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Stereoselective Lithiation and Carboxylation of Boc-Protected Bicyclopyrrolidine: Synthesis of a Key Building Block for HCV Protease Inhibitor Telaprevir

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ABSTRACT: A stereoselective process for the manufacture of bicyclopyrrolidine **7** to **2** has been developed. The process utilizes a stereoselective lithiation/carboxylation sequence. The achiral diamine ligand **DPBP** induces excellent diastereocontrol, and resolution with **(*S*)-THNA** provides the corresponding salt of **8** in high er and dr. Subsequent processing of **8** gives **2** as the oxalate salt in an overall yield of 27% from **7** (based on total molar charge of **7**). Compound **2** was obtained with high chemical and chiral purities. The process was successfully demonstrated on >100 kg scale.

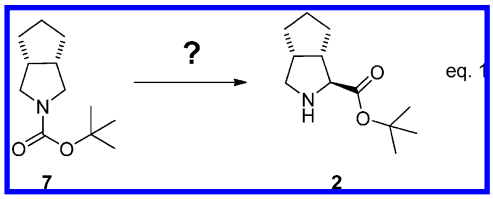
INTRODUCTION

The global prevalence of hepatitis C virus (HCV) infection is estimated to be 130−170 million people, approximately 2−3% of the world population,[1] with more than 365,000 deaths per year resulting from long-term complications.[2] Approximately 55−85% of infections become chronic, and chronic hepatitis C (CHC) can lead to serious liver disease.[3] Cirrhosis develops within 20 years in 4−20% of patients with CHC.[4] Patients diagnosed with cirrhosis have an 18−29% risk of developing decompensated liver disease within 5−10 years, and a 10−30% risk of developing hepatocellular carcinoma after 20 years.[5] An approved treatment for patients with genotype 1 CHC and compensated liver disease includes the HCV protease inhibitor telaprevir (**1**) in combination with pegylated interferon (Peg-IFN) and ribavirin (RBV).

Telaprevir is a polyamide containing two unique subunits: a *β*-amino-*α*-ketoamide and a bicyclic proline analogue. Scheme 1 shows a retrosynthetic disconnection of telaprevir. Retroanalysis by amide bond cleavages reveals four amino acids and one pyrazine carboxylic acid as appropriate building blocks for the construction of **1**. Pyrazine carboxylic acid, *N*-protected cyclohexylglycine, and *N*-protected *tert*-butyl glycine are available commercially, but building blocks **2** and **3** require synthetic preparation. In this report, we will detail the development of a stereoselective chemical process for the manufacture of bicycloproline, **2**.

ENANTIOSELECTIVE LITHIATION/CARBOXYLATION

An initial evaluation of the structural similarity between **2** and its monocyclic analogue proline guided us to the evaluation of an enantioselective lithiation/carboxylation process based on the groundbreaking work of Beak.[6] From Beak's work, (*R*)-proline can be prepared from Boc-protected pyrrolidine in high enantiomeric purity via enantioselective *α*-lithiation with *sec*-butyllithium in the presence of (−)-sparteine (Scheme 2, top reaction sequence). Treatment of an ethereal solution of Boc-protected pyrrolidine with *sec*-butyllithium at low temperature in the presence of a stoichiometric amount of (−)-sparteine provided the (*R*)-proline *α*-functionalized products in up to 98:2 er, via formation of intermediate **4**. A wide range of electrophiles was used for quenching the lithium anion, with CO_2 being the most relevant to our endeavors. O'Brien extended Beak's work, providing access to the (*S*)-proline enantiomer via (−)-cytisine-based chiral ligand **6** (Scheme 2, lower reaction sequence).[7] Under identical reaction conditions, O'Brien's chemistry gave the (*S*)-proline *α*-functionalized product in up to 96:4 er. On the basis of these results, we were intrigued as to whether **2** could be prepared from Boc-protected 3-azabicyclo[3.3.0]-octane **7** (eq 1).



Although seemingly straightforward, direct application of the Beak−O'Brien chemistry to bicyclopyrrolidine **7** was hampered by the stereochemical features and the unknown behavior of the aza-[3.3.0]-bicyclooctane system. Specifically, we were concerned with the consequences of poor stereocontrol for the lithiation/carboxylation steps. Scheme 3 depicts our concerns. In the case of pyrrolidine, poor stereocontrol would result in the production of two enantiomers, which have the potential for interconversion via epimerization of the *α* carbon atom.[8] For **7**, however, poor stereocontrol would give in a mixture of enantiomers (**8** and **ent-8**) which cannot be interconverted. Epimerization of the bicycloproline enantiomers would result in generation of diastereomers (**endo-8** and **endo/ent-8**) via exo/endo interconversion. This property of bicyclopyrrolidine

