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Enantiopure Synthesis of All Four Stereoisomers of Carbapenam-3-carboxylic Acid Methyl Ester

Alberto Avenoza,* José I. Barriobero, Jesús H. Busto, and Jesús M. Peregrina*

Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de La Rioja, U.A.-C.S.I.C., E-26006 Logroño, Spain

alberto.avenoza@dq.unirioja.es

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The retro-Dieckmann reaction has been used as a stereodivergent synthetic tool on *N*-Boc-7-azabicyclo[2.2.1]heptan-2-one-1-carboxylic acid methyl ester to obtain enantiopure *trans*- and *cis*-5-(carboxymethyl)pyrrolidine-2-carboxylic acid methyl esters. These disubstituted pyrrolidines have been used as starting materials to develop concise and straightforward syntheses of all four stereoisomers of carbapenam-3-carboxylic acid methyl esters. In this way, we have confirmed unequivocally the stereochemistry of two carbapenams isolated from strains of *Serratia* and *Erwinia* species.

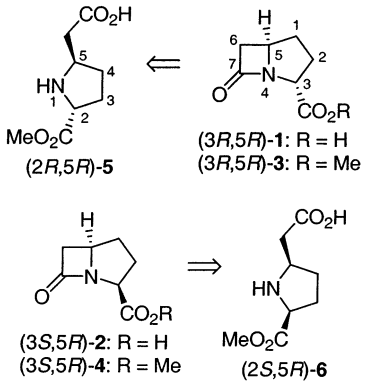
Introduction

The carbapenam system is a very important skeleton in β-lactam antibiotics[1] and is also an efficient intermediate in the carbapenem synthetic route.[2] Given the interest in these materials, several synthetic strategies to obtain carbapenam and carbapenem systems have been developed.[3] To date, *trans*- and *cis*-carbapenam-3-carboxylic acids (**1** and **2**) have been isolated from strains of *Serratia* and *Erwinia* species[4] and have been evaluated in terms of their biosynthetic implications.[5] The (3*R*,5*R*) configuration was provisionally assigned to the major trans isomer isolated from the natural source on the basis of comparative circular dichroism data.[4] Later, the same authors reported a convenient stereoselective synthesis of the major stereoisomer (3*R*,5*R*)-carbapenam-3-carboxylic acid and its methyl and *p*-nitrobenzyl esters from (*R*)-glutamic acid. On the basis of this study the assignment of the major natural stereoisomer was subsequently revised to the opposite configuration (3*S*,5*S*)[6] (Scheme 1).

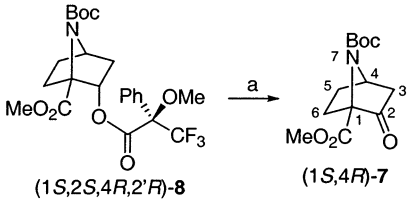
However, very recently Ogasawara and co-workers[7] achieved a stereoselective synthesis of **3** (methyl ester of **1**) that proved the configuration of the naturally occurring *trans*-carbapenam-3-carboxylic acid to be not the revised configuration but the originally assigned (3*R*,5*R*) configuration. In these syntheses, the key compounds required to obtain the β-lactam ring are the 5-(carboxymethyl)pyrrolidine-2-carboxylic acid methyl esters **5** and **6** (Scheme 1).

Recently, and using racemic serine as a starting material, we synthesized the two enantiomers of a new β-keto ester:[8] *N*-Boc-7-azabicyclo[2.2.1]heptan-2-one-1-carboxylic acid methyl ester [(1*R*,4*S*)-**7** and (1*S*,4*R*)-**7**] (Scheme 2). Considering that strained β-keto esters are

SCHEME 1



SCHEME 2[a]



[a] Reagents and conditions: ref 8: (i) MeONa, MeOH, rt, 87%, (ii) Dess−Martin reagent, CH_2Cl_2, rt, 89%.

(1) *The Organic Chemistry of β-Lactams*; George, G. I., Ed.; VCH Press: New York, 1993.

(2) Asada, S.; Kato, M.; Asai, K.; Ineyama, T.; Nishi, S.; Izawa, K.; Shono, T. *J. Chem. Soc., Chem. Commun.* **1989**, 486−488.

(3) (a) Berryhill, S. R.; Price, T.; Rosenblum, M. *J. Org. Chem.* **1983**, *48*, 158−162. (b) Williams, M. A.; Hsiao, C.-N.; Miller, M. J. *J. Org. Chem.* **1991**, *56*, 2688−2694. (c) Alcaide, B.; Polanco, C.; Sáez, E.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 7125−7132. (d) Goo, Y. M.; Seo, M. H.; Lee, Y. Y. *Bull. Korean Chem. Soc.* **1996**, *17*, 909−918. (e) Gilchrist, T. M.; Lemos, A.; Ottaway, C. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3005−3012. (f) Hanessian, S.; Reddy, B. *Tetrahedron* **1999**, *55*, 3427−3443. (g) Mori, M.; Kozawa, Y.; Nishida, M.; Kanamaru, M.; Onozuka, K.; Takimoto, M. *Org. Lett.* **2000**, *2*, 3245−3247. (h) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2001**, *42*, 4869−4873.

(4) Bycroft, B. W.; Maslen, C.; Box, S. J.; Brown, A. G.; Tyler, J. W. *J. Chem. Soc., Chem. Commun.* **1987**, 1623−1625.

(5) (a) Bycroft, B. W.; Maslen, C.; Box, S. J.; Brown, A. G.; Tyler, J. W. *J. Antibiot.* **1988**, *41*, 1231−1242. (b) Li, R.; Stapon, A.; Blanchfield, J. T.; Townsend, C. A. *J. Am. Chem. Soc.* **2000**, *122*, 9296−9297.

