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Process Research and Development for a Tetrazole-Based Growth Hormone Secretagogue (GHS) Pharmaceutical Development Candidate

Akin H. Davulcu,* Douglas D. McLeod, Jun Li, Kishta Katipally, Adam Littke, Wendel Doubleday, Zhongmin Xu, Cary W. McConlogue, Chiajen J. Lai, Margaret Gleeson, Mark Schwinden, and Rodney L. Parsons, Jr.*

Process Research and Development, Bristol-Myers Squibb Company, One Squibb Drive, New Brunswick, New Jersey 08903

akin.davulcu@bms.com; rodney.parsons@bms.com

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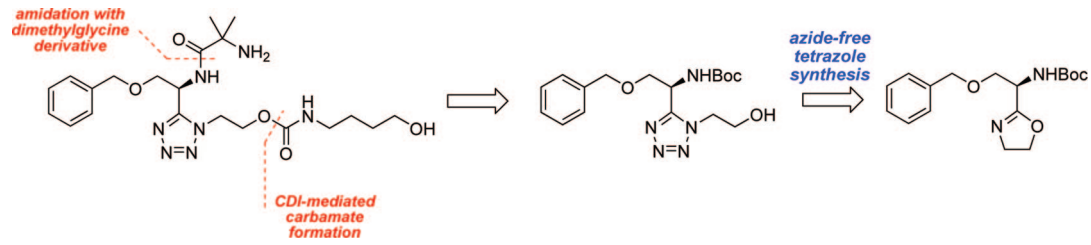

BMS-317180 (**1**) is a potent, orally active agonist of the human growth hormone secretagogue (GHS) receptor. This manuscript details the process research and development efforts that enabled the synthesis of the phosphate salt of **1** on a multi-kilogram scale. Key considerations in the development of this process focused on safe execution and the requirement for telescoped synthetic transformations (i.e., without isolation of intermediate products) to contend with a lack of suitably crystalline products.

Introduction

Over the next 25 years, the worldwide population of individuals over 65 years of age is expected to double, resulting in an elderly population of ca. 1 billion people.[1] By 2050, it is projected that 10% of the worldwide population will be at least 65 years of age. Current estimates suggest that 30−60% of elderly individuals suffer from frailty or other disorders (e.g., decline in musculoskeletal function and metabolic profile, interference with normal sleep cycles, and development of cardiovascular risk factors) associated with age-related functional decline. These health issues have a profound negative impact on these individuals' ability to carry out many of the activities of daily life. Contemporary medicine associates many of these pathological conditions with human growth hormone (hGH) deficiency that results from neuroendocrine dysregulation; this notion is corroborated by clinical studies with recombinant hGH that demonstrate the beneficial effects of hormone replacement therapy.[2] However, administration of recombinant hGH has significant disadvantages. First, hGH therapy is accompanied by a number of serious side effects, including edema, arthralgia, and carpal tunnel syndrome. Second, intravenous (IV) dosing at a frequency of 3−5 times per week presents compliance issues among the patient population. Lastly, hGH therapy is very expensive.[3] The identification of the growth hormone secretagogue (GHS) receptor triggered a paradigm shift in this field by advancing the notion that a small-molecule GHS agonist might restore normal pulsatile GH secretion by the pituitary gland while avoiding the side effects associated with IV administration of hGH.[4] This advance resulted in the identification of several small-molecule GHS agonists, including BMS-317180 (**1**), a potent, orally effective agent that has been advanced into clinical development by the Bristol-Myers Squibb Company.

(1) (a) Li, J.; Chen, S. Y.; Li, J. J.; Wang, H.; Hernandez, A. S.; Tao, S.; Musial, C. M.; Qu, F.; Swartz, S.; Chao, S. T.; Flynn, N.; Murphy, B. J.; Slusarchyk, D. A.; Seethala, R.; Yan, M.; Sleph, P.; Grover, G.; Smith, M. A.; Beehler, B.; Giupponi, L.; Dickinson, K. E.; Zhang, H.; Humphreys, W. G.; Patel, B. P.; Schwinden, M.; Stouch, T.; Cheng, P. T. W.; Biller, S. A.; Ewing, W. R.; Gordon, D.; Robl, J.A.; and; Tino, J. A. *J. Med. Chem.* **2007**, *50*, 5890, and references cited therein. (b) Strobl, J. S.; Thomas, M. J. *Pharmacol. Rev.* **1993**, *46*, 1.

(2) Jørgensen, J. O. L.; Christiansen, J. S. *Lancet* **1993**, *341*, 1247.

(3) Lehrman, S. *Nature (London)* **1993**, *364*, 179.

(4) (a) Bowers, C. Y.; Reynolds, G. A.; Durham, D.; Barrera, C. M.; Pexxoli, S. S.; Thorner, M. O. *J. Clin. Endocrinol. Metab.* **1990**, *70*, 975. (b) Reichlin, S.; Saperstain, R.; Jackson, I. M. D.; Boyd, A. E.; Patel, Y. *Annu. Rev. Physiol.* **1976**, *38*, 389. (c) Gertz, B. J.; Barrett, J. S.; Eisenhandler, R.; Krups, D. A.; Wittreich, J. M.; Seibold, J. R.; Schneider, S. H. *J. Clin. Endocrinol. Metab.* **1993**, *77*, 1393.

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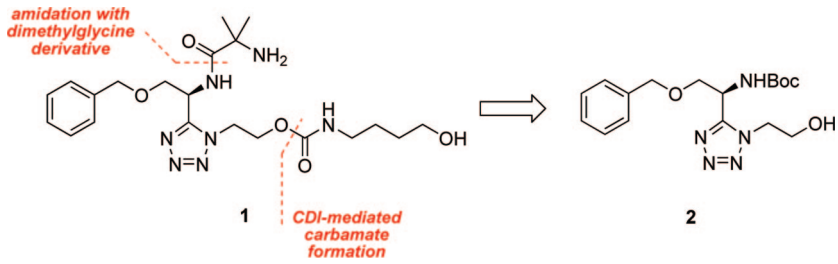
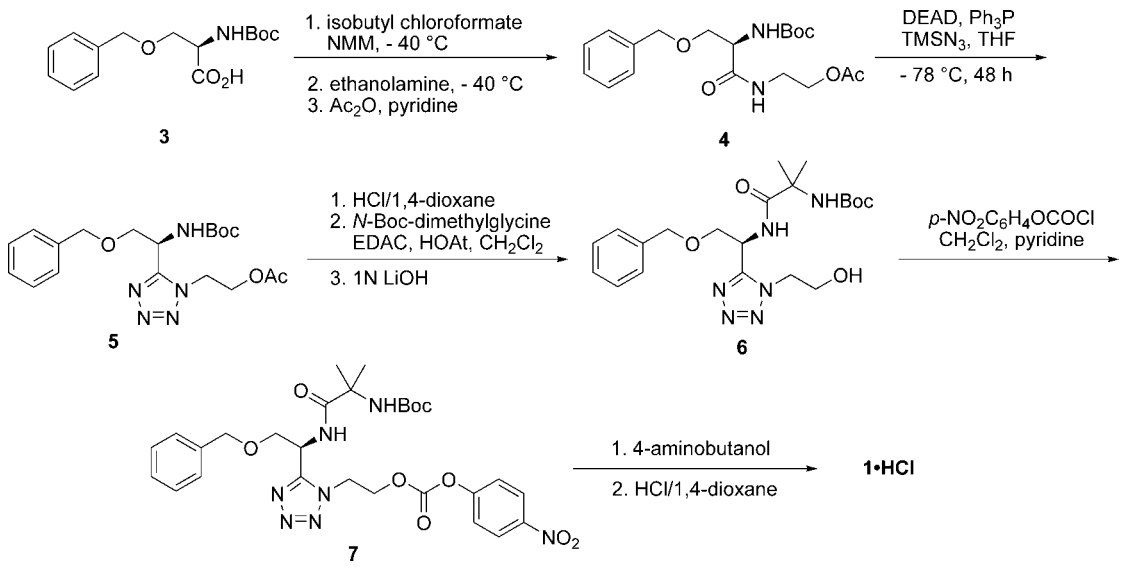
SCHEME 1. Retrosynthetic Analysis for 1



SCHEME 2. Discovery Synthesis of 1•HCl



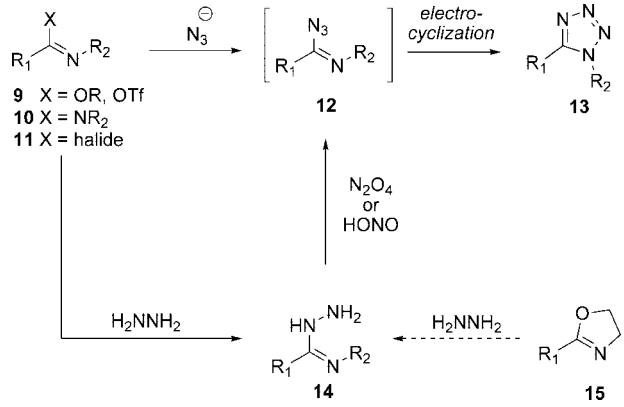
Results and Discussion

Consideration of structure **1** from the process research and development perspective revealed two primary challenges. Given the fact that tetrazoles are generally regarded as energy-rich, thermodynamically unstable compounds, the first challenge involved the identification of safe, scaleable chemistry for the synthesis of this heterocyclic core. Many of the known synthetic methods for tetrazole formation require the use of azide reagents, and while employing such chemistry on a large scale is feasible, execution is oftentimes far from routine, generally requiring stringent safety and engineering controls. As such, avoidance of azide chemistry was an important practical goal for us. The second challenge derived from the reactive primary amine and alcohol functionalities displayed by the molecule. Orchestrating a sequence that would contend with their intrinsic reactivity while minimizing reliance on protecting groups would be critical to defining a practical route. Tactical and strategic issues were also foreseen with regard to the resident stereogenic center. Strategically, options employing asymmetric synthesis versus exploiting the rich "chiral pool" would require thorough evaluation. Tactically, the chemistry would require fine-tuning to contend with the stereochemical lability (e.g., racemization upon exposure to base, as was observed with **1**) of the intermediates encountered throughout the sequence. In planning the path forward, a route that would intersect crystalline intermediates (whereupon isolation would provide the opportunity for purity control) was regarded as ideal. Toward this end, retrosynthetic analysis of **1** (Scheme 1) suggested that late-stage construction of the amide and carbamate linkages would lead to tetrazole fragment **2** as a key intermediate. Since our Discovery group had demonstrated that **2** was a stable, crystalline intermediate, our synthetic efforts quickly focused on this target.

