  $C^{3'}$  for the less polar isomer **1b** resonates at  $\delta_{\text{H}}$  3.56 ppm as a singlet, and according to the HSQC spectrum, its carbon atom corresponds to the signal at  $\delta_{\text{C}}$  51.20 ppm. The chemical shifts of the remaining carbon atoms in the lactone part were determined from the cross-peaks in the HMBC spectrum:  $\delta_{\text{C}}(C^{2'}) = 174.01$ ,  $\delta_{\text{C}}(C^{4'}) = 40.44$ ,  $\delta_{\text{C}}(C^{5'}) = 77.74$  ppm.

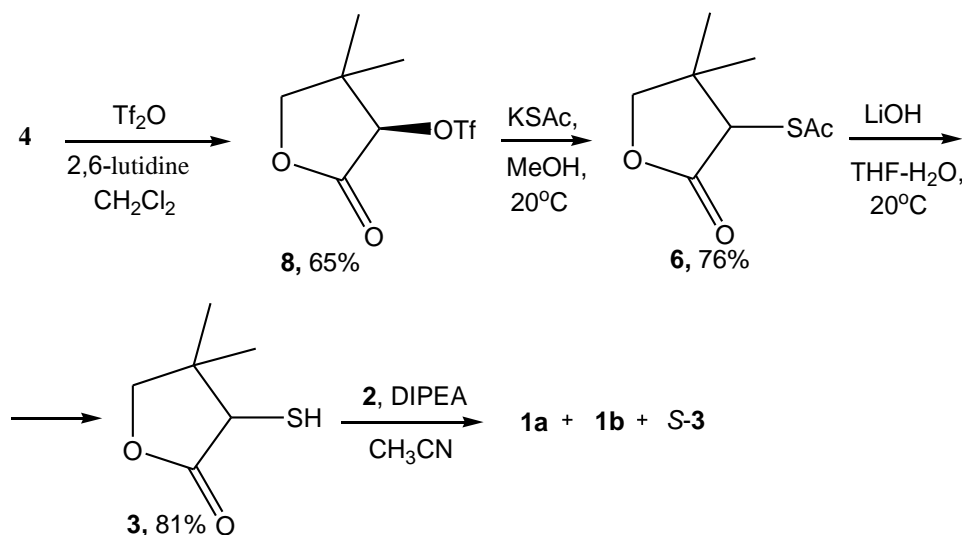
For the more polar isomer **1a**, the signals of the proton and carbon at  $C^{3'}$ -H position are observed at  $\delta_{\text{H}}$  3.65 ppm and  $\delta_{\text{C}}$  54.26 ppm, correspondingly.

Furthermore, the structures of diastereomers **1a** and **1b** were accurately assigned by NOESY spectra, where the cross peaks of the  $C^{3'}$ -H coupling at  $\delta_{\text{H}}$  3.65 and  $\delta_{\text{C}}$  3.56 ppm with the protons at  $C^4$  and with the protons of the methyl group at  $C^4$  were observed (Figure 1, 2). The observed NOE interactions indicate that in both diastereomers of **1**, the conformations in which  $C^{3'}$ -H is oriented to  $C^4$  predominate. According to the models, this situation is possible if two orientations of the lactone ring with *syn*- or *anti*-arrangement of the *gem*-dimethyl groups at the  $C^{4'}$  atom with respect to the  $C^4$ -CH<sub>3</sub> are realized.

Figure 1. Structures and main NOESY interactions in **1a** and **1b**.Figure 2. NOESY interactions in **1a**.Figure 3. NOESY interactions in **1b**.Figure 4. NOESY interactions in **1a**.Figure 5. NOESY interactions in **1b**.

Thus, the diastereomer with an *R* configuration at the C<sup>3'</sup> center is the more polar isomer **1a** and the less polar diastereomer **1b** has the *S* configuration at the C<sup>3'</sup> center with an *anti* C<sup>4'</sup>Me<sub>2</sub> position relative to the methyl group at the C<sup>4</sup> bicycle. The steric hindrance that arises in this case results in downfield shift of the signals of one of the methyl groups at C<sup>4'</sup> ( $\delta_c$  26.13 ppm). Considering that in the reaction of ( $\pm$ )-**3** with **2**, the predominant formation of **1a** is observed at first, the *S*-configuration of the chiral center should be assigned to the residual thiol (Scheme 2).

In the next stage, in order to improve the yields and optical purity of thiol **3**, the sequence **4**  $\rightarrow$  **8**  $\rightarrow$  **6** was used to synthesize thiol **3** from pantolactone **4** under milder conditions via trifluoromethanesulfonate derivative **8**<sup>14</sup> followed by hydrolysis (LiOH-THF-H<sub>2</sub>O). The thiol **3** obtained in this case had a  $[\alpha]_D^{20} = +3^\circ$  (ee=7.8). Its reaction with enol phosphate **2** also occurs with predominant formation of the more polar diastereomer **1a** (**1a** : **1b** ~ 2 : 1, by <sup>1</sup>H NMR).

