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Efficient One-Pot Synthesis of the 2-Aminocarbonylpyrrolidin-4-ylthio-Containing Side Chain of the New Broad-Spectrum Carbapenem Antibiotic Ertapenem

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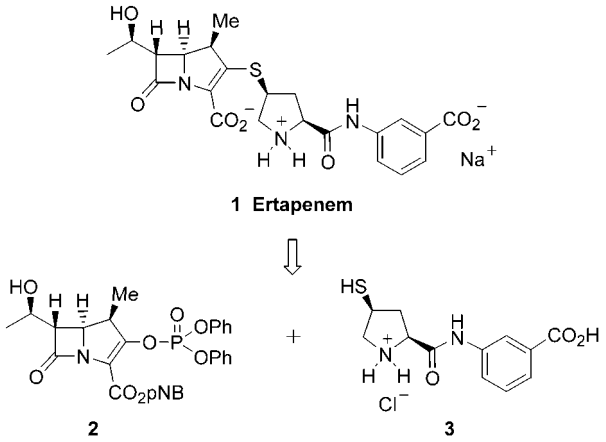
An efficient synthesis of the 2-aminocarbonylpyrrolidin-4-ylthio containing side chain of ertapenem (MK-0826) is described. Starting material *N*-(*O*,*O*-diisopropyl phosphoryl)-*trans*-4-hydroxy-L-proline is converted in a one-pot process to (2*S*)-*cis*-3-[[(4-mercapto-2-pyrrolidinyl)carbonyl]amino]benzoic acid monohydrochloride in 70−75% overall yield via a series of six reactions. The development of each of these reactions and the isolation of the product is discussed in detail.

Introduction

The discovery and development of new antibiotics has drawn significant attention in recent years due to the rising prevalence of multidrug resistant bacteria.[1] Ertapenem (**1**) is a new parenteral broad-spectrum carbapenem antibiotic[2,3] with a unique efficacy profile which is in late stages of development at Merck.[4,5] The compound is stable against renal dehydropeptidase-I and resistant to most β-lactamases.[6] Once-daily intramuscular or I. V. dosing is expected to be sufficient for treatment of most serious upper and lower respiratory tract, urinary tract, skin, obstetric and gynecologic infections due to its long pharmacokinetic half-life.[7]

SCHEME 1



Following conventional carbapenem retrosynthetic analysis, ertapenem can be assembled from 4-nitrobenzyl-protected β-methyl carbapenem enolphosphate **2**[8] and the 2-aminocarbonylpyrrolidin-4-ylthio-containing side chain **3** (Scheme 1). Many efficient approaches to **2** have been reported in the literature,[9] and this compound is now commercially available on a large scale.[10] In this paper, we will describe an efficient and practical one-pot synthesis of **3** that is amenable to large-scale produc-

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(10) Carbapenem enolphosphate **2** is commercially available from Takasago, Kaneka, and Nisso companies.

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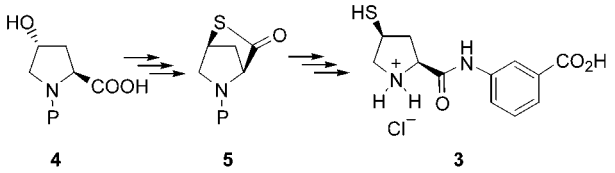
SCHEME 2



4 **5** **3**

tion. The coupling of **3** with **2** and the conversion to ertapenem (**1**) will be disclosed separately.[11]

