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Efficient and Practical Synthesis of a Potent Anti-MRSA β-Methylcarbapenem Containing a Releasable Side Chain

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Abstract: We describe a convergent synthesis of the MRSA β-methyl carbapenem **1**, wherein the molecule is assembled from the naphthosultam side chain **2** and the allylic carbonate of the β-Me carbapenem piece **6**. The β-Me stereochemistry of **6** is set up in a novel titanium enolate addition into the TBDMS acetoxy azetidinone **5**. The benzenesulfonate salt of **1** is endowed with exceptional stability.

The ability of pathogenic bacteria to rapidly develop resistance to the existing repertoire of antibacterial agents poses a constant challenge for medicinal chemistry and the pharmaceutical industry. Consequently, an urgent need exists to expand the quality of the arsenal of compounds at the disposal of the medical community in order to prevent an upsurge of often-fatal bacterial infections. Prominent among the many antibacterial agents are the β-lactams, and especially the carbapenems, such as imipenem.[1] Carbapenems are endowed with broad-spectrum antibacterial properties combined with good tolerability and are consequently one of the most potent weapons in the fight against bacterial infections. Work from numerous laboratories has revealed some important structure−activity relationships: addition of a β-Me group in the 1-position increases the metabolic and chemical stability, while attachment of aryl groups either directly or through a heteroatom linker to the 2-position of the carbapenem results in exquisitely potent antibacterial agents.[2] A recent, very promising carbapenem development candidate with anti-MRSA (Methicillin-resistant *Staphylococcus aureus*) activity is **1**, which attaches a naphthosultam side chain **2** through a methylene linker to the carbapenem nucleus[3] (Scheme 1). This arrangement results in expulsion of the side chain when the β-lactam has acylated the surface of red blood cells. Consequently, the red blood cells are not labeled with the potentially immunogenic naphthosultam side chain and it could be hoped that hemolytic anemia, i.e., the lysis of the marked red blood cells by the immune system, would not pose a problem for this compound.[4] Retrosynthetically, we planned to assemble **1** by a Pd-catalyzed coupling[5] between the allylic carbonate of the β-methyl carbapenem **6** and the fully elaborated naphthosultam side chain **2**[6] (Scheme 2). Two different strategies were pursued for the preparation of the carbapenem coupling partner **6**. In the first approach, a Pd-catalyzed Stille coupling between the enoltriflate **3** and *n*-Bu_3SnCH_2OH is used to install the methylene linker on the carbapenem nucleus.[7] While this approach has been used to successfully prepare material, the route is long and requires significant efforts to ensure that the

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(1) Backes, J. In *Methoden der Organischen Chemie (Houben Weyl*); Klamann, D., Ed.; Georg Thieme Verlag: Stuttgart, 1991; Band E16b.

(2) Kawamoto, I. *Drugs Future* **1998**, *23*, 181.

(3) (a) Ratcliffe, R. W.; Wilkening, R. R.; Wildonger, K. J.; Waddell, S. T.; Santorelli, G. M.; Parker, D. L., Jr.; Morgan, J. D.; Blizzard, T. A.; Hammond, M. L.; Heck, J. V.; Huber, J.; Kohler, J.; Dorso, K. L.; St. Rose, E.; Sundelof, J. G.; May, W. J.; Hammond, G. G. *Bioorg. Med. Chem. Lett* **1999**, *9*, 679. (b) Wilkening, R. R.; Ratcliffe, R. W.; Wildonger, K. J.; Cama, L. D.; Dykstra, K. D.; DiNinno, F. P.; Blizzard, T. A.; Hammond, M. L.; Heck, J. V.; Dorso, K. L.; Rose, E. St.; Kohler, J.; Hammond, G. G. *Bioorg. Med. Chem. Lett* **1999**, *9*, 673.

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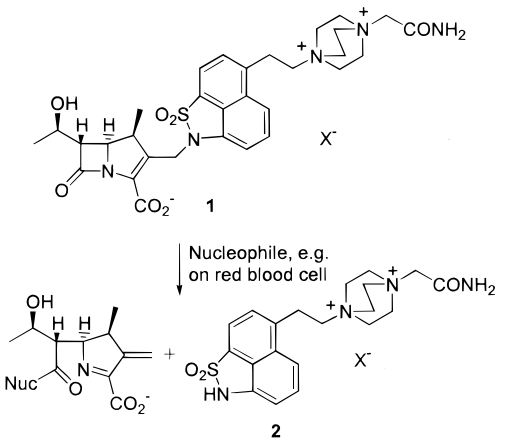
Scheme 1

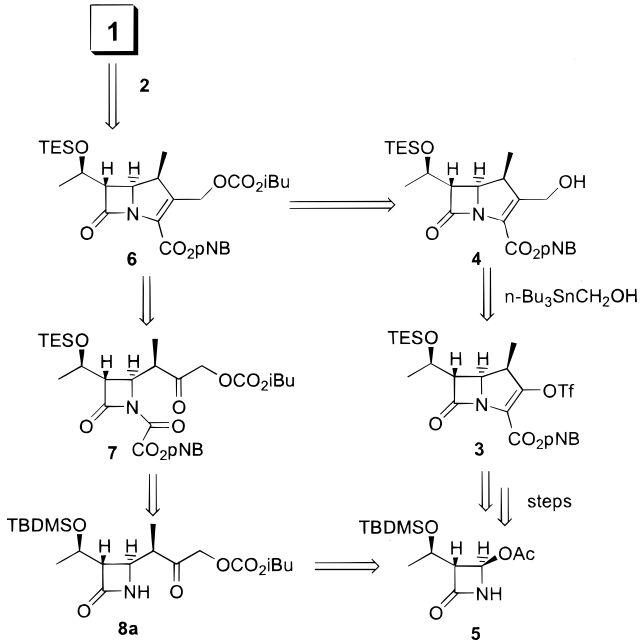


final drug is free from the organotin byproducts. Our goal was develop a short, practical, and high yielding, as well as environmentally benign, route to **1** that prepares the carbapenem nucleus containing the activated methylene linker (**6**) directly from the commercially available TBDMS acetoxy azetidinone **5**. To this end, the β-methyl carbapenem coupling partner **6** would be made using a reductive cyclization of the oxalimide **7**,[8] which should in turn be easily attainable from the ketone **8a**. The key problem is thus the ability to prepare the β-methyl-containing hydroxymethyl ketone **8a** in an efficient manner from **5**.

