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Quaternary Chiral Center *via* Diastereoselective Enolate Amination Enables the Synthesis of an Anti-inflammatory Agent†

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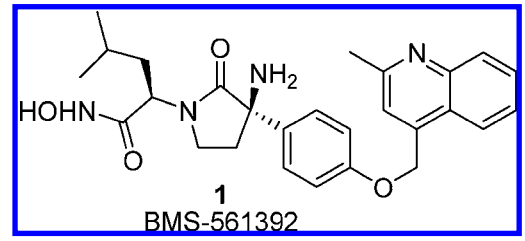
Abstract:

The D-leucine amino acid residue necessary for the synthesis of BMS-561392, 1, was employed as a chiral directing group for a diastereoselective enolate amination to establish the quaternary chiral center. Enhanced diastereomeric ratios were observed while conducting the enolate amination with 1-chloro-1-nitrosocyclopentane 6 in the presence of LiCl. Analogies are drawn between known tertiary amide amino alcohol chiral auxiliaries which have been used to effect diastereoselective enolate alkylations and aminations. Once the stereochemical features of 1 were established, an efficient reaction sequence was devised to complete its synthesis. During the course of this research, accelerated reaction calorimetry (ARC) data substantiated that the aminating agent 1-chloro-1-nitrosocyclopentane 6 was not safe to use as a neat compound. Consequently, a preparation and use of 6 as a stock solution in methyl *tert*-butyl ether (MTBE) was developed that rendered it safe for use.

Introduction

Tumor necrosis factor alpha (TNFα) is a cytokine produced primarily by activated monocytes, macrophages, and T-cells, which exhibits a wide range of biological actions relevant to acute and chronic inflammation. The administration of neutralizing anti-TNFα antibodies or fusion proteins has been demonstrated to be effective in the treatment of inflammatory diseases in a clinical setting including rheumatoid arthritis, psoriasis, Crohn's diseases, and ankylosing spondylitis.[1] The clinical candidate synthesized in this article arose from a discovery program targeted to identify an orally administered, selective, small molecule capable of reducing the levels of circulating TNFα. An oral agent was judged desirable from the perspective of ease of administration, reduced cost of therapy, and patient compliance. The clinical development candidate, BMS-561392, **1**, is a TACE inhibitor, an inhibitor of the enzyme which processes proTNFα to yield the soluble TNFα cytokine product.[2] The previously reported syntheses of **1** utilized racemic methods to establish the tetra-substituted carbon stereocenter and relied on a subsequent chromatographic separation of diastereomers[2d] or an enzymatic resolution[2e] to establish the absolute stereochemistry. This article describes a diastereoselective synthesis that affords the desired single diastereomer of **1**.



1
BMS-561392

Results and Discussion

The objective of the research described herein was to devise an efficient asymmetric synthesis for potential commercialization of **1** with a focus on the key tetra-substituted carbon atom. The preparation outlined in Scheme 1 gives access to the γ-lactam **5**. The methyl ester **2** in Scheme 1 is a known compound.[3] Allylation and ozonolysis of similar compounds is described in the literature.[4] The ozonolysis was run in EtOAc to permit facile purification of the aldehyde **4** *via* crystallization from EtOAc/heptane, and the intermediate ozonide was reduced by the combination of zinc and acetic acid to enable removal of the byproduct salts by filtration. Next, an efficient reductive

† This manuscript is dedicated to Professor Philip D. Magnus, FRS, in honor of his 66th birthday.

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(1) (a) Klareskog, L.; Gaubitz, M.; Rodriguez-Valverde, V.; Malaise, M.; Dougados, M.; Wajdula, J. *Ann. Rheum. Dis.* **2006**, *65* (12), 1578. (b) Tutrone, W. D.; Weinberg, J. M. *Expert Rev. Dermatol.* **2006**, *1* (2), 207. (c) Bhatia, J. K.; Korelitz, B. I.; Panagopoulos, G.; Lobel, E.; Mirsky, F.; Sultan, K.; DiSanti, W.; Chun, A.; Keenan, G.; Mamun, K. *J. Clin. Gastroenterol.* **2007**, *41* (7), 677. (d) Gorman, J. D.; Sack, K. E.; Davis, J. C., Jr. *N. Engl. J. Med.* **2002**, *346* (18), 1349.

(2) (a) Lee, D. C.; Sunnarborg, S. W.; Hinkle, C. L.; Myers, T. J.; Stevenson, M.; Russell, W. E.; Castner, B. J.; Gerhart, M. J.; Paxton, R. J.; Black, R. A.; Chang, A.; Jackson, L. F. *Ann. N.Y. Acad. Sci.* **2003**, *995*, 22. (b) Newton, R. C.; Decicco, C. P. *J. Med. Chem.* **1999**, *42* (13), 2295. (c) DasGupta, S.; Murumkar, P. R.; Giridhar, R.; Yadav, M. R. *Bioorg. Med. Chem.* **2009**, *17* (2), 444. (d) Maduskuie, T. P., Jr.; Duan, J.; Mercer, S. E. Novel Lactam Metalloprotease Inhibitors. (Dupont Pharmaceuticals Company, U.S.A.). PCT Int. Appl. WO 2002004416 A2 20020117, 2002. (e) Savage, S. A.; Waltermire, R. E.; Campagna, S.; Bordawekar, S.; Dalla Riva Toma, J. *Org. Process Res. Dev.* **2009**, *13*, 510.

(3) (a) Williams, D. R.; Sing-Yeun, S. *J. Org. Chem.* **1982**, *47*, 2846. (b) Weiss, P. *J. Am. Chem. Soc.* **1948**, *70*, 4263.

(4) (a) Edgar, M. T.; Pettit, G. R.; Smith, T. H. *J. Org. Chem.* **1978**, *43*, 4115. (b) Pour, M.; Spulák, M.; Buchta, V.; Kubanová, P.; Voprsalová, M.; Wsól, V.; Fáková, H.; Koudelka, P.; Pourová, H.; Schiller, R. *J. Med. Chem.* **2001**, *44*, 2701.

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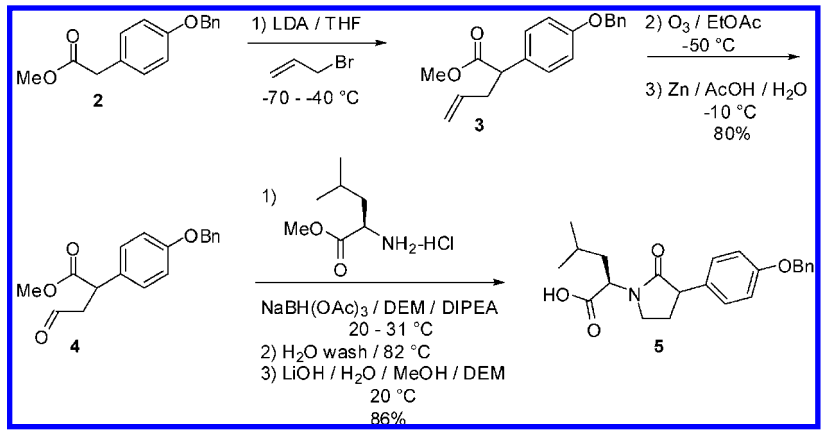
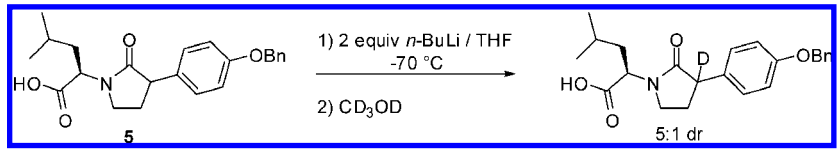
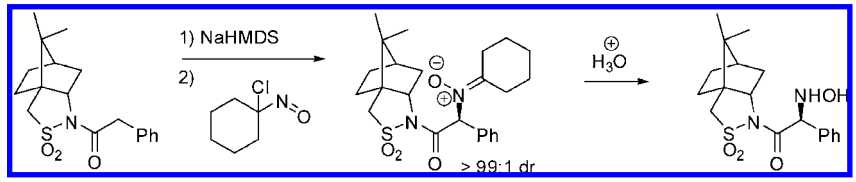
Scheme 1