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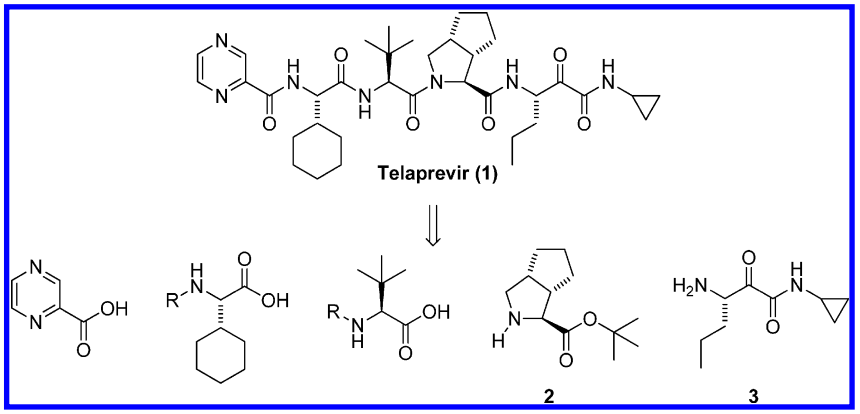
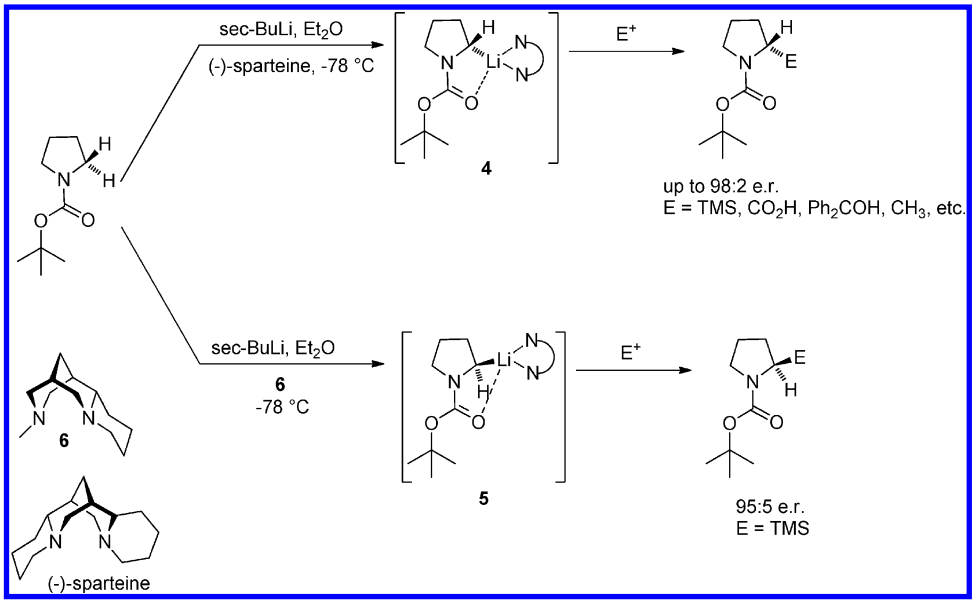
Scheme 1. Retrosynthetic Analysis of Telaprevir



Scheme 2. Stereochemical course for litiations using (−)-sparteine and (−)-cytisine derivative 6 as ligands



renders the development of a dynamic epimerization process unobtainable.

Our second concern was the kinetic behavior of the lithiation/carboxylation process relative to pyrrolidine. Following the mechanistic and kinetic work of Beak,[9] reaction of bicyclopyrrolidine with *sec*-BuLi would result in the formation of four possible precomplexes, whose equilibrium ratios would be dictated by the K_{eq} for each isomer (Scheme 4). The precomplex(es) would undergo the subsequent deprotonation step, whose rate is dictated by k_2, then quenching by CO_2 at a rate controlled by k_3. If the stereochemical-controlling step is deprotonation, the rate of product formation (and the stereochemical ratio) is determined by eq 2. Our concern was the unknown K_{eq} for precomplexes **10**−**13**, and the relative rates of deprotonation for each of these isomers. The possibility of generating four precomplexes rendered the kinetic (and thermodynamic) behavior of our system more complex relative to pyrrolidine.

$$\frac{d[\mathbf{P}]}{dt} = \frac{k_2 K_{eq}[\mathbf{9}][7]}{1 + K_{eq}[\mathbf{9}]}. \text{ For } K_{eq} \text{ large, } \frac{d[\mathbf{P}]}{dt} = k_2[7] \quad (2)$$

Having considered the stereochemical, kinetic and thermodynamic properties of our bicyclopyrrolidine system, we proposed three strategic directions to realize a successful stereoselective process (Scheme 5). The most direct route would be a highly enantio- and diastereoselective reaction, route **A**. With a lack of literature examples describing the chemistry of bicyclopyrrolidine, the effect of the propylidene bridge on the stereochemical outcome was unknown.[17a] Route **B** proposes a resolution of an amino ester, formed by diastereoselective carboalkoxylation and *N*-deprotection, using a chiral acid. Product decomposition during quench of the lithiated intermediate by an appropriate chloroformate was a concern, as the lithiated intermediate would be highly reactive toward the product ester during chloroformate addition.[10] Route **C** proposes diastereoselective formation of a carboxylic acid via quench of the lithiated intermediate with CO_2, followed by resolution with a chiral amine. The performance of the resolution process required not only rejection of the unwanted enantiomer but rejection of the two unwanted diastereomers also.

INITIAL ENANTIOSELECTIVE RESULTS

Having outlined the strategies to prepare the desired product in high enantiomeric and diastereomeric excesses, we began our studies by examination of the stereoselective lithiation process.

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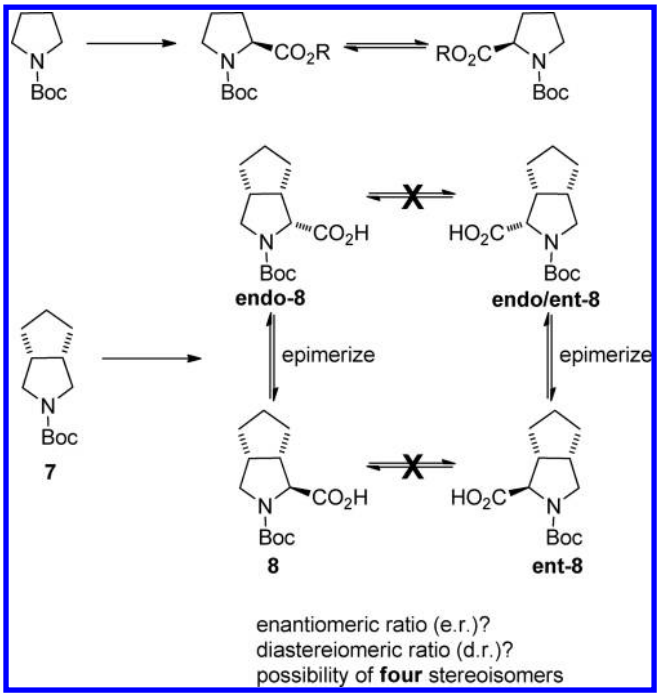
Scheme 3. Comparison and Contrast of Pyrrolidine and Bicyclopyrrolidine Carboxylation Products