The synthetic approach employed by our Discovery colleagues is detailed in Scheme 2.[5] In their preparation, commercially available *N*-Boc-*O*-benzyl-D-serine (**3**) was coupled with ethanolamine via the intermediacy of an isobutyl chloroformate-derived mixed carbonic anhydride, followed by *O*-acylation of the derived 2-hydroxyethyl amide, affording acetate **4** in ca. 90% overall yield. The conversion of **4** to tetrazole **5** was carried out according to the method of Duncia and coworkers, wherein exposure of **4** to a mixture of trimethylsilyl azide (1.0 equiv), triphenylphosphine (1.0 equiv), and diethyl azodicarboxylate (DEAD, 1.0 equiv) in THF, followed by the addition of equivalent supplemental quantities of reagents after 24 and 48 h, afforded tetrazole **5** in 85% yield after chromatographic purification.[6] Removal of the Boc protecting group was effected through the action of HCl in dioxane, and subsequent coupling with *N*-Boc dimethylglycine under EDAC/HOAt-mediated amidation conditions, followed by exposure of the resulting amide to aqueous lithium hydroxide, afforded the tetrazole core **6** in 71% yield over the three-step sequence. Next, treatment of alcohol **6** with *p*-nitrophenyl chloroformate afforded carbonate **7** in 83% yield after chromatographic purification. Subsequent reaction with 4-amino-1-butanol formed the penultimate **8** (not shown), and final exposure to HCl in dioxane yielded **1** as the corresponding HCl salt. Although this sequence

(5) See ref 1a.
(6) Duncia, J. V.; Pierce, M. E.; Santella, J. B., III. *J. Org. Chem.* **1991**, *56*, 2395.

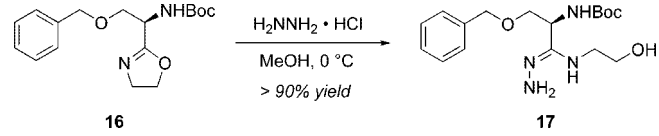
SCHEME 3. Routes to 1,5-Disubstituted Tetrazoles



met the Discovery material requirements, consideration from the process perspective revealed significant concerns. First, the sequence required extensive use of column chromatography, primarily due to the noncrystalline nature of the intermediates. In order to maximize throughput, eliminating the requirement for chromatographic purification would be a key objective. The successful achievement of this objective would rely on the identification of crystalline intermediates along the sequence that could serve as purity control points. Second, the tetrazole-forming chemistry employed by the Discovery group was found to be highly exothermic and thus presented safety concerns for pilot-scale manufacture. Auxiliary concerns regarding scaleup of this reaction were (1) sourcing and safe handling of trimethylsilyl azide and (2) efficient removal of the triphenylphosphine oxide and diethyl hydrazodicarboxylate byproducts formed in the reaction. Indeed, laboratory evaluation of this reaction revealed that several chromatographic separations were required to deliver **5** at an acceptable purity level.

Given the issues associated with this tetrazole synthesis, coupled with a lack of suitably crystalline intermediates in the sequence, we sought to define a new synthesis that would be better suited for scale up. A survey of the literature reveals that most approaches to 1,5-disubstituted tetrazoles (e.g., **13**) rely on the facile electrocyclization of iminoazides (Scheme 3).[7] Representative examples include the reactions of imidoyl esters or triflates (**9**),[8] amidines (**10**),[9] and imidoyl halides (**11**)[10] with sodium azide to afford the corresponding iminoazide (**12**), which undergoes a rapid electrocyclization to yield the corresponding 1,5-disubstituted tetrazole (**13**). From the process development perspective, these approaches are hampered by the necessary use of sodium azide (or azide salts, in general). A conceptually similar approach that does not require azide salts involves the treatment of activated imidoyl derivatives (**15**) with hydrazine, thereby affording the corresponding amidrazone **14**. Exposure to a nitrosating agent (e.g., N_2O_4, HONO) then gives rise to the aforementioned iminoazide, in turn affording tetrazole **13** via electrocyclization.[11] From the process perspective, this is compelling because it avoids the use of azide salts. Furthermore, it represents a straightforward combination of chemistries that are well-precedented on scale. It was recognized that the potential for hydrazoic acid formation did still exist in this chemistry (vide infra), but we were confident, based on literature precedent, that the relative stoichiometries of hydrazine, sodium nitrite, and HCl could be adjusted to cope with this issue.[12] However, it was evident that implementation of this chemistry toward our target would almost certainly require protection of the primary hydroxyl group, since the conditions required to activate the amide would, in all likelihood, affect this hydroxyl group preferentially. Consequently, the incipient intermediate would be expected to undergo facile cyclocondensation to the corresponding oxazoline. This line of reasoning raised a question that would prove vital to our process development effort: *Would hydrazine react with an oxazoline in a manner analogous to the known reaction between hydrazine and an imidoyl ester to afford an amidrazone (e.g.,* **15** → **14***)?* If so, this would address both of the issues associated with the projected amide to tetrazole conversion—amide activation and hydroxyl protection—in an efficient and powerfully simplifying manner. We were unable to find a precedent for this approach in the literature, so we set out to investigate it in the laboratory and were delighted to find that oxazoline **16** was smoothly converted to the corresponding amidrazone **17** upon exposure to hydrazine hydrochloride in methanol at 0 °C (Scheme 4). With this key result secured, our efforts were directed toward the development of this chemistry into a scaleable process.[13]

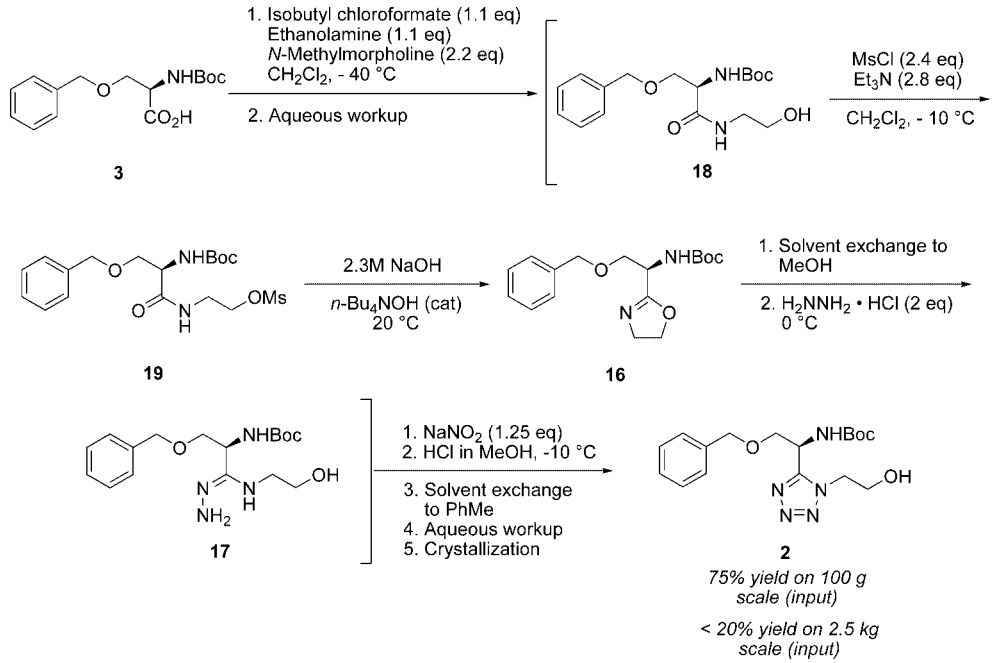
SCHEME 4



First Generation Tetrazole Process. Given the aggressive development timeline associated with this program, we opted to take advantage of the pool of chiral substances to supply our starting material. From previous Discovery efforts, *N*-Boc-*O*-Benzyl-D-serine **3** was identified as a commercial (albeit expensive at ca. $11000/kg) starting material, available in bulk quantity, and served as our point of departure. Conversion to the corresponding 2-hydroxyethyl amide **18** was accomplished using the Discovery conditions (Scheme 5). After aqueous workup, the resulting dichloromethane stream was subjected to methanesulfonyl chloride (MsCl) in the presence of triethylamine to provide **19**. The requirement for excess MsCl stemmed from the fact that the isobutanol byproduct from the amidation chemistry remained in solution, consuming 1 equiv of the reagent. Upon reaction completion, the mixture was subjected to aqueous sodium hydroxide and catalytic tetrabutylammonium hydroxide (under biphasic conditions), thereby effecting cyclocondensation to the corresponding oxazoline **16**. The resulting dichloromethane solution was subjected to solvent exchange distillation to methanol and subsequently treated with hydrazine hydrochloride at 0 °C, thus affording the amidrazone **17**. Sodium nitrite was introduced to the solution, and the resulting slurry was treated with methanolic HCl at −10 °C, initiating the nitrosation/tetrazole-forming chemistry. Upon reaction completion, the methanol solution was subjected to solvent exchange distillation to toluene. An aqueous workup, followed by crystallization from a toluene/heptanes mixed solvent system, afforded tetrazole **2** in ca. 75% isolated yield. This process worked well on the laboratory scale (ca. 100 g input), but further

(7) Wittenberger, S. J. *Org. Prep. Proced. Int.* **1994**, *26*, 499, and references cited therein.
(8) Thomas, E. W. *Synthesis*, **1993**, *767*.
(9) Gaponik, P. N.; Grigorev, Y. V.; Karavai, V. P. *Khim. Geterotsikl. Soedin.* **1985**, *566*.
(10) (a) von Braun, J.; Rudolf, W. *Chem. Ber.* **1941**, *74*, 264. (b) Harvill, E. K.; Herbst, R. M.; Schreiner, E. C.; Roberts, C. W. *J. Org. Chem.* **1950**, *15*, 662.
(11) Temple, C., Jr.; McKee, R. L.; Montgomery, J. A. *J. Org. Chem.* **1962**, *27*, 1671.

