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Enantioselective Synthesis of Antiinfluenza Compound A-315675

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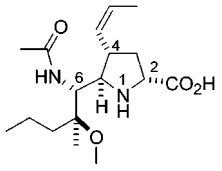
Drug discovery efforts at Abbott Laboratories have led to the identification of influenza neuraminidase inhibitor A-315675 (**1**) as a candidate for development as an antiinfluenza drug. A convergent, stereoselective synthesis of this highly functionalized pyrrolidine is reported that utilizes pyrrolinone **2** as the key intermediate. The C5, C6 stereochemistry was established through a diastereoselective condensation of chiral imine compound **3** with silyloxypyrrole **4** to give pyrrolinone **2**. The stereochemical outcome of this reaction depended critically on the choice of the imine functional group (FG), with tritylsulfenyl and (*R*)-toluenesulfinyl providing the desired products in good yields as crystalline intermediates. Conversion of pyrrolinone **2** into **1** was accomplished in seven subsequent steps, including Michael addition of *cis*-1-propenylcuprate at C4 and introduction of a cyano group as a carboxylic acid equivalent at C2.

Introduction

The viral surface glycoproteins haemagglutinin and neuraminidase mediate attachment and release of the influenza virus at the surface of infected cells. The use of inhibitors of viral neuraminidase has been shown to be an effective therapy for the treatment and prevention of influenza A and B infections,[1] and three potent inhibitors, namely, zanamavir (Relenza), oseltamivir (Tamiflu), and RWJ-270201 (BCX-1812), have already been developed (RWJ-270201 is in clinical trials). Recently, Abbott scientists have discovered a novel inhibitor series based on a pyrrolidine core structure, and structure−activity relationship (SAR) studies have led to the identification of A-315675 (**1**, Figure 1) as a highly potent, broad spectrum agent that is orally bioavailable when administered as a prodrug ester of the carboxylic acid.[2,3] The unique structural features found in **1**, such as its five stereogenic centers, the *cis*-propenyl group, and the tertiary ether side chain, are not only crucial for its biological activity but also add significant complexity to its synthesis. In the initial discovery, A-315675 was prepared through a racemic synthesis with low overall diastereoselectivity and was resolved by chiral chromatography at the end. To provide adequate material for preclinical studies, however, an efficient enantioselective synthesis of this highly functionalized pyrrolidine was needed. In this paper, a convergent, stereoselective synthesis of A-315675 is reported that utilized the condensation of chiral imine **3** (Scheme 1) with silyloxypyrrole **4** to provide pyrrolinone **2** as the key intermediate.[4]



1; A-315675

FIGURE 1. Structure of A-315675.

(1) Gubareva, L. V.; Kaiser, L.; Hayden, F. G. *Lancet* **2000**, *355*, 827−835.

(2) Maring, C.; McDaniel, K.; Krueger, A.; Zhao, C.; Sun, M.; Madigan, D.; DeGoey, D.; Chen, H.-J.; Yeung, M. C.; Flosi, W.; Grampovnik, D.; Kati, W.; Klein, L.; Stewart, K.; Stoll, V.; Saldivar, A.; Montgomery, D.; Carrick, R.; Steffy, K.; Kempf, D.; Molla, A.; Kohlbrenner, W.; Kennedy, A.; Herrin, T.; Xu, Y.; Laver, W. G. Presented at 14th International Conference on Antiviral Research, *Antiviral Res.* **2001**, *50*, A76; Abstract 129.

(3) Raja, S. N.; George, K. ST.; Fan, L.; Nequist, G.; Reisch, T.; Maring, C.; McDaniel, K.; DeGoey, D.; Darbyshire, K. *Abstracts of Papers*, 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL; American Society for Microbiology: Washington, DC, 2001; Abstract F-1683.

(4) This work has been presented in preliminary form. DeGoey, D. A.; Chen, H.-J.; Flosi, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. Presented at the 221st National Meeting of the American Chemical Society, San Diego, CA, April 2001; paper ORGN 320.

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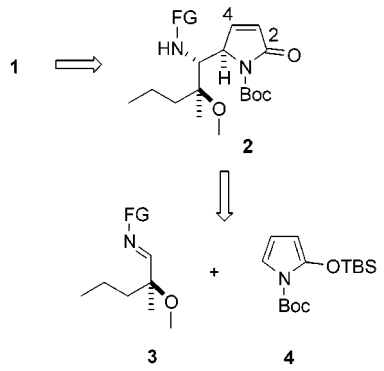
SCHEME 1

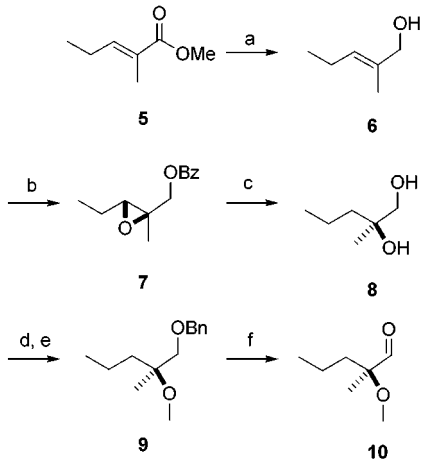


Results and Discussion

Retrosynthetic analysis of A-315675 led to the synthetic strategy shown in Scheme 1, which proposes pyrrolinone **2** as an intermediate. It has been shown in the literature that the 3-pyrrolin-2-one moiety can serve as a Michael acceptor for organocuprate reagents at the C4 position[5] and that the resulting lactam can be used to introduce a nitrile group as a carboxylic acid equivalent at C2.[6] In addition, several synthetic methods have been developed for the synthesis of pyrrolinones,[7] and Casiraghi and co-workers have conducted extensive research on their preparation from condensation reactions of silyloxypyrrole **4**.[8] An advantage of the strategy chosen in Scheme 1 was that the reaction between imine **3** and silyloxypyrrole **4** introduced the complex tertiary ether side chain of **1** as a preassembled fragment. While reactions of imines with 2-silyloxyfuran[8] and silyl enolates[9] have been reported, reactions of aliphatic aldimines with silyloxypyrroles have received little attention[10] and required investigation. Although the stereochemical outcome of the reaction with sterically hindered imine **3** was difficult to predict, the tertiary ether stereocenter could be envisioned to direct the facial selectivity of nucleophilic attack on the imine, and the choice of Lewis acid and solvent could influence the C5, C6 *erythro*/*threo* selectivity. Selection of the optimal functional group (FG) on the imine would influence its reactivity and allow for deprotection in the presence of other functionality in the molecule.

The aldehyde **10** (Scheme 2), the precursor to imines **3**, was prepared in seven steps starting from the commercially available ester **5**.[11] The ester was reduced with

SCHEME 2[a]



[a] Reagents and yields: (a) LAH (80%); (b) (i) AE; (ii) BzCl, Et_3N (65%); (c) LAH (63%); (d) BnBr, NaH (98%); (e) NaHMDS, MeI (98%); (f) (i) Pd on C, H_2; (ii) PCC (60%).

LAH, and the resulting allylic alcohol **6** was subjected to Sharpless asymmetric epoxidation.[12] For convenience, the volatile epoxide was isolated as the benzoate ester **7**, which underwent reductive ring opening and removal of the benzoate upon treatment with LAH to give the diol **8**.[13] The primary hydroxyl group of **8** was protected as a benzyl ether, and the tertiary alcohol was methylated to give **9**. Catalytic hydrogenolysis and PCC oxidation gave the aldehyde **10**.

Aldehyde **10** was converted into imines **3a**−**3f** under standard conditions and reacted with silyloxypyrrole **4**[14] (Scheme 3). Some conventional imine derivatives were prepared, and their reactions with **4** were examined to evaluate the viability of the condensation step. For example, conversion of aldehyde **10** into a benzylic imine, such as *p*-methoxybenzyl, benzhydryl, or trityl imine, and subsequent condensation with **4** using various Lewis acids, solvents, and temperatures led to no reaction and mainly to decomposition of the imines. Conversion of aldehyde **10** into *p*-methoxyphenyl (PMP) imine **3a** and subsequent condensation with **4** (Table 1, entries 1 and 2) using $SnCl_4$, $TiCl_4$, or $ZnCl_2$ as Lewis acids led to no reaction in CH_2Cl_2 and to only a trace of product using $BF_3{\cdot}Et_2O$. Lanthanide triflates have been shown to efficiently activate imines,[9,10] and reaction of **3a** with **4** using catalytic $Yb(OTf)_3$ yielded two C5, C6 *erythro* products, **11a** and **11b** (Scheme 3), in nearly equal amounts (Table 1, entry 3) as the only products. Varying the solvent and temperature for this condensation proved to have only minor effects on the product ratio, although

(5) For examples of organocuprate additions to pyrrolinones, see: (a) Hanessian, S.; Ratovelomanana, V. *Synlett* **1990**, 501−503. (b) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814−3819. (c) Herdeis, C.; Hubmann, H. P. *Tetrahedron: Asymmetry* **1992**, *3*, 1213−1221. (d) Herdeis, C.; Hubmann, H. P.; Lotter, H. *Tetrahedron: Asymmetry* **1994**, *5*, 351−345. (e) Baussanne, I.; Royer, J. *Tetrahedron Lett.* **1998**, *39*, 845−848.