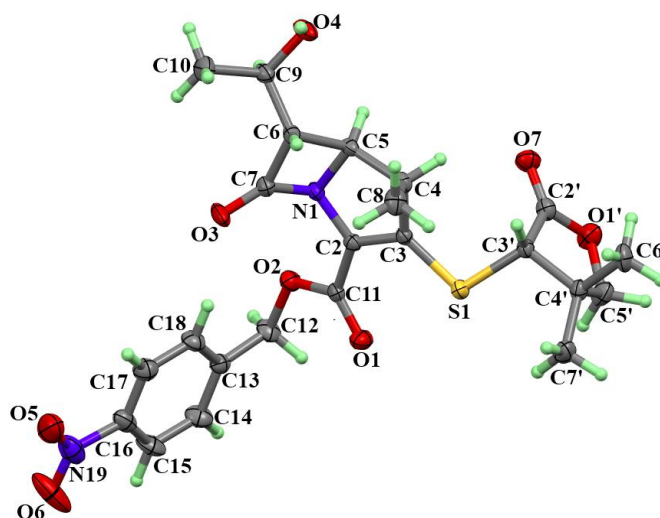


**Scheme 3.** Synthesis of thiol **3** via trifluoromethanesulfonate **8** and diastereomers **1a,1b**.

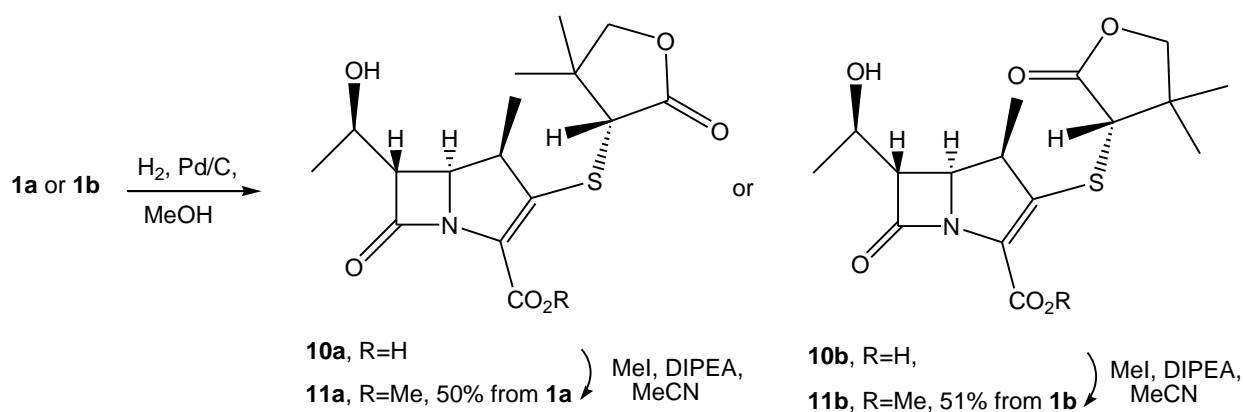
The assignment of **1a** and **1b** was confirmed by quantum chemical calculations. For the stationary points corresponding to the NOESY interactions found, we performed optimization of the geometric parameters, vibrational frequency calculation, calculation of the total energy and geometric corrections in the B3LYP / 6-311 + G (*d,p*) approximation for standard conditions (298.15 K, 1 atm) in the Gaussian program.<sup>15</sup> Estimation of the relative thermodynamic stability of the isomers,  $\Delta G^{298}$ , showed that diastereomer **1b** is the most favorable with  $\Delta G^{298}_{rel} = 2.7$  kJ/mol. The structure of **1b** was confirmed by X-ray diffraction data (Figure 6).

Due to the significant degradation during the isolation and purification, unstable acids **10a,b** after hydrogenolysis of **1a,b** were converted to methyl esters **11a, 11b** by treatment with MeI in MeCN-DIPEA. Unlike the acids **10a,b**, the latter were stable under the conditions of chromatographic purification on SiO<sub>2</sub> and were characterized by spectral methods.

We believe that methyl esters **11a,b** are more lipophilic prodrugs than **10a,b**, since the methyl esters are rapidly hydrolyzed enzymatically *in vivo* to the corresponding acids.



**Figure 6.** The molecular structure of **1b** with atom labelling. The atoms are drawn as thermal ellipsoids at the 50% probability level.

