JOC*Article*

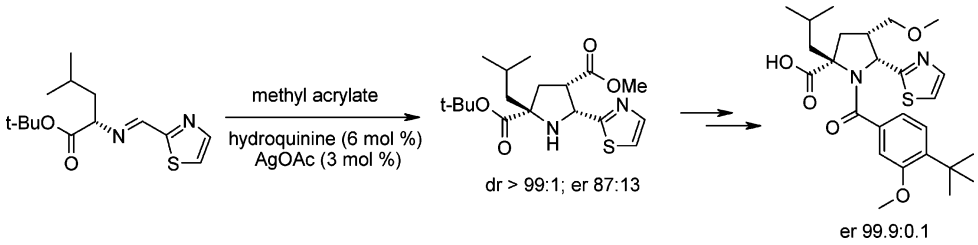
Asymmetric Synthesis of an *N*-Acylpyrrolidine for Inhibition of HCV Polymerase

Armel A. Agbodjan,[†] Bob E. Cooley,[†] Royston C. B. Copley,[‡] John A. Corfield,[§] Roy C. Flanagan,[†] Bobby N. Glover,[†] Rossella Guidetti,[§] David Haigh,[§] Peter D. Howes,[§] Mary M. Jackson,[†] Richard T. Matsuoka,[†] Katrina J. Medhurst,[§] Alan Millar,[†] Matthew J. Sharp,[†] Martin J. Slater,*[,§] Jennifer F. Toczko,[†] and Shiping Xie*[,†]

Chemical Development, GlaxoSmithKline, Research Triangle Park, North Carolina 27709, Analytical Chemistry, GlaxoSmithKline, New Frontiers Science Park (North), Third Avenue, Harlow, Essex CM19 5AW, United Kingdom, and Infectious Diseases CEDD and Medicinal Discovery Research, GlaxoSmithKline, GSK Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, United Kingdom

shiping.x.xie@gsk.com

Received January 10, 2008



A practical asymmetric synthesis of a highly substituted *N*-acylpyrrolidine on multi-kilogram scale is described. The key step in the construction of the three stereocenters is a [3+2] cycloaddition of methyl acrylate and an imino ester prepared from L-leucine *t*-butyl ester hydrochloride and 2-thiazolecarboxaldehyde. The cycloaddition features novel asymmetric catalysis via a complex of silver acetate and a cinchona alkaloid, particularly hydroquinine, with complete diastereomeric control and up to 87% enantiomeric control. The alkaloid serves as a ligand as well as a base for the formation of the azomethine ylide or 1,3-dipole. Experiments have shown that the hydroxyl group of hydroquinine is a critical element for the enantioselectivities observed. The cycloaddition methodology is also applicable to methylvinyl ketone, providing access to either α- or β-epimers of 4-acetylpyrrolidine depending on the reaction conditions utilized. The synthesis also highlights an efficient *N*-acylation, selective *O*- versus *N*-methylation, and a unique ester reduction with $NaBH_4$−MeOH catalyzed by $NaB(OAc)_3H$ that not only achieves excellent chemoselectivity but also avoids formation of the undesired but thermodynamically favored epimer. The highly functionalized target is synthesized in seven linear steps from L-leucine *t*-butyl ester hydrochloride with all three isolated intermediates being highly crystalline.

Introduction

Hepatitis C virus (HCV) infection has been identified as the most common risk factor for developing hepatocellular carcinoma and the main cause of adult liver transplants in developed nations.[1] Worldwide, over 170 million people are estimated to be infected with HCV.[2] Following acute HCV infection, most patients develop a slowly progressive chronic disease that can eventually lead to cirrhosis and liver failure. The current standard treatment for HCV infection is a combination therapy employing some form of interferon-α, particularly the pegylated form, plus ribavirin. Unfortunately, only about 50−80% of the patients achieve sustained virological response as measured by a reduction in serum HCV RNA levels and normalization of liver

[†] Chemical Development.
[‡] Analytical Chemistry.
[§] Infectious Diseases CEDD and Medicinal Discovery Research.

(1) Willems, M.; Metselaar, H. J.; Tilanus, H. W.; Schalm, S. W.; de Man, R. A. *Transplant Int.* **2002**, *15*, 61.

(2) (a) Wasley, A.; Alter, M. J. *Semin. Liver Dis.* **2000**, *20*, 16. (b) Alter, M. J. *Hepatology* **1997**, *26*, 62S.

10.1021/jo800062c CCC: $40.75
Published on Web 03/22/2008

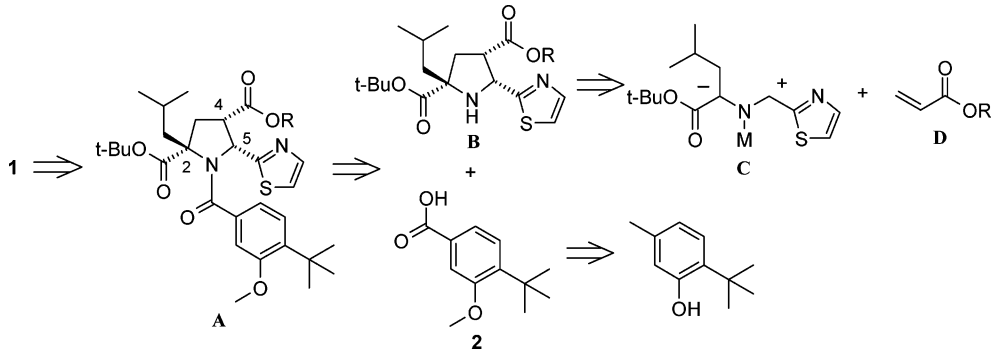
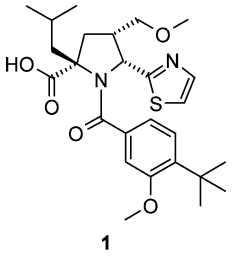


FIGURE 1. Strategy for synthesis of **1**.

enzymes. The response rate is about 50% for infections with HCV of genotype 1, the prevalent type of HCV infection in the United States.[3] In addition, the current treatment is also accompanied with significant systemic side effects. Clearly, new therapies are needed to address the issues of safety, broad antiviral response, and viral resistance mutations.

Several pharmaceutical companies, in search of a new treatment for HCV infections, are pursuing an approach that inhibits the HCV polymerase which synthesizes the new viral RNA strands.[4] Compound **1**, a highly substituted *N*-acylpyrrolidine with three stereocenters, is a non-nucleoside small molecule which acts as a potent inhibitor of RNA-dependent RNA polymerase (NS5B) in enzymatic assays and inhibits viral RNA replication in cell-based replicon assays.[5]



1

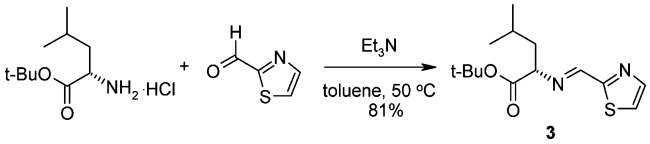
Our synthetic strategy is shown in Figure 1. The C2 carboxylic acid group in the target molecule (**1**) is protected as a bulky *tert*-butyl ester (intermediate **A**) throughout the synthesis. The C4 methoxymethyl group of **1** is derived from selective reduction of an ester precursor (CO_2R) in the presence of two other acyl groups in **A**. Intermediate **A** is obtained from the acylation of a pyrrolidine moiety (**B**) with a benzoic acid (**2**), which is prepared from commercially available 2-*t*-butyl-3-methylphenol by methylation followed by oxidation with potassium permanganate.[6] The overall efficiency of the synthesis depends on the efficiency in preparation of **B** with the three stereocenters and the level of selectivity in the ester reduction. A common approach to substituted pyrrolidine like **B** is the [3+2] cycloaddition of a *N*-metalated azomethine ylide 1,3-dipole such as **C** with an electron deficient dipolarophile such as acrylic ester **D**.[7]

We herein report a practical and efficient synthesis of target **1**, which includes diastereo- and enantioselective synthesis of the acylpyrrolidine moiety through a [3+2] cycloaddition catalyzed by a novel silver−cinchona complex, a unique and highly selective reduction of a carboxylic ester group with $NaBH_4$−MeOH catalyzed by $NaB(OAc)_3H$, as well as other efficient downstream functionalizations of the pyrrolidine core.