SCHEME 5. First-Generation Process for the Preparation of 2



scaleup was hampered by four main issues. First, the isobutanol byproduct generated in the amidation step was not separable from **18** either through extraction or azeotropic distillation and was thus carried through the entire sequence. Second, while an organic base (e.g., triethylamine) was required for the mesylation reaction (**18** → **19**), its presence resulted in downstream issues. Specifically, organic bases catalyzed the dimerization of amidrazone **17** to the corresponding triazole **20** and tetrazine **21** impurities (Figure 1). These dimeric impurities led to coloration of the isolated product, and since their levels increased with time, they represented a major liability for scaleup. To complicate matters further, the extraction of triethylamine at the oxazoline stage was precluded by the facile racemization of **16** upon exposure to acid. In fact, **16** was found to racemize simply on standing in dichloromethane, presumably due to the residual HCl found in many common chlorinated solvents. Third, it was found that the diazotization reaction exhibited a substantial exotherm after an induction period, with much of the heat evolution occurring during the addition of the last 20−30% of the methanolic HCl solution. Closer examination (vide infra) revealed the basis for this delayed exotherm. Fourth, and most troubling, was the fact that the yield for the sequence became progressively worse as the reaction scale was increased, with ca. 30% isolated yields at 1 kg (input) scale and <20% isolated yields at 2.5 kg (input) scale. The root cause for decreasing yield upon scaleup was traced to two factors, both of which are related to the inherent time delays associated with running at large scale. Normal time lapses in processing led to racemization of **16** at a higher level than was anticipated from laboratory runs, resulting in entrainment of the desired compound in the crystallization liquors as the corresponding racemate. Also, the solvent exchange distillation from methanol to toluene post-nitrosation required much more time on a multi-kilogram scale than was expected (based on laboratory data). This, in turn, led to substantial decomposition of the product via cleavage of the Boc protecting group, with subsequent loss of the water-soluble amine hydrochloride to the aqueous layer during workup.

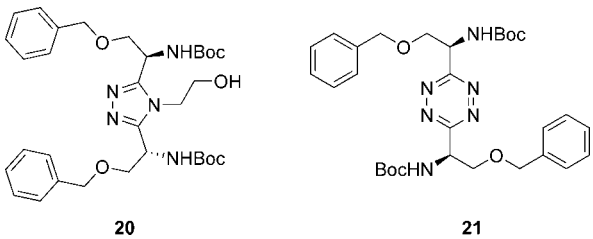


FIGURE 1. Triazole (**20**) and tetrazine (**21**) impurities resulting from amidrazone dimerization.

Addressing the Issues and Refining the Process. Although significant progress had been made toward the goal of achieving a safe, azide-free synthesis of tetrazole **2**, a robust, scaleable process was not yet in place. In order to bring this objective to fruition, the aforementioned issues would have to be addressed. From a safety perspective, the delayed exotherm observed in the nitrosation chemistry was a major concern. However, closer examination revealed that the underlying cause was quite straightforward and could be traced back to the triethylamine that was implemented in the mesylation chemistry. As mentioned earlier, this base could not be extracted from the product stream, and as a result, it was simply carried through the entire sequence. Hence, during the course of the methanolic HCl addition at the nitrosation stage, the first portions of the HCl charge served simply to engage the triethylamine in acid−base chemistry, with a minimal associated heat signature. Once the triethylamine was neutralized, excess HCl lowered the apparent pH of the reaction medium. Eventually, significant levels of HONO ($pK_a = 3.2$) were accumulated, which initiated the highly exothermic tetrazole formation (Figure 2). This thermochemical issue, coupled with the base-catalyzed dimerization of amidrazone **17** to form impurities **20** and **21**, highlighted the need to purge triethylamine from the process. This was achieved by modifying the route such that the mesylation reaction was avoided. Specifically, ethanolamine was replaced with chloroethylamine hydrochloride in the first step of the sequence (Scheme 6). In doing so, the derived amide **22**

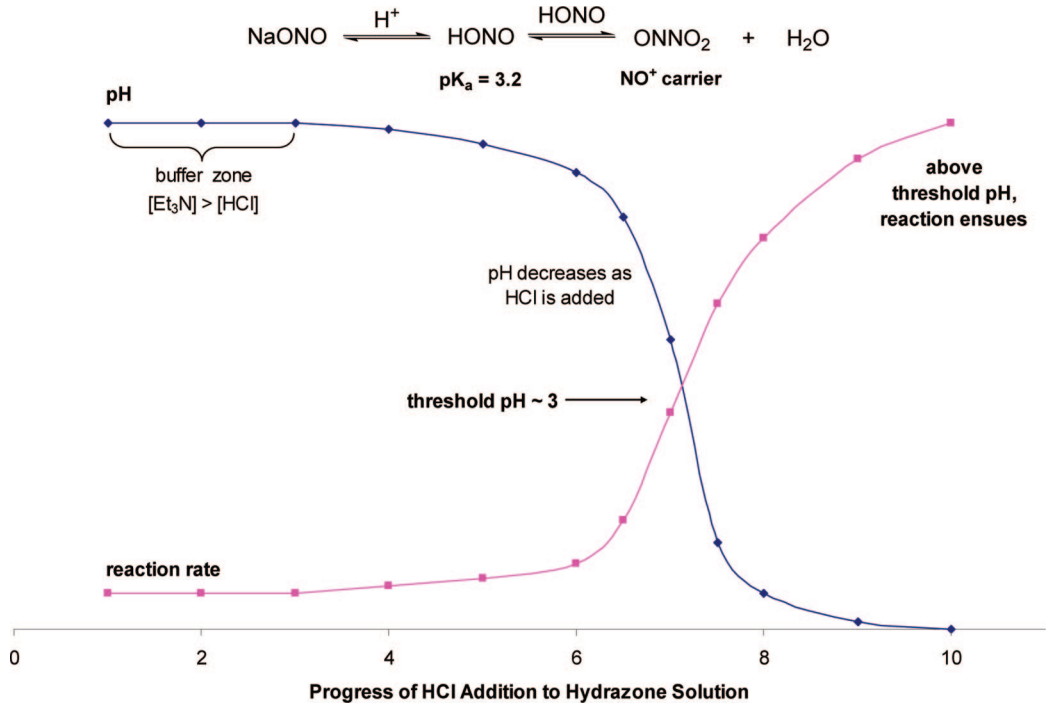
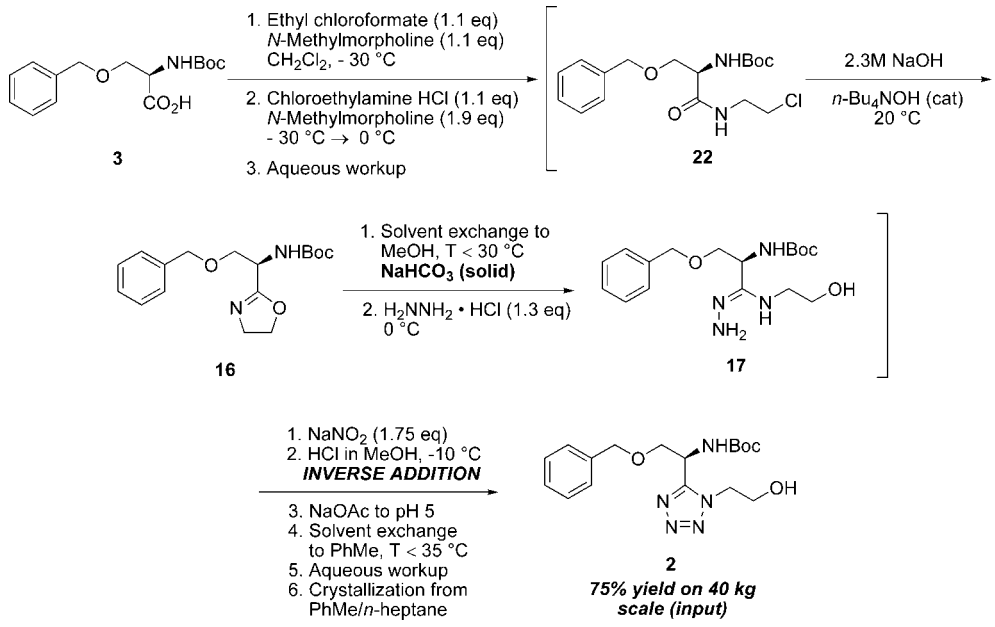


FIGURE 2. Depiction of the relationship between reaction pH and rate of diazotization.

SCHEME 6. Second-Generation Process for the Preparation of 2



contained the requisite leaving group at the β position, thus heralding a smooth intramolecular cyclocondensation to the oxazoline **16** upon exposure to aqueous NaOH/*n*-Bu_4NOH. By removing the mesylation chemistry, this process modification allowed for more expedient access to **16** and provided a way to eliminate triethylamine from the sequence. It should be noted that although chloroethylamine is a strong vesicant,[14] the corresponding hydrochloride salt is safe to handle and is widely available in bulk quantity. During the development of this process, we were cognizant of the rapid conversion of chloroethylamine to ethanolamine under basic aqueous conditions.[15] Indeed, the simple addition of water as the first step of the reaction workup served to reduce residual chloroethylamine to levels that were not detectable by GC analysis.