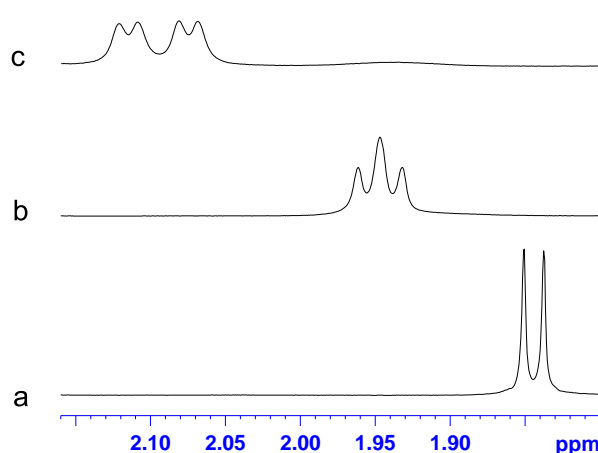


**Scheme 4.** Synthesis of methyl esters **11a,b** from **1a,b**.

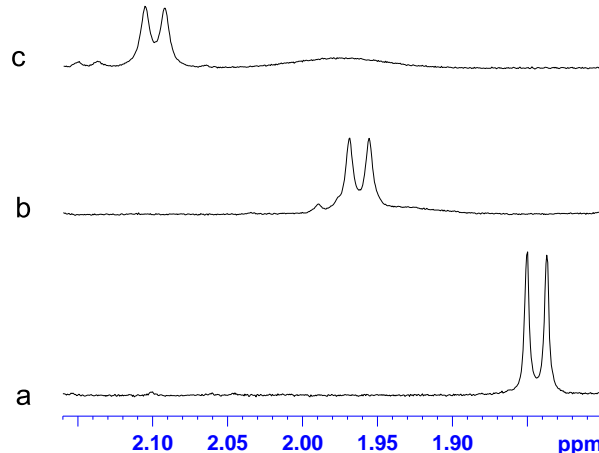
The enantiomeric purity of the thiol **3** obtained was determined by  $^1\text{H}$  NMR with a chiral shift reagent  $(-)\text{-Eu(hfc)}_3$  (Figures 7, 8). Accordingly, sequential addition of  $(-)\text{-Eu(hfc)}_3$  to a solution of  $(\pm)\text{-3}$  causes a shift and doubling of the SH signal in the  $^1\text{H}$  NMR spectra. In the case of *S*-**3**, doublet signals of both enantiomers are observed in the  $^1\text{H}$  NMR spectra upon addition of the europium complex (Figure 8), which indicates the high enantiomeric purity of the thiol  $(-)\text{-3}$  obtained (ee=89%).

The fact that a mixture of **1a** and **1b** with predominance of **1a** (**1a:1b** = 2:1) along with enantiomerically enriched residual thiol  $(-)\text{-3}$  are isolated quickly by flash chromatography in the reaction of  $(\pm)\text{-3}$  with chiral **2** indicates that the substitution occurs under conditions of considerable kinetic control.

However, during the chromatography of mixture **1a, 1b** on  $\text{NEt}_3$ -deactivated silica gel, the equilibrium in the **1a+1b** mixture shifts towards the thermodynamically more stable **1b**. The reason for this lies in the steric hindrance in structures **1a,b**. As a result, predominantly the thermodynamically favorable product is formed (product development control). There is no need to start from  $(-)\text{-pantolactone}$  in the synthesis of **1a,b**. The same result can be obtained using the cheap  $(\pm)\text{-pantolactone}$ .



**Figure 7.** SH signals in the spectrum of (±)-**3** (a) and in the presence of (-)-Eu (hfc)<sub>3</sub> (b, c). (b) and (c) have a different concentration of (-)-Eu (hfc)<sub>3</sub>



**Figure 8.** SH signals in the spectrum of S-**3** (a) and in the presence of (-)-Eu (hfc)<sub>3</sub> (b, c). (b) and (c) have a different concentration of (-)-Eu (hfc)<sub>3</sub>

## Conclusions

New carbapenems **1**, **11** containing a (±)-4,4-dimethyl-3-mercaptodihydrofuran-2(3*H*)-one fragment at C<sup>3</sup> have been synthesized. In the NOESY spectra, the characteristic NOE interactions between the C<sup>3'</sup>-H proton of the lactone with C<sup>4</sup>-Me and C<sup>4</sup>-H protons in the bicyclic part of both diastereomers was the determining factor in the structural assignments of **1a** and **1b**. The main structural differences in the diastereomers are caused by the *syn*- or *anti*-orientation of the *gem*-dimethyl groups in the lactone part with respect to the C<sup>4</sup>-Me of the bicycle. This assignment of diastereomers was subsequently confirmed by X-ray single-crystal diffraction analysis of **1b**.

Hydrogenolysis of the PNB-protecting groups of **1a**, **1b** gave the corresponding unstable acids, which were converted to methyl esters **11a**, **11b** without isolation.

A potentially important aspect of the application **1**, **11** is as follows: as it is well known, pantolactone **4** undergoes ring opening under mild conditions under the action of *N*-nucleophiles and anionic *O*-nucleophiles. In addition, the compounds **1**, **11** obtained are of interest as carbapenems sterically screened at C<sup>3</sup>, which increases their chemical stability. In the case of **1**, **11** the lactone ring is a potential moiety that reacts with *N*-nucleophiles (serine β-lactamases)<sup>16</sup> and *O*-nucleophiles (metallo-β-lactamases).<sup>17</sup> Thus, incorporation of a γ-lactone moiety into carbapenems simultaneously allows one to suppress the degrading action of lactamases.

Also, the tandem transformations with kinetic resolution of thiol **3** and the thermodynamically controlled selection in a mixture of **1a** + **1b** are of a significant synthetic interest.

## Experimental Section

**General.** IR spectra were recorded on a Shimadzu IR Prestige-21 spectrophotometer in films or Nujol mulls. NMR spectra were recorded on a Bruker Avance-III 500MHz spectrometer [operating frequencies 500.13 (<sup>1</sup>H) and 125.77 (<sup>13</sup>C) MHz], in CDCl<sub>3</sub>, in Acetone-*d*<sub>6</sub> for internal reference (δ<sub>H</sub> 7.27, 2.05, δ<sub>C</sub> 77.00, 29.84 ppm). The elemental compositions were determined with a Euro EA3000 CHNS analyzer. Atmospheric pressure chemical