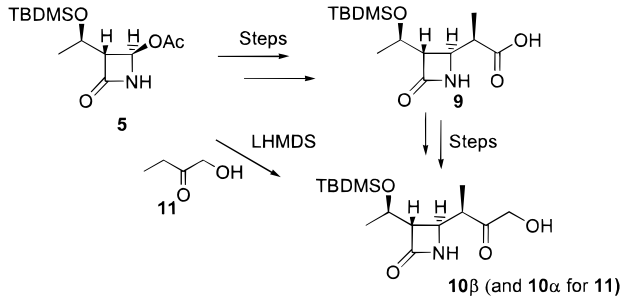
The highly desirable properties of β-methyl-containing carbapenems and the difficult synthetic accessibility of this class of compounds have resulted in a large body of publications, mostly from industrial laboratories.[9] Unfortunately, the published approaches target the β-Me carboxylic acid **9** and require complex and cumbersomely prepared synthons of the propionic acid enolate to achieve the desired diastereoselectivity in the addition. Additionally, while the required extension from the carboxylic acid to the hydroxymethyl ketone can be accomplished, a direct approach from the TBDMS acetoxy azetidinone **5** would be preferable.[10]

To this end, we decided to examine enolates and enolate equivalents of the commercially available 1-hydroxy-2-butanone (**11**) (Scheme 3). Initial results appeared promising: addition

Scheme 2



Scheme 3



of the enolate prepared from **11** by the addition into LHMDS resulted in a 33% yield of **10**, albeit as a 1:1 mixture of α- and β-Me diastereomers. A systematic variation of reaction conditions was undertaken at this point.

Surprisingly, no reports on the use of the 1-hydroxy-2-butanone enolate could be found in the literature and it was clear that both the regiochemistry and enolate geometry would have to be controlled. Addition of **11** to an excess of LHMDS followed by a quench with TMSCl resulted in poor regioselectivity of enolate formation, but with good selectivity for the Z(O) enol ether **12**. All attempts to improve on this result by use of different bases or the addition of salts resulted in lower selectivities. Fortunately, the combination of TMSOTf and Et_3N at -60 °C in CH_2Cl_2 cleanly led to the desired Z(O) enol ether **12**. Reaction of **12** with acetoxy azetidinone **5** using $ZnCl_2$ catalysis gave a small selectivity for the undesired α-Me stereochemistry (66:34). Changing the NH group of the lactam for the NTBDMS group (**13**) and use of TMSOTf as catalyst improved the diastereoselectivity of the reaction to give a 10:1 ratio of the undesired α-diastereomer (Scheme 4).While the high diastereoselectivity to the undesired α-diastereomer was disappointing, it was encouraging to obtain the desired enolate regiochemistry using a combination of Lewis acid and base. To expand on this lead **11** was protected as the carbonate using standard conditions (isobutylchloroformate, pyridine, toluene) and the resulting **14** was treated with $TiCl_4$ in toluene (Scheme

(4) (a) Rosen, H.; Hajdu, R.; Silver, L.; Kropp, H.; Dorso, K.; Kohler, J.; Sundelof, J.G.; Huber, J.; Hammond, G. G.; Jackson, J. J.; Gill; C. J.; Thompson, R.; Pelak, B. A.; Epstein, T.; Jeffrey H.; Lankas, G.; Wilkening, R. R.; Wildonger, K. J.; Blizzard, T. A.; DiNinno, F. P.; Ratcliffe, R. W.; Heck, J. V.; Kozarich, J. W.; Hammond, M. L. *Science* **1999**, *283*, 703. (b) Lankas, G. R.; Coleman, J. B.; Klein, H. J.; Bailly, Y. *Toxicology* **1996**, *108*, 207.

(5) For a review of Pd-catalyzed π-allyl coupling, see: Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 585.

(6) The synthesis of the side chain **2** is disclosed in a separate publication: Miller, R. A.; Humphrey, G. R.; Lieberman, D. R.; Ceglia, S. S.; Grabowski, E. J. J. *J. Org. Chem*., manuscript submitted.

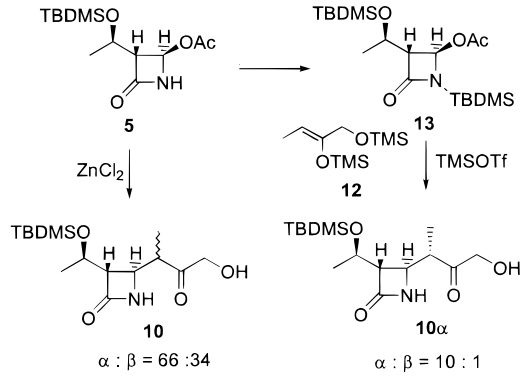
(7) Yasuda, N.; Yang, C.; Wells, K. M.; Jensen, M. S.; Hughes, D. L. *Tetrahedron Lett*. **1999**, *40*, 427.

(8) For some recent applications of this reductive cyclization, see: (a) King, S. A.; Pipik, B.; Thompson, A. S.; DeCamp, A.; Verhoeven, T. R. *Tetrahedron Lett*. **1995**, *36*, 4563. (b) Hanesian, S.; Rozema, M. J. *J. Am. Chem. Soc*. **1996**, *118*, 9884.

