PRELIMINARY EXPERIMENTS FOR ASYMMETRIC TOTAL SYNTHESIS OF THE THIENAMYCIN-LIKE γ-LACTAM†

Hiroshi Matsunaga,[a] Toshio Kumagai,[a] Yoshinori Inoue,[a] and Yoshimitsu Nagao[b*]

[a] The Chemical and Formulation Research Laboratories, Lederle (Japan), Ltd., Kashiwa-cho, Shiki, Saitama 353, Japan

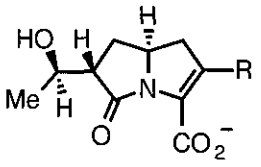
b Faculty of Pharmaceutical Science, The University of Tokushima, Sho-machi, Tokushima 770, Japan

Abstract - Optically active bicyclic γ-lactam carboxylates (**3** and **4**) were readily synthesized by employing chiral 5-alkylated pyrrolidin-2-one (**9b**) obtained from an asymmetric alkylation with tin(II) enolate (**6a**) onto 5-acetoxypyrrolidin-2-one (**7b**).

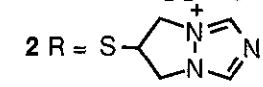
In recent years, a number of γ-lactam analogues of β-lactam antibiotics have been investigated in order to develop a new class of non-natural antibacterial agents.[1] Recently, we have reported the first asymmetric total synthesis of thienamycin like γ-lactam (**1**) and its analogue (**2**) by utilizing a highly diastereoselective alkylation (**8a**→**9a**) of a chiral tin(II) enolate (**6b**) onto the cyclic acylimine obtained from chiral 3-substituted 5-acetoxypyrrolidin-2-one (**7a**).[2] Before achievement of the total synthesis of compounds (**1** and **2**), we examined an asymmetric synthesis of bicyclic chiral γ-lactam derivatives (**3** and **4**) as the preliminary study, which is herein described in detail.

(4*S*)-3-Acetyl-4-ethyl-1,3-thiazolidine-2-thione (**5a**)[3] was treated with tin(II) trifluoromethane-

† This paper is dedicated to Dr. Arnord Brossi, Scientist Emeritus NIH, on the occasion of his 70th birthday.



1 R = $S(CH_2)_2\overset{+}{N}H_3$



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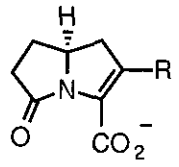

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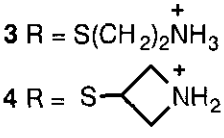
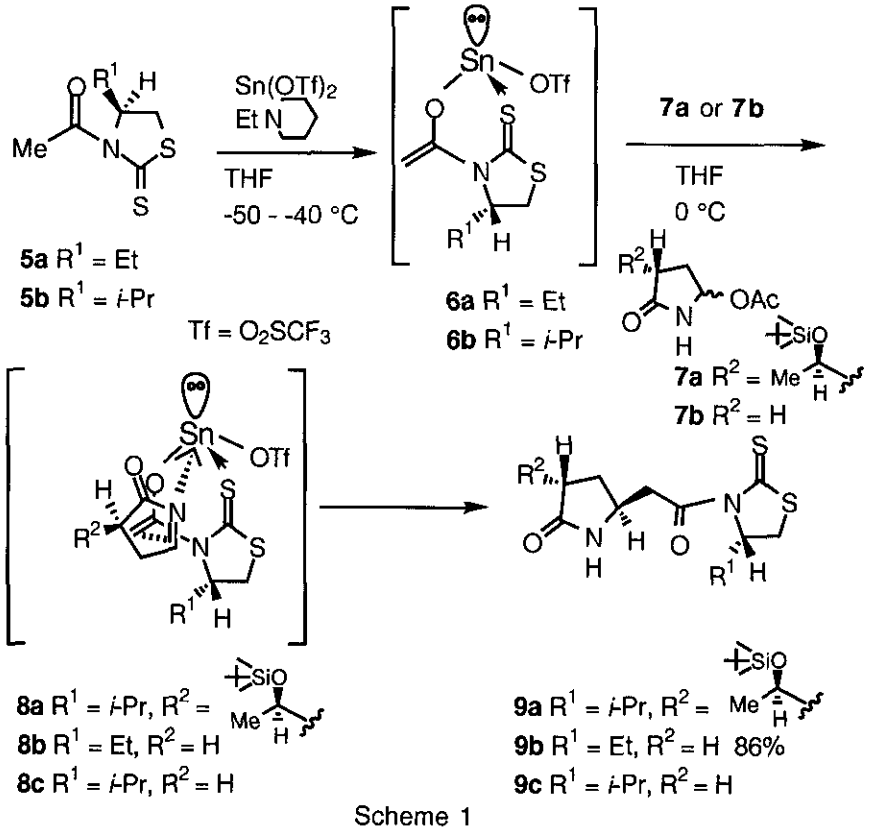


