Synthesis of 2-(Hydroxymethyl)-1β-methylcarbapenem. Chemoselective Organometallic Addition to 3-Substituted 4-[(*R*)-1-Carboxyethyl]azetidin-2-one

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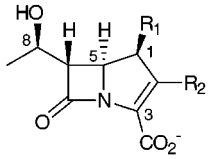
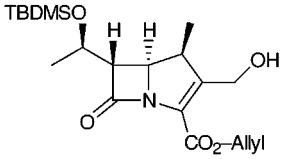
Thienamycin (**1**), an early carbapenem reported by the Merck research group,[1] exhibited an unusually broad spectrum of antibacterial activity.[2] Its discovery triggered intense synthetic activity to explore carbapenem congeners, such as **2**, with enhanced or retained antibacterial activity but with improved chemical and metabolic stability.[3] The structural characteristics of this class of stable carbapenem antibiotics include 6-hydroxyethyl and 1β-methyl substitutions. As richly documented in the literature, chemical manipulation with 2-(alkylthio) substitution around the basic skeleton of the carbapenem has continued to be the major subject of a synthetic focus area.[4] However, the discovery of carbamate **3** of 2-(*O*-functionalized methyl) carbapenem, which was among the most active and exceeded the activity of thienamycin against most bacterial strains except for *P. aeruginosa*,[5] has led to the synthesis of several 2-alkyl-1β-methylcarbapenems with pronounced antibacterial activity.[6]



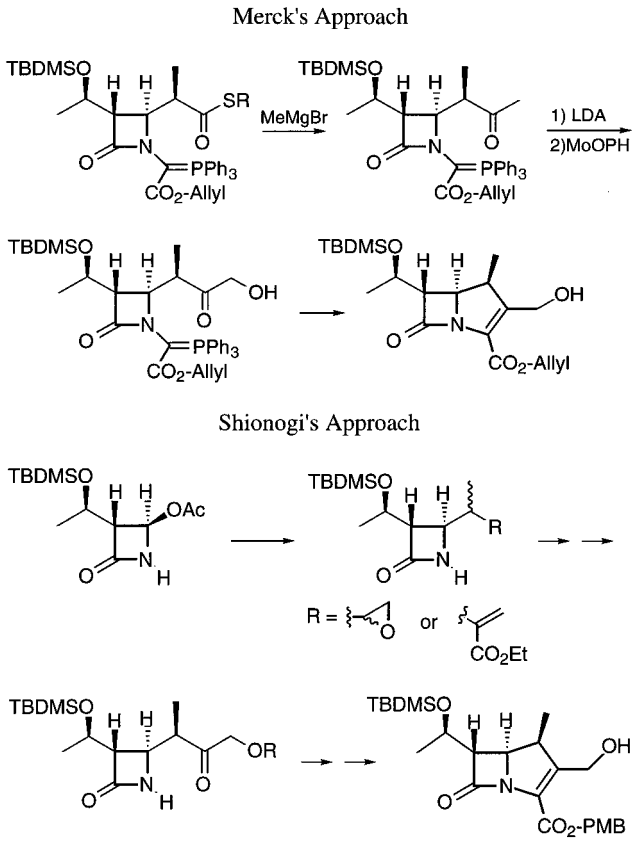


1. $R_1 = H$, $R_2 = S(CH_2)_2NH_2$
2. $R_1 = CH_3$, $R_2 = SCH_2C(=NH)N(CH_3)_2$
3. $R_1 = CH_3$, $R_2 = CH_2OCONH_2$

4

2-(Hydroxymethyl)-1β-methylcarbapenem (**4**) has been used as a versatile building template to prepare potent carbapenem antibiotics.[6,7] Chemical stability of such a multifunctionalized molecule having an extremely high level of ring strain was a major concern for the introduction of the 2-(hydroxymethyl) group to the carbapenem. To date, only a limited number of methodologies for the synthesis of 2-(hydroxymethyl)-1β-methylcarbapenems have been published.[6−8] One representative method, developed at Merck,[5,8] involved the introduction of the hydroxy group α to the methyl ketone by oxidation of a lithium enolate using MoOPH reagent followed by Wittig cyclization (Scheme 1). Another method, reported by a Shionogi group, described the construction of the hydroxymethyl ketone functionality from an azetidinone epoxide derivative,[9a] or preferably from a protected allylic alcohol by ozonolysis.[9b] Unfortunately, none of these methods was suitable to meet our needs for large-scale synthesis due either to low chemical yield and poor reproducibility or to tedious separation of two diastereomers and lengthy synthetic sequences. These problems

Scheme 1



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were sufficient to warrant development of a new and more convergent method for the synthesis of 2-(hydroxymethyl)-1β-methylcarbapenems. Our synthetic strategy is based on the addition of a hydroxymethyl anion equivalent to an azetidinone carboxyl at a very early stage and in a relatively short synthetic sequence.