Our strategy for the synthesis of **3** (Scheme 2) is based on a general and expedient synthesis for protected 2-thia-5-azabicyclo[2.2.1]heptan-3-ones, which we recently disclosed in a preliminary communication.[12] Thus, a suitably protected 4-hydroxyproline derivative **4** was expected to deliver the key thiolactone **5**, which was projected to undergo aminolysis with *m*-aminobenzoic acid (MABA). A team from Sumitomo Pharmaceuticals reported recently on their independent arrival at a similar strategy.[13] Thiolactones of the type of **5** have been synthesized previously.[14] However, inefficient multistep approaches using impractical protecting groups (P = Ts, Ac) were used in those studies. We recognized significant advantages in entering a coupling of **2** with a completely unprotected side chain. Therefore, we carefully selected the nature of protecting group P in **5** such that deprotection of the aminoysis product would afford salt **3** directly. The little-used diisopropyl phosphoryl group (DIPP)[15] met all of our criteria. It is economical, and only nonvolatile and innocuous cleavage products are generated under mild acidic conditions. We recently reported on a novel and practical method for the preparation of *N*-(*O*,*O*-diisopropylphosphoryl)-*trans*-4-hydroxy-L-proline (**6**; DIPP-Hyp).[16] The projection that all transformations leading from **4** to **3** could be performed in the same pot promised to make our approach particularly practical and economical.

The thiolactone functionality in **5** performs a pivotal role in our strategy. It not only allows the stereoselective introduction of a protected mercapto group but also activates the carbonyl group toward reaction with *m*-aminobenzoic acid. Thus, the synthesis of **3** will require only a single protecting group. Our strategy also guarantees high enantiomeric purity of the end product. Any loss of stereochemical integrity at C-2 or C-4 before the formation of the thiolactone would result in species that would not be expected to cyclize and would be readily separated in a judiciously chosen workup. Only the unlikely event of a combination of epimerization at C-2 and retention of configuration during the intramolecular substitution at C-4 would result in the formation of the enantiomer of **5**.

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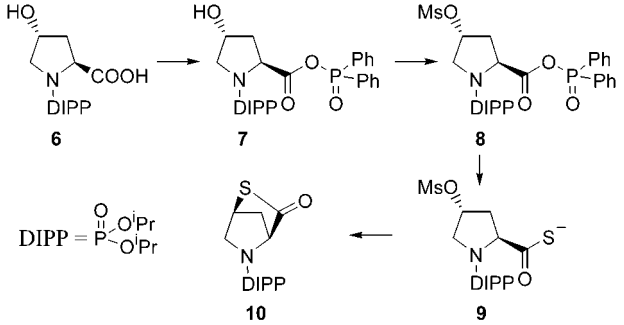
SCHEME 3



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

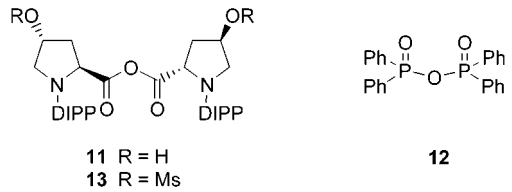
TABLE 1. Yield of 10 as a Function of the Solvent(s)[a]

entry	solvent	% yield for **10**[b]
1	THF[c]	<10
2	DME[d]	<5
3	EtOAc[c,e]	36
4	MeCN[c]	75
5	DMF[d]	58
6	DMA[d]	42
7	NMP[d]	33
8	CH_2Cl_2[d]	92
9	$ClCH_2CH_2Cl$[c,e]	86
10	cyclohexanone[d]	64
11	fluorobenzene[c]	83
12	$PhCF_3$[c]	45
13	THF/MeCN 1:1[c]	83
14	MeCN/EtOAc 1:2[c]	75
15	DMF/toluene 1:5[c]	53
16	CH_2Cl_2/toluene 1:2[c]	77

[a] According to the procedure detailed in the Experimental Section, 1.0 equiv of **6** as a 0.15 M solution in solvent(s) at −15 °C was treated consecutively with 2.1 equiv of DIPEA, 1.05 equiv of DPPC, 1.1 equiv of pyridine, 1.1 equiv of MsCl and 1.2 equiv of Na_2S. [b] Yields of **10** determined by HPLC. [c] The reaction mixture became a heavy slurry after DPPC addition and became homogeneous again after MsCl addition. [d] The reaction mixture was homogeneous throughout the entire sequence. [e] The starting material is barely soluble in this solvent at a concentration of 0.15 M.

