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An Expedient One-pot Synthesis for Protected 2-Thia-5-azabicyclo[2.2.1]heptan-3-ones. Versatile Intermediates in the Synthesis of Carbapenem Sidechains.

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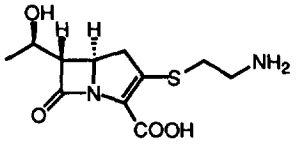
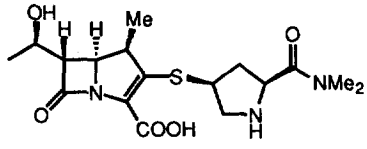
Abstract: A convenient and high yielding one-pot process for the preparation of protected 2-thia-5-azabicyclo-[2.2.1]heptan-3-ones from 4-hydroxyproline and their use in the synthesis of carbapenem sidechains is described. Copyright © 1996 Elsevier Science Ltd

Considerable effort has been directed towards the discovery and development of new broad spectrum carbapenem antibiotics that are chemically and metabolically more stable than thienamycin (**1**) and related naturally occurring compounds.[1] Meropenem (**2**) is the most prominant member of a class of carbapenems that contain a 2'-aminocarbonyl pyrrolidin-4'-ylthio sidechain.[2]



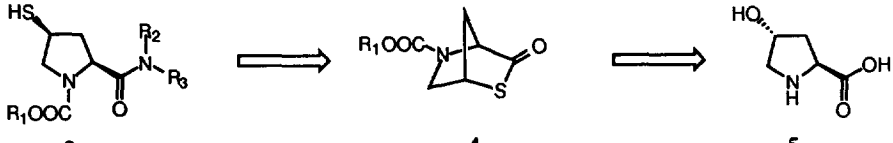
1 Thienamycin



2 Meropenem

The original Sumitomo synthesis of the sidechain thiol of meropenem (**2**) starting from natural *trans*-4-hydroxy-L-proline (**5**) is fairly straightforward and relies heavily on the use of protecting groups.[2] More recently the same group published a more expedient approach[3] based upon the use of thiolactone synthon **4** (Scheme 1).[4] Independently, we developed a practical and high-yield process for making compounds **4** starting from *N*-protected *trans*-4-hydroxy-L-proline. This process can be carried out in one pot and facilitates access to a wide variety of protected carbapenem sidechains **3**.

Scheme 1

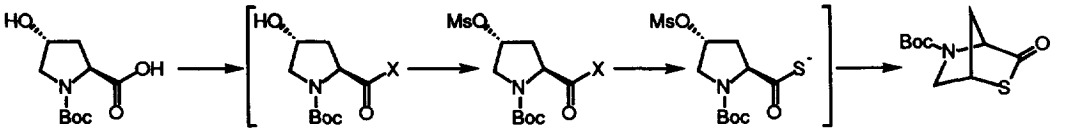


3 **4** **5**

The proposed synthetic sequence (**5** → **4** → **3**) requires a minimum of protecting groups since the thiolactone functionality simultaneously protects the thiol group and activates the carboxyl group towards aminolysis. In addition, high stereochemical purity of aminolysis product **3** is ensured. Since the thiolactone will be generated through intramolecular displacement of a suitably activated 4-hydroxy group by a 2-thiocarboxylate, any epimerization at C-2 before the formation of the thiolactone will result in uncyclized species that will be readily removed in a judiciously chosen workup. Conversion of *N*-Boc-*trans*-4-hydroxy-L-proline (**6**)[5] to thiolactone **10** in one pot by first activating the 2-carboxy group and then adding methanesulfonyl chloride followed by sulfide is described in Scheme 2. Thiolactone **10** can either be isolated

by crystallization after an extractive workup or, preferably, reacted directly with an amine in the same pot to give amides **3**.

Scheme 2



6 **7** **8** **9** **10**

In general the carboxylic acid was activated in the presence of an excess of diisopropylethylamine (DIPEA; 2.5 equivalents) as the base at -10 °C. Then the 4-hydroxy group was sulfonylated at the same temperature generating **8**. It was found that the efficiency of the mesylation step was highly dependent on the presence of an equivalent of pyridine[6] and not on the solvent (CH_2Cl_2, MeCN or THF were equally effective). Various ways to introduce an equivalent of sulfide were probed: a solution of NaSH in anhydrous DMF with addition of an extra equivalent of DIPEA, a solution of NaSH in water with an extra equivalent of DIPEA introduced into the reaction mixture, a solution of TMS_2S in THF treated with MeLi to generate an anhydrous and homogeneous solution of Li_2S in THF[7] or a solution of $Na_2S \cdot 9H_2O$ or Li_2S in water. In a direct comparison, introduction of sodium sulfide dissolved in water gave the highest yields.[8] Careful monitoring of the reaction by HPLC showed that upon rapid exothermic addition of aqueous sodium sulfide to a solution of **8** (X = $OPOPh_2$) in THF at -10 °C thiocarboxylate **9** was formed instantaneously (the temperature rises rapidly to ≈ +10 °C following this addition). Complete conversion of **9** to **10** was achieved in 5-6 hours at 25 °C. A number of common activating agents for the conversion of **6** to **7** were evaluated[9], comparing the overall yield of **10** from **6**. The most important results (all reactions were performed on 1 g scale) are given in Table 1. The yields were determined by HPLC analysis of the crude reaction mixture.[10]