Scheme 2



Scheme 3



amination/cyclization[5]/hydrolysis sequence was conducted without isolation of the intermediates. Aldehyde **4** was dissolved in diethoxymethane and treated with D-leucine methyl ester hydrochloride, followed by Hunig's base. This mixture was exposed to sodium triacetoxyborohydride to afford the corresponding secondary amine. Lactamization was induced thermally and the ester hydrolyzed by the action of aqueous lithium hydroxide to afford γ-lactam **5** in 86% overall yield from **4** to **5**.

The proposal for the asymmetric synthesis of **1** was to generate the dianion (carboxylate, enolate) of γ-lactam **5** and trap the enolate on carbon with an electrophilic source of nitrogen (i.e., electrophilic enolate amination).[6] The hypothesis, based on models, was that the existing chiral center of the amino acid would influence the stereochemistry of the newly formed quaternary chiral center (*vide infra*). To probe the question of diastereoselection and dianion formation, a deuteration experiment was performed. γ-Lactam **5** was dissolved in THF and 2 equiv of *n*-butyllithium was added at −70 °C to generate the dianion (Scheme 2). The dianion mixture was warmed to 0 °C briefly, and cooled back to −70 °C in an attempt to effect complete double deprotonation. CD_3OD was subsequently added to the reaction mixture.

The deuterated product was examined by ^{1}H NMR integration, which indicated a 5:1 diastereomer ratio (dr). This result demonstrated that the dianion had formed and that the enolate quench had been influenced stereochemically by the amino acid residue. With the diastereoselection concept validated, the research was next directed towards selecting an appropriate electrophilic aminating agent.[6]

Oppolzer employed chloronitroso reagents to efficiently aminate the enolate of a sultam tertiary amide (Scheme 3).[7] This methodology was expected to be compatible with the proposed chemistry in Scheme 2, and therefore considered worth investigation.

The dianion of γ-lactam **5** was generated as before, and the resulting reaction mixture was treated with 1-chloro-1-nitrosocyclopentane **6**[8] as a MTBE stock solution (Scheme 4). The amination of the dianion of γ-lactam **5** proceeded at the rate of addition of **6** to give greater than 95% conversion to the desired product as indicated by HPLC. After an aqueous acidic workup,

(5) (a) Trybulski, E. J.; Zhang, J.; Kramss, R. H.; Mangano, R. M. *J. Med. Chem.* **1993**, *36*, 3533. (b) Moss, N.; Beaulieu, P.; Duceppe, J. S.; Ferland, J. M.; Gauthier, J.; Ghiro, E.; Goulet, S.; Guse, I.; Llinàs-Brunet, M.; Plante, R.; Plamondon, L.; Wernic, D.; Déziel, R. *J. Med. Chem.* **1996**, *39*, 2178. (c) Shiniji, F.; Shuichi, N.; Yoshikazu, S.; Shigeo, N. *Heterocyles* **1981**, *15*, 819.

(6) Erdik, E. *Tetrahedron* **2004**, *60*, 8747, and references cited therein.

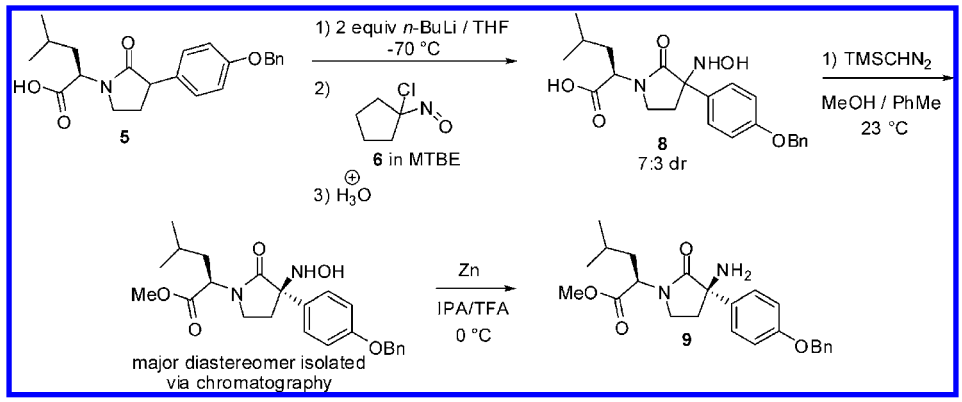
(7) (a) Oppolzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991. (b) Oppolzer, W.; Tamura, O.; Deerberg, J. *Helv. Chim. Acta* **1992**, *75*, 1965.

(8) Müller, E.; Metzeger, H.; Fries, D. *Chem. Ber.* **1954**, *87*, 1449.

(9) Hashimoto, N.; Aoyama, T.; Shioi, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.

(10) (a) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322. (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (c) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (d) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428. (e) Myers, A. G.; Yoon, T. *Tetrahedron Lett.* **1995**, *36*, 9429. (f) Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488. (g) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361. (h) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *Tetrahedron Lett.* **1978**, 3961. (i) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *J. Organomet. Chem.* **1979**, *177*, 5.

Scheme 4



the hydroxylamine **8** was isolated. A 7:3 mixture of diastereomers was apparent by NMR and HPLC. In order to determine which diastereomer was favored in the amination it was necessary to convert hydroxylamine **8** into the known intermediate **9** from the original synthesis of **1**.[2d] To this end, hydroxylamine **8** was esterified by reaction with trimethylsilyldiazomethane in the presence of a mixture of MeOH and toluene,[9] and the N−O bond was cleaved reductively by the action of zinc in acidic media.[7] The relative configuration of ester **9** was confirmed by comparison of its NMR spectra with those of an authentic sample.

As indicated above, **6** (Scheme 4) was selected as the aminating agent. We selected **6** after comparing its performance with that of 1-chloro-1-nitrosocyclohexane in the amination reaction.[8] It was found that **6** gave moderately cleaner reaction profiles, perhaps due to less hindrance (more reactive) and corresponding attenuation of competing processes. Accelerated reaction calorimetry (ARC) analysis revealed that neat **6** was already decomposing at 22 °C when the analysis began, and a maximum "self heat" rate of 400 °C min^{-1} was measured (Figure 1a). To enable the safe use of **6**, solutions of **6** were evaluated to determine their relative safety. As a 33 weight percent (wt %) solution in MTBE, **6** had an onset of decomposition at 70 °C with a maximum "self heat" rate of 4 °C min^{-1} (Figure 1b). As MTBE has a boiling point of 55−56 °C, this gave the additional safety that the solvent would boil before decomposition of the reagent could occur. As a result, all further studies and scale-up were performed with **6** as a 33 wt % solution in MTBE.