(6) Bycroft, B. W.; Chhabra, S. R. *J. Chem. Soc., Chem. Commun.* **1989**, 423−425.

(7) Tanaka, H.; Sakagami, H.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 93−96.

(8) Avenoza, A.; Barriobero, J. I.; Busto, J. H.; Cativiela, C.; Peregrina, J. M. *Tetrahedron: Asymmetry* **2002**, *13*, 625−632.

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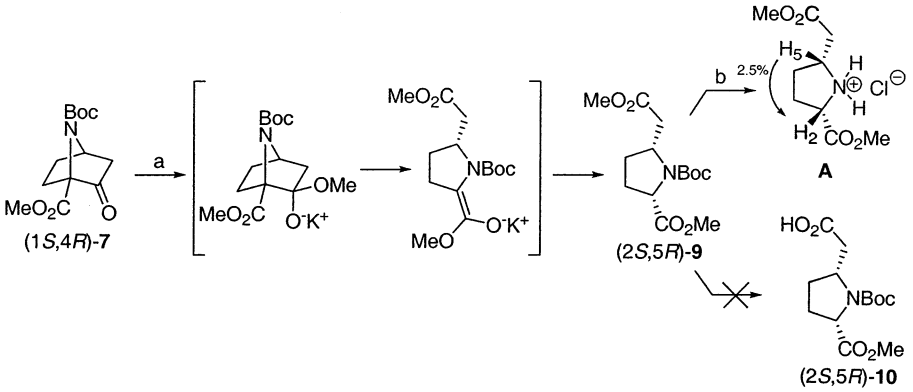
SCHEME 3[a]



[a] Reagents and conditions: (a) K_2CO_3, MeOH, rt, 80%; (b) AcCl, MeOH, rt, quantitative yield.

good candidates to undergo the retro-Dieckmann reaction, we decided to carry out this procedure on the aforementioned substrates. The retro-Dieckmann reaction is a process of synthetic significance at the organic[9] and enzymatic levels.[10] The most comprehensive studies on this reaction and its application to organic synthesis have been reported by Rodriguez and co-workers, who used base-promoted conditions in conjunction with bicyclooctanol derivatives.[11] Our goal was to obtain all stereoisomers of 5-(carboxymethyl)pyrrolidine-2-carboxylic acid methyl ester [i.e. the trans compounds (2*R*,5*R*)- and (2*S*,5*S*)-**5** and the cis compounds (2*S*,5*R*)- and (2*R*,5*S*)-**6**, as well as the corresponding β-lactam systems (3*R*,5*R*)-**3**, (3*S*,5*S*)-**3**, (3*S*,5*R*)-**4**, and (3*R*,5*S*)-**4**] by retro-Dieckmann reactions on β-keto esters (1*S*,4*R*)-**7** and (1*R*,4*S*)-**7**.

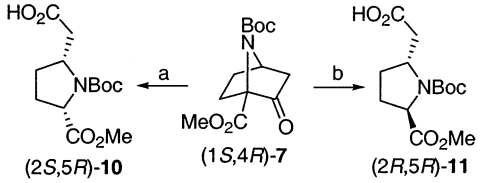
Results and Discussion

We have recently synthesized the (*R*)-Mosher ester derivative **8**[8] and the absolute configuration of this compound has been determined by X-ray diffraction.[12] Hydrolysis of the chiral ester and subsequent oxidation gave compound (1*S*,4*R*)-**7** (Scheme 2).

In an attempt to perform the retro-Dieckmann reaction on β-keto ester (1*S*,4*R*)-**7**, we used Rodriguez's conditions promoted by K_2CO_3 in methanol. The cis isomer of *N*-Boc-5-(methoxycarbonylmethyl)pyrrolidine-2-carboxylic acid methyl ester (2*S*,5*R*)-**9** was obtained exclusively in excellent yield (Scheme 3). The stereochemistry for **9** was unambiguously determined by transformation of this compound into *cis*-2-methoxycarbonyl-5-(methoxycarbonylmethyl)pyrrolidinium chloride **A** to simplify the ^{1}H NMR spectrum, since the spectrum of **9** is complicated by conformational isomerism of the Boc group. According to ^{1}H−^{1}H correlation in CD_3OD, hydrogens H_2 and H_5 were well assigned. In this new compound **A**, the cis disposition of the hydrogens H_2 and H_5 was determined by nOe experiments,[12] so when H_5 was presaturated an enhancement of 2.5% was observed in H_2 (Scheme 3). With the aim of obtaining the pyrrolidine (2*S*,5*R*)-**10**, we attempted the hydrolysis of the methyl ester from the 5-methoxycarbonylmethyl group of (2*S*,5*R*)-**9**. However, selective hydrolysis of the ester failed under several sets of conditions (Scheme 3).

Another alternative to obtain the target compound (2*S*,5*R*)-**10** involved the retro-Dieckmann reaction, using

SCHEME 4[a]



[a] Reagents and conditions: (a) LiOH·H_2O, ^{i}PrOH/H_2O, −30 °C, 100%; (b) $NMe_4OH·5H_2O$, THF, rt, 67%.