Scheme 5. Three Plausible Routes for Providing Stereochemical Purity

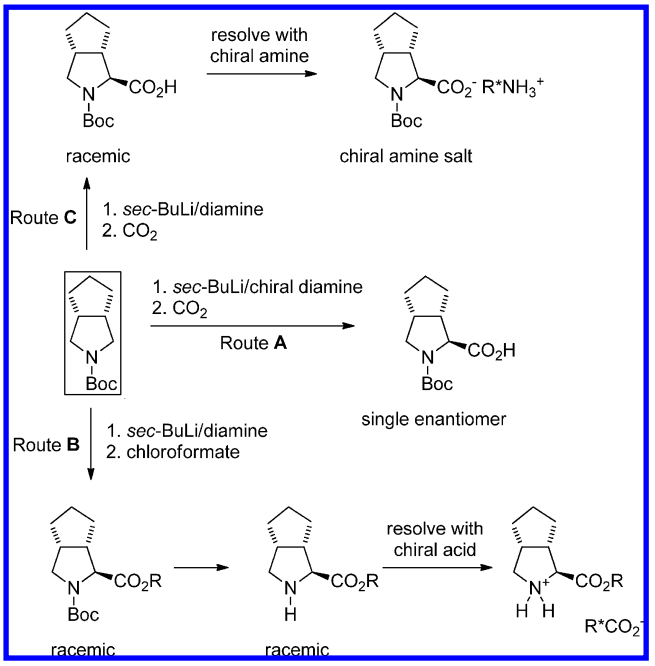


Table 1 gives the results using (−)-sparteine and **6** as chiral ligands. TMEDA was included in this study for comparisons of exo/endo selectivities. The high enantioselectivity and good diastereoselectivity were very encouraging: both chiral ligands gave 94:6 er and 90:10 dr. Comparison with the diastereoselectivity results of TMEDA indicated that the 3,7-diazabicyclo[3.3.1]-octane core may be responsible for the improved diastereocontrol with (−)-sparteine and **6**. Further investigations were performed with analogues **14**−**17** (Figure 1 and Table 1) showing comparable diastereoselectivies for **6** and **14**−**17** but inferior enantioselectivies for **14**−**17** relative to **6**. The added steric hindrance encountered between methyl, ethyl, isopropyl, and isobutyl had minimal impact on the diastereoselectivity, but had significant impact on the enantioselectivity. Neopentyl derivative **17** gave poor results for both selectivity criteria. Evidently, increasing the size of the isopropyl moiety of **16** to a neopentyl moiety had a major impact on the stereocontrolling capacity of the system. Recrystallization of the crude products (non-optimized) obtained from **6**, **14**, and **16** resulted in very high stereochemical purities.

Scheme 4. Mechanisitic Rationale for Enantioselectiive Lithiation of 7

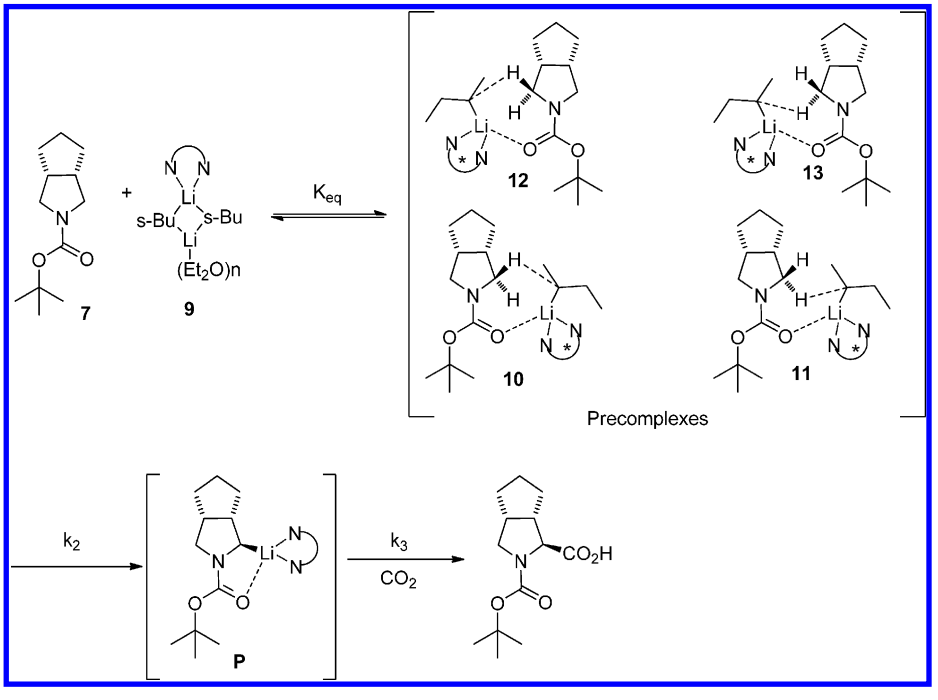


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Table 1. Enantio- and Diastereoselectivities[a] for Chiral Diamine Ligands and TMEDA

		crude product		recryst. product	
diamine	yield (%)	dr	er (**8**:ent-**8**)	dr	er (**8**:ent-**8**)
(−)-sparteine	−[e]	96:4	90:10	–	–
TMEDA	−[e]	1:2	–	–	–
6	44[b,c]	92:8	94:6	97:3	99.6:0.4
14	35[b,c]	92:8	88:12	98:2	100:0
15	−[d]	94:6	87:13	–	–
16	25[b,c]	93:7	91:9	98:2	100:0
17	−[c]	88:12	63:37	–	–

[a]dr: diastereomeric ratio (determined by HPLC Method 1, see Experimental Section); er: enantiomeric ratio (determined by Chiral HPLC Method 1, see Experimental Section). [b]Yield after recrystallization from EtOAc/heptane mixtures. [c]Conversion >95%. [d]Conversion <50%. [e]>98% conversion, isolated yield not determined.