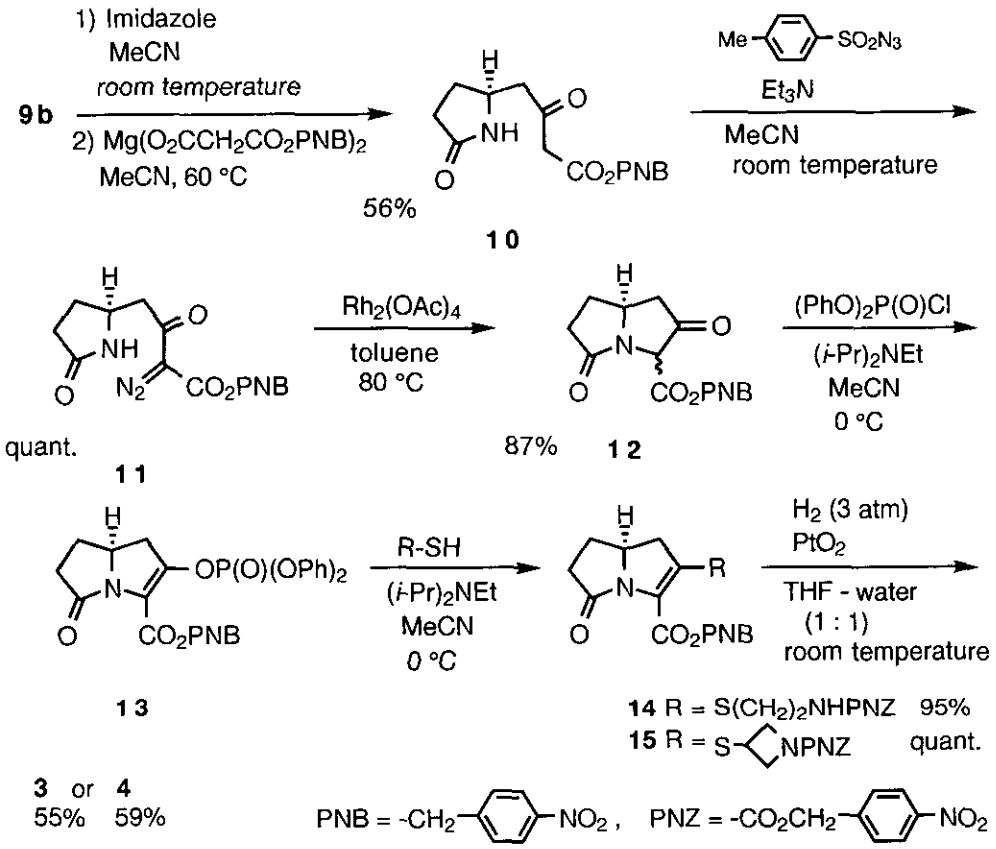
4 R = S-

sulfonate[4] in the presence of *N*-ethylpiperidine[4] in THF at -50 - -40°C to give the chiral tin(II) enolate (**6a**). Treatment of the THF solution of **6a** with 5-acetoxypyrrolidin-2-one (**7b**) at 0°C afforded a crude alkylated product (**9b**) [94% diastereomer excess (hplc analysis)], which was purified on a silica gel column to give pure compound (**9b**) in 86% yield as shown in Scheme 1. Stereochemistry of the newly formed asymmetric carbon atom (C5) of **9b** must be the same as that of the known compound (**9c**)[5] because these compounds can be provided *via* a common transition state (**8b,c**) from **5a, b**.