Table 1: Comparison of Various Activating Agents in the Preparation of Thiolactone **10**.

entry	activating agent	solvent	sulfide source	yield (%) [10]
1	$ClSO_2Me$/DIPEA [a]	THF	Na_2S/H_2O	64
2	$ClCO_2{}^iBu$/DIPEA	THF	Na_2S/H_2O	87
3	$ClCOMe_3$/DIPEA	THF	Na_2S/H_2O	23
4	CDI [b]	MeCN [c]	$NaHS/H_2O$ [d]	74
5	$ClPO(OPh)_2$/DIPEA	THF	Na_2S/H_2O	59
6	$ClPO(Ph)_2$/DIPEA	THF	Na_2S/H_2O	92

[a] No pyridine was used in this reaction. When this reaction was carried out in the presence of 1 equiv. of lutidine an assay yield for **10** of 55 % was obtained.
[b] An extra equivalent of methanesulfonyl chloride/DIPEA was added to mesylate the imidazole.
[c] In THF the yield is only slightly lower.
[d] No reaction was observed when a solution of Na_2S in water was added to the solution of **8** (X = imidazolide). However addition of TFA to the resulting mixture resulted in conversion to **10** (34% assay yield).

Although at the outset it seemed attractive to use methanesulfonyl chloride for activation of both the carboxylic acid and the alcohol, entry 1 of Table 1 shows, not unexpectedly,[11] that this procedure gave only a

mediocre yield of **10**. Remarkably, the yield in using a mixed carboxylic anhydride was substantially less than using a mixed carbonic carboxylic anhydride (entry 2 vs. 3). When carbonyldiimidazole (CDI) was used as the activator (entry 4), it was necessary to use an additional amount of methanesulfonyl chloride and DIPEA (in total 2.1 and 2.5 eq., respectively) since mesylation of imidazole (liberated in the reaction of CDI with the acid) competes with mesylation of the 4-hydroxy group. The best yields were obtained using diphenylphosphinic chloride as the carboxylic acid activator (entry 6). The effect of various sulfide sources on the yield was repeated for diphenylphosphinic chloride activation and aqueous sodium sulfide again proved superior. It was also found that it was critical to keep the concentration of the reaction at ≤ 0.15 mol/L in order to obtain the best yields. The one-pot process using diphenylphosphinic chloride activation was easily scaled to multikilogram scale while maintaining > 90% yields. After completion of the thiolactone formation, the aqueous layer can be separated and the organic layer containing **10** can be used directly for the ensuing aminolysis reaction. However, one can also opt to isolate thiolactone **10** in 85% yield after an aqueous workup and crystallization. Since this one-pot process consists of four chemical steps the average yield per step is better than 96%. The procedure works equally well for the synthesis of thiolactones **4** with other protecting groups. In particular, a *p*-nitrobenzylcarbamate-protected thiolactone **4** (R_1=*p*NB) was obtained in 93 % yield (as determined by HPLC).

As stated above, thiolactone **10** can be treated with a variety of amines yielding compounds of general formula **3** in good yields (Table 2). Facile reactions (complete conversion in less than 30 minutes at room temperature) were observed with several aliphatic amines under a variety of conditions. The primary amide **3a** was obtained by treatment with NH_4Cl and triethylamine (4 equiv each) in methanol (entry 1). Addition of benzylamine or pyrrolidine (1.1 equiv; reaction in THF and ethyl acetate, respectively) gave **3b** and **3e**, respectively (entries 2 and 5). Treatment of a solution of **10** in THF with a solution of dimethylamine in water (1.25 equiv) afforded **3c**. Reaction of **10** with the less reactive aniline (1.25 equiv) required heating. The aminolysis was slow in refluxing THF but was complete after two hours in toluene at 100 °C (entry 4). The product thiols are readily oxidized to the corresponding disulfides. In order to prevent disulfide formation tri-*n*-butylphosphine (typically 5 mol%) can be included in the aminolysis.

Table 2: Reaction of Isolated Thiolactone **10** (R_1 = *tert*-Bu) with Amines.

entry	product **3** [a]	R_2	R_3	yield (%)[b]
1	**3a**	H	H	66 [c]
2	**3b**	CH_2Ph	H	76
3	**3c**	Me	Me	91
4	**3d**	Ph	H	70
5	**3e**	- C_4H_8N -		90

[a] All products showed satisfactory ^1H and ^{13}C-NMR data and microanalysis.
[b] Reported yields are based on unoptimized reactions followed by crystallization of products.
[c] The yield for this product was low because of its water solubility.

In summary, we have developed an efficient one-pot synthesis of protected 2-thia-5-azabicyclo[2.2.1]heptan-3-ones from protected *trans*-4-hydroxyproline. We have demonstrated that these thiolactones react smoothly with a variety of amines. Both transformations can be carried out in the same pot. Thus, rapid assembly of optically pure carbapenem sidechains is accomplished from commercially available starting materials allowing detailed SAR studies on this class of promising carbapenem antibiotics.