Results and Discussion

Preparation of imino ester **3**, the precursor to the *N*-metalated azomethine ylide, is shown in Scheme 1. Condensation of

SCHEME 1



3

L-leucine *t*-butyl ester hydrochloride with 2-thiazolecarboxaldehyde in the presence of triethylamine afforded imino ester **3** in 81% yield. The stereocenter in **3** is irrelevant because of the subsequent formation of the planar 1,3-dipole. Thus L-leucine was used for its low cost and wide availability. No dehydrating reagent was needed under this set of reaction conditions. While there have been many reports of racemic synthesis of substituted pyrrolidines from an imino ester like **3**,[7] the enantioselective synthetic strategy using a substoichiometric amount of a catalyst is relatively new. The most notable ligands for the enantioselective catalysis via cycloadditions of *N*-metalated azomethine ylides include chiral bisferrocenyl amide phosphines (FAP) from Zhang's group,[8] chiral bisoxazolines from Jørgensen's group,[9] and QUINAP P,N-ligands from Schreiber's group.[10] These

(3) (a) Fried, M. W. *Hepatology* **2002**, *36*, 237. (b) Cornberg, M.; Wedemeyer, H.; Manns, M. P. *Curr. Gastroenterol. Rep.* **2002**, *4*, 23. (c) Hügle, T.; Cerny, A. *Rev. Med. Virol.* **2003**, *13*, 361.

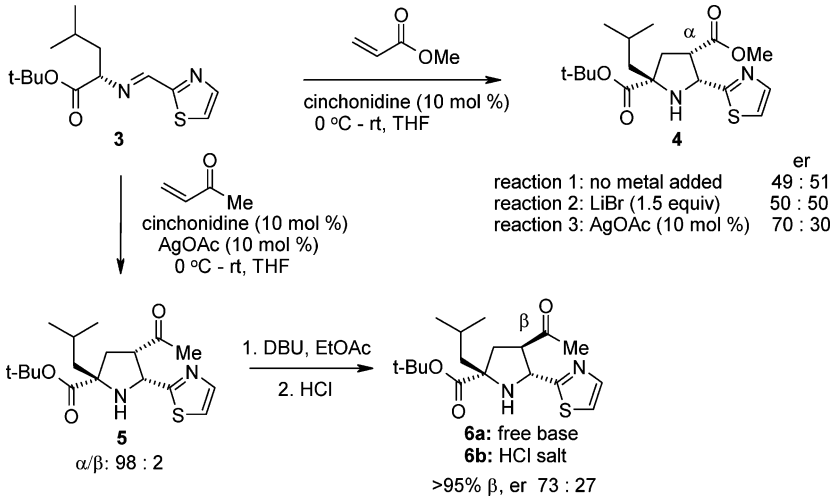
(4) For recent reviews on the progress and development of small-molecule HCV antivirals, see: (a) Nie, Z-J.; Wagman, A. S. *Curr. Opin. Drug Discovery Dev.* **2004**, *7*, 446. (b) Beaulieu, P. L.; Tsantrizos, Y. S. *Curr. Opin. Invest. Drugs* **2004**, *5*, 838. (c) Wu, J. Z.; Yao, N.; Walker, M.; Hong, Z. *Mini-Rev. Med. Chem.* **2005**, *5*, 1103.

(5) (a) Slater, M. J.; Amphlett, E. M.; Andrews, D. M.; Bravi, G.; Burton, G.; Cheasty, A. G.; Corfield, J. A.; Ellis, M. R.; Fenwick, R. H.; Fernandes, S.; Guidetti, R.; Haigh, D.; Hartley, C. D.; Howes, P. D.; Jackson, D. L.; Jarvest, R. L.; Lovegrove, V. L. H.; Medhurst, K. J.; Parry, N. R.; Price, H.; Shah, P.; Singh, O. M. P.; Stocker, R.; Thommes, P.; Wilkinson, C.; Wonacott, A. *J. Med. Chem.* **2007**, *50*, 897. (b) Burton, G.; Ku, T. W.; Carr, T. J.; Kiesow, T.; Sarisky, R. T.; Lin-Goerke, J.; Baker, A.; Earnshaw, D. L.; Hofmann, G. A.; Keenan, R. M.; Dhanak, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1553. (c) Burton, G.; Ku, T. W.; Carr, T. J.; Kiesow, T.; Sarisky, R. T.; Lin-Goerke, J.; Hofmann, G. A.; Slater, M. J.; Haigh, D.; Dhanak, D.; Johnson, V. K.; Parry, N. R.; Thommes, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1930.

(6) 4-(1,1-Dimethylethyl)-3-(methyloxy)benzoic acid is available from CarboGen, Bubendorf, Switzerland, through custom synthesis.

(7) For reviews, see: (a) Grigg, R.; Sridharan, V. *Adv. Cycloaddit.* **1993**, *3*, 161. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kabayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; pp 211−245.

SCHEME 2



ligands, when used with silver acetate or zinc triflate, provide excellent selectivities for certain imine substrates usually derived from glycine. Tertiary amines such as *N*,*N*-diisopropylethylamine or triethylamine are used as a base along with these cited catalysts. However, these ligands are not readily available and can be costly when used as a catalyst in industrial-scale production. In addition, leucine-derived imines are much less reactive toward a dipolarophile than glycine-derived imines.

A common feature of all of the reported ligands is their bidentate chemical structure. This feature brought to our attention the cinchona alkaloids which have an amino group and an adjacent hydroxyl group. Examples of some cinchona alkaloids include cinchonidine, quinine, and hydroquinine, as shown in Figure 2. In addition to the chelation potential of the

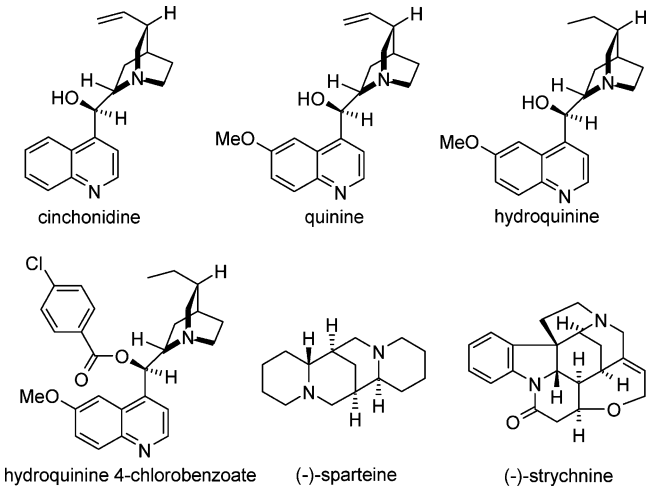


FIGURE 2. Structures of some alkaloids screened for the cycloadditions.

hydroxyl and amino groups, the tertiary amino group could function as a base for the formation of ylides or four-electron 1,3-dipoles. Such a built in basic moiety would eliminate the need to add an achiral tertiary amine such as *N*,*N*-diisopropylethylamine and triethylamine as used in the reported catalytic systems.[8−10] The availability of the pseudo enantiomers and the abundant supply at low cost of those alkaloids were also attractive for the industrial use that we were pursuing.[11] We were also interested in knowing what would happen if the hydroxyl group of the cinchona alkaloids was capped as an ester such 4-chlorobenzoate (Figure 2). Other alkaloids such as (-)-sparteine and (-)-strychnine were also included in the screening for comparison.