Scheme 1

Aminolysis of **9b** with imidazole in MeCN followed by decarboxylative Claisen-type reaction with $Mg(O_2CCH_2CO_2PNB)_2$ at 60°C gave β-keto PNB ester (**10**) as colorless needles in 56% yield. Crystalline compound (**11**), derived from **10** by diazotization with *p*-toluenesulfonyl azide and Et_3N, was submitted to the carbenoid insertion reaction[6] using $Rh_2(OAc)_4$ (0.6 w/w%) to give a bicyclic



Scheme 2

product (**12**) in 87% yield. The bicyclic β-keto PNB ester (**12**) was treated with diphenyl chlorophosphate in the presence of $(i\text{-Pr})_2NEt$ in MeCN to give the diphenylphosphoryloxy derivative (**13**) in 82% yield. On treatment with *N*-*p*-nitrobenzyloxycarbonylaminoethanethiol[7] or *N*-*p*-nitrobenzyloxycarbonylazetidinethiol[8] in the presence of $(i\text{-Pr})_2NEt$, compound (**13**) was readily converted to the corresponding thioether (**14**) or (**15**) in excellent yield respectively as pale yellow crystals. Hydrogenolysis of **14** and **15** on PtO_2 under H_2 (3 atm) in THF-water (1:1) furnished the corresponding bicyclic γ-lactam carboxylates (**3**) in 55% yield as amorphous powder [mp 145-146°C

(water)] and (**4**) in 59% yield as amorphous powder [mp 182-183°C (water)], respectively. Thus, the preliminary experiments as described above proved to be useful for the asymmetric total synthesis of thienamycin-like γ-lactam (**1**).[2]

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus, and are uncorrected. The ir spectra were recorded on a Hitachi 260-50 spectrophotometer. ^{1}H Nmr spectra were determined on a JEOL JNM-FX 200 (200 MHz) spectrometer in $CDCl_3$ or D_2O solution and chemical shifts are reported in δ (ppm) relative to tetramethylsilane. Mass spectra were taken on a JEOL JMS-D300 instrument. Optical rotations were measured with a JASCO-DIP-181 polarimeter. Elemental analyses were obtained on a Yanaco CHN MT-3 CORDER. Column chromatography was performed on silica gel (Fuji-Davision, BW-127ZH). All reactions were monitored by silica gel F_{254} plates (Merck). All organic extracts were dried over anhydrous sodium sulfate.

(5*S*)-[(4*S*)-(4-Ethyl-1,3-thiazolidine-2-thion-3-yl)carbonylmethyl]pyrrolidin-2-one (9b). To a stirred suspension of $Sn(OSO_2CF_3)_2$ (697 mg, 1.67 mmol) in THF (2.5 ml) were added *N*-ethylpiperidine (0.26 ml, 1.89 mmol) and (4*S*)- 3-acetyl-4-ethyl-1,3-thiazolidine-2-thione (243 mg, 1.29 mmol) in THF (1.5 ml) at -50 - -40°C and the mixture was kept stirring at -50 - -40°C for 3.5 h. After addition of 5-acetoxypyrrolidin-2-one (239 mg, 1.67 mmol) in THF (1.5 ml), the mixture was stirred at 0°C for 2 h, and then 10% citric acid and $CHCl_3$ were added. After filtration of the reaction mixture with celite, the filtrate was washed with brine, dried, and evaporated *in vacuo*. The hplc (HITACHI 635S Liquid Chromatograph) analysis (column, Nucleosil 50-5, 4.6 mm i.d. x 15 cm; eluent, 4:1 AcOEt-hexane; flow rate, 1.5 ml/min; detection UV 254 nm) of the curde residue showed the presence of **9b** and its diastereomer in a 97:3 ratio. The residue was purified by column chromatography with 33% acetone in CH_2Cl_2 to give **9b** (302 mg, 86%) as a yellow oil. $[\alpha]_D^{21}$ +211.5° (*c* 0.30, $CHCl_3$). Ir υ_{max} (neat) cm^{-1}: 3200, 1685. ^{1}H Nmr ($CDCl_3$) δ: 1.02 (t, 3H, J = 7.3 Hz), 1.60-2.10 (m, 3H), 2.12-2.50 (m, 3H), 2.97 (d, 1H, J = 11.2 Hz), 3.13 (dd, 1H, J = 9.3, 17.6 Hz), 3.60 (dd, 1H, J = 7.8, 11.2 Hz), 3.79 (dd, 1H, J =3.4, 17.6 Hz), 3.86-4.24 (m, 1H), 4.96-5.30 (m, 1H), 6.33 (br s, 1H). High-resolution ms *m/z* Calcd for $C_{11}H_{16}N_2O_2S_2$ (M^+): 272.0655. Found: 272.0682.