Results and Discussion

Synthesis of the DIPP-Protected Thiolactone. Scheme 3 shows the sequential reactions that were used to convert DIPP-protected hydroxyproline **6** to thiolactone **10** in a single pot. In the first step, the carboxyl group was activated as mixed carboxylic phosphinic anhydride **7** via a reaction with diphenylphosphinic chloride (DPPC) in the presence of diisopropylethylamine (DIPEA). This intermediate was directly reacted with methanesulfonyl chloride in the presence of pyridine to produce mixed anhydride mesylate **8.** The latter was then quenched with aqueous sodium sulfide yielding **9** instantaneously, which then slowly cyclized to **10**. It was found that the overall yield for this sequence of reactions was critically dependent on the solvent. Table 1 compiles the most important results of solvent optimization studies. While THF was the preferred solvent in the preparation of the *tert*-butyloxycarbonyl (BOC) and 4-nitrobenzyloxycarbonyl (pNZ) protected analogues of **5**,[12] it provided the DIPP-protected **10** in a disappointingly low yield (Table 1, entry 1). The data of Table 1 clearly show that the best yield is obtained using dichloromethane as the solvent. In many solvent systems, mixed anhydride alcohol **7** crystallizes from the reaction mixture as it is formed. Indeed, this reactive intermediate could be isolated, purified via



11 R = H
13 R = Ms

12

FIGURE 1.

recrystallization, and characterized. Typically, crystalline **7** went back into solution to form the more soluble **8** during the reaction with methanesulfonyl chloride. However, there is no correlation between low solubility of **7** and poor overall reaction performance. For entries 1, 3, 4, 9, and 11−16 in Table 1, a slurry was formed immediately after addition of DPPC. For some of these experiments, the overall yield was quite acceptable (>75% for entries 4, 9, 13, 14, and 16). On the other hand, not all homogeneous reaction mixtures provided **10** in good yield (cf. entries 2, 5−7, and 10). A relationship between solvent polarity and reaction performance is not evident either. Good yields are obtained in systems of widely varying polarity (cf. entries 4, 8, 9, 11, 13, 14, and 16). Surprisingly, overall yields were significantly lower in solvents closely related to dichloromethane or proposed as dichloromethane alternatives[17] (entries 9, 11, and 12). NMR studies provided an explanation for the lower yields of **10** in particular solvent systems. When **6** was allowed to react with 1.05 equiv of DPPC in the presence of 1.10 equiv of DIPEA in DMF-d_7 at −30 °C, three distinct proline-containing species were formed in a 73/18/9 ratio. In situ ^{13}C NMR studies were used to characterize the major species as **7**, the expected mixed anhydride, and the more abundant minor species as **11**, a *sym*-anhydride (Figure 1). In the ^{1}H-decoupled ^{13}C spectrum, the nitrogen-bearing methine of **7** was a doublet of doublets (J_{CP} = 6.4, 4.0 Hz) due to spin−spin coupling to two phosphorus atoms. In **11**, the analogous methine was a doublet (J_{CP} = 6.4 Hz) with coupling to only one phosphorus. A triple-resonance NMR experiment (^{13}C observed with simultaneous ^{1}H and ^{31}P decoupling) was used to verify these assignments. The structure of the third species could not be elucidated. The *sym*-phosphinic anhydride **12** (which is also always present as a small impurity in the starting DPPC), was also detected in the sample. Significant *sym*-anhydride formation obviously detracts from the maximum achievable yield for **10** in this process. A reverse addition protocol (slow addition of a solution of **6** and DIPEA in DMF to a cold solution of DPPC in DMF, followed by a typical sodium sulfide quench) resulted in more *sym*-anhydride **11** formation and a lower overall yield for **10** than the normal addition protocol. The thermal stability of phosphinic carboxylic mixed anhydrides of N-protected amino acids has been reported in the literature.[18] Solutions of **7** in a variety of solvents (dichloromethane, DMF, acetonitrile, and THF) were quite stable according to ^{31}P NMR (no disproportionation at −25 °C; 10−20% of **11** formed after 16 h at rt). Addition of DIPEA to the dichloromethane solution at −25 °C had no effect. However, at rt, significant formation of **11** occurred. Mixed anhydride mesylate **8** is more prone to disproportionation than **7** under the reaction conditions, which caused some concern for scale-up. It was demonstrated in a series of control experiments in dichloromethane that mesylation at higher than optimal temperatures (−10 °C vs <−15 °C) and/or aging of solutions of **8** for longer than required to achieve complete conversion (2 h vs 30 min) resulted in more disproportionation of **8** into **12** and **13**. Consequently, significantly lower yields for **10** were obtained under these conditions (80% vs 90−95% under optimal conditions).