To contend with the persistent isobutanol byproduct that formed in the first-generation amidation reaction, we opted to replace isobutyl chloroformate with ethyl chloroformate as the

(12) (a) Perrott, J. R.; Stedman, G.; Uysal, N. *J. Chem. Soc., Dalton Trans.: Inorg. Chem.* **1976**, *2058*. (b) Doherty, A. M.; Howes, K. R.; Stedman, G. Naji, M. Q. *J. Chem. Soc., Dalton Trans.: Inorg. Chem.* **1995**, *3103*.

(13) The scope/generality of this chemistry has not been evaluated.

(14) Ward, K., Jr. *J. Org. Chem.* **1935**, *57*, 914.

(15) (a) Chan, S. C.; Leh, F. *Aust. J. Chem.* **1966**, *19*, 2271. (b) Cohen, B.; van Artsdalen, E.; Harris, J. *J. Am. Chem. Soc.* **1952**, *74*, 1875.

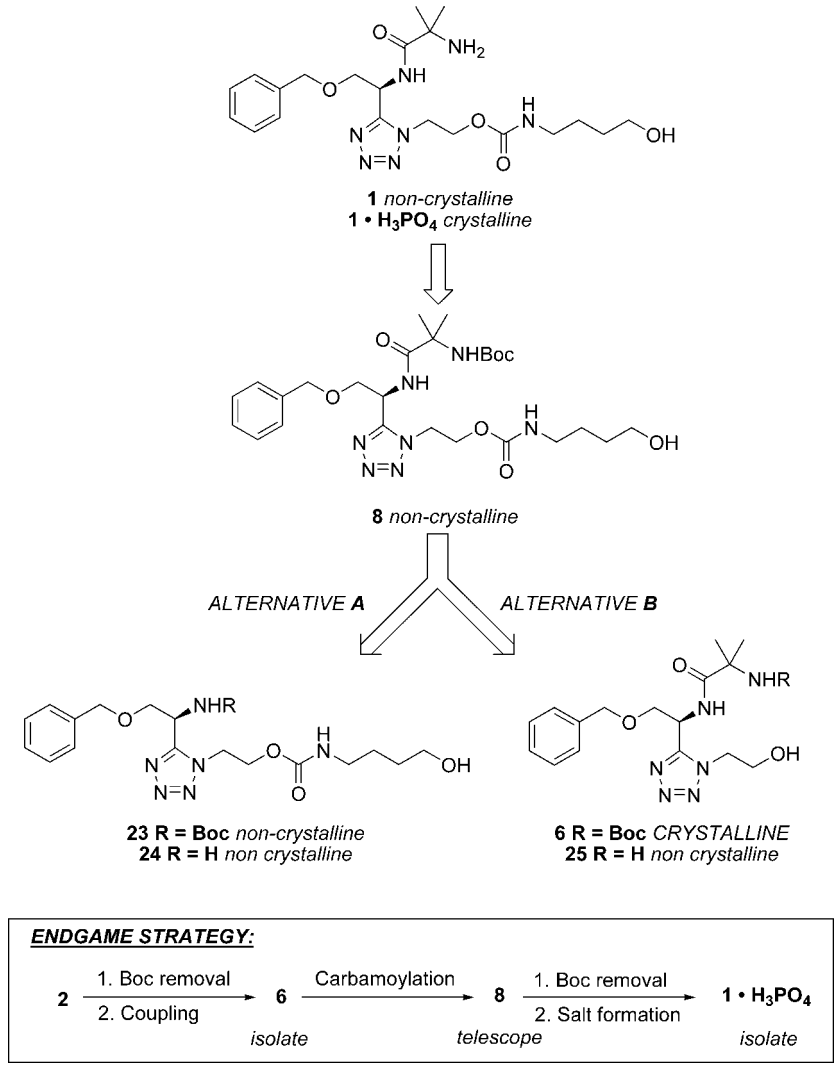
coupling reagent. This modification led to the generation of ethanol, a byproduct that was easily removed by aqueous extraction. Although isobutyl chloroformate is generally regarded as a superior coupling reagent, due to an intrinsically higher level of chemoselectivity in the reaction of the amine with the derived mixed carbonic anhydride intermediate, it was determined that control of two key reaction variables, temperature and base charge, could effectively mitigate the chemoselectivity and racemization issues commonly associated with the use of ethyl chloroformate in this arena. Specifically, by employing a temperature profile wherein the reaction was first aged at −30 °C for 45 min, then warmed to 0 °C over 30 min, the extent of racemization was controlled to ≤2%. Furthermore, adducts arising from nucleophilic attack at the undesired carbonyl of the mixed carbonic anhydride intermediate were maintained at nondetectable levels. Given our laboratory data which showed that the mixed carbonic anhydride intermediate suffered racemization primarily via base catalysis, it was important that this intermediate had only minimal contact with base. Hence, the *N*-methylmorpholine charge was split, with 1.1 equiv introduced at the activation step, and the balance introduced concurrent with the chloroethylamine hydrochloride charge. Following an aqueous workup to remove ethanol, *N*-methylmorpholine and excess chloroethylamine (vide supra), the resulting dichloromethane stream was subjected to base-induced cyclocondensation (conditions identical to the first-generation process), thus affording a dichloromethane solution of oxazoline **16** in greater than 95% solution yield. Recall that **16** is subject to facile acid-catalyzed racemization and was found to undergo substantial stereochemical degradation upon standing in dichloromethane for only a few hours. In order to perform the required solvent exchange to methanol, a process that would require ca. 15 h on a pilot scale, we found it beneficial to add solid sodium bicarbonate to the product stream prior to distillation. Presumably by quenching residual acid present in the solution, this base allowed for successful solvent exchange with only minimal (≤2%) racemization. Due to the intrinsically low solubility of sodium bicarbonate in methanol, the base could be conveniently removed at the end of the solvent exchange by simple filtration. Having advanced to this stage of the telescoped sequence with a high level of enantiomeric purity (≥96% ee) and no residual organic base, we were delighted to find that subsequent treatment with hydrazine hydrochloride to form amidrazone **17** proceeded in essentially quantitative solution yield, with dimeric impurities **20** and **21** controlled at ≤1.5% (total). The amidrazone solution was then treated with sodium nitrite (1.75 equiv), and the resulting slurry was metered *into* a cold solution of methanolic HCl (2.0 equiv), resulting in efficient conversion to tetrazole **2**. Notably, the strategy of expunging residual base from the reaction stream, coupled with an inverse addition protocol, resulted in a smooth, addition-controlled exotherm. Furthermore, the relative stoichiometries of hydrazine hydrochloride, sodium nitrite, and hydrochloric acid served to preclude hydrazoic acid formation. In preparation for solvent exchange to toluene, the methanol solution of **2** required neutralization in order to avoid losses associated with cleavage of the Boc protecting group. Cognizant of the potential racemization of **2** under basic conditions, sodium acetate was selected as a neutralizing agent, thus quenching the HCl in solution while simultaneously eliminating any potential for excursion into the high pH regime. Subsequent aqueous workup, followed by crystallization from toluene:heptanes, afforded a 75% isolated yield of tetrazole **2** in high chemical [>99.5% HPLC area, > 97% (wt/wt)] and enantiomeric (>99.5%) purity. Importantly, this process proved to be robust and practical, with no erosion of yield or quality when employed on pilot scale (ca. 40 kg input).

Route-Scouting and Securing a Viable Synthetic Endgame. With a suitable process for the preparation of **2** in hand, laboratory research efforts shifted toward defining a viable synthetic endgame. Preliminary route-scouting efforts demonstrated that while advancing **2** via initial installation of the carbamate side chain was synthetically feasible, it led to a series of intermediates **23**, **24**, and **8** that were noncrystalline (Scheme 7). This was a concern because it provided no recourse for purity control/upgrade by recrystallization until the final stage of the synthesis (i.e., recrystallization of **1** as its phosphate salt). Alternatively, conversion of **2** via initial installation of the *N*-Boc-dimethylglycine side chain led to a crystalline intermediate, **6**, and while the corresponding carbamate **8** was not crystalline, the known crystallinity of **1**·H_3PO_4 suggested the possibility of telescoping the conversion of **6** to **1** without isolating **8**. Given that this latter option (alternative B) presented two isolable, crystalline intermediates (versus one in alternative A), it was selected for further development and optimization.

