The Power of Visual Imagery in Synthesis Planning. Stereocontrolled Approaches to CGP-60536B, a Potent Renin Inhibitor

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Two strategies were developed toward the stereocontrolled synthesis of 8-aryl-3-hydroxy-4-amino-2,7-diisopropyloctanoic acids with predetermined stereogenic centers. This is a generic motif in a new class of potent inhibitors of the enzyme renin, exemplified by CGP-60536B. The synthesis relies on the utilization of L-pyroglutamic acid as chiron, and proceeds through the incorporation of required functionality by exploiting internal induction. One of the strategies shows the power of visual imagery in synthesis planning, akin to a Dali-like representation of objects that can be viewed in more than one way. Thus, the entire carbon skeleton of the target molecule is encompassed in a partially functionalized bicyclic indolizidinone precursor. In a second strategy, an intermediate common to the first approach is elaborated into an appended γ-lactone which is alkylated through enolate chemistry and ultimately transformed into the intended target compound. X-ray crystallography was used to corroborate the structures and stereochemistries of several intermediates.

Introduction

The aspartic protease renin[1] has been associated with the cascade of events involving the selective cleavage of a Leu−Val bond in angiotensinogen to angiotensin I, in the so-called renin−angiotensin system (RAS). Further enzymatic cleavage produces the octapeptide angiotensinogen II, a vasoconstricting peptide resulting eventually in hypertension in man.[2] A major advance was made in 1982 when renin inhibitors were synthesized on the basis of a transition-state structure to replace the scissile bond.[3] Dipeptide hydroxyethylene and related isosteres of the Leu−Val bond in the natural substrate were actively pursued by many groups.[4] Intensive efforts on the chemical and biological fronts followed over the past two decades, leading to a better understanding of the molecular events involved in the release of renin in animal models, and its inhibition by designed transition-state-based inhibitors.[5] Nonpeptidic inhibitors of renin based on substituted piperidines with remarkable activity have been reported.[6] The amide backbone of renin inhibitors has been replaced with nonpeptidic vinylogous amides showing low micromolar inhibition in vitro.[7] Several drug candidates were successfully developed

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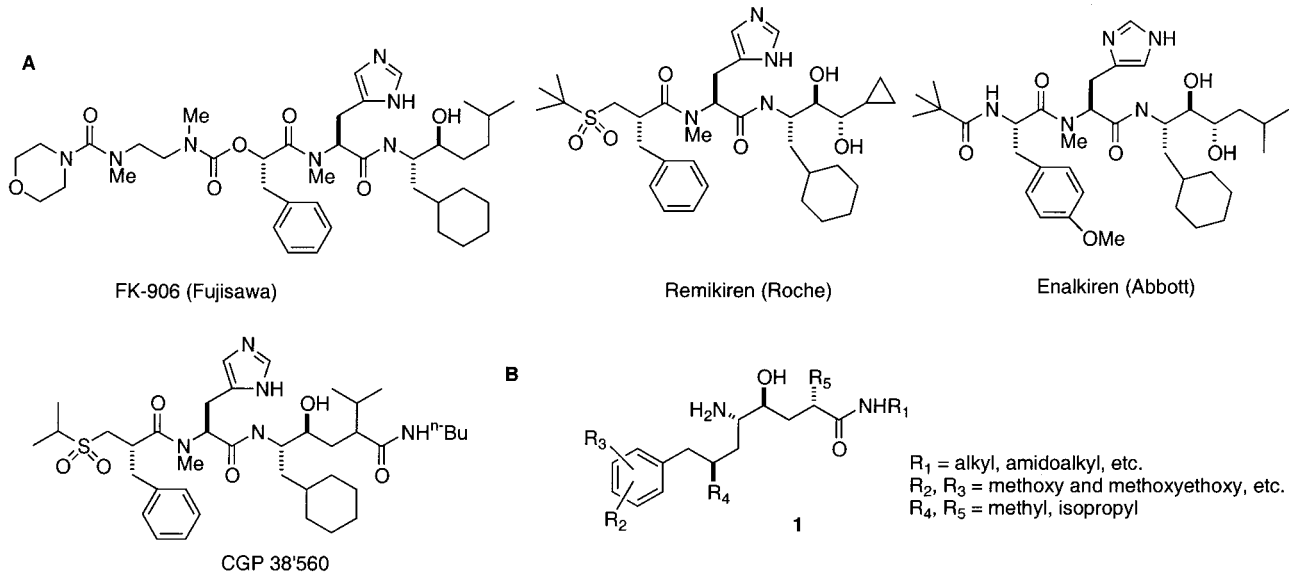

Figure 1.

worldwide, culminating with compounds that exhibited potent in vitro and in vivo activities, although good bioavailability remained as a major challenge. Unfortunately, these programs were eventually terminated virtually in every pharmaceutical company, primarily for strategic marketing reasons. Although good pharmacokinetics and excellent antihypertensive activity were achieved with some compounds in experimental animals, a major obstacle was concerned with oral bioavailability in man, and in devising cost-effective syntheses. The structures of some of these compounds, harboring four or more stereogenic centers, with heterocyclic, alkyl, and hydroxy appendages on a peptidic backbone are shown in Figure 1A. More recently, a new class of inhibitors having the general structure **1** (Figure 1B), and exhibiting sub-nanomolar specific binding affinity to human renin, with excellent oral activity in primates, was reported.[8] The generic structure **1**, varying in the nature of the aromatic substituents, the amide moiety, and the alkyl groups, represents a novel carbon backbone with unique binding affinities to renin. Of particular significance was the nonpeptidic nature of the truncated tetrasubstituted 8-aryloctanoic acid amide backbone in **1**, in which the P_1–P_4 units of peptide-type inhibitors (Figure 1B) were modified by directly linking P_1–P_3 moieties as shown in another series.[9,10] X-ray crystal structure data of recombinant glycosylated renin with a representative analogue of **1** revealed favorable hydrophobic and hydrogen-bonding interactions within the S_3–$S_{2'}$ subsites, which were not utilized by peptidic inhibitors.[11] Extensive optimization of the backbone appendages in the 8-aryloctanoic acid motif revealed a distinct preference for two isopropyl groups with 2*R*,7*R*-configurations rather than methyl or combinations thereof, as indicated in the generic structure **1**.[11]

Very recently, two synthesis routes to CGP-60536B, an analogue of **1** (where R_1 = 2,2-dimethylpropionamide, R_2, R_3 = dialkoxy; R_4, R_5 = isopropyl), representing original efforts at ex.Ciba-Geigy in Basel[12] and the U.K.,[13] respectively, were published. Both groups utilized a convergent approach where a derivative of 2*R*-isopropyl-4*R*-hydroxymethylbutyrolactone, obtained by auxiliary-mediated asymmetric alkylation[14] of appropriate amide enolates, was a key chiron. Despite the need for chromatographic separation of mixtures of diastereomers, it was possible to develop viable routes to the target structure. The source of nitrogen in the β-hydroxy amino alcohol portion of **1** was azide ion, introduced via an S_N2-type inversion of a suitably protected diol intermediate. A third synthesis was based on nitrone chemistry, and led to the target compound as a minor diastereomer.[15] A synthesis of *N*-substituted 2,7-dialkyl-4-hydroxy-5-amino-8-aryloctanoylamides has been reported in the recent patent literature.[16]

We report herein a full account of our efforts toward the development of stereocontrolled synthesis routes aimed at the generic structure **1**, while allowing flexibility for variations in the aromatic substituents and the nature of the amide moiety. In considering various practical approaches, we chose to capitalize on a synthesis plan that utilizes readily available *N*-containing chiral templates as starting materials, thus avoiding the potential hazards of azide reagents. Added to this daunting task was the desire to combine practicality with innovation, even if the project was an academically based endeavor.[17]

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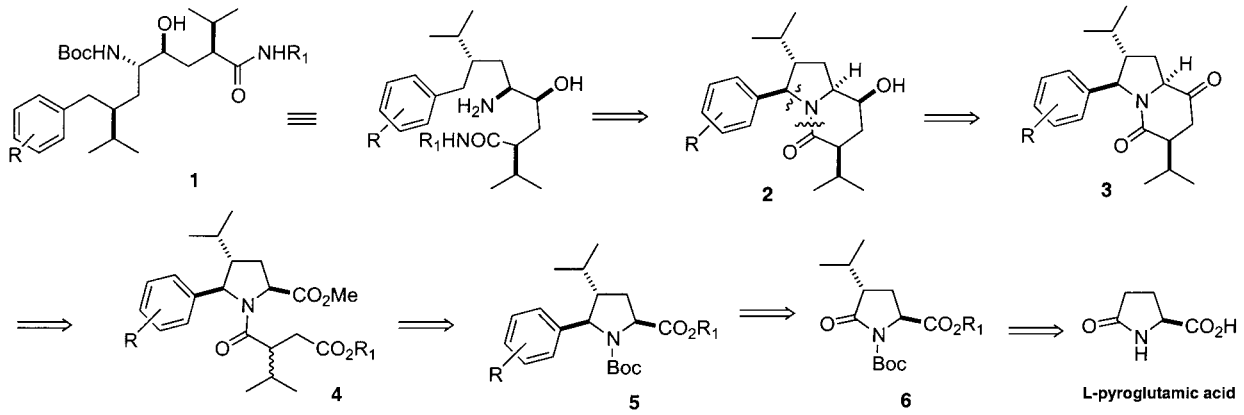

Figure 2.

The retrosynthetic analysis of an 8-aryl-2*R*-isopropyl-3*S*-hydroxy-4*S*-amino-6*S*-isopropyloctanoic acid amide representing the prototypical structure of **1** ($R_2 \simeq$ H, *p*-methoxy; $R_3 \simeq$ H; R_4, R_5 = isopropyl) is shown in Figure 2. Inspection of the generic backbone structure of **1** with the required substituents reveals that it may be derived from **2** by two logical disconnections, involving cleavage of the lactam and the hydrogenolysis of the *N*-benzyl bond in the pyrrolidine motif (Figure 2). The alcohol **2** may, in turn, be obtained by a simple diastereoselective reduction of ketolactam **3**, originating from an intramolecular Dieckmann cyclization reaction between the two ester moieties of **4**. To simplify the process, our original plan called for the utilization of a racemic 2-isopropyl succinate side chain as in **4**, with the hope that the correct stereochemistry could be attained by equilibration of the unwanted isomer en route to the intended target **3**. Amide **4** would be obtained from the pyrrolidine **5**, itself synthesized from pyrrolidinone **6** via the diastereoselective addition of aryl cuprates[18] to an intermediate iminium ion precursor.[19] Finally, pyrrolidinone **6** would be prepared from the readily available L-pyroglutamic acid[20] by a stereocontrolled introduction of the isopropyl group. The synthesis plan shown in Figure 2 presented a number of practical advantages, in addition to being innovative in design.

The principle of using conformational constraint to control stereochemistry, as well as to avoid protective group manipulations, is particularly noteworthy in this strategy. It is also of heuristic interest to point out the value of visual imagery in synthesis planning.[21] Depicting the familiar acyclic representation of the target structure **1** as one whose backbone overlaps better *visually* with the bicyclic lactam **2** reveals a strategy that may not have been so obvious otherwise. Once assembled as **2**, it would suffice to cleave two bonds, thereby unveiling the intended acyclic target structure **1**. Attractive as this Dalièsque synthetic plan appeared to be,[22] it was imperative to test its feasibility, particularly as related to stereochemistry issues and overall efficacy.

Results

The first task in this synthesis was the introduction of the 2*R*-isopropyl group in a suitably protected L-pyroglutamic acid. Unlike many examples of lactam enolate alkylations with reactive halides such as methyl, benzyl, or allyl in a pyroglutamic ester motif,[23] the introduction of an isopropyl group has few precedents.[24] In fact, the treatment of the lithium, potassium, or magnesium enolates of *N*-Boc-L-pyroglutamic acid methyl ester **7** (Scheme 1) with isopropyl iodide failed to give any of the desired 4-isopropylated lactam. We were successful in adding acetone to the lithium enolate of **7** to give **8** in 85% yield as a 5:1 mixture of *anti*- and *syn*-isomers, respectively, with no evidence of racemization of the ester.[25] The diastereoselectivity of the acetone addition reaction could be raised to >10:1 in favor of the desired *anti*-isomer by using the bulkier benzylhydryl ester to direct the approach of the electrophile. It was decided to proceed with the methyl ester and to separate diastereomers further downstream. Moreover, we surmised that the methyl ester would be a better intermediate in the intended intramolecular Dieckmann condensation. Thus, protection of the tertiary alcohol of the 5:1

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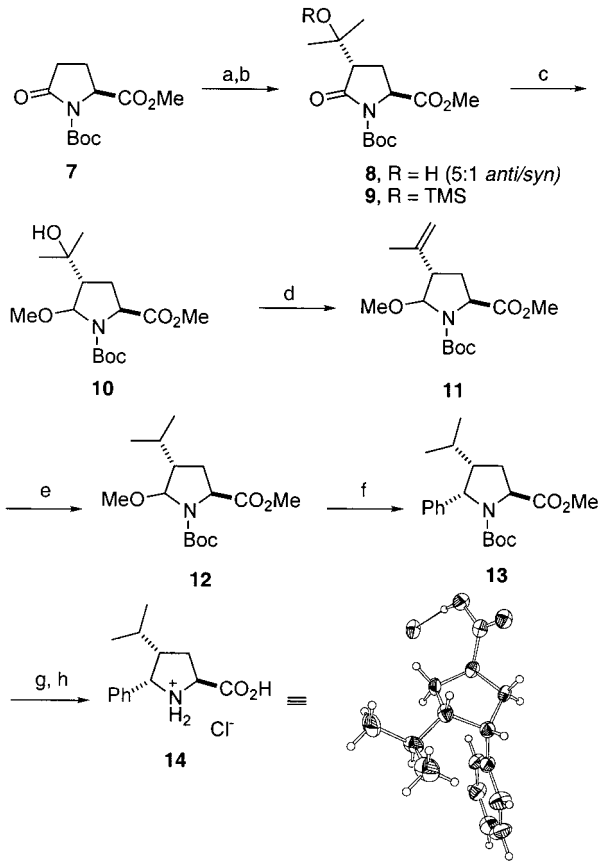
Scheme 1[a]