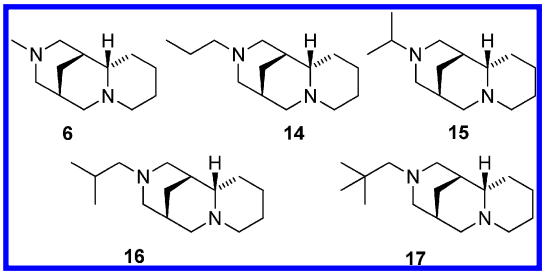
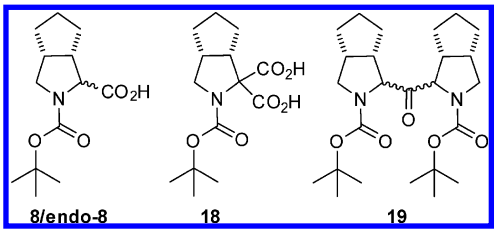


Figure 1. (−)-Cytisine-derived ligands evaluated for enantioselectivity.

The preliminary results in Table 1 prompted us to investigate the reactions using ReactIR.[11] Figure 2 shows IR traces of the reaction mixtures at time = 0 (blue trace), at a representative intermediate time point during a 3 h addition of *sec*-BuLi (green trace), and after *sec*-BuLi addition was complete (red trace). In all cases, the starting bicyclopyrrolidine (1698 cm^{-1}) is consumed after all *sec*-BuLi has been added. However, the behavior of the system differs radically among the chiral ligands employed. The cleanest conversion to the lithiated intermediate (1644 cm^{-1}) was for **6**, as indicated by a relatively clean IR signal after complete addition of the organolithium reagent. For **14**−**17**, a peak between the SM and product was observed (1660−1680 cm^{-1}), most likely pertaining to the precomplex.[12] The preponderance of the precomplex increased as the size of the*N*-substituent on the diazabicycle increased. For neopentyl analogue **17**, only a minor amount of the lithiated intermediate was generated (shoulder at 1644 cm^{-1}), while the majority of material remained at the precomplex stage. The exciting results from the cytisine systems, especially **6** and **14**, were dampened by the unpredictability and associated risk for the long-term cytisine supply required for large-scale manufacture.[13] Hence, a diastereoselective process with subsequent resolution was pursued.

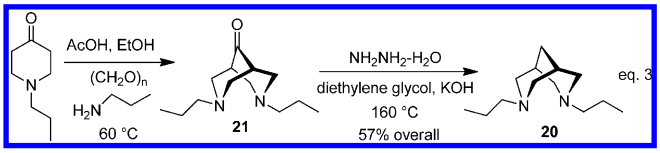
AN EXOSELECTIVE RESOLUTION ROUTE

Our initial approach to an exoselective route, and subsequent resolution, began with a further analysis of the TMEDA results. A comparison of the ReactIR spectra of the reaction progress for TMEDA (Figure 3, spectrum A) and (−)-sparteine (spectrum B) showed clean conversion for both systems to the lithiated intermediate. However, upon addition of CO_2, the IR spectra became very complex, with the TMEDA system showing formation of multiple products. An analysis of the ^1H NMR spectrum of the crude product mixture indicated the presence of at least four products: the expected exo and endo isomers (**8**/**endo-8**), the bis-carboxylated product **18**, and ketone **19**. Compound **18** was most likely generated by reaction of the dianion of **8**/**endo-8** with CO_2, while ketone **19** resulted from condensation of lithiated **7** with **8**/**endo-8**. The complex reaction mixture and the preference for the undesired (endo) diastereomer caused us to terminate the TMEDA approach. However, although (−)-sparteine did not provide a promising option for large-scale manufacturing, the relative cleanliness of the ReactIR spectrum after CO_2 addition encouraged us to pursue achiral analogues of (−)-sparteine.



A close examination of the diastereoselective results obtained for (−)-sparteine vs TMEDA suggested to us that evaluation of ligands based on the core 3,7-diazabicyclo[3.3.1]nonane architecture could provide the required diastereoselectivity (Scheme 6). Additionally, an appropriately designed "achiral" sparteine ligand could obviate the sparteine- and cystisine-related supply risks for large-scale manufacture. Following this logic, we turned our attention to the bispidine series of diamines.[14,15]

To begin our investigations, we chose the dipropyl bispidine analogue **20**.[16,17] Preparation of **20** (DPBP) was accomplished in two steps starting from a three-component Aldol/Mannich reaction between *N*-propylpiperidone, *n*-propylamine, and formalin in an AcOH/EtOH solvent mixture to give bispidinone **21** (eq 3).[18] Wolff−Kishner reduction of the bispidinone gave DPBP in 57% overall yield by direct azeotropic distillation from the reaction mixture.