Addition of organometallic reagents to activated azetidinone carboxylic acids is known in the literature to give the corresponding ketones.[7,10] We envisaged that if a protected hydroxymethyl synthon ($^-CH_2OR$) could be used as a nucleophile, the resulting oxygenated methyl ketone would provide an intermediate with the desired functionality. This approach would eliminate the need for the oxidation of the enolate.[5] Furthermore, since the direct addition of nucleophiles to lithium salts of carboxylic acids is a well-known procedure,[11] the application of this method to the azetidinone carboxylic acid would eliminate activation, protection, and deprotection steps in the synthetic sequence. We therefore anticipated that this approach would overall be more expeditious and practical.

To develop a general method, we initially chose to use MeLi (**5a**) and *n*-BuLi (**5b**) as both base and nucleophile to examine the feasibility of direct organometallic addition to the lithium salt of the azetidinone carboxylic acid. In addition, we planned to incorporate such a suitable protecting group into the oxygenated carbon nucleophile so that it could be readily removed under mild conditions in a late stage of the synthetic sequence. According to literature procedures, lithium reagents $MOMOCH_2Li$ (**5c**) and $PMBOCH_2Li$ (**5d**) were derived from organometallic exchange of tributyltin compounds $MOMOCH_2Sn(Bu\text{-}n)_3$ (**6c**)[12] and $PMBOCH_2Sn(Bu\text{-}n)_3$ (**6d**).[13] These lithium reagents were used immediately after their preparation for the next addition reaction.

The 3-substituted 4-[(*R*)-1-carboxyethyl]azetidin-2-one **7**,[14] a useful carbapenem precursor having four contiguous stereogenic centers and the requisite carboxylic acid, was treated with slightly in excess of 2 equiv of an organic base to form either dilithium **8** or dimagnesium salt **9** below −60 °C (Scheme 2). The amount of the base added for the deprotonation was critical, and therefore, it was monitored by the color change of triphenylmethane indicator in the reaction solution in order to achieve the maximum deprotonation of both the acid and the β-lactam nitrogen protons of **7**. The use of excess base complicated the reaction, since it could act as a nucleophile to compete with the desired addition. The consequence was difficulty in separation of the products and reduced chemical yields. The formed dilithium salt (**8**) in turn reacted in situ with lithium reagents **5a**−**d** at −78 °C, and then the temperature was slowly raised to 0 °C. In

Scheme 2

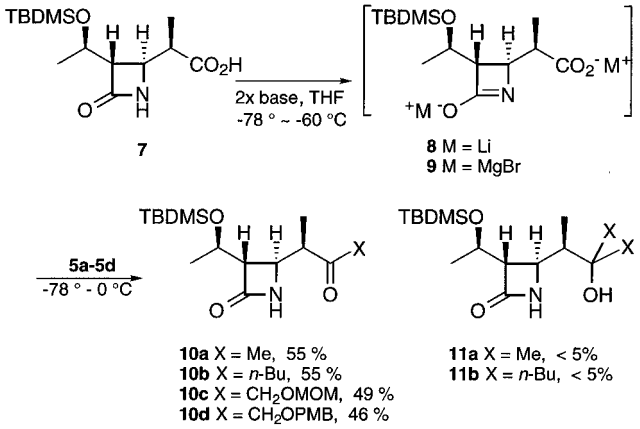


Table 1

entry	base	nucleophile	isolated yield
1	MeLi	MeLi (**5a**)	55
2	*n*-BuLi	*n*-BuLi (**5b**)	50
3	*n*-BuLi	$LiCH_2OMOM$ (**5c**)	49
4	*n*-BuLi/$CeCl_3$	$LiCH_2OMOM$ (**5c**)	45
5	*n*-BuLi	$LiCH_2OPMB$ (**5d**)	19
6	MeMgBr	$LiCH_2OPMB$ (**5d**)	46