ionization (APCI) mass spectra were obtained on an HPLC LCMS-2010EV mass-spectrometer (Shimadzu) (direct syringe sample inlet; sample solution in acetonitrile; acetonitrile/water (95:5) mobile phase) in positive and negative ion mode at ionizing electrode potentials of 4.5 kV and  $-3.5$  kV, respectively. The mobile phase flow rate was  $0.1 \text{ mL min}^{-1}$ . The temperature of the interface for APCI was  $250^\circ\text{C}$ , the heater and desolvation line temperatures were  $200$  and  $230^\circ\text{C}$ , respectively. The nebulizer gas (nitrogen) flow rate was  $2.5 \text{ L min}^{-1}$ . The progress of the reactions was monitored by TLC on Sorbfil plates; the spots were detected by treatment with a 10% solution of 4-methoxybenzaldehyde in ethanol acidified with sulfuric acid. Optical rotations were determined on a Perkin-Elmer 341 M polarimeter. To determinate enantiomeric purity of thiol **3**, a 0.05% solution of (-)-Eu(hfc)<sub>3</sub> in CDCl<sub>3</sub> was sequentially added (in 0.02 mL portions) with a syringe to a solution of thiol **3** in CDCl<sub>3</sub>. An NMR spectrum was recorded after each addition. This work was performed using the equipment of the “Khimiya” Center for Collective Use of the Ufa Institute of Chemistry UFCR RAS. X-Ray diffraction data were obtained using the equipment in the “Agidel” Regional Center for Collective Use at the UFCR RAS.

**(3R)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl methanesulfonate (5).** To a solution of D-(-)-pantolactone (1.0 g, 7.68 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (15 ml) was added Et<sub>3</sub>N (1.59 ml, 11.53 mmol), then MsCl (0.83 ml, 10.76 mmol). The reaction mixture was stirred for 12 h, then washed with H<sub>2</sub>O (2×10 ml). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. After purification of the residue by column chromatography on SiO<sub>2</sub> (petroleum ether-ethyl acetate, 9:1 → 4:1) mesylate **5** was obtained in 91% (1.45 g) yield as a white solid. Mp  $54\text{--}55^\circ\text{C}$ ,  $[\alpha]_D^{20} +16^\circ$  (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  1.17 (s, 3H, CH<sub>3</sub>), 1.27 (s, 3H, CH<sub>3</sub>), 3.28 (s, 3H, CH<sub>3</sub>), 4.05 (d,  $J$  9.1 Hz, 1H, H<sup>5A</sup>), 4.10 (d,  $J$  9.1 Hz, 1H, H<sup>5B</sup>), 4.99 (s, 1H, H<sup>3</sup>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  19.56 (CH<sub>3</sub>), 22.18 (CH<sub>3</sub>), 39.74 (CH<sub>3</sub>), 40.31 (C<sup>4</sup>), 76.24 (C<sup>5</sup>), 81.41 (C<sup>3</sup>), 171.37 (C=O). IR ( $\nu_{\text{max}}$ , cm<sup>-1</sup>): 1781, 1480, 1350, 1183, 1070, 979, 852. Anal. calcd for C<sub>7</sub>H<sub>12</sub>O<sub>5</sub>S (208.23): C, 40.38; H, 5.81; S, 15.40. Found: C, 40.49; H, 5.70; S, 15.51.

**S-(4,4-Dimethyl-2-oxotetrahydrofuran-3-yl) ethanethioate (6).** To a solution of mesylate **5** (0.20 g, 0.96 mmol) in of anhydrous CH<sub>3</sub>CN (10 ml) at room temperature was added CH<sub>3</sub>COSK (0.25 g, 2.21 mmol). The reaction mixture was refluxed for 6 h (TLC control), evaporated, the residue was diluted with EtOAc, washed with 5% HCl solution to pH 5 then with saturated solutions of NaHCO<sub>3</sub> and NaCl. The combined organic layers were dried over MgSO<sub>4</sub>, filtered, evaporated. After purification of the residue by column chromatography on SiO<sub>2</sub> (petroleum ether-ethyl acetate, 9:1 → 6:1), thioacetate **6** (0.13 g, 73%) was obtained. A pale yellow oily substance.  $[\alpha]_D^{20} 0^\circ$  (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  1.07 (s, 3H, CH<sub>3</sub>), 1.17 (s, 3H, CH<sub>3</sub>), 2.46 (s, 3H, CH<sub>3</sub>), 4.08 (d,  $J$  8.8 Hz, 1H, H<sup>5A</sup>), 4.10 (d,  $J$  8.8 Hz, 1H, H<sup>5B</sup>), 4.36 (s, 1H, H<sup>3</sup>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  22.53 (CH<sub>3</sub>), 23.27 (CH<sub>3</sub>), 30.31 (CH<sub>3</sub>), 40.68 (C<sup>4</sup>), 52.55 (C<sup>3</sup>), 78.02 (C<sup>5</sup>), 174.03 (C=O), 192.66 (S-C=O). IR ( $\nu_{\text{max}}$ , cm<sup>-1</sup>): 1780, 1703, 1699, 1362, 1128, 1028, 1012, 952, 931. MS (APCI):  $m/z$  189 (M+H<sup>+</sup>, 100). Anal. calcd for C<sub>8</sub>H<sub>12</sub>O<sub>3</sub>S (188.24): C, 51.04; H, 6.43; S, 17.03. Found: C, 51.12; H, 6.34; S, 17.11.

**Hydrolysis of the acetate group.** To a solution of thioacetate **6** (0.20 g, 1.06 mmol) in a THF-H<sub>2</sub>O mixture (10 ml, 2:1) at room temperature was added LiOH (0.08 g, 3.18 mmol) and stirred for 3 h (TLC). The reaction mixture was concentrated in vacuo, the residue was acidified with 5% HCl solution to pH 4, and the reaction product was extracted with CHCl<sub>3</sub>. The organic extracts were dried over MgSO<sub>4</sub>, filtered, and the solution was concentrated in vacuo. After purification of the residue by column chromatography on SiO<sub>2</sub> (petroleum ether-ethyl acetate, 9:1 → 6:1), thiol **3** (0.08 g, 53%) and dimer **7** (0.04 g, 13%) were obtained.