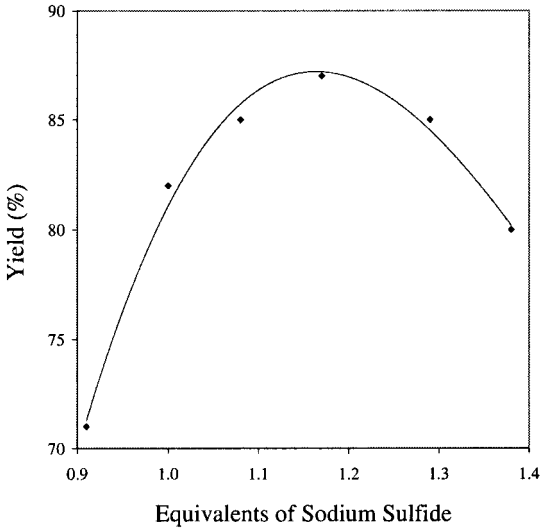


FIGURE 2. Optimization of the amount of sodium sulfide in the reaction with **8**. (Varying amounts of a 1.0 M solution of sodium sulfide trihydrate in water were rapidly added to a solution of **8** prepared in the standard manner at −20 °C. The yield for **10** was determined by HPLC after an identical age and workup.)

It should be noted that several other methods for activating the carboxyl group in **6** were also examined, but none of these compared favorably with the mixed carboxylic phosphinic anhydride method. The best results were obtained with chloroformates, particularly isobutyl chloroformate. Combinations with various bases and solvents and various addition protocols were probed with this reagent. The optimal yield for **10** (73% according to HPLC) was obtained when 1.1 equiv of isobutyl chloroformate was added to **6** in dichloromethane at −40 °C in the presence of both DIPEA and pyridine followed by addition of methanesulfonyl chloride and a quench with aqueous sodium sulfide as usual (vide infra). Again, dramatic solvent effects were noted with significantly lower overall yields in THF or acetonitrile (38 and 25%, respectively).

A careful definition of the sodium sulfide quench protocol also proved crucial in obtaining the best yields for our process. The results of a study determining the optimum amount of sodium sulfide is given in Figure 2. The best yield was obtained with 1.2 equiv of sodium sulfide (the optimal amount of water for the quench was determined at 0.4 mL water per mL of dichloromethane). It proved critical to add the aqueous sodium sulfide solution into the cold solution of **8** in dichloromethane as fast as possible with vigorous agitation. With a relatively slow addition (10 min rather than <2 min), the