the case of **5a** and **5b** (entries 1 and 2 in Table 1), the bases used for the deprotonation were the same as the nucleophiles for the addition. In the case of **5c** and **5d**, *n*-BuLi was used for the deprotonation (entries 3 and 5, Table 1). Reaction of **8** with **5c** gave results consistent with the previous findings. However, an unexpectedly low chemical yield (19%) was obtained when the PMB protected carbon anion (**5d**) was added to the lithium salt (**8**). Replacement of the dilithium salt **8** with its magnesium counterpart (intermediate **9**, prepared by treatment of **8** with 2 equiv of MeMgBr) improved the yield to 46% (entry 6, Table 1). The protected hydroxymethyl ketones (**10a**−**d**) were isolated by chromatography in moderate yield, and the unreacted starting material was recovered in 14−25% yield by a simple aqueous workup.[15] In two cases, byproducts **11a** and **11b** were isolated in less than 5% yield and characterized by NMR and MS analyses as evidence of competing double addition via ketone intermediates.[11a] During the course of this study, the use of $CeCl_3$ reagent in the addition of organometallic reagents to less complex carboxylic acids appeared in the literature, and improved chemical yields were reported.[16] Therefore, we tried to use $CeCl_3$ reagent in the addition of **5c** to carbapenem lithium salt **8** but found the reagent was not effective in improving the chemical yield (entry 4, Table 1). Finally, it should be pointed out that under our reported conditions[17a] the additions of vinyllithium, ethynyllithium, and [[(*tert*-butyldimethylsilyl)oxy]methyl]lithium to the azetidinone **8** were unsuccessful.[17b]

Subsequent application of the literature procedure for cyclization to the carbapenem[5,18] led to the successful synthesis of the 2-(hydroxymethyl)-1β-methyl carbapenem (Scheme 3). The keto ylides **12a** and **12b** were

(10) (a) Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. *J. Med. Chem.* **1987**, *30*, 871. (b) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1987**, *28*, 1857.

(11) (a) Knudsen, C. G.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2260. (b) Maurer, P. J.; Knudsen, C. G.; Palkowitz, A. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 325.

(12) (a) Johnson, C. R.; Medich, J. R. *J. Org. Chem.* **1988**, *53*, 4131. (b) Compound **6c** was purified by chromatography using EtOAc:hexanes (0:1 → 1:10).

(13) (a) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930. (b) For the preparation of (iodomethyl)tributyltin compound, see: Ahman, J.; Somfai, P. *Synth. Commun.* **1994**, *24*, 1117. (c) Compound **6d** was purified by chromatography using EtOAc:hexanes (0:1 → 1:10).

(14) (a) This compound was purchased from Kaneka Inc. (b) For the preparation of this azetidinone, see a recent review: Berks, A. H. *Tetrahedron* **1996**, *52*, 331.

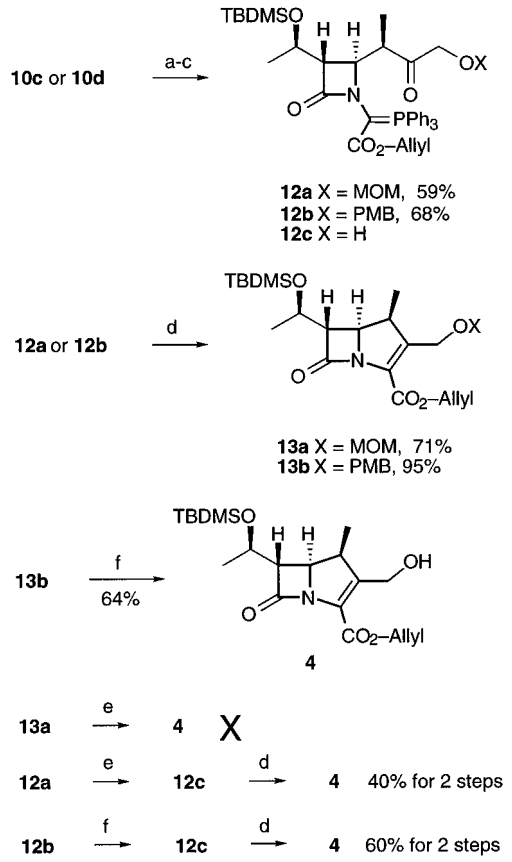
(15) The azetidinone was collected as a white solid by filtration of the acidified aqueous layer after extraction of the product. The material was pure by ^1H NMR analysis and recycled.

(16) Ahn, Y.; Cohen, T. *Tetrahedron Lett.* **1994**, *35*, 203.