For the proof of concept studies, three reactions with imine **3** and methyl acrrylate were set up at ambient temperature, each containing 10 mol % cinchonidine (Scheme 2). When no metal salt was added (reaction 1), cycloaddition occurred but was only about 50% complete after several days. Essentially no enantioinduction was seen even though cinchonidine served as the catalytic base. Reaction times were decreased to 2 h with the addition of 1.5 equiv of lithium bromide, but the presence of lithium bromide completely eliminated all enantioselectivity. For the third reaction, addition of 10 mol % silver acetate significantly increased the reaction rate. The reaction was complete within 1 h after addition of silver acetate. Furthermore, the reaction was cleaner, and the enantiomeric ratio of the cycloadduct was 7:3 as measured by chiral HPLC analysis.[12] In all reactions, only the C4 α-epimer was detected by HPLC-MS analysis, which indicated excellent diastereoselectivity. The C4 α-epimer corresponds to the addition of methyl acrylate to the 1,3-dipole derived from the imino ester via an endo transition state. For the reaction with silver acetate and cinchonidine, both

(8) Longmire, J. M; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400.

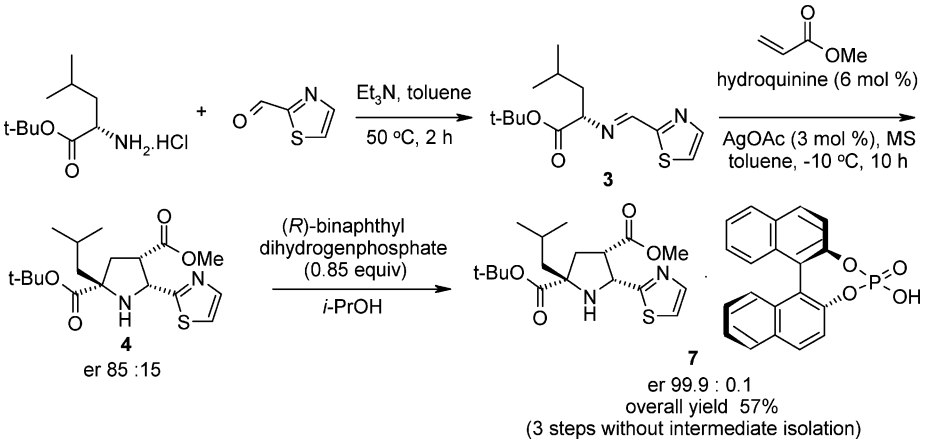
(9) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236.

(10) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174.

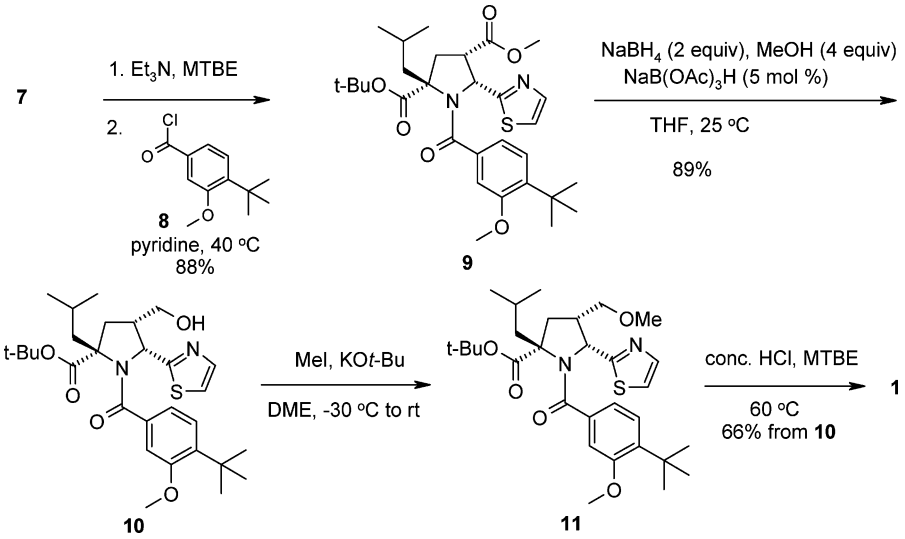
(11) Jørgensen and co-workers recently published their work on cycloadditions of glycine-derived imino esters with acrylates catalyzed by hydrocinchonine and silver fluoride. See: Alemparte, C.; Blay, G.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 4569. Our work involving glycine as well as the less reactive leucine-derived imines was independently initiated in the fall of 2002. The results from our study including many more examples varying amino acids and aldehydes were presented in the GlaxoSmithKline International Chemistry Symposium at Tonbridge, U.K., in 2004, and a part of it was published in an internal journal (Xie, S.; Agbodjan, A. A.; Cooley, B. E.; Flanagan, R. C.; Glover, B. N.; Jackson, M. M.; Matsuoka, R. T.; Sharp, M. J.; Toczko, J. F. *Chemicus* **2004**, *20*, 3).

(12) Conditions for chiral analysis of **4** and **6a** were as follows. Column: Chiracel OD-H, 4.6 × 250 mm, 5 micron; mobile phase: 90:10 heptane/*i*-PrOH; flow rate: 1 mL/min; detection: 230 nm; temperature: 20 °C; retention time: 7.0 min for **4** and 5.9 min for ***ent*-4**, 5.4 min for **6a**, and 6.8 min for ***ent*-6a**.

SCHEME 3



SCHEME 4

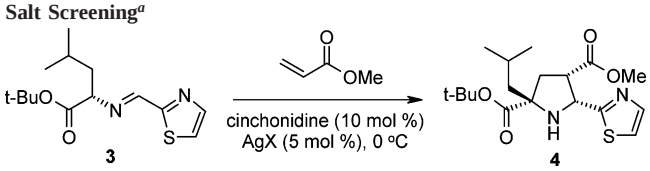


the rate acceleration and the enantioinduction clearly indicated the presence of chiral catalysis. The absolute stereochemistry of **4** was subsequently confirmed by X-ray analysis on the crystal of a derivative of **4**, namely, compound **10** (Scheme 4).

The Ag−cinchonidine catalysis worked similarly for the cycloaddition of methylvinyl ketone to give predominantly the C4 α-epimer **5** (α/*β* ratio 98:2); this result suggests the involvement of the same endo addition as observed in the acrylate addition. We found that the C4 α-epimer readily converted to the *β*-epimer **6a** when stirred with 10 mol % 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ethyl acetate at 40 °C (*β*/α ratio >95:5). The enantiomeric ratio of **6a** was 73:27 by chiral HPLC analysis.[12] The hydrochloride salt **6b** was prepared for analysis. The **5**/**6a** ratio was determined by HPLC-MS analysis. The structures of compounds **5** and **6b** were assigned based on extensive NMR studies including gDQCOSY (gradient double quantum filtered correlation spectroscopy), ^{1}H {^{13}C} gHSQC (gradient heteronuclear single quantum coherence), and GOESY (gradient enhanced nuclear Overhauser effect spectroscopy). These studies clearly indicated that the substituents on positions 4 and 5 of the pyrrolidine ring are geometrically cis for **5** and trans for **6b**. Further details of this analysis are provided in the Supporting Information. In a scale-up using 10 g of imine **3**, the epimerization from **5** to **6** was cleanly carried out in just 6 h with a stoichiometric amount of DBU at ambient temperature. Compound **6** was of interest to our drug discovery program; however, access to **6** had proven extremely difficult under other conditions including racemic synthesis with lithium bromide. In contrast, the C4 epimerization of cycloadduct **4** required much stronger conditions such as heating in refluxing THF with powdered potassium carbonate. From the data obtained, we propose that the endo cycloadduct is kinetically favored for both the acrylate and the vinyl ketone dipolarophiles and that the *β*-epimer, which corresponds to exo addition, is the thermodynamic product. Thus, the cycloaddition, when combined with the base-catalyzed epimerization, in essence, provides access to both endo and exo products depending on the conditions applied.