1-Chloro-1-nitrosocyclopentane **6** was prepared by reacting cyclopentanone oxime with chlorine in MTBE with a ReactIR 1000 Dicomp probe submerged into the reaction mixture. The React IR data indicated a complete conversion of the starting oxime to **6** with no side reactions detected. An unidentified, transient, thick precipitate was observed during the course of the reaction that was at maximum concentration at the point when the oxime was completely consumed. The ReactIR plots in Figures 2 and 3 show complete consumption of the oxime OH and production of the N═O double bond. The component profiles (Figure 4) illustrate complete consumption of the oxime

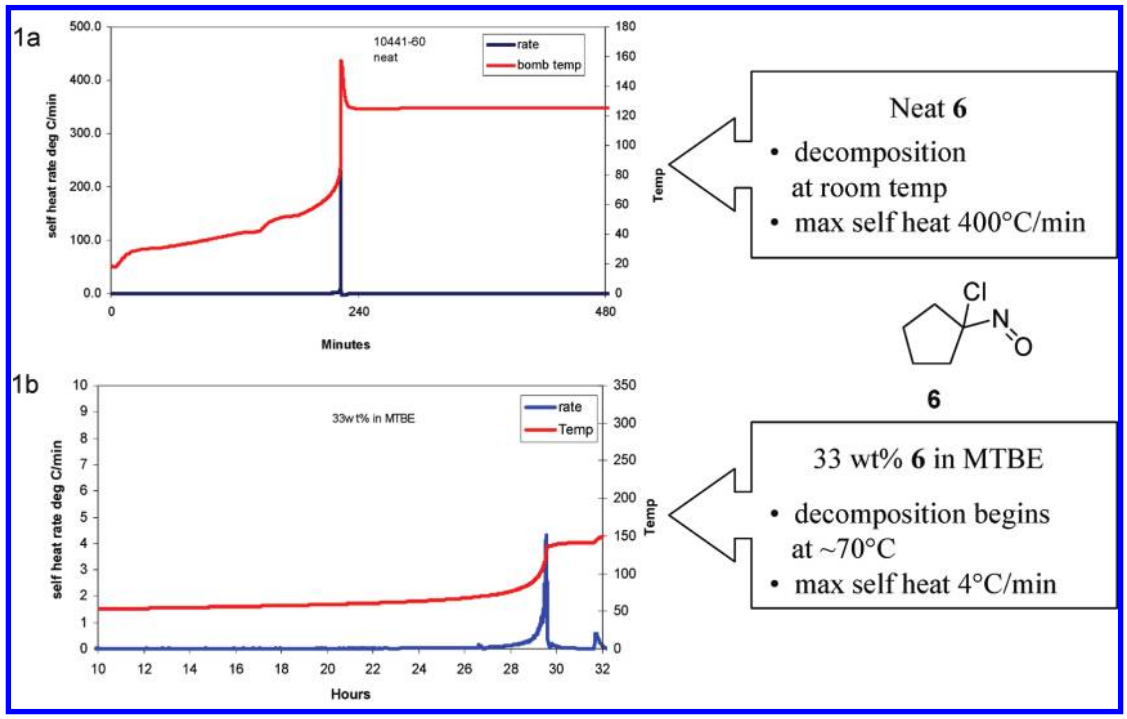


Figure 1. **ARC data comparing neat 6 to 33 wt % 6 in MTBE.**

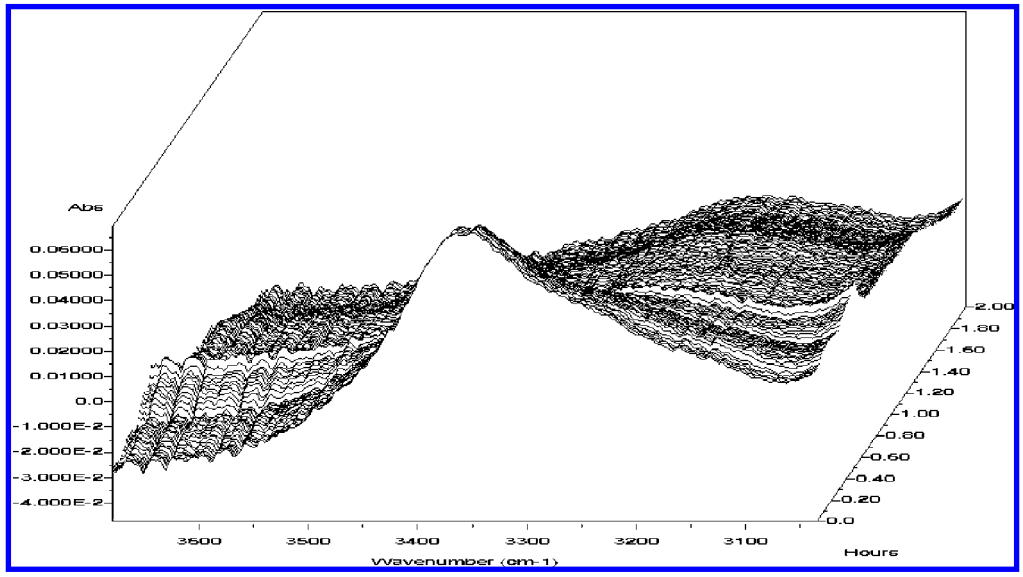


Figure 2. **Profile of peak consumption at 3363 cm^{-1} of the oxime OH of cyclopentanone oxime in MTBE.**

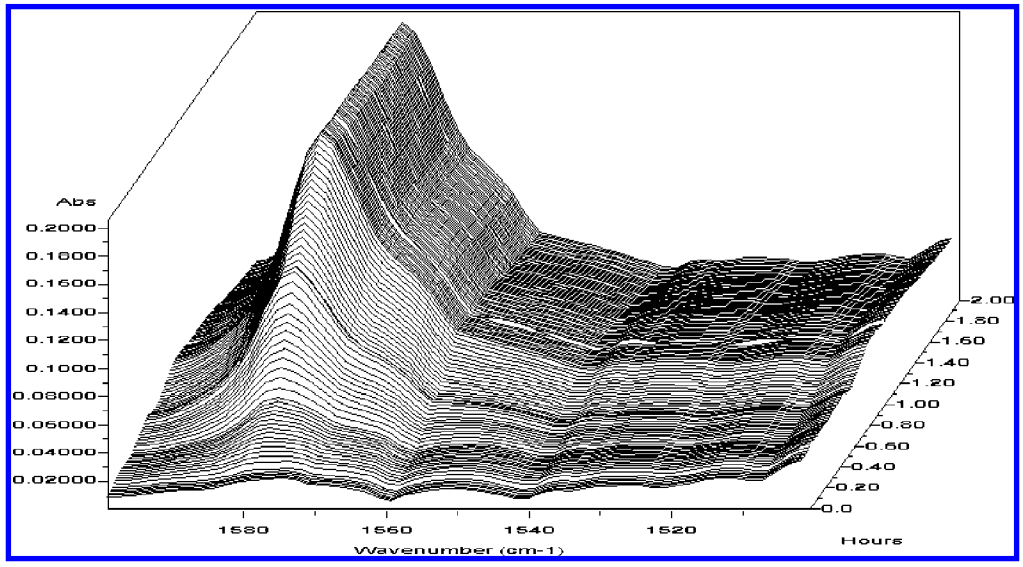


Figure 3. **Profile of peak production at 1578 cm^{-1} of the nitroso N═O of 6 in MTBE.**