Reaction of **7** under our previous conditions using DPBP as ligand resulted in 96% reaction completion and provided the desired carboxylic acid as a 95:5 mixture of racemic exo/endo isomers in 86% isolated yield (eq 4). Analysis of the reaction by ReactIR (Figure 4) showed a very clean conversion to the lithiated intermediate and smooth formation of the lithium carboxylate upon quenching with CO_2 gas. The carbonyl stretching frequency of the Boc group smoothly shifted from 1698 to 1644 cm^{-1} upon addition of *sec*-BuLi, indicating formation of the desired lithiated intermediate. Upon addition of CO_2 gas, the IR band corresponding to the free carbonyl stretch of the Boc group reappeared. Completion of the quench of the lithiated intermediate and the presence of excess CO_2 were identified by growth of a band at 2350 cm^{-1}, the CO_2 stretching frequency. The DPBP ligand was recovered (95−98%) from the reaction mixture via aqueous acidic workup and reused five times with identical yields and selectivities. If necessary,

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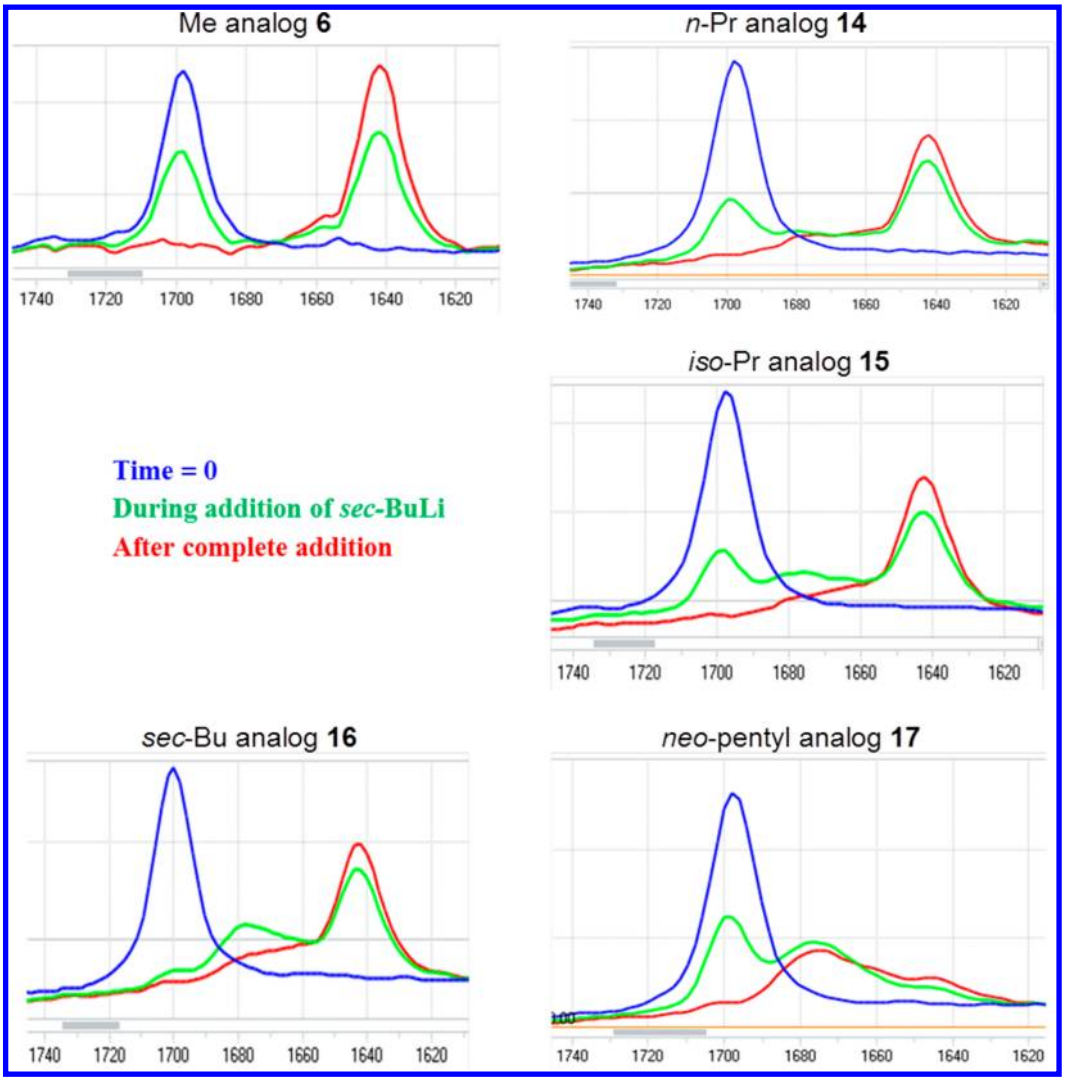
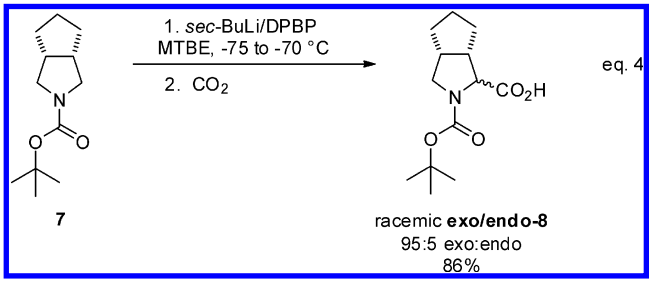


Figure 2. ReactIR spectra for lithiation of **7** with ligands **6**, **14**−**17**.

recycled DPBP could be purified by azeotropic distillation from water.



RESOLUTION OF ENANTIOMERS AND ENRICHMENT OF THE EXO DIASTEREOMER

The requisite next step in the process was to develop a chiral resolution of the exo diastereomer while concomitantly purging both enantiomers of the undesired endo products: the isolation of a single enantiomer from a mixture of four stereoisomers. A resolution screen was used to provide initial insight into the structural requirements of the resolving agent. Table 2 gives the results (er, **8**:**ent-8**) for multiple chiral amines in a variety of process-friendly solvents. The results provided two leads: readily available α-methylbenzyl amine **22** (entry 1) and tetrahydronaphthylamine (THNA) **23** (entry 5). Although salt formation and crystallization with **22** resulted in a respectable resolution providing the exo isomer with 91:9 er, a decrease in diastereoselectivity from 95:5 to 92:8 occurred. Recrystallization of the salt from **22** increased the er to 99:1 but further eroded the dr to 88:12. Contrary to these results, use of **23** for the resolution provided the THNA salt with 95:5 er and no decrease in dr. Recrystallization of this salt provided material with 99:1 er and 100:0 dr.