(6) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927−964, and references cited therein.

(7) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1759−1769, and references cited therein.

(8) Review: Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109−118.

(9) For examples, see: Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233−234, and references cited therein.

(10) Reactions of a silyloxypyrrole with aromatic aldimines have recently been reported: Dudot, B.; Royer, J.; Sevrin, M.; George, P. *Tetrahedron Lett.* **2000**, *41*, 4367−4371.

(11) Available from Aldrich.

(12) Asymmetric expoxidation of **6** has been reported: Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464−465.

(13) The ee was found to be 96%, as determined by conversion of **8** to the Mosher ester (mono-MTPA) under standard conditions and ^{19}F NMR analysis (^{19}F NMR ($CDCl_3$) δ −71.92 for 2-(*S*)-**8** and −71.96 for 2-(*R*)-**8**). Preparation of diol **8** by asymmetric dihydroxylation of 2-methyl-1-pentene was examined and shown to provide material with low ee (ca. 60%) using a modified Sharpless condition, which was reported to show improvement in ee for some terminal olefins. See: Torii, S.; Liu, P.; Bhuvaneswari, N.; Amatore, C.; Jutand, A. *J. Org. Chem.* **1996**, *61*, 3055−3060.

(14) For preparation of **4**, see: Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L. *J. Org. Chem.* **1992**, *57*, 3760−3763, and references cited therein.

SCHEME 3

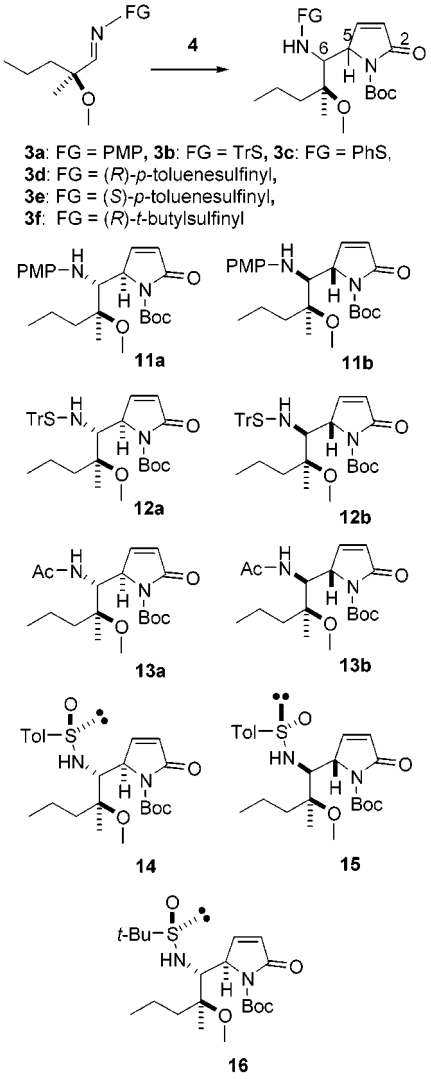


TABLE 1. Condensation of Imines 3a−f with Silyloxypyrrole 4[a]

entry	imine	Lewis acid	solvent, temp (°C)	products, (ratio), yield[b]
1	**3a**	$SnCl_4$	CH_2Cl_2, −30	no reaction
2	**3a**	$BF_3{\cdot}Et_2O$	CH_2Cl_2, −30	trace product
3	**3a**	$Yb(OTf)_3$	CH_2Cl_2, rt	**11a:11b**, (1:1.1), 66%
4	**3a**	$Yb(OTf)_3$	CH_3CN, −25	**11a:11b**, (1:1.7)
5[c]	**3a**	TMSOTf	Et_2O, −30	**11a:11b**, (1:2.3)
6[d]	**3b**	$BF_3{\cdot}Et_2O$	Et_2O, −78 to −50	**12a:12b**, (3:1 to 7:1), 60% to 90%
7	**3b**	$Yb(OTf)_3$	CH_2Cl_2, 0	**12a:12b**, (3.6:1), 61%
8[d,e]	**3c**	$BF_3{\cdot}Et_2O$	Et_2O, −78	**13a:13b**, (1:1.9), 41%
9[f]	**3d**	TMSOTf	CH_2Cl_2, −23	**14**, 59% to 82%
10[f]	**3e**	TMSOTf	CH_2Cl_2, −30	**15**, 61%
11[f]	**3f**	TMSOTf	CH_2Cl_2, −30	**16**, 36%

[a] All reactions were carried out with 1.0 equiv of **4** and Lewis acid or catalytic lanthanide triflates (0.1 equiv) unless otherwise indicated. [b] Ratio determined by ^1H NMR; isolated yield based on imine, where available. [c] Used 1.5 equiv of TMSOTf. [d] Used 2.0 equiv of **4** and 2.5 equiv of $BF_3{\cdot}Et_2O$. [e] Treatment of unstable PhS products with 80% AcOH/H_2O and acetylation with Ac_2O provided **13a** and **13b**. [f] Used 1.5 equiv of TMSOTf and **4**.

a slight excess of the undesired product **11b** could be obtained (Table 1, entry 4). Using other catalytic metal triflates, including $La(OTf)_3$, $Sc(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, and $Mg(OTf)_2$, also led to a mixture of **11a** and **11b**, but the choice of metal had little influence on the product ratio. The use of TMSOTf as Lewis acid gave modest selectivity, but the conversion of imine to product was only 25% by NMR (Table 1, entry 5). Various means of deprotecting the PMP-amine product **11a** were attempted and were problematic, leading to only traces of product.

A higher degree of stereocontrol was realized by conversion of aldehyde **10** into tritylsulfenimine (TrS) **3b** (Table 1, entries 6 and 7).[15] Condensation of **3b** with silyloxypyrrole **4** in the presence of $BF_3{\cdot}Et_2O$ in ether or CH_2Cl_2 led to a mixture of C5, C6 *erythro* isomers **12a** and **12b** (Scheme 3), favoring the desired isomer **12a**. The ratio of products (**12a**:**12b)** was found to be somewhat variable, and selectivities ranged from 3:1 to 7:1. The desired isomer **12a** was crystalline, and the structural assignment was determined by single-crystal X-ray analysis, while the minor isomer **12b** was obtained as an oil. Optimized conditions for larger scale reactions required larger amounts of $BF_3{\cdot}Et_2O$ (2.5 equiv) and silyloxypyrrole **4** (2 equiv) in order to obtain a complete reaction, and yields ranged from 60% to 90%. A similar product ratio for this condensation was observed using catalytic $Yb(OTf)_3$ (**12a**:**12b**, 3.6:1) in various solvents, and this choice of Lewis acid made it possible to obtain a reasonable yield of products by combining aldehyde **10**, tritylsulfenamide, and silyloxypyrrole **4** in one pot in the presence of $MgSO_4$.

To address the generality of the product ratio observed using sulfenimines, phenylsulfenimine (PhS) **3c** (Table 1, entry 8) was prepared.[16] Condensation of **3c** with silyloxypyrrole **4** using $BF_3{\cdot}Et_2O$ resulted in **13a** and **13b** (Scheme 3, after hydrolysis of the labile phenylsulfenyl group and acetylation of the amine), which were obtained in a ratio of 1:1.9, favoring the undesired isomer and in contrast with the ratio observed using tritylsulfenimine **3b**.

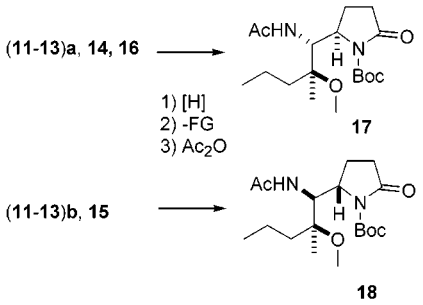
Stereoselective transformations using chiral auxiliary-containing imines have recently attracted the attention of organic chemists, and sulfinimines are especially attractive due to the high degree of stereoselectivity observed in their addition reactions and the mild conditions required for removing the sulfinyl groups.[17] As entries 9 and 10 (Table 1) indicate, a level of complete stereocontrol was observed in the condensation of the diastereomeric toluenesulfinimines **3d** and **3e** with silyloxypyrrole **4**. Condensation of (*R*)-*p*-toluenesulfinimine **3d** with **4** in the presence of TMSOTf resulted in the production of the crystalline C5, C6 *erythro* isomer **14**, exclusively (Scheme 3). The structural assignment of **14** was determined by single-crystal X-ray analysis. Employing the diastereomeric (*S*)-*p*-toluenesulfinimine

(15) Branchaud reported the preparation and synthetic use of TrS imines previously. Branchaud, B. P. *J. Org. Chem.* **1983**, *48*, 3531−3538.