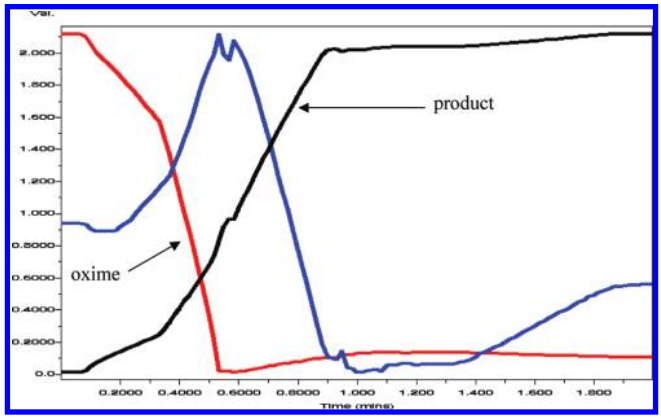


Figure 4. **Component profiles from the ReactIR experiment.**

(red line), an intermediate buildup which coincided with the transient precipitate (blue line), and clean production of **6** (black line).

The ReactIR data gave us the confidence to assume a quantitative yield of **6** after consumption of the starting oxime was complete.

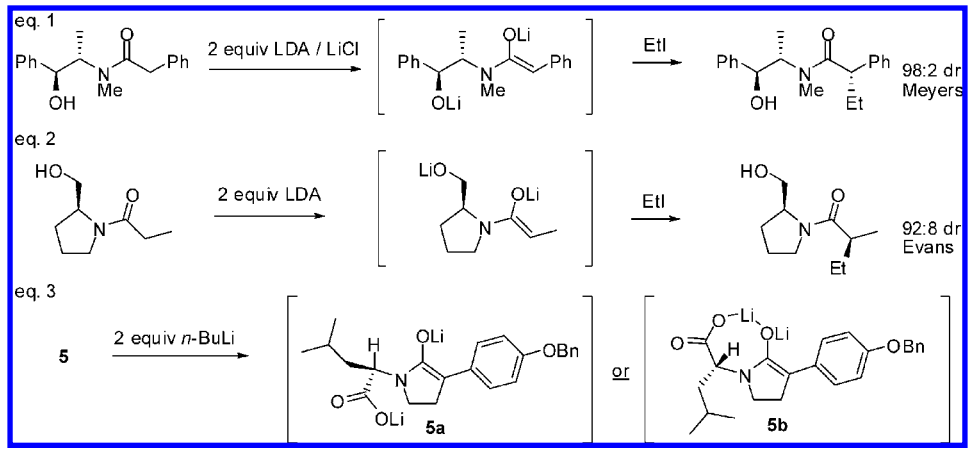
The work of A. G. Myers[10] and D. A. Evans[11] (Scheme 5, eqs 1 and 2; concerning the diastereoselective alkylation of a tertiary amide enolate dianion) and the enolate amination work of Badia[12] appeared to have similarities to the chemistry in Scheme 4. The specific similarities are a tertiary amide bearing a chiral directing group, a lithium alkoxide of an amino alcohol as part of the directing group which is similar in arrangement to the lithium carboxylate **5a** (Scheme 5), and a tertiary amide dianion nucleophile that is trapped on the enolate carbon by an electrophile.

The origin of the diastereoselectivity in the alkylations presented in eqs 1 and 2 (Scheme 5) are proposed to be a result of the *Z*-enolate geometry (alkyl group on the same side of the enolate as oxygen). In the *Z*-enolate configuration, the alkoxide-bearing side chain can adopt a staggered confirmation in which

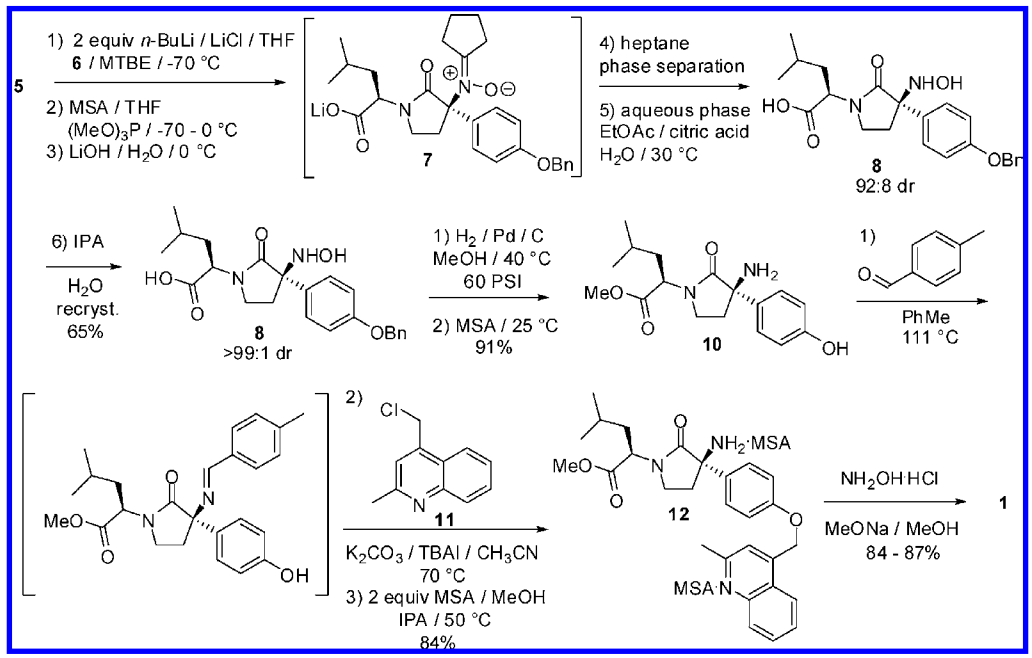
(11) (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233. (b) Sonnet, P.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137.

(12) (a) Anakabe, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Yoldi, V. *Eur. J. Org. Chem.* **2001**, 4343. (b) Vicario, J. L.; Badía, D.; Domínguez, E.; Crespo, A.; Carrillo, L.; Anakabe, E. *Tetrahedron Lett.* **1999**, *40*, 7123.

Scheme 5



Scheme 6



the C−H bond α to nitrogen lies in the plane of the enolate oxygen, in keeping with allylic strain arguments. This places the alkoxide (perhaps solvent coordinated or aggregated) side chain in a position to block one of the faces of the enolate and enhance the diastereoselectivity of the ensuing enolate trapping. The possible intermediates **5a** and **5b** illustrate that only the *Z*-enolate can form due to ring constraints (Scheme 5, eq 3). In addition, if the enolate carboxylate of γ-lactam **5** is configured with the C−H bond α to nitrogen lying in the plane of the enolate oxygen **5a**, the carboxylate does occupy the face opposite to the newly introduced amino hydroxyl group of compound **8** (Scheme 6). In Scheme 5, a cyclic transition state **5b** is also drawn as an alternative predictive tool[13] with the proposition that the electrophile is introduced to the opposite face with respect to the alkyl group of the amino acid.