Having identified **23** as the resolving agent of choice, a process was developed to combine the lithiation/carboxylation and resolution steps into a single-stage process. The reaction mixture generated from the conversion of **7** to a 95:5 mixture of **8**:**endo-8** was washed with an aqueous HCl solution to remove the DPBP ligand, followed by a water wash. The solvent was switched from MTBE to EtOAc by distillation and subsequent addition of a solution of 1.1 equiv of **23** provided **8** (*S*)-**THNA** in 95:5 er and 95:5 dr. Recrystallization of **8** (*S*)-**THNA** from EtOAc/IPA gave the desired product in 99:1 er and 100:0 dr in 31% overall yield (Scheme 7).

The final steps of the process required breaking the salt, conversion of the carboxylic acid to the *tert*-butyl ester and chemoselective removal of the Boc group in the presence of the *tert*-butyl ester. These steps were accomplished as shown in Scheme 8. The salt break and *tert*-butyl ester formation performed as expected, but optimization of the chemoselective

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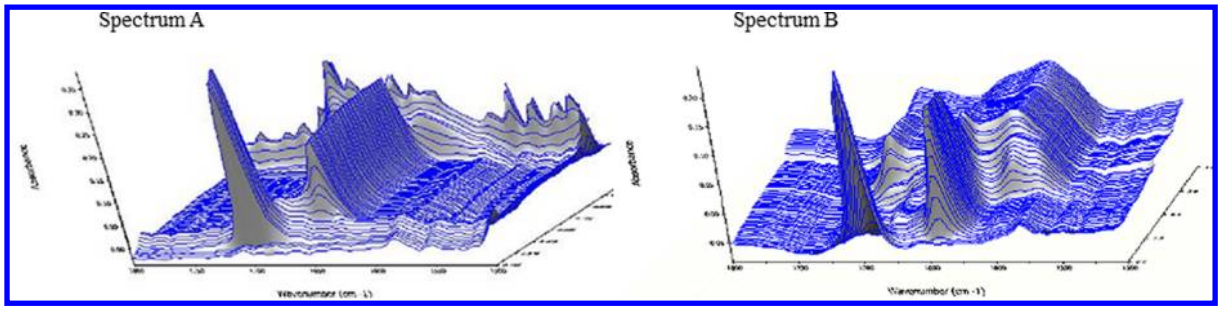
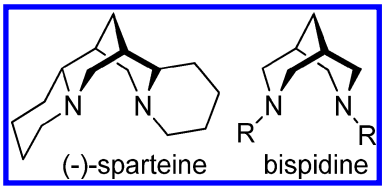


Figure 3. ReactIR spectra for lithiation/carboxylation of **7** using TMEDA (Spectrum A) and (−)-sparteine (Spectrum B). Carbonyl stretch for **7** at 1698 cm^{-1} and for the lithiated intermediate at 1644 cm^{-1}.

Scheme 6. Structural Comparison of (−)-Sparteine and Bispidine Ligands



Boc removal required exploration. Development of a process for the removal rested on leveraging the differences in solvent-dependent deprotection rates and pH stabilities of the Boc group and the *tert*-butyl ester; a pH too low resulted in removal of both moieties while a pH too high resulted in no reaction. The correct pH was dialed-in by use of the appropriate acid, solvent, and reaction temperature. In our case, MsOH in THF at 22−25 °C provided a scaleable process that resulted in exclusive removal of the Boc group without affecting the *tert*-butyl ester.

The entire process for the conversion of **7** to the oxalate salt of **2** was accomplished in 27% overall yield, and with >99.5:0.5 er and dr. The process has been used to manufacture over 200 kg of this key intermediate of telaprevir.

CONCLUSION

We have demonstrated an innovative process for the stereoselective preparation of **2**. The process involved a stereoselective α-lithiation of Boc-protected bicyclopyrrolidine mediated by DPBP ligand **20**, providing racemic **8**/**ent-8** with excellent diastereocontrol via a lithiation/carboxylation process. The racemic mixture was resolved using enantiomerically pure tetrahydronaphthyl amine. Subsequent recrystallization provided the requisite **8** in superior enantio- and diastereomeric purities. Further manipulation of **8** gave **2**, a key building block for HCV protease inhibitor telaprevir. The process provided a practical route to **2** for manufacture on several hundred kilogram scale.