[a] Reagents and conditions: (a) LiHMDS, −78 °C, THF, then acetone, 85%; (b) TMSCl, imidazole, DCM, 70%; (c) DIBAL, −78 °C, THF, then MeOH, pTSA, 95%; (d) MsCl, DMAP, Et_3N, 72%; separation of minor *syn*-isomer; (e) H_2, Pd/C, EtOAc, $NaHCO_3$, 82%; (f) PhMgBr, CuBr−Me_2S, BF_3·OEt_2, THF, 89%; (g) LiOH, THF/H_2O; (h) HCl, dioxane, 80% (two steps).

mixture of diastereomers **8** as a TMS ether afforded **9**, which was reduced with DIBAL-H to give the corresponding mixture of hemiaminals. Subsequent treatment with acidic methanol afforded the methoxy analogue **10** in high overall yield. Mesylation of **10**, followed by base-catalyzed elimination, proceeded regioselectively to give the alkene **11** exclusively, which could be separated from the minor *syn*-2-propenyl isomer by chromatography. Hydrogenation over Pd/C in the presence of sodium carbonate gave the desired *O*-methyl hemiaminal **12** in excellent yield. An alternative synthesis of **12** in our laboratory relied on a radical-induced deoxygenation[26,27] of the half methyloxalate ester of **8**.[28] Thus, we had successfully introduced an isopropyl group with the desired regio- and enriched stereochemistry in six high-yielding steps starting from the readily available **7**. The next task was to explore methods for the introduction of an aryl group following the synthesis plan outlined in Figure 1. We focused on introducing phenyl and *p*-methoxyphenyl groups as prototypes, and further exploring chemistry toward the elaboration of the generic structure **1**. Thus, treatment of **12** with 4 equiv of a mixture of phenylmagnesium bromide, copper bromide−dimethyl sulfide complex, and boron trifluoride diethyl etherate[18i] resulted in the formation of an adduct, **13**, in 89% yield (Scheme 1). Deprotection of the *N*-Boc and ester groups afforded a crystalline proline analogue, **14**, whose structure was ascertained by single-crystal X-ray crystallography. Contrary to expectations based solely on steric effects, the phenyl group had been introduced from a trajectory of attack on the intermediate iminium ion that was *opposite* the ester group and *syn* to the isopropyl group. The coordination of the ester group with the excess organometallic reagent, coupled with a possible conformational change as a result of such a steric encumberment, may explain the observed result. It is of interest that the steric effect imposed by the 4-isopropyl group is counterbalanced by the bulk of the coordinated ester in directing the attack on the iminium ion. The formation of *anti*-adducts in the reaction of *N*-Boc iminium ions derived from L-pyroglutamic esters with organocopper reagents has been rationalized on the basis of complexation with the ester, resulting in a shielding of the *syn*-face.[18c,d,h] This tendency also overrides the 1,2-induction of a C-4 substitutent,[18h] as observed in the case of **13**. However, exceptions to this stereochemical course of *anti*-addition can be found.[18a]

In an alternative approach, we opted to introduce the phenyl group prior to deoxygenation of the tertiary alcohol (Scheme 2). In this strategy one would expect the nucleophile to approach the iminium ion from the side opposite the bulky metal alkoxide organic complex, provided excess reagent was used. Thus, treatment of **10** with 5 equiv of the phenylmagnesiocuprate reagent gave the corresponding adduct **15** in 55% yield as a 5:1 mixture of diastereomers. Reaction of the alcohol with mesyl chloride, triethylamine, and DMAP gave the corresponding alkene **17**, which could be separated from the minor *syn*-isomer by column chromatography. Catalytic hydrogenation afforded **19** as a single isomer in high overall yield. There was no evidence of any product arising from ring opening by hydrogenolysis. Hydrolysis of the ester with lithium hydroxide gave the acid **21**, which after X-ray analysis showed that the phenyl group had, in fact, added to the iminium ion in an *anti* fashion to the alkoxy isopropyl group. The same sequences were performed in the *p*-methoxyphenyl series to give **16**, which was further transformed to **20** as described for the phenyl analogue (Scheme 2). With both 4,5-*syn*-proline **14** and 4,5-*anti*-prolines **19** and **20**, available in enantiopure form, we turned to the introduction of the second isopropyl group and to test the prospects of a Dieckmann cyclization.[29] It was interesting that a cursory literature search for carrying out the synthesis of substituted indolizidinones such as **3** (Figure 2) by a Dieckmann cyclization showed no precedents,[30] which heightened our interest to pursue this strategy. The more directly accessible 4,5-*anti*-proline analogue **19** was investigated. Removal of the Boc group, and converting the resulting product to the monobenzyl 2-isopropylsuccinamide **22** proceeded smoothly to give a 1:1 mixture of diastereomers (Scheme 3).

Subsequent treatment with KHMDS at −50 °C gave a bicyclic product, **23**, which after hydrogenolysis and decarboxylation was converted to **24**, isolated as a single isomer in only 30% yield. Numerous attempts at improving the yield by variations of bases proved futile. Having reached this stage in our planned sequence, we decided to continue the synthesis despite this apparent setback.

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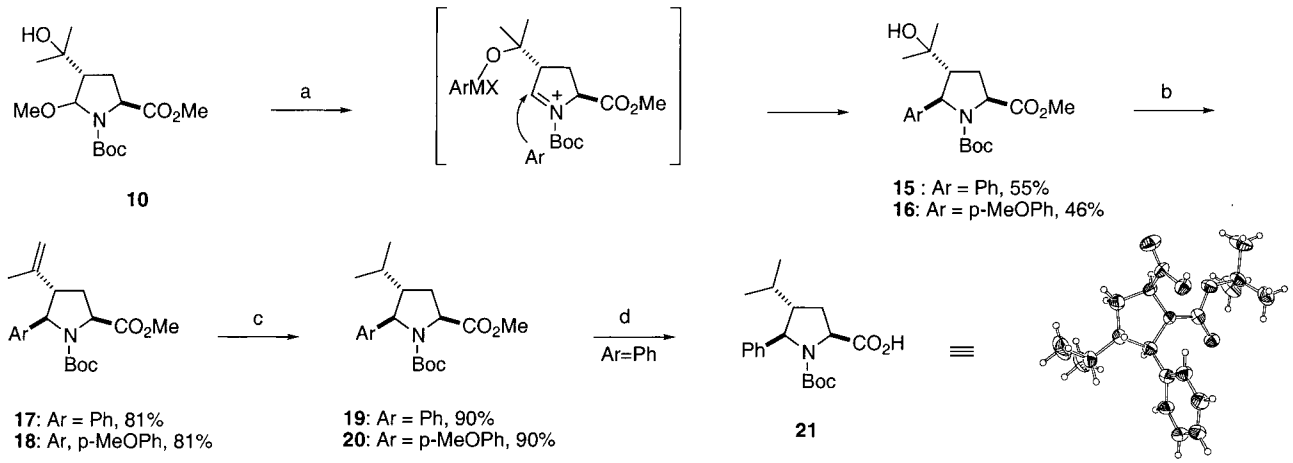
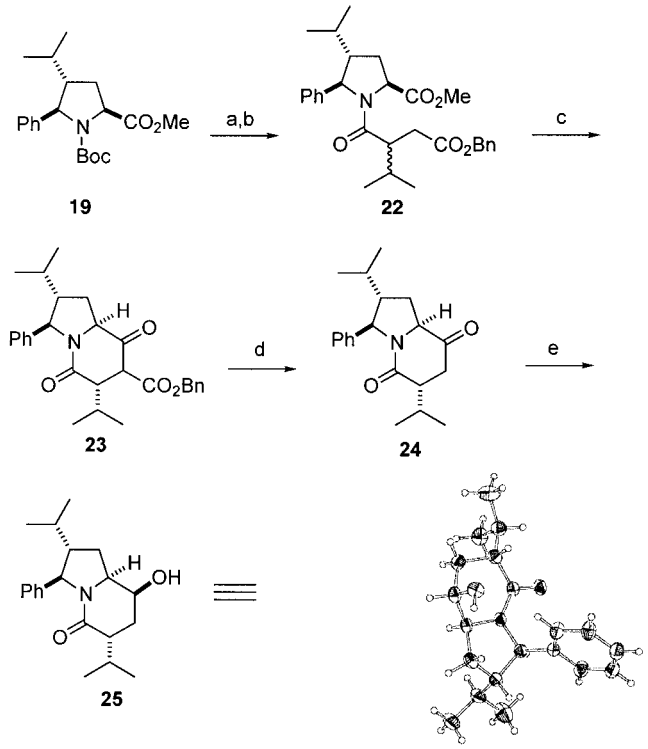
Scheme 2[a]



[a] Reagents and conditions: (a) PhMgBr (or *p*-$MeOC_6H_4Li$, CuBr−Me_2S, BF_3·OEt_2, THF; (b) MsCl, DMAP, Et_3N; (c) H_2, 10% Pd/C, EtOAc; (d) LiOH, MeOH, H_2O, 95%.

Reduction of the carbonyl group in **24** with L-Selectride gave the corresponding alcohol whose structure and absolute stereochemistry were definitively shown to be **25** on the basis of a single-crystal X-ray analysis. Except for an important stereochemical caveat revealed in the opposite orientation of the new isopropyl group, we had indeed succeeded in elaborating the entire carbon skeleton and required functionalities in **1**. Each chemical step leading to the bicyclic product **25** had proceeded with excellent stereoselectivity, thus validating to a large measure our original synthetic plan (Figure 2). Attempts to epimerize the 2*S*-isopropyl-bearing carbon using a variety of conditions[31] resulted in the recovery of starting material with no trace of the desired epimer. A simple rationalization of the results is illustrated in Scheme 4. On the basis of the presence of equal proportions of amides **22a** and **22b**, it is clear why isomer **23**, possibly arising from a hypothetical chairlike conformation in the *pro-S*-isomer **22a** with a predisposed pseudoequatorial isopropyl group, is the observed product. An analogous pathway from the enolate formed from the desired *pro-R*-isomer **22b** would be unfavorable (Scheme 4).

Scheme 3[a]



[a] Reagents and conditions: (a) TFA, toluene, 95%; (b) BOPCl, $^iPr_2NEt$, $HO_2CCH(CHMe_2)CH_2CO_2Bn$, 85%; (c) KHMDS, THF, −50 °C; (d) H_2, Pd/C, 30% (two steps); (e) L-Selectride, THF, −78 °C, 60%.

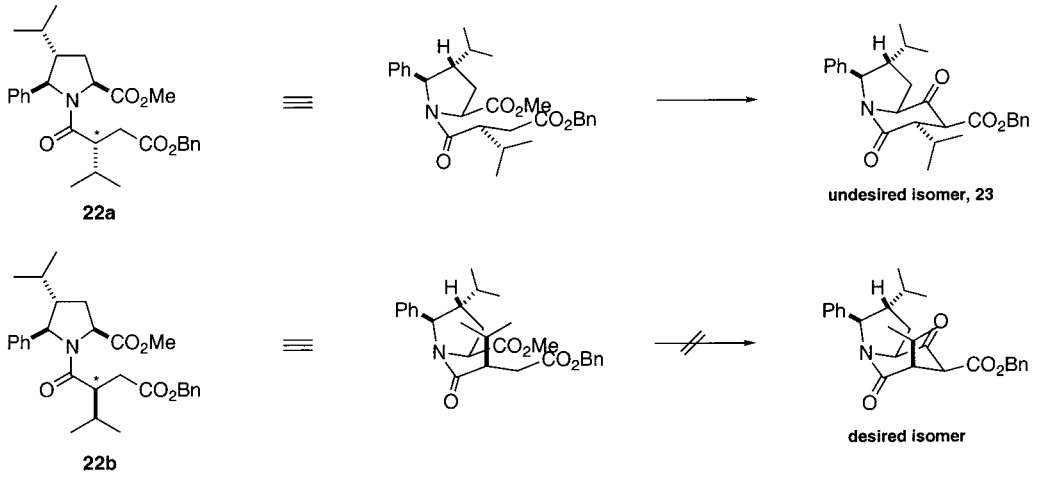
Considering the modest 30% yield in the Dieckmann cyclization, and excluding the possibility of equilibration between the two isomers via the corresponding enolate prior to cyclization, we assumed that the ester enolate of the *pro-R*-isomer **22b** must follow a different course during the reaction, leading to unidentified products. To lend credence to this supposition, we prepared **22b** independently, and subjected it to a Dieckmann cyclization under the same conditions as for the mixture (Scheme 5). A complex mixture of unidentifiable products was obtained with no trace of the expected bicyclic lactam **23**.

(29) For examples of monocyclic nitrogen heterocycles, see: (a) Blake, J.; Willson, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1964**, *86*, 5293. (b) Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145. (c) Toda, F.; Suzuki, T.; Higa, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3521. (d) Sibi, M. P.; Christensen, J. W.; Kim, S.-G.; Eggen, M.; Stessman, C.; Oien, L. *Tetrahedron Lett.* **1995**, *36*, 6209. (e) Knight, D. W.; Lewis, N.; Share, A. C.; Haigh, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3673. (f) Ma, D.; Sun, H. *Tetrahedron Lett.* **1999**, *40*, 3609. For examples of bicyclic and polycyclic nitrogen heterocyles, see: (g) Leonard, N. G.; Fulmer, R. W.; Hay, A. S. *J. Am. Chem. Soc.* **1956**, *78*, 3457. (h) Davies, W. A. M.; Pinder, A. R.; Morris, I. G. *Tetrahedron* **1962**, *18*, 405. (i) Holden, R. T.; Raper, R. *J. Chem. Soc.* **1963**, 2545. (j) Beckett, A. H.; Lingard, R. G.; Theobald, A. E. E. *J. Med. Chem.* **1969**, *12*, 563. Fulmer, R. W.; Hay, A. S. *J. Am. Chem. Soc.* **1956**, *78*, 3457. (k) Gensler, W. J.; Hu, M. W. *J. Org. Chem.* **1973**, *38*, 3848. (l) Howard, A. S.; Gerrans, G. C.; Meerholtz, C. A. *Tetrahedron Lett.* **1980**, *21*, 1373. (m) Hatamaka, M.; Ishimaru, T. *Tetrahedron Lett.* **1983**, *24*, 4837. (n) Jackson, B. G.; Gardner, J. P.; Heath, P. C. *Tetrahedron Lett.* **1990**, *31*, 6317. (o) Neyer, G.; Ugi, I. *Synthesis* **1991**, 743. (p) Bureau, R.; Mortier, J.; Joucla, M. *Tetrahedron* **1992**, *48*, 8947. (q) Liu, R.; Castelles, J.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 4069. (r) Andrews, M. D.; Brewster, A. G.; Crapnell, K. M.; Ibbett, A. J.; Jones, T.; Moloney, M. G.; Prout, K.; Watkin, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, *223*. (s) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998. (t) Harrison, J. R.; O'Brien, P.; Porter, D. W.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3623. (u) Haudrechey, A.; Chassaing, C.; Riche, C.; Langlois, N. *Tetrahedron* **2000**, *56*, 3181.