(17) (a) *n*-BuLi was used as a base. (b) Presumably, β-lactam ring opening occurred to give a water-soluble amino acid, because material recovery was very poor.

(18) Baxter, A. J. G.; Dickinson, K. H.; Roberts, P. M.; Smale, T. C.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1979**, 236.

Scheme 3[a]



[a] Key: (a) $OHCCO_2$−allyl, toluene, reflux; (b) $SOCl_2$, 2,6-lutidine, THF; (c) PPh_3, 2,6-lutidine, DMF; (d) toluene, reflux; (e) TMSBr, CH_2Cl_2, −35 °C, 15 min; (f) DDQ, CH_2Cl_2, H_2O, rt, 2.5 h.

prepared via a three-step sequence: condensation of azetidinones **10c** and **10d**, respectively with allyl glyoxylate, chlorination of the corresponding hemiaminals, and then ylide formation. It was noticed that the hemiaminals were stable enough to undergo purification by flash chromatography, and the purified hemiaminals proved to give higher overall yields in the three-step sequence. Cyclization of the keto ylides in boiling toluene afforded carbapenems **13a** and **13b**. Unexpectedly, considerable difficulty was encountered in the removal of the MOM protecting group in **13a**, with most of the conventional and mild MOM deprotection methods (including HCl,[19] TMSBr,[20] Py·TsOH,[21] and $LiBF_4$[22]) proving ineffective. Therefore, an alternative route was chosen in which the MOM group was removed prior to the cyclization. Deblocking the hydroxy ketone **12a** with TMSBr produced hydroxymethyl ketone **12c**, and the intramolecular Wittig annulation of the ylide completed the synthesis of 2-(hydroxymethyl)-1β-methylcarbapenem (**4**) in 40% yield for the last two steps. In contrast, carbapenem **13b** underwent debenzylation under very mild conditions using DDQ[23] to give 2-(hydroxymethyl-)penem **4** in good yield. Similarly, the debenzylation of **12b** prior to the cyclization also proceeded smoothly under DDQ conditions to provide **12c**, which cyclized in refluxing toluene to afford **4**.

In conclusion, the development of a method for the addition of organometallic carbon nucleophiles directly to the preformed dilithium or dimagnesium salt of an azetidinone acid as a key step allows the introduction of the hydroxymethyl functionality at the 2-position of the carbapenem system at a very early stage. The advantages of the chemistry described above include the elimination of activation, protection, and deprotection steps in the synthetic sequence. Thus, our method is indeed more streamlined for the synthesis of 2-(hydroxymethyl)-1β-methyl carbapenems. It is noteworthy that this method was reproducible in our laboratory from a 0.5-g scale to a 50-g scale, and the overall yields were between 12 and 19% for the five discrete steps.

Experimental Section

General Experimental Procedures. All reagents were commercial grade and were used as received without further purification, unless otherwise specified. Commercially available anhydrous solvents were used for reactions conducted under an inert atmosphere. Reagent-grade solvents were used in all other cases, unless otherwise specified. Flash chromatography was performed on E. Merck silica gel 60 (230−400 mesh). Thin-layer chromatography was performed on E. Merck 60 F-254 precoated silica plates (250 μm layer thickness). ^{1}H NMR spectra were recorded at 300 MHz. Chemical shifts for ^{1}H NMR spectra are expressed in parts per million downfield from tetramethylsilane. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; br, broad. Coupling constants are given in hertz (Hz). The ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts for ^{13}C NMR spectra are expressed in parts per million downfield from chloroform. Mass spectra were obtained by electrospray mass spectrometry using an electrospray ionization (ESI) interface in flow injection analysis (FIA) mode equipped with an ESI interface. Melting points were taken on a capillary melting point apparatus. High-resolution mass spectra were obtained by fast atom bombardment (FAB) with a *p*-nitrobenzyl alcohol matrix. IR spectra were recorded using attenuated total reflectance spectroscopy with a germanium internal reflection element. Optical rotations were measured with the use of a 10-cm cell at 20 °C.

Representative Procedure for the Addition of Alkyllithium Reagents to 4-[(*R*)-1-Carboxyethyl]azetidin-2-one. Synthesis of (3*S*,4*R*)-3-[(1′*R*)-1′-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1″*R*)-1″-[[(methoxymethoxy)methyl]carbonyl]ethyl]azetidin-2-one (10c). To a solution of 10.0 g (33.2 mmol) of azetidinone **7** and 10 mg of triphenylmethane as an indicator dissolved in 200 mL of anhydrous THF was added 41.5 mL (66.4 mmol) of 1.6 M *n*-BuLi solution in heptane below −60 °C under an argon atmosphere. After addition, an additional 1.5 mL of *n*-BuLi was added, the color of the solution changed from pale yellow to pink, and then the mixture was stirred at −75 °C for 30 min.