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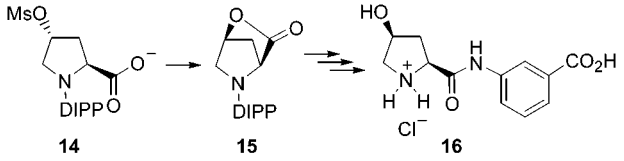
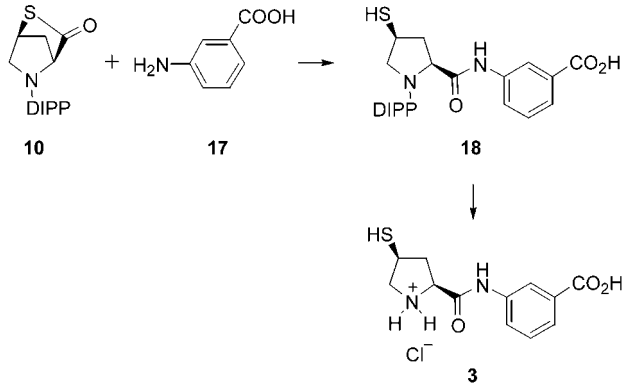
SCHEME 4



overall assay yield for **10** was significantly lower (84 vs 90%, in a direct comparison). During the quench, **8** is instantaneously converted to **9**. Completion of the intramolecular displacement of the mesylate in **9** requires approximately 2 h at 20−25 °C. In the quench, small amounts of carboxylate **14** are also formed. It was demonstrated in a control experiment that the ring closure of **14** to oxylactone **15** is significantly slower than in the sulfur series, presumably due to a combination of better nucleophilicity of the thiocarboxylate and higher ring strain in the oxylactone (Scheme 4).[19] An authentic sample of oxylactone **15** was independently synthesized from **6** via a Mitsunobu reaction. Any amount of oxylactone **15** carried forward into the aminolysis and deprotection reactions (vide infra) eventually produced **16**, an impurity which is poorly rejected in the final crystallization of **3**. Recognition of the different cyclization rates of **9** and **14** suggested an extraction immediately after completion of thiolactone formation as a practical way to control the level of **15** in **10** at less than 0.1%. Thiolactone **10** can be crystallized after an aqueous workup. However, using the dichloromethane solution directly for aminolysis with MABA is preferred since product losses in the isolation are avoided. Typically, the overall yield from **6** to **10** is in the 90−95% range under the fully optimized conditions.

Aminolysis and Deprotection. While the reaction of **10** with aliphatic amines is very fast at rt in most solvents, the reaction with MABA is relatively slow. This is probably caused by the combined effects of low nucleophilicity of the free aniline and the significant presence of zwitterionic MABA. Upon warming in several solvents, the aminolysis of **10** with MABA was not particularly clean. An important solvent effect was discovered when the aminolysis was performed in acetic acid. In this solvent the aminolysis is significantly accelerated at rt, typically resulting in a complete conversion within 3 h. Presumably, acid catalysis of the aminolysis via protonation of the tetrahedral intermediate formed upon addition of the amine to the carbonyl group more than offsets the higher degree of protonation of MABA under these conditions. In practice, the dichloromethane solution containing **10**, prepared as described above, was added to a solution of 1.0 equiv of MABA in acetic acid while removing the dichloromethane by distillation. It proved possible to isolate the aminolysis product **18** via a workup and crystallization as the corresponding dicyclohexylammonium salt. However, once again, the direct use of the acetic acid solution of **18** for the next step was preferred. Deprotection of **18** was readily achieved via addition of a small amount of concentrated hydrochloric acid to the mixture. This reaction is typically completed

SCHEME 5



in 2−3 h at rt and yields crude **3** in 90−95% overall yield for the aminolysis and deprotection reactions (Scheme 5).