TABLE 1. Retro-Dieckmann Reaction with Different OH^- Sources

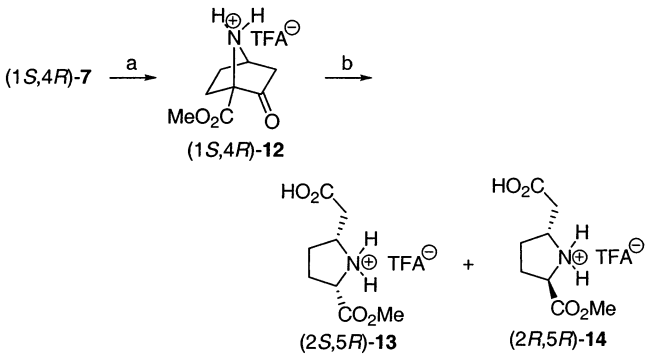
entry	OH^- source (equiv)	solvent system	*T* (°C)	*t* (h)	cis/trans[a]
1	LiOH·H_2O (5)	MeOH/H_2O	rt	2	>95/−
2	LiOH·H_2O (1.2)	MeOH/H_2O	rt	4	>95/−
3	LiOH·H_2O (1.3)	^{i}PrOH/H_2O	rt	0.75	83/17
4	LiOH·H_2O (1.3)	^{i}PrOH/H_2O	−30	0.5	>95/−
5	NMe_4OH (1.3)	^{i}PrOH/H_2O	35	0.3	77/23
6	LiOH·H_2O (1.5)	THF	40	96	75/25
7	NaOH (10%)	CH_2Cl_2	rt	96	40/60
8	$NMe_4OH·5H_2O$ (1.3)	THF/H_2O	40	0.5	76/24
9	$NMe_4OH·5H_2O$ (1.3)	THF	40	96	30/70
10	$NMe_4OH·5H_2O$ (1.3)	THF	rt	72	9/91

[a] Measured by ^{1}H NMR spectroscopy of the H-2 proton in the pyrrolidine ring.

conditions to obtain directly the carboxymethyl group at the 5-position. The first step in the mechanism of the retro-Dieckmann[13] reaction (Scheme 3) is nucleophilic attack on the ketone group. Under Rodriguez's conditions the nucleophile is the MeO^- group but it was envisaged that the use of an OH^- source would allow us to achieve our goal. With this aim in mind, the MeOH/H_2O solvent system and LiOH·H_2O as an OH^- source was employed (Scheme 4). Table 1 shows several sets of conditions for the retro-Dieckmann reaction. When an excess of LiOH·H_2O (entry 1) was used the reaction gave only the cis isomer but, in this case, the product contained two carboxylic acid groups due to hydrolysis of the methyl ester. Smaller quantities of LiOH·H_2O in conjunction with other solvent systems, such as THF/H_2O or dry THF, gave a mixture of compounds. However, it was found that the change from MeOH to ^{i}PrOH along with a decrease in temperature from room temperature to −30 °C was successful in providing the compound (2*S*,5*R*)-**10** as the only stereoisomer (Scheme 4. entry 4, Table 1).

To obtain inversion at C-2 and achieve the trans stereoisomer, we tried the retro-Dieckmann reaction with hydroxides other than LiOH·H_2O [e.g. NMe_4OH, Ba-

SCHEME 5[a]



[a] Reagents and conditions: (a) TFA, CH_2Cl_2, rt, 98%; (b) (i) $LiOH·H_2O$, $^iPrOH/H_2O$, −30 °C, or $NMe_4OH·5H_2O$, THF, rt, (ii) TFA, CH_2Cl_2, rt,

$(OH)_2$, CsOH, NBu_4OH in a protic solvent system ($^iPrOH/H_2O$ and THF/H_2O)] but the ratio in these cases varied from 86/14 to 76/24. Nevertheless, on using NaOH in CH_2Cl_2 with NBu_4Br as an additive (entry 7) the reaction did lead to a greater proportion of the trans stereoisomer, but the products contained a mixture of ester and acid groups. Finally, the combination of a noncoordinative salt and aprotic solvent system did give inversion at C-2. These conditions involved the use of dry THF and NMe_4-OH as the OH^- source and gave rise to a 1/9 ratio in favor of the trans stereoisomer (2*R*,5*R*)-**11**.

The cis stereochemistry of (2*S*,5*R*)-**10** was determined by transformation of this compound, arising from (1*S*,4*R*)-**7** following the conditions of entry 4 in Table 1, into compound **A** by treatment with AcCl in MeOH. In this way, the stereochemistry of compound (2*R*,5*R*)-**11** arising from (1*S*,4*R*)-**7** (conditions of entry 10, Table 1) is therefore trans.

In all cases, the retro-Dieckmann reactions with different OH^- sources gave good yields of *cis*- or/and *trans*-*N*-Boc-5-(carboxymethyl)pyrrolidine-2-carboxylic acid methyl esters (2*S*,5*R*)-**10** or/and (2*R*,5*R*)-**11** and the total amounts of the side products were no more than 4% with the exceptions of entries 2 and 7 of Table 1, where a 33% and a 40% yield of other pyrrolidinecarboxylic diacids were detected, respectively.

To evaluate the influence of the Boc group, we carried out the reaction of the β-keto ester (1*S*,4*R*)-**12**, obtained from ketone (1*S*,4*R*)-**7** by hydrolysis of the Boc group with trifluoroacetic acid (TFA), under retro-Dieckmann conditions to give a mixture of cis and trans compounds: (2*S*,5*R*)-**13** and (2*R*,5*R*)-**14**. Therefore, when we used the $LiOH·H_2O$ conditions the cis/trans ratio was 60/40, but under NMe_4OH conditions the ratio was 34/66 in favor of the trans stereoisomer (Scheme 5). The stereochemistry of (2*S*,5*R*)-**13** and (2*R*,5*R*)-**14** was determined in the same way that was described above for (2*S*,5*R*)-**10** and (2*R*,5*R*)-**11**.