EXPERIMENTAL SECTION

General. GC Method 1: RTX 5A column, 50 °C hold 2 min, ramp to 280 °C at a rate of 20 °C/min, hold at 280 °C for 6.5 min. Run time = 20 min. Typical retention times: 1-propyl-4-piperidone (10.0 min); **20** (12.2 min); **21** (13.8 min). GC Method 2: RTX 5A column, 50 °C hold 2 min, ramp to 280 °C at a rate of 20 °C/min, hold at 280 °C for 6.5 min. Run time = 20 min. Typical retention times: 3-azabicyclo[3.3.0]octane (9.9 min), **7** (12.2 min). GC Method 3: HP-5 column, 50 °C hold 2 min, ramp to 280 °C at a rate of 20 °C/min, hold at 280 °C for 6.5 min. Run time = 20 min. Typical retention times: **2** (8.1 min); **24** (10.2 min). Chiral GC Method 1: Cyclosil B, 30 m × 0.25 mm, 0.25 μm film; 100 °C ramp to 160 °C at a rate of 2 °C/min. Run time = 20 min. Typical retention times: **ent-2** (21.5 min); **2** (21.8 min); **diastereomer A-2** (24.4 min); **diastereomer B-2** (24.6 min). HPLC Method 1: Zorbax SB-C_{18}, 3.0 × 150 mm; (H_2O, 0.1% TFA):(ACN, 0.1% TFA); gradient: at 90:10 for 3 min, to 5:95 over 22 min, at 5:95 for 3 min; flow rate = 0.65 mL/min, 215 nm, Run time = 33 min; temp = 50 °C. Typical retention times: **(*S*)-THNA** (7.6 min); **endo-8** (12.6 min); **8** (13.1 min); **7** (18.4 min). HPLC Method 2: Symmetry C_{18}, 4.6 mm × 150 mm; (H_2O, 0.1% TFA)/(ACN, 0.1% TFA); gradient 95:5 to 5:95 over 15 min, hold 3 min, flow rate = 1.0 mL/min, 210 nm, run time = 20 min. Typical retention times: **8** (10.6 min); **2**, TFA derivative (14.7 min). Chiral HPLC Method 1: Chiral Pack IA, 4.6 mm × 250 mm, 5 μm; hexane/IPA/ethanesulfonic acid 96.5:3.5:0.025, flow rate = 1.2 mL/min, 205 nm, run time = 20 min. Typical retention times: **ent-8** (8.2 min); **8** (9.9 min).

NMR data were collected on a 400 MHz spectrometer. ^{1}H NMR and ^{13}C NMR spectra were referenced using tetramethylsilane in the respective deuterated solvents. Chemical shifts are in parts per million, multiplicity (*s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *m*, multiplet), coupling constants (*J*) are in hertz, and number of protons. The resonances of infrared (IR) spectra are reported in wavenumbers (cm^{-1}). High-resolution

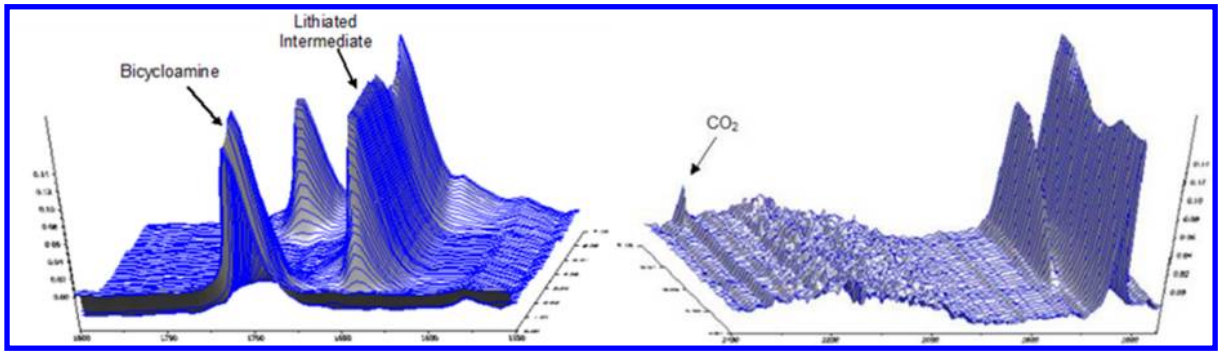


Figure 4. ReactIR waterfall plots for the lithiation and carboxylation steps using DPBP.

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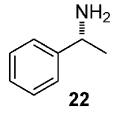
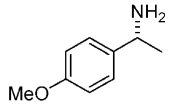
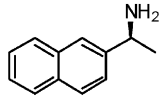
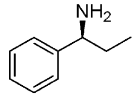
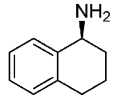
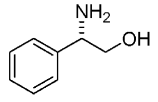
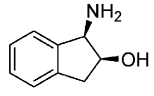
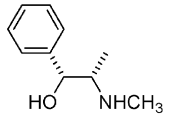
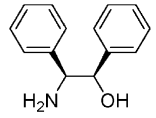
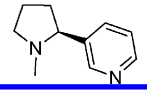
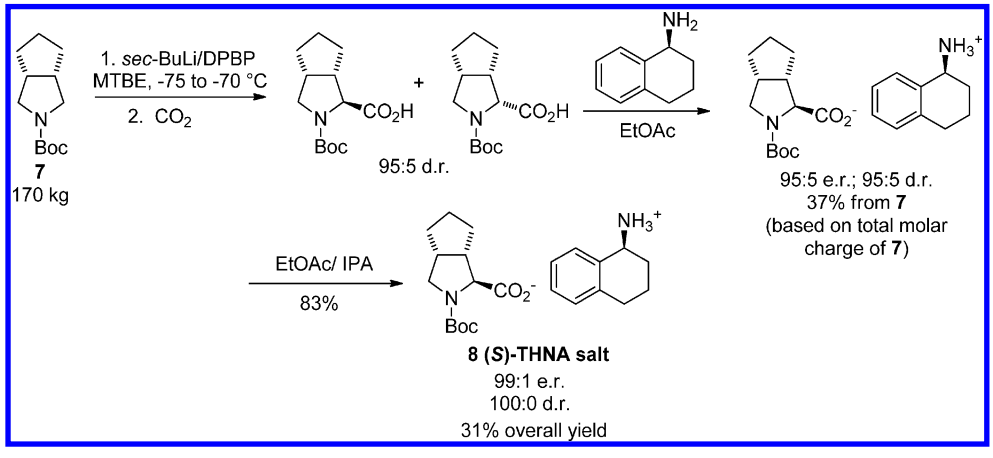
Table 2. Evaluation of Resolving Agents and Solvents for rac-8[a]

Entry	Amine	EtOAc	IPAc	ACN	Toluene	MTBE
1	 **22**	**92:8**	88:12	**96:4**	56:44	73:26
2				32:68		
3				45:52		49:51
4		24:76	27:73	17:83		67:33
5	 **23**	**89:11**	74:26	85:15	85:15	18:82
6		54:46	53:47	31:68		50:50
7		79:21	77:23	23:77		not soluble
8				77:23		
9				25:75		
10		49:51				

[a]Values given are enantiomeric ratios, **8:ent-8**.