Isolation of 3. With a one-pot process from **6** to **3** in hand, a practical isolation of the product from the mixture of acetic acid and hydrochloric acid was needed. The solubility of the hydrochloride **3** in this system increases dramatically with increasing amounts of water. It was indeed established that **3** can be crystallized by removing most of the water via distillation at reduced pressure. Although the recovery from this crystallization was very good (95%), the purity of the solids was not satisfactory. Moreover, it proved difficult to reduce residual acetic acid in **3** to the very low levels required via washing and/or drying. Screening of various other crystallization solvents led to the identification of 1-propanol and 1-butanol as excellent alternatives. From these alcohols, **3**·HCl crystallizes with >99 area % purity according to HPLC analysis. Thus, a crystallization protocol was developed in which water and acetic acid were efficiently removed from the crude solution of **3**·HCl by azeotropic vacuum distillation with 1-butanol.[20] Two pseudopolymorphic crystal forms for **3**·HCl were obtained using this procedure: an unsolvated product and a thermodynamically less stable (and more soluble) 1:1 solvate with 1-butanol. The control over the desired crystal form critically depended on seeding in a defined solvent composition window during the vacuum distillation. This process was not very robust since there was also the added complication of formation of significant amounts of butyl acetate during large scale distillations. Therefore, a two-stage crystallization was developed. Crude **3**·HCl was first crystallized from acetic acid via removal of water, as described above, and filtered. The resulting crude wet cake was then dissolved in a 9:1 mixture of 1-butanol and water. Slow removal of the water via an azeotropic distillation in vacuo led to a reproducible crystallization of the unsolvated product with a high recovery (85−90% over the two crystallizations).

Not surprisingly, **3** forms the corresponding disulfide **19** quite readily (Figure 3). It was discovered that addition of a small amount of tri-*n*-butylphosphine (1−5 mol % relative to **3**) during the crystallization process

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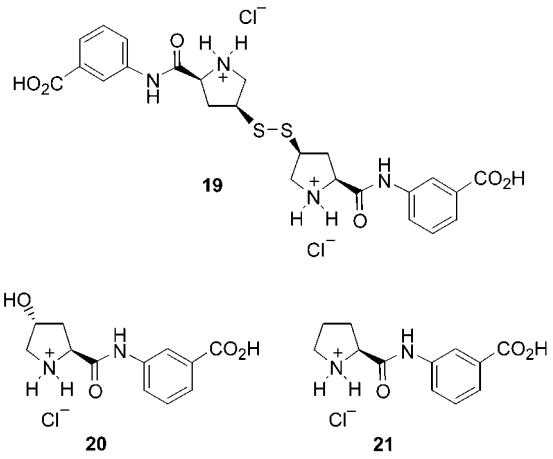

FIGURE 3.

assured low levels of **19** in the isolated product (<0.2 area % by HPLC).[21] However, it was also determined that the addition of tri-*n*-butylphosphine carried some risk. Adding larger amounts and/or using extended recrystallization times at elevated temperatures led to significant formation of **16**, **20**, and **21**, with the latter predominating.[22] The structures of **16**, **20**, and **21** were initially proposed based on LC−MS analysis of the crystallization mixtures and later corroborated via their independent synthesis.[23]

Conclusions

An exceedingly efficient and practical synthesis for side chain **3** of the novel broad-spectrum carbapenem antibiotic ertapenem (**1**) was developed. Compound **3** can be synthesized in a one-pot operation comprising six chemical reactions starting from DIPP−hydroxyproline (**6**). The product is isolated as the hydrochloride salt with an overall yield of 70−75%, corresponding to an average yield of >95% per chemical step. The above-described process has been implemented on a multikilogram scale and consistently provides isolated **3**·HCl with >99.5 area % purity according to HPLC analysis. This chemistry appears quite general for use in the synthesis of other 2-aminocarbonylpyrrolidin-4-ylthio-containing carbapenem side chains.

Experimental Section

All commercially available materials and solvents were used as received. Reaction temperatures were measured internally, unless indicated otherwise (rt = 20−23 °C). Melting points are not corrected. Optical rotations were measured at 25 °C.