Considering all of the aspects related to the reaction conditions used, the following conclusions can be drawn: a coordinative salt favors cis selectivity, a polar solvent system gives rise to a large proportion of cis isomer, and the presence of the Boc group is critical for control of the selectivity.

In summary, the enantiomerically pure *cis*- and *trans*-pyrrolidines (2*S*,5*R*)-**10** and (2*R*,5*R*)-**11** were obtained by retro-Dieckmann reaction on the β-keto ester (1*S*,4*R*)-**7**, using the conditions shown in entries 4 and 10 in Table 1, respectively. The enantiomers of these pyrrolidines were obtained by using the same strategy on the β-keto ester (1*R*,4*S*)-**7** under the best conditions (entries 4 and 10 in Table 1) to give the cis and trans stereoisomers (2*R*,5*S*)-**10** and (2*S*,5*S*)-**11**, respectively. These target molecules, and other related compounds, are valuable building blocks in organic synthesis and have been used in the design of interesting biomolecules.[3e,14]

In the next step of our synthetic route we followed the standard protocol to obtain the β-lactam core. This protocol was applied to the four stereoisomers described above. The cleavage of the Boc group was carried out on compounds (2*S*,5*R*)-**10**, (2*R*,5*S*)-**10**, (2*R*,5*R*)-**11**, and (2*S*,5*S*)-**11** with TFA in CH_2Cl_2 at room temperature to give the triflouroacetate salts (2*S*,5*R*)-**13**, (2*R*,5*S*)-**13**, (2*R*,5*R*)-**14**, and (2*S*,5*S*)-**14**, respectively. With these β-amino acids in hand, the next step was the cyclization of the amino acid to form the bicyclic β-lactams (3*S*,5*R*)-**4**, (3*R*,5*S*)-**4**, (3*R*,5*R*)-**3**, and (3*S*,5*S*)-**3** (Scheme 6).

A common method used to activate carboxylic acids toward nucleophilic substitution involves the use of Mukaiyama's reagent, 2-chloro-*N*-methylpyridinium iodide, which has also been successfully used to generate the β-lactam ring.[15] In this case Mukaiyama's reagent was applied as a coupling agent and diisopropylethylamine (DIEA) as a base with the β-amino acid (2*R*,5*R*)-**14**. The required carbapenam (3*R*,5*R*)-**3** was obtained in 23% yield after column chromatography. In the same way the β-amino acid (2*S*,5*R*)-**13** gave the carbapenam (3*S*,5*R*)-**4** in 20% yield. The yields obtained in these cyclizations are similar those described in the formation of other β-lactams.[7,15] The spectroscopy data for (3*R*,5*R*)-**3** are identical with those reported when the same com-

(9) (a) O'Neil, B. T. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 806−817. (b) Mahajan, J. R. *Synthesis* **1976**, 110−111. (c) Duthaler, R. O.; Maienfisch, P. *Helv. Chim. Acta* **1984**, *67*, 832−844. (d) Duthaler, R. O.; Maienfisch, P. *Helv. Chim. Acta* **1984**, *67*, 845−855. (e) Han, W. C.; Takahashi, K.; Cook, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 318−321. (f) Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28−34. (g) Buono, F.; Tenaglia, A. *Synlett* **1998**, 1153−1155. (h) Al-Busafi, S.; Whitehead, R. C. *Tetrahedron Lett.* **2000**, *41*, 3467−3470. (i) Al-Busafi, S.; Doncaster, J. R.; Drew, M. G. B.; Regan, A. C.; Whitehead, R. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 476−484.

(10) (a) Grogan, G.; Graf, J.; Jones, A.; Parons, S.; Turner, N. J.; Flitsch, S. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1111−1114. (b) Grogan, G. *J. Mol. Catal. B-Enzym.* **2002**, *780*, 1−10.

(11) (a) Filippini, M.-H.; Rodriguez, J.; Santelli, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1647−1648. (b) Filippini, M.-H.; Faure, R.; Rodriguez, J. *J. Org. Chem.* **1995**, *60*, 6872−6882. (c) Filippini, M.-H.; Rodriguez, J. *J. Org. Chem.* **1997**, *62*, 3034−3035. (d) Lavoisier-Gallo, T.; Charonnet, E.; Rodriguez, J. *J. Org. Chem.* **1998**, *63*, 900−902. (e) Rodriguez, J. *Synlett* **1999**, 505−517. (f) Lavoisier-Gallo, T.; Charonnet, E.; Pons, J.-M.; Rajzman, M.; Faure, R.; Rodriguez, J. *Chem. Eur. J.* **2001**, *7*, 1056−1068.

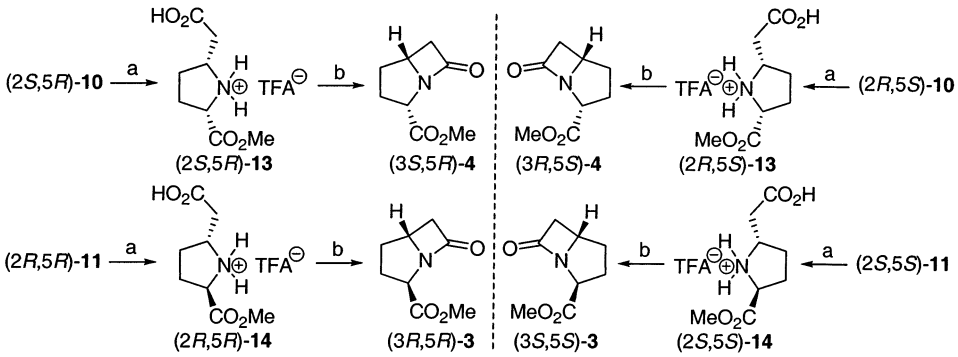
(12) See Supporting Information.