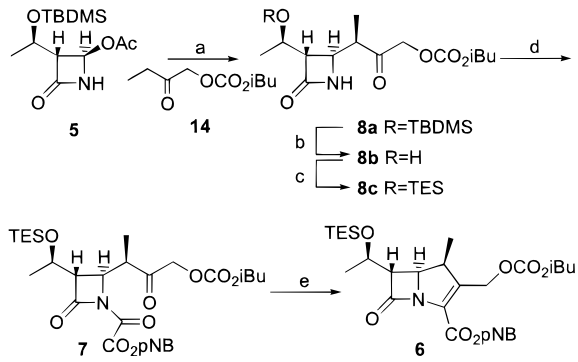
(9) For a comprehensive review of the chemistry of **9**, see: Berks, A. H. *Tetrahedron* **1996**, *52*, 331.

(10) (a) Yang, C. Yasuda, N. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 255. (b) Hu, X. E.; Demuth, T. P. *J. Org. Chem.* **1998**, *63*, 1719. (c) We have realized an alternative, much simpler approach from the acid **9** to the hydroxymethyl ketone β-**10**: activation of **9** using carbonyldiimidazole is followed by reaction with the glycolic acid enolate. Acid workup with concomitant decarboxylation gives β-**10** in 72% isolated yield. (d) Choi, W. B. *Chem. Commun. (Cambridge)* **1998**, *17*, 1817.

Scheme 4



Scheme 5[a]



[a] Conditions: (a) **14**, $TiCl_4$, Bu_3N, PhMe, −40 °C to −5 °C; (b) 2 N HCl (aq), MeCN, PhMe, 64% from **5**; (c) TESCl, imid, PhMe, MeCN; (d) pyr, $ClOCCO_2pNB$, PhMe, 97% from **8b**; (e) $POEt_3$, heptane, 92 °C, 85%.

5). A yellow precipitate formed,[11] which was treated at −40 °C with 4 equiv of *n*-Bu_3N.[12] To the resulting deep red solution of the Ti enolate was added a solution of **5** in toluene, and the mixture was allowed to stir for 5 h at 5 °C. An inverse quench into 2 N HCl resulted in a *82% yield of the desired product* ***8a*** *with excellent 95:5 β:α stereoselectivity* (Scheme 5).

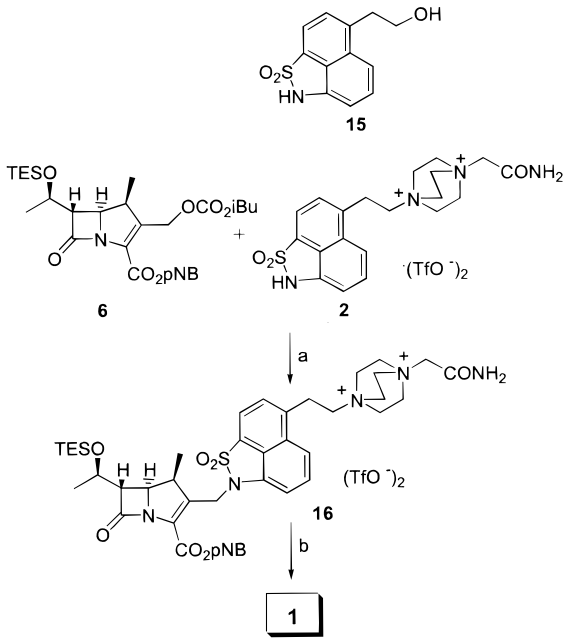
To gain some understanding of the mechanism, we attempted to elucidate the nature of the intermediate Ti enolate. Direct quench of the Ti enolate with electrophiles other than DCl/D_2O failed, but low-temperature transmetalation with MeLi followed by addition of TMSCl gave predominantly the Z(O) silyl enolate **12** (>10:1 *Z*:*E*). This apparent regio- and stereoselective formation of the Z(O) enolate was confirmed by NMR experiments, where the enolate was generated in toluene-d_8 using Et_3N-d_{15}. Again, the resulting enolate was the Z(O) enolate (10:1 *Z*:*E*). While conclusive statements on the mechanism of the reaction between the Ti enolate with acetoxy azetidinone are clearly not possible without extensive experimental work, the observed enolate geometry is consistent with a closed cyclic transition state in the addition of the titanium Z(O) enolate to the putative acyl iminium intermediate.

With an efficient access to **8a** at hand, we were now in a position to complete the synthesis of the key penem nucleus **6** (Scheme 5). The lability of carbapenem **1** made it necessary to use protecting groups throughout the sequence that could be removed using a mild set of conditions for the final elaboration of the drug substance. Consequently, a protecting group change

(11) Poll, T.; Metter; J. O.; Helmchen G. *Angew. Chem., Int. Ed. Engl* **1985**, *24*, 112.

(12) (a) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc*. **1991**, *113*, 1047. (b) Yoshida, Y.; Hayashi, R.; Sumbara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38*, 8727.

