Pergamon

Tetrahedron Letters 43 (2002) 93–96

TETRAHEDRON LETTERS

# Diastereoselective synthesis of 3,5-*trans*-(+)-(3*R*,5*R*)-3-carbomethoxycarbapenam from 3-hydroxypyridine: questioning the stereochemical assignment of the natural product

Hideyuki Tanaka, Hideki Sakagami and Kunio Ogasawara*

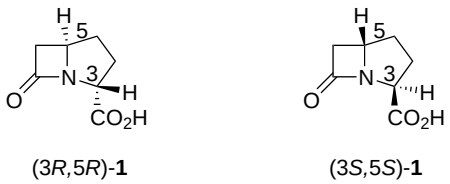
*Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan*

Received 11 October 2001; revised 26 October 2001; accepted 1 November 2001

**Abstract**—An enantio- and diastereoselective synthesis of the methyl ester of 3,5-*trans*-(3*R*,5*R*)-carbapenam-3-carboxylic acid from 3-hydroxypyridine via (2*R*,5*S*)-*trans*-5-acetoxy-2-allylpiperidine has been achieved by employing the piperidine–pyrrolidine ring-contraction reaction as the key step. The synthesis indicates that the configuration of the naturally occurring 3,5-*trans*-carbapenam-3-carboxylic acid is not the revised (3*S*,5*S*), but rather the originally assigned (3*R*,5*R*) configuration. 

The isolation of 3,5-*trans*-carbapenam-3-carboxylic acid **1** from strains of *Serratia* and *Erwinia* spp. was reported by Bycroft and co-workers.[1] Although its absolute configuration was assigned as (3*R*,5*R*) based on spectroscopic analysis, this assignment was later revised[2] to be the opposite (3*S*,5*S*) configuration, since the synthetic carbapenam methyl ester (3*R*,5*R*)-**2** synthesized from (*R*)-glutamic acid was found to be the antipode of the one obtained from the natural compound (Fig. 1).

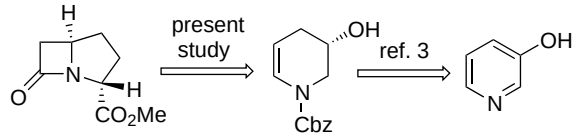
Because carbapenems and carbapenams with a 5*S* configuration had not been known before, this finding was of particular interest to the biosynthetic researchers. Since we had discovered[3,4] the unprecedented *N*-acylative reduction of 3-hydroxypyridine **3** to produce the 3-hydroxytetrahydropyridine enamide **4** and its diastereoselective transformation into the enantiopure *trans*-2,5-disubstituted piperidine **7**, we decided to explore the enantio- and diastereocontrolled synthesis of the methyl ester **2** of the carbapenam-3-carboxylic acid **1** to extend the synthetic utility of our chiral product. We report here the stereoselective synthesis of the methyl ester **2** of the carbapenam **1** having the (3*R*,5*R*) configuration. This configuration argues strongly that the natural 3,5-*trans*-carbapenam-3-carboxylic acid **1** has the originally assigned (3*R*,5*R*) configuration, and not the revised (3*S*,5*S*) configuration (Scheme 1).




(3*R*,5*R*)-**1** (3*S*,5*S*)-**1**

**Figure 1.**

The starting enantiopure (2*R*,5*S*)-*trans*-5-acetoxy-2-allylpiperidine was prepared from 3-hydroxypyridine **3** following the five-step sequence of our established route[3,4] using *N*-acylative reduction, lipase-mediated resolution, methanol addition, acetylation, and diastereoselective allylation. Oxidative cleavage of the olefin functionality followed by esterification[5] transformed the allyl piperidine (+)-**7** into the *tert*-butyl ester (−)-**8**, $[\alpha]_D^{25}$ −9.1 (*c* 1.1, $CHCl_3$). The *N*-carbobenzoxy (*N*-Cbz) functionality of the ester (−)-**8** was then replaced by the *N*-benzyl functionality by sequential