(5*S*)-5-(3-*p*-Nitrobenzyloxycarbonyl-2-oxopropyl)pyrrolidin-2-one (10). To a stirred solution of optically pure **9b** (326 mg, 1.2 mmol) in MeCN (12 ml) was added imidazole (204 mg, 3.0 mmol) at room temperature and the stirring was continued at the same temperature for 5.5 h. To the mixture was added $Mg(O_2CCH_2CO_2PNB)_2$ (899 mg, 1.8 mmol) and then the mixture was stirred at 60°C for 18 h. After cooling, the reaction mixture was acidified with 1N HCl and extracted with AcOEt. The extract was washed with 5% $NaHCO_3$ and brine, dried, and evaporated *in vacuo*. The residue was purified by column chromatography with 33% acetone in CH_2Cl_2 to give **10** (214 mg, 56%) as a colorless viscous oil which crystallized on standing. Recrystallization from AcOEt gave colorless needles. mp 115-116°C. $[\alpha]_D^{21}$ +55.5° (*c* 0.5, $CHCl_3$). Ir υ_{max} (Nujol)cm^{-1}: 2900, 1735, 1695. ^1H Nmr ($CDCl_3$) δ: 1.61-1.81 (m, 1H), 2.18-2.43 (m, 3H), 2.74 (dd, 1H, J = 8.9, 18.5 Hz), 2.89 (dd, 1H, J = 4.0, 18.5 Hz), 3.57 (s, 2H), 3.97-4.09 (m, 1H), 5.28 (s, 2H), 6.23 (br s, 1H), 7.53 (d, 2H, J = 8.9 Hz), 8.24 (d, 2H, J = 8.9 Hz). High-resolution ms *m/z* Calcd for $C_{15}H_{16}N_2O_6(M^+)$: 320,1009. Found: 320,1037. *Anal.* Calcd for $C_{15}H_{16}N_2O_6$; C, 56.25; H, 5.03; N, 8.75. Found: C, 56.26; H, 5.04; N, 8.76.

***(5S)*-5-(3-Diazo-3-*p*-nitrobenzyloxycarbonyl-2-oxopropyl)pyrrolidin-2-one (11).** To a stirred solution of **10** (214 mg, 0.6 mmol) in MeCN (3.5 ml) were added *p*-toluenesulfonyl azide (170 mg, 0.86 mmol) and Et_3N (0.12 ml, 0.87 mmol) under N_2. The mixture was stirred at room temperature for 20 min. After removal of the solvent, the residue was purified by column chromatography (33% acetone in CH_2Cl_2) to give **11** (230 mg, quant.) as a pale yellow, amorphous powder. Its crystallization from a mixture of AcOEt and hexane gave colorless needles. mp 95-96°C. $[\alpha]_D^{21}$ +70.1° (*c* 0.5, $CHCl_3$). Ir υ_{max} (neat)cm^{-1}: 3400, 1720, 1690 . ^1H Nmr ($CDCl_3$) δ: 1.71-1.88 (m, 1H), 2.26-2.41 (m, 3H), 2.92 (dd, 1H, J = 9.6, 18.1 Hz), 3.23 (dd, 1H, J = 3.6, 18.1 Hz), 4.02-4.14 (m, 1H), 5.36 (s, 2H), 6.08 (s, 1H), 7.54 (d, 2H, J = 8,9 Hz), 8.26 (d, 2H, J = 8.9 Hz). *Anal.* Calcd for $C_{15}H_{14}N_4O_6$: C, 52.03; H, 4.07; N, 16.18. Found: C, 52.04; H, 4.08; N, 16.16.