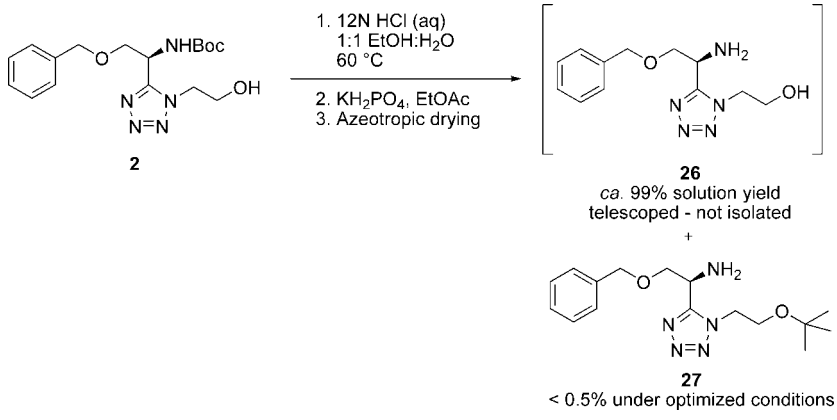
The first step in the advancement of **2**, removal of the Boc protecting group to afford **26**, was complicated by the formation of *tert*-butyl impurity **27** at levels of ca. 3% (Scheme 8). Given that **26** was not crystalline and telescoping the product stream into the subsequent reaction (rather than isolation) was anticipated, efforts were focused on controlling purity through reaction optimization. From a three-factor (equivalent amounts of HCl, EtOH, and water content), two-level statistical design of experiment (DOE) analysis,[16] water content was found to have the strongest influence on the formation of **27**. Application of this knowledge led to the design of a reaction medium comprising 1:2 (vol/vol) ethanol/water containing 4 equiv of HCl. Gratifyingly, implementation of these reaction conditions on a kilogram scale afforded practically quantitative conversion to **26**, with levels of **27** maintained at ≤0.5% (HPLC area). A variety of amidation protocols were evaluated for the conversion of **26** to **6**. It was found that the mixed carbonic anhydrides (derived by treating **28** with either ethyl or isobutyl chloroformate) led to unacceptable levels of the corresponding carbamate impurities upon reaction with **26**. Likewise, evaluation of other commonly employed coupling reagents (e.g., DMT-MM or MsCl) led to similarly unacceptable results. However, application of the ubiquitous EDAC/HOBt amide bond-forming methodology proved quite satisfactory, affording **6** in both high yield and purity, enabling a fully telescoped conversion of **2** to **6**. Thus, the acidic stream of **26** from the preceding Boc deprotection reaction was adjusted to pH 8.3−8.6 with aqueous potassium phosphate, and subsequently extracted with ethyl acetate. The resulting extract was subjected to azeotropic distillation to render it dry, and then introduced directly into the EDAC/HOBt mediated coupling chemistry (Scheme 9). Workup and crystallization from a ternary solvent system (EtOAc/MTBE/*n*-heptane) afforded high purity **6** in 79% isolated yield on kilo scale. The major process-related impurities present in the isolated material were the *tert*-butyl analogue **29** (vide supra), at ca. 0.1%, and the acylated analogue **30**, derived

(16) Box, G. E. P.; Hunter, W. G. ; Hunter, J. S. *Statistics for Experimenters*; Wiley: New York, 1978. Carlson, R. *Design and Optimisation in Organic Synthesis*; Elsevier: Amsterdam, 199.

SCHEME 7



SCHEME 8

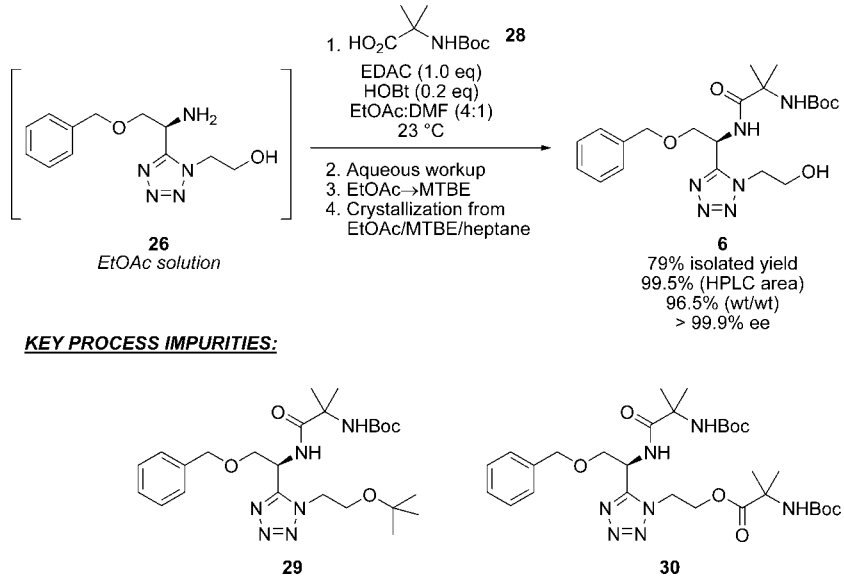


from EDAC/HOBt mediated esterification at the primary hydroxyl group of **6**, at ca. 0.1%.

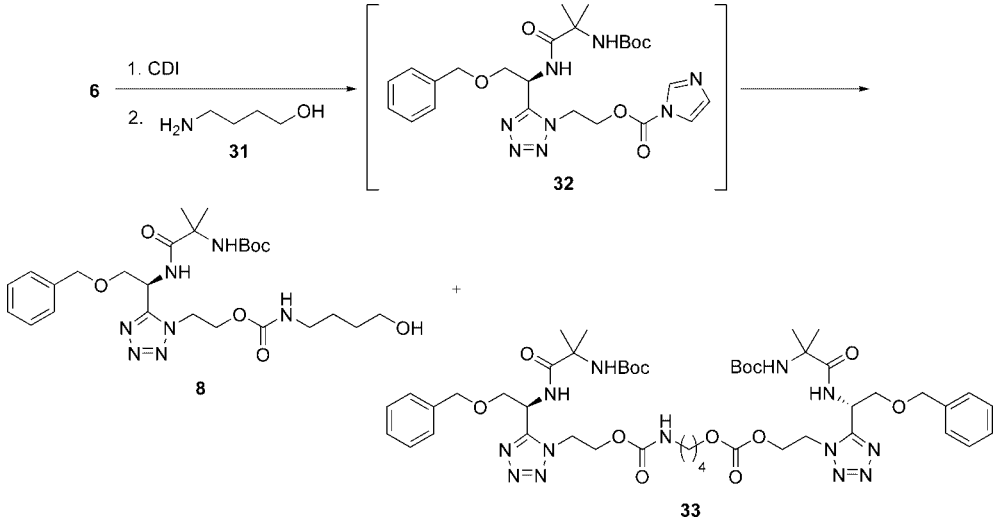
In order to secure the carbamate-linked aminobutanol side chain of the target, 1,1-carbonyldiimidazole (CDI) was selected as the reagent of choice. However, we found that implementation of unprotected 4-amino-1-butanol (**31**) in the coupling reaction resulted in unacceptable levels of the pseudodimer **33**, presumably via reaction of the free hydroxyl of the desired product **8** with the imidazolide intermediate **32** (Scheme 10).

The most expedient solution to this problem involved transient protection of the hydroxyl group present in **31**. The trimethylsilyl (TMS) protecting group was preferred since removal could be accomplished under very mild conditions, ideally during the reaction workup. Laboratory evaluation of this strategy was encouraging. Deployment of the TMS-protected nucleophile 4-(trimethylsilyloxy)butan-1-amine (**34**) effectively suppressed the formation of the pseudodimer **33**, and protodesilylation could be accomplished by exposure to a dilute aqueous hydrochloric

SCHEME 9

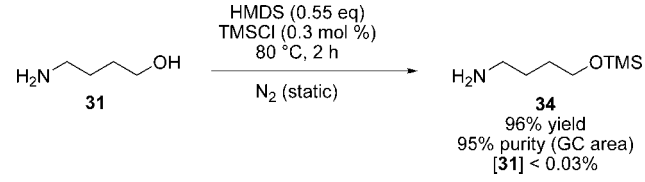


SCHEME 10



acid solution. The preparation of **34** from **31**, employing hexamethyldisilizane (HMDS) and catalytic chlorotrimethylsilane, had been described in the literature,[17] but the procedure was found to be difficult to implement on scale for a number of reasons. First of all, catalyst loadings were not specified in the original paper. To address this, we carried out a series of experiments which showed that catalyst loadings as low as 0.3% gave acceptable results. Reaction stalling, resulting in only partial protection of **31**, was another vexing problem. We found that stalling could be remedied through the introduction of supplemental hexamethyldisilizane charges during the course of the reaction. The observation that conversion was directly proportional to the initial HMDS charge led us to suspect that reaction stalling might be due to loss, through volatilization, of the intermediate silylating agent (trimethylsilylamine), suggesting that the problem could be overcome by simply performing the reaction in the absence of a nitrogen sweep. Gratifyingly, this modification did resolve the stalling issue, decreasing the residual levels of **31** to ≤0.1%. Furthermore, the resulting process proved to be robust and reproducible, with typical yields of 96% and purities ranging from 89−96% (by GC analysis) on a kilogram scale (Scheme 11). Also, the fact that crude **34** could be employed directly in the subsequent step without the need for purification was of great practical value and proved to be a key factor in enabling a the CDI-mediated synthesis of **8**.