Scheme 6[a]



[a] Conditions: (a) 0.5 equiv of 2,6-lutidine, 3 mol % $Pd(OAc)_2$, 9 mol % $(BuO)_3P$, NMP, 35 °C; (b) TfOH, H_2O, IPA pH = 2.6; pH = 6.85 MOPS buffer, 5% Pd/C, 40 psi H_2; $PhSO_3Na$, H_2O, IPA.

from TBDMS to the more labile TES group is performed. Removal of the TBDMS ether in **8a** was best accomplished using aqueous 2 N HCl in a homogeneous CH_3CN/toluene mixture, followed by neutralization of the acid with solid $NaHCO_3$ and isolation of **8b** after a filtration to remove salts and a concentration from toluene. This simple procedure gave **8b** in 64% overall yield from **5** and additionally served to improve the diastereomeric purity in the crystallization of **8b** (>99% β-Me in isolated product). Reprotection of the hydroxyethyl side chain was accomplished using standard conditions (TESCl, imidazole, toluene/CH_3CN), and the resulting **8c** was not isolated but used directly in the next step. The elaboration of **8c** to the oxalimide **7** was accomplished by addition of **8c** to a slurry of the pyridinium salt of *p*-nitrobenzyl oxalyl chloride in toluene. Aqueous work up and crystallization gave the oxalimide **7** in 97% overall yield. The reductive cyclization of **7** was easily accomplished using 5 equiv of $P(OEt)_3$ in refluxing heptane for 3 days.[13,8] Oxidation of the excess phosphite to triethyl phosphate (H_2O_2 in pH 6 phosphate buffer) was followed by aqueous washes to remove the phosphate. A subsequent solvent switch from heptane to 2-butoxyethanol and addition of water precipitated the desired **6** in 85% yield (Scheme 5).

The next synthetic challenge for the elaboration of **1** was the coupling of the naphthosultam side chain **2** to **6** (Scheme 6). The desirable convergent route would bring in the fully elaborated side chain to convert **6** in one step to the protected precursor of **1** (**16**), thus, minimizing manipulations with the sensitive carbapenem. The choice of carbonate protection of the hydroxymethyl side chain of **6** offers the opportunity to exploit this protecting group as an activating group by utilizing the chemistry of cationic Pd−π-allyl systems.[14] Significantly, both the generation of the Pd−π-allyl species and its coupling with the complex dicationic 1,8-naphthosultam DABCO aceta-

(13) Heptane was chosen for its commercial availability; running the reaction in nonane or in heptane under pressure at 120 °C allows completion of the reaction in 3 h.

mide nucleophile **2** would clearly rank among the most complex and challenging examples for this reaction recorded in the literature.[7]

Conventionally, the activation of allylic carbonates to the Pd−π-allyl species is done using Ph_3P both to reduce the $Pd(OAc)_2$ catalyst precursor to the catalytically active Pd(0) species and to prevent the precipitation of metallic Pd black. Indeed, coupling of the partly elaborated side chain **15** with the isobutyl carbonate **6** occurs in essentially quantitative yield with 3 mol % $Pd(OAc)_2$ and 9 mol % of Ph_3P in a biphasic toluene/aqueous Rochelle's salt solution system at 80 °C in 2 h. Unfortunately, it was not possible to use these conditions with the fully elaborated side chain **2**, as Hofmann elimination of the quaternary DABCO piece became dominant. Thus, reaction conditions were varied with the goal of finding a more highly reactive catalyst system that would avoid this problem. Contrary to literature reports, phosphite ligands resulted in catalysts of exquisite reactivity: use of $(BuO)_3P$ instead of Ph_3P with **15** gives complete conversion at 35 °C in less than 30 min! Indeed, application of this highly active catalyst system makes it possible to couple the carbapenem piece **6** with the fully elaborated side chain **2** using NMP as solvent and 2,6-lutidine as base in quantitative assay yield.[15] Isolation of the protected **1** (**16**) is accomplished in a straightforward manner from the reaction mixture by the addition of water and isopropyl alcohol, which furnishes crystalline product in excellent purity in 97% yield. A key issue for the use of metal-catalyzed reactions for the preparation of pharmaceuticals is the removal of the metal catalysts down to trace levels in the bulk drug. Fortunately, the crystallization after the Pd−π allyl coupling leaves the Pd metal largely in the mother liquors, the Pd level in the isolated bulk is very low at <100 ppm Pd.

The completion of the synthesis requires the removal of the TES and p-PNB protecting groups from **16**, as well as the development of a procedure that allows for the isolation of the unprotected **1**. To this end, the TES group was removed using 3.5 mol % of triflic acid in IPA at 20 °C for 18 h. Adjustment of the pH to 6.9 by the addition of aqueous MOPS buffer, addition of 5% Pd/C catalyst and hydrogenolysis at 3 bar H_2 for 1 h gave the desired free **1**. After the filtration of the Pd/C catalyst, the nonpolar byproducts of the deprotection steps could be removed by washing the buffered aqueous phase with toluene to give **1** in 90% yield.

The isolation of pure, crystalline, stable carbapenem products from deprotection solutions is a formidable problem as these products have limited stability in aqueous buffered solutions due, principally, to β-lactam solvolysis. Initial purification is usually achieved via resin chromatography followed by reverse osmosis concentration of the rich cuts. Crystallization, if possible at all, is typically difficult even for the chromatographed material. Initial isolations of **1** were done in this standard manner. While typical salts of **1** are not suitable for direct isolation (i.e., chloride or sulfate), we were pleased to note that addition of sodium benzenesulfonate to a worked-up hydrogenation reaction mixture led to the ready crystallization of **1** as its benzenesulfonate salt trihydrate (X = $PhSO_3^-$) in 75% yield. The isolated product has excellent purity and is essentially free from palladium (<2 ppm). In addition to providing a simple and elegant method for the isolation of **1**, the benzenesulfonate salt is endowed with exceptional thermal stability in the crystalline state: essentially no decomposition is observed after heating the solid salt for 2 h at 100 °C, in marked contrast to observations for other salts of **1**, or other carbapenems in general.