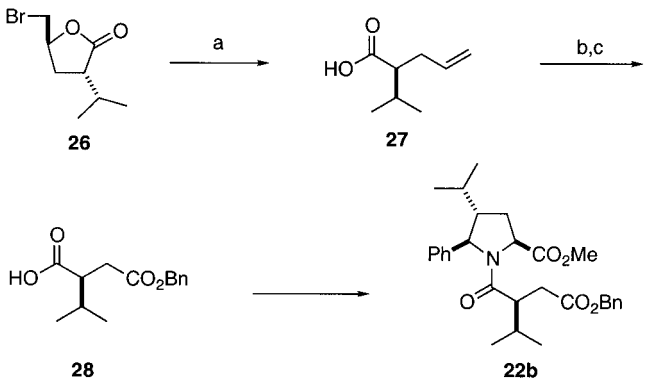
(30) For the synthesis of indolizidinones and pyrrolizidinones by Dieckmann condensations of proline-derived precursors, see refs 29t and 29k,p, respectively.

(31) Baker, W. R.; Pratt, J. K. *Tetrahedron* **1993**, *49*, 8739.

Scheme 4



Scheme 5[a]



[a] Reagents and conditions: (a) Zn, ^{i}PrOH, H_2O, 60%; (b) OsO_4/$NaIO_4$, then Jones oxidation; (c) BnOH, EDC, Et_3N, DCM, 40% (three steps).

This could account for the modest yield of cyclization when the mixture of 2-isopropyl-2*R*- and 2-isopropyl-2*S*-succinates **22a** and **22b** was used in the Dieckmann reaction, since only the 2*S*-isomer reacted. The synthesis of enantiopure succinate **28** from a known precursor[27] is shown in Scheme 5.

At this juncture, we decided to introduce the second isopropyl group later in the sequence, without compromising the original plan shown in Figure 2 (Scheme 6). Removal of the *N*-Boc group in **19** followed by amide formation with succinic acid monobenzyl ester afforded **29**. In this case Dieckmann cyclization was best achieved using sodium *tert*-pentoxide as a base. However, the yield of the product **30** after decarboxylation was modest. In the presence of other bases (NaH, KH, LiHMDS) yields were substantially lower. Clearly the possibility of multiple enolate formation sites and different reactivities must be controlling factors in the Dieckmann cyclizations of polysubstituted proline analogues such as **29**. Nevertheless, we continued this sequence with the phenyl analogue **30**. Reduction with L-Selectride afforded the alcohol **31** as the only detectable isomer (NMR). Treatment with hydrochloric acid in methanol resulted in the hydrolysis of the lactam to afford the corresponding lactone hydrochloride.[32] Protection of the pyrrolidine moiety as the *N*-Boc derivative afforded the lactone **32**. Formation of the lithium enolate and treatment with acetone afforded the corresponding adduct **33** as a single isomer. Treatment of **33** with phosphorus pentachloride in dichloromethane,[33] in the absence of base, gave the side chain alkene derivative **34** in excellent yield. Reduction of the double bond, followed by ring opening of the resulting lactone **35** with 2-propylamine in the presence of trimethylaluminum,[34] and catalytic hydrogenation afforded the prototypical target **36**.

We turned our attention to an alternative route that utilized the disubstituted proline scaffolds prepared from L-pyroglutamic acid (Scheme 7). The reaction of the *p*-methoxyphenyl derivative **20** with the lithium salt of dimethyl methylphosphonate[35] gave the corresponding phosphonate in 88% yield. Horner−Emmons−Wadsworth reaction in the presence of LiCl[36] with methyl glyoxal gave the unsaturated ester **38** as a mixture of *cis*- and *trans*-isomers in 68% yield. Hydrogenation of the double bond and subsequent reduction of both the ester and the ketone groups with sodium borohydride in methanol gave the diol **39** in 88% yield as a single diasteroisomer, as ascertained by ^{1}H NMR. Selective oxidation of the primary alcohol with TEMPO and iodobenzene diacetate[37] gave the corresponding lactone **40** in 75% yield. We were now poised to introduce the isopropyl group via the corresponding lithium enolate as in the phenyl series (Scheme 6). Thus, treatment of **40** with LiHMDS, followed by addition of acetone, gave the aldol product **41** as a single isomer in 87% yield. Treatment of **41** with phosphorus pentachloride[33] at −60 °C in dichloromethane in the absence of added base gave the desired alkene **42** in 80% yield, whose structure and absolute configuration were ascertained by X-ray crystallographic analysis. The remaining steps followed closely the chemistry already described in Scheme 6. In this series, we opened the lactone ring with 1-butylamine[8,38] in the presence of trimethylaluminum[34] to afford the amide **43** in 75% yield.

(32) For a related acid-catalyzed lactam to lactone transformation, see: Plata, D. J.; Leanna, M. R.; Morton, H. E. *Tetrahedron Lett.* **1991**, *32*, 3623.

(33) Rehders, F.; Hoppe, D. *Synthesis* **1992**, 859.

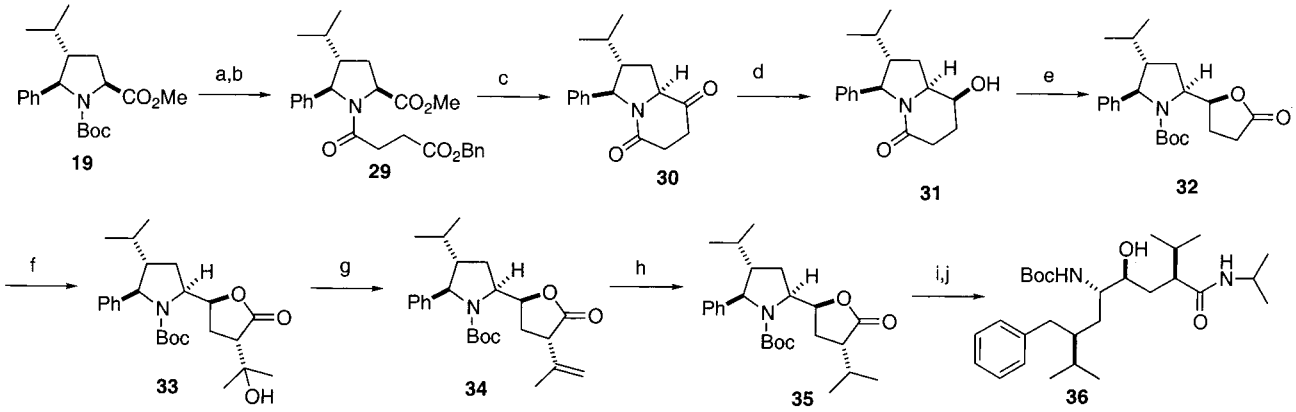
(34) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 2815.

(35) Chakravarty, P. K.; Combs, P.; Roth, A.; Greenlee, W. J. *Tetrahedron Lett.* **1981**, *28*, 611.

(36) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

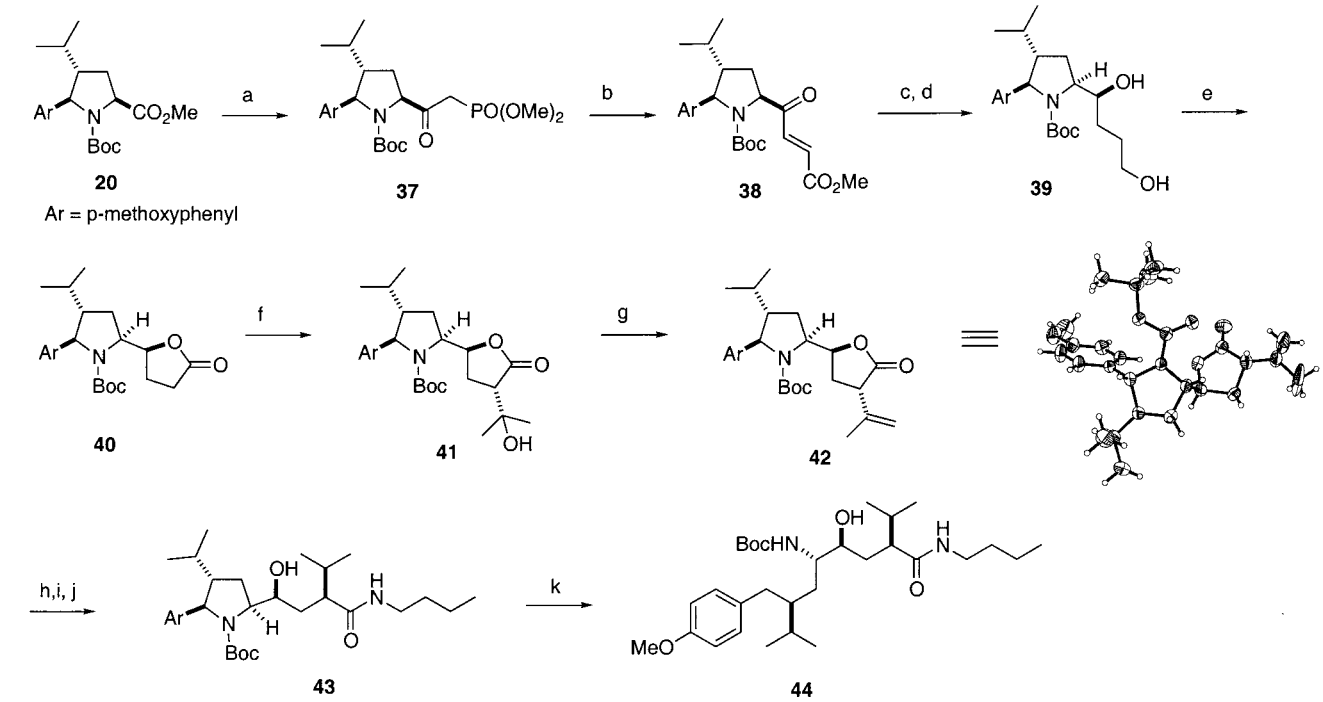
(37) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

Scheme 6[a]



[a] Reagents and conditions: (a) TFA, benzene, quantitative; (b) BOPCl, Et_3N, $^iPr_2NEt$, $HO_2C(CH_2)_2CO_2Bn$, 85%; (c) sodium *tert*-pentoxide, THF, −20 °C, then H_2, 10% Pd/C, 46%; (d) L-Selectride, −78 °C, THF, 66%; (e) concentrated HCl, MeOH, reflux, then Boc_2O, 60%; (f) LiHMDS, −78 °C, THF, then acetone, 85%; (g) PCl_5, DCM, 80%; (h) H_2, 10% Pd/C, EtOAc, 90%; (i) NH_2CHMe_2, $AlMe_3$, DCM; (j) H_2, 10% Pd/C, EtOAc, 60 psi, 3 days, 50% (two steps).

Scheme 7[a]



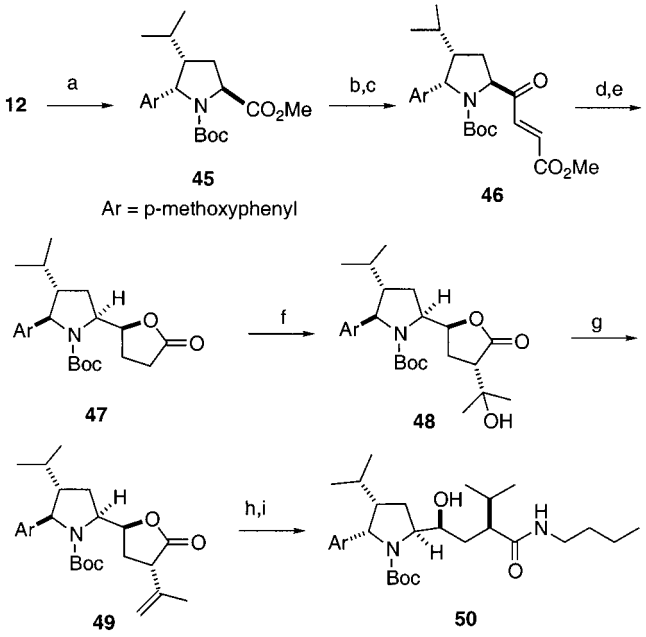
[a] Reagents and conditions: (a) $MePO(OMe)_2$, ^nBuLi, THF, −78 °C, 88%; (b) $CHOCO_2Me$, LiCl, MeCN, $^iPr_2NEt$, 68%; (c) H_2, 10% Pd/C, EtOAc, 90%; (d) $NaBH_4$, MeOH, 88%; (e) TEMPO, DCM, $PhI(OAc)_2$, 75%; (f) LiHMDS, THF, −78 °C, then acetone, 87%; (h) PCl_5, DCM, −60 °C, 80%; (i) H_2, 10% Pd/C, EtOAc, 90%; (j) $^nBuNH_2$, $AlMe_3$, DCM, 75%; (k) H_2, 10% Pd/C, MeOH, 3 days, 60%.