(5*S*)-1-Aza-2,7-dioxo-8-*p*-nitrobenzyloxycarbonylbicyclo[3.3.0]octane (12.). A mixture of **11** (88 mg, 0.25 mmol), $Rh_2(OAc)_4$ (1 mg), and AcOEt (1.0 ml) was refluxed for 15 min under N_2. After removal of the solvent of the reaction mixture, the residue was submitted to chromatographic purification with 14% acetone in CH_2Cl_2 to give **12** (70 mg, 87%) as a pale yellow, amorphous powder. Ir υ_{max} (neat)cm^{-1}: 1775, 1690. ^1H Nmr ($CDCl_3$) δ: 1.72-3.04 (m, 6H), 4.25-4.56 (m, 1H), 4.85 (s, 1H), 5.32 (dd, 2H, J = 13.2, 17.6 Hz), 7.55 (d, 2H, J = 8.8 Hz), 8.24 (d, 2H, J = 8.8 Hz).

(5*S*)-3-Diphenylphosphoryloxy-2-*p*-nitrobenzyloxycarbonyl-8-oxo-1-azabicyclo[3.3.0]oct-2-ene (13). To a stirred solution of **12** (80 mg, 0.25 mmol) in MeCN (1.0 ml) were added diphenylphosphoryl chloridate (0.06 ml, 0.30 mmol) and diisopropylethylamine (0.05 ml, 0.30 mmol) at 0°C. The mixture was stirred at 0°C for 1 h. After removal of the solvent, the residue was purified by column chromatography with 11% acetone in CH_2Cl_2 to give **13** (116 mg, 82%) as a yellow oil. Ir υ_{max} (neat)cm^{-1}: 1730, 1710. ^1H Nmr ($CDCl_3$) δ: 1.86-2.02 (m, 1H), 2.41-2.52 (m, 2H), 2.64-2.83 (m, 1H), 2..90 (ddd, 1H, J = 2.6, 10.6, 17.5 Hz), 3.09 (ddd, 1H, J = 1.5, 9.7, 17.5 Hz), 4.50-4.63 (m, 1H), 5.28 , 5.37 (AB, 2H, J = 13.5 Hz), 7.17-7.37 (m, 10H), 7.54 (d, 2H, J = 8.6 Hz), 8.13 (d, 2H, J = 8.6 Hz). High-resolution ms *m/z* Calcd for $C_{27}H_{23}N_2O_9P(M^+)$: 550.1142. Found: 550.1173. *Anal.* Calcd for $C_{27}H_{23}N_2O_9P$: C, 58.91; H, 4.21; N, 5.09. Found: C, 58.93; H, 4.19; N, 5.08.

(5*S*)-2-*p*-Nitrobenzyloxycarbonyl-3-(2-*p*-nitrobenzyloxycarbonylamino)ethylthio-8-oxo-1-azabicyclo[3.3.0]oct-2-ene (14). To a stirred solution of **13** (320 mg, 0.58 mmol) in MeCN (2.5 ml) were added *N*-*p*-nitrobenzyloxycarbonylaminoethanethiol[7] (170 mg, 0.7 mmol) and diisopropylethylamine (0.12 ml, 0.70 mmol) at 0°C. The mixture was stirred at 0°C for 2 h. The usual work-up of the reaction mixture gave **13** (309 mg, 95%) as pale yellow needles. mp 170-171°C (from $CHCl_3$-cyclohexane). $[\alpha]_D^{20}$ -1.1° (*c* 0.53, $CHCl_3$), Ir υ_{max} (neat)cm^{-1}: 3400, 1700. ^1H Nmr ($CDCl_3$) δ: 1.90-2.01 (m, 1H), 2.45-2.54 (m, 2H), 2.68-3.01 (m, 3H), 3.04 (dd, 1H, J = 6.9, 13.5 Hz), 3.18 (dd, 1H, J = 9.2, 16.8 Hz), 3.34-3.46 (m, 2H), 4.49-4.62 (m, 1H), 5.20 (s, 2H), 5.26, 5.50 (AB, 2H, J = 13.5 Hz), 7.50 (d, 2H, J = 8.6 Hz), 7.67 (d, 2H, J = 8.6 Hz), 8.21 (d, 2H, J = 8.6 Hz), 8.23 (d, 2H, J = 8.6Hz). High-resolution ms *m/z* Calcd for $C_{25}H_{24}N_4O_9S(M^+)$: 556.1289. Found: 556.1285. *Anal.* Calcd for $C_{25}H_{24}N_4O_9S$: C, 53.95; H, 4.35; N, 10.07. Found: C, 53.55; H, 4.24; N, 9.92.