In summary, we have described a simple and convergent process for the preparation of the anti-MRSA β-Me carbapenem **1**, which allows the preparation of this important antibiotic in 38% overall yield from the readily available acetoxy azetidinone **5**. Preparation of the β-Me carbapenem coupling partner **6** is accomplished in five steps from the readily available acetoxy azetidinone in 52% yield, whereby the required β-Me stereochemistry is set up in a highly diastereoselective reaction using a novel titanium enolate. Subsequent attachment of the complete side chain **2** uses a Pd−π-allyl cation intermediate and occurs in near quantitative yield. Subsequent deprotections and isolation of the desired **1** as the exceptionally stable benzenesulfonate salt occurs in a remarkable 73% yield from **6**. The route described uses environmentally acceptable chemistry, is amenable to large-scale preparations, and has been used to prepare **1** on a multikilogram scale.

Experimental Section

General Procedure. All reactions were carried out in glassware that was dried in a N_2 stream overnight. All reagents were commercial grade and were used as received. BASF is a commercial supplier of 1-hydroxy-2-butanone. *tert*-Butyldimethylsilyl acetoxy azetidinone was purchased from Takasago. HPLC purities refer to area % measured at 210 nm.

***p*-Nitrobenzyloxalyl Chloride.**[16] A 100-L flask equipped with an overhead stirrer, thermocouple, nitrogen inlet, and an outlet leading to a 50% aqueous sodium hydroxide scrubber was charged with dichloromethane (44 L) and the temperature was adjusted to 6 °C. Oxalyl chloride (5.81 kg) was added followed by *p*-nitrobenzyl alcohol (4.49 kg) in ~500 g portions over 30 min. The reaction mixture was aged at 6 °C for 2 h. Dichloromethane (40 L) was removed by distillation over 4 h. Toluene (9.4 L) was added and heating was resumed. When the distillation was complete the temperature was allowed to rise to 73 °C for 10 min. The heating was stopped and cyclohexane (1 L) was added to precipitate the undesired bis *p*-nitrobenzyl oxalate. Bis-*p*-nitrobenzyl oxalate was removed by filtration under a blanket of nitrogen. Cyclohexane (33 L) was added and the slurry was aged for 2 h at 11 °C. The precipitated *p*-nitrobenzyloxalyl chloride was filtered off and allowed to dry under a nitrogen sweep to afford *p*-nitrobenzyloxalyl chloride (5.31 kg, 74% yield).

2-Oxobutyl Isobutyl Carbonate (14). A 100-L flask equipped with an overhead stirrer, thermocouple, and a nitrogen inlet was charged with 1-hydroxy-2-butanone (5.14 kg, 58.4 mol), hexanes (12 L), cyclohexane (18 L), and pyridine (6.16 L). The temperature was adjusted to 10 °C. iso-Butyl chloroformate (7.90 L) was added over 2.5 h. At the end of the reaction, water (20 L) was added, and the mixture was aged with stirring for 30 min. The lower aqueous layer was cut away, and the organic layer was further washed with aqueous HCl (0.5 N; 20.7 L) and water (2 × 20 L). The organic phase was concentrated to afford 9.68 kg of the 2-oxobutyl isobutyl carbonate (**14**) as a pale yellow oil: ^{1}H NMR (400.25 MHz, $CDCl_3$) δ 4.60 (s, 2 H), 3.89 (d, J = 6.8 Hz, 2 H), 2.39 (q, J = 7.2 Hz, 2 H), 1.93 (m, 1 H), 1.02 (t, J = 7.2 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 6 H); ^{13}C NMR (100.64 MHz, $CDCl_3$) δ 204.0, 154.7, 74.4, 70.0, 31.6, 27.6, 18.6, 6.8; IR (neat) 2966, 2878, 1755.7 cm^{-1}. Anal. Calcd for $C_9H_{16}O_4$: C, 57.41; H, 8.57. Found: C, 57.36; H, 8.59.

Hydroxymethyl Ketone Isobutyl Carbonate (8a). A 100-L flask equipped with an overhead stirrer, thermocouple, and a nitrogen inlet was charged with 2-oxobutyl isobutyl carbonate (**14**) (5.47 kg, 58.4 mol) and toluene (28 L) and the temperature was adjusted to −40 °C. Titanium(IV) chloride (3.05 L) was added over 45 min and the slurry

(14) Mitsunobu reactions of a 2-(hydroxymethyl)carbapenem with N-nucleophiles have been reported: Arnould, J. C.; Landier, R.; Pasquet, M. J. *Tetrahedron Lett*. **1992**, *33*, 7133.

(15) A strong ligand dependence is noted for the coupling between **6** and **2** in NMP/2,6-lutidine with 3 mol % $Pd(OAc)_2$. The conversion after 5 h at 30 °C is 10% for Ph_3P, 93% for $(BuO)_3P$ and <2% for Ph_3As.

(16) Togo, H.; Fujii, M.; Yokoyama, M. *Bull. Chem. Soc. Jpn*. **1991**, *64*, 57.

was aged for a further 30 min at −45 °C. Tributylamine (13.5 L) was added over 1.5 h. The reaction mixture was warmed to −20 °C over 1 h. A solution of *tert*-butyldimethylsilyl acetoxy azetidinone **5** (4.01 kg, 14.8 mol) in toluene (22 L) was added to the 100-L flask over 1 h. After 5 h the reaction was quenched by an inverse addition into water at 5 °C. The organic layer was washed further with aqueous HCl (1.2 N; 2 × 72 L). The organic layer was collected (44.8 kg; β:α = 96:4;) and used in the subsequent step: mp 64.0−66.0 °C; $[\alpha]^{25}_D$ −5.56° (*c* 2.50, $CHCl_3$); ^{1}H NMR (400.25 MHz, $CDCl_3$) δ 6.14 (s, 1H), 4.74 (d, J = 17.0 Hz, 1H), 4.68 (d, J = 17.0 Hz, 1H), 4.16 (m, 1H), 3.95 (d, J = 6.8 Hz, 2H), 3.89 (dd, J = 2.0, 4.8 Hz, 1H), 2.93−2.86 (m, 2H), 1.99 (m, 1H), 1.20 (d, J = 7.2 Hz, 3H), 1.18 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.8 Hz, 6H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100.64 MHz, $CDCl_3$) δ 205.6, 168.2, 154.8, 74.8, 69.7, 65.5, 61.8, 51.0, 44.6, 27.8, 25.8, 22.5, 18.8, 17.9, 11.6, −4.3, −5.0; IR (KBr) 3468, 2955, 1763, 1748, 1734, 1722 cm^{-1}. Anal. Calcd for $C_{20}H_{37}NO_6Si$: C, 57.69; H, 8.89; N, 3.61 Si, 7.70. Found: C, 57.69; H, 8.70; N, 3.31; Si, 7.20.