**4,4-Dimethyl-3-thiodihydrofuran-2(3H)-one (3).** A pale yellow oil.  $[\alpha]_D^{20} 0^\circ$  (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  1.12 (s, 3H, CH<sub>3</sub>), 1.21 (s, 3H, CH<sub>3</sub>), 1.84 (d,  $J$  6.7 Hz, 1H, SH), 3.46 (d,  $J$  6.7 Hz, 1H, H<sup>3</sup>), 3.96 (d,  $J$  8.8 Hz, 1H, H<sup>5A</sup>), 4.13 (d,  $J$  8.8 Hz, 1H, H<sup>5B</sup>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  20.95 (CH<sub>3</sub>), 24.36 (CH<sub>3</sub>), 40.77 (C<sup>4</sup>), 48.21 (C<sup>3</sup>),



77.67 (C<sup>5</sup>), 175.65 (C=O). IR ( $\nu_{\max}$ , cm<sup>-1</sup>): 1778, 1463, 1277, 1021, 1005, 952, 931. MS (APCI):  $m/z$  145 (M-H<sup>+</sup>, 100). Anal. calcd for C<sub>6</sub>H<sub>10</sub>O<sub>2</sub>S (146.21): C, 49.29; H, 6.89; S, 21.93. Found: C, 49.38; H, 6.77; S, 22.02.

**3,3'-Thiobis(4,4-dimethyldihydrofuran-2(3H)-one) (7).** A pale yellow oil. <sup>1</sup>H NMR (500 MHz, Acetone-*d*<sub>6</sub>):  $\delta_{\text{H}}$  1.10 (s, 3H, CH<sub>3</sub>), 1.11 (s, 3H, CH<sub>3</sub>), 1.30 (s, 3H, CH<sub>3</sub>), 1.31 (s, 3H, CH<sub>3</sub>), 2.85 (s, 2H, H<sup>3</sup>, H<sup>3'</sup>), 4.07-4.10 (m, 4H, H<sup>5</sup>, H<sup>5'</sup>). <sup>13</sup>C NMR (125 MHz, Acetone-*d*<sub>6</sub>):  $\delta_{\text{C}}$  20.64 (CH<sub>3</sub>), 20.80 (CH<sub>3</sub>), 23.20 (CH<sub>3</sub>), 23.43 (CH<sub>3</sub>), 41.06 (C<sup>4</sup>), 41.20 (C<sup>4'</sup>), 61.78 (C<sup>3</sup>, C<sup>3'</sup>), 77.32 (C<sup>5</sup>, C<sup>5'</sup>), 173.94 (C=O), 174.42 (C'=O). IR ( $\nu_{\max}$ , cm<sup>-1</sup>): 1781, 1705, 1433, 1252, 1028, 1011, 931. MS (APCI):  $m/z$  291 (M+H<sup>+</sup>, 100). Anal. calcd for C<sub>12</sub>H<sub>18</sub>O<sub>4</sub>S<sub>2</sub> (290.40): C, 49.63; H, 6.25; S, 22.08. Found: C, 49.51; H, 6.31; S, 22.01.

**Synthesis of carbapenems 1a and 1b.** Thiol **3** (0.092 g, 0.63 mmol) and DIPEA (0.11 ml, 0.63 mmol) were added to a stirred solution of carbapenem enol phosphate **2** (0.3 g, 0.50 mmol) in anhydrous CH<sub>3</sub>CN (15 ml) at 0 °C and the reaction mixture was stirred until the disappearance of **2** (3 h, TLC). The solvent was evaporated, a mixture **1a** + **1b** (0.22 g, 90%) in a ratio of 2:1 (<sup>1</sup>H NMR) and 0.015 g of unreacted thiol **5-3** with [ $\alpha$ ]<sub>D</sub><sup>20</sup> -34° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>) were isolated by flash chromatography of the residue on silica gel (CHCl<sub>3</sub>:MeOH, 100:1).

Individual diastereomers **1a** and **1b** were isolated by repeated column chromatography of the **1a+1b** mixture (SiO<sub>2</sub>, eluent: CHCl<sub>3</sub>:MeOH, 150:1).

On chromatographing a mixture of **1a+1b** on a column with silica gel deactivated with NEt<sub>3</sub>, the ratio of **1a** and **1b** changes from ~2:1 to ~1:3.3, but the total yield decreases (78%) due to partial decomposition of the less stable **1a** and its epimerization to **1b**.