(2*S*)-*cis*-3-[[(4-Mercapto-2-pyrrolidinyl)carbonyl]amino]benzoic Acid Monohydrochloride (3). A solution of **6** (2.50 kg; 8.46 mol) in dichloromethane (50 L; dried over 4 Å molsieves) was cooled to −20 °C, and diisopropylethylamine (2.35 kg; 18.18 mol; dried over 4 Å molsieves) was added at such a rate that the temperature was kept below −18 °C (20 min). To the resulting solution was added a solution of diphenylphosphinic chloride (98%; 2.10 kg; 8.90 mol) in dichloromethane (4 L) at such a rate that the temperature was kept below −18 °C (20 min). After aging at −20 °C for 40 min, a solution of pyridine (0.72 kg; 9.10 mol; dried over 4 Å molsieves) in dichloromethane (1 L) was added in one portion, immediately followed by a solution of methanesulfonyl chloride (1.07 kg; 9.34 mol) in dichloromethane (5 L) at such a rate that the temperature was kept below −18 °C (30 min). After aging at −20 °C for an additional 30 min, a solution of sodium sulfide trihydrate (1.35 kg; 10.22 mol) in water (19 L) was added under vigorous agitation as fast as possible (<2 min). The resulting biphasic mixture (+ 3 °C) was warmed to 25 °C over 5 min and vigorously agitated for another 2 h. Agitation was stopped, and the layers were separated. The organic layer was extracted with 1.0 M hydrochloric acid (20 L), a solution of sodium bicarbonate (1.65 kg) in water (20 L), and water (15 L). The resulting dichloromethane solution (approximately 55 L) was assayed to contain 2.35 kg of **10** (95% yield). This solution was added under vacuum into a slurry of 3-aminobenzoic acid (98%; 1.15 kg; 7.86 mol) in glacial acetic acid (12.5 L) while distilling the dichloromethane. When all dichloromethane had been distilled out, the resulting clear solution was aged at rt overnight. After conversion to **18** was confirmed by HPLC, concentrated hydrochloric acid (3.0 L) was added. The resulting mixture was stirred under N_2 for 2 h. After completion of the deprotection was confirmed by HPLC, the solution was concentrated to a total volume of approximately 15 L. The solution was flushed in vacuo with additional fresh glacial acetic acid (30 L), and then toluene (15 L) was added over 1 h at atmospheric pressure. The slurry was stirred under N_2 overnight, cooled to 0−5 °C, aged for another 1 h, and filtered. The solids were washed with a mixture of glacial acetic acid and toluene in a 1:5 ratio (7.5 L), followed by toluene (15 L). The wet cake was dried in vacuo at rt and then redissolved in a mixture of water (5 L) and 1-butanol (40 L). To the clear solution was added tri-*n*-butylphosphine (75 g). The mixture was concentrated in vacuo to a total volume of approximately 20 L while maintaining the pot temperature below 40 °C. The solution was flushed with additional 1-butanol (40 L). The resulting crystal slurry was filtered after aging for 5 h at 0−5 °C. The solids were washed with 1-butanol (5 L) and toluene (3 × 5 L) and dried in vacuo at 100 °C under a stream of N_2. In this way, 1.88 kg of **3** was obtained (73% overall yield from **6**). The solids contained >99 wt % of **3** at >99 area % purity according to HPLC analysis (Zorbax Eclipse XDB−C18; 150 × 4.6 mm; 5 μm particle size; UV detection at 225 nm; 0.1% perchloric acid/acetonitrile gradient from 90:10 to 50:50 over 50 min; 1.0 mL/min): mp 212 °C; $[\alpha]_{365} = +41$ ($c = 1.0$; 20 mM phosphoric acid); ^{1}H NMR (400 MHz, D_2O) δ 7.96 (s, 1H), 7.76 (d, $J = 7.8$ Hz, 1H), 7.61 (d, $J = 7.5$ Hz, 1H), 7.45 (m, 1H), 4.69 (br s, 1H), 4.57 (t, $J = 8.4$ Hz, 1H), 3.78 (dd, $J =$ 11.7, 6.9 Hz, 1H), 3.68 (m, 1H), 3.32 (dd, $J = 11.7$, 7.5 Hz, 1H), 2.96 (m, 1H), 2.13 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 169.3, 166.8, 136.5, 130.2, 129.3, 126.4, 125.6, 121.6, 59.9, 53.9, 39.1, 34.6. Anal. Calcd for $C_{12}H_{15}ClN_2O_3S$: C, 47.60; H, 4.99; Cl, 11.71; N, 9.25; S, 10.59. Found: C, 47.66; H, 4.93; Cl, 11.76; N, 9.11; S, 10.57.