Finally, cleavage of the pyrrolidine *N*-benzyl bond with 10% Pd/C under an atmosphere of hydrogen at 60 psi gave the intended prototype **44** in 60% yield. The same sequence was adopted in the case of the *syn*-oriented analogue **45**, prepared essentially as described for the phenyl analogue **13** (Scheme 1). The sequence proceeding through the steps shown in Scheme 8 led to the lactone intermediate **49**, which was transformed to the *n*-butyl amide **50**. Unfortunately, the same conditions that resulted in smooth hydrogenolysis of the pyrrolidine *N*-benzyl bond in **35** and **43** were not successful with **50**. A survey of other catalysts and conditions were tried, but only unchanged starting material was recovered (10% Pd/C, 10% $Pd(OH)_2$, Pd black in methanol, at 60 psi for 3 days).

We have reported our strategies for the stereocontrolled synthesis of 2*R*-isopropyl-4*S*-hydroxy-5*S*-amino-7*S*-isopropyl-8-aryloctanoic acid amides representing the generic renin inhibitor structure **1**, starting from the readily available L-pyroglutamic acid. The resident chirality in this versatile template was efficiently exploited to control the stereochemistry of the 4*R*-isopropyl group and to introduce the 5-aryl group, as well as being the source of the 5-amino group in the target structures (Schemes 1 and 2). The difficulty in achieving lactam enolate alkylations with 2-propyl halides was circumvented by an aldol-type condensation with acetone, followed by

(38) See, for example: (a) Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* **1992**, *33*, 1411. (b) Kotsuki, H.; Miyazaki, A.; Ochi, M. *Tetrahedron Lett.* **1991**, *32*, 4503.

Scheme 8[a]



[a] Reagents and conditions: (a) *p*-$MeOC_6H_4Li$, CuBr−Me_2S, BF_3·OEt_2, 70%; (b) $MePO(OMe)_2$, ^{n}BuLi, THF, −78 °C, 80%; (c) $CHOCO_2Me$, LiCl, MeCN, $^i Pr_2NEt$, 60%; (d) H_2, 10% Pd/C, EtOAc, 90%; (e) $NaBH_4$, MeOH, then pTSA, toluene, reflux, 40%; (f) LiHMDS, THF, −78 °C, then acetone, 66%; (g) PCl_5, DCM, −60 °C, 62%; (h) H_2, 10% Pd/C, EtOAc, 95%; (i) $^n BuNH_2$, $AlMe_3$, DCM, 60%.

elimination to a 2-propenyl appendage, and subsequent reduction. Further chemical elaboration of the 4,5-disubstituted proline analogues afforded the enantiopure 8-aryl-7-isopropyl-5-amino-4-hydroxyoctanoic acid skeleton disguised as a pyrrolidinolactone, **40**. Stereocontrolled enolate alkylation with acetone as a 7*S*-isopropyl equivalent, amide formation, and cleavage of the benzylic pyrrolidine bond led to the intended targets exemplified by **36** and **44**. The entire sequence shown in Schemes 1, 2, and 7 adopting the "β-ketophosphonate" route constitutes 18 linear steps starting with *N*-Boc-pyroglutamic acid methyl ester and proceeds in an overall yield of 2.5%. Several intermediates were crystalline, and purifications were easily accomplished in other cases.

Although the original plan as outlined in Figure 2 could not be realized past the Dieckmann cyclization step, it served as a visual stimulus to devise alternative strategies that were successfully executed. The implementation of these and related strategies to other aryl-substituted congeners of **1**, and variations in the amide portion, should prove useful in further fine-tuning the biological profile of this class of novel inhibitors of renin.

Experimental Section

General Procedures. All commercially available reagents were used without further purification. Solvents were distilled under positive pressure of dry nitrogen before use, THF and ether were distilled from K/benzophenone, and CH_2Cl_2 and toluene were distilled from $CaCl_2$. NMR (^{1}H, ^{13}C, ^{31}P) spectra were recorded on 300, 400, and 600 MHz spectrometers in $CDCl_3$, and DEPT experiments were performed routinely. Low- and high-resolution mass spectra were measured using fast atom bombardment (FAB) or electrospray techniques. Optical rotations were measured at the sodium line at ambient temperature. Flash column chromatography[39] was performed in the usual way using silica gel (40−60 μm). Melting points are uncorrected.

4*R*- and 4*S*-(1-Hydroxy-1-methylethyl)-5-oxopyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, 8. To a solution of **7** (15 g, 61.7 mmol) in dry THF (600 mL) at −78 °C was added LiHMDS (62.6 mL, 62.6 mmol, 1 M solution in THF), and the mixture was stirred at −78 °C for 2 h. Dry acetone (17.6 g, 5 equiv, 0.3 mol) was then added, and the mixture was stirred at −78 °C for an additional 4 h. The reaction mixture was quenched with saturated ammonium chloride solution and allowed to warm to room temperature. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 100 mL). The organic extracts were combined, dried over anhydrous sodium sulfate, and then filtered. The solvent was removed, and the residual pale yellow oil consisted of a 5:1 mixture of **8** and its 4-epimer, which was used directly without further purification (18.5 g, quantitative): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (dd, 1H, J = 2, 9 Hz), 3.77 (s, 3 H), 2.79 (dd, 1H, J = 9, 12 Hz), 2.10 (m, 2 H), 1.48 (s, 9H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 171.4, 148.9, 83.9, 71.0, 56.5, 52.6, 51.1, 27.8, 25.1, 24.9; LRMS (*m*/*z*) (M^+ + 1) 302.2.

4*R*- and 4*S*-(1-Methyl-1-trimethylsilanyloxyethyl)-5-oxopyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, 9. To a solution of **8** (18.5 g, 61.4 mmol) in dry dichloromethane (600 mL) was added imidazole (4.54 g, 2 equiv, 0.13 mol), and the mixture was stirred for 5 min. Chlorotrimethylsilane (6.48 g, 60 mmol) was then added in one portion, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was then filtered, and the filtrate was washed rapidly with distilled water (30 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the solvent was removed under reduced pressure to give a yellow oil which was used without further purification (16.04 g, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.52 (dd, 1H, J = 2, 9 Hz), 3.77 (s, 3H), 2.55 (m, 1H), 2.37 (m, 1H), 2.01 (m, 1H), 1.48 (s, 9H), 1.42 (s, 3H), 1.38 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 172.2, 149.0, 83.1, 74.5, 57.0, 52.9, 52.3, 29.8, 27.8, 26.1, 24.4, 2.2; MS (*m*/*z*) (M^+ + 1) 374.2; HRMS (*m*/*z*) (M^+ + 1) calcd for C_{17} $H_{31}NO_6Si$ 374.1982, found 374.1999.

4*R*- and 4*S*-(1-Hydroxy-1-methylethyl)-5-methoxypyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, 10. To a solution of **9** (16.0 g, 42.9 mmol) in dry THF (400 mL) was added at −78 °C DIBAL-H (80 mL, 80 mmol, 1 M solution in toluene), and the mixture was stirred at that temperature for 2 h. The reaction mixture was quenched with distilled water, and the organic solvents were removed under vacuum. The residue was suspended in 3 M NaOH solution, and the suspension was rapidly washed with ethyl acetate (3 × 150 mL). The organic extracts were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure to give the hemiaminal (15 g, 40 mmol) as a yellow oil which was dissolved in dry methanol (150 mL), pTSA(cat.) was added, and the mixture was stirred overnight. Solid sodium bicarbonate was added, and the mixture was stirred for 20 min before the solvent was removed under vacuum. The residue was dissolved in ethyl acetate and washed with distilled water. The organic phase was dried over anhydrous sodium sulfate and filtered, and the solvent was removed under reduced pressure to give a yellow oil. The oil was dissolved in benzene, and any residual water was removed azeotropically. The oil was then used directly without further purification (11.4 g, 95%): IR (neat) 3516, 2976, 1750, 1710, 1479, 1458, 1438, 1368, 1300, 1203 cm^{-1}.

4*S*-Isopropyl-5*S*-phenylpyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, 13. To a solution of **10** (1.0 g, 3.15 mmol) in DCM (50 mL) were added DMAP (15.4 g, 12.6 mmol), triethylamine (12.7 g, 12.6 mmol), and MsCl (14.4 g, 12.6 mmol), and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure,

(39) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

and the crude was dissolved in ethyl acetate and washed sequentially with dilute HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure, and the crude was purified by column chromatography (1:9 ethyl acetate/hexane) to separate the minor 4*R*-isomer to give **11** as a colorless oil (0.68 g, 72%). To a solution of **11** (600 mg, 2.0 mmol) in ethyl acetate were added solid sodium bicarbonate (large excess) and 10% Pd/C. The reaction mixture was stirred under an atmosphere of hydrogen gas. The solids were removed by filtration, and the solvent was removed to give **12** as a colorless oil, which was used without further purification (500 mg, 82%). To a suspension of copper(II) bromide−dimethyl sulfide complex (1.22 g, 4.4 equiv, 5.95 mmol) in anhydrous ether (5 mL) at −78 °C was added phenylmagnesium bromide (5.95 mL, 4.4 equiv, 5.95 mmol), and the reaction mixture was stirred at −40 °C for 45 min. $BF_3{\cdot}OEt_2$ (0.84 mL, 4.4 equiv, 5.95 mmol) was added at −78 °C, and the mixture was stirred for a further 30 min. The aminal **12** (0.41 g, 1.36 mmol) was then added, and the reaction mixture was stirred at −78 °C for 1 h and then slowly warmed to room temperature. The reaction mixture was quenched with a 1:1 mixture of NH_4OH/NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The mixture was concentrated and purified by column chromatography (1:4 ethyl acetate/hexane) to yield **13** (yield 420 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.10 (m, 5H), 4.97 (and rotamer at 5.1) (d, 1H, J = 7.19 Hz), 4.68 (and rotamer at 4.58) (d, 1H, J = 10 Hz), 3.78 (s, 3H), 2.35−2.20 (m, 2H), 2.10−2.01 (m, 1H), 1.15 (s, 9H), 0.91−0.85 (m, 4H), 0.78−0.72 (m, 3H); HRMS (*m*/*z*) calcd for $C_{20}H_{29}NO_4$ 347.2096, found 347.2084.

4*S*-Isopropyl-5*S*-phenyl-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester, 14. To a solution of **13** (100 mg, 0.29 mmol) in THF (5 mL) and water (2 mL) was added lithium hydroxide (24 mg, 2 equiv, 0.57 mmol), and the reaction mixture was stirred overnight. The THF was removed under vacuum, and the solution was extracted with diethyl ether and then acidified to pH 1. The aqueous phase was extracted with ethyl acetate, the organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed to give an oil which was treated with HCl in dioxane overnight. The solvent was removed under reduced pressure to give an oil which was triturated with diethyl ether to **14** as a white solid (76 mg, 80%): mp 162−164 °C dec; ^{1}H NMR (free amino acid) (300 MHz, $CDCl_3$) δ 9.4−8.9 (br s, 2 H), 7.38−7.25 (m, 5H), 5.18 (d, 1H, J = 7 Hz), 4.91 (s, 1H), 2.40−2.05 (m, 3H), 1.26 (m, 1H), 0.8 (dd, 6H, J = 4, 6 Hz); ^{13}C (free amino acid) (75 MHz, $CDCl_3$) δ 171.5, 132.7, 129.1, 128.6, 128.7, 65.9, 58.6, 49.6, 32.1, 27.6, 21.6, 21.3; LRMS (*m*/*z*) (M^+ + 1) 234; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{14}H_{20}NO_2$ 234.1485, found 234.1494.

4*R*- and 4*S*-(1-Hydroxy-1-methylethyl)-5*R*-phenylpyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, 15. Copper(II) bromide−dimethyl sulfide complex (20.4 g, 99.6 mmol) was suspended in dry THF (450 mL), and the mixture was cooled to −40 °C. Phenylmagnesium bromide (99.6 mL, 99.6 mmol, 1 M in THF) was then added slowly at such a rate so as to keep the reaction temperature between −40 and −30 °C. After complete addition of the Grignard reagent, the yellow suspension was stirred at −30 °C for 1 h. The reaction mixture was then cooled to −78 °C whereupon $BF_3{\cdot}OEt_2$ (14.04 g, 99 mmol) was added, and the mixture was stirred at this temperature for 30 min. A solution of **10** (7.5 g, 24.8 mmol) in dry THF (60 mL) was then added, and the mixture was allowed to slowly warm to room temperature and then stirred for 1 h. The black suspension was quenched with a 1:1 mixture of aqueous ammonia and ammonium chloride (60 mL), and the THF was removed under vacuum. The residue was dissolved in diethyl ether (100 mL) and washed with ammonium chloride solution. The aqueous phase was extracted with diethyl ether (3 × 100 mL), and the organic extracts were combined, dried over anhydrous sodium sulfate, and then filtered. The solvent was removed, and the dark oil was purified by column chromatography (1:4 ethyl acetate/hexane) to afford **15** (5:1 mixture) as an off-white solid (4.97 g, 55%): mp 122−124 °C; $[\alpha]_D$ −11.92 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (m, 5H), 6.96 (br, 1H), 5.00 (d, 1H, J = 14 Hz), 4.54 (m, 1H), 3.89 (s, 3H), 2.71−2.40 (m, 3H), 1.21 (s, 3H), 0.97 (s, 3H) (free amine); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 153.1, 144.0, 128.3, 128.0, 126.6, 80.1, 71.4, 63.9, 59.5, 57.9, 52.1, 30.2, 28.1, 27.9, 27.7; LRMS (*m*/*z*) (M^+ + 1) 364.1; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{20}H_{30}NO_5$ 364.2130, found 364.2124.