(16) For the preparation of phenylsulfenimines, see: Davis, F. A.; Slegeir, W. A. R.; Evans, S.; Schwartz, A.; Goff, D. L.; Palmer, R. *J. Org. Chem.* **1973**, *38*, 2809−2813.

(17) For a review on *p*-toluenesulfinimines, see: Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13−18. For preparation of *p*-toluenesulfinimines, see: Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang H. *J. Org. Chem.* **1999**, *64*, 1403−1406. For preparation and uses of *tert*-butylsulfinimines, see: Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278−1284, and references cited therein.

SCHEME 4

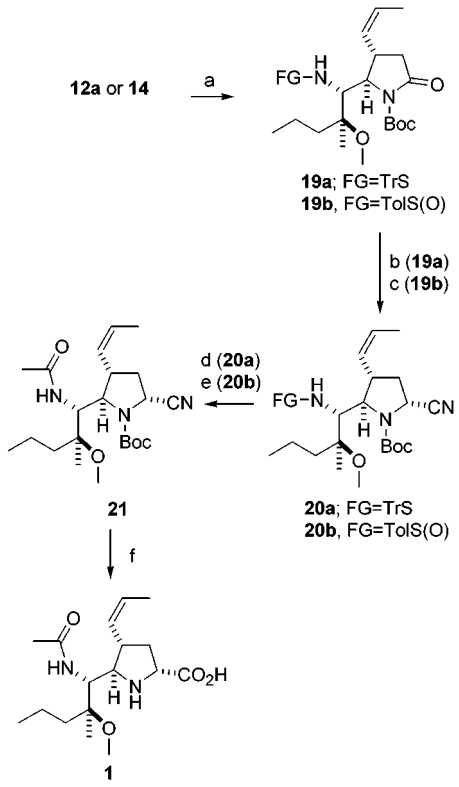


3e led to a reversal of the facial selectivity on the imine, giving **15** (Scheme 3), exclusively, and demonstrating the strong influence of the chirality of the sulfinyl group on the stereochemical outcome of these reactions. Other Lewis acids, such as $Yb(OTf)_3$, $BF_3{\cdot}Et_2O$, $TiCl_4$, and TMSCl, were also examined and found to be less effective, in that they led to sluggish coupling reactions. The condensation with *tert*-butyl sulfinimine **3f** (Table 1, entry 11) also yielded the desired product **16** selectively (Scheme 3), but the reaction was incomplete even under prolonged reaction time, possibly due to the steric hindrance associated with this sulfinyl group.

It is interesting to note that while the ratio of products in reactions between **3a**−**3f** and silyloxypyrrole **4** could be controlled by the functional group on the imine, only C5, C6 *erythro* stereoisomers were observed in each case. The C5, C6 *threo* products could not be detected by ^{1}H NMR, regardless of the choice of functional group, solvent, or Lewis acid. In contrast, *erythro*/*threo* selectivity in the direct condensation of aldehyde **10** with **4** depended upon the choice of Lewis acid and solvent, as Casiraghi demonstrated previously for the condensation of **4** with other aldehydes.[18] Reaction of aldehyde **10** with **4** using $BF_3{\cdot}Et_2O$ in ether favored the C5, C6 erythro isomer (*erythro*/*threo*, 19:1), while using $SnCl_4$ in ether gave the C5, C6 *threo* isomer, exclusively. The facial selectivity of nucleophilic attack on the aldehyde resulted only in compounds with the *R* configuration at the resulting stereocenter bearing the hydroxyl group.[19]

The structural determination of each product from the condensations of imines **3a**−**3f** with **4** was accomplished through a combination of X-ray crystallography and the synthesis of correlation compounds (Scheme 4). Since many of the products were not crystalline, two correlation compounds, **17** and **18**, were prepared through the following sequence: (1) reduction of the pyrrolinone double bond (H_2/Pd on C, or $NaBH_4/NiCl_2$) in order to avoid possible epimerization at acidic C5, (2) removal of the functional group under the appropriate conditions (ozonolysis for PMP, PPTS/MeOH for TrS, and TFA/MeOH or HCl/MeOH for sulfinyl groups), and (3) acetylation (Ac_2O, Et_3N) of the amine. Compounds **12a** and **14**, the structures of which were determined by single-crystal X-ray analyses, were used to prepare and establish the stereochemistry of compound **17**. Correlation compound **18** was crystalline, and its stereochemistry was proven through single-crystal X-ray analysis. All condensation products that were not crystalline were subjected to the sequence above and correlated with either **17** or **18** by ^{1}H NMR.

SCHEME 5[a]



[a] Reagents and yields: (a) *cis*-1-propenylmagnesium bromide, Cu(I)Br·DMS, TMSCl (89% from **12a**; 74% from **14**); (b) (i) DIBALH (87%); (ii) PPTS, MeOH; (iii) TMSCN, $BF_3{\cdot}Et_2O$ (77%); (c) (i) DIBALH; (ii) TMSCN, TMSOTf (97%); (d) (i) PPTS, MeOH, reflux; (ii) Ac_2O, Et_3N (69%); (e) (i) TFA, MeOH; (ii) Ac_2O, Et_3N (76%); (f) 6 N HCl, 60 °C (99%).

Compounds **12a** and **14** were converted to the final product **1** (Scheme 5). Introduction of the *cis*-propenyl group at C4 required a stereoselective *trans*-addition (relative to the C5 ring substituent) of a *cis*-propenyl cuprate reagent, and excellent *trans*-selectivity with no ring-opening has already been reported for the addition of organocuprate reagents to pyrrolinones in the presence of TMSCl.[5] Although *cis*-vinylic cuprates with high isomeric purity have been prepared from *cis*-propenyllithium[20] or through carbocupration of acetylenes,[21] ease of preparation prompted us to explore addition of propenyl cuprates prepared from Grignard reagents. *cis*-1-Propenylmagnesium bromide, prepared under the standard conditions from magnesium and *cis*-1-bromopropene (reportedly leading to isomerization (10%) of olefin geometry[22]), was reacted with Cu(I)Br·DMS to form the required cuprate reagent. Reaction of this cuprate (5 equiv) with **12a** in the presence of TMSCl gave 89%

(18) Zanardi, F.; Battistini, L.; Nespi, M.; Rassu, G.; Spanu, P.; Cornia, M.; Casiraghi, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1167−1180.

(19) Experimental details of reaction of **10** with **4** are available in the Supporting Information.

(20) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379−1389. Linstrumelle, G.; Krieger, J. K.; Whitesides, G. M. *Org. Synth.* **1976**, *55*, 103−113.

(21) Lipshutz, B. H. In *Organometallics in Synthesis*; Schlosser, M., Ed.; John Wiley and Sons: New York, 1994; p 293.

(22) Isomerization of the propenyl olefin geometry has been reported to occur under these conditions. Mechin, B.; Naulet, N. *J. Organomet. Chem.* **1972**, *39*, 229−236.

yield of lactam **19a** (Scheme 5) that was contaminated with traces (from 2% to undetectable) of the *trans*-propenyl isomer.[23] We speculated that *cis*-1-propenylcuprate may react with **12a** more rapidly than the corresponding *trans*-propenyl isomer, since the *cis*/*trans* ratio of products did not appear to reflect the ratio presumed for the reagent. In support of this hypothesis, **12a** was reacted with cuprate reagent (5 equiv) prepared from *trans*-1-propenylmagnesium bromide (prepared from magnesium turnings with *trans*-1-bromopropene under the standard conditions, and reported to result in 20% isomerization of olefin geometry[22]), resulting in a mixture of **19a** and the *trans*-propenyl isomer in a ratio of 1.5:1, respectively. Compound **19a** was also the major product, along with 11.5% of the *trans*-propenyl isomer, observed using commercially available 1-propenylmagnesium bromide (contains a mixture of olefin isomers)[11] to prepare the cuprate.

Partial reduction of **19a** to the hemiaminal with DIBALH (Scheme 5) was followed by conversion to the α-methoxycarbamate through treatment with PPTS in methanol. Reaction of this compound with TMSCN in the presence of $BF_3{\cdot}Et_2O$ gave compound **20a** in 77% yield, along with 4% of the epimeric cyano compound[24] that was removed by chromatography. A high degree of *trans* selectivity (relative to the C5 substituent) for nucleophilic addition to *N*-acyliminium ions generated from pyrrolidines has been reported previously.[6] The tritylsulfenyl protecting group in **20a** proved to be susceptible to acidic hydrolysis and was removed by refluxing in methanol with PPTS.[25] Acetylation of the amine gave crystalline intermediate **21** (69% yield, X-ray crystallographic analysis was obtained), and treatment with 6 N HCl at 60 °C gave **1** in high yield.