**4-Nitrobenzyl (4R,5S,6S)-3-[[[(3R)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1a).** White solid. Mp 76 °C, [ $\alpha$ ]<sub>D</sub><sup>20</sup> +185° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  1.10 (s, 3H, C<sup>4'</sup>-CH<sub>3</sub>), 1.17 (s, 3H, C<sup>4'</sup>-CH<sub>3</sub>), 1.25 (d, *J* 7.2 Hz, 3H, C<sup>8</sup>H<sub>3</sub>), 1.29 (d, *J* 6.2 Hz, 3H, C<sup>10</sup>H<sub>3</sub>), 3.26 (dd, *J* 6.5 Hz, *J* 2.6 Hz, 1H, H<sup>6</sup>), 3.32 (dq, 1H, *J* 9.2 Hz, *J* 7.2 Hz, H<sup>4</sup>), 3.65 (s, 1H, H<sup>3</sup>), 3.91 (d, *J* 8.9 Hz, 1H, H<sup>5A</sup>), 4.03 (d, *J* 8.9 Hz, 1H, H<sup>5B</sup>), 4.20 (dd, 1H, *J* 9.2 Hz, *J* 2.6 Hz, H<sup>5</sup>), 4.21 (dq, 1H, *J* 6.5 Hz, *J* 6.2 Hz, H<sup>9</sup>), 5.19 (d, 1H, *J* 13.6 Hz, OCH<sup>A</sup>), 5.46 (d, *J* 13.6 Hz, 1H, OCH<sup>B</sup>), 7.60 (d, *J* 8.7 Hz, 2H, H<sub>Ar</sub>), 8.16 (d, *J* 8.7 Hz, 2H, H<sub>Ar</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  15.45 (C<sup>8</sup>H<sub>3</sub>), 20.37 (C<sup>4'</sup>-CH<sub>3</sub>), 20.90 (C<sup>10</sup>H<sub>3</sub>), 23.55 (C<sup>4'</sup>-CH<sub>3</sub>), 40.71 (C<sup>4</sup>), 43.59 (C<sup>4</sup>), 54.26 (C<sup>3</sup>), 54.85 (C<sup>5</sup>), 59.10 (C<sup>6</sup>), 64.56 (OCH<sub>2</sub>), 64.80 (C<sup>9</sup>), 76.75 (C<sup>5</sup>), 122.77 (CH<sub>Ar</sub>), 126.64 (C<sup>2</sup>), 127.28 (CH<sub>Ar</sub>), 141.56 (C<sub>Ar</sub>), 145.64 (C<sup>3</sup>), 146.75 (C<sub>Ar</sub>), 158.91 (CO<sub>2</sub>), 171.33 (C<sup>7</sup>), 172.57 (C<sup>2'</sup>).

**4-Nitrobenzyl (4R,5S,6S)-3-[[[(3S)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1b).** White solid. Mp 189-191 °C, [ $\alpha$ ]<sub>D</sub><sup>20</sup> -9° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  1.23 (s, 3H, C<sup>4'</sup>-CH<sub>3</sub>), 1.24 (d, *J* 7.2 Hz, 3H, C<sup>8</sup>H<sub>3</sub>), 1.32 (s, 3H, C<sup>4'</sup>-CH<sub>3</sub>), 1.36 (d, *J* 6.2 Hz, 3H, C<sup>10</sup>H<sub>3</sub>), 3.28 (dd, *J* 6.8 Hz, *J* 2.7 Hz, 1H, H<sup>6</sup>), 3.56 (s, 1H, H<sup>3</sup>), 3.74 (dq, *J* 9.2 Hz, *J* 7.2 Hz, 1H, H<sup>4</sup>), 4.00 (d, *J* 8.9 Hz, 1H, H<sup>5A</sup>), 4.15 (d, *J* 8.9 Hz, 1H, H<sup>5B</sup>), 4.26 (dq, *J* 6.8 Hz, *J* 6.2 Hz, 1H, H<sup>9</sup>), 4.33 (dd, *J* 9.2 Hz, *J* 2.7 Hz, 1H, H<sup>5</sup>), 5.24 (d, *J* 13.7 Hz, 1H, OCH<sup>A</sup>), 5.51 (d, *J* 13.7 Hz, 1H, OCH<sup>B</sup>), 7.65 (d, *J* 8.6 Hz, 2H, H<sub>Ar</sub>), 8.22 (d, *J* 8.6 Hz, 2H, H<sub>Ar</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  16.55 (C<sup>8</sup>H<sub>3</sub>), 20.88 (C<sup>4'</sup>-CH<sub>3</sub>), 21.85 (C<sup>10</sup>H<sub>3</sub>), 26.13 (C<sup>4'</sup>-CH<sub>3</sub>), 40.44 (C<sup>4</sup>), 43.46 (C<sup>4</sup>), 51.20 (C<sup>3</sup>), 56.46 (C<sup>5</sup>), 59.73 (C<sup>6</sup>), 65.45 (OCH<sub>2</sub>), 66.11 (C<sup>9</sup>), 77.74 (C<sup>5</sup>), 123.78 (CH<sub>Ar</sub>), 126.70 (C<sup>2</sup>), 128.16 (CH<sub>Ar</sub>), 142.88 (C<sub>Ar</sub>), 147.68 (C<sub>Ar</sub>), 147.70 (C<sup>3</sup>), 160.29 (CO<sub>2</sub>), 172.61 (C<sup>7</sup>), 174.01 (C<sup>2'</sup>). IR ( $\nu_{\max}$ , cm<sup>-1</sup>): 3438, 1757, 1734, 1700, 1527, 1346, 1206, 1152, 1088, 1011, 993. MS (APCI):  $m/z$  491 (M+H<sup>+</sup>, 100). Anal. calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub>S (490.53): C, 56.32; H, 5.34; N, 5.71; S, 6.54. Found: C 56.41, H 5.25, N 5.62, S 6.62.