With the concept of a metal alkaloid catalysis proven, we next proceeded to optimize the cycloaddition reaction. We first screened a number of metal salts including Mg^{2+}, Co^{3+}, Mn^{2+}, Zn^{2+}, and Li^{+} with various counterions. The use of these metal salts resulted in much lower enantioselectivity and,[13] in the reactions employing $CoBr_3$, $CoCl_3$, and $MnCl_2$, less clean reactions due to formation of impurities including the undesired C4 *β*-epimer. In the end, Ag^{+} was, by far, the best metal salt to use with respect to both diastereo- and enantioselectivities. As a result, our efforts were focused on silver salts for further optimization of the cycloaddition. The screening of silver salts was carried out with 10 mol % cinchonidine and 5 mol % silver

TABLE 1. Cycloaddition of Imine 3 and Methyl Acrylate: Silver Salt Screening[a]



3 4

entry	AgX, $X =$	solvent	enantio ratio of **4**
1	CF_3CO_2	THF	60:40
2	CF_3CO_2	toluene	73:27
3	OTf	THF	63:37
4	OTf	toluene	72:28
5	OAc	THF	68:32
6	OAc	toluene	73:27
7	PF_6	THF	56:44
8	PF_6	toluene	72:28
9	NO_3	THF	65:35
10	NO_3	toluene	73:27

[a] The general procedure for screening was followed, and the enantio ratio was analyzed by chiral HPLC.[12,14]

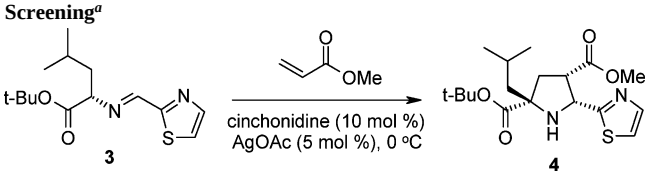
salt in two solvents, with the results shown in Table 1. Of the five silver salts screened, it was found that there was not much difference among the various silver salts in regards to the enantioselectivity when the same solvent was used. All salts gave enantio ratios of about 6:4 in THF and 7:3 in toluene. Silver acetate was chosen for alkaloid optimization because it gave a faster and slightly cleaner reaction probably because of its better solubility in THF and toluene.

The choice of solvent had a dramatic impact on the enantioselectivity in the cycloaddition. Results from screening of 14 solvents with cinchonidine as the ligand are shown in Table 2. In general, solvents containing a phenyl group such as toluene, chlorobenzene, benzene, and anisole (entries 1−4) gave better selectivity. On the other hand, too much substitution on the phenyl ring, as in *p*-xylene and mesitylene (entries 7 and 11), lowered the selectivity. Ethers such as THF, methyl *t*-butyl ether (MTBE), and 1,4-dioxane (entries 6, 8 and 9) were not good solvents, even though THF was the solvent initially used in the study. Interestingly, the use of acetonitrile as the solvent (entry 14) gave no enantioselectivity at all.

The alkaloid screening was conducted with 10 mol % alkaloids and 5 mol % silver acetate, with the results shown in Table 3. Pseudo enantiomeric alkaloids gave opposite enantioselectivities (entries 1 and 2), as did quinine and quinidine (entries 3 and 4). The use of hydroquinine improved the selectivity to above 80% (entry 5). Interestingly, addition of 50 wt % 4 Å molecular sieves (MS) increased the enantioselectivity to 87% (entry 6). We postulate that molecular sieves facilitate the exchange of imine **3** and cycloadduct **4** from the silver−ligand complex and thus increase the catalytic efficiency and reduce, relatively, the various background reactions. When the conditions for entry 6 were applied to *t*-butyl acrylate, the enantiomeric ratio increased to 92:8. However, the use of C4 *t*-butyl ester would theoretically make the subsequent selective ester reduction in the presence of the *N*-acyl group and the C2 *t*-butyl ester (see Scheme 4) more difficult. For practicality, we focused our efforts on methyl acrylate, despite the 5% lower selectivity. Minimum enantiomeric induction was observed

(13) Zinc triflate, in combination with (*S*,*S*)-2,2′-isopropylidene-bis(4-*t*-butyl-2-oxazoline) (*t*-Bu-BOX, 10 mol %) and triethylamine (10 mol %), as described by Jørgensen and coworkers,[9] did not yield any enantioselectivity when applied to the cycloaddition of imine **3** and methyl acrylate in THF.

TABLE 2. Cycloaddition of Imine 3 and Methyl Acrylate: Solvent Screening[a]

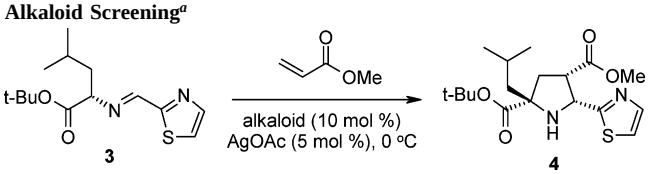


3 4

entry	solvent	enantio ratio	entry	solvent	enantio ratio
1	toluene	75:25	8	1,4-dioxane	66:34
2	chlorobenzene	72:28	9	MTBE	65:35
3	benzene[b]	72:28	10	CH_2Cl_2	63:37
4	anisole	70:30	11	mesitylene	62:38
5	*i*-PrOAc	69:31	12	trifluorotoluene	60:40
6	THF	69:31	13	isooctane	59:41
7	*p*-xylene	68:32	14	MeCN	50:50

[a] The general procedure for screening was followed, and the enantio ratio was analyzed by chiral HPLC.[12,14] [b] The reaction in benzene was run at 7 °C.

TABLE 3. Cycloaddition of Imine 3 and Methyl Acrylate: Alkaloid Screening[a]



3 4

entry	alkaloid	solvent	enantio ratio of **4**
1	cinchonidine	THF	69:31
2	cinchonine	THF	33:67
3	quinine	THF	62:38
4	quinidine	THF	31:69
5	hydroquinine	toluene	81:19
6	hydroquinine	toluene with 4 Å MS	87:13
7	(-)-strychnine	THF	45:55
8	(-)-sparteine	THF	46:54
9	hydroquinine 4-chlorobenzoate	toluene	57:43
10	hydroquinine 1,4-phthalazinediyl diether	toluene	68:32

[a] The general procedure for screening was followed, and the enantio ratio was analyzed by chiral HPLC.[12,14]

(entries 7 and 8) when using (-)-strychnine or (-)-sparteine as the ligand. This is presumably due to lack of a hydroxyl group and hence an inability to form a bidentate complex with the silver cation. As expected, when the hydroxyl group of hydroquinine was capped as an ester (entry 9) or as an ether (entry 10), the selectivity was significantly lower by as much as 24% compared to ratios obtained with hydroquinine (entry 5). We believed that the hydroxyl group of the cinchona alkaloids is an important component of the ligand structure for the silver−cinchona catalyst. It is possible that the hydroxyl group and the amino group of the alkaloid chelate to the silver ion for a more stable complex of the catalyst.

The process as shown in Scheme 3 was scaled up in 500 gallon reactors. The HCl salt of L-leucine *t*-butyl ester reacted with the 2-thiazolecarboxaldehyde in the presence of triethylamine to give imine **3**. Although **3** is crystalline, this compound is a hygroscopic and low melting solid. For the sake of practicality, the crude **3** from the aqueous workup and partial concentration in vacuo to remove triethylamine was used for cycloaddition directly without any purification. The catalyzed [3+2] cycloaddition was carried out with 6 mol % hydroquinine

and 3 mol % silver acetate in the presence of 50 wt % 4 Å molecular sieves at −10 °C. The enantioselectivity was 85:15, slightly lower than the typical 87:13 ratio that we were able to consistently achieve with isolated crystalline imine **3**. Cycloadduct **4** as a crude toluene solution was partially concentrated and diluted with isopropanol. For the purpose of isolation, (*R*)-1,1′-binapthyl-2,2′-dihydrogen phosphate was used to form crystalline salt **7** in 57% overall yield from L-leucine *t*-butyl ester hydrochloride. Use of the chiral acid not only secured excellent recovery of the desired cycloadduct **4**, but it also enhanced the enantiomeric ratio of the product to 99.9:0.1. On the smaller scale with one-liter fixed equipment, an overall yield as high as 65% was achieved for the three steps. Compared with the racemic synthesis that we scaled up to 50 L to support the early research program, the asymmetric route as shown in Scheme 3 more than doubled the overall yield, and the process was extremely robust and consistently reproducible on a large scale.