(13) Nishimura, T.; Sunagawa, M.; Okajima, T.; Fukazawa, Y. *Tetrahedron Lett.* **1997**, *40*, 7063−7066.

(14) (a) Petersen, S. P.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539−4547. (b) van der Werf, A.; Kellogg, R. M. *Tetrahedron Lett.* **1991**, *32*, 3727−3730. (c) Collado, I.; Ezquerra, J.; Vaquero, J. J.; Pedregal, C. *Tetrahedron Lett.* **1994**, *35*, 8037−8040. (d) Bulychev, A.; Massova, I.; Miyashita, K.; Mobashery, S. *J. Am. Chem. Soc.* **1997**, *119*, 7619−7625. (e) Muzler, J.; Schülzchen, F.; Bats, J.-W. *Tetrahedron* **2000**, *56*, 4289−4298.

(15) Avenoza, A.; Busto, J. H.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **2002**, *67*, 598−602.

SCHEME 6[a]



[a] Reagents and conditions: (a) TFA, CH_2Cl_2, rt, 100% cis sequences and 93% trans sequences; (b) 2-chloro-*N*-methylpyridinium iodide, DIEA, MeCN, 70 °C, 20% cis sequences and 23% trans sequences.

pound was obtained from (*R*)-glutamic acid[6] and 3-hydroxypyridine.[7] However, the *β*-lactam (3*R*,5*R*)-**3** obtained from (2*R*,5*R*)-**14** showed the opposite sign for its optical rotation compared to the product reported from the (*R*)-glutamic acid route but the same sign as the product from the 3-hydroxypyridine route. The *β*-lactam resulting from (2*S*,5*S*)-**14** showed the same optical rotation as the product reported for the (*R*)-glutamic acid route. Therefore, our synthesis confirms that the absolute configuration of the natural compound *trans*-carbapenam-3-carboxylic acid is (3*R*,5*R*), as described by Ogasawara and co-workers, and not the opposite (3*S*,5*S*).

Conclusion

We have developed a concise synthesis of all four stereoisomers of carbapenam-3-carboxylic acid methyl esters **3** and **4** using two stereodivergent synthetic routes. These routes involve retro-Dieckmann reactions on each enantiomer of *N*-Boc-7-azabicyclo[2.2.1]heptan-2-one-1-carboxylic acid methyl ester **7** to obtain *N*-Boc-5-(carboxymethyl)pyrrolidine-2-carboxylic acid methyl esters **10** and **11**, followed by the corresponding *β*-lactam cyclizations. In summary, the skeleton of the 1-azabicyclo-[3.2.0]heptan-7-one-2-carboxylic acid methyl ester has been obtained from the system of 7-azabicyclo[2.2.1]-heptan-2-one-1-carboxylic acid methyl ester through a retro-Dieckmann reaction. The synthesis of other azabicyclo[2.2.1]heptane functionalized systems to obtain alternative *β*-lactams is in progress.

Experimental Section

General Procedures. Melting points are uncorrected. Solvents were purified according to standard procedures. Organic solutions were dried over anhydrous Na_2SO_4 and, when necessary, concentrated under reduced pressure with a rotary evaporator. NMR spectra were recorded at 300 (^{1}H) and 75 MHz (^{13}C) and signals are reported in ppm downfield from TMS. Mass spectra were obtained by electrospray ionization (ESI).

(2*S*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-5-(methoxycarbonylmethyl)pyrrolidine-2-carboxylic Acid Methyl Ester, (2*S*,5*R*)-9. Method A: K_2CO_3 (8 mg, 0.055 mmol) was added to a solution of ketone (1*S*,4*R*)-**7** (13.5 mg, 0.05 mmol) in MeOH (2 mL). The reaction mixture was stirred for 7 h at room temperature, 2 N HCl (0.6 mL) was added, and the resulting solution was stirred for 5 min. This mixture was diluted with H_2O and extracted with $CHCl_3$/^{i}PrOH (4:1) (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated to give a residue that was purified by silica gel column chromatography, eluting with hexane/EtOAc (8:2), to yield 12 mg (80%) of (2*S*,5*R*)-**9** as a colorless oil. **Method B:** LiOH·H_2O (39 mg, 0.928 mmol) was added to a solution of ketone (1*S*,4*R*)-**7** (50 mg, 0.186 mmol) in MeOH/H_2O 3:2 (6 mL) at room temperature. The reaction mixture was stirred for 2 h at room temperature and 2 N HCl (1.5 mL) was added. The mixture was stirred for a further 5 min, diluted with H_2O (20 mL), and extracted with $CHCl_3$/^{i}PrOH (4:1) (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was dissolved in CH_2Cl_2, an excess of an ethereal solution of diazomethane was added, and the mixture was stirred for 1 h. After this time the solvent was evaporated and the residue purified by silica gel column chromatography, eluting with hexane/EtOAc (8:2), to yield 56 mg (100%) of (2*S*,5*R*)-**9** as a colorless oil. $[\alpha]^{24}_D$ (*c* 0.99, $CHCl_3$) −7.5. ^{1}H NMR ($CDCl_3$) (as a mixture of conformers due to the Boc group isomerism) *δ* 1.35−1.45 (m, 9H), 1.70−2.00 (m, 2H), 2.01−2.30 (m, 2H), 2.35−2.55 (m, 1H), 2.95−3.20 (m, 1H), 3.63−3.67 (m, 3H), 3.70 (s, 3H), 4.15−4.40 (m, 2H). ^{13}C NMR ($CDCl_3$) (as a mixture of conformers due to the Boc group isomerism) *δ* 27.3, 28.1, 28.3, 28.5, 28.7, 29.8, 30.7, 38.2, 39.1, 51.6, 52.1, 52.3, 55.1, 59.7, 60.0, 80.4, 80.6, 153.3, 153.9, 172.1, 173.6, 173.8. Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.91; H, 7.66; N, 4.63.