**(3R)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl trifluoromethanesulfonate (8).** To a solution of D-(-)-pantolactone (0.24 g, 1.84 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (8 ml) under argon atmosphere at -20 °C was added 2,6-lutidine (0.54 ml, 4.61 mmol) then at -78 °C (0.72 ml, 4.29 mmol) of Tf<sub>2</sub>O. The reaction mixture was stirred at -78 °C for 30 minutes, then warmed to room temperature and stirred for 2 hours. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with H<sub>2</sub>O (3-5 ml). The organic layers were dried over MgSO<sub>4</sub>, filtered, and the

solvent was distilled off in vacuo. After purification of the residue by column chromatography on SiO<sub>2</sub> (petroleum ether-ethyl acetate, 7:1 → 4:1), triflate **8**<sup>14</sup> (0.32 g, 65%) was obtained. White solid, Mp 29-30 °C,  $[\alpha]_D^{20} +4.0^\circ$  (c 1.0, MeOH) (lit.<sup>14</sup> Mp 29-30 °C,  $[\alpha]_D^{20} +3.8^\circ$  (c 1.0, MeOH)). <sup>1</sup>H NMR (500 MHz, Acetone-*d*<sub>6</sub>): δ<sub>H</sub> 1.20 (s, 3H, CH<sub>3</sub>), 1.36 (s, 3H, CH<sub>3</sub>), 4.26 (d, *J* 9.0 Hz, 1H, H<sup>5A</sup>), 4.31 (d, *J* 9.0 Hz, 1H, H<sup>5B</sup>), 5.73 (s, 1H, H<sup>3</sup>). <sup>13</sup>C NMR (125 MHz, Acetone-*d*<sub>6</sub>): δ<sub>C</sub> 19.83 (CH<sub>3</sub>), 21.70 (CH<sub>3</sub>), 41.43 (C<sup>4</sup>), 76.31 (C<sup>5</sup>), 87.89 (C<sup>3</sup>), 119.47 (q, <sup>1</sup>J<sub>CF</sub> 319 Hz, CF<sub>3</sub>), 169.95 (C=O). IR, ν, cm<sup>-1</sup>: 1792, 1419, 1248, 1362, 1208, 1139, 1034, 996, 868.

**S-(4,4-Dimethyl-2-oxotetrahydrofuran-3-yl) ethanethioate (6).** CH<sub>3</sub>COSK (0.29 g, 2.92 mmol) was added to a solution of triflate **8** (0.24 g, 0.92 mmol) in anhydrous MeOH (7 ml) under an argon atmosphere. The reaction mixture was stirred for 2 hours (TLC), then MeOH was evaporated. The residue was diluted with ethyl acetate, then washed with H<sub>2</sub>O (2–5 ml) and saturated NaCl solution. The organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. After purification of the residue by column chromatography on SiO<sub>2</sub> (petroleum ether-ethyl acetate, 9:1 → 6:1), thioacetate **6** (0.13 g, 76%) was obtained. A pale yellow oil,  $[\alpha]_D^{20} +3^\circ$  (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>).

**4,4-Dimethyl-3-thiodihydrofuran-2(3H)-one (3).** To a solution of thioacetate **6** (0.08 g, 0.42 mmol) in 6 ml a mixture of THF-H<sub>2</sub>O (2:1) was added LiOH (0.03 g, 1.26 mmol). The reaction mixture was stirred for 3 hours (TLC), concentrated in vacuo, the residue was acidified with 5% HCl solution to pH 4, and the reaction product was extracted with CHCl<sub>3</sub>. The organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether-ethyl acetate, 6:1 → 4:1) to give a pale yellow oily thiol **3** (0.05 g, 81%) with  $[\alpha]_D^{20} +3^\circ$  (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>).

The reaction of this thiol **3** with enol phosphate **2** leads to the same result as for (±)-**3**.

**Synthesis of carbapenems 11a and 11b.** A mixture of carbapenems **1b** (0.16 g, 0.33 mmol) and 10% Pd/C (0.15 g) in anhydrous MeOH (10 ml) was stirred under hydrogen atmosphere for 3 hours at room temperature until complete conversion of the starting compound (TLC). The catalyst was filtered off in an argon atmosphere and washed with MeOH, then the filtrate was concentrated in vacuo. The residue was diluted with 10 ml of CH<sub>3</sub>CN, then 0.08 ml (1.29 mmol) of MeI and 0.12 ml (0.66 mmol) of DIPEA were added and the reaction mixture was stirred an argon atmosphere until the disappearance of **10b** (1 day, TLC). The solvent was removed under reduced pressure. After purification of the residue by column chromatography on SiO<sub>2</sub> (petroleum ether-ethyl acetate, 1:1→1:2), methyl ether **11b** was obtained in 51% (0.06 g) yield for 2 stages. Methyl carbapenem **11a** was obtained from **1a** (0.10 g, 0.20 mmol) in 50% (0.037 g) yield according to the above procedure.