Compound **14** also underwent smooth Michael addition of the *cis*-1-propenylcuprate to give **19b** along with a minor side product identified as the toluenesulfenamide from deoxygenation of the toluenesulfinamide.[26] In this case, introduction of the cyano group proceeded with slight modifications to give exclusively the desired nitrile **20b**. The intermediate hemiaminal was transformed directly to the cyano compound by treatment with TMSCN, and the choice of TMSOTf as Lewis acid resulted in a much faster reaction rate than with $BF_3{\cdot}Et_2O$. Deprotection of the toluenesulfinamide **20b** proceeded under standard conditions (TFA, methanol).[17] The final product **1** was obtained by sequential acetylation of the amine and hydrolysis with 6 N HCl.

Conclusion

In summary, an efficient, enantioselective synthesis of the promising antiinfluenza compound A-315675 was carried out.[27] The key step involving condensation of imine **3** with silyloxypyrrole **4** established the main skeleton of the compound and also two important stereocenters in one step. Selection of tritylsulfenyl or (*R*)-toluenesulfinyl as functional groups on imine **3** led to a synthetically useful degree of stereocontrol in the condensation reactions. The resultant pyrrolinone products **12a** and **14** were crystalline intermediates and served as chiral templates that directed the subsequent stereoselective Michael addition of *cis*-1-propenylcuprate and the introduction of the cyano group.

Experimental Section

General Methods. Tetrahydrofuran (THF) and ether were freshly distilled from sodium benzphenone ketyl. All other solvents and reagents were obtained from commercial suppliers and were used without further purification. Where appropriate, reactions were carried out in flame or oven-dried glassware under an inert atmosphere. ^{1}H NMR spectra were obtained at either 300 or 500 MHz and chemical shifts are reported in parts per million (ppm, δ), using as a reference the appropriate signal for residual solvent protons. ^{13}C NMR spectra were obtained at 75 MHz without proton decoupling, and chemical shifts are reported in parts per million, using the center signal of the solvent signal as a reference. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison NJ. Column chromatography was carried out using 230−400 mesh silica gel.

(2*E*)-2-Methylpent-2-en-1-ol (6). To a slurry of lithium aluminum hydride (4.72 g, 124.2 mmol) in ether (180 mL) at 0 °C was added a solution of methyl (2*E*)-2-methylpent-2-enoate (6.37 g, 49.6 mmol) in ether (120 mL). After stirring at 0 °C for 30 min, the reaction mixture was stirred at room temperature for 1.5 h. The reaction was cooled to 0 °C and quenched very carefully with water (4.7 mL), 15% NaOH (4.7 mL), and water (14.1 mL). The mixture was filtered, dried ($MgSO_4$), filtered again, and concentrated. The crude product was distilled (55 Torr, 85−87 °C) to give **6** (3.96 g, 80%): ^{1}H NMR ($CDCl_3$) δ 5.44−5.38 (m, 1H), 4.00 (d, J = 5.4 Hz, 2H), 2.10−2.00 (m, 2H), 1.67 (s, 3H), 0.97 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 134.1, 128.2, 68.9, 20.8, 13.9, 13.5. Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.57; H, 12.12.

[(2*R*,3*R*)-3-Ethyl-2-methyloxiran-2-yl]methyl Benzoate (7). To a mixture of (−)-dimethyl D-tartrate (0.545 g, 3.06 mmol), titanium tetraisopropoxide (0.76 g, 2.55 mmol), molecular sieves (4 Å, 1.8 g), and *tert*-butylhydroperoxide (5 M solution in decane, 20 mL) in dichloromethane (180 mL) at −20 °C was added a solution of **6** (5.1 g, 51 mmol) in dichloromethane (35 mL) over 30 min, and the reaction mixture was stirred for 3.5 h. To this mixture at −20 °C were added (cautiously) trimethyl phosphite (9 mL, 76.5 mmol), triethylamine (8.5 mL, 61.2 mmol), and benzoyl chloride (5.92 mL, 51 mmol), and the mixture was stirred for 1.5 h before being washed with 10% tartaric acid (2 × 200 mL), saturated sodium bicarbonate (3 × 150 mL), and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by chromatography (gradient, hexanes to 85% hexanes/15% ethyl acetate) to give **7** (7.35 g, 65%): ^{1}H NMR ($CDCl_3$) δ 8.09−8.05 (m, 2H), 7.61−7.24 (m, 3H), 4.42 (d, J = 11.7 Hz, 1H), 4.20 (d, J = 11.7 Hz, 1H), 2.94 (t, J = 7.5 Hz, 1H), 1.71−1.53 (m, 2H), 1.40 (s, 3H), 1.06 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.2, 133.1, 129.7, 128.4, 118.8, 69.1, 62.6, 58.6, 21.5, 14.3, 10.40. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.76; H, 7.20.

(2*S*)-2-Methylpentane-1,2-diol (8). To a suspension of lithium aluminum hydride (3.8 g, 0.1 mol) in THF (160 mL) at 0 °C was added **7** (7.35 g, 0.033 mol) in THF (40 mL). After stirring for 0.5 h, the mixture was warmed to room temperature, cooled to 0 °C, and quenched cautiously with water (5 mL), 15% NaOH (5 mL), and water (15 mL). The mixture was filtered, and the filtrate was concentrated. The residue was purified by chromatography (gradient, hexanes to 60% hex-

(23) The ratio was determined by ^{1}H NMR integration.
(24) NOE analysis was consistent with this assignment.
(25) The tritylsulfenamide group has been reported to be generally quite stable to acidic hydrolysis. Branchaud, B. P. *J. Org. Chem.* **1983**, *48*, 3538−3544.
(26) Careful attention had to be paid to the amount of reagents used, as excess cuprate or TMSCl led to a significant amount of side product.
(27) An enantioselective total synthesis of A-315675 has recently been completed by Stephen Hanessian and co-workers. We thank Prof. Hanessian for informing us of the details of his synthesis; personal communication.

anes/40% ethyl acetate) to give **8** (2.48 g, 63%): ^{1}H NMR ($CDCl_3$) δ 3.47 (dd, J = 5.8, 10.9 Hz, 1H), 3.40 (dd, J = 5.8, 10.9 Hz, 1H), 1.97 (t, J = 5.8 Hz, 1H), 1.82 (s, 1H), 1.50−1.31 (m, 4H), 1.17 (s, 3H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 73.0, 69.8, 41.1, 23.2, 17.0, 14.6. Anal. Calcd for $C_6H_{14}O_2$: C, 60.98; H, 11.94. Found: C, 60.84; H, 11.60.

({[(2*S*)-2-Methoxy-2-methylpentyl]oxy}methyl)benzene (9). To a suspension of sodium hydride (95% powder, 5.08 g, 0.212 mol) in THF (210 mL) at 0 °C was added **8** (10.02 g, 0.085 mol) in THF (85 mL). After stirring for 1 h, benzyl bromide (12.1 mL, 0.102 mol) was added, and the reaction mixture was warmed to room temperature and stirred for 16 h. The mixture was quenched with saturated NH_4Cl (30 mL), and the solvent was removed via Rotovap. The residue was partitioned between water and ether, and the ether layer was separated and dried ($MgSO_4$). The crude product was purified by chromatography (gradient, hexanes to 85% hexanes/15% ethyl acetate) to give (2*S*)-1-(benzyloxy)-2-methylpentan-2-ol (17.26 g, 98%): ^{1}H NMR ($CDCl_3$) δ 7.39−7.27 (m, 5H), 4.56 (s, 2H), 3.31 (dd, J = 8.8, 17.0 Hz, 2H), 1.52−1.23 (m, 4H), 1.16 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.3, 128.4, 127.7, 127.6, 77.4, 73.4, 72.2, 41.5, 23.7, 17.0, 14.7. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.92; H, 9.55.

To a solution of the above alcohol (17.26 g, 0.083 mol) in THF (280 mL) at 0 °C was added sodium bis(trimethylsilyl)-amide (NaHMDS) (1 M in THF, 166 mL, 0.166 mol). The mixture was stirred for 1 h followed by the addition of methyl iodide (25.8 mL, 0.415 mol). The mixture was warmed to room temperature and stirred for 16 h. Upon completion, the reaction mixture was quenched with saturated NH_4Cl (25 mL) and water (250 mL). The organic layer was separated, and the aqueous layer was extracted with ether. The organic layers were combined, washed with brine, and dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (gradient, hexanes to 90% hexanes/10% ethyl acetate) to give **9** (18.03 g, 98%): ^{1}H NMR ($CDCl_3$) δ 7.35−7.26 (m, 5H), 4.55 (s, 2H), 3.36−3.29 (m, 2H), 3.21 (s, 3H), 1.58−1.42 (m, 2H), 1.34−1.22 (m, 2H), 1.14 (s, 3H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.5, 128.3, 127.6, 127.5, 76.5, 74.2 73.4, 49.5, 37.6, 20.5, 16.6, 14.7. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.56; H, 9.79.