Noted in the Meyers' work is the use of LiCl to increase the reaction rate and in some cases the diastereoselectivity.[10] The work of Seebach indicates that LiCl may modify the aggregation state of enolates, and thereby the reactivity of an enolate in solution.[14] The addition of LiCl to the amination reaction mixture increased the dr of hydroxylamine **8** to 92:8 at −70 °C (Scheme 6). Conducting the amination at 0 °C with LiCl present gave a dr of hydroxylamine **8** of 9:1, with increased levels of impurities when compared to the reaction at −70 °C.

It was observed that the impurity profile of the amination reaction worsened when warmed prior to quenching for the workup. To neutralize the carboxylate nitrone intermediate **7** (Scheme 6), an equivalent of methanesulfonic acid (MSA) as a solution in THF was added to the reaction mixture at −70 °C, which improved the purity of the reaction mixture as it was brought to 0 °C. In addition, it was found that unreacted **6**, which was apparent by its deep-blue color, also contributed to increased impurity levels during the workup/warm-up. Trimethylphosphite was added to the reaction mixture at −70 °C as a titration, removing the blue color of **6** on contact, and improving the purity of the reaction mixture. This workup sequence resulted in a crude reaction mixture containing the nitrone carboxylic acid of intermediate **7** (Scheme 6). The crude mixture was treated with aqueous lithium hydroxide to reform the lithium carboxylate nitrone intermediate **7** (Scheme 6) and extract it into the aqueous phase. The aqueous phase was washed twice with heptane to remove impurities and subse-

quently treated with aqueous citric acid and EtOAc to establish conditions amenable to hydrolysis of the nitrone **7** (Scheme 6). The crude hydroxylamine **8** was ultimately extracted into the EtOAc phase. The EtOAc was replaced with IPA *via* azeotropic distillation, followed by a water addition to induce crystallization of the major diastereomer of hydroxylamine **8** (65% overall yield and 99:1 dr as determined by HPLC). Colorless "irregular block" tetragonal crystals of the major diastereomer of hydroxylamine **8** were found to crystallize from $CDCl_3$, and its absolute configuration was subsequently confirmed by single-crystal X-ray analysis (Scheme 6).[15]

The hydrogenation of **8** with palladium in methanol first removed the benzyl group, followed by reduction of the N−O bond (Scheme 6).[16] After the double reduction was complete, the catalyst was removed by filtration, and MSA was added to induce Fischer esterification which afforded methyl ester **10** in 91% overall yield from hydroxylamine **8**. Direct alkylation of the phenol moiety of **10** with 4-chloromethyl-2-methylquinoline **11** with cesium carbonate to give quinoline adduct **12** was not completely selective, affording a minor byproduct due to alkylation of the primary amine. To counter this problem, a Schiff base (imine) was formed *in situ via* condensation of **10** with *p*-tolualdehyde in refluxing toluene. The imine was concentrated to an oil and redissolved in acetonitrile, followed by the addition of potassium carbonate, catalytic tetrabutylammonium iodide (TBAI), and **11**. The resulting reaction mixture was heated to 70 °C for an hour to give complete consumption of the intermediate imine, and after imine hydrolysis, the free base of **12** was obtained as a yellow oil. The free base of **12** was dissolved in a mixture of MeOH and IPA, and 2 equiv of MSA was slowly added to the mixture to effect crystallization of the bis-MSA salt **12** in 84% yield from **10**. The last chemical transformation required to synthesize **1** was conversion of the methyl ester **12** into the requisite hydroxamic acid. The hydroxamic acid **1** was prepared in 84−87% yield by exposing the methyl ester **12** to hydroxylamine hydrochloride in a mixture of sodium methoxide in methanol.[2e,17,18]

In an attempt to shorten the synthesis, the possibility of replacing the benzyl protection group with the required 2,4-dimethylquinoline of **1** was explored. After investigating this possibility, it was found that the quinoline moiety was labile to the required N−O cleavage reaction conditions and therefore not compatible.

Conclusions

An asymmetric synthesis was discovered[18] and developed to enable the preparation of **1**. The synthesis consists of an efficient sequence of fifteen chemical transformations with only seven isolations of crystalline intermediates in an overall yield of 27%. The quaternary chiral center of **1** was established by diastereoselective enolate amination with the requisite D-leucine serving as the chiral directing group. To enable this chemistry, a safe and "scalable" stock solution form of the electrophilic aminating reagent **6** was developed.[18] This synthesis was selected for the preparation of **1** required to support late-stage clinical development studies.[19]

Experimental Section

General. Melting points were taken by differential scanning calorimetry (DSC). Accurate mass spectra were recorded on a Micromass LCT mass spectrometer (ESI-TOF-MS). Reagents and solvents were purchased and used as received.

(4-Benzyloxyphenyl)acetic Acid Methyl Ester (2). Under a nitrogen atmosphere, methyl-4-hydroxyphenylacetate (1.0 kg, 6.0 mol), potassium carbonate (325 mesh powder, 1.25 kg, 9.0 mol), and acetonitrile (8 L) were charged to a reactor. Benzyl bromide (1.08 kg, 6.3 mol) was charged to the reaction, and the resulting mixture was warmed to 75 °C. After 3 h, HPLC indicated >95A% conversion of the methyl-4-hydroxyphenylacetate to **2**. The reaction was cooled to 20 °C, and the solids were filtered off. The solids were washed with acetonitrile (3 L), and the wash was combined with the original filtrate. The combined solution was heated to reflux and 9−10 L of distillate was removed. Heptane (5 L) was added to the mixture, and the distillation was continued to remove a further 5 L of distillate. The distillation temperature reached 97 °C, indicating that the reaction solvent had been switched from acetonitrile to heptane. Heptane (10 L) was added to the mixture while holding the temperature above 60 °C. The mixture was cooled to 50 °C and seeded with 10 g of (4-benzyloxyphenyl)acetic acid methyl ester **2**. The mixture was held at 50 °C for 30 min before cooling to 3 °C over 3 h. The mixture was held for 30 min, then filtered to obtain the product. The product was washed with cold heptane (3 L) and dried at 45 °C under vacuum to constant weight. The (4-benzyloxyphenyl)acetic acid methyl ester **2** (1.46 kg; 95% isolated yield) had a purity of >99.5A% by HPLC analysis (see reference3 for spectroscopic data on (4-benzyloxyphenyl)acetic acid methyl ester **2**).

2-(4-Benzyloxyphenyl)-4-oxobutyric Acid Methyl Ester (4). Under a nitrogen atmosphere, diisopropylamine (0.35 kg, 3.5 mol) and THF (3.75 L) were charged to a reactor. The resulting mixture was cooled to −70 °C, and 2.5 M *n*-butyllithium in hexanes (1.29 L, 3.2 mol) was added to the mixture, maintaining a reaction temperature below −20 °C. The reaction mixture was warmed briefly to −5 °C to ensure the formation of lithium diisopropylamide (LDA) and cooled back to −70 °C. In a separate vessel under a nitrogen atmosphere, (4-benzyloxyphenyl)acetic acid methyl ester **2** (0.75 kg, 2.9 mol) was dissolved

(13) (a) Smitrovich, J. H.; DiMichele, L.; Qu, C.; Boice, G. N.; Nelson, T. D.; Huffman, M. A.; Murry, J. *J. Org. Chem.* **2004**, *69*, 1903. (b) Smitrovich, J. H.; Boice, G. N.; Qu, C.; DiMichele, L.; Nelson, T. D.; Huffman, M. A.; Murry, J.; McNamara, J.; Reider, P. *J. Org. Lett.* **2002**, *4*, 1963.