***tert*-Butyldimethylsilyl Ether Deprotection: Free Hydroxyl (8b).** The toluene solution containing **8a** from the previous step was concentrated to 20 L under vacuum. Acetonitrile (50 L) was charged to the vessel, and with stirring aqueous HCl (2 N; 2.5 L) was added. After 3.5 h the reaction was complete and solid sodium bicarbonate (2.5 kg) was added to quench the reaction. Stirring was continued for 30 min. Solka floc was added, and the slurry was filtered. The filtrate was evaporated with the addition of toluene until ∼30 L of solution was left. The product **8b** precipitated during the solvent switch. The organics contained 10% acetonitrile. The slurry of the product was cooled to 4 °C and aged for 3 h. The solids were isolated by filtration and then washed with the liquors. The wet cake was slurry-washed with 20% MTBE/hexanes (3 × 8 L) and then surface washed with 20% MTBE/hexanes (4 L). The cake was dried under a nitrogen sweep for 18 h to furnish 2.64 kg of **8b** as a white solid (63.4%, containing 0.5 A% α isomer): mp 136.0−138.5 °C; $[\alpha]^{25}_D$ −39.96° (*c* 2.5, MeOH); ^{1}H NMR (400.25 MHz, $CDCl_3$) δ 6.40 (s, 1H), 4.78 (d, J = 16.9 Hz, 1H), 4.74 (d, J = 16.9 Hz, 1H), 4.11 (m, 1H), 3.97 (d, J = 6.8 Hz, 2H), 3.83 (dd, J = 2.4, 6.8 Hz, 1H), 2.93−2.85 (m, 2H), 2.63 (broad s, 1H), 1.98 (m, 1H), 1.30 (d, J = 6.4 Hz, 3H), 1.25 (d, J = 7.2 Hz, 3H), 0.96 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100.64 MHz, $CDCl_3$) δ 206.0, 168.1, 154.9, 75.0, 69.7, 65.7, 62.2, 52.6, 45.8, 27.8, 21.4, 18.8, 12.6; IR (KBr) 3500, 3200, 1734, 1703 cm^{-1}. Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.63; H, 7.62; N, 4.97. Found: C, 55.91; H, 7.30; N, 4.70.

Triethylsilyl Ether (8c). A 100-L cylindrical vessel equipped with internal coils, a thermocouple, a nitrogen inlet, and an overhead stirrer was charged with **8b** (4.66 kg), imidazole (1.37 kg), toluene (30 L), and acetonitrile (6 L). TES chloride was added slowly over 1 h. After a 1 h age the reaction was quenched by the addition of water (30 L) and the organic layer was collected and washed again with water (20 L). The solvent was switched into toluene (25 L) and this solution was used in the subsequent step. Evaporation gave the triethylsilyl ether **8c** as a thick oil; ^{1}H NMR (400.25 MHz, $CDCl_3$) δ 5.91 (s, 1H), 4.76 (d, J = 16.9 Hz, 1H), 4.70 (d, J = 16.9 Hz, 1H), 4.21−4.14 (m, 1H), 3.97 (d, J = 6.8 Hz, 2H), 3.89 (dd, J = 2.4, 4.8 Hz, 1H), 2.93−2.89 (m, 2H), 2.06−1.96 (m, 1H), 1.23 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 7.2 Hz, 3H), 0.97 (d, J = 6.4 Hz, 6H), 0.95 (t, J = 8.0 Hz, 9H), 0.60 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100.64 MHz, $CDCl_3$) δ 205.7, 167.9, 154.9, 70.4, 69.7, 65.7, 61.8, 51.4, 44.6, 27.8, 22.7, 18.8, 11.3, 6.8, 5.0; exact mass [M + H] calcd 416.2468 found 416.2441.

Oxalimide (7). A 100-L cylindrical vessel equipped with internal coils, a thermocouple, a nitrogen inlet and an overhead stirrer was charged with *p*-nitrobenzyl oxalyl chloride (4.90 kg) and toluene (30 L) and the temperature was adjusted to 10 °C. Pyridine (3.25 L) was slowly added over 15 min to the slurry. The cooling was stopped and the reaction mixture aged for 30 min. The solution of **8c** in toluene was added over 10 min. After 17 h the reaction was quenched by the addition of aqueous citric acid (20 L), and the organic layer was collected. After hot extraction of the organics (60 °C) with aqueous sodium bicarbonate (20 L) then water (2 × 20 L) Ecosorb-C (400 g) was added and the batch was filtered. The solvent was switched into heptane (25 L). The solids were isolated by filtration and the wet cake was washed with heptane. The solids were allowed to dry under a nitrogen sweep to afford 9.37 kg of **7** as a pale yellow solid (97% yield): mp 60−62 °C; $[\alpha]^{25}_D$ −81.59° (*c* 2.50, $CHCl_3$); ^{1}H NMR (400.25 MHz, $CDCl_3$) δ 8.24 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 5.41 (s, 2H), 4.76 (d, J = 17.3 Hz, 1H), 4.63 (d, J = 17.3 Hz, 1H), 4.46 (m, 1H), 4.32 (m, 1H), 3.93 (d, J = 6.8 Hz, 2H), 3.60−3.51 (m, 2H), 1.98 (m, 1H), 1.27 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.8 Hz, 6H), 0.89 (t, J = 8.0 Hz, 9H), 0.54 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100.64 MHz, $CDCl_3$) δ 204.5, 164.8, 159.4, 156.0, 154.7, 148.1, 141.1, 129.0, 123.8, 74.8, 69.9, 66.7, 64.7, 61.4, 54.5, 40.9, 27.8, 22.5, 18.8, 14.0, 6.7, 4.8; IR (KBr) 1810, 1754, 1729, 1685, 1607 cm^{-1}. Anal. Calcd for $C_{29}H_{42}N_2O_{11}Si$: C, 55.71; H, 6.73; N, 4.81; Si, 4.49. Found: C, 55.91; H, 6.47; N, 4.24; Si, 4.24.