(2*S*)-2-Methoxy-2-methylpentanal (10). To a solution of **9** (5 g, 22.5 mmol) in dichloromethane (75 mL) was added 20% $Pd(OH)_2$ on carbon (1.6 g), and the flask was fitted with a hydrogen balloon. The mixture was stirred for 3.5 h after which the catalyst was filtered and rinsed with dichloromethane (75 mL). The filtrate was reacted directly with pyridinium chlorochromate (14.5 g, 67.5 mmol) at 0 °C in the presence of molecular sieves (4 Å, 5 g) and Celite (5 g). The mixture was stirred at room temperature for 1.5 h, diluted with ether (200 mL), and filtered through a short pad of silica gel with additional ether. The solvent was removed by short-path distillation, and the remaining liquid was distilled (60 Torr, 72−75 °C) to give **10** (1.74 g, 60% for two steps): ^{1}H NMR ($CDCl_3$) δ 9.58 (s, 1H), 3.28 (s, 3H), 1.64−1.51 (m, 2H), 1.38−1.23(m, 2H), 1.22 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.3, 82.4, 51.5, 36.8, 17.4, 16.2, 14.5. Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 61.27; H, 10.31.

***tert*-Butyl (2*R*)-2-{(1*R*,2*S*)-2-Methoxy-1-[(4-methoxyphenyl)amino]-2-methylpentyl}-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (11a) and *tert*-Butyl (2*S*)-2-{(1*S*,2*S*)-2-Methoxy-1-[(4-methoxyphenyl)amino]-2-methylpentyl}-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (11b).** To a suspension of $Yb(OTf)_3$ (12 mg, 0.019 mmol) and $MgSO_4$ (70 mg, 0.58 mmol) in dichloromethane (0.50 mL) were added **10** (22 mg, 0.19 mmol) in dichloromethane (0.35 mL) and *p*-anisidine (24 mg, 0.19 mmol) in dichloromethane (0.25 mL), and the mixture was stirred at room temperature for 0.5 h. Compound **4** (59 mg, 0.19 mmol) in dichloromethane (0.35 mL) was added, and the reaction was stirred for 1 h and then quenched with water. The reaction was diluted with ethyl acetate, and the organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by gradient chromatography (hexanes to 35% EtOAc/65% hexanes) to provide **11a** (25 mg, 31% yield, R_f 0.48 in 35% EtOAc/65% hexanes) and **11b** (28 mg, 35% yield, R_f 0.36 in 35% EtOAc/65% hexanes). **11a**: ^{1}H NMR ($CDCl_3$) δ 7.42 (dd, J = 2.0, 6.1 Hz, 1H), 6.65 (m, 2H), 6.41 (m, 2H), 6.06 (dd, J = 1.7, 6.1 Hz, 1H), 4.91 (m, 1H), 4.28 (dd, J = 3.4, 10.5 Hz, 1H), 3.70 (s, 3H), 3.42 (d, J = 10.8 Hz, 1H), 3.26 (s, 3H), 1.90−1.29 (m, 4H), 1.52 (s, 9H), 1.18 (s, 3H), 1.02 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 168.9, 151.7, 150.4, 148.6, 143.5, 127.3, 115.0, 114.0, 82.7, 79.7, 63.7, 60.3, 55.8, 49.3, 38.4, 28.1, 20.6, 17.5, 14.9. Anal. Calcd for $C_{23}H_{34}N_2O_5$: C, 66.0; H, 8.19; N, 6.69. Found: C, 65.70; H, 7.82; N, 6.81. **11b**: ^{1}H NMR ($CDCl_3$) δ 7.39 (dd, J = 2.4, 6.1 Hz, 1H), 6.65 (m, 2H), 6.40 (m, 2H), 6.05 (dd, J = 1.7, 6.1 Hz, 1H), 4.93 (m, 1H), 4.29 (dd, J = 2.4, 10.5 Hz, 1H), 3.70 (s, 3H), 3.45 (d, J = 10.5 Hz, 1H), 3.26 (s, 3H), 1.58 (s, 9H), 1.55−1.10 (m, 4H), 1.39 (s, 3H), 0.69 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 169.0, 151.7, 150.1, 148.9, 143.0, 127.4, 115.0, 114.0, 82.7, 79.6, 64.3, 59.6, 55.8, 48.7, 37.4, 28.2, 20.6, 18.3, 14.5. Anal. Calcd for $C_{23}H_{34}N_2O_5$: C, 66.0; H, 8.19; N, 6.69. Found: C, 65.97; H, 8.11; N, 6.65.

***tert*-Butyl (2*R*)-2-{(1*R*,2*S*)-2-Methoxy-2-methyl-1-[(tritylthio)amino]pentyl}-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (12a) and *tert*-Butyl (2*S*)-2-{(1*S*,2*S*)-2-Methoxy-2-methyl-1-[(tritylthio)amino]pentyl}-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (12b).** A mixture of **10** (3.87 g, 29.8 mmol), triphenylmethanesulfenamide (8.7 g, 29.8 mmol), $MgSO_4$ (10.8 g, 89.4 mmol), and PPTS (150 mg, 0.60 mmol) in 60 mL of ether was stirred at room temperature for 18 h. The mixture was filtered, and the filtrate was concentrated. **3b**: ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1H), 7.32−7.23 (m, 15H), 2.97 (s, 3H), 1.39−1.34 (m, 2H), 1.17−1.04 (m, 2H), 0.99 (s, 3H), 0.80 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.9, 144.2, 130.0, 127.9, 127.0, 80.1, 50.7, 39.8, 19.4, 16.7, 14.6. Anal. Calcd for $C_{26}H_{29}NOS$: C, 77.38; H, 7.24; N, 3.47. Found: C, 77.55; H, 7.11; N, 3.46.

To imine **3b** (12.0 g, 29.8 mmol) and **4** (17.7 g, 59.6 mmol) in ether (100 mL) at −78 °C was added $BF_3{\cdot}Et_2O$ (9.4 mL, 74.4 mmol) dropwise and the reaction was stirred at −78 °C for 2 h and then at −50 °C for 1 h. The reaction was quenched with saturated sodium bicarbonate (180 mL) and allowed to warm to room temperature. The mixture was diluted with chloroform (500 mL), and the organic layer was separated and washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (20% ethyl acetate/80% hexanes) to provide **12a** (9.1 g, 52% yield, R_f 0.54 in 35% EtOAc/65% hexanes) and **12b** (2.85 g, 16% yield, R_f 0.41 in 35% EtOAc/65% hexanes). **12a**: ^{1}H NMR ($CDCl_3$) δ 7.32 (dd, J = 2.0, 6.1 Hz, 1H), 7.29−7.19 (m, 15H), 6.02 (dd, J = 1.4, 6.1 Hz, 1H), 4.83(m, 1H), 3.86 (dd, J = 3.1, 11.5 Hz, 1H), 3.05 (s, 3H), 2.62 (d, J = 11.2 Hz, 1H), 1.62−1.50 (m, 2H), 1.36 (s, 9H), 1.36−1.26 (m, 1H), 1.15−0.97 (m, 1H), 0.92 (t, J = 6.6 Hz, 3H), 0.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.2, 144.8, 130.1, 127.6, 126.6, 82.4, 79.2, 66.9, 64.6, 48.9, 38.7, 27.9, 19.3, 17.1, 14.9. Anal. Calcd for $C_{35}H_{42}N_2O_4S$: C, 71.64; H, 7.21; N, 4.77. Found: C, 71.45; H, 7.06; N, 4.59. **12b**: ^{1}H NMR ($CDCl_3$) δ 7.28−7.18 (m, 16H), 6.02 (dd, J = 1.7, 6.1 Hz, 1H), 4.90 (m, 1H), 3.89 (dd, J = 2.0, 11.5 Hz, 1H), 3.06 (s, 3H), 2.42 (d, J = 11.5 Hz, 1H), 1.54 (s, 9H), 1.28−0.85 (m, 4H), 1.16 (s, 3H), 0.57 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 148.2, 144.3, 130.0, 127.7, 126.5, 82.6, 79.2, 67.2, 65.3, 49.2, 37.3, 28.3, 20.9, 17.5, 14.7. Anal. Calcd for $C_{35}H_{42}N_2O_4S$: C, 71.64; H, 7.21; N, 4.77. Found: C, 70.61; H, 7.05; N, 4.66.

***tert*-Butyl (2*R*)-2-[(1*R*,2*S*)-1-(Acetylamino)-2-methoxy-2-methylpentyl]-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (13a) and *tert*-Butyl (2*S*)-2-[(1*S*,2*S*)-1-(Acetylamino)-2-methoxy-2-methylpentyl]-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (13b).** Ammonia gas was bubbled through a suspension of phenyl disulfide (34 mg, 0.15 mmol) and silver nitrate (26 mg, 0.15 mmol) in methanol (2.5 mL) at 0 °C for 15 min. To the mixture was added a solution of **10** (40 mg,

0.31 mmol) in methanol (0.5 mL), and the mixture was stirred at room temperature for 68 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was dissolved in ether and refiltered. The resulting filtrate was washed with water, dried ($MgSO_4$), and concentrated to give crude imine **3c** (42 mg, 57%).