***N*-(*O*,*O*-Diisopropylphosphoryl)-*trans*-4-hydroxy-L-proline (6).** Trans-4-Hydroxy-L-proline (200 g; 1.52 mol) was dissolved in water (500 mL), and the resulting solution was cooled to 0−5 °C. The pH was adjusted from 5 to 6 to 9 using a 25% sodium hydroxide solution (18 mL). Diisopropyl phosphite (280 g; 1.68 mol) was added in one portion. Sodium hypochlorite (20 wt %; 640 mL; concentration determined before use at 2.6 M via iodometric titration) was added over 2.5 h while the pH was maintained at 9.0 (using 25% sodium hydroxide) and the temperature at 0−5 °C. Excess bleach was then quenched via addition of sodium bisulfite (30 g; 0.28 mol). The pH of the resulting solution was adjusted to 2 via slow addition of concentrated hydrochloric acid (230 mL) while the temperature was maintained at 0−5 °C. The solution was

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(22) (a) Hoffmann, F. W.; Ess, R. J.; Simmons, T. C.; Hanzel, R. S. *J. Am. Chem. Soc.* **1956**, *78*, 6414. (b) Walling, C.; Rabinowitz, R. *J. Am. Chem. Soc.* **1959**, *81*, 1243−1249. (c) Corey, E. J.; Shimoji, K. *J. Am. Chem. Soc.* **1983**, *105*, 1662−1664.

(23) Details are reported in the Supporting Information.

saturated with sodium chloride (170 g) and extracted with isopropyl acetate (2 × 2 L). The product crystallized from the combined organic extracts upon partial concentration in vacuo. The slurry was flushed with fresh isopropyl acetate. The crystals were filtered, washed, and dried in vacuo at rt to yield 359 g of the product (80% yield): mp 94−95 °C; $[\alpha]_{589} = -45$ ($c = 1.00$; EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (br, 2H), 4.76 (m, 1H), 4.56 (m, 1H), 4.42 (m, 1H), 4.34 (dd, $J = 12.9$, 7.2 Hz, 1H), 3.28 (m, 1H), 3.20 (m, 1H), 2.27 (m, 1H), 2.14 (m, 1H), 1.28 (d, $J = 6.3$ Hz, 12H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 5.1; ^{13}C NMR (100 MHz, $CDCl_3$; resolution enhanced) δ 175.7, 71.4 (d, $J = 6.0$ Hz), 71.3 (d, $J = 6.0$ Hz), 70.5 (d, $J = 8.0$ Hz), 59.0 (d, $J = 5.9$ Hz), 54.5 (d, $J = 2.9$ Hz), 39.1 (d, $J = 8.1$ Hz), 23.6 (d, $J = 14.6$ Hz), 23.5 (d, $J = 12.3$ Hz), 23.5 (d, $J = 14.9$ Hz), 23.4 (d, $J = 11.9$ Hz). Anal. Calcd for $C_{11}H_{22}NO_6P$: C, 44.75; H, 7.51; N, 4.74; P, 10.50. Found: C, 44.80; H, 7.28; N, 4.57; P, 10.64.

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Supporting Information Available: Experimental details and physical data for compounds **7**, **10**, **15**, **16**, and **18**−**21** as well as ^{1}H and ^{13}C NMR spectra of **19**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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