[4*S*-[4α,5*β*,6*β*(*S)]]-4-Methyl-3-[[[(2-methylpropoxy)carbonyl]-oxy]methyl]-7-oxo-6-[1-[(triethylsilyl)oxy]ethyl]-1-azabicyclo[3.2.0]-hepten-2-ene-2-carboxylic Acid (4-Nitrophenyl)methyl Ester (6).** A 72-L flask equipped with an overhead stirrer, thermocouple, and nitrogen was charged with **7** (3.50 kg) and heptane (42 L). To this slurry was added triethyl phosphite (3.50 L), and the reaction mixture was heated to 92 °C over 1 h. Heating was continued for 72 h and the reaction was allowed to cool to 22 °C over 14 h. pH 6 phosphate buffer (20 L) was charged to the vessel followed by 30% hydrogen peroxide (1.2 L) over 2 h with the temperature maintained below 30 °C. MTBE (20 L) was added, and after 5 min the layers were allowed to settle. The lower aqueous phase was removed and the organic layer was washed with water (4 × 20 L) and dried with sodium sulfate (300 g). The organic layer was passed through a filter pot containing silica gel-60 (300 mm dia × 10 mm) and the silica gel was washed with 20%MTBE/heptane (15 L). The solvent was switched into 2-butoxy-ethanol (7.3 L). Water (2.5 L) was added slowly and the batch was seeded. After 30 min the batch crystallized, water (20 L) was added, and the slurry was aged overnight. The solids were collected by filtration and washed twice with 20% 2-butoxyethanol/water (2 × 5 L) and then four times with water (4 × 5 L). The solids were dried under a nitrogen sweep to afford 2.82 kg of the **6** as an off white solid (85% yield, 93 area %, 95 wt %): mp 53−58 °C; $[\alpha]^{25}_D$ = +52.6° (5.20, $CHCl_3$); ^{1}H NMR (400.25 MHz, DMSO-d_6) δ 8.19 (d, J = 8.6 Hz, 2H), 7.72 (d, J = 8.6 Hz, 2H), 5.46−5.31 (m, 3H), 4.83 (d, J = 14.2 Hz, 1H), 4.25−4.21 (m, 2H), 3.89 (d, J = 6.5 Hz, 2H), 3.48−3.46 (m, 1H), 3.32−3.26 (m, 2H), 1.88 (m, 1H), 1.15 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 7.4 Hz, 3H), 0.89 (t, J = 8.0, 9H), (d, J = 6.4, 6H), 0.54 (q, J = 8.0, 6H); ^{13}C NMR (100.64 MHz, DMSO-d_6) δ 176.0, 160.6, 154.9, 147.6, 145.3, 143.8, 128.8, 128.3, 123.8, 74.1, 65.7, 65.3, 61.9, 60.7, 55.1, 40.3, 27.7, 22.3, 19.1, 15.4, 7.1, 4.9; IR (KBr) 2963, 1791, 1746, 1716 cm^{-1}; MS (EI) *m*/*e* 399, 429, 443, 461, 517, 561. Anal. Calcd for $C_{29}H_{42}N_2O_9Si$: C, 58.96; H, 7.17; N, 4.74; Si, 4.75. Found: C, 59.10; H, 7.17; N, 4.68; Si, 4.74.

Triethylsilyl-*p*-nitrobenzyl-Protected 1 (16). A 100-L round-bottom flask equipped with an overhead stirrer, temperature probe, and nitrogen inlet was charged with **6** (1500 g, 2.54 mol). Next, 6.93 L of 1-methyl-2-pyrrolidinone was added, followed by **2** (1600 g, 2.3 mol) and 2,6-lutidine (122.4 g, 1.15 mol). This solution was aged at ambient temperature for 5 min. The mixture was degassed at ambient temperature with two nitrogen/vacuum cycles. Pd $(OAc)_2$ (17.4 g, 0.076 mol)) was added followed by tributyl phosphite (57.2 g, 0.229 mol). The reaction mixture was heated to 35 °C, and aged 12−16 h until reaction was complete by HPLC. The reaction mixture was cooled back to ambient temperature and quenched with water (0.7 L). Isopropyl alcohol (10.8 L) was added, and the reaction mixture was seeded and aged at ambient temperature for 40 min, at which time the product crystallized. An additional 16.2 L of isopropyl alcohol was then added slowly over a 40-min period, and the mixture was aged for 30 min at ambient temperature. The mixture was cooled to 5 °C and aged for 1 h. The solid was isolated by filtration and washed with cold isopropyl alcohol (2 × 5.4 L). A total of 2.98 kg (97% yield) of off-white solid was obtained as the di-2-propanoate solvate of **16**: mp 143 °C (dec); $[\alpha]^{25}_D$ = +28.65° (9.98, MeOH); ^{1}H NMR (400.25 MHz, acetone-d_6) δ 8.25 (m, 2H), 8.14 (d, J = 7.4 Hz, 1H), 8.01 (d, J = 7.5 Hz, 1H), 7.88 (m, 3H), 7.74 (br s, 1H), 7.66 (m, 1H), 7.29 (br s, 1H), 7.01 (d, J = 7.4 Hz, 1H), 5.62 (d, J = 14.1 Hz, 1H), 5.45 (d, J = 14.1 Hz, 1H), 5.40 (d, J = 17.1 Hz, 1H), 4.83 (d, J = 17.1 Hz, 1H), 4.71 (s, 2H), 4.64 (s, 12H), 4.30 (om, 4H), 4.01 (m, 2H), 3.89 (m, isopropyl alcohol O−C*H*−