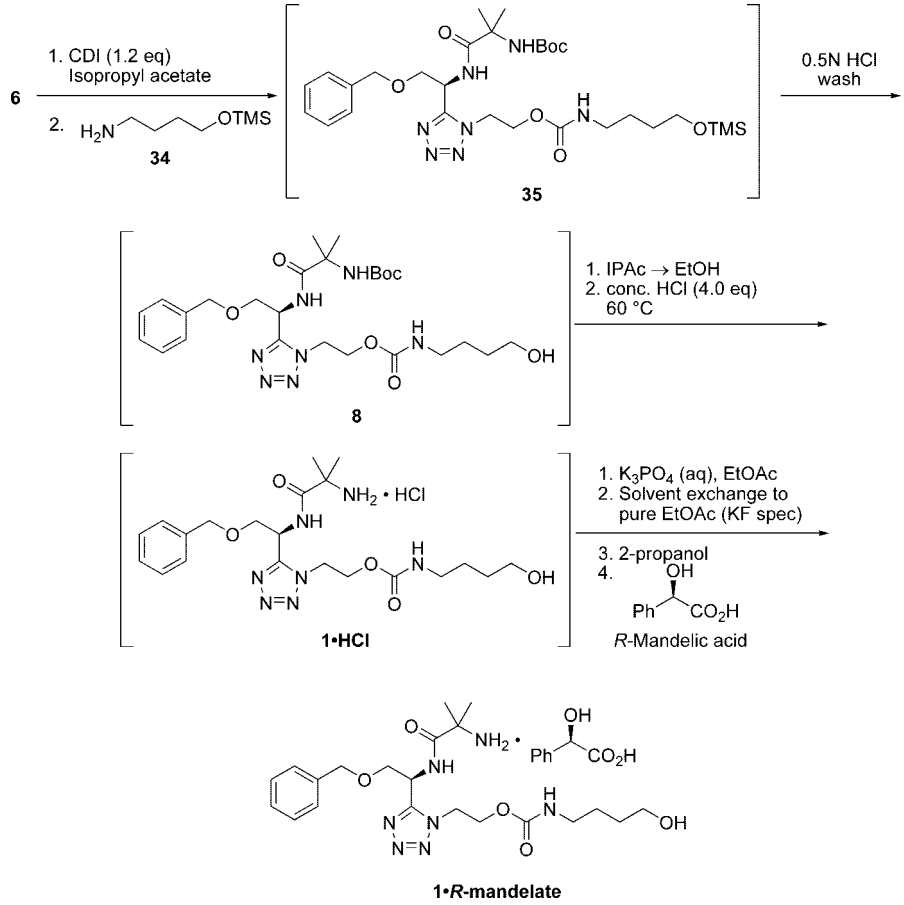
SCHEME 11



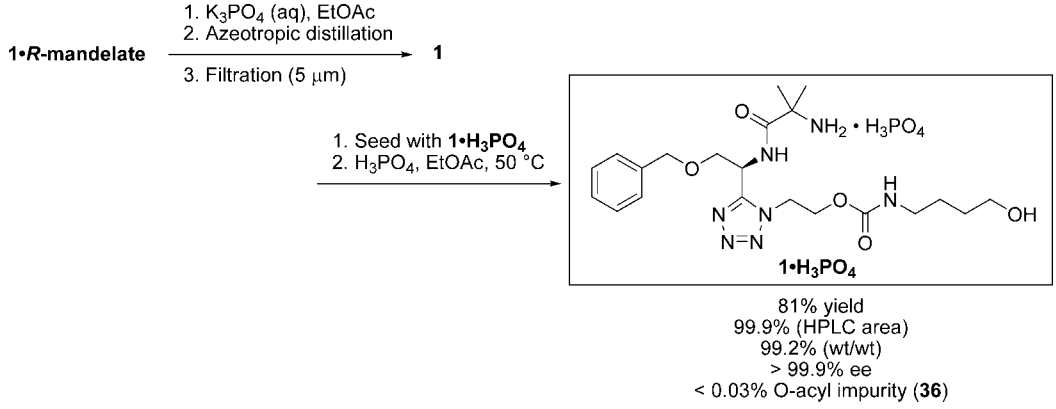
Considering the lack of crystallinity in **8**, the plan from the outset was to telescope a stream containing **8**, without isolation, into the Boc cleavage reaction to furnish **1**. While **1** was also noncrystalline, its phosphate salt *was* found to be crystalline, and we anticipated that isolation of the phosphate salt would be accompanied by purity upgrade. Unfortunately, screening of a number of conditions showed that isolation of **1**·H_3PO_4

(17) Mormann, W.; Leukel, G. *Synthesis* **1988**, *990*, 992.

SCHEME 12. Telescoped Preparation of 1·*R*-Mandelate



SCHEME 13. Conversion of 1·*R*-Mandelate to 1·H_3PO_4



was accompanied by only minimal purity upgrade, inadequate to purge the impurities present in the material to acceptable levels. Thus, an automated, high-throughput salt screen was initiated, with the goal of identifying a "bridging salt" that would confer an element of purity control at this late stage of the process. In this screen, a total of 60 acids were screened in five different solvent systems. This screen revealed the **1·*R*-mandelate** and **1·glycolate** salts as two previously unidentified crystalline forms. Further experimentation showed that the mandelate salt, when isolated from ethyl acetate/2-propanol, provided the desired level of purity/impurity and crystallization control with optimal mass recovery. This was a key finding and proved to be instrumental in enabling the endgame of this synthetic sequence, culminating in the isolation of **1·H_3PO_4** (Scheme 12 and 13). In the process, a solution of **6** in isopropyl acetate was first treated with CDI, eliciting conversion to the corresponding imidazolide (**32**), followed by introduction of crude **34**, to afford **35**. Washing of the reaction stream with 0.5 N hydrochloric acid induced protodesilyation, thus giving rise to **8**. The resulting organic solution was subjected to vacuum distillation, thereby effecting solvent exchange to ethanol, and subsequently treated with concentrated hydrochloric acid at 60 °C to effect removal of the Boc protecting group. Upon reaction completion, the ethanolic solution of **1·HCl** was diluted with ethyl acetate, then neutralized with potassium phosphate solution, and the derived organic layer was distilled to an end point of ≤1% EtOH (GC) and ≤1000 ppm water [Karl Fischer (KF) titration]. Introduction of 2-propanol, followed by *R*-mandelic

acid, furnished the **1·*R*-mandelate** salt in 83% overall isolated yield for the four-step sequence. The expected purity upgrade was realized, evidenced by assay values of 99.5% (HPLC area), 99.2% (wt/wt), and >99.9% ee.

With high-purity **1·*R*-mandelate** salt in hand, all that remained was conversion to the desired phosphate salt **1·H_3PO_4** (note that mandelic acid is not a pharmaceutically preferred counterion). Thus, **1·*R*-mandelate** was partitioned between ethyl acetate and aqueous potassium phosphate, and the resulting free-base solution was rendered anhydrous through azeotropic distillation. After filtration to remove insoluble contaminants, **1·H_3PO_4** seed crystals were charged, followed by aqueous phosphoric acid, at 50 °C. During laboratory development, this process was found to have two major problems. One was the tendency to form the *O*-acylated impurity **36** (not shown), via acid-catalyzed esterification, during the crystallization. This side reaction was minimized through the careful quantitation of **1** and implementation of a substoichiometric (0.95 equiv.) charge of H_3PO_4. The second problem was ascribed to the exceedingly low solubility of **1·H_3PO_4** in the crystallization medium. As a consequence of the high level of supersaturation, the addition of phosphoric acid resulted in uncontrolled crystallization on the reactor walls. To contend with this issue, we opted to charge **1·H_3PO_4** seed crystals *prior to* the slow, controlled introduction of phosphoric acid. Demonstration of this protocol at kilo scale was met with success, resulting in an 81% isolated yield of **1·H_3PO_4** with greater than 99.5% purity and only 0.03% of the *O*-acylated impurity **36**.

Conclusion

In summary, this manuscript discloses the development and execution of a robust, efficient and practical synthesis of the growth hormone secretagogue **1·H_3PO_4**. Expansion of the established amidrazone formation/diazotization methodology to include oxazolines as competent electrophiles eliminated the need for azide salts and allowed for the development of a safe, scaleable synthesis of the tetrazole core (**2**). This process employed a complex, four-step telescoped sequence that enabled the preparation of **2** from *N*-Boc-*O*-benzyl-D-serine in 75% yield with only one isolation. The ambident reactivity of 4-amino-1-butanol in the carbamoylation of **6** led to the implementation of the labile trimethylsilyl protecting group, solving a critical chemoselectivity issue while only minimally impacting process throughput. The endgame of the synthesis also leveraged extensive telescoping to contend with a lack of crystalline intermediates. In order to more fully control the quality attributes (e.g., color, purity, etc.) of the final product, an isolation was *added* to the endgame sequence, exploiting an intermediate *R*-mandelate salt as a chemical purity gatekeeper. A highly optimized sequence of eight chemical operations furnished the active pharmaceutical intermediate (API) **1·H_3PO_4** in 53% overall yield (from **2**).

Experimental Procedures

Telescoped Preparation of 1-(*β*-Hydroxyethyl)-5-(α-*R*-*tert*-butyloxycarbonylamino-*β*-benzyloxyethyl)tetrazole (2). Step 1: Amidation (3 → 22). To an 800 L Hastalloy reactor were charged *N*-Boc-*O*-senzyl-D-serine (**3**) (40.0 kg, 135 mol, 1.0 equiv) and dichloromethane (200 L). The resulting solution was cooled to −35 °C, *N*-methylmorpholine (15.0 kg, 148 mol, 1.1 equiv) was introduced while maintaining the reaction temperature below −30 °C, and the charge was chased with 10 L of dichloromethane. Ethyl chloroformate (16.3 kg, 150 mol, 1.1 equiv) was subsequently introduced while maintaining the reaction temperature below −30 °C. The charge was chased with 10 L of dichloromethane, and the resulting white slurry was aged at −30 ± 3 °C for 50 min. Next, *N*-methylmorpholine (26.0 kg, 257 mol, 1.9 equiv) was charged while maintaining the reaction temperature below −30 °C. Upon completion of the addition, the mixture was cooled to −40 °C, and milled chloroethylamine hydrochloride (17.3 kg, 149 mol, 1.1 equiv) was added in one portion via the reactor manway, causing the internal temperature to rise to approximately −28 °C. Once the addition was complete, the reaction temperature was adjusted to −30 °C and the slurry was agitated for 45 min. The slurry was then warmed to 0 °C over the course of 40 min and aged at said temperature until complete consumption of starting material was achieved [specification: [**3**] ≤ 2.0% (HPLC area)]. The reaction was quenched at 0 °C with deionized water (140 L), and the resulting mixture was warmed to 20 °C over 30 min. Agitation was stopped, the mixture was allowed to separate, and the resulting aqueous (top) layer was discarded. The derived organic layer was treated with 0.5 N hydrochloric acid solution (140 L) and agitated for 30 min. Again agitation was stopped, the mixture was allowed to separate, and the resulting aqueous (top) layer was discarded. In the same manner, the organic layer was washed with deionized water (140 L), and the resulting aqueous (top) layer was discarded.