(14) (a) Seebach, D.; Bossler, H.; Gründler, H.; Shoda, S.-I. *Helv. Chim. Acta* **1991**, *74*, 197. (b) Miller, S. A.; Griffiths, S. L.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 563. (c) Bossler, H. G.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 1124.

(15) The following crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 237521. http://www.ccdc.cam.ac.uk.

(16) Basheerudddin, K.; Siddiqui, A. A.; Khan, N. H.; Saleha, S. *Synth. Commun.* **1979**, *9*, 705.

(17) Thouin, E.; Lubell, W. D. *Tetrahedron Lett.* **2000**, *41*, 457.

(18) Waltermire, R. E.; Savage, S. A.; Campagna, S.; Magnus, N. A.; Confalone, P. N.; Yates, M.; Meloni, D. J. Asymmetric synthesis of aminopyrrolidinones. (Bristol-Myers Squibb Company, U.S.A.). PCT Int. Appl. WO 2003104220 A1 20031218, 2003, and U.S. Patent 6770763 B2 20040803, 2004.

(19) After further optimization, a large-scale campaign was initiated to support full development. The initial portion of the campaign delivered 450 kg of lactam **5**. Two pilot-scale batches, 20 kg input of lactam **5** per batch, of the key diastereoselective amination were conducted to afford hydroxylamine **8** with >99:1 dr in 56% yield.

in 2.2 L of THF. The THF solution of **2** was slowly charged to the LDA solution while holding the temperature at −70 °C. The resulting mixture was stirred at −70 °C for 1 h while a light-green enolate slurry formed. Allyl bromide (0.46 kg, 3.8 mol) was added to the reactor, and the resulting mixture slowly warmed to −40 °C and stirred for 1 h. A sample was taken for HPLC analysis which indicated >97% conversion of **2**. In a separate vessel, an aqueous solution of dihydrogen sodium phosphate monohydrate (0.75 kg, 5.4 mol) and water (8 L) was prepared. The aqueous phosphate solution was charged to the reaction mixture, allowing the reaction temperature to increase to 20 °C. EtOAc (2.2 L) was charged to the reaction mixture, and after mixing, the layers were allowed to separate. The lower aqueous phase was removed, and the organic layer was washed two times with water (2 × 6 L). Using vacuum distillation at <40 °C, the solution was concentrated until the distillation rate slowed substantially. EtOAc (2.2 L) was charged to the mixture, and the vacuum distillation continued. When the distillation rate slowed substantially, distillation was ceased and a sample of the intermediate 2-(4-benzyloxyphenyl)-pent-4-enoic acid methyl ester **3** was submitted for HPLC analysis. (The area percent of **3** was >90%. Note: if the area percent of **3** is <90%, crystallization of **4** becomes difficult.) The crude 2-(4-benzyloxyphenyl)-pent-4-enoic acid methyl ester **3** was diluted with EtOAc (7.5 L) and the resulting mixture cooled to −50 to −55 °C. Ozone was introduced to the reaction mixture below the surface of the liquid with rapid agitation. (**Caution**: the combination of oxygen and EtOAc can present a fire hazard! To mitigate risk, the outgas stream was diluted with nitrogen gas.) When the solution turned light-gray/blue, a sample was submitted for HPLC analysis which indicated >99A% conversion of **3**. The reaction mixture was warmed to −30 °C while purging with nitrogen to remove excess ozone from solution. Acetic acid (0.75 L) and water (0.75 L) were added to the reaction mixture, followed by zinc (the zinc used was ∼325 mesh, 99.9% pure). The temperature was kept between −10 and −20 °C during the addition of four portions of zinc (total of 0.37 kg, 5.6 mol of zinc added). Note: we waited a minimum of 20 min between additions of zinc to avoid large exotherms). After the zinc additions were complete, the mixture was stirred at 0 to −10 °C for 30 min. A sample was submitted for HPLC analysis which indicated >99.8A% conversion of the ozonide. At 0 to −10 °C, the reaction mixture was filtered through a 3-in. bed of Celite. The Celite/zinc cake was washed with EtOAc (3.0 L), the resulting filtrates were combined and washed two times with water (2 × 4.5 L). Aqueous sodium bicarbonate (4 wt %) (5 L) was combined with the organic phase and the resulting mixture stirred for 15 min to give a pH of >7. The aqueous layer was removed, and vacuum distillation at <30 °C was employed to reduce the volume of the organic phase by approximately 4 L. Heptane (6 L) was charged to the mixture, and the vacuum distillation was continued to give an ending volume of approximately 8 L. A sample was removed for GC analysis, which indicated <20% EtOAc by volume when compared to a reference solvent mixture. The mixture was cooled to 0−10 °C and stirred for 1 h; the product was filtered off, washed with heptane (3 L), and dried under vacuum to constant weight at 45 °C. The title aldehyde **4** (698 g; 80% isolated yield) was afforded as a tan solid. Mp (DSC) (10 °C/min) onset 70.68 °C, peak 84.58 °C. IR (KBr pellet) 3441, 2952, 2833, 2727, 1729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, s), 7.46−7.34 (5H, m), 7.22 (2H, d, J = 8.8 Hz), 6.96 (2H, d, J = 8.8 Hz), 5.07 (2H, s), 4.11 (1H, dd, J = 5.0, 9.6 Hz), 3.69 (3H, s), 3.39 (1H, dd, J = 9.6, 18.7 Hz), 2.81 (1H, dd, J = 5.0, 18.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 173.4, 158.1, 136.7, 129.8, 128.7, 128.5, 127.9, 127.3, 115.0, 69.8, 52.2, 47.2, 43.8. HRMS (ESI) calcd for $C_{18}H_{19}O_4$ (M^+) 299.128, found 299.128.