Experimental procedure (preparation of 10 using diphenylphosphinic chloride activation):

To a solution of 35.0 g of **6** (151 mmol) and 60.0 mL of DIPEA (344 mmol) in 1.0 L of dry THF at -10 °C was slowly added over 20 min a solution of 37.5 g of diphenylphosphinic chloride (155 mmol) in 50 mL of THF. The reaction mixture was stirred at -10 °C for 90 min before 13.0 mL of pyridine (161 mmol) was added, followed by a solution of 19.8 g of methanesulfonyl chloride (171 mmol) in 50 mL of THF over 15 min. The reaction mixture was stirred at -10 °C for 3 h and allowed to warm to -5 °C over an additional 30 min before a solution of 45.0 g of $Na_2S \cdot 9H_2O$ (187 mmol) in 60 mL of water was added in one portion. The biphasic reaction mixture was allowed to warm to room temperature and was stirred for 8 hours. The resulting mixture was partitioned between toluene and water. The organic layer was washed with 2.0 M HCl, 1.0 M $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. Crystallization of the oily residue (pure according to ^{1}H-NMR and HPLC analysis) from ether/ethyl acetate yielded 29.4 g of **10** (88 mmol; 85 %); m.p. 91 °C; $[\alpha]_D$ = - 88.0° (c = 1.01; $CHCl_3$).[12]

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Ms. L.M. DiMichele and Dr. J.M. Ballard are acknowledged for recording variable temperature NMR spectra and mass spectra, respectively.

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1 a) Ratcliffe, R.W.; Albers-Schönberg, G. *Chemistry and Biology of β-Lactam Antobiotics*; Morin, R.B. and Gorman, M. (Eds.); Academic, 1982; Vol. 2; 227-313; b) Salzman, T.N.; DiNinno, F.P.; Greenlee, M.L.; Guthikonda, R.N.; Quesada, M.L.; Schmitt, S.M.; Herrman, J.J.; Woods, M.F. in *Recent Advances in the Chemistry and Biology of β-Lactam Antibiotics*; Bentley, P.H. and Southgate, J.J. (Eds.); Royal Society of Chemistry: London, 1989; Special Publication No.70; 171-189.

2 Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M; Kato, M. *J. Antibiot.* **1990**, *43*, 519-532.

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4 Three early reports on the synthesis of 2-thia-5-azabicyclo[2.2.1]heptan-3-ones are: a) Yamada, S.; Murakami, Y.; Koga, K. *Tetrahedron Lett.* **1968**, 1501-1506; b) Murakami, Y.; Koga, K.; Matsuo, H.,Yamada, S. *Chem. Pharm. Bull.* **1972**, *20*, 543-549; c) Verbiscar, A.J.; Witkop, B. *J. Org. Chem.* **1970**, *35*, 1924-1927.

5 Keller, O.; Keller, W.E.; van Look, G.; Wersin, G. *Org. Synth. Coll. Vol. VII*, **1993**, 70-75.

6 We speculate that under these conditions the sulfonating agent is a methylsulfonyl pyridinium species which is presumed to be a more stable reagent than the corresponding sulfene (cf. Opitz, G.; Ehlis, T.; Rieth, K. *Chem. Ber.* **1990**, *123*, 1989-98).

7 Steliou, K; Salama, P.; Corriveau, J. *J. Org. Chem.* **1985**, *50*, 4969-4971.

8 Addition of solid $Na_2S \cdot 9H_2O$ to a solution of **8** (X = $OCO_2{}^tBu$) in THF led only to low yields of **10**.

9 Bodanszky, M. *Principles of Peptide Synthesis*; Springer: Heidelberg, 1993; 2nd Edition; 9-55.

10 Assay yield as determined by HPLC; conditions using a HP1090 chromatograph: YMCbasic 4.6 x 250 mm column and a MeCN/ 0.1% aq. H_3PO_4 30/70 (0 min) to 60/40 (30 min) gradient (flowrate 1.0 mL/min); detection at 210 nm. The retention time for **10** under these conditions is 14.2 min.

11 For a recent detailed discussion of the application of carboxylic sulfonic mixed anhydrides see: Wirth, D.D. *Tetrahedron* **1993**, *49*, 1535-1540.

12 ^{1}H-NMR (CD_2Cl_2, -20 °C; 400 MHz) δ 1.42 (s, 3H), 2.07 (dt, *J* 2.5, *J* 11.3, 1H), 2.13 (m, *J* 11.3, 1H), 3.48 and 3.53 (m, *J* 1.1, *J* 10.2, 1H), 3.74 (m, *J* 2.8, *J* 10.1, 1H), 4.11 (m, 1H), 4.42 and 4.53 (m, *J* 0.9, 1H); ^{13}C-NMR (CD_2Cl_2, -20 °C; 100 MHz) δ 29.9/30.0 (q), 43.3/43.9 (t), 49.9/50.6 (d), 54.3/54.7 (t), 65.3/66.1 (d), 82.5/82.6 (s), 155.5/155.7 (s), 201.1/201.6 (s).

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