Step 2: Cyclocondensation (22 → 16). The dichloromethane solution (from step 1) was treated with deionized water (97 L), 15% (wt/wt) sodium hydroxide solution (105 L), and 40% (wt/wt) tetrabutylammonium hydroxide solution (4.4 kg, 17 mol, 0.05 equiv), and the resulting biphasic mixture was stirred at 20 °C for 10.5 h. Upon complete consumption of **22** [specification: [**22**] ≤ 1.0% (HPLC area)], agitation was stopped, the layers were allowed to separate, and the aqueous (top) layer was discarded. The dichloromethane layer was then washed with 5% (wt/wt) sodium bicarbonate solution (224 L), followed by 5% (wt/wt) sodium chloride solution (224 L), and the spent aqueous (top) phases were discarded. The derived dichloromethane solution was then treated with solid sodium bicarbonate (7.9 kg) and distilled under 200 − 500 mbar pressure, while maintaining the internal temperature ≤35 °C, to a final volume of 1.2 − 1.5 L per kg of *N*-Boc-*O*-benzyl-D-serine (**3**) input. Methanol was added (100 L) and the distillation was continued at 50−500 mbar pressure, while maintaining the internal temperature ≤35 °C, to an end point of ≤1.0% (wt/wt) CH_2Cl_2 (determined by GC). Finally, the concentrate was diluted with methanol (80 L) and filtered for use in the next step.

Step 3: Amidrazone Formation (16 → 17). To an 800 L Hastalloy reactor were charged hydrazine monohydrochloride (12.1 kg, 176.6 mol, 1.30 equiv) and methanol (520 L), and the stirred solution was cooled to 0 °C. The methanolic solution of **16** (product stream from step 2) was then transferred *into* the hydrazine monohydrochloride solution, while maintaining the reaction temperature below 5 °C, and the resulting solution was aged at 0 °C for 1.5 h, effecting complete conversion to amidrazone **17** [specification: [**16**] < 1.0% (HPLC area)].

Step 4: Nitrosation (17 → 2). To a 2000 L Hastalloy reactor was charged methanol (400 L), which was cooled to 0 °C and treated with acetyl chloride (21.3 kg, 271 mol, 2.0 equiv) while maintaining the reaction temperature between 0 and 5 °C. The resulting solution was aged at 0 °C for 30 min and then cooled to −50 °C. Next, sodium nitrite (16.4 kg, 238 mol, 1.75 equiv) was charged to a solution of **17** (product stream from step 3) contained in an 800 L reactor at 0 °C. The resulting mixture was agitated for 15 min at 0 °C, then cooled to −30 °C and metered into the 2000 L Hastalloy reactor containing methanolic HCl, while maintaining the reaction temperature ≤ −10 °C. Once this transfer was complete, the resulting mixture was stirred at −10 °C for 20 min. HPLC analysis of the reaction mixture at this point indicated ≤0.1% (area) **17** remaining. The enantiomeric purity of **2** (in solution) was ca. 97% ee, and the pH of the reaction mixture was ca. 1 (by water−wet pH paper). To neutralize the reaction mixture, anhydrous

sodium acetate (26.0 kg, 316 mol, 2.3 equiv) was charged, and the agitated mixture was warmed to 20 °C to afford a pH of 5−6 (by water−wet pH paper). Toluene (600 L) was then charged, and the mixture was concentrated to ca. 530 L via reduced-pressure distillation, maintaining the internal temperature at ≤40 °C. A second portion of toluene (600 L) was added, and again the mixture was concentrated to ca. 530 L under identical conditions. Subsequent GC analysis of the filtered reaction mixture indicated ≤3.0% (vol/vol) methanol, thus verifying that the solvent exchange was complete. The reaction temperature was adjusted to 20 °C, and the mixture was treated with deionized water (320 L). After 15 min, agitation was stopped, the mixture was allowed to separate for 30 min, and the aqueous (bottom) layer was discarded. The organic layer was subsequently treated with 5% (wt/wt) sodium bicarbonate solution (320 L) and agitated for 15 min. Again, agitation was stopped, the mixture was allowed to separate for 30 min, and the aqueous (bottom) layer was discarded. The organic layer was finally treated with 5% (wt/wt) sodium chloride solution (320 L) and agitated for 15 min. Again, agitation was stopped, the mixture was allowed to separate for 30 min, and the aqueous (bottom) layer was discarded. The resulting toluene solution was concentrated to ca. 266 L via reduced-pressure distillation, while maintaining the internal temperature ≤35 °C, to a KF titration end point of ≤500 ppm H_2O. The mixture was clarified by filtration, and the resulting solution was transferred to an 800 L Hastalloy reactor. With agitation, the solution was warmed to 50 °C and then treated with *n*-heptane (180 L) while maintaining the internal temperature between 45 and 50 °C, yielding a homogeneous solution (GC analysis of the mixture indicated a 56:44 toluene/*n*-heptane (vol/vol) composition). The solution was cooled to 20 °C over 3 h, and spontaneous crystallization commenced at ca. 35 °C. The slurry was further cooled to 0 °C over 1 h, aged for an additional hour, and then discharged to a Nutsche filter. The resulting wetcake was washed twice with heptanes (2 × 60 L) and subsequently dried under vacuum (35 °C, 25 mmHg) to 0.02% LOD, furnishing 36.9 kg of **2** (75% yield) as a white, crystalline solid, mp 77.1 °C with 97.8% HPLC area purity, 99.3% (wt/wt) assay purity, and enantiomeric purity of 99.4% ee: $[\alpha]^{25}_D$ +17.2 (*c* 1.03, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (app d, J = 8.5 Hz, 1 H), 7.25−7.35 (m, 5 H), 5.28 (app q, J = 6.4 Hz, 1 H), 5.11 (t, J = 5.5 Hz, 1 H), 4.51−4.55 (m, 4 H), 3.93 (app t, J = 8.9 Hz, 1 H), 3.79−3.85 (m, 2 H), 3.68−3.75 (m, 1 H), 1.37 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.4, 154.8, 138.0, 128.2, 127.5, 127.4, 78.8, 72.1, 69.5, 59.4, 49.5, 44.3, 28.1; IR (KBr pellet) ν_{max} 3488 (br), 3325, 2983, 2938, 2883, 1681, 1527, 1458, 1369, 1337, 1279, 1159. Anal. Calcd for $C_{17}H_{25}N_5O_4$: C, 56.18; H, 6.93; N, 19.27. Found: C, 56.29; H, 7.04; N, 19.40.

Telescoped Preparation of (*S*)-*tert*-Butyl-1-(2-(benzyloxy)-1-(1-(2-hydroxyethyl)-1*H*-tetrazol-5-yl)ethylamino)-2-methyl-1-oxopropan-2-ylcarbamate (6). Step 1: Deprotection (2 → 26). To a 100 L glass-lined reactor were charged **2** (2.41 kg), SDA 3A ethanol (3.21 kg), water (8.09 kg), and concentrated hydrochloric acid (2.62 kg of a 37% solution). The resulting mixture was heated at 60 °C for 1.5 h, at which point HPLC analysis indicated complete consumption of **2**. Upon cooling to 20 °C, the pH of the batch was adjusted to ca. 8 by the addition of 2.0 M potassium phosphate solution, and the resulting mixture was extracted with ethyl acetate (54.1 kg). The derived organic phase was concentrated to ca. 55 L via reduced pressure distillation, while maintaining the internal temperature ≤40 °C, to a KF titration end point of 0.8% H_2O, and then cooled to 20 °C.

Step 2: Amidation (26 → 6). To the stirred solution of **26** in ethyl acetate (product stream from step 1) were introduced HOBt (180 g), *N*-Boc-2-aminoisobutyric acid (1.40 kg), EDAC (1.37 kg), and DMF (3.41 kg). The resulting mixture was aged at 20 °C for 4.5 h, at which point HPLC analysis indicated complete consumption of **26**. The mixture was diluted with water (12.2 kg) and ethyl acetate (54.2 kg). After 15 min, agitation was stopped, the mixture was allowed to separate for 30 min, and the aqueous (bottom) layer was discarded. The derived organic layer was successively washed with 0.1 N HCl solution (12.0 kg), 5% (wt/wt) $NaHCO_3$ solution (24.0 kg), and water (2 × 24.0 kg). The derived solution was then concentrated to ca. 65 L via reduced pressure distillation, while maintaining the internal temperature ≤40 °C, to a KF titration end point of ≤0.2% H_2O. The mixture was clarified by filtration, concentrated to 10.0 L, and diluted with MTBE (7.12 kg). While maintaining the batch temperature between 45 and 50 °C, *n*-heptane (11.85 kg) was introduced, followed by a portion of **6** seed material (24..0 g, 1%). The batch was aged at 50 °C for 2 h, resulting in a thin slurry. Additional *n*-heptane (7.9 kg) was charged, and the slurry was aged for 1 h at 50 °C and then cooled to 20 °C over 2 h. The product was collected by filtration, washed with a solution of *n*-heptane (1.64 kg) and MTBE (1.78 kg), and subsequently dried under vacuum (50 °C, 25 mmHg), affording 2.35 kg of **6** (79.3% yield) as a white, crystalline solid, mp = 110 °C, with 99.6% purity (HPLC area): $[\alpha]^{25}_D$ +12.4 (*c* 1.02, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.18 (m, 5H), 5.66 (q, J = 6.0 Hz, 1 H), 4.94 (s, 1 H), 4.46−4.60 (m, 4 H), 3.95−4.0 (m, 4 H), 3.83 (m, 1 H), 3.49 (t, J = 6.3 Hz, 1 H), 1.43 (s, 3 H), 1.40 (s, 3 H), 1.33 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 154.1, 154.0; 136.5, 128.0, 127.6, 127.3, 80.6, 73.4, 70.2, 61.0, 56.8, 50.6, 43.9, 28.5, 25.9, 25.7; IR (KBr pellet) ν_{max} 3401 (br), 2981, 1709, 1668, 1542, 1509, 1459, 1366, 1276, 1186, 1160, 1122, 1083. Anal. Calcd for $C_{21}H_{32}N_6O_5$: C, 56.23; H, 7.19; N, 18.73. Found: C, 56.19; H, 7.25; N, 18.82.