Meanwhile, a solution of [(methoxymethoxy)methyl]lithium was prepared by addition of 34.2 mL (54.8 mmol) of 1.6 M *n*-BuLi to a solution of 20 mL (54.8 mmol) of [(methoxymethoxy)methyl]-tributylstannane in 100 mL of anhydrous THF at −75 °C under an argon atmosphere and stirred for 15 min.

To the THF solution of azetidinone dilithium salt was added the THF solution of [(methoxymethoxy)methyl]lithium immediately through a double-tipped needle by applying a slight vacuum pressure in the reaction flask at −78 °C. The addition was finished as fast as possible. After addition, the mixture was stirred for 3 h with a slow increase of reaction temperature to 0 °C. The mixture was quenched by addition of 200 mL of water and extracted with ethyl acetate (200 mL m~ 2). The combined extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed and eluted with hexane:ethyl acetate (3:1, 250 mL; 1:1, 400 mL; 0:1,

(19) Auerbach, J.; Weinreb, S. M. *J. Chem. Soc., Chem. Commun.* **1974**, 298.
(20) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515.
(21) Monti, H.; Leandri, G.; Klos-Ringquet, M.; Corriol, C. *Synth. Commun.* **1983**, *13*, 1021.
(22) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635.
(23) Tanaka, T.; Yoshioka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3651.

200 mL) (R_f = 0.68, EtOAc) to give 5.78 g (16.1 mmol, 49%) of **10c** as a white solid: mp 55−56 °C; IR ($CHCl_3$) 3298, 2954, 2931, 1761, 1733; $[\alpha]^{27}_D$ −20.0° (c 0.20 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (br, 1H), 4.70 (s, 2H), 4.23 (s, 2H), 4.20 (pentet, J = 6.3 Hz), 3.90 (dd, J = 2.4, 4.8 Hz), 3.41 (s, 3H), 3.08 (m, 1H), 2.93 (dd, J = 2.4, 4.8 Hz, 1H), 1.21 (d, J = 6.3 Hz, 3H), 1.20 (d, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 168.4, 96.7, 71.8, 65.6, 61.8, 56.0, 51.2, 44.4, 25.9, 22.8, 18.1, 11.8, −4.1, −4.8. Anal. Calcd for $C_{17}H_{33}NO_5Si$: C, 56.79; H, 9.25; N, 3.90. Found: C, 56.82; H, 9.30; N, 3.89.

The aqueous layer after the extraction was acidified with concentrated HCl to pH <1, and the precipitate was collected by filtration, washed with water, and dried under reduced pressure overnight to give 2.34 g of a white solid. ^{1}H NMR analysis confirmed the compound was the starting azetidinone (recovered yield 63%).

(3*S*,4*R*)-3-[(1′*R*)-1′-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1″*R*)-1″-(methylcarbonyl)ethyl]azetidin-2-one (10a). According to the procedure described above, addition of MeLi to the dilithium salt of azetidinone **8** (10.0 g, 0.033 mol) gave 5.48 g (0.018 mol, 55%) of **10a** as a white solid: mp 108−110 °C (R_f = 0.70, EtOAc); $[\alpha]^{20}_D$ −3.6° (*c* 2.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (b, 1H), 4.17 (pentet, J = 6.3 Hz, 1H), 3.89 (dd, J = 2.7, 4.8 Hz, 1H), 2.85 (dd, J = 1.8, 5.1 Hz, 1H), 2.80 (m, 1H), 2.20 (s, 3H), 1.18 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 6.3 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 168.0, 65.4, 61.4, 50.9, 48.7, 29.2, 25.5, 22.3, 17.7, 11.1, −4.5, −5.2; IR (NaCl)) 3298, 2954, 2931, 1761, 1733. Anal. Calcd for $C_{15}H_{29}NO_3Si$: C, 60.16; H, 9.76; N, 4.68. Found: C, 60.10; H, 9.56; N, 4.59.