To a solution of the above imine **3c** (42 mg, 0.18 mmol) and **4** (53 mg, 0.18 mmol) in dichloromethane (1.5 mL) at −78 °C was added $BF_3{\cdot}Et_2O$ (0.034 mL, 0.27 mmol). After stirring at −78 °C for 2 h, the reaction was quenched with saturated sodium bicarbonate (2 mL) and extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated to give the crude mixture of unstable phenylsulfenamide products. These crude products were treated with 80% acetic acid (2 mL) at room temperature for 1 h, and the volatiles were evaporated. The crude residue was purified by chromatography (5% methanol in dichloromethane with 0.2% ammonium hydroxide) to give the amine (28 mg, 50%).

The amine product (28 mg, 0.09 mmol) in dichloromethane (1 mL) was treated with acetic anhydride (0.017 mL, 0.18 mmol), triethylamine (0.028 mL, 0.2 mmol), and 4-(dimethylamino)pyridine (2 mg, 0.02 mmol) for 1 h. The material was purified directly by eluting with 5% methanol in dichloromethane to give **13a** and **13b** (26 mg, 82%) as a mixture (1:1.9, respectively) of two inseparable disastereomers. **13a**: ^{1}H NMR ($CDCl_3$) δ 7.33 (dd, J = 2.0, 6.1 Hz, 1H), 6.08 (dd, J = 1.4, 6.1 Hz, 1H), 5.37 (d, J = 10.0 Hz, 1H), 4.89 (dd, J = 3.4, 9.8 Hz, 1H), 4.85 (m, 1H), 3.23 (s, 3H), 1.91 (s, 3H), 1.59 (s, 9H), 1.18 (s, 3H), 1.01 (t, J = 7.1 Hz, 3H). **13b**: ^{1}H NMR ($CDCl_3$) δ 7.28 (dd, J = 2.4, 6.1 Hz, 1H), 6.10 (dd, J = 1.7, 6.4 Hz, 1H), 5.33 (d, J = 10.5 Hz, 1H), 4.98 (dd, J = 2.7, 10.2 Hz, 1H), 4.89 (m, 1H), 3.24 (s, 3H), 1.90 (s, 3H), 1.60 (s, 9H), 1.40 (s, 3H), 0.89 (t, J = 7.1 Hz, 3H).

The mixture of **13a** and **13b** (20 mg, 0.06 mmol) was subjected to catalytic hydrogenation with 20% $Pd(OH)_2$ on carbon (10 mg) in 2 mL of EtOAc for 2 h under balloon pressure. The reaction was filtered and evaporated to give a mixture of **17** and **18** (18 mg) in a 1:1.9 ratio by ^{1}H NMR, respectively.

***tert*-Butyl (2*R*)-2-((1*R*,2*S*)-2-Methoxy-2-methyl-1-{[(*R*)-(4-methylphenyl)sulfinyl]amino}pentyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (14).** To a solution of (*R*)-*p*-toluenesulfinimine **3d** (2.9 g, 10.84 mmol) and **4** (6.1 g, 20.5 mmol) in dichloromethane (80 mL) at −78 °C was added trimethylsilyl triflate (2.8 mL, 16.23 mmol). After stirring at −78 °C for 10 min and then at −23 °C for 7 h, the reaction was quenched with saturated sodium bicarbonate (100 mL) and diluted with dichloromethane. The organic layer was separated, dried (Na_2SO_4), and concentrated. The crude residue was triturated with ether, and the resulting precipitate was collected by filtration to give **14** as a white solid (2.86 g, 59%): ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 2H), 7.29−7.26 (m, 3H), 6.00 (dd, J = 6.1, 1.4 Hz, 1H), 4.81 (m, 1H), 4.28 (dd, J = 9.2, 3.1 Hz, 1H), 4.18 (d, J = 8.8 Hz,1H), 3.17 (s, 3H), 2.38 (s, 3H), 1.93 (m, 1H), 1.72−1.38 (m, 3H), 1.59 (s, 9H), 1.43 (s, 3H), 1.03 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.4, 149.7, 148.0, 142.7, 141.4, 129.5, 127.4, 125.1, 83.5, 77.9, 63.2, 62.5, 49.0, 37.8, 28.3, 21.3, 21.0, 17.5, 14.8. Anal. Calcd for $C_{23}H_{34}N_2O_5S$: C, 61.31; H, 7.61; N, 6.22. Found: C, 61.35; H, 7.51; N, 6.14.

***tert*-Butyl (2*S*)-2-((1*S*,2*S*)-2-Methoxy-2-methyl-1-{[(*S*)-(4-methylphenyl)sulfinyl]amino}pentyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (15).** To a solution of (*S*)-*p*-toluenesulfininimine **3e** (37.4 mg, 0.14 mmol) and **4** (63.6 mg, 0.21 mmol) in dichloromethane (0.6 mL) at −78 °C was added trimethylsilyl triflate (0.038 mL, 0.21 mmol). After stirring at −30 °C for 18 h, the reaction was quenched with saturated sodium bicarbonate (4 mL) and diluted with dichloromethane and warmed to room temperature. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude residue was purified by chromatography (gradient, dichloromethatne to 50% ethyl acetate/50% dichloromethane) to provide **15** as a foaming solid (38.6 mg, 61%): ^{1}H NMR ($CDCl_3$) δ 7.54 (d, J = 7.9 Hz, 2H), 7.27 (d, J = 7.3 Hz, 2H), 7.25 (dd, J = 1.8, 6.1 Hz, 1H), 6.02 (dd, J = 1.2, 6.1 Hz, 1H), 4.85 (m, 1H), 4.39 (dd, J = 3.1, 9.2 Hz, 1H), 4.22 (d, J = 9.2 Hz, 1H), 3.18 (s, 3H), 2.37 (s, 3H), 1.94 (m, 1H), 1.64−1.55 (m, 2H), 1.60 (s, 9H), 1.40 (s, 3H), 1.21 (m, 1H), 1.07 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.7, 149.2, 148.1, 142.7, 141.3, 129.5, 127.6, 125.1, 83.4, 77.6, 63.6, 61.1, 48.4, 36.4, 28.2, 21.3, 20.2, 18.3, 14.5. Anal. Calcd for $C_{23}H_{34}N_2O_5S$: C, 61.31; H, 7.61; N, 6.22. Found: C, 61.02; H, 7.41; N, 6.04.

***tert*-Butyl (2*R*)-2-((1*R*,2*S*)-2-Methoxy-2-methyl-1-{[(*R*)-(*tert*-butyl)sulfinyl]amino}pentyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (16).** The procedure of preparation of **15** was followed with **3f** (20 mg, 0.086 mmol). Purification by chromatography (gradient, 6% to 50% ethyl acetate/dichloromethane) provided **16** (12.9 mg, 36%): ^{1}H NMR ($CDCl_3$) δ 7.37 (dd, J = 1.8, 6.1 Hz, 1H), 6.05 (dd, J = 1.2, 6.1 Hz, 1H), 4.73 (m, 1H), 4.09 (dd, J = 3.7, 8.5 Hz, 1H), 3.79 (d, J = 8.5 Hz, 1H), 3.25 (s, 3H), 1.92 (m, 1H), 1.69−1.43 (m, 3H), 1.57 (s, 9H), 1.39 (s, 3H), 1.15 (s, 9H), 1.02 (t, J = 2.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.4, 149.6, 148.2, 127.4, 83.2, 78.2, 63.5, 61.6, 56.4, 49.2, 37.9, 28.3, 23.0, 21.0, 17.4, 14.8.

***tert*-Butyl (2*R*)-2-[(1*R*,2*S*)-1-(Acetylamino)-2-methoxy-2-methylpentyl]-5-oxopyrrolidine-1-carboxylate (17):** ^{1}H NMR ($CDCl_3$) δ 5.87 (d, J = 9.9 Hz, 1H), 4.57 (dd, J = 2.4, 9.8 Hz, 1H), 4.40 (m, 1H), 3.20 (s, 3H), 2.55−2.32 (m, 3H), 1.98 (s, 3H), 2.02−1.87 (m, 1H), 1.84−1.62 (m, 1H), 1.58 (s, 9H), 1.50−1.08 (m, 3H), 1.15 (s,3H), 0.98 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.1, 170.0, 149.9, 83.0, 78.6, 58.0, 54.7, 49.0, 37.3, 32.6, 28.1, 23.2, 20.5, 18.4, 17.3, 14.8. Anal. Calcd for $C_{18}H_{32}N_2O_5$: C, 60.65; H, 9.05; N, 7.86. Found: C, 60.92; H, 9.18; N, 7.66.