4*R*- and 4*S*-(1-Hydroxy-1-methylethyl)-5*R*-(4-methoxyphenyl)pyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2S-Methyl Ester, 16. To a solution of *p*-bromoanisole (23.6 g, 0.126 mol) in dry THF (150 mL) at −78 °C was added *n*-butyllithium (63.2 mL, 0.126 mol, 2 M in hexanes), and the reaction mixture was stirred at −78 °C for 20 min. The lithium reagent was added to a stirring suspension of copper(II) bromide−dimethyl sulfide complex (26 g, 0.126 mol) at −78 °C in THF (150 mL), and the resultant black solution was stirred at −78 °C for 1 h. $BF_3{\cdot}OEt_2$ (35.8 g, 0.25 mol) was then added in one portion, and the reaction mixture was stirred for a further 30 min. A solution of **10** as described above (8 g, 25.2 mmol) in dry THF (20 mL) was then added, and the reaction mixture was then allowed to slowly warm to room temperature. The black suspension was quenched with a 1:1 mixture of ammonium chloride solution and aqueous ammonia and extracted with ethyl acetate (4 × 30 mL). The organic fractions were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure, and the resultant yellow oil was purified by column chromatography (1:4 ethyl acetate/hexane) to give a clear oil consisting of 5:1 mixture of diastereomers (4.56 g, 46%): $[\alpha]_D$ − 9.3 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 2H, J = 9 Hz), 6.84 (d, 2H, J = 8 Hz), 4.90−4.46 (m, 2H), 3.79 (s, 6 H), 2.40−2.08 (m, 3 H), 1.35−1.10 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 158.3, 154.2, 136.6, 113. 3, 80.1, 71.2, 63.2, 60.3, 57.8, 55.1, 52.1, 30.1, 28.7, 28.1, 27.9, 27.8; LRMS (*m*/*z*) (M^+ + 1) 394; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{21}H_{32}NO_6$ 394.2236, found 394.2229.

4*S*-Isopropenyl-5*R*-phenylpyrrolidine-1,2S-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, 17. To a solution of **15** (3.2 g, 8.77 mmol) in dry dichloromethane (240 mL) were added dry triethylamine (3.56 g, 4 equiv, 35.2 mmol) and DMAP (4.3 g, 4 equiv, 35.2 mmol), and the mixture was stirred for 5 min at 0 °C. Methanesulfonyl chloride (4.01 g, 4 equiv, 35.2 mmol) was slowly added, and the deep red solution was allowed to stir at room temperature overnight. The reaction mixture was quenched by the addition of ammonium chloride solution (20 mL) and ethyl acetate (100 mL). The organic phase was separated, and the aqueous phase was washed with ethyl acetate (3 × 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under vacuum, and the crude red oil was purified by column chromatography (1:9 ethyl acetate/hexane) to give **17** as a colorless oil which solidified on standing (2.46 g, 81%): mp 46−48 °C; $[\alpha]_D$ –36.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.17 (m, 5H), 4.8 (br, 1H), 4.67 (br, 1H), 4.3 (dd, 2H, J = 9, 20 Hz), 3.84 (s, 3H), 3.76 (d, 1H, J = 3 Hz), 2.84 (m, 1H), 2.15 (m, 2H), 1.75−1.09 (br m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 143.0, 127.8, 127.6, 126.6, 125.9, 113.0, 80.3, 66.4, 59.1, 54.9, 52.1, 33.4, 28.1, 27.8, 20.2; MS (*m*/*z*) (M^+ + 1) 346; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{20}H_{28}NO_4$ 346.2013, found 346.2018.

4*S*-Isopropenyl-5*R*-(4-methoxyphenyl)pyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, 18. To a solution of **16** (3.1 g, 7.9 mmol) in dry dichloromethane (200 mL) were added dry triethylamine (3.19 g, 4 equiv, 31.6 mmol) and DMAP (3.86 g, 4 equiv, 31.6 mmol), and the mixture was stirred for 5 min at 0 °C. Methanesulfonyl chloride (3.6 g, 4 equiv, 31.6 mmol) was then slowly added, and the deep red solution was allowed to stir at room temperature overnight. The reaction mixture was quenched by the addition of ammonium chloride solution (20 mL) and ethyl acetate (100 mL), and the organic phase was separated and processed as described for **17** to give a red oil which was purified by column chromatography (1:9 ethyl acetate/hexane) to give **18** as a colorless oil (2.40 g, 81%): $[\alpha]_D$ −12.55 (*c* 1,

$CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, 2H, $J = 8$ Hz), 6.74 (d, 2H, $J = 7$ Hz), 4.72−4.35 (m, 3H), 3.70 (s, 4H), 3.66 (s, 3H), 2.05 (m, 2H), 1.29 (m, 4H), 1.45−1.02 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 158.3, 141.8, 135.1, 128.1, 127.6, 113.0, 79.7, 65.7, 60.0, 58.9, 54.8, 33.2, 28.0, 20.7, 13.9; LRMS (*m*/*z*) ($M^+ + 1$) 376; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{21}H_{30}NO_5$ 376.2126, found 376.2124.

4*S*-Isopropyl-5*R*-phenylpyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, 19. To a solution of **17** (2.46 g, 7.13 mmol) in ethyl acetate (100 mL) was added 10% Pd/C (150 mg), and the mixture was reduced under an atmosphere of hydrogen at 40 psi for 24 h. The catalyst was filtered, and the solvent was removed under reduced pressure to give a colorless oil which solidified on standing and was used without further purification (2.23 g, 90%): mp 48−50 °C; $[\alpha]_D$ −31.6 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 4.6 (br, 1H), 4.36 (m, 1H), 3.82 (dd, 1H, $J = 4$, 9 Hz), 3.72 (s, 3H), 2.1−2.0 (m, 3H), 1.6 (m, 1H), 1.39 (s, 3H), 1.09 (s, 6H), 0.85 (d, 3H, $J = 7$ Hz), 0.70 (d, 3H, $J = 6$ Hz) (free amine); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 143.9, 128.2, 127.9, 126.9, 126.6, 126.2, 80.3, 65.9, 59.1, 53.7, 52.1, 29.6, 28.1, 27.8, 26.9, 21.7, 17.6; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{20}H_{30}NO_4$ 348.2168, found 348.2175.

4*S*-Isopropyl-5*R*-(4-methoxyphenyl)pyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2*S*-Methyl Ester, 20. To a solution of **18** (2.3 g, 6.1 mmol) in ethyl acetate (100 mL) was added 10% Pd/C (200 mg), and the mixture was reduced under an atmosphere of hydrogen at 40 psi for 24 h. The catalyst was filtered, and the solvent was removed under reduced pressure to give **20** as a colorless oil which was used without further purification (2.08 mg, 90%): $[\alpha]_D$ −22.9 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, 2H, $J = 9$ Hz), 6.85 (d, 2H, $J = 8$ Hz), 4.61−4.30 (m, 2H), 3.80 (s, 6H), 2.13−1.94 (m, 3H), 1.70−1.60 (m, 1H), 1.37 (s, 3H), 1.11 (s, 6H), 1.0−0.73 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 158.3, 154.3, 135.9, 128.1, 113.1, 79.6, 65.4, 59.9, 51.9, 29.6, 27.8, 21.6, 17.7.

4*S*-Isopropyl-5*R*-phenylpyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester, 21. To a solution of **19** (100 mg, 0.29 mmol) in 10:1 MeOH/water (5 mL) was added lithium hydroxide (1.5 equiv, 0.44 mmol), and the reaction mixture was stirred at room temperature overnight. Methanol was removed under reduced pressure, and the aqueous phase was extracted with diethyl ether (2 × 10 mL), acidified to pH 1, and then extracted with diethyl ether. The solvent was removed under reduced pressure to give a white solid (91.7 mg, 95%): mp > 200 °C; 1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 4.51 (d, 1H, $J = 8$ Hz), 4.33 (d, 1H, $J = 7$ Hz), 2.43 (m, 1H), 2.16 (m, 1H), 1.88 (m, 1H), 1.69 (m, 1H), 1.1 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 142.9, 128.2, 127.0, 126.8, 66.4, 60.2, 53.7, 27.8, 21.6, 17.8; LRMS (*m*/*z*) ($M^+ + 1$) 334; HRMS (*m*/*z*) calcd for $C_{19}H_{28}NO_4$ 334.2025, found 334.2018.

1-(2-Benzyloxycarbonylmethyl-3-*R*,*S*-methylbutyryl)-4*S*-isopropyl-5*R*-phenylpyrrolidine-2*S*-carboxylic Acid Methyl Ester, 22. To a solution of 2-isopropylsuccinic acid monobenzyl ester (405 mg, 2 equiv, 1.62 mmol) in dry dichloromethane (4 mL) at 0 °C was added BOPCl (411 mg, 2 equiv, 1.62 mmol), and the reaction mixture was stirred at 0 °C for 2 h. A solution of the free amine of **19**, obtained by treatment with TFA (200 mg, 0.81 mmol), and diisopropylethylamine (627 mg, 6 equiv, 4.86 mmol) in dry dichloromethane (5 mL) was then added, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and then washed sequentially with dilute hydrochloric acid (15 mL), sodium bicarbonate solution (15 mL), and brine (15 mL). The organic layer was dried over sodium sulfate and then filtered, and the solvent was removed under vacuum to give a brown oil. Purification by column chromatography (1:2 diethyl ether/hexane) gave **22** (1:1 mixture of diastereomers) as a colorless oil (330 mg, 85%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.66−7.17 (m, 10H), 5.15−4.81 (m, 3H), 4.64−4.56 (m, 1H), 3.85−3.52 (m, 3H), 2.87−2.74 (m, 1H), 2.64−2.56 (m, 1H), 2.49−2.24 (m, 2H), 2.17−1.92 (m, 3H), 1.68−1.60 (m, 2H), 1.50−1.43 (m, 1H), 1.06−0.29 (multiple dd, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 173.2, 172.9, 143.8, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.4, 127.2, 127.1, 126.5, 66.2, 59.4, 55.6, 52.0, 45.2, 44.2, 33.3, 31.7, 29.7, 28.7, 28.2, 21.6, 20.8, 20.6, 18.9, 17.9, 14.0; LRMS (*m*/*z*) ($M^+ + 1$) 480; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{29}H_{38}NO_5$ 480.2762 found 480.2750.

2*S*,6*R*-Diisopropyl-3*R*-phenylhexahydroindolizine-5,8-dione, 24. To a solution of **22** (275 mg, 0.57 mmol) in dry THF (50 mL) at −78 °C was added KHMDS (4.56 mL, 2.28 mmol, 0.5M in toluene), and the reaction mixture was allowed to warm to −50 °C and stirred at that temperature for 3 h. The reaction mixture was quenched with saturated ammonium chloride solution (10 mL), and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 × 30 mL), the combined organic phases were dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure to give **23** as a crude oil. The oil was dissolved immediately in methanol (5 mL), 10% Pd/C was added, and the mixture was stirred under an atmosphere of hydrogen gas for 3 h. The catalyst was removed by passage through a pad of Celite, and the solvent was removed. Purification of the resultant oil by column chromatography (1:4 ethyl acetate/hexane) gave **24** as a colorless oil (54 mg, 30%, two steps): $[\alpha]_D$ −25.8 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.05 (m, 5H), 5.30 (s, 1H), 4.29−4.10 (m, 1H), 2.86−2.74 (m, 2H), 2.43−2.38 (m, 1H), 2.25−2.05 (m, 2H), 1.93−1.87 (m, 1H), 1.83−1.72 (m, 1H), 1.71−1.67 (m, 1H), 1.10 (t, 3H, $J = 6$ Hz), 0.99 (t, 3H, $J = 6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 142.4, 128.5, 128.3, 124.1, 64.6, 63.8, 52.3, 49.6, 39.2, 30.1, 29.6, 28.3, 28.0, 22.6, 21.2, 20.8, 20.8, 20.1; LRMS (*m*/*z*) ($M^+ + 1$) 313.

8*S*-Hydroxy-2*S*,6*R*-diisopropyl-3*R*-phenylhexahydroindolizin-5-one, 25. To a solution of **24** (54 mg, 0.173 mmol) in dry THF (2 mL) was added L-Selectride (0.21 mL, 0.21 mmol, 1 M solution in THF), and the reaction mixture was stirred at −78 °C. After 2 h, the reaction was quenched by the addition of saturated ammonium chloride solution, and the mixture was warmed to room temperature. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over anhydrous sodium sulfate, and then filtered. The solvent was removed under vacuum to give a clear oil. Purification by column chromatography (1:3 ethyl acetate/hexane) gave **25** as a white solid (33 mg, 60%): mp > 180 °C; $[\alpha]_D$ +4.0 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3684, 3620, 3019, 1658, 1602, 1522, 1476, 1423, 1046, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.11 (m, 5H), 4.91 (br s, 1H), 4.18 (br s, 1H), 3.68 (dd, 2H, $J = 5$, 12 Hz), 2.58−2.53 (m, 2H), 2.26−2.18 (dt, 1H, $J = 6$, 12 Hz), 2.06−2.0 (m, 1H), 1.77−1.65 (m, 4H), 1.13 (d, 3H, $J = 6$ Hz), 0.96 (d, 3H, $J = 6$ Hz), 0.90 (d, 3H, $J = 7$ Hz), 0.84 (d, 3H, $J = 7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 144.2, 128.1, 126.0, 125.3, 64.9, 64.3, 60.9, 52.8, 42.0, 30.1, 29.6, 27.8, 27.6, 21.3, 20.5, 19.8, 17.3; LRMS (*m*/*z*) ($M^+ + 1$) 316; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{20}H_{30}NO_2$ 316.2291, found 316.2276.

2*S*-Isopropylpent-4-enoic Acid, 27. To a solution of **26** (500 mg, 2.26 mmol) in a 2-propanol/water mixture (10:1, 50 mL) was added zinc metal (8.81 g, 135.6 mmol, 60 equiv), and the mixture was heated to reflux for 5 h. The reaction mixture was cooled, and the 2-propanol was removed under vacuum. The aqueous phase was acidified to pH 1 and extracted with ethyl acetate. The organic fractions were combined and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give **27** as a dark oil which was purified by column chromatography (ethyl acetate) to give a colorless oil (193 mg, 60%): ^1H NMR (400 MHz, $CDCl_3$) δ 5.70 (m, 1H), 5.03 (m, 1H), 4.97 (m, 1H), 2.19 (m, 2H), 2.38 (m, 1H), 2.15 (m, 1H), 1.01 (d, 6H).