(3*S*,4*R*)-3-[(1′*R*)-1′-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1″*R*)-1″-(1-butylcarbonyl)ethyl]azetidin-2-one (10b). According to the procedure described above, addition of *n*-BuLi to the dilithium salt of azetidinone **8** (0.600 g 1.99 mmol) gave 0.341 g (1.00 mmol, 50%) of **10b** as a white solid: mp 66−67 °C (R_f = 0.45, EtOAc:hexane 1:2); $[\alpha]^{20}_D$ −5.6° (*c* 3.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (b, 1H), 4.16 (pentet, J = 6.3 Hz, 1H), 3.86 (dd, J = 2.4, 4.5 Hz, 1H), 2.85 (dd, J = 2.4, 5.1 Hz, 1H), 2.81 (m, 1H), 2.48 (m, 2H), 1.55 (pentet, J = 7.5 Hz, 2H), 1.32 (m, 2H), 1.19 (d, J = 6.3 Hz, 3H), 1.18 (d, J = 6.3 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 168.0, 65.4, 61.4, 50.1, 47.8, 41.8, 25.5, 25.3, 22.1, 22.3, 17.7, 13.6, 11.4, −4.4, −5.2; IR (NaCl) 3161, 2958, 2928, 1757, 1710. Anal. Calcd for $C_{18}H_{35}NO_3Si$: C, 63.30; H, 10.33; N, 4.10. Found: C, 63.30; H, 10.09; N, 4.02.

(3*S*,4*R*)-3-[(1′*R*)-1′-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1″*R*)-1″-[[[(*p*-methoxybenzyl)oxy]methyl]carbonyl]ethyl]-azetidin-2-one (10d). According to the procedure described above, addition of [[(*p*-methoxybenzyl)oxy]methyl]lithium to the dimagnesium salt of azetidinone **9** (51.0 g, 0.169 mol) gave 33.83 g (0.078 mol, 46%) of **10b** as a colorless oil (R_f = 0.68, EtOAc): $[\alpha]^{20}_D$ +28.0° (*c* 0.3.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 5.85 (s, 1H), 4.54 (s, 2H), 4.23−4.11 (m, 1H), 4.08 (s, 2H), 3.86 (dd, J = 2.1, 4.5 Hz, 1H), 3.84 (s, 3H), 3.14 (m, 1H), 2.91 (dd, J = 1.8, 4.8 Hz, 1H), 1.19 (d, J = 6.3 Hz, 3H), 1.18 (d, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9, 168.1, 159.5, 129.7, 128.8, 114.0, 74.0, 73.1, 65.3, 61.4, 55.3, 51.0, 43.9, 25.7, 22.5, 17.9, 11.4, −4.3, −5.1; IR (NaCl)) 3155, 2954, 2926, 1757, 1716. Anal. Calcd for $C_{23}H_{37}NO_5Si$: C, 63.41; H, 8.56; N, 3.22. Found: C, 63.60; H, 8.39; N, 3.10.

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1′*R*)-1′-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1″*R*)-1″-[[(methoxymethoxy)methyl]carbonyl]ethyl]azetidin-2-one (12a). A solution of 5.76 g (16.0 mmol) of keto azetidinone **10c** and 3.67 g (32.0 mmol) of allyl glyoxylate in 80 mL of toluene was heated at reflux for 16 h, and the small amount of water was removed by azeotropic distillation using a Dean−Stark trap. The solvent was evaporated under reduced pressure, and the residue was chromatographed using eluent hexane:ethyl acetate (4:1, 300 mL; 2:1, 300 mL; 1:1, 300 mL) to give 6.39 g (13.5 mmol, 84%) of the hemiaminal as a thick oil.

A solution of 6.38 g (13.5 mmol) of the hemiaminal intermediate and 4.72 mL (40.5 mmol) of 2,6-lutidine in 150 mL of dry THF was cooled to −40 °C, and to it was added 2.95 mL (40.5 mmol) of thionyl chloride dropwise under an argon atmosphere. The mixture was stirred at −40 to −30 °C for 1 h, and the formed salt solid was removed by immediate filtration. The filtrate was dried in vacuo. The residue was dissolved in 150 mL of molecular sieve-dried ethyl acetate, and the precipitate was removed by filtration. The filtrate was dried in vacuo again. The filtration should be performed as fast as possible under an argon atmosphere to avoid exposure to moisture. The residue was dissolved in 100 mL of DMF dried with molecular sieves, and 7.082 g (27.0 mmol) of triphenylphosphine was added followed by 3.14 mL (27.0 mmol) of 2,6-lutidine. The resulting solution was stirred at room temperature for 15 h and then partitioned between 200 mL of saturated aqueous NaCl solution and 300 mL of ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with 200 mL of ethyl acetate. The combined organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was flash chromatographed using hexane:ethyl acetate (4:1, 500 mL; 1:1, 800 mL) (R_f = 0.45, hexane:EtOAc 1:1) to give 6.772 g (9.45 mmol, 70%) of ylide **12a** as a light brown thick oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82−7.40 (m, 15H), 6.02−5.85 (m, 1H), 5.40−5.05 (m, 2H), 4.75−4.49 (m, 4H), 4.26−3.98 (m, 4H), 3.37 (s, 3H), 2.77−2.58 (m, 2H), 1.40−0.98 (m, 6H), 0.90−0.65 (m, 9H), +0.04 to −0.06 (m, 6H).