***tert*-Butyl (2*S*)-2-[(1*S*,2*S*)-1-(Acetylamino)-2-methoxy-2-methylpentyl]-5-oxopyrrolidine-1-carboxylate (18):** ^{1}H NMR ($CDCl_3$) δ 5.87 (d, J = 9.5 Hz, 1H), 4.68 (dd, J = 2.0, 9.5 Hz, 1H), 4.44 (m, 1H), 3.20 (s, 3H), 2.52−2.33 (m, 3H), 1.97 (s, 3H), 2.02−1.89 (m, 1H), 1.58 (s, 9H), 1.55−1.12 (m, 4H), 1.29 (s, 3H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.3, 169.9, 149.3, 82.6, 78.1, 58.4, 53.1, 48.4, 38.3, 32.3, 28.0, 22.9, 20.0, 18.0, 17.7, 14.7. Anal. Calcd for $C_{18}H_{32}N_2O_5$: C, 60.65; H, 9.05; N, 7.86. Found: C, 59.92; H, 8.94; N, 7.61.

***tert*-Butyl (2*R*,3*S*)-2-{(1*R*,2*S*)-2-Methoxy-2-methyl-1-[(tritylthio)amino]pentyl}-5-oxo-3-[(1*Z*)-prop-1-enyl]pyrrolidine-1-carboxylate (19a).** *cis*-1-Bromopropene (21 mL, 0.24 mmol), Mg turnings (7 g), and 5 drops of 1,2-dibromoethane were refluxed in THF (470 mL) for 3 h and then cooled to room temperature. To a slurry of Cu(I)Br·DMS (12.6 g, 61.5 mmol) in THF (230 mL) at −78 °C was added *cis*-1-propenylmagnesium bromide (0.5M in THF, 246 mL, 123 mmol) dropwise over 1.5 h followed by dropwise addition of trimethylsilyl chloride (4.6 mL, 36.9 mmol) over 10 min. To this solution was added **12a** (7.2 g, 12.3 mmol) in THF (230 mL) at −78 °C, and the reaction mixture was stirred at this temperature for 1 h. The reaction was quenched with saturated NH_4Cl (290 mL) and warmed to room temperature. The mixture was extracted twice with ethyl acetate (0.5 L), and the organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by chromatography (10% ethyl acetate/ 90% hexanes) to give **19a** (6.9 g, 89%): ^{1}H NMR ($CDCl_3$) δ 7.30−7.19 (m, 15H), 5.44−5.33 (m, 2H), 3.99 (d, J = 1.4 Hz, 1H), 3.69 (m, 1H), 3.58 (dd, J = 2.4, 10.5 Hz, 1H), 3.05 (d, J = 10.9 Hz, 1H), 3.03 (s, 3H), 2.80 (dd, J = 9.5, 18.0 Hz, 1H), 1.94 (dd, J = 17.6, 1.4 Hz, 1H), 1.66−1.36 (m, 2H), 1.58 (d, J = 4.7 Hz, 3H), 1.43 (s, 9H), 1.26−0.92 (m, 2H), 0.86 (t, J = 6.6 Hz, 3H), 0.51 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.3, 144.7, 133.1, 130.1, 127.7, 126.6, 123.2, 82.6, 79.8, 77.2, 66.5, 65.3, 48.9, 39.8, 37.9, 28.1, 27.4, 19.9, 16.9, 14.8, 13.0. Anal. Calcd for $C_{38}H_{48}N_2O_4S$: C, 72.58; H, 7.69; N, 4.45. Found: C, 72.16; H, 7.70; N, 4.38.

***tert*-Butyl (2*R*,3*S*,5*R*)-5-Cyano-2-{(1*R*,2*S*)-2-methoxy-2-methyl-1-[(tritylthio)amino]pentyl}-3-[(1*Z*)-prop-1-enyl]-pyrrolidine-1-carboxylate (20a).** To a solution of **19a** (6.4 g, 10.2 mmol) in THF (27 mL) at −78 °C was added diisobutylaluminum hydride (1 M in hexane, 30.6 mL). After stirring at −78 °C for 45 min, the reaction was quenched with saturated NH_4Cl (150 mL) and a 10% sodium potassium tartrate solution (250 mL), diluted with ethyl acetate (250 mL), and stirred at room temperature for 1 h. The organic layer was separated, and the aqueous extracted again with ethyl acetate (250 mL). The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated to give a crude oil (5.6 g, 87% yield), which was used directly in the next step.

The above crude hemiaminal (8.9 mmol) was stirred in methanol (100 mL) with pyridinium *p*-toluenesulfonic acid (0.11 g, 0.43 mmol) at room temperature for 1 h. The reaction was diluted with ethyl acetate (500 mL), washed with water (150 mL) and brine (100 mL), and then dried ($MgSO_4$) and evaporated to give 6.1 g of an oil which was used directly for the next step.

To a solution of crude product from above in dichloromethane (90 mL) at −78 °C were added trimethylsilyl cyanide (3.5 mL, 26.7 mmol) and $BF_3{\cdot}Et_2O$ (1.2 mL, 9.5 mmol) in dichloromethane (8 mL). After 30 min at −78 °C, triethylamine (2.5 mL) was added and the reaction was quenched with saturated sodium bicarbonate (150 mL) and warmed to room temperature. Ethyl acetate (500 mL) was added, and the organic was washed with water and brine and dried ($MgSO_4$). The solvents were evaporated, and the crude residue was purified by chromatography (5% EtOAc/95% hexanes) to give **20a** (4.4 g, 77%): ^{1}H NMR ($CDCl_3$) δ 7.36−7.20 (m, 15H), 5.74−5.67 (m, 1H), 5.49−5.38 (m, 1H), 4.60 (d, J = 9.2 Hz, 1H), 3.82 (dd, J = 7.8, 10.5 Hz, 1H), 3.79 (d, J = 1.7 Hz, 1H), 3.68 (dd, J = 2.0, 10.5 Hz, 1H), 3.02 (d, J = 10.5 Hz, 1H), 3.01 (s, 3H), 2.59−2.48 (m, 1H), 1.84 (d, J = 13.2 Hz, 1H), 1.67−1.39 (m, 2H), 1.60 (dd, J = 1.7, 6.8 Hz, 3H), 1.34 (s, 9H), 1.12−0.91 (m, 2H), 0.86 (t, J = 6.6 Hz, 3H), 0.45 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.5, 144.6, 132.3, 130.1, 127.7, 126.7, 123.5, 120.5, 80.9, 79.7, 65.7, 62.9, 48.7, 47.0, 37.9, 36.8, 35.3, 28.2, 19.8, 16.8, 14.9, 12.8. Anal. Calcd for $C_{39}H_{49}N_3O_3S$: C, 73.20; H, 7.72; N, 6.57. Found: C, 72.96; H, 7.84; N, 6.53. The epimeric nitrile was also obtained (0.22 g. 4%, removed during chromatography) and was identified as ***tert*-butyl (2*R*,3*S*,5*S*)-5-cyano-2-{(1*R*,2*S*)-2-methoxy-2-methyl-1-[(tritylthio)amino]pentyl}-3-[(1*Z*)-prop-1-enyl]pyrrolidine-1-carboxylate**: ^{1}H NMR ($CDCl_3$) δ 7.34−7.17 (m, 15H), 5.49−5.39 (m, 1H), 5.27−5.20 (m, 1H), 4.42 (t, J = 7.0 Hz, 1H), 3.75−3.65 (m, 3H), 3.33 (d, J = 10.8 Hz, 1H), 3.01 (s, 3H), 2.42 (m, 1H), 1.89−1.81 (m, 1H), 1.68−1.47 (m, 2H), 1.61 (dd, J = 1.7. 6.8 Hz, 3H), 1.38 (s, 9H), 1.12−0.82 (m, 2H), 0.80 (t, J = 6.5 Hz, 3H), 0.50 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.9, 145.0, 131.5, 130.2, 127.6, 126.5, 124.5, 118.9, 79.9, 66.8, 64.2, 48.6, 47.3, 38.0, 37.1, 35.6, 28.2, 19.6, 16.7, 14.9, 13.0. Anal. Calcd for $C_{39}H_{49}N_3O_3S$: C, 73.20; H, 7.72; N, 6.57; Found: C, 73.38; H, 7.54; N, 5.37.