(3*R*,5*R*)-**2** (+)-**4** **3**

**Scheme 1.**

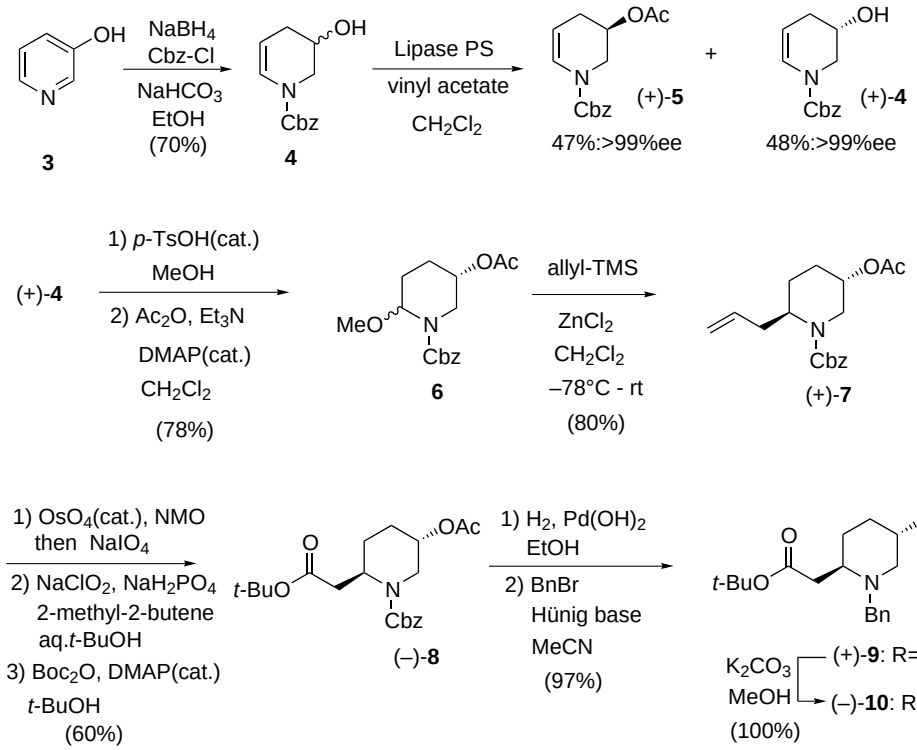
* Corresponding author. E-mail: konol@mail.cc.tohoku.ac.jp

0040-4039/02/$ - see front matter 
PII: S0040-4039(01)02073-1

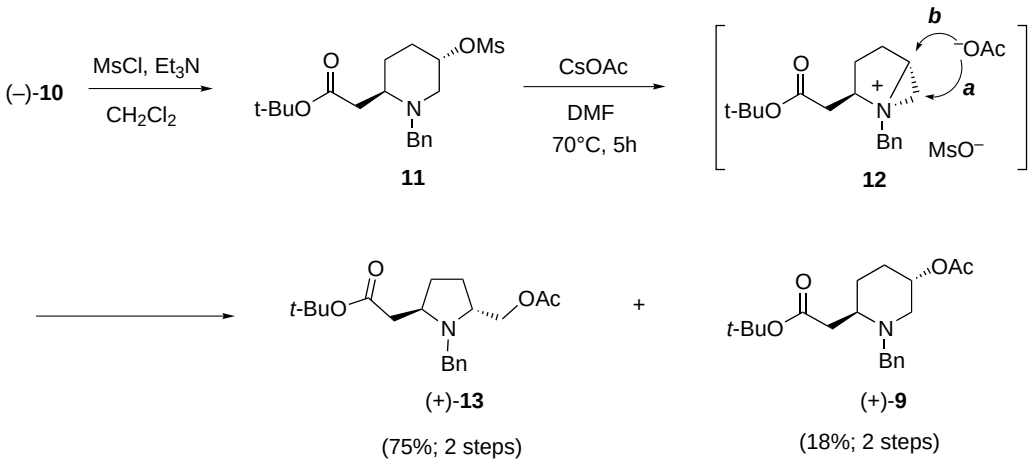
hydrogenolysis and *N*-benzylation to give the tertiary amine (+)-**9**, $[\alpha]_D^{26}$ +15.8 (*c* 1.3, $CHCl_3$), the acetyl functionality of which was removed by alkaline methanolysis to yield the (2*R*,5*S*)-5-piperidinol (–)-**10**, $[\alpha]_D^{27}$ –4.4 (*c* 0.8, $CHCl_3$) (Scheme 2).

To carry out the key piperidine–pyrrolidine ring-contraction reaction, the (2*R*,5*S*)-piperidinol **10** was transformed into the mesylate **11** which was exposed to cesium acetate[6a,c] in warm (~70°C) DMF for 5 h to furnish the (2*R*,5*R*)-*trans*-2,5-disubstituted pyrrolidine (+)-**13**, $[\alpha]_D^{23}$ +64.1 (*c* 0.9, $CHCl_3$), and the *trans*-2,5-disubstituted piperidinol acetate (+)-**9**, $[\alpha]_D^{27}$ +15.4 (*c* 1.1, $CHCl_3$), in yields of 75 and 18%, respectively. The resulting acetate was identical to the above intermediate acetate (+)-**9** and was subsequently recycled. Both products presumably came about via an intervention of the common aziridinium intermediate **12**, generated initially from the mesylate **10** by an intramolecular $S_N2$ reaction. The two products were formed diastereoselectively by two competitive intermolecular $S_N2$ pathways, namely, the pyrrolidine (+)-**13** via route ***a*** and the piperidine (+)-**9** via route ***b*** (Scheme 3).