(2*R*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-5-(methoxycarbonylmethyl)pyrrolidine-2-carboxylic Acid Methyl Ester, (2*R*,5*S*)-9. As described for (2*S*,5*R*)-**9**, compound (2*R*,5*S*)-**9** (56 mg, 100%) was obtained starting from ketone (1*R*,4*S*)-**7** (50 mg, 0.186 mmol). $[\alpha]^{24}_D$ (*c* 0.99, $CHCl_3$) +7.2. Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.89; H, 7.68; N, 4.61.

(2*S*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-5-(carboxymethyl)-pyrrolidine-2-carboxylic Acid Methyl Ester, (2*S*,5*R*)-10. To a solution of ketone (1*S*,4*R*)-**7** (50 mg, 0.186 mmol) in ^{i}PrOH (9 mL) was added dropwise a solution of LiOH·H_2O (10 mg, 0.241 mmol) in H_2O (1 mL) at −30 °C. The mixture was stirred for 30 min at −30 °C and the reaction was then quenched by the addition of 2 N HCl (1 mL). The reaction was stirred for 5 min at the same temperature. The resulting mixture was diluted with H_2O (20 mL) and extracted with $CHCl_3$/^{i}PrOH (4:1) (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated to give the acid (2*S*,5*R*)-**10** (53 mg, 100%) as a colorless oil. This compound was used in the next step without purification, although an analytical sample was purified by silica gel column chromatography with EtOAc/MeOH (95:5) to determine its elemental analysis. $[\alpha]^{24}_D$ (*c* 0.99, $CHCl_3$) −22.6. ^{1}H NMR ($CDCl_3$) (as a mixture of conformers due to the Boc group isomerism) *δ* 1.35−1.50 (m, 9H), 1.70−2.00 (m, 2H), 2.01−2.30 (m, 2H), 2.35−2.55 (m, 1H), 2.85−3.20 (m, 1H), 3.70 (s, 3H), 4.15−4.40 (m, 2H). ^{13}C NMR ($CDCl_3$) (as a mixture of conformers due to the Boc group isomerism) *δ* 28.0, 28.3, 28.7, 29.8, 30.1, 30.8, 38.5, 39.5, 52.2, 52.5, 54.9, 59.6, 60.0, 80.8, 81.0, 153.6, 153.9, 173.8, 174.1,

176.4. Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.43; H, 7.45; N, 4.79.

(2*R*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-5-(carboxymethyl)-pyrrolidine-2-carboxylic Acid Methyl Ester, (2*R*,5*S*)-10. As described for (2*S*,5*R*)-**10**, compound (2*R*,5*S*)-**10** (53 mg, 100%) was obtained starting from (1*R*,4*S*)-**7** (50 mg, 0.186 mmol). This compound was used in the next step without purification, although an analytical sample was purified by silica gel column chromatography with EtOAc/MeOH (95:5) to determine its elemental analysis. $[\alpha]^{24}_D$ (*c* 0.99, $CHCl_3$) +21.7. Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.46; H, 7.40; N, 4.81.

(2*R*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-5-(carboxymethyl)-pyrrolidine-2-carboxylic Acid Methyl Ester, (2*R*,5*R*)-11. To a solution of ketone (1*S*,4*R*)-**7** (90 mg, 0.334 mmol) in dry THF (33 mL) was added at room temperature $NMe_4OH{\cdot}5H_2O$ (78 mg, 0.434 mmol). The mixture was stirred for 3 d at 25 °C, the reaction was then quenched by the addition of saturated aqueous NH_4Cl (17 mL), and the mixture was stirred for a further 5 min. This mixture was extracted with $CHCl_3$/^{i}PrOH (4:1) (3 × 40 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated to give the acid (2*R*,5*R*)-**11** (64 mg, 67%) as a colorless oil. This compound was used in the next step without purification, although an analytical sample was purified by silica gel column chromatography with EtOAc/MeOH (95:5) to determine its elemental analysis. ^{1}H NMR ($CDCl_3$) (as a mixture of conformers due to the Boc group isomerism) δ 1.35−1.50 (d, 9H), 1.70−2.00 (m, 2H), 2.05−2.25 (m, 2H), 2.25−2.40 (m, 1H), 2.77−3.00 (m, 1H), 3.68 (s, 3H), 4.20−4.40 (m, 2H). ^{13}C NMR ($CDCl_3$) (as a mixture of conformers due to the Boc group isomerism) δ 27.1, 27.9, 28.1, 28.3, 28.4, 29.1, 29.6, 38.4, 39.0, 52.0, 52.1, 54.4, 54.5, 59.3, 59.6, 80.5, 80.7, 153.7, 154.0, 173.0, 173.3, 176.1, 176.4. Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.30; H, 7.31; N, 4.90.

(2*S*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-5-(carboxymethyl)-pyrrolidine-2-carboxylic Acid Methyl Ester, (2*S*,5*S*)-11. As described for (2*R*,5*R*)-**11**, compound (2*S*,5*S*)-**11** (71 mg, 67%) was obtained starting from ketone (1*R*,4*S*)-**7** (100 mg, 0.37 mmol). This compound was used in the next step without purification, although an analytical sample was purified by silica gel column chromatography with EtOAc/MeOH (95:5) to determine its elemental analysis. Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.41; H, 7.42; N, 4.91.