2*S*-Isopropylsuccinic Acid Monobenzyl Ester, 28. To a solution of **27** (150 mg, 1.06 mmol) in THF/water (9:1, 5 mL) was added sodium metaperiodate (0.45 g, 2.1 mmol), and the reaction mixture was stirred. Osmium tetroxide solution was added (cat.), and the reaction mixture was stirred overnight. The solvent was removed, and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and then concentrated. The crude aldehyde was dissolved in acetone and treated with the Jones reagent at 0 °C. The reaction mixture was quenched

with excess 2-propanol, the solvents were removed, and the crude acid was purified by column chromatography (ethyl acetate) to give 2*S*-isopropylsuccinic acid as a colorless oil. To a solution of the diacid (100 mg, 6.25 mmol) in dichloromethane (5 mL) were added benzyl alcohol (101 mg, 9.35 mmol), Et_3N (94 mg, 9.31 mmol), and EDC (178 mg, 9.3 mmol), and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate and then washed sequentially with dilute HCl (10 mL), $NaHCO_3$ solution (10 mL), and finally brine solution (10 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated. The crude monoester was purified by column chromatography (1:4 ethyl acetate/hexane) to give **28** as a colorless oil (62.5 mg, 40%): ^{1}H NMR δ 7.19 (m, 5H), 5.34 (s, 2H), 2.98 (m, 1H), 2.48 (m, 2H), 2.15 (m, 1H), 1.01 (d, 6H).

1-(3-Benzyloxycarbonylpropionyl)-4*S*-isopropyl-5*R*-phenylpyrrolidine-2*S*-carboxylic Acid Methyl Ester, 29. To a solution of succinic acid monobenzyl ester (2.35 g, 11.3 mmol, 2 equiv) in a mixture of dry dichloromethane and DMF (50 mL, 4:1) was added BOPCl (2.9 g, 11.4 mmol, 2 equiv), and the mixture was stirred at 0 °C for 1 h. A solution of the amine of **19**, obtained by treatment with TFA (1.4 g, 5.7 mmol), in dichloromethane (20 mL) and Hunig's base (4.4 g, 34 mmol, 6 equiv) were then added, and the reaction mixture was stirred at room temperature overnight. The solvents were removed, and the residue was dissolved in ethyl acetate (10 mL). The organic phase was washed sequentially with dilute HCl, saturated sodium bicarbonate solution, and then brine. The organic phase was dried over anhydrous sodium sulfate, and the solvent was then removed to give a dark oil. Purification by column chromatography (1:4 ethyl acetate/hexane) gave **29** as a pale yellow oil (2.2 g, 89%): $[\alpha]_D$ −22.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.18 (m, 10H), 5.10−5.02 (dd, 2H, J = 24, 12 Hz), 4.69 (d, 1H, J = 13 Hz), 4.63 (t, 1H, J = 7 Hz), 3.79 (s, 3H), 2.77−2.69 (m, 1H), 2.52−2.31 (m, 2H), 2.13−1.85 (m, 4H), 1.67 (m, 1H), 0.94 (d, 6H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 172.5, 171.7, 142.4, 135.9, 128.7, 128.4, 128.1, 127.97, 127.9, 66.2, 66.1, 60.2, 59.4, 55.3, 52.1, 29.4, 29.0, 28.8, 28.7, 27.6, 21.6, 20.9, 18.3, 14.1; LRMS (*m*/*z*) (M^+ + 1) 438; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{26}H_{32}NO_5$ 438.2288, found 438.2280.

2*S*-Isopropyl-3*R*-phenylhexahydroindolizine-5,8-dione, 30. To a solution of **29** (2.0 g, 4.6 mmol) in dry THF (450 mL) at −20 °C was added sodium *tert*-pentoxide (1.5 g, 13.6 mmol), and the reaction mixture was stirred at that temperature until there was no remaining starting material detected by TLC. The reaction mixture was quenched by the addition of saturated ammonium chloride solution, and the THF was then separated. The aqueous phase was extracted with ethyl actetate (3 × 30 mL), the organic extracts were combined and dried over anhydrous sodium sulfate, and the solvent was removed to give a yellow oil. The crude product was dissolved in methanol (50 mL), 10% Pd/C was added, and the reaction mixture was stirred under an atmosphere of hydrogen gas. The catalyst was removed by filtration, the solvent was removed, and the residue was purified by column chromatography (1:1 ethyl acetate/hexane) to give **30** as a yellow oil (570 mg, 46%): $[\alpha]_D$ +15.07 (*c* 0.7, $CHCl_3$); IR (neat) 2962, 1732, 1693, 1602, 1429 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.02 (m, 5H), 5.04 (s, 1H), 4.26 (t, 1H, J = 8 Hz), 2.75 (m, 4H), 2.18 (m, 2H), 2.0−1.5 (m, 2H), 1.10−0.99 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 169.2, 141.9, 130.3, 126.9, 126.1, 124.8, 64.9, 63.6, 34.9, 31.1, 30.8, 26.9, 20.9, 20.1; LRMS (*m*/*z*) (M^+ + 1) 272; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{17}H_{22}O_2N$ 272.1659, found 272.1650.

8*S*-Hydroxy-2*S*-isopropyl-3*R*-phenylhexahydroindolizin-5-one, 31. To a solution of **30** (451 mg, 1.6 mmol) in dry THF (10 mL) at −78 °C was added L-Selectride (2.5 mL, 2.5 mmol, 1 M solution in THF), and the reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was quenched by the addition of saturated ammonium chloride, and the solution was extracted with ethyl acetate (3 × 10 mL) and dichloromethane (3 × 10 mL). The organic extracts were combined and then dried over anhydrous sodium sulfate. The solvents were removed, and the resultant oil was purified by column chromatography (ethyl acetate) to give **31** as a white solid (300 mg, 66%): mp > 200 °C; $[\alpha]_D$ +6.12 (*c* 0.8, $CHCl_3$); IR ($CDCl_3$) 3428, 2972, 1731, 1635, 1451, 1410, 1373, 1250 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.13 (m, 5H), 4.94 (s, 1H), 4.17 (s, 1H), 3.70 (dd, 1H, J = 12, 5 Hz), 2.6−2.5 (m, 1H), 2.35−2.31 (m, 1H), 2.1−1.9 (m, 3H), 1.77 (dd, 1H, J = 13, 6 Hz), 1.66 (s, 2H), 1.14 (d, 3H, J = 6 Hz), 0.95 (d, 3H, J = 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 143.7, 128.2, 126.2, 64.4, 63.8, 61.3, 53.1, 29.8, 29.2, 27.3, 27.1, 21.4, 20.5; LRMS (*m*/*z*) (M^+ + 1) 274; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{17}H_{24}NO_2$ 274.1819, found 274.1807.

3*S*-Isopropyl-5*S*-(5-oxotetrahydrofuran-2*S*-yl)-2*R*-phenylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 32. To a solution of **31** (300 mg, 1.1 mmol) in methanol (4 mL) was added concentrated HCl (4 mL), and the reaction mixture was heated to reflux for 3 days. The solvents were removed, the crude lactone was dissolved in dry acetonitrile (5 mL), DMAP (268 mg, 2 equiv, 2.2 mmol), triethylamine (450 mg, 4 equiv, 4.4 mmol), and Boc anhydride (650 mg, 2 equiv, 2.2 mmol) were added, and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the crude was dissolved in ethyl acetate and then washed sequentially with dilute HCl, saturated sodium bicarbonate solution, and brine. The organic phase was collected and dried over anhydrous sodium sulfate, and the solvent was removed to give a dark oil which was purified by column chromatography (1:3 ethyl acetate/hexane) to give **32** as a colorless oil (245 mg, 60%, two steps): $[\alpha]_D$ −27.05 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.18 (m, 5H), 4.63−4.61 (m, 1H), 4.40 (s, 1H), 4.21 (m, 1H), 2.59−2.49 (m, 2H), 2.36−2.15 (m, 3H), 1.96−1.88 (m, 1H), 1.77−1.73 (m, 2H), 1.24 (s, 9H), 0.94 (d, 3H, J = 7 Hz), 0.82 (d, 3H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 155.9, 143.7, 128.0, 126.6, 82.7, 80.1, 66.5, 59.5, 52.3, 29.5, 28.7, 28.5, 28.3, 28.0, 27.6, 25.4, 21.9, 17.5; LRMS (*m*/*z*) (M^+ + 1) 374; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{22}H_{32}NO_4$ 374.2320, found 374.2331.

5*S*-[4*S*-(1-Hydroxy-1-methylethyl)-5-oxotetrahydrofuran-2*S*-yl]-3*S*-isopropyl-2*R*-phenylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 33. To a solution of **32** (240 mg, 0.63 mmol) in dry THF (8 mL) at −78 °C was added LiHMDS (0.7 mL, 1.15 equiv, 0.7 mmol, 1 M solution in THF), and the reaction mixture was stirred for 1 h. Dry acetone (187 mg, 5 equiv, 3.2 mmol) was then added, and the reaction mixture was stirred for an additional 1 h. The reaction mixture was quenched by the addition of a saturated ammonium chloride solution and extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed to give a dark oil. Purification by column chromatography (1:4 ethyl acetate/hexane) gave **33** as a colorless oil (235 mg, 85%): $[\alpha]_D$ +2.18 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.19 (m, 5H), 4.48 (s, 1H), 4.15 (t, 1H, J = 8 Hz), 2.85 (t, 1H, J = 10 Hz), 2.27−2.10 (m, 2H), 1.97−1.88 (m, 1H), 1.76−1.67 (s, 2H), 1.31 (s, 17H), 0.94 (d, 3H, J = 7 Hz), 0.84 (d, 3H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 143.6, 128.2, 126.7, 126.4, 80.3, 70.9, 59.7, 52.3, 48.9, 29.6, 28.6, 28.4, 29.9, 27.1, 25.4, 21.9, 17.3; LRMS (*m*/*z*) (M^+ + 1) 432; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{25}H_{38}NO_5$ 432.2750, found 432.2749.

5*S*-(4*S*-Isopropenyl-5-oxotetrahydrofuran-2*S*-yl)-3*S*-isopropyl-2*R*-phenylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 34. To a solution of **33** (100 mg, 0.23 mmol) in dry dichloromethane (4 mL) at −60 °C was added PCl_5 (53 mg, 1.1 equiv, 0.25 mmol), and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with saturated sodium bicarbonate solution and then extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed to give a yellow oil. Purification by column chromatography (1:9 ethyl acetate/hexane) gave **34** as a colorless oil (77 mg, 80%): $[\alpha]_D$ +3.63 (*c* 0.6, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.16 (m, 5H), 5.0 (s, 2H), 4.55 (s, 1H), 4.40 (s, 1H), 4.20 (t, 1H, J = 7 Hz), 3.38 (t, 1H, J = 8 Hz), 2.40−2.26 (m, 3H), 1.97−1.62 (m, 5H), 1.50−1.0 (s, 9H), 1.0−0.8 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.1, 176.3, 143.7, 139.7, 128.1,

126.6, 126.5, 114.3, 80.2, 68.8, 59.4, 52.3, 46.9, 30.9, 30.8, 28.9, 27.9, 27.4, 24.3, 21.9, 21.8, 17.4, 14.0; LRMS (*m*/*z*) ($M^+ + 1$) 414; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{25}H_{36}NO_4$ 414.2632, found 414.2644.

3*S*-Isopropyl-5*S*-(4*S*-isopropyl-5-oxotetrahydrofuran-2*S*-yl)-2*R*-phenylpyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 35. To a solution of **34** (75 mg, 0.18 mmol) in ethyl acetate (5 mL) was added 10% Pd/C, and the reaction mixture was stirred under an atmosphere of hydrogen gas. The catalyst was removed by filtration, the solvent was removed, and the residue was purified by column chromatography (1:9 ethyl acetate/hexane) to give **35** as a colorless oil (68 mg, 90%): $[\alpha]_D$ +0.74 (*c* 0.6, $CHCl_3$); IR ($CDCl_3$) 2965, 2932, 1777, 1739, 1691, 1650, 1604, 1440, 1369, 1336, 1312 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.15 (m, 5H), 4.95 (s, 1H), 4.62 (s, 1H), 3.93 (t, 1H, J = 6 Hz), 2.60 (m, 1H), 2.35−2.24 (m, 4H), 1.96−1.60 (m, 4H), 1.48−1.0 (s, 8H), 1.0−0.8 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 160.3,139.7, 128.1, 125.7, 126.5, 82.8, 70.9, 54.9, 54.2, 51.7, 41.9, 28.6, 25.7, 25.4, 19.5; LRMS (*m*/*z*) ($M^+ + 1$) 416; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{25}H_{38}NO_4$ 416.2788, found 416.2801.

[1*S*-(2-Benzyl-3*S*-methylbutyl)-2*S*-hydroxy-4*S*-isopropylcarbamoyl-5-methylhexyl]carbamic Acid *tert*-Butyl Ester, 36. To a solution of isopropylamine (43 mg, 4 equiv, 0.72 mmol) in dry dichloromethane (1 mL) was added trimethylaluminum (0.37 mL, 2 M solution in toluene, 0.74 mmol), and the reaction mixture was stirred at room temperature for 5 min. This solution was then transferred via cannula to a solution of **35** (75 mg, 0.18 mmol) in dry dichloromethane (2 mL). The reaction mixture was then stirred at room temperature overnight and quenched with a saturated solution of ammonium chloride. The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and then filtered. The solvent was removed to give a dark oil which was used directly in the next step. To a solution of the amide (20 mg, 0.042 mmol) in methanol (3 mL) was added 10% Pd/C (40 mg), and the reaction mixture was stirred under an atmosphere of hydrogen gas at 60 psi for 3 days. The reaction mixture was filtered, and the solvent was removed under reduced pressure to give a pink oil. Purification by column chromatography (1:3 ethyl acetate/hexane) gave **36** as a colorless oil (10 mg, 50%): $[\alpha]_D$ −15 (*c* 0.6, $CHCl_3$); IR ($CDCl_3$) 3330, 2950, 1697, 1620, 1513, 1359, 1438, 1246, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.14 (m, 5H), 5.53 (s, 1H), 4.64 (d, 1H, J = 9 Hz), 4.11 (m, 1H), 3.53 (d, 9H, J = 7 Hz), 3.43 (m, 1H), 2.66 (dd, 1H, J = 7, 5 Hz), 2.47 (dd, 1H, J = 13, 7 Hz), 2.0−1.83 (m, 3H), 1.76−0.76 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 157.0, 139.4, 128.3, 125.7, 73.0, 70.2, 52.8, 44.1, 41.6, 39.6, 31.6, 30.5, 28.7, 26.4, 23.7, 20.1, 19.1; LRMS (*m*/*z*) ($M^+ + 1$) 477; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{28}H_{48}N_2O_4$ 477.3686, found 477.3692.