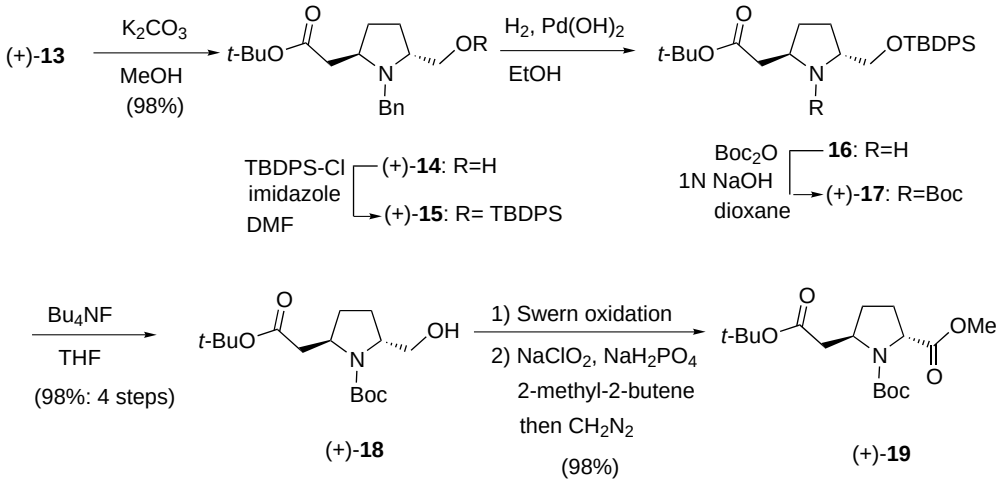
To adjust the oxidation stage of the C5 functionality to that of the target molecule **2**, the 5-substituted prolinol acetate (+)-**13** thus obtained was first transformed into the 5-substituted prolinol (+)-**14**, $[\alpha]_D^{28}$ +52.7 (*c* 1.4, $CHCl_3$), by alkaline methanolysis. Since its direct oxidation was found to be difficult, the benzylamine (+)-**14**




**Scheme 2.**



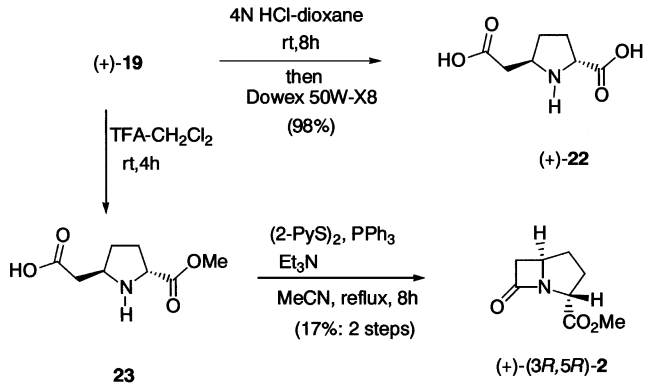

**Scheme 3.**




**Scheme 4.**

was transformed into the *tert*-butyl carbamate (Boc) (+)-**18**, $[\alpha]_D^{23}$ +44.5 (*c* 1.1, $CHCl_3$), by a four-step sequence of reactions involving *O*-protection, hydrogenolysis, carbamoylation, and *O*-deprotection via the *tert*-butyldiphenylsilyl (TBDPS) ether **15**, the secondary amine **16**, and the *N*-*tert*-butylcarbamate (*N*-Boc) **17**. Oxidation of the carbamate (+)-**18** proceeded without difficulty to give the methyl ester, (+)-**19**, $[\alpha]_D^{26}$+56.6 (*c* 1.1, $CHCl_3$), by sequential Swern oxidation,[7] chlorite-mediated oxidation,[4] and esterification (Scheme 4).