Trifluoroacetate Salt of (1*S*,4*R*)-7-Azabicyclo[2.2.1]-heptan-2-one-1-carboxylic Acid Methyl Ester, (1*S*,4*R*)-12. TFA (0.21 mL, 2.79 mmol) was added dropwise to a solution of ketone (1*S*,4*R*)-**7** (50 mg, 0.186 mmol) in dry CH_2Cl_2 (5 mL) at room temperature. The mixture was stirred for 3 d and the solvent was evaporated. The residue was dissolved in Et_2O (5 mL) and then evaporated to remove excess TFA. The process was repeated three times and the residue was purified with use of a C_{18} Sep-pack cartridge to yield (1*S*,4*R*)-**12** (51 mg, 98%) as a colorless oil. $[\alpha]^{24}_D$ (*c* 0.96, $CHCl_3$) −20.0. ^{1}H NMR ($CDCl_3$) δ 1.85−2.00 (m, 1H), 2.10−2.25 (m, 1H), 2.41 (d, 1H, J = 18.3 Hz), 2.45−2.65 (m, 2H), 3.10−3.22 (m, 1H), 3.88 (s, 3H), 4.62 (m, 1H), 8.20−8.80 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ 26.1, 26.7, 42.6, 53.8, 55.9, 74.8, 105.0, 164.2, 197.8. Anal. Calcd for $C_{10}H_{12}F_3NO_5$: C, 42.41; H, 4.27; N, 4.95. Found: C, 42.50; H, 4.29; N, 4.92.

Trifluoroacetate Salt of (1*R*,4*S*)-7-Azabicyclo[2.2.1]-heptan-2-one-1-carboxylic Acid Methyl Ester, (1*R*,4*S*)-12. As described for (1*S*,4*R*)-**12**, compound (1*R*,4*S*)-**12** (26 mg, 100%) was obtained starting from ketone (1*R*,4*S*)-**7** (25 mg, 0.093 mmol). $[\alpha]^{24}_D$ (*c* 1.05, $CHCl_3$) +20.3. Anal. Calcd for $C_{10}H_{12}F_3NO_5$: C, 42.41; H, 4.27; N, 4.95. Found: C, 42.48; H, 4.25; N, 4.96.

Trifluoroacetate Salt of (2*S*,5*R*)-5-Carboxymethyl-2-methoxycarbonylpyrrolidine, (2*S*,5*R*)-13. TFA (0.21 mL, 2.79 mmol) was added dropwise to a solution of acid (2*S*,5*R*)-**10** (53 mg, 0.186 mmol) in dry CH_2Cl_2 (5 mL) at room temperature. The mixture was stirred overnight, evaporated, and purified with use of a C_{18} Sep-pack cartridge to yield (2*S*,5*R*)-**13** (56 mg, 100%) as a colorless oil. $[\alpha]^{24}_D$ (*c* 1.00, MeOH) −31.4. ^{1}H NMR (CD_3OD) δ 1.65−1.90 (m, 1H), 2.10−2.50 (m, 3H), 2.85−2.95 (m, 2H), 3.84 (s, 3H), 3.90−4.10 (m, 1H), 4.40−4.55 (m, 1H). ^{13}C NMR (CD_3OD) 28.3, 29.8, 36.5, 53.9, 58.5, 60.9, 170.5, 173.4. Anal. Calcd for $C_{10}H_{14}F_3NO_6$: C, 39.87; H, 4.68; N, 4.65. Found: C, 39.80; H, 4.65; N, 4.67.

Trifluoroacetate Salt of (2*R*,5*S*)-5-Carboxymethyl-2-methoxycarbonylpyrrolidine, (2*R*,5*S*)-13. As described for (2*S*,5*R*)-**13**, compound (2*R*,5*S*)-**13** (56 mg, 100%) was obtained starting from (2*R*,5*S*)-**10** (53 mg, 0.186 mmol). $[\alpha]^{24}_D$ (*c* 1.14, MeOH) +30.6. Anal. Calcd for $C_{10}H_{14}F_3NO_6$: C, 39.87; H, 4.68; N, 4.65. Found: C, 39.77; H, 4.63; N, 4.61.

Trifluoroacetate Salt of (2*R*,5*R*)-5-Carboxymethyl-2-methoxycarbonylpyrrolidine, (2*R*,5*R*)-14. TFA (0.26 mL, 3.34 mmol) was added dropwise to a solution of acid (2*R*,5*R*)-**11** (64 mg, 0.22 mmol) in dry CH_2Cl_2 (6 mL) at room temperature. The mixture was stirred for 15 h, evaporated, and purified with use of a C_{18} Sep-pack cartridge to yield (2*R*,5*R*)-**14** (62 mg, 93%) as a colorless oil. $[\alpha]^{24}_D$ (*c* 0.9, MeOH) +1.3. ^{1}H NMR (CD_3OD) δ 1.75−1.90 (m, 1H), 2.00−2.20 (m, 1H), 2.25−2.40 (m, 1H), 2.41−2.55 (m, 1H), 2.85 (d, 2H, J = 6.9 Hz), 3.85 (s, 3H), 3.95−4.10 (m, 1H), 4.50 (t, 1H, J = 8.4 Hz). ^{13}C NMR (CD_3OD) 28.9, 30.7, 36.5, 53.9, 58.2, 60.3, 170.3, 173.3. Anal. Calcd for $C_{10}H_{14}F_3NO_6$: C, 39.87; H, 4.68; N, 4.65. Found: C, 39.94; H, 4.72; N, 4.63.