(3*S*,4*R*)-3-[(1′*R*)-1′-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-1-[1-hydroxy-1-[(allyloxy)carbonyl]methyl]-4-[(1″*R*)-1″-[[(methoxymethoxy)methyl]carbonyl]ethyl]azetidin-2-one (12b). According to the procedure described above, keto azetidinone **10d** (35.43 g, 81.45 mmol) was converted to the hemiaminal intermediate (37.24 g, 70.0 mmol, 83%) as a thick oil. The hemiaminal (2.29 g, 4.18 mmol) was then transferred to the corresponding ylide **12b** (2.714 g, 3.42 mmol, 82%) as a foaming material: ^{1}H NMR (300 MHz) in $CDCl_3$ δ 7.82−6.83 (m, 19H), 6.02−5.85 (m, 1H), 5.40−5.03 (m, 2H), 4.64−4.33 (m, 4H), 4.32−3.72 (m, 4H), 3.81 (s, 3H), 2.75−2.60 (m, 2H), 1.51−0.95 (m, 6H), 0.92−0.75 (m, 9H), 0.15 to −0.50 (m, 6H).

(3*S*,4*R*)-1-[[(Allyloxy)carbonyl](triphenylphosphoranylidene)methyl]-3-[(1′*R*)-1′-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-[(1″*R*)-1″-[(hydroxymethyl)carbonyl]ethyl]-azetidin-2-one (12c) from 12a. To a solution of 46 mg (0.064 mmol) of ylide **12a** in 3 mL of dry CH_2Cl_2 was added 34 μL (0.258 mmol, 4 equiv) of trimethylsilyl bromide at −35 °C, and the mixture was stirred at −35 to −30 °C. TLC analysis showed no starting material in 15 min (R_f = 0.40, hexane:EtOAc 1:1). The mixture was washed with 5 mL of saturated aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to afford 44 mg of the crude hydroxymethyl ketone, which was used in the next step without further purification.

Allyl (1*S*,5*R*,6*S*)-2-(Hydroxymethyl)-6-[(1′*R*)-1′-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-methylcarbapen-2-em-3-carboxylate (4) from 12c. A solution of 44 mg of hydroxymethyl ketone ylide **12c** in 2 mL of toluene was heated at reflux for 1 h, and the solvent was evaporated under reduced pressure to give 45 mg of crude product, which was flash chromatographed using hexane:ethyl acetate (4:1 and then 1:1) (R_f = 0.80, hexane:EtOAc 1:1) to afford 10 mg (0.025 mmol, 40% for two steps) of carbapenem **4** as a colorless oil: IR ($CHCl_3$) 3500, 2955, 2859, 1774, 1720, 1651, 1624; $[\alpha]^{27}_D$ +60.0° (*c* 0.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (ddt, J = 5.1, 10.8, 17.1 Hz, 1H), 5.52 (dq, J = 1.5, 17.1 Hz, 1H), 5.15 (dq, J = 1.5, 17.1 Hz, 1H), 4.72−4.55 (m, 3H), 4.28−4.06 (m, 3H), 3.28−3.17 (m, 1H), 3.15 (dd, J = 2.7, 5.7 Hz, 1H), 1.16 (d, 3H), 1.10 (d, 3H), 0.80 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 161.7, 152.6, 131.4, 127.2, 118.2, 66.2, 65.9, 60.1, 57.4, 56.4, 41.1, 25.8, 22.4, 18.0, 15.4, −4.1, −4.9. Anal. Calcd for $C_{20}H_{33}NO_5Si\cdot 1/5H_2O$: C, 60.18; H, 8.43; N, 3.51. Found: C, 59.84; H, 8.19; N, 3.45.