After the *trans*-2,5-disubstituted pyrrolidine (+)-**19** with the two distinguishable ester functionalities was obtained, it was exposed to trifluoroacetic acid in dichloromethane at room temperature to give the half ester **23** by selective removal of the *tert*-butyl ester functionality. When the methyl ester **23**, after conversion into the hydrochloride, was dissolved in water, facile hydrolysis occurred to give the diacid (+)-**22**, mp 130–131°C, $[\alpha]_D^{30}$ +113.0 (*c* 1.0, $H_2O$), after purification using an ion-exchange resin (Dowex 50W-X8). In order to obtain the target carbapenam ester **2**, the half ester **23** was refluxed with di(2-pyridyl) disulfide, triphenylphosphine and triethylamine in acetonitrile[8] for 8 h. Although the reaction did not proceed as efficiently as we had hoped, the expected carbapenam ester **2**, $[\alpha]_D^{30}$ +199.1 (*c* 0.2, $CHCl_3$), having the (3*R*,5*R*) configuration, was nevertheless obtained in 17% yield. Its spectroscopic data were identical in all respects with those reported for the (3*R*,5*R*)-ester **2**,[2,9] $[\alpha]_D^{30}$ −197 (*c* 0.5, $CHCl_3$), obtained from (*R*)-glutamic acid. However, the present product showed the opposite sign in its optical rotation, indicating that it was enantiomeric with the one reported.[2] Although we cannot account for this discrepancy, we still believe that our product has the correct structure since the starting material was carefully checked and the absolute structure has been defined by its conversion into several structurally-defined compounds[3a,10] including *tert*-butyl (+)-2,5-*trans*-(2*R*,5*R*)-1-*tert*-butoxycarbonyl-5-(2-hydroxyethyl)




**Scheme 5.**

prolinate[11,12] from the same intermediate (+)-**17** used in the present synthesis (Scheme 5).

In conclusion, using the enantiopure piperidine precursor, we have synthesized the (3*R*,5*R*)-3-carbomethoxycarbapenam that is identical with the methyl ester of the naturally occurring carbapenam-3-carboxylic acid. The key step of this synthesis is utilizing the ring contraction. The present synthesis indicates unambiguously that the absolute configuration of the naturally occurring 3,5-*trans*-carbapenam-3-carboxylic acid is (3*R*,5*R*) and not the opposite (3*S*,5*S*), as had previously been proposed.

## Acknowledgements

We thank the Ministry of Education, Culture, Sports, Science and Technology, Japan, for financial support. We also thank the Japan Society for the Promotion of Science for a fellowship (to H.S.).

## References


1. (a) Bycroft, B. W.; Maslen, C.; Box, S. J.; Brown, A. G.; Tyler, J. W. *J. Chem. Soc., Chem. Commun.* **1987**, 1623; (b) Bycroft, B. W.; Marslen, C.; Box, S. J.; Brown, A. G.; Tyler, J. W. *J. Antibiot.* **1988**, *41*, 1231.
2. Bycroft, B. W.; Chhabra, S. R. *J. Chem. Soc., Chem. Commun.* **1989**, 423.
3. (a) Sakagami, H.; Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1996**, 1433; (b) Sakagami, H.; Ogasawara, K. *Synthesis* **2000**, 521.
4. Lindgren, B. O.; Nolsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.
5. Takeda, K.; Akiyama, A.; Nakamura, H.; Takizawa, S.; Mizuno, H.; Takayanagi, H.; Harigaya, Y. *Synthesis* **1994**, 1063.
6. (a) Poitout, L.; LeMerrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1996**, *37*, 1609; (b) Tehrani, K. A.; Syngel, K. V.; Boelens, M.; Contreras, J.; DeKimpe, N.; Knight, D. W. *Tetrahedron Lett.* **2000**, *41*, 2507; (c) Sakagami, H.; Ogasawara, K. *Synlett* **2001**, 45.
7. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
8. Kobayashi, S.; Iimori, T.; Izawa, T.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 2405.
9. For a racemic synthesis of the 3,5-*trans*-ester (±)-**2**, see: Gilchrist, T. L.; Lemos, A.; Ottaway, C. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3005.
10. (a) Sakagami, H.; Kamikubo, T.; Ogasawara, K. *Synlett* **1997**, 221; (b) Sakagami, H.; Ogasawara, K. *Heterocycles* **2001**, *54*, 43.
11. Mulzer, J.; Schülzchen, F.; Bats, J.-W. *Tetrahedron* **2000**, *56*, 4289.
12. Compound (+)-**17** afforded *tert*-butyl (+)-2,5-*trans*-(2*R*,5*R*)-1-*tert*-butoxycarbonyl-5-(2-hydroxyethyl)prolinate, $[\alpha]_D^{27}$ +32.3 (*c* 0.2, $CHCl_3$) {lit.[11] for the (2*S*,5*S*)-enantiomer: $[\alpha]_D^{20}$ −31.2 (*c* 1.12, $CHCl_3$)}, on a sequence of six steps of reactions.