1-((R)-2-Amino-4-methylpentanoic acid)-3-(4-benzyloxyphenyl)pyrrolidin-2-one (5). Under a nitrogen atmosphere, aldehyde **4** (628 g; 2.1 mol) was dissolved in diethoxymethane (DEM) (6 L), and D-leucine methyl ester hydrochloride (419 g; 2.31 mol) was added, followed by diisopropylethylamine (320 g; 2.48 mol). The resulting mixture was stirred at 20 °C for 30 min and treated with sodium triacetoxyborohydride (540 g; 2.55 mol), giving a temperature rise to 31 °C. After 1 h, HPLC indicated complete consumption of the starting material. The resulting mixture was washed with water (2 × 4 L) and heated to reflux. Distillate (2 L) was removed, and at a pot temperature of 82 °C the reaction was held for 14 h giving complete lactamization by HPLC. The reaction mixture was cooled to 5 °C, and aqueous LiOH (60 g; 2.5 mol in 1 L water) and MeOH (1.5 L) were charged to the reaction. The resulting mixture was warmed to 20 °C, and held for 4 h. HPLC indicated >95A% conversion to γ-lactam **5**. The pH was adjusted to between 2 to 3 with 1 N HCl and EtOAc (2 L) was charged. The aqueous layer was removed, and the organic layer was washed with water (2 × 3 L), concentrated *via* distillation to 3.5 L, and held at 65 °C. Heptane (3 L) was slowly added while holding at 65 °C. After 1 h, the resulting slurry was slowly cooled to 20 °C and held for 4 h. The solids were filtered and washed with 30% EtOAc/heptane (1 L) and finally with heptane (2 × 1 L). The product was dried to constant weight at 50 °C giving γ-lactam **5** (692 g: 86% isolated yield) with a purity of >99.5A% by HPLC analysis as a tan powder. Mp (DSC) (10 °C/min) onset 129.52 °C, peak 131.55 °C. IR (KBr pellet) 3449, 2958, 2873, 2583, 1735, 1632 cm^{-1}. Mixture of diastereomers: ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (1H, bs), 7.46−7.33 (5H, m), 7.22 (1H, d, J = 8.6 Hz), 7.17 (1H, d, J = 8.6 Hz), 6.96 (2H, d, J = 8.6 Hz), 5.07 (1H, s), 5.05 (1H, s), 4.92 (1H, dd, J = 8.0, 15.6 Hz), 3.75 (1H, m), 3.62 (1H, m), 3.42, (1H, m), 2.54 (1H, m), 2.12 (1H, m), 1.81 (2H, m), 1.55 (1H, m), 0.99 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 174.7, 174.4, 157.7, 136.8, 131.9, 131.5, 129.1, 128.8, 128.4, 127.7, 127.3, 114.9, 69.8, 52.4, 47.4, 42.3, 42.0, 37.3, 36.8, 28.5, 28.3, 24.9, 23.0, 21.1, 20.9. HRMS (ESI) calcd for $C_{23}H_{28}NO_4$ (M^+) 382.201, found 382.202.

1-Chloro-1-nitrosocyclopentane (6). Under a nitrogen atmosphere, cyclopentanone oxime (600 g, 6.06 mols), and MTBE (4.0 L) were combined. The reaction vessel was marked at the solvent line for later reference, and the agitation was started. After obtaining a solution, the mixture was held at 20−25 °C. *Safety Note*: The following addition was exothermic, and the reactor was vented to an aqueous NaOH scrubber. The NaOH charge to the scrubber was 5 times the excess of chlorine gas (1 equiv of the chlorine was consumed by the cyclopen-

tanone oxime which produced 1 equiv of HCl, and the chlorine gas had a maximum excess of 0.3 equiv). Chlorine (roughly 600 g, 8.46 mols) was charged to the reaction mixture through a glass frit. (Note: lighting was kept as subdued as possible due to the light-sensitive product). The chlorine addition produced a deep-blue color and was charged at a rate to keep the temperature between 20−35 °C. Good agitation was needed because a thick slurry was produced during the addition. The reaction was complete when the mixture returned to homogeneous and a halo of green (chlorine) was observed on the reaction surface. The reaction was sparged with nitrogen to remove any excess chlorine and HCl. The mixture was cooled to 0−10 °C, and 2 N NaOH (4 to 5 L) was added at a rate that kept the temperature between 0 to 25 °C until the pH was constant at 14 (Note: The 2 N NaOH addition produced an exotherm). The phases were separated, and the bottom aqueous phase was removed. The organic phase was washed twice with water (2 × 5.0 L) at 0−25 °C. The reactor was set up for vacuum distillation with a Dean−Stark trap in place and an addition funnel to add MTBE. (Note: the reaction volume was not reduced below the starting volume of roughly 4 L marked on the vessel after the initial oxime/MTBE charge due to the enhanced stability of the product when diluted.) An initial volume of MTBE ((needs to be <150 ppm water) or azeotropic distillation was futile)) was charged to the mixture equal to the volume of the Dean−Stark trap. During the vacuum distillation, MTBE was charged to the vessel at roughly the same rate as it was being distilled off, between 40 to 50 °C (the distillate had a light-blue color). The Dean−Stark trap was emptied periodically, and after 8 L was removed, the reaction was checked by Karl Fischer titration for water (criteria for completion was <150 ppm water). If the criteria were not met, the analysis was repeated after every 4 L of distillate was collected until the criteria were met. It was important that the weight and volume of the reactor contents were measured, so that a weight percent strength of the product could be estimated. The final volume was roughly 4.0 L and was charged to amber glass bottles, leaving as little head space as possible. Nitrogen was blown into the head space, and the bottles were capped and parafilmed (stored in a refrigerator at <7 °C in the dark). A quantitative yield was assumed.

(R)-3-Aminohydroxy-1-((R)-2-amino-4-methylpentanoic acid)-3-(4-benzyloxyphenyl)pyrrolidin-2-one (8). Under a nitrogen atmosphere, LiCl (30 g; 708 mmol) was charged to a vessel, followed by THF (1.05 L). The resulting mixture was stirred at 20 °C for 30 min at which point the mixture was almost homogeneous. γ-Lactam **5** (45 g; 118 mmol) was added, and the mixture cooled to −50 °C. *n*-Butyllithium (2.5 N; 97.2 mL; 242 mmol) in hexanes was added over 30 min, and the resulting mixture cooled to −70 °C. To the reaction mixture an estimated 23.5 wt % solution of **6** (113.2 mL; 153 mmol) in MTBE was added over 30 min (HPLC indicated >95A% conversion and a 13:1 diastereomer ratio), followed by a THF solution of MSA (8 mL; 124 mmol; in 90 mL of THF) over 15 min. Trimethylphosphite (12.52 mL; 106.17 mmol) was added to the reaction mixture, followed by warming to 0 °C over 30 min, and holding for an additional 30 min. An aqueous lithium hydroxide solution (4.3 g; 177 mmol; in 1.35 L of water) was added to the reaction mixture (aqueous pH >12), followed by heptane (400 mL). After vigorous mixing, the phases were separated, and the aqueous phase was washed with a further 300 mL of heptane. EtOAc (450 mL) was added to the aqueous phase, and the resulting mixture was warmed to 30 °C with vigorous mixing. Aqueous citric acid (10%; 250 mL) was added to the mixture until pH 3.6 was reached. After 30 min of vigorous mixing to effect hydrolysis of the nitrone intermediate **7**, the organic phase was separated and washed with brine (500 mL water + 100 mL saturated aqueous brine), and the solvent was exchanged for IPA *via* azeotropic distillation (final volume of 400 mL). The reaction mass was held at 60 °C, and water (600 mL) was added to the mixture over 2.0 h, inducing precipitation. The resulting slurry was cooled to 20 °C over 2.0 h, filtered, and washed with 40% IPA/water (2 × 100 mL). After drying at 70 °C to constant weight, the product hydroxylamine **8** (32.0 g; 65% isolated yield) was afforded as a light-yellow solid, as a single diastereomer as determined by HPLC and NMR. The absolute stereochemistry of hydroxylamine **8** was confirmed by single-crystal X-ray analysis.[15] Mp (DSC) (10 °C/min) onset 140.63 °C, peak 147.46 °C. IR (KBr pellet) 3378, 2968, 2878, 1692 cm^{-1}. Single diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, s), 7.45−7.37 (5H, m), 7.33 (2H, d, J = 8.8 Hz), 6.94 (2H, d, J = 8.8 Hz), 5.09 (2H, s), 4.71 (1H, dd, J = 4.0, 11.6 Hz), 3.34−3.20 (4H, m), 2.63−2.56 (1H, m), 2.13−2.09 (1H, m), 1.81−1.74 (1H, m), 1.62−1.49 (2H, m), 0.92 (3H, d, J = 6.6 Hz), 0.87 (3H, d, J = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 172.6, 157.6, 137.1, 132.3, 128.4, 127.9, 127.7, 127.5, 114.3, 70.5, 69.1, 51.8, 39.0, 36.3, 29.7, 24.1, 23.1, 21.0. HRMS (ESI) calcd for C_{23} H_{29} N_2O_5 (M^+) 413.209, found 413.209. $[\alpha]_D$ (25 °C) −29.0 (*c* 1.064, MeOH).