Completion of the synthesis of the target *N*-acylpyrrolidine (**1**) is shown in Scheme 4. The slurry of salt **7** in MTBE was treated with 1 equiv of triethylamine to provide free base **4** as a solution in MTBE. (*R*)-Binaphthyl hydrogenphosphate was fully recovered as the crystalline triethylamine salt via filtration. For the formation of acid chloride **8** from carboxylic precursor **2** and $SOCl_2$ in CH_2Cl_2, the use of a catalytic amount (0.25 equiv) of pyridine to ensure that conversion to the acid chloride was reproducible proved to be vital. The formation of the highly reactive and corrosive acid chloride was monitored by online ReactIR. This technique offered advantages in safety and accuracy compared with the traditional analysis of an amide derivative by HPLC. The carbonyl stretch at 1691 cm^{-1} was used to monitor the carboxylic acid **2**, and the carbonyl stretches at 1743 and 1768 cm^{-1} were used to monitor the formation of the acid chloride **8**. Acylation of free base **4** with acid chloride **8** provided crystalline *N*-acylpyrrolidine **9** in up to 88% yield.

Reduction of the methyl ester to alcohol **10** was a significant challenge. Both the amide bond and the *t*-butyl ester were susceptible to reduction by a variety of reducing agents. In addition to the chemoselectivity, the C4 position of **9** is prone to epimerization to the thermodynamically more stable β-epimer prior to the methyl ester reduction. As a result, common reagents for reduction of an ester to an alcohol such as *i*-Bu_2AlH, $LiBH_4$, Super-hydride, and $NaBH_4$ in combination with various alcohols led to a large amount of overreduction and C4 epimerization on the multigram scale. The use of $LiAlH_4$ was successful on a small scale when the reaction temperature was carefully controlled within a narrow and low range.[5a] Unfortunately, this $LiAlH_4$-based reduction, on scale up to just under 100 grams, led to the formation of over 50% of 4-(1,1-dimethylethyl)-3-(methyloxy)benzaldehyde, a byproduct from the partial reduction of the amide bond of ester **9** or alcohol **10**. HPLC-MS was used to monitor and analyze the ratios of **9** and **10** versus their respective epimers.[15] After extensive reagent screening and process optimization, we came up with a unique set of reduction conditions involving $NaBH_4$−MeOH (1:2) in the presence of a catalytic amount of $NaB(OAc)_3H$ (2.5 mol % relative to $NaBH_4$). These conditions were an extension of previously reported work by our colleagues on the reduction of a *t*-butoxycarbonyl (BOC)-protected amide with $NaBH_4$−MeOH in the presence of acetic acid.[16] We postulated that conversion of $NaBH_4$ to $NaB(OMe)_{4-n}H_n$ ($n = 1-3$) was catalyzed by $NaB(OAc)_3H$. To our surprise, the commercially available $NaB(OMe)_3H$ led to up to 50% C4 epimerization in the reduction of **9** to **10**. We believed that the in-situ-formed $NaB(OMe)_{4-n}H_n$ was more reactive and less basic, contributing to both the fast and essentially epimerization-free reduction.[17] The reduction was carried out conveniently by charging the three solids (**9**, $NaBH_4$, and $NaB(OAc)_3H$) to the reactor followed by the sequential addition of THF and methanol with stirring. The selective reduction was complete within 5 h at 25 °C, affording **10** as a crystalline solid in 89% yield (as high as 97% if a second crop was included). A molecule of alcohol **10** from a single-crystal X-ray diffraction study is shown in Figure 3. The structure confirmed the structural assignment for the [3+2] cycloaddition as well as the retention of the integrity of the stereocenter from the selective reduction.[18]

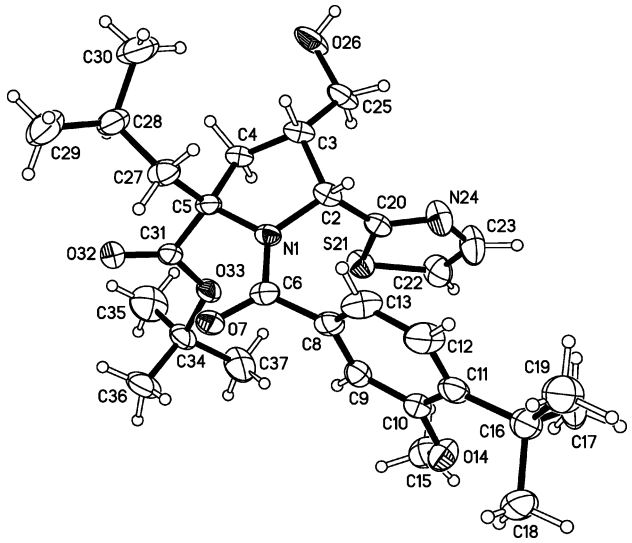


FIGURE 3. Atomic displacement ellipsoid plot (50% probability) for **10** from the crystal structure. A molecule of acetonitrile, also present in the asymmetric unit and with partial occupancy, has been omitted for clarity.

The *O*-methylation of **10** proceeded smoothly with iodomethane or dimethyl sulfate and a strong base such as 1 equiv of sodium hydride or 2 equiv of sodium *t*-butoxide, as shown

(14) General procedure for screening: To a solution of 282 mg (1.00 mmol) of imino ester **3** in 10 mL of toluene or another solvent was added 29.4 mg (0.10 mmol) of cinchonidine or equivalent mmolar quantities of another alkaloid, followed by addition of 8.3 mg (0.05 mmol) of silver acetate or equivalent mmolar quantities of another silver salt. After being stirred with ice cooling for 15 min, the mixture was treated with 0.10 mL (1.10 mmol) of methyl acrylate. The mixture was stirred for 30 min with ice cooling and was allowed to gradually warm to ambient temperature. Upon completion of the reaction (1−12 h), the reaction was quenched with water. The organic layer was sampled for analysis by chiral HPLC.[12]

(15) (a) Conditions for HPLC analysis of **9** and its β-epimer were as follows. Column: Phenomenex, Develosil Diol 100A, 4.6 × 250 mm, 5 micron; mobile phase: 85:15 heptane/EtOAc; flow rate: 1.5 mL/min; detection: 250 nm; temperature: 25 °C; retention time: 5.95 min for **9** and 5.05 min for its β-epimer. (b) Conditions for HPLC analysis of **10** and its β-epimer were as follows. Column: Phenomenex, Develosil Diol 100A, 4.6 × 250 mm, 5 micron; mobile phase: 60:40 heptane/EtOAc; flow rate: 1.0 mL/min; detection: 250 nm; temperature: 25 °C; retention time: 7.59 min for **10** and 5.26 min for its β-epimer.

(16) Daluge, S. M.; Martin, M. T.; Sickles, B. R.; Livingston, D. A. *Nucleosides, Nucleotides Nucleic Acids* **2000**, *19*, 297.

(17) The process research work leading to the discovery of this unique set of reduction conditions and the solution to process safety issues identified during reaction calorimetry assessment will be the subject of a future publication.

(18) The numbering method for the X-ray structure in Figure 3 is different from the one used in the rest of the structure drawings and text.

in Scheme 4. When a weak base such as potassium hydroxide or cesium carbonate was used, up to 50% quarternization of the thiazole nitrogen occurred. The formation of the more nucleophilic alkoxide in the presence of the strong base was critical to avoid the undesired *N*-methylation. The methylation was over 99% complete within 1 h after the reaction was warmed from −30 °C to room temperature. For an unknown reason, we could not achieve 100% methylation with 2 equiv of methyl iodide, and the unreacted residual alcohol **10** could not be removed by recrystallization. As a result, the initial isolated methyl product **11** was subject to the methylation process with additional 0.2 equiv of methyl iodide to convert the residual amount (<1%) of **10** to **11**. Finally, the hydrolysis of the crude *t*-butyl ester was facile with concentrated aqueous hydrochloric acid in MTBE. The target **1** was isolated as a crystalline solid in 66% overall yield for the two steps from **10**.