$(CH_3)_2$), 3.46 (om, 2H), 3.44 (isopropyl alcohol O*H*), 1.33 (d, $J = 7.4$ Hz, 3H), 1.24 (d, $J = 6.1$ Hz, 3H), 1.10 (d, isopropyl alcohol CH_3), 0.94 (t, $J = 7.8$ Hz, 9H), 0.62 (q, $J = 7.8$ Hz, 6H); ^{13}C NMR (100.64 MHz, acetone-d_6) δ 174.3, 164.5, 161.1, 147.7, 146.2, 143.6, 137.7, 137.2, 130.3, 129.8, 129.7, 129.6, 129.2, 128.4, 123.4, 121.1 (q, $J =$ 320.1 Hz), 120.1, 119.2, 115.2, 104.5, 65.4, 65.3, 64.2, 62.9, 62.3, 60.4, 55.2, 52.2, 51.5, 40.7, 38.1, 24.9, 24.8, 21.5, 15.0, 6.25, 4.6; IR (KBr) 2960, 1778, 1701, 1669 cm^{-1}; MS (EI) *m*/*e* calcd for 874.4 found 873.1. Anal. Calcd for $C_{46}H_{58}F_6N_6O_{15}S_3Si$: C, 47.09; H, 4.98; N, 7.16; F, 9.72; S 8.20; Si, 2.39. Found C, 47.12; H, 5.03; N, 7.13; F, 9.72; S, 8.43; Si, 2.38.

Preparation of Benzenesulfonate of 1. To a 12-L round-bottom-flask equipped with an overhead stirrer, N_2 inlet, and temperature probe was charged **16** (600 g). In a separate flask, 2 mL triflic acid was added to 2 L water (pH 1.95), and then added to 6 L of isopropyl alcohol, (pH 2.6). The resulting solution was added to the TES penultimate, and the slurry (pH = 2.9) was stirred at ambient temperature until reaction was complete (~18 h).

A buffered solution of 4-morpholinepropanesulfonic acid was prepared by dissolving 356 g in 6 L water followed by addition of ~168 mL 5 N NaOH, resulting in a final solution pH of 7.17. The MOPS buffered solution (4.8 L) was added to neutralize the reaction slurry (final pH 6.85). The mixture was degassed, 150 g 5% Pd/C (dry reduced) was added and the system was placed under hydrogen (40 psi) until completion of the H_2 uptake (30 min). The catalyst was removed by filtration and the cake slurry was washed with 7 L of 50% aqueous isopropyl alcohol. The filtrate was immediately cooled to 5 °C to improve the stability of the free cation. The filtrate was partitioned with toluene (4 L), and the layers were separated. The aqueous solution was added to a solution of sodium benzenesulfonate (1.35 kg) in 4 L water at 20 °C. The reaction mixture was seeded and aged 1 h until crystallization occurred. The resulting slurry was cooled to 5 °C and filtered, and the slurry was washed with 0.5 L of 50% aqueous isopropyl alcohol. The solid was dried under nitrogen at ambient temperature to give 255 g of **1** (99.3 area % pure, 73.4% overall yield): mp 150−168 °C (dec); $[\alpha]^{25}_{436} = +136°$ (0.5, H_2O, after anion exchange to Cl^-); ^{1}H NMR (400.25 MHz, DMSO-d_6) δ 8.34 (br s, 1H), 8.18 (d, $J = 7.4$ Hz, 1H), 7.88 (br s, 1H), 7.84 (d, $J = 7.4$ Hz, 1H), 7.72 (d, $J = 8.6$ Hz, 1H), 7.61−7.59 (m, 2H), 7.43−7.39 (m, 1H), 7.32−7.28 (m, 3H), 7.11 (d, $J = 7.4$ Hz, 1H), 5.72 (d, $J = 15.9$ Hz, 1H), 4.99 (m, 1H), 4.55−4.46 (m, 3H), 4.42−4.24 (m, 12H), 4.05−3.80 (m, 4H), 3.75−3.55 (m, 2H), 3.1−3.0 (m, 1H), 2.99−2.85 (m, 1H), 1.09 (d, $J = 6.4$, 3H), 1.06 (d, $J = 7.2$, 3H); ^{13}C NMR (100.64 MHz, DMSO-d_6) δ 174.6, 165.2, 164.7, 148.4, 139.7, 138.7, 136.7, 132.6, 130.4, 129.8, 129.3, 129.2, 129.1, 128.2, 126.0, 120.8, 118.7, 115.6, 105.0, 64.7, 63.1, 62.1, 58.9, 55.3, 51.9, 50.9, 39.2, 37.2, 24.8, 22.1, 15.8; IR(KBr) 3426, 1751, 1698 cm^{-1}; MS (EI) cation *m*/*e* 401.2, 624.1, 625.1. Anal. Calcd for $C_{37}H_{49}N_5O_{13}S_2$: H, 5.91; C, 53.16; N, 8.38; S, 7.67. Found H, 6.08; C, 52.94; N, 8.38; S, 7.66.

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