**Methyl (4R,5S,6S)-3-[(3R)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (11a).** White solid. Mp 154-156 °C,  $[\alpha]_D^{20} +183^\circ$  (c 0.5, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 1.19 (s, 3H, C<sup>4'</sup>-CH<sub>3</sub>), 1.25 (s, 3H, C<sup>4'</sup>-CH<sub>3</sub>), 1.30 (d, *J* 7.2 Hz, 3H, C<sup>8</sup>H<sub>3</sub>), 1.35 (d, *J* 6.2 Hz, 3H, C<sup>10</sup>H<sub>3</sub>), 3.30 (dd, *J* 6.6 Hz, *J* 2.7 Hz, 1H, H<sup>6</sup>), 3.37 (dq, 1H, *J* 9.2 Hz, *J* 7.2 Hz, H<sup>4</sup>), 3.72 (s, 1H, H<sup>3</sup>), 3.88 (s, 3H, OCH<sub>3</sub>), 3.98 (d, *J* 9.0 Hz, 1H, H<sup>5A</sup>), 4.11 (d, *J* 9.0 Hz, 1H, H<sup>5B</sup>), 4.24 (dd, *J* 9.2 Hz, *J* 2.7 Hz, 1H, H<sup>5</sup>), 4.26 (dq, 1H, *J* 6.6 Hz, *J* 6.2 Hz, H<sup>9</sup>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 16.39 (C<sup>8</sup>H<sub>3</sub>), 21.40 (C<sup>4'</sup>-CH<sub>3</sub>), 21.83 (C<sup>10</sup>H<sub>3</sub>), 24.56 (C<sup>4'</sup>-CH<sub>3</sub>), 41.75 (C<sup>4</sup>), 44.43 (C<sup>4</sup>), 52.50 (OMe), 55.29 (C<sup>3</sup>), 55.90 (C<sup>5</sup>), 60.03 (C<sup>6</sup>), 65.92 (C<sup>9</sup>), 77.81 (C<sup>5</sup>), 128.40 (C<sup>2</sup>), 145.25 (C<sup>3</sup>), 160.91 (CO<sub>2</sub>Me), 172.42 (C<sup>7</sup>), 173.86 (C<sup>2</sup>).

**Methyl (4R,5S,6S)-3-[(3S)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (11b).** White solid. Mp 178-180 °C,  $[\alpha]_D^{20} -29^\circ$  (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 1.22 (d, *J* 7.2 Hz, 3H, C<sup>8</sup>H<sub>3</sub>), 1.25 (s, 3H, C<sup>4'</sup>-CH<sub>3</sub>), 1.32 (s, 3H, C<sup>4'</sup>-CH<sub>3</sub>), 1.35 (d, *J* 6.2 Hz, 3H, C<sup>10</sup>H<sub>3</sub>), 3.25 (dd, *J* 7.1 Hz, *J* 2.6 Hz, 1H, H<sup>6</sup>), 3.56 (s, 1H, H<sup>3</sup>), 3.69 (dq, *J* 9.2 Hz, *J* 7.2 Hz, 1H, H<sup>4</sup>), 3.85 (s, 3H, OCH<sub>3</sub>), 4.00 (d, *J* 9.0 Hz, 1H, H<sup>5A</sup>), 4.17 (d, *J* 9.0 Hz, 1H, H<sup>5B</sup>), 4.23 (dq, *J* 7.1 Hz, *J* 6.2 Hz, 1H, H<sup>9</sup>), 4.30 (dd, *J* 9.2 Hz, *J* = 2.6 Hz, 1H, H<sup>5</sup>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 16.46 (C<sup>8</sup>H<sub>3</sub>), 20.86 (C<sup>4'</sup>-CH<sub>3</sub>), 21.74 (C<sup>10</sup>H<sub>3</sub>), 26.12 (C<sup>4'</sup>-

CH<sub>3</sub>), 40.43 (C<sup>4'</sup>), 43.30 (C<sup>4</sup>), 51.10 (C<sup>3'</sup>), 52.43 (OMe), 56.53 (C<sup>5</sup>), 59.61 (C<sup>6</sup>), 66.15 (C<sup>9</sup>), 77.73 (C<sup>5'</sup>), 127.06 (C<sup>2</sup>), 146.47 (C<sup>3</sup>), 161.32 (CO<sub>2</sub>Me), 172.73 (C<sup>7</sup>), 174.19 (C<sup>2'</sup>). IR ( $\nu_{\max}$ , cm<sup>-1</sup>): 3420, 1775, 1730 1706, 1653, 1559, 1506, 1457, 1349, 1218, 1147, 1010. MS (APCI): *m/z* 370 (*M*+H<sup>+</sup>, 100), 284 (*M*-[C<sub>4</sub>H<sub>6</sub>O<sub>2</sub>]+H<sup>+</sup>, 50). Anal. calcd for C<sub>17</sub>H<sub>23</sub>NO<sub>6</sub>S (369.43): C, 55.27; H, 6.28; N, 3.79; S, 8.68. Found: C 55.41, H 6.13, N 3.91, S 8.52.

**X-ray Crystallography.** The X-ray diffraction measurements for compound **1b** was performed on a Agilent XCalibur (Gemini, Eos) diffractometer with graphite-monochromated MoK $\alpha$  radiation ( $\lambda$  = 0.71073 Å). The structure was solved with the ShelXS<sup>18</sup> structure solution program using Direct Methods and refined with the ShelXL<sup>19</sup> refinement package using Least Squares minimization. All hydrogen atoms are generated using the proper HFIX command and refined isotropically using the riding model.

Crystal data for **1b**. C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub>S (*M* = 490.52), monoclinic, space group C2: *a* = 23.6710(14), *b* = 6.1115(3) and *c* = 17.4616(10) Å,  $\beta$  = 109.925(6)°, *V* = 2374.9(2) Å<sup>3</sup>, *Z* = 4, *d*<sub>calc</sub> = 1.372 g cm<sup>-3</sup>,  $\mu$ (MoK $\alpha$ ) = 0.187 mm<sup>-1</sup>, *F*(000) = 1032.0. Total of 5824 were collected (4480 independent reflections, *R*<sub>int</sub> = 0.0350), GOOF 0.997. The final *R*<sub>1</sub> was 0.0468 (*I* > 2 $\sigma$ (*I*)) and *wR*<sub>2</sub> was 0.0957 (all data).

CCDC 2009010 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>.

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## Supplementary Material

Copy of <sup>1</sup>H and <sup>13</sup>C NMR spectra of synthesized compounds are provided in supplementary materials.

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