Allyl (1*S*,5*R*,6*S*)-2-[(Methoxymethoxy)methyl]-6-[(1′*R*)-1′-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-methylcarbapen-2-em-3-carboxylate (13a). The procedure used for the preparation of carbapenem **4** was employed to prepare carbapenem **13a** as a white solid from the ylide in 71% after flash chromatography using hexane:ethyl acetate (4:1 and then 1:1) (R_f = 0.70, hexane:ethyl acetate 4:1): mp 23−25 °C; MS (ion spray) 440 (M + 1); $[\alpha]^{20}_D$ +65.2° (*c* 1.2 in $CHCl_3$) (*c* 2.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddt, J = 5.4, 10.5, 17.1 Hz, 1H), 5.35 (dq, J = 1.5, 17.1 Hz, 1H), 5.18 (dq, J = 1.5, 17.1 Hz,

1H), 4.86 (dd, J = 0.6, 14.1 Hz, 1H), 4.66 (dtq, J = 1.5, 5.4, 13.8 Hz, 2H), 4.57 (d, J = 1.5 Hz, 2H), 4.17 (dd, J = 1.2, 14.1 Hz, 1H), 4.16−4.06 (m, 1H), 3.31 (s, 3H), 3.34−3.23 (m, 1H), 3,14 (dd, J = 3.0, 6.6 Hz, 1H), 1.18 (d, J = 6.0, 3H), 1.12 (dd, J = 7.2 Hz, 3H), 0.81 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 161.0, 148.4, 131.7, 127.6, 118.6, 96.6, 66.6, 65.9, 62.1, 60.4, 56.4, 55.7, 40.6, 25.9, 22.6, 18.1, 15.5, −4.0, −4.8. Anal. Calcd for $C_{22}H_{37}NO_6Si$: C, 60.11; H, 8.48; N, 3.19. Found: C, 59.75; H, 8.18; N, 3.02.

Allyl (1*S*,5*R*,6*S*)-2-[(*p*-methoxybenzyl)oxy]-6-[(1′*R*)-1′-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-methylcarbapen-2-em-3-carboxylate (13b). The procedure used for the preparation of carbapenem **4** was employed to prepare carbapenem **13b** as a colorless oil in 95% after flash chromatography using hexane:ethyl acetate (8:1 and then 4:1) (R_f = 0.45, hexane:ethyl acetate 4:1): IR (NaCl) 2955, 2884, 1778, 1720 cm^{-1}, $[\alpha]^{20}_D$ +62.0° (*c* 2.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 12.0 Hz, 2H), 6.88 (d, J = 12.0 Hz, 2H), 5.93 (m, 1H),5.42 (dtq, J = 1.2, 5.4, 13.5 Hz, 2H), 4.50 (d, J = 11.4 Hz, 1H), 4.40 (d, J = 11.4 Hz, 1H), 4.24−4.12 (m, 3H), 3.807 (s, 3H), 3.35 (dq, J = 2.7, 7.2 Hz, 1H), 3.19 (dd, J = 3.0, 6.6 Hz, 1H), 1.25 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 7.5 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 161.2, 159.6, 149.2, 131.7, 130.1, 129.7, 127.4, 118.6, 114.0, 72.9, 66.6, 65.8, 64.3, 60.4, 56.3, 55.5, 40.6, 25.9, 22.7, 18.2, 15.6, −4.0, −4.7. Anal. Calcd for $C_{28}H_{41}NO_6Si$: C, 65.21; H, 8.01; N, 2.72. Found: C, 65.5; H, 7.61; N, 2.61.

Allyl (1*S*,5*R*,6*S*)-2-(Hydroxymethyl)-6-[(1′*R*)-1′-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1-methylcarbapen-2-em-3-carboxylate (4) from 13b. To a solution of 5.00 g (9.70 mmol) of [[(*p*-methoxybenzyl)oxy]methyl]carbapenem **13b** dissolved in 250 mL of CH_2Cl_2 was added 3.306 g (12.6 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) followed by 25 mL of H_2O, and the mixture was stirred at room temperature for 2.5 h. The solid was removed by filtration, and the filtrate was washed by saturated $NaHCO_3$. The organic phase was dried over anhydrous $MgSO_4$ and evaporated. The residue was chromatographed using hexane:ethyl acetate (8:1 → 2:1) to give 2.437 g (6.09 mmol, 63%) of hydroxymethyl carbapenem **4** as a pale yellow thick oil.

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