Conclusions

An efficient synthesis of the highly substituted *N*-acylpyrrolidine target (**1**) was achieved in seven linear steps from L-leucine *t*-butyl ester hydrochloride. The synthesis features a novel asymmetric synthesis of pyrrolidines through a [3+2] cycloaddition of an azomethine ylide with methyl acrylate catalyzed by a complex of silver acetate and a cinchona alkaloid. The cycloaddition is completely diastereoselective and 87% enantioselective with readily available hydroquinine. The alkaloid serves as a base for the formation of the azomethine ylide or 1,3-dipole as well as a ligand for the catalyst. The cycloaddition methodology also proved applicable to methylvinyl ketone, providing access to either α- or *β*-epimer of the 4-acetylpyrrolidine, depending on the reaction conditions utilized. A unique $NaBH_4$−MeOH reduction condition with catalysis by $NaB(OAc)_3H$ was developed to secure a mild and selective reduction of an ester to an alcohol. With all three isolated intermediates being highly crystalline solids, the synthesis is practical and has been scaled up to 500 gallon reactors to produce multi-kilogram quantities of **1**.

Experimental Section

1,1-Dimethylethyl *N*-(1,3-Thiazol-2-ylmethylidene)-l-leucinate (3): To a suspension of 50.0 g (223 mmol) of L-leucine *t*-butyl ester hydrochloride in 500 mL of toluene was successively added 19.6 mL (223 mmol) of 2-thiazolecarboxaladehyde and 31.8 mL (228 mmol) of triethylamine. The reaction was heated at 50 °C for 3 h. The reaction was cooled to ambient temperature and diluted with 40 mL of MTBE and 200 mL of water. The organic layer was successively washed with 150 mL of water and 200 mL of saturated brine, dried with anhydrous sodium sulfate, and evaporated in vacuo to near dryness. The thick oil was diluted with 50 mL of MTBE and treated with about 100 mL of heptane. After being cooled at 0 °C for 4 h, the solids were filtered, washed with 50 mL of heptane, and dried at 50 °C overnight to give 32.1 g (51%) of imine **3** as a light-yellow crystalline solid. The combined filtrate and washing were concentrated to about 50 mL and stood at ambient temperature for 2 days. The resultant solids were filtered, washed with 10 mL of heptane, and dried to give 18.9 g (30%) of the second crop of **3**: $[\alpha]^{25}_D$ −62.2 (*c* 2.21, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.42 (s, 1H), 7.90 (d, *J* = 3.0 Hz, 1H), 7.41 (d, *J* = 3.0 Hz, 1H), 4.03 (t, *J* = 6.0 Hz, 1H), 1.80 (m, 2H), 1.43 (s, 9H), 0.86 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.9, 166.9, 156.7, 144.3, 122.2, 81.7, 71.5, 42.0, 28.2, 24.8, 23.3, 21.7. Anal. Calcd for $C_{14}H_{22}N_2O_2S$: C, 59.54; H, 7.85; N, 9.92, S, 11.35. Found: C 59.56; H, 7.88; N, 9.91, S, 11.36.

2-(1,1-Dimethylethyl) 4-Methyl (2*S*,4*S*,5*R*)-2-(2-Methylpropyl)-5-(1,3-thiazol-2-yl)-2,4-pyrrolidinedicarboxylate (4): A general procedure for cycloaddition of **3** and methyl acrylate to form **4** as used in the screening is described in the note.[14] For the synthesis of target **1**, free base **4** was not isolated. It was conveniently converted to salt **7** for purification and isolation. See the procedure for compound **7** for details.

An analytical sample of **4** was obtained by neutralization of compound **7**, which was the salt of **4** and (*R*)-1,1′-binapthyl-2,2′-dihydrogen phosphate, with triethylamine in MTBE. The procedure for this free base preparation is described in the procedure for **9**. Crystallization from the concentrated MTBE solution provided **4** as a crystalline solid; enantiomeric ratio by chiral HPLC[12] > 99.9:0.1 favoring target enantiomer **4**: $[\alpha]^{25}_D$ −29.9 (*c* 1.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.66 (d, *J* = 3.0 Hz, 1H), 7.22 (d, *J* = 3.0 Hz, 1H), 4.87 (d, *J* = 6.0 Hz, 1H), 3.44 (s, 3H), 3.48 (m, 1H), 3.30 (br s, 1H), 2.70 (m, 1H), 2.06 (m, 1H), 1.75 (m, 2H), 1.60 (m, 1H), 1.47 (s, 9H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.89 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) *δ* 174.7, 172.3, 171.3, 142.7, 119.2, 100.2, 81.6, 69.0, 61.9, 51.9, 48.9, 39.0, 28.2, 25.4, 24.5, 23.7. Anal. Calcd for $C_{18}H_{28}N_2O_4S$: C, 58.67; H, 7.66; N, 7.60, S, 8.70. Found: C 58.47; H, 7.62; N, 7.57, S, 8.68.

1,1-Dimethylethyl (4*S*,5*R*)-4-Acetyl-2-(2-methylpropyl)-5-(1,3-thiazol-2-yl)-l-prolinate (5) and 1,1-Dimethylethyl (4*R*,5*R*)-4-Acetyl-2-(2-methylpropyl)-5-(1,3-thiazol-2-yl)-l-prolinate (6): A 1 L round-bottom flask was charged with 10.0 g (35.4 mmol) of imine **3**, 300 mL of THF, 1.05 g (3.54 mmol) of (-)-cinchonidine, and 600 mg (3.54 mmol) of AgOAc. The reaction mixture was cooled to −20 °C, and 3.6 mL (42.5 mmol) of methylvinyl ketone was added. The reaction mixture was allowed to warm to 0 °C. After 4 h, 100 mL of MTBE and 100 mL of H_2O were added, and the layers were separated. The organic layer was washed with 100 mL of H_2O and 100 mL of brine successively, dried over $MgSO_4$, and concentrated to give 12.5 g of crude cis product 1,1-dimethylethyl (4*S*,5*R*)-4-acetyl-2-(2-methylpropyl)-5-(1,3-thiazol-2-yl)-L-prolinate (**5**) as a thick oil. The ratio of **5** to its C4 *β*-epimer was determined to be 98:2 by HPLC analysis on the crude product (HPLC conditions: Column: Luna C_{18}(2) 50 × 2 mm, 3 *μ*m; mobile phase A: H_2O (0.05% TFA), mobile phase B: MeCN (0.05% TFA); gradient: 0−95% B over 8 min; detection: 220 nm; temperature: 40 °C; retention time: 4.07 min for **5** and 4.68 min for the *β*-epimer). The crude oil was dissolved in 250 mL of THF, and 6.50 mL (42.5 mmol) of DBU was added. After being stirred at room temperature for 6 h, the HPLC analysis showed conversion to the C4 *β*-epimer (**6a**). The mixture was treated with 100 mL of 20% aqueous NH_4Cl and 150 mL of EtOA. The organic layer was washed with an additional 100 mL of 20% NH_4Cl, dried over $MgSO_4$, and concentrated in vacuo to give 12.4 g of trans product **6a** as a yellow oil (er 73:27 by chiral HPLC analysis).[12] A hydrochloride salt (**6b**) was obtained by stirring a mixture of 353 mg (1.00 mmol) of **6a** and 0.5 mL (2.00 mmol) of 4 M HCl in 1,4-dioxane in 5 mL of MTBE. Filtration and washing with cold MTBE provided **6b** as a light-yellow crystalline solid. The structures of compounds **5** and **6b** were assigned based on extensive NMR studies including gDQCOSY, ^{1}H {^{13}C} gHSQC, and GOESY experiment. Details are included in the Supporting Information. These studies clearly indicated that the substituents on positions 4 and 5 of the pyrrolidine ring were cis for **5** and trans for **6b**. **5**: ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.64 (d, *J* = 3.0 Hz, 1H), 7.22 (d, *J* = 3.0 Hz, 1H), 4.98 (d, *J* = 9.0 Hz, 1H), 3.54 (m, 1H), 3.04 (br s, 1H), 2.70 (m, 1H), 2.01 (s, 3H), 1.98 (m, 1H), 1.76 (m, 2H), 1.60 (m, 1H), 1.47 (s, 9H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.88 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 207.3, 175.0, 171.7, 142.6, 119.5, 81.6, 68.7, 62.0, 56.0, 49.6, 38.3, 30.8, 28.2, 25.4, 24.6, 23.6. HRMS calcd for $C_{18}H_{29}N_2O_3S$ (MH^+): 353.1894. Found: 353.1905. **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.69 (d, *J* = 3.0 Hz, 1H), 7.25 (d, *J* = 3.0 Hz, 1H), 4.57 (m, 1H), 3.10 (m, 1H), 2.60 (m, 1H), 2.50 (m, 1H), 2.23 (s, 3H), 1.98 (m, 1H), 1.79 (m, 2H), 1.71 (m, 1H), 1.39 (s, 9H), 0.98 (d, *J* = 6.0 Hz, 3H), 0.91 (d, *J* = 6.0 Hz,

3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 173.3, 172.8, 142.6, 119.1, 82.6, 72.8, 61.9, 58.9, 47.6, 37.5, 31.5, 28.0, 25.8, 25.1, 24.0. HRMS calcd for $C_{18}H_{29}N_2O_3S$ (MH^+): 353.1894. Found: 353.1893.