5*S*-[2-(Dimethoxyphosphoryl)acetyl]-4*S*-isopropyl-2*R*-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 37. To a solution of dimethyl methylphosphonate (2.98 g, 6 equiv, 24.0 mmol) in dry THF (50 mL) at −78 °C was added *n*-butyllithium (10.56 mL, 6.6 equiv, 26.4 mmol, 2.5 M in hexane), and the mixture was stirred for 30 min at −78 °C. A solution of **20** (1.5 g, 4.0 mmol) in THF (50 mL) was added, and the reaction mixture was stirred for 3 h at −78 °C. The reaction mixture was quenched with saturated ammonium chloride solution and then extracted with ethyl acetate (3 × 30 mL). The organic phases were combined, dried over anhydrous sodium sulfate solution, and filtered. The solvent was removed to give a colorless oil which was purified by column chromatography (1:1 ethyl acetate/hexane) to give **37** as a colorless oil (1.64 g, 88%): $[\alpha]_D$ −106.3 (*c* 0.8, $CHCl_3$); IR ($CDCl_3$) 2959, 1726, 1687, 1613, 1514, 1463, 1392, 1366, 1248, 1178, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, 2H, J = 8 Hz), 6.83 (d, 2H, J = 8 Hz), 4.60−4.30 (m, 2H), 3.32−3.78 (2s, 9H), 3.60−3.2 (m, 2H), 2.16−1.94 (m, 3H), 1.63 (m, 1H), 1.37−1.30 (m, 3H), 1.11 (s, 6H), 0.92−0.79 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 158.3, 154.7, 135.8, 128.2, 127.6, 113.2, 80.1, 65.6, 55.1, 53.5, 52.9, 39.4, 38.1, 27.9, 21.6, 18.1; LRMS (*m*/*z*) ($M^+ + 1$) 470; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{23}H_{36}NNaO_7P$ 492.2140, found 492.2127.

4*S*-Isopropyl-5*S*-(3-methoxycarbonylacryloyl)-2*R*-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 38. To a solution of the β-ketophosphonate (1.5 g, 3.2 mmol) in dry acetonitrile (75 mL) were added LiCl (536 mg, 4 equiv, 12.8 mmol), $CHOCO_2Me$ (1.12 g, 4 equiv, 12.8 mmol), and Hunig's base (1.65 g, 4 equiv, 12.8 mmol), and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate and washed sequentially with dilute HCl, saturated sodium bicarbonate solution, and brine. The organic phase was dried over anhydrous sodium sulfate and then filtered. The solvent was removed under reduced pressure to give a dark oil which was purified by column chromatography (1:4 ethyl acetate/hexane) to give **38** as a yellow oil (935 mg, 68%): $[\alpha]_D$ −33 (*c* 0.8, $CHCl_3$); IR ($CDCl_3$) 2960, 1731, 1693, 1613, 1513, 1392, 1304, 1247, 1175, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.26 (m, 3H), 6.86−6.83 (m, 3H), 4.76−4.32 (m, 2H), 3.78 (s, 6H), 2.0 (s, 3H), 1.60 (s, 1H), 1.33−0.70 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 165.6, 158.4, 154.6, 137.1, 136.7, 131.2, 128.2, 127.5, 113.2, 80.1, 65.5, 64.6, 55.1, 53.5, 52.2, 28.1, 27.9, 21.7, 17.8; LRMS (*m*/*z*) ($M^+ + 1$) 432; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{24}H_{34}NO_6$ 432.2400, found 432.2386.

5*S*-(1,4*S*-Dihydroxybutyl)-4*S*-isopropyl-2*R*-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 39. To a solution of **38** (900 mg, 2.1 mmol) in ethyl acetate (40 mL) was added 10% Pd/C, and the reaction mixture was stirred under an atmosphere of hydrogen gas. The catalyst was filtered, and the solvent was removed under reduced pressure to give a colorless oil which was purified by column chromatography (1:9 ethyl acetate/hexane) to give a colorless oil (813 mg, 90%): $[\alpha]_D$ −29.89 (*c* 0.8, $CHCl_3$); LRMS (*m*/*z*) ($M^+ + 1$) 434; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{24}H_{36}NO_6$ 434.2556, found 434.2542. To a solution of the above compound (750 mg, 1.73 mmol) in methanol (40 mL) was added sodium borohydride (excess), and the reaction was stirred until no remaining starting material was observed by TLC. The reaction mixture was quenched with saturated ammonium chloride solution, and the solvent was removed under reduced pressure. The crude was dissolved in ethyl acetate and washed with water. The organic phase was dried over anhydrous sodium sulfate and then filtered. The solvent was removed under reduced pressure to give a colorless oil which was purified by column chromatography (ethyl acetate) to give **39** as a colorless oil (620 mg, 88%): $[\alpha]_D$ −37.88 (*c* 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, 2H, J = 8 Hz), 6.82 (d, 2H, J = 8 Hz), 4.37 (d, 1H, J = 8 Hz), 3.91 (t, 1H, J = 9 Hz), 3.77 (s, 3H), 3.68 (m, 3H), 1.82 (m, 1H), 1.80−1.61 (m, 8H), 1.13 (s, 9H), 0.89 (d, 3H, J = 7 Hz), 0.82 (d, 3H, J = 9 Hz);^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 135.9, 127.5, 113.4, 80.8, 75.9, 65.6, 63.3, 62.8, 60.2, 55.1, 52.8, 32.9, 29.1, 28.9, 27.9, 27.5, 21.7, 17.9, 14.0; LRMS (*m*/*z*) ($M^+ + 1$) 408; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{23}H_{38}NO_5$ 408.2742, found 408.2750.

4*S*-Isopropyl-2*R*-(4-methoxyphenyl)-5*S*-(5-oxotetrahydrofuran-2*S*-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 40. To a solution of **39** (510 mg, 1.25 mmol) in dichloromethane (12 mL) were added TEMPO (19 mg) and iodobenzene diacetate (807 mg, 2 equiv, 2.5 mmol), and the reaction mixture was stirred for 6 h. The reaction mixture was quenched with sodium thiosulfate solution and then extracted with dichloromethane (3 × 30 mL). The organic phases were combined, then dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure to give a dark oil which was purified by column chromatography (1:2 ethyl acetate/hexane) to give **40** as a colorless oil (379 mg, 75%): $[\alpha]_D$ −8.53 (*c* 0.8, $CHCl_3$); IR ($CDCl_3$) 2961, 1778, 1691, 1613, 1513, 1389, 1366, 1247, 1173, 111, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, 2H, J = 9 Hz), 6.83 (d, 2H, J = 9 Hz), 4.59 (m, 1H), 4.30 (s, 1H), 4.20 (m, 1H), 3.78 (s, 3H), 2.52 (m, 2H), 2.34−2.20 (m, 3H), 2.04−1.70 (m, 3H), 1.25 (s, 9H), 0.92 (d, 3H, J = 7 Hz), 0.80 (d, 3H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 158.2, 135.7, 127.9, 113.4, 80.1, 66.2, 59.6, 55.4, 53.4, 52.3, 29.1, 28.5, 28.0, 26.0, 25.4, 21.8, 17.8;

LRMS (*m*/*z*) ($M^+ + 1$) 404; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{23}H_{34}NO_5$ 404.2427, found 404.2437.

5*S*-[4*S*-(1-Hydroxy-1-methylethyl)-5-oxotetrahydrofuran-2*S*-yl]-4*S*-isopropyl-2*R*-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 41. To a solution of **40** (300 mg, 0.74 mmol) in dry THF (10 mL) at −78 °C was added LiHMDS (0.82 mL, 1.1 equiv, 1 M solution in THF), and the reaction mixture was stirred for 1 h. Dry acetone (215 mg, 5 equiv, 3.7 mmol) was then added, and the reaction mixture was stirred for an additional 1 h. The reaction mixture was quenched by the addition of a saturated ammonium chloride solution and then extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, and then the solvent was removed to give **41** as a dark oil. Purification by column chromatography (1:4 ethyl acetate/hexane) gave the product as a colorless oil (299 mg, 87%): $[\alpha]_D$ +3.06 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, 2H, *J* = 9 Hz), 6.84 (d, 2H, *J* = 8 Hz), 4.61−4.1 (m, 2H), 3.79 (s, 3H), 2.83 (t, 1H, *J* = 10 Hz), 2.40−2.1 (m, 2H), 1.91 (m, 1H), 1.66 (s, 2H), 1.31 (m, 17H), 0.93 (d, 3H, *J* = 6 Hz), 0.82 (d, 3H, *J* = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 158.3, 135.6, 127.6, 113.5, 80.2, 70.9, 59.7, 55.1, 52.2, 51.0, 48.9, 29.1, 28.9, 28.3, 28.0, 27.5, 25.4, 21.9, 17.5; LRMS (*m*/*z*) ($M^+ + 1$) 462; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{26}H_{40}NO_6$ 462.2845, found 462.2855.

5*S*-(4*S*-Isopropenyl-5-oxotetrahydrofuran-2*S*-yl)-4*S*-isopropyl-2*R*-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 42. To a solution of **41** (150 mg, 0.33 mmol) in dry dichloromethane (6 mL) at −60 °C was added PCl_5 (74 mg, 1.1 equiv, 0.36 mmol), and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed to give a yellow oil. Purification by column chromatography (1:9 ethyl acetate/hexane) gave **42** as a white solid (115 mg, 80%): $[\alpha]_D$ +5 (*c* 1, $CHCl_3$); IR ($CDCl_3$) 2967, 1781, 1752, 1686, 1613, 1513, 1457, 1387, 1290, 1247, 1172, 1148 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, 2H, *J* = 8 Hz), 6.82 (d, 2H, *J* = 9 Hz), 4.99 (s, 1H), 4.92 (s, 1H), 4.53 (s, 1H), 4.35 (s, 1H), 4.15 (t, 1H, *J* = 7 Hz), 3.76 (s, 3H), 3.34 (t, 1H, *J* = 8 Hz), 2.33−2.24 (m, 3H), 2.02−1.71 (m, 6H), 1.23 (s, 9H), 0.90 (d, 3H, *J* = 7 Hz), 0.79 (d, 3H, *J* = 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 158.3, 139.7, 127.8, 113.4, 80.1, 66.1, 59.6, 55.1, 52.2, 46.9, 30.9, 29.3, 28.0, 27.8, 21.8, 17.7; LRMS (*m*/*z*) ($M^+ + 1$) 444; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{26}H_{38}NO_5$ 444.2736, found 444.2750.

5*S*-(3-Butylcarbamoyl-1*S*-hydroxy-4*S*-methylpentyl)-3*S*-isopropyl-2*R*-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 43. To a solution of **42** (100 mg, 0.26 mmol) in ethyl acetate (7 mL) was added 10% Pd/C, and the reaction mixture was stirred under an atmosphere of hydrogen gas. The catalyst was removed by filtration, then the solvent was removed, and the residue was purified by column chromatography (1:9 ethyl acetate/hexane) to give a colorless oil (90 mg, 90%): $[\alpha]_D$ +2.4 (*c* 0.8, $CHCl_3$); LRMS (*m*/*z*) ($M^+ + 1$) 446; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{26}H_{38}NO_5$ 446.2910, found 444.2906. To a solution of *n*-butylamine (52.6 mg, 4 equiv, 0.72 mmol) in dry dichloromethane (1 mL) was added trimethylaluminum (0.36 mL, 2 M solution in toluene, 0.71 mmol), and the reaction mixture was stirred at room temperature for 5 min. This solution was then transferred via cannula to a solution of the above compound (80 mg, 0.18 mmol) in dry dichloromethane (2 mL). The reaction mixture was stirred at room temperature overnight and quenched with a saturated solution of ammonium chloride. The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and filtered, and the solvent was removed. The residue was purified by column chromatography (1:3 ethyl acetate/hexane) to give **43** as a colorless oil (70 mg, 75%): $[\alpha]_D$ −31.9 (*c* 0.8, $CHCl_3$); IR ($CDCl_3$) 3322, 2959, 1740, 1651, 1538, 1514, 1464, 1401, 1367, 1289, 1247, 1175, 1153 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, 2H, *J* = 8 Hz), 6.81 (d, 2H, *J* = 8 Hz), 5.89 (s, 1H), 4.36 (d, 1H, *J* = 8 Hz), 3.87 (t, 1H, *J* = 8 Hz), 3.79 (s, 3H), 3.51 (t, 1H, *J* = 10 Hz), 3.34−3.20 (m, 2H), 2.24 (m, 1H), 2.17−1.62 (m, 6H), 1.51 (m, 2H), 1.41−1.15 (m, 14H), 1.0−0.73 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 158.2, 136.2, 127.6, 113.3, 80.7, 73.7, 65.5, 63.9, 55.1, 52.8, 50.5, 38.8, 36.6, 31.7, 30.2, 28.8, 27.8, 27.8, 21.6, 21.2, 21.1, 20.1, 19.9, 18.1, 13.6; LRMS (*m*/*z*) ($M^+ + 1$) 519; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{30}H_{50}N_2O_5$ 519.3806, found 519.3798.