Preparation of 4-(Trimethylsilyloxy)butan-1-amine (34). To a 4 L glass reactor were charged 4-amino-1-butanol (**31**) (1.64 L, 1.59 kg, 17.8 mol, 1.0 equiv) and 1,1,1,3,3,3-hexamethyldisilazane (2.1 L, 1.61 kg, 9.95 mol, 0.56 equiv). With agitation, chlorotrimethylsilane (6.78 mL, 5.8 g, 0.053 mol, 0.003 equiv) was introduced via syringe; the resulting mixture was warmed to 80 °C over the course of 90 min and subsequently aged at said temperature for ca. 3 h. GC analysis of the reaction mixture at this point indicated 0.049% (area) **31** remaining (specification: [**31**] ≤ 0.25%). The mixture was cooled to 20 °C and discharged to a 20 L carboy, affording 2.98 kg of crude, unpurified **34** [97.4% yield (corrected for purity)] as a light yellow oil. GC analysis of the product stream indicated purity of 94.5% (area), with 0.024% (area) residual **31**. Spectral data were consistent with those reported in the literature.

Telescoped Preparation of 1·*R*-Mandelate. Step 1: Carbamate Formation (6 → 8). To a 100 L glass-lined reactor were charged CDI (1,1′-carbonyldiimidazole) (910 g, 5.61 mol, 1.1 equiv) and isopropyl acetate (2.45 kg). To a 20 L carboy were charged **6** (2.1 kg, 4.68 mol, 1.0 equiv) and isopropyl acetate (15.3 kg). To the agitated CDI slurry was introduced the solution of **6**, and the resultant mixture was aged for 2 h at 22−25 °C, effecting complete consumption of starting material [specification: [**6**] ≤ 1.0% (HPLC area)]. Next, neat **34** (1.13 kg, 7.0 mol, ca. 1.5 equiv) was introduced to reaction mixture, followed by an isopropyl acetate (1.0 kg) rinse, and the resulting solution was aged at 22−25 °C until the imidazolide intermediate was reduced to a level of ≤0.5% (HPLC area). Upon completion, 0.5 N HCl (17.32 kg) was introduced to the mixture. After 30 min, agitation was stopped, the mixture was allowed to separate for 30 min, and the aqueous (bottom) layer was discarded. Two additional 0.5 N HCl treatments were carried out in an identical manner, followed by HPLC analysis to verify that desilylation was complete [completion criteria: [**35**] ≤ 0.5% (HPLC area); result: 0.3%]. The organic layer was successively washed with 5.0% (wt/wt) potassium phosphate solution (15.0 kg) and 5.0% (wt/wt) NaCl solution (15.0 kg). The derived solution was concentrated to ca. 8 L via reduced-pressure distillation, maintaining the internal temperature ≤50 °C, then subjected to a constant-volume distillative solvent exchange to ethanol, to a GC end point of ≤0.1% (vol/vol) isopropyl acetate in ethanol.

Step 2: Deprotection (8 → 1). To the filtered reaction stream from step 1 were charged water (25.2 kg) and 37% aqueous hydrochloric acid solution (1.85 kg), and the resulting mixture was heated 60 °C for 3.25 h, at which point HPLC analysis indicated complete consumption of **8**. Upon cooling to 20 °C, the pH of the

batch was adjusted to ca. 8 by the addition of 2.0 M potassium phosphate solution, and the resulting mixture was extracted twice with ethyl acetate (2 × 15.8 kg). The derived organic phase was then subjected to distillative solvent exchange to ethyl acetate, while maintaining the internal temperature ≤50 °C, to a KF titration end point of 0.02% H_2O.

Step 3: Salt Formation (1 → 1·*R*-Mandelate). After clarification, the mixture was treated with a solution of mandelic acid (0.72 kg) in ethyl acetate (7.58 kg) at 50 °C. The resulting slurry was aged at 50 °C for 1 h, cooled to 10 °C over 1.5 h, and aged for an additional 1 h at 10 °C. The product was collected by filtration, washed with ethyl acetate (16.3 kg), and subsequently dried under vacuum (50 °C, 25 mmHg) to ≤1.0% LOD, affording 2.38 kg of **1·*R*-Mandelate** (83.1% yield) as a white, crystalline solid, mp = 113.7 °C (dec), with an HPLC area purity of 99.45% and enantiomeric purity of >99.9% ee: $[\alpha]^{25}_D$ −18.12 (*c* 1.01, H_2O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (s, 3 H), 1.32 (s, 3 H), 1.33−1.43 (m, 4 H), 2.83−2.97 (m, 2 H), 3.29−3.40 (m, 2 H), 3.88 (dd, J = 6.32, 9.71 Hz, 1 H), 3.96 (dd, J = 7.83, 9.74 Hz, 1H), 4.25−4.42 (m 2 H), 4.49−4.57 (m, 2 H), 4.61−4.76 (m, 3 H), 5.50 (t, J = 6.34 Hz, 1 H), 7.12−7.41 (m, 10 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.1, 26.2, 27.1, 30.8, 44.3, 47.6, 56.6, 61.3, 62.3, 69.9, 73.1, 73.9, 126.7, 126.8, 127.8, 127.9, 127.9, 128.6, 138.1, 142.9, 154.4, 155.6, 174.2, 174.3; IR (KBr pellet) ν_{max} 3477, 3322 (br), 2944 (br), 1737, 1683, 1637, 1542, 1456, 1366, 1342, 1256, 1193; HRMS (ESI-MS) calcd for $C_{21}H_{34}N_7O_5$ 464.2616 [(M + H)$^+$], found 464.2614. Anal. Calcd for $C_{29}H_{41}N_7O_8$: C, 56.57; H, 6.71; N, 15.93. Found: C, 56.30; H, 6.55; N, 15.86.

Telescoped Preparation of 1·H_3PO_4. Step 1: Free-Base Formation (1·*R*-Mandelate → 1). To a glass-lined 100 L reactor were charged **1·*R*-mandelate** (2.37 kg) and water (40.17 kg), and the resulting mixture was agitated to effect dissolution. Next, ethyl acetate (14.5 kg) was charged, and the batch pH was adjusted to 8.5−9.0 by the addition of ca. 2.5 kg of a 2.0 M K_3PO_4 solution. After 15 min, agitation was stopped, and the phases were allowed to separate. The organic phase was retained, the aqueous layer was extracted twice with ethyl acetate (14.5 kg), and the resulting organic solutions were combined. After washing with 0.075 M K_3PO_4 (10.2 kg), followed by 5.0% aqueous NaCl (10.5 kg), the solution was concentrated via vacuum distillation (batch temperature 35−50 °C, ca. 300 mmHg) to a target volume of ca. 30 L. The cooled mixture was transferred to another glass-lined 100 L reactor through a 5 μm cartridge filter, and the resulting clarified solution of **1** was adjusted to a final volume of 36 L through the addition of filtered ethyl acetate.

Step 2: Crystallization and Isolation of 1·H_3PO_4. To the solution of **1** in ethyl acetate was charged water (0.36 kg, 1.0% (vol/vol)), and the batch was heated to 50 °C. A phosphoric acid solution was prepared by combining concentrated phosphoric acid (0.365 kg, 0.97 equiv based on quantitation of **1**), water (0.36 kg), and ethyl acetate (32.0 kg). With vigorous agitation, ca. 500 mL of the phosphoric acid solution was introduced to the reactor at a rate of ≤100 mL/min, affording a cloudy mixture. A portion of **1·H_3PO_4** seeds (34 g, 2.0%) was charged, followed by introduction of the remaining acid solution over ca. 3 h. Upon completion of the acid charge, the batch was cooled to 20 °C over ca. 1 h, subsequently aged at said temperature for 1 h, and ultimately discharged to a Nutsche filter. The resulting wetcake was washed with ethyl acetate (18.1 kg) and dried under vacuum (50 °C, 25 mmHg) to ≤1.0% LOD, furnishing 1.8 kg of **1·H_3PO_4** (81.2% yield) as a white, crystalline solid, mp = 104 − 105 °C, with 99.9% HPLC area purity, 99.2% (wt/wt) assay purity, and enantiomeric purity of >99.9% ee: $[\alpha]^{25}_D$ +3.03 (*c* 1.01, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24−7.37 (m, 5 H), 7.15 (app t, J = 5.7 Hz, 1 H), 5.51 (app t, J = 7.01 Hz, 1 H), 4.65−4.74 (br m, 2 H), 4.54 (br s, 2 H), 4.36−4.44 (m, 1 H), 4.28−4.35 (m, 1 H), 4.00 (dd, J = 7.49, 9.77 Hz, 1 H), 3.92 (dd, J = 6.51, 9.60 Hz, 1 H), 3.32−3.38 (m, 2 H), 2.89−2.96 (m, 2 H), 1.43 (s, 3 H), 1.40 (s, 3 H), 1.33−1.41 (m, 4 H); ^{13}C NMR (100 MHz, D_2O) δ 172.6, 157.0, 153.9, 136.6, 128.7, 128.4, 128.3, 73.5, 68.8, 62.6, 61.8, 57.7, 47.9, 44.6, 40.8, 29.2, 23.9, 23.7; IR (KBr pellet) ν_{max} 3345 (br, 2943 (br), 1733, 1718, 1692, 1675, 1542, 1470, 1376, 1253, 1199, 1124, 1101; HRMS (ESI-MS) calcd. for $C_{21}H_{34}N_7O_5$ 464.2616 [(M + H)$^+$], found 464.2614.

Supporting Information Available: General experimental details, along with copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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