Trifluoroacetate Salt of (2*S*,5*S*)-5-Carboxymethyl-2-methoxycarbonylpyrrolidine, (2*S*,5*S*)-14. As described for (2*R*,5*R*)-**14**, compound (2*S*,5*S*)-**14** (68 mg, 93%) was obtained starting from (2*S*,5*S*)-**11** (70 mg, 0.24 mmol). $[\alpha]^{28}_D$ (*c* 1.14, MeOH) −1.6. Anal. Calcd for $C_{10}H_{14}F_3NO_6$: C, 39.87; H, 4.68; N, 4.65. Found: C, 39.92; H, 4.70; N, 4.66.

(2*S*,5*R*)-1-Azabicyclo[3.2.0]heptan-7-one-2-carboxylic Acid Methyl Ester, (3*S*,5*R*)-4. To a solution of 2-chloro-1-methylpyridinium iodide (171 mg, 0.67 mmol) in dry CH_3CN (20 mL) was added DIEA (0.27 mL, 1.58 mmol) and the mixture was warmed to 70 °C. At this temperature, a solution of β-amino acid (2*S*,5*R*)-**13** (56 mg, 0.186 mmol) in CH_3CN (20 mL) was added dropwise to the reaction mixture over 4 h. When the addition was complete, the reaction was stirred for 30 min at 70 °C and then allowed to stand at room temperature. The mixture was stirred for 17 h at room temperature, the reaction was quenched by the addition of H_2O (20 mL), and the product was extracted with EtOAc (3 × 40 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography eluting with hexane/EtOAc (6:4) to give the carbapenam (3*S*,5*R*)-**4** (6.3 mg, 20%) as a yellow oil. $[\alpha]^{24}_D$ (*c* 0.41, $CHCl_3$) +87. ^{1}H NMR ($CDCl_3$) δ 1.70−1.90 (m, 1H), 2.05−2.20 (m, 1H), 2.25−2.40 (m, 2H), 2.77 (dd, 1H, J = 15.6, 2.4 Hz), 3.11 (ddd, 1H, J = 15.6, 4.8, 1.5 Hz), 3.65−3.76 (m, 1H), 3.77 (s, 3H), 3.86−3.93 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 29.8, 36.8, 41.6, 52.5, 53.4, 59.8, 170.9, 173.3. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.89; H, 6.59; N, 8.28.

(2*R*,5*S*)-1-Azabicyclo[3.2.0]heptan-7-one-2-carboxylic Acid Methyl Ester, (3*R*,5*S*)-4. As described for (3*S*,5*R*)-**4**, compound (3*R*,5*S*)-**4** (6 mg, 20%) was obtained starting from (2*R*,5*S*)-**13** (56 mg, 0.186 mmol). $[\alpha]^{24}_D$ (*c* 0.28, $CHCl_3$) −87.7. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.91; H, 6.57; N, 8.24.

(2*R*,5*R*)-1-Azabicyclo[3.2.0]heptan-7-one-2-carboxylic Acid Methyl Ester, (3*R*,5*R*)-3. To a solution of 2-chloro-1-methylpyridinium iodide (183 mg, 0.72 mmol) in dry CH_3CN (20 mL) was added DIEA (0.29 mL, 1.69 mmol) and the mixture was warmed to 70 °C. At this temperature, a solution of β-amino acid (2*R*,5*R*)-**14** (50 mg, 0.166 mmol) in CH_3CN (20 mL) was added dropwise to the reaction mixture over 4 h. When the addition was complete, the reaction was stirred for 30 min at 70 °C and then allowed to stand at room temperature. The mixture was stirred for 17 h at room temperature, the reaction was quenched by the addition of H_2O (20 mL),

and the product was extracted with EtOAc (3 × 40 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography eluting with hexane/EtOAc (6:4) to give carbapenam (3*R*,5*R*)-**3** (6.4 mg, 23%) as a yellow oil. $[\alpha]^{25}_D$ (*c* 0.64, $CHCl_3$) +198. ^1H NMR ($CDCl_3$) δ 1.40−1.60 (m, 1H), 2.20−2.35 (m, 2H), 2.50−2.59 (m, 1H), 2.64 (dd, 1H, J = 15.9, 2.1 Hz), 3.29 (dd, 1H, J = 15.9, 5.1 Hz), 3.74 (s, 3H), 3.85−3.90 (m, 1H), 4.41 (t*, 1H, J = 7.8, 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 31.3, 35.6, 42.8, 52.6, 53.2, 59.2, 172.0, 176.4. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.93; H, 6.56; N, 8.31.

(2*S*,5*S*)-1-Azabicyclo[3.2.0]heptan-7-one-2-carboxylic Acid Methyl Ester, (3*S*,5*S*)-3. As described for (3*R*,5*R*)-**3**, compound (3*S*,5*S*)-**3** (6 mg, 23%) was obtained starting from (2*S*,5*S*)-**14** (56 mg, 0.186 mmol). $[\alpha]^{24}_D$ (*c* 0.5, $CHCl_3$) −198.5. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.85; H, 6.52; N, 8.27.

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Supporting Information Available: A full listing of ^1H and ^{13}C NMR data for all the new compounds with peak assignments, as well as ^1H and ^{13}C NMR spectra and $^1H-^1H$ and $^1H-^{13}C$ correlations for **3**, **4**, **9**, **10**, **11**, **12**, **13**, and **14**; ^1H and ^{13}C NMR spectra, $^1H-^1H$ and $^1H-^{13}C$ correlations, and nOe data for a chloride derivative of **9**; and crystal structure data for **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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