Salt of (2*S*,4*S*,5*R*)-2-(2-Methylpropyl)-5-(1,3-thiazol-2-yl)-2,4-pyrrolidinedicarboxylate and (*R*)-1,1′-Binapthyl-2,2′-dihydrogen Phosphate (7): To a 300 gallon reactor were successively added 45.0 kg (201 mol) of *t*-butyl L-leucine hydrochloride, 450 L of toluene, and 22.8 kg (201 mol) of 1,3-thiazole-2-carbaldehyde at ambient temperature. The white slurry was stirred for 2 min under nitrogen; then, 20.7 kg (205 mol) of Et_3N was added. The mixture was heated at 50 °C for 2 h. The reaction was cooled to 20 °C and quenched with 180 L of water. Layers were separated, and the toluene layer was washed with 130 L of water. The toluene layer was concentrated in vacuo at 35−55 °C to about 180 L. After being diluted with 270 L of toluene, the solution was further distilled to about 270 L. The toluene solution of the crude 1,1-dimethylethyl *N*-(1,3-thiazol-2-ylmethylidene)-L-leucinate (**3**) was used for the cycloaddition without further purification.

The toluene solution of **3** as prepared above was diluted with 540 L of toluene, followed by sequential addition of 3.9 kg (11.9 mmol) of hydroquinine and 22.5 kg of 4 Å powdered molecular sieves at ambient temperature. The thin slurry was stirred for 5 min followed by addition of 1.02 kg (6.11 mol) of AgOAc. The mixture was cooled to −10 °C, and then, 19.1 kg (222 mol) of methyl acrylate was added. The reaction was stirred for 6 h. The reaction was warmed to ambient temperature and filtered through an in-line filter. The filtrate was successively washed with 2 × 180 L of water and 180 L of 15% brine. The organic layer was concentrated in vacuo at 35−65 °C to about 360 L. The mixture was diluted with 360 L of *i*-PrOH and further concentrated to 360 L. This dilution−concentration protocol was repeated once. The crude cycloadduct 2-(1,1-dimethylethyl) 4-methyl (2*S*,4*S*,5*R*)-2-(2-methylpropyl)-5-(1,3-thiazol-2-yl)-2,4-pyrrolidinedicarboxylate (**4**), prepared as such, was used for the next step without further purification.

A 500 gallon reactor was charged with 59.4 kg (171 mol) of (*R*)-1,1′-binapthyl-2,2′-dihydrogen phosphate and 765 L of *i*-PrOH, and the slurry was heated to 80 °C for 30 min. The solution of cycloadduct **4** in *i*-PrOH prepared as above in the 300 gallon reactor was then added to the 500 gallon reactor, maintaining a temperature of 70−80 °C during the addition. After being stirred for 1 h, the reaction mixture was cooled to 20 °C at a rate of 1 °C/min. The solids were filtered, and the cake was washed with 225 L of *i*-PrOH. The solids were dried at 50−60 °C under house vacuum to afford 81.6 kg (overall yield of 57% for three steps from *t*-butyl L-leucine hydrochloride) of the salt of (2*S*,4*S*,5*R*)-2-(2-methylpropyl)-5-(1,3-thiazol-2-yl)-2,4-pyrrolidinedicarboxylate and (*R*)-1,1′-binapthyl-2,2′-dihydrogen phosphate (**7**); enantiomeric ratio by chiral HPLC analysis of the free base **4**[12] > 99.9:0.1 favoring target enantiomer **4**. Analytical data of **7**: $[\alpha]^{25}_D$ −36.9 (*c* 1.33, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.10 (d, J = 6.0 Hz, 2H), 8.06 (d, J = 6.0 Hz, 2H), 7.76 (m, 2H), 7.73 (m, 2H), 7.48 (m, 4H), 7.33 (m, 2H), 7.23 (m, 2H), 5.22 (br s, 1H), 3.75 (m, 1H), 3.38 (s, 3H), 2.90 (m, 1H), 2.23 (m, 1H), 1.80 (m, 2H), 1.61 (m, 1H), 1.41 (s, 9H), 0.90 (d, J = 6.0 Hz, 3H), 0.83 (d, J = 6.0 Hz, 3H). Anal. Calcd for $C_{38}H_{41}N_2O_8SP$: C, 63.68; H, 5.77; N, 3.91, S, 4.47. Found: C 63.45; H, 5.74; N, 3.76, S, 4.39.

2-(1,1-Dimethylethyl) 4-Methyl (2*S*,4*S*,5*R*)-1-{[4-(1,1-Dimethylethyl)-3-(methyloxy)phenyl]carbonyl}-2-(2-methylpropyl)-5-(1,3-thiazol-2-yl)-2,4-pyrrolidinedicarboxylate (9): A 300 gallon reactor was charged with 74 kg (103 mol) of **7**, followed by 370 L of MTBE and 15.8 L (11.0 mol) of triethylamine. The slurry was stirred at room temperature for 1 h, and the solids were filtered off and washed with 222 L of MTBE. The reactor was rinsed with MTBE, the filtrate containing free base **4** was recharged to the reactor via an in-line filter (0.4−1 micron) to remove residual solids, and 20.9 L (260 mol) of pyridine was added. Meanwhile, 25.8 kg (120 mol) of carboxylic acid **2** was charged to a 500 gallon reactor, followed by 222 L of dichloromethane, 2.50 L (30 mol) of pyridine, and 9.80 L (130 mol) of $SOCl_2$. After being stirred at 20 °C for 2 h, the resultant acid chloride **8** was cooled to 0 °C. The previous filtrate in the other reactor containing **4** was slowly added to the cold acid chloride (**8**) solution, the temperature was raised to 35 °C, and it was stirred overnight.

The reaction mixture was concentrated under vacuum, with mild heating, to approximately 370 L and cooled to 20 °C. To the mixture was added 148 L of 1 N HCl, followed by 740 L of heptane, and the slurry was cooled to 0 °C. After 2 h at 0 °C, the solids were filtered off, washed with 370 L of water, followed by 370 L of heptane, and dried to a constant weight to provide 50.8 kg (88%) of **9** as a white crystalline solid: $[\alpha]^{25}_D$ +73.0 (*c* 1.20, MeOH); ^{1}H NMR (300 MHz, DMSO−d_6) δ 7.53 (d, J = 3.0 Hz, 1H), 7.49 (d, J = 3.0 Hz, 1H), 7.19 (d, J = 6.0 Hz, 1H), 6.85 (d, J = 6.0 Hz, 1H), 6.62 (s, 1H), 5.82 (d, J = 9.0 Hz, 1H), 3.90 (m, 1H), 3.67 (s, 3H), 3.27 (s, 3H), 2.83 (t, J = 12 Hz, 1H), 2.50 (s, 1H), 2.36 (m, 1H), 2.20 (m, 2H), 1.93 (m, 2H), 1.36 (s, 9H), 1.31 (s, 9H), 1.01 (d, J = 6.0 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 170.5, 169.5, 168.1, 156.9, 139.6, 137.8, 134.0, 124.9, 118.9, 115.4, 107.5, 80.4, 69.7, 62.4, 59.5, 52.6, 33.0, 27.3, 25.9, 23.6, 23.2, 22.5. Anal. Calcd for $C_{30}H_{42}N_2O_6S$: C, 64.49; H, 7.58; N, 5.01, S, 5.74. Found: C 64.48; H, 7.54; N, 5.06, S, 5.69.