***tert*-Butyl (2*R*,3*S*)-2-((1*R*,2*S*)-2-Methoxy-2-methyl-1-{[(*R*)-(4-methylphenyl)sulfinyl]amino}pentyl)-5-oxo-3-[(1*Z*)-prop-1-enyl]pyrrolidine-1-carboxylate (19b).** To a suspension of Cu(I)Br·DMS (62.53 mg, 0.30 mmol) in THF (0.6 mL) at −78 °C was added *cis*-1-propenylmagnesium bromide (0.5 M in THF, 1.22 mL, 0.61 mmol), and the solution was stirred at −78 °C for 30 min. To the solution was added trimethylsilyl chloride (0.017 mL, 0.13 mmol) followed by a solution of **14** (54.96 mg, 0.12 mmol) in dichloromethane (0.4 mL). The reaction mixture was stirred at −78 °C for 1.5 h and quenched with saturated NH_4Cl and warmed to room temperature for 1 h. The mixture was partitioned between saturated NH_4Cl (10 mL) and dichloromethane (45 mL). The organic layer was washed with H_2O (10 mL), and the combined aqueous layers were extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography (gradient, 17% to 33% ethyl acetate/hexane) to give **19b** (44.31 mg, 74%): ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 5.43 (m, 2H), 4.58 (d, J = 7.8 Hz, 1H), 3.99 (br d, J = 2.7 Hz, 1H), 3.93 (dd, J = 7.8, 2.7 Hz, 1H), 3.71 (m, 1H), 3.19 (s, 3H), 2.57 (dd, J = 17.8, 9.7 Hz, 1H), 2.40 (s, 3H), 1.97 (dd, J = 17.8, 1.5 Hz, 1H), 1.82 (m, 1H), 1.59 (s, 9H), 1.55 (s, 3H), 1.52 (m, 1H), 1.42 (s, 3H), 1.27 (m, 2H), 0.96 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.1, 150.5, 136.5, 133.2, 129.5, 127.7, 123.3, 82.6, 79.4, 69.2, 65.8, 49.0, 40.3, 37.7, 28.0, 21.1, 21.0, 16.9, 14.8, 13.0. Anal. Calcd for $C_{26}H_{40}N_2O_5S$: C, 63.38; H, 8.18; N, 5.69. Found: C, 63.33; H, 8.09; N, 5.68.

***tert*-Butyl (2*R*,3*S*,5*R*)-5-Cyano-2-((1*R*,2*S*)-2-methoxy-2-methyl-1-{[(*R*)-(4-methylphenyl)sulfinyl]amino}pentyl)-3-[(1*Z*)-prop-1-enyl]pyrrolidine-1-carboxylate (20b).** To a solution of **19b** (2.12 g, 4.31 mmol) in dichloromethane (21 mL) at −78 °C was added diisobutylaluminum hydride (1 M in hexane, 10.77 mL, 10.77 mmol). After stirring at −78 °C for 0.4 h, the reaction was quenched with saturated NH_4Cl (35 mL) and 10% sodium potassium tartrate solution (35 mL), diluted with ethyl acetate, and stirred at room temperature for 1 h. The organic layer was separated, dried (Na_2SO_4), and concentrated to give a crude oil (2.1 g), which was used directly in the next step.

To the above hemiaminal in dichloromethane (20 mL) at −78 °C were added trimethylsilyl cyanide (1.7 mL, 12.78 mmol) and trimethylsilyl triflate (1.12 mL, 6.18 mmol). After stirring for 5 min, the reaction was quenched with triethylamine (1.7 mL, 12.8 mmol) followed by saturated sodium bicarbonate and warmed to room temperature and extracted with dichloromethane. The solvents were evaporated, and the crude residue was purified by chromatography (30% ethyl acetate/hexane) to give **20b** (2.1 g, 97% over two steps): ^{1}H NMR ($CDCl_3$, rotamers) δ 7.53 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 5.73 (m, 1H), 5.48 (m, 1H), 4.58−4.46 (m, 2H), 4.01−3.69 (m, 3H), 3.18 (s, 0.6H), 3.16 (s, 2.4H), 2.42 (s, 3H), 2.38 (m, 1H), 1.81−1.66 (m, 3H), 1.61−1.55 (m, 12H), 1.26−1.17 (m, 5H), 0.92 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 152.6, 132.0, 129.9, 129.7, 124.1, 124.0, 123.8, 120.2, 81.8, 78.7, 65.4, 60.5, 48.9, 47.9, 47.5, 37.6, 36.8, 35.5, 28.6, 28.5, 21.4, 21.0, 17.1, 14.9, 12.7. Anal. Calcd for $C_{27}H_{41}N_3O_4S$: C, 64.38; H, 8.20; N, 8.34. Found: C, 64.26; H, 7.91; N, 8.30.

***tert*-Butyl (2*R*,3*S*,5*R*)-5-Cyano-2-[(1*R*,2*S*)-1-(acetylamino)-2-methoxy-2-methylpentyl]-3-[(1*Z*)-prop-1-enyl]-pyrrolidine-1-carboxylate (21). Preparation from 20a.** Compound **20a** (4.4 g, 6.9 mmol) was suspended in methanol (75 mL), and PPTS (3.45 g, 13.7 mmol) was added. The mixture was heated to reflux for 18 h and cooled to room temperature, and the solvent was evaporated. To the crude residue dissolved in dichloromethane (75 mL) were added acetic anhydride (2.0 mL, 20.7 mmol) and triethylamine (5.8 mL, 41.3 mmol), and the mixture was stirred for 1 h. The reaction was quenched with methanol (6 mL) and evaporated. The residue was purified by chromatography (gradient, chloroform to 50% ethyl acetate/50% chloroform) to give **21** (1.92 g, 69%).

Preparation from 20b. To a solution of **20b** (8.4 mg, 0.017 mmol) in MeOH (0.17 mL) was added trifluoroacetic acid (0.0055 mL, 0.071 mmol) at room temperature. The solution was stirred overnight and concentrated at reduced pressure. The residue was azeotroped with chloroform and toluene. To the crude amine in dichloromethane (0.17 mL) was added triethylamine (0.0238 mL, 0.17 mmol) followed by acetic anhydride (0.0081 mL, 0.086 mmol) at room temperature. The solution was stirred for 20 min and concentrated in vacuo. The residue was purified by chromatography (gradient, 33% to 67% ethyl acetate/hexane) to give **21** (5.16 mg, 76%): ^{1}H NMR ($CDCl_3$, rotamers) δ 5.91 (m, 1H), 5.80−5.68 (m, 1H), 5.55−5.45 (m, 1H), 4.55 (dd, J = 2.4, 9.5 Hz, 1H), 4.47−4.35 (m, 1H), 3.98−3.85(m, 1H), 3.73 (dd, J = 9.2, 9.8 Hz, 1H), 3.21 and 3.20 (2s, 3H), 2.55−2.39 (m, 1H), 2.00 (s, 3H), 1.97−1.88 (m, 1H), 1.82−1.60 (m, 2H), 1.66 (dd, J = 1.7, 6.8 Hz, 3H), 1.36−1.20 (m, 2H), 1.57 and 1.55 and 1.53 (3s, 9H), 1.18 and 1.14 and 1.12 (3s, 3H), 0.95 (t, J = 6.8 Hz, 3H); ^{13}C NMR

($CDCl_3$, rotamers) δ 169.6, 152.5, 131.9, 123.9, 123.8, 81.4, 78.9, 64.6, 64.3, 54.9, 54.4, 49.0, 47.2, 46.6, 37.6, 37.2, 37.0, 36.8, 36.1, 35.86, 28.5, 28.3, 28.2, 23.5, 20.5, 20.4, 20.3, 17.5, 16.9, 14.9, 14.5, 12.8. Anal. Calcd for $C_{22}H_{37}N_3O_4$: C, 64.84; H, 9.15; N, 10.31. Found: C, 64.82; H, 9.07; N, 10.27.

(−)-(2*R*,4*S*,5*R*)-5-[(1*R*,2*S*)-1-(Acetylamino)-2-methoxy-2-methylpentyl]-4-[(1*Z*)-prop-1-enyl]pyrrolidine-2-carboxylic Acid (1). Compound **21** (6.1 g, 14.9 mmol) was combined with hydrochloric acid (6 N, 350 mL) and stirred at 60 °C for 42 h. The reaction was evaporated to give 6.4 g of crude solid, which was purified by flash chromatography (reversed phase, Biotage KP-C18-HS column, gradient elution starting with 100% water (0.1% TFA) and ending with 100% acetonitrile) to give 6.56 g (99%) of material (TFA salt form). An analytical sample of **1** was prepared by ion exchange chromatography (Dowex 50WX8-400): $[\alpha]_D = -50.2$ (*c* 0.25, water); ^{1}H NMR (D_2O) δ 5.66−5.59 (m, 1H), 5.33−5.28 (m, 1H), 4.38 (d, $J = 10.4$ Hz, 1H), 4.16 (t, $J = 8.9$ Hz, 1H), 3.65 (t, $J = 10.4$ Hz, 1H), 3.26 (s, 3H), 3.22−3.11 (m, 1H), 2.60−2.54 (m, 1H), 1.95 (s, 3H), 1.74−1.61 (m, 2H), 1.59 (dd, $J = 1.5$, 7.0 Hz, 3H), 1.39−1.26 (m, 3H), 1.24 (s, 3H), 0.85 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (D_2O) δ 177.0, 176.5, 131.6, 129.3, 82.7, 65.3, 62.6, 56.2, 51.4, 43.9, 38.5, 37.2, 24.7, 20.2, 18.0, 16.2, 15.1. Anal. Calcd for $C_{17}H_{30}N_2O_4$: C, 62.55; H, 9.26; N, 8.58. Found: C, 62.32; H, 9.12; N, 8.34.

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Supporting Information Available: X-ray crystal structure data and ORTEP diagrams of compounds **12a**, **14**, **18** and **21**. Experimental details and spectral data for reaction of aldehyde **10** with **4** and additional spectral data for compounds **13a**, **13b**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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