2*R*-Isopropyl-4*S*-hydroxy-5*S*-*N*-butoxycarbamoylamino-7*S*-isopropyl-8-*p*-methoxyphenyloctanoic Acid *N*-Butylamide, 44. To a solution of **43** (30 mg, 0.058 mmol) in methanol (3 mL) was added 10% Pd/C (50 mg), and the reaction mixture was stirred under an atmosphere of hydrogen gas at 60 psi for 3 days. The reaction mixture was filtered, and the solvent was removed under reduced pressure to give a colored oil which was purified by column chromatography (1:2 ethyl acetate/hexane) to give **44** as a colorless oil (18 mg, 60%): $[\alpha]_D$ +17.2 (*c* 0.7, $CHCl_3$); IR ($CDCl_3$) 3333, 2958, 1693, 1633, 1513, 1455, 1366, 1246, 1175, 1044 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, 2H, *J* = 9 Hz), 6.79 (d, 2H, *J* = 8 Hz), 5.85 (s, 1H), 4.66 (d, 1H, *J* = 10 Hz), 3.77 (s, 3H), 3.52−3.17 (m, 4H), 2.61 (m, 1H), 2.38 (m, 1H), 2.05−1.90 (m, 2H), 1.60 (m, 4H), 1.5 (s, 9H), 1.08−0.71 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 156.6, 133.6, 129.9, 113.4, 79.1, 71.0, 55.1, 53.7, 51.3, 42.4, 39.6, 34.6, 32.2, 31.8, 31.6, 29.6, 29.2, 28.3, 27.9, 22.6, 21.1, 20.4, 20.0, 16.6, 14.0, 13.6, 12.1; LRMS (*m*/*z*) ($M^+ + 1$) 521; HRMS (*m*/*z*) ($M^+ + 1$) calcd for $C_{30}H_{53}N_2O_5$ 521.3941, found 521.3954.

4*S*-Isopropyl-5*S*-(4-methoxyphenyl)pyrrolidine-1,2*S*-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester, 45. To a solution of *p*-bromoanisole (18.7 g, 5 equiv, 0.1 mol) in dry THF (150 mL) at −78 °C was added *n*-butyllithium (44 mL, 0.11 mmol, 2.5 M in hexanes), and the reaction mixture was stirred at −78 °C for 1 h. The lithium reagent was then added to a stirring solution of copper(II) bromide−dimethyl sulfide complex (20.5 g, 5 equiv, 0.1 mol) at −78 °C, and the resultant black solution was stirred at −78 °C for 1 h. BF_3·OEt_2 (28.4 g, 10 equiv, 0.2 mol) was added in one portion, and the reaction mixture was stirred for a further 30 min. A solution of the aminal **12** (6 g, 20.0 mmol) in dry THF (20 mL) was added, and the reaction mixture was allowed to slowly warm to room temperature (black suspension). The mixture was quenched with a 1:1 mixture of ammonium chloride solution and aqueous ammonium hydroxide and extracted with ethyl acetate (4 × 50 mL). The organic fractions were combined, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure, and the resultant yellow oil was purified by column chromatography (1:4 ethyl acetate/hexane) to give **45** as a clear oil (5.29 g, 70%): IR (neat) 3019, 2976, 1746, 1686, 1612, 1586, 1512, 1395, 1368, 1298, 1215, 1178, 1160, 1036, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09−6.77 (m, 4H), 4.90 (d, 1H, *J* = 7 Hz), 4.63 (d, 1H, *J* = 9 Hz), 3.77 (s, 3H), 3.71 (s, 3H), 2.22−2.0 (m, 4H), 1.33−1.15 (s, 9H), 0.84−0.7 (t, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 158.4, 152.9, 133.2, 128.7,115. 8, 113. 1, 79.9, 63. 8, 59. 3, 55.0, 52.2, 49.9, 31.9, 27.9, 27.6, 21.7, 20.9; LRMS (*m*/*z*) (M^+) 377; HRMS (*m*/*z*) (M^+) calcd for $C_{21}H_{31}NO_5$ 377.2210, found 377.2202.

4*S*-Isopropyl-5*S*-(3-methoxycarbonylacryloyl)-2*S*-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 46. To a solution of dimethyl methylphosphonate (3.9 g, 6 equiv, 31.9 mmol) in dry THF (80 mL) at −78 °C was added *n*-butyllithium (13.6 mL, 6.4 equiv, 34.1 mmol, 2.5M solution in hexanes), and the mixture was stirred for 30 min at −78 °C. A solution of **45** (2 g, 5.31 mmol) was then added, and the reaction mixture was stirred for 3 h at −78 °C. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (3 × 30 mL). The organic phases were combined, dried over anhydrous sodium sulfate solution, and then filtered. The solvent was removed to give a colorless oil (1.99 g, 80%) which was used immediately in the next step. To a solution of the β-ketophosphonate (1.94 g, 4.14 mmol) in dry acetonitrile (10 mL) were added LiCl (870 mg, 5 equiv, 20.7 mmol), methyl glyoxalate (1.82 g, 5 equiv, 20.7 mmol), and Hunig's base (2.67 g, 5 equiv,

21 mmol), and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate and washed sequentially with dilute HCl, saturated sodium bicarbonate solution, and brine. The organic phase was dried over anhydrous sodium sulfate and then filtered. The solvent was removed under reduced pressure to give a brown oil which was purified by column chromatography (1:4 ethyl acetate/hexane) to give **46** as a yellow oil (1.0 g, 60%): $[\alpha]_D$ −4.76 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) 2959, 1730, 1693, 1611, 1521, 1394, 1247, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 1H, J = 16 Hz), 7.04 (d, 1H, J = 8 Hz), 6.85−6.79 (m, 4H), 4.93 (m, 2H), 3.77 (m, 6H), 2.24−1.91 (m, 4H), 1.25−1.14 (s, 9H), 0.82 (t, 3H, J = 6 Hz), 0.68 (t, 3H, J = 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 165.7, 158.5, 136.3, 133.0, 131.6, 128.7, 113.1, 79.9, 64.3, 63.9, 55.4, 52.2, 49.7, 30.6, 27.9, 27.6, 21.6, 20.9; LRMS (*m*/*z*) (M^+ + 1) 432; HRMS (*m*/*z*) (M^+ + 1) calcd, for C_{24} $H_{34}NO_6$ 432.2386, found 432.2396.

4*S*-Isopropyl-2*S*-(4-methoxyphenyl)-5*S*-(5-oxotetrahydrofuran-2*S*-yl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 47. To a solution of **46** (1 g, 2.32 mmol) in ethyl acetate (15 mL) was added 10% Pd/C, and the reaction mixture was stirred under an atmosphere of hydrogen gas. The catalyst was filtered, and the filtrate was processed as usual to give a colorless oil which was purified by column chromatography (1:9 ethyl acetate/hexane) to give the saturated ketoester as a colorless oil (904 mg, 90%): $[\alpha]_D$ −5.8 (*c* 0.5, $CHCl_3$); LRMS (*m*/*z*) (M^+ + 1) 434; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{24}H_{36}NO_6$ 434.2542, found 434.2551. To a solution of the above compound (500 mg, 1.15 mmol) in methanol (20 mL) was added sodium borohydride (excess), and the reaction was stirred at 0 °C until there was no remaining starting material (observed by TLC). The reaction mixture was quenched by the addition of a solution of ammonium chloride, and the solvents were removed. The mixture was triturated with diethyl ether, and the solvent was removed under reduced pressure to give a dark oil. The oil was dissolved in toluene (5 mL), pTSA(cat.) was added, and the mixture was heated to reflux for 5 h. The toluene was removed, and the crude was purified by column chromatography (ethyl acetate) to give **47** as a colorless oil (186 mg, 40%): $[\alpha]_D$ −16 (*c* 0.7, $CHCl_3$); IR ($CDCl_3$) 2929, 1780, 1693, 1611, 1513, 1462, 1365, 1250, 1178, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, 2H, J = 8 Hz), 6.74 (d, 2H, J = 8 Hz), 4.93 (m, 1H), 4.62 (s, 1H), 4.04 (m, 1H), 3.73 (s, 3H), 2.48−2.20 (m, 5H), 2.06−1.70 (m, 3H), 1.31 (s, 9H), 1.01 (d, 3H, J = 8 Hz), 0.92 (d, 3H, J = 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 159.2, 159.1, 131.6, 129.3, 113.4, 83.8, 68.2, 56.0, 54.9, 51.0, 41.9, 35.8, 25.4, 25.4, 20.1, 17.8; LRMS (*m*/*z*) (M^+ + 1) 404; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{23}H_{34}NO_5$ 404.2427, found 404.2448.

5*S*-[4*S*-(1-Hydroxy-1-methylethyl)-5-oxotetrahydrofuran-2*S*-yl]-3*S*-isopropyl-2*S*-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 48. To a solution of **47** (150 mg, 0.037 mmol) in dry THF (4 mL) at −78 °C was added LiHMDS (0.41 mL, 1.1 equiv, 1 M solution in THF), and the reaction mixture was stirred for 1 h. Dry acetone (107 mg, 5 equiv, 0.18 mmol) was then added, and the reaction mixture was stirred for an additional 1 h. The reaction mixture was quenched by the addition of a saturated ammonium chloride solution and then extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed to give a dark oil. Purification by column chromatography (1:4 ethyl acetate/hexane) gave **48** as a colorless oil (113 mg, 66%): $[\alpha]_D$ −6.5 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, 2H, J = 8 Hz), 6.81 (d, 2H, J = 9 Hz), 4.78 (d, 1H, J = 7 Hz), 4.60 (m, 1H), 4.41 (m, 1H), 3.78 (m, 3H), 2.75 (m, 2H), 2.40−1.70 (m, 3H), 1.34−1.17 (2s, 9H), 1.05 (s, 9H), 0.90−0.75 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.1, 162.6, 160.1, 138.1, 132.7, 117.3, 85.4, 83.8, 75.2, 70.0, 63.4, 59.4, 54.2, 53.3, 35.8, 32.4, 32.1, 31.7, 29.3, 25.9, 25.4; LRMS (*m*/*z*) (M^+ + 1) 462; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{26}H_{40}NO_6$ 462.2864, found 462.2855.

5*S*-(4*S*-Isopropenyl-5-oxotetrahydrofuran-2*S*-yl)-4*S*-isopropyl-2*S*-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 49. To a solution of **48** (100 mg, 0.22 mmol) in dry dichloromethane (2 mL) at −60 °C was added PCl_5 (50 mg, 1.1 equiv, 0.24 mmol), and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with saturated sodium bicarbonate solution and then extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed to give a yellow oil which was purified by column chromatography (1:9 ethyl acetate/hexane) to give **49** as a colorless oil (59 mg, 62%): $[\alpha]_D$ −65 (*c* 1, $CHCl_3$); IR ($CDCl_3$) 2692, 1776, 1693, 1651, 1513, 1456, 1456, 1366, 1298, 1271, 1249, 1179, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, 2H, J = 9 Hz), 6.80 (d, 2H, J = 9 Hz), 5.0−4.5 (m, 5H), 3.77 (s, 3H), 3.32 (t, 1H, J = 8 Hz), 2.63 (m, 1H), 2.32−2.20 (m, 3H), 2.09−1.65 (m, 5H), 1.04 (s, 9H), 0.98−0.75 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 158.4, 155.7, 140.0, 133.9, 128.5, 114.3, 133.1, 81.0, 79.5, 65.7, 58.7, 55.1, 50.0, 47.1, 31.2, 30.5, 28.2, 27.7, 21.6, 21.1, 20.3; LRMS (*m*/*z*) (M^+ + 1) 444; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{26}H_{38}NO_5$ 444.2741, found 444.2750.

5*S*-(3-Butylcarbamoyl-1*S*-hydroxy-4*S*-methylpentyl)-4*S*-isopropyl-2*S*-(4-methoxyphenyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester, 50. To a solution of **49** (50 mg, 0.11 mmol) in ethyl acetate (3 mL) was added 10% Pd/C, and the reaction mixture was stirred under an atmosphere of hydrogen gas. The catalyst was filtered, solvent was removed, and the residue was purified by column chromatography (1:9 ethyl acetate/hexane) to give a colorless oil (48 mg, 95%): $[\alpha]_D$ −28.8 (*c* 1, $CHCl_3$); LRMS (*m*/*z*) (M^+ + 1) 446; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{26}H_{38}NO_5$ 446.2914, found 446.2906. To a solution of *n*-butylamine (26 mg, 4 equiv, 0.36 mmol) in dry dichloromethane (1 mL) was added trimethylaluminum (0.18 mL, 2 M solution in toluene, 0.36 mmol), and the reaction mixture was stirred at room temperature for 5 min. This solution was transferred via cannula to a solution of the lactone (40 mg, 0.09 mmol) in dry dichloromethane (2 mL). The reaction mixture was stirred at room temperature overnight and quenched with a saturated solution of ammonium chloride, and the organic phase was separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL), and the combined organic extracts were dried over anhydrous sodium sulfate and filtered. The solvent was removed to give a dark oil which was purified by column chromatography (1:3 ethyl acetate/hexane) to give **50** as a colorless oil (28 mg, 60%): $[\alpha]_D$ −30.1 (*c* 0.9, $CHCl_3$); IR ($CDCl_3$) 3307, 2958, 1660, 1513, 1464, 1394, 1366, 1248, 1178, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, 2H, J = 8 Hz), 6.81 (d, 2H, J = 9 Hz), 5.91 (m, 1H), 4.76 (d, 1H, J = 7 Hz), 4.11 (t, 1H, J = 9 Hz), 3.79 (s, 3H), 3.35 (t, 1H, J = 11 Hz), 3.30−3.19 (m, 2H), 2.19−1.20 (m, 17H), 1.08 (s, 9H), 0.95−0.71 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 158.3, 133.6, 128.4, 113.4, 80.2, 74.7, 65.0, 63.3, 55.1, 49.7, 38.7, 36.8, 31.7, 30.3, 30.3, 27.8, 27.6, 21.8, 21.1, 21.0, 20.0, 13.7; LRMS (*m*/*z*) (M^+ + 1) 519; HRMS (*m*/*z*) (M^+ + 1) calcd for $C_{30}H_{51}N_2O_5$ 519.3800, found 519.3798.

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Supporting Information Available: Selected ^1H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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