1,1-Dimethylethyl (4*S*,5*R*)-1-{[4-(1,1-Dimethylethyl)-3-(methyloxy)phenyl]carbonyl}-4-(hydroxymethyl)-2-(2-methylpropyl)-5-(1,3-thiazol-2-yl)-l-prolinate (10): To a 50 L reactor were added 6.48 kg (11.6 mol) of ester **9**, 880 g (23.2 mol) of $NaBH_4$, 120 g (0.58 mol) of $NaB(OAc)_3H$, and 16.2 L of THF at ambient temperature under nitrogen. The mixture was cooled to −10 °C. To the white slurry was added 1.87 L (46.4 mol) of methanol over about 1 h. The reaction was gradually warmed to 25 °C over 1.5 h and stirred for 5 h. The reaction was cooled to 5 °C and treated with 740 mL (23.2 mol) of MeOH over 30 min and 1.95 kg of concentrated HCl (19.8 mol) over 30 min. The mixture was diluted with 19.4 L of water and 6.5 L of MTBE. About 115 g more of concentrated HCl was added to adjust the pH of the aqueous layer to about 3.0 to ensure full hydrolysis of any residual reducing reagent. Layers were separated, and the aqueous layer was extracted with 19.5 L of MTBE. The combined organic layers were washed with 13 L of 15% brine and concentrated in vacuo to about 15 L. To the solution was added 19.5 L of MeCN, and the mixture was further concentrated to about 16 L, at which point the crystallization started. After being cooled to −5 °C and stirred for 2h, the white mixture was filtered, washed with 2.5 L of MTBE, and dried at 55 °C in vacuo to give 5.49 kg (89%) of alcohol **10** as a white crystalline solid.

The filtrate from the above isolation was combined with filtrates from two other reactions involving 3.1 and 6.2 kg of ester **9**. The combined filtrates were concentrated to 13 L, diluted with 10 L of MeCN, and further concentrated in vacuo to 7.5 L. After being cooled at −8 °C for 2 h, the mixture was filtered, washed with 0.8 L of MTBE, and dried to give 1.57 kg (8%) of a second crop of product. The overall yield including the second crop would be 97% of **10**: $[\alpha]^{25}_D$ +81.6 (*c* 1.10, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.36 (s, 2H), 7.05 (d, J = 9.0 Hz, 1H), 6.62 (d, J = 3.0 Hz, 1H), 6.34 (s, 1H), 5.46 (d, J = 9.0 Hz, 1H), 3.63 (m, 1H), 3.52 (s, 3H), 3.27 (m, 1H), 3.09 (m, 1H), 2.74 (m, 1H), 2.27 (m, 1H), 2.18 (m, 2H), 1.93 (m, 2H), 1.50 (s, 9H), 1.20 (s, 9H), 1.01 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 170.5, 169.5, 168.1, 156.9, 139.6, 137.8, 134.0, 124.9, 118.9, 115.4, 107.5, 80.4, 69.7, 62.4, 59.5, 52.6, 33.0, 27.3, 25.9, 23.6, 23.2, 22.5. Anal. Calcd for $C_{29}H_{42}N_2O_5S{\cdot}0.5H_2O$: C, 64.53; H, 8.02; N, 5.18; S, 5.94. Found: C 64.84; H, 8.00; N, 5.23; S, 5.91. HRMS *m*/*z* calcd for $C_{29}H_{42}N_2O_5SNa$ ($M+Na^+$): 553.2707. Found: 553.2688.

(4*S*,5*R*)-1-{[4-(1,1-Dimethylethyl)-3-(methyloxy)phenyl]carbonyl}-4-[(methyloxy)methyl]-2-(2-methylpropyl)-5-(1,3-thiazol-2-yl)-l-proline (1): A 300 gallon reactor was charged with 139 L of 1,2-dimethoxyethane and 34.7 kg (65.4 mol) of **10**. The mixture was cooled to −30 °C. A solution of 12.6 kg (131 mol) of sodium *t*-butoxide in 139 L of 1,2-dimethoxyethane was charged to the

cold reaction mixture over 30 min and rinsed with 29 L of 1,2-dimethoxyethane. While maintaining the reaction temperature below −25 °C, 18.5 kg (131 mol) of methyl iodide was added. The mixture was held at −30 °C for 30 min and then warmed to 25 °C over 1 h. The alkylation at this point was >99% complete. The following recycling process was used to convert all of the starting material **10**. The reaction was quenched with 139 L of 0.1 N HCl and cooled to 0 °C. The intermediate methylated *t*-butyl ester **11** was collected by filtration and washed with 52 L of water. The material was charged to a clean 300 gallon reactor along with 347 L of 1,2-dimethoxyethane. The solution was concentrated in vacuo to 220 L to azeotropically dry the solution. To the mixture was added 90 L of 1,2-dimethoxyethane, and the solution was cooled to −30 °C. A solution of 1.26 kg (13.1 mol) of sodium *t*-butoxide in 14 L of 1,2-dimethoxyethane was charged to the cold reaction mixture and rinsed with 3.5 L of 1,2-dimethoxyethane. While maintaining the reaction temperature below −25 °C, 1.90 kg (13.1 mol) of methyl iodide was added. The mixture was warmed to 25 °C; then, 69 L of MTBE and 69 L of 0.1 N HCl were added. The aqueous phase was removed, and the organic solution was concentrated in vacuo to 170 L. The reactor was charged with 3.30 kg of concentrated HCl. The mixture was heated to 60 °C and stirred for 7 h. After being cooled to 25 °C, the mixture was diluted with 139 L of MTBE and 104 L of water. The aqueous layer was removed, and the organic solution was concentrated in vacuo to 140 L. After being treated with 34 L of MTBE and 35 L of 2,2,4-trimethylpentane, the mixture was aged for 30 min at 25 °C. An additional 35 L of 2,2,4-trimethylpentane was added, and the mixture was stirred for 30 min. A final 35 L of 2,2,4-trimethylpentane was charged, and the mixture was stirred for an additional 30 min. The suspension was cooled to 0 °C and held for 2 h. The product was collected by filtration and washed with 70 L of a 1:1 mixture of MTBE and 2,2,4-trimethylpentane. The product was dried in vacuo to give a 66% yield of **1**: $[\alpha]^{25}_{D}$ +50.0 (*c* 1.43, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.87 (d, J = 6.0 Hz, 1H), 7.61 (d, J = 3.0 Hz, 1H), 7.22 (d, J = 9.0 Hz, 1H), 6.71 (d, J = 6.0 Hz, 1H), 6.36 (d, J = 3 Hz, 1H), 5.67 (d, J = 9.0 Hz, 1H), 3.64 (s, 3H), 3.19 (s, 1H), 3.11 (m, 1H), 3.10 (s, 3H), 2.68 (t, J = 9 Hz, 1H), 1.95−2.35 (m, 5H), 1.32 (s, 9H), 1.14 (d, J = 6.0 Hz, 3H), 1.12 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 171.2, 158.6, 140.2, 135.0, 126.5, 121.8, 116.9, 108.7, 100.2, 70.8, 63.9, 57.9, 54.3, 47.0, 43.4, 42.7, 34.6, 28.8, 24.9, 24.6, 23.7. Anal. Calcd for $C_{26}H_{36}N_2O_5S$: C, 63.91; H, 7.43; N, 5.73, S, 6.56. Found: C 63.82; H, 7.37; N, 5.72, S, 6.58.

Acknowledgment. We thank Dr. Thomas O'Connell (University of North Carolina at Chapel Hill) for the NMR studies, Dr. David Black (GlaxoSmithKline) for the HRMS analysis, and Professor William Clegg and Dr. Neil Brooks (University of Newcastle) for the GSK-funded X-ray crystallographic analysis.

Supporting Information Available: NMR spectra for compounds **1**, **3**, **4**, **5**, **6a**, **7**, **9**, and **10**, gDQCOSY and gHSQC analysis on compounds **5** and **6b**, and X-ray crystallographic data for compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800062C