(5*S*)-2-*p*-Nitrobenzyloxycarbonyl-3-((1-*p*-nitrobenzyloxycarbonyl)azetidin-3-yl)thio-8-oxo-1-azabicyclo[3.3.0]oct-2-ene (15). To a stirred solution of **13** (304 mg, 0.55 mmol) in MeCN (2.5 ml) were added *N*-*p*-nitrobenzyloxycarbonylazetidinethiol[8] (169 mg, 0.66 mmol) and diisopropylethylamine (0.11 ml, 0.66 mmol) at 0°C. The mixture was stirred at 0°C for 2 h. After removal of the solvent, the residue was treated as usual to give **15** (290 mg,. quant.) as pale yellow plates. mp 181-182°C (from $CHCl_3$-cyclohexane). $[\alpha]_D^{21}$ -30.7° (*c* 0.53, $CHCl_3$). Ir υ_{max} (neat)cm^{-1}: 3400, 1710, 1530, 1350. ^1H Nmr ($CDCl_3$) δ: 1.86-2.01 (m, 1H), 2.43-2.55 (m, 2H), 2.67 (dd, 1H, J = 10.9, 16.5 Hz), 2.76-2.90 (m, 2H), 3.96-4.06 (m, 3H), 4.42 (br s, 2H), 4.50-4.63 (m, 1H), 5.19 (s, 2H), 5.27, 5.50 (AB, 2H, J = 13.5 Hz), 7.50 (d, 2H, J = 8,6 Hz), 7.67 (d, 2H, J = 8.6 Hz), 8.22 (d, 4H, J = 8.6 Hz).

High-resolution ms *m/z* Calcd for $C_{26}H_{24}N_4O_9S(M^+)$: 568.1264. Found: 568.1264. *Anal.* Calcd for $C_{26}H_{24}N_4O_9S$: C, 54.93; H, 4.25; N, 9.85. Found: C, 54.82; H, 4.26; N, 9.49.

(5*S*)-3-(2-Aminoethyl)thio-8-oxo-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (3). A solution of **14** (205 mg, 0.37 mmol) in 1:1 THF-water (2.0 ml) was treated with PtO_2 (40 mg) under H_2 (3 atm) at room temperature for 1 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* and then the residue was charged on a HP-40 column and eluted with 5% acetone in water to give **3** (53 mg, 55%) as a colorless amorphous powder. mp 145-146°C (from water). $[\alpha]_D^{20}$ +18.5° (*c* 0.26, H_2O). Ir υ_{max} (KBr)cm^{-1}: 3450, 2950, 1650. ^1H Nmr (D_2O) δ: 1.99-2.11 (m, 1H), 2.41-2.56 (m, 2H), 2.72 (dd, 1H, J = 10.6, 15.8 Hz), 2.82-3.17 (m, 4H), 3.23 (t, 2H, J = 6.4 Hz), 4.58-4.71 (m, 1H). *Anal.* Calcd for $C_{10}H_{14}N_2O_3S{\cdot}H_2O$: C, 46.14; H, 6.20; N, 10.76. Found: C, 45.87; H, 5.90; N, 10.58.

(5*S*)-3-(3-Azetidinyl)thio-8-oxo-1-azabicyclo[3.3.0]oct-2-ene-2-carboxylic acid (4). A solution of **15** (232 mg, 0.41 mmol) in 1:1 THF-water (2.0 ml) was similarly treated with PtO_2 (40 mg) under H_2 (3 atm) to the case of **14** to afford carboxylic acid (**4**) (84 mg, 59%) as a colorless amorphous powder. mp 182-183°C (from water). $[\alpha]_D^{21}$ +18.5° (*c* 0.26, H_2O). Ir υ_{max} (KBr)cm^{-1}: 3400, 2970, 1650. ^1H Nmr (D_2O) δ: 1.97-2.09 (m, 1H), 2.40-2.55 (m, 2H), 2.68 (dd, 1H, J = 10.6, 16.2 Hz), 2.78-2.96 (m, 2H), 4.02-4.11 (m, 2H), 4.29-4.40 (m, 1H), 4.53-4.67 (m, 3H), *Anal.* Calcd for $C_{11}H_{14}N_2O_3S{\cdot}2H_2O$): C, 45.50; H, 6.25; N, 9.65. Found: C, 45.66; H, 5.89; N, 9.26.

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