(R)-3-Amino-1-((R)-2-amino-4-methylpentanoic acid methyl ester)-3-(4-hydroxyphenyl)pyrrolidin-2-one (10). Under a nitrogen atmosphere, hydroxylamine **8** (10 g; 24.27 mmol) was suspended in MeOH (250 mL) and heated to 40 °C for 30 min giving a homogeneous mixture. Palladium on carbon (6.0 g; 54% wet; 8% palladium based on dry weight; 220 mg Pd; Degussa) was charged to the reaction, and the nitrogen was replaced with hydrogen. The reactor pressure was increased with hydrogen to 60 psi and returned to atmospheric pressure three times, and finally held at 60 psi. After 3.5 h, HPLC indicated complete conversion to the corresponding phenol/primary amine intermediate. The reaction mixture was cooled to 25 °C, and filtered through a bed of Celite on filter paper. The clarified mixture was held at 25 °C, and treated with MSA (3.15 mL; 48.54 mmol). After 18 h, HPLC indicated complete conversion to the title ester **10**. The resulting mixture was neutralized with saturated aqueous sodium bicarbonate and extracted with dichloromethane (2 × 500 mL). After drying the organic phase with sodium sulfate and removing the solvent *in vacuo*, a white solid was obtained. Drying the white solid at 50 °C and 25 inHg to constant weight afforded ester **10** (7.0 g; 91% isolated yield). The product was recrystallized from EtOAc/heptane to give colorless needles as an EtOAc solvate. Mp (DSC) (10 °C/min) onset 62.23 °C, peak 73.61 °C. IR (KBr pellet) 3406, 3358, 3298, 3144, 2964, 2874, 1746, 1688 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, d, J = 8.8 Hz), 6.62 (2H, d, J = 8.8 Hz), 5.00−4.96 (1H, m, apparent J = 7.6 Hz), 3.98 (3H, bs), 3.70

(3H, s), 3.38−3.29 (2H, m), 2.51−2.46 (1H, m), 2.18−2.10 (1H, m), 1.81−1.77 (2H, m, apparent $J = 7.6$ Hz), 1.56−1.49 (1H, m), 0.99 (3H, d, $J = 4.5$ Hz), 0.97 (3H, d, $J = 4.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 171.3, 156.0, 132.5, 126.7, 115.5, 62.8, 52.4, 52.1, 39.6, 36.8, 36.6, 24.6, 23.0, 21.1. HRMS (ESI) calcd for C_{17} H_{25} N_2O_4 (M^+) 321.181, found 321.181. $[\alpha]_D$ (25 °C) −6.4 (*c* 0.962, MeOH).

(R)-3-Amino-1-((R)-2-amino-4-methylpentanoic acid methyl ester)-3-[4-(4-methanol-2-methylquinoline)phenyl]pyrrolidin-2-one-bis-mesylate (12). Under a nitrogen atmosphere, ester **10** (1.0 g; 3.13 mmol) was dissolved in toluene (10 mL), and *p*-tolualdehyde (380 μL, 3.13 mmol) was added to the mixture. A Dean−Stark trap (prefilled with dry toluene) was fitted to the reactor, and the mixture heated to reflux for 1 h to remove water. The trap was emptied, and the reaction mixture cooled to 40 °C. The pressure was reduced to 60 mbar to remove toluene by distillation to afford the intermediate imine (confirmed by HPLC and MS) as a colorless oil. At atmospheric pressure and 20 °C, the oil was taken up in acetonitrile (10 mL), and potassium carbonate (864 mg; 6.25 mmol) was added, followed by TBAI (115 mg; 0.31 mmol). 4-Chloromethyl-2-methyl-quinoline **11** (605 mg; 3.15 mmol) was added to the reaction mixture, and the temperature increased to 70 °C. After 1 h, HPLC indicated a complete conversion to quinoline adduct **12**. The reaction mixture was cooled to 20 °C, and 1N HCl (20 mL) was added (aqueous pH 1). The resulting mixture was washed with EtOAc (2 × 10 mL), and subsequently neutralized with saturated aqueous sodium bicarbonate. Extraction with EtOAc (2 × 40 mL), drying with sodium sulfate, and removing the solvent *in vacuo* gave a pale-yellow oil. The oil was dissolved in 10% MeOH/IPA (20 mL) and heated to 50 °C. Slow addition of MSA (405 μL; 6.25 mmol) at 50 °C caused a precipitate to form, and subsequently, the reaction was cooled to 20 °C over 1 h. The solids were filtered, rinsed with IPA (2 × 10), and dried at 50 °C and 25 inHg for 18 h. The bis-MSA salt of quinoline adduct **12** (1.25 g; 84% isolated yield) was isolated as a white crystalline solid. Mp (DSC) (10 °C/min) onset 251.32 °C, peak 252.82 °C. IR (KBr pellet) 3449, 3008, 2959, 2733, 2515, 2186, 1747, 1704 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11−9.02 (2H, m), 8.46 (1H, d, $J = 8.3$ Hz), 8.25 (1H, d, $J = 8.3$ Hz), 8.13 (1H, dd, $J = 7.6$ Hz), 8.09 (1H, s), 7.94 (1H, dd, $J = 7.6$ Hz), 7.57 (2H, d, $J = 8.6$ Hz), 7.37 (2H, d, $J = 8.6$ Hz), 5.93 (2H, s), 4.78 (1H, dd, $J = 4.5, 11.6$ Hz), 3.60 (3H, s), 3.52−3.47 (1H, m), 3.23−3.17 (1H, m), 2.97 (3H, s), 2.72−2.68 (1H, m), 2.50−2.43 (1H, m), 2.35 (6 H, s), 1.88−1.80 (1H, m), 1.69−1.59 (1H, m), 1.58−1.53 (1H, m), 0.95 (3H, d, $J = 6.6$ Hz), 0.92 (3H, d, $J = 6.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.5, 158.0, 153.1, 137.3, 134.0, 128.9, 128.4, 127.9, 125.0, 123.6, 121.0, 120.2, 115.3, 66.0, 62.1, 52.3, 52.0, 40.1, 39.8, 38.8, 36.0, 32.1, 23.7, 23.1, 21.0, 20.9. HRMS (ESI) calcd for C_{28} H_{34} N_3O_4 (M^+) 476.254, found 476.256. $[\alpha]_D$ (25 °C) −16.3 (*c* 1.228, MeOH).

Note: for conversions of the methyl ester **12** into hydroxamic acid **1** see references 2e, 17, and 18.

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