Scheme 7. Process for Manufacture of 8 (*S*)-THNA from 7



mass spectra (HRMS) were obtained by electron spray ionization (ESI) and time-of-flight (TOF). Solvents were used directly from their containers. When necessary, solvents were dried by azeotropic distillation.

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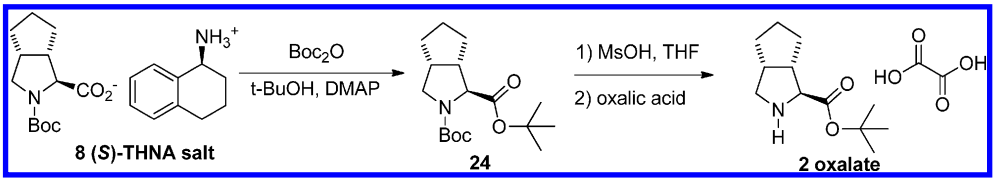
Scheme 8. Process for the Conversion of 8 (*S*)-THNA to 2



Preparation of 3,7-Dipropyl-3,7-diazabicyclo[3.3.1]-nonane (20). To paraformaldehyde (75.0 kg) was added ethanol (1210 kg), 1-propyl-4-piperidone (150 kg), and acetic acid (139 kg). The batch was warmed to 37−42 °C. To the reaction mixture was added a solution of propylamine (69 kg) in ethanol (315 kg) over 7 h, maintaining a reaction temperature of 37−42 °C. The batch was stirred for 9 h. GC analysis (GC Method 1) of the batch showed 100% conversion. The batch was filtered, and the filtrate was concentrated under vacuum to approximately 400 L. Diethylene glycol (754 kg) was charged, and the batch was concentrated under vacuum to approximately 1050 L. KOH (238 kg) was charged to the batch, keeping the temperature below 85 °C. The batch was warmed to 80−90 °C, and hydrazine hydrate (150 kg) was added. The batch was stirred at 80−90 °C for 1 h and then warmed to 149−152 °C. The distillate was collected in a Dean−Stark apparatus. When the volume of the lower aqueous layer was approximately 10 L, the lower aqueous was charged back into the reactor. The distillation was continued until the product no longer distilled as an azeotrope with water. The upper organic phase (approximately 150 L of crude batch material) was collected. GC analysis (GC Method 1) of the crude batch showed 93.0% purity. Heptane (222 kg) and the batch were agitated for 15 min. The batch was washed twice with water (2 × 160 kg), and the combined aqueous layers were extracted with heptane (110 kg). Na_2SO_4 (22.5 kg) was added to the combined organic layers, the batch was agitated for 2 h, and then filtered. The solution was concentrated to approximately 225 L, MTBE (231 kg) was charged, and the batch was concentrated again to approximately 225 L. The solution was collected to give 169 kg of a 70 wt % solution of **20** in MTBE. GC analysis showed 96.4% purity (GC Method 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69−2.61 (m, 2H), 2.29−2.21 (m, 2H), 2.19−2.10 (m, 2H), 1.88−1.82 (m, 1H), 1.46−1.35 (m, 3H), 0.81 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 60.78, 57.84, 29.83, 29.17, 20.00, 11.82. IR (cm^{-1}, neat): 2930.60, 2872.48, 2758.46, 1461.44, 1145.92, 1067.07, 1001.17. ESI-HRMS (m/z) calcd for $C_{10}H_{14}N$ $[M + H]^+$ 141.1121, found 141.1126.

(1*S*,3a*R*,6a*S*)-2-(*tert*-Butoxycarbonyl)octahydrocyclo-penta[*c*]pyrrole-1-carboxylic Acid (*S*)-1,2,3,4-Tetrahydro-1-naphthylammonium salt (8 (*S*)-THNA). To 3-azabicyclo-[3.3.0]nonane hydrochloride (170 kg, mol) was charged *tert*-butyl methyl ether (MTBE) (1864 kg) and a solution of potassium carbonate (318 kg, mol) in water (280 kg). The mixture was agitated for 30 in, allowed to stand for 30 min, and the lower aqueous phase was removed. A solution of Boc_2O (246 kg, 0.644 mol) in MTBE (250 kg), was added, and the solution was stirred for 1.5 h at 15−25 °C. GC analysis (GC method 1) of an aliquot of the reaction mixture showed the starting material was completely consumed. The mixture was filtered, and the filtrate was collected. The filtrate was stirred for 30 min at 20−30 °C and then allowed to stand for 30 min. The lower water layer was removed. The batch was washed twice with a solution of $NaHSO_4$ (12.7 kg) in water (255 kg) and then with water (270 kg). Na_2SO_4 (23 kg) was charged, and the batch was stirred for 2 h and then filtered. The batch was concentrated to remove residual water, giving 215 kg of **7** (93.5% yield), as a 65 wt % solution (HPLC method 1) in MTBE. An aliquot was removed to provide a sample for characterization. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65−3.33 (m, 2H), 3.03 (dd, J = 11.3, 3.8 Hz, 2H), 2.65−2.34 (m, 2H), 1.89−1.25 (m, 15H). IR (cm^{-1}, neat): 1692.25, 1391.21, 1169.05. ESI-HRMS (m/z) calcd for $C_{12}H_{22}NO_2$ $[M + H]^+$ 212.1645, found 212.1654. 99.4% purity, HPLC method 1.

To a solution of **7** in MTBE (105 kg of **7** as a 65 wt % solution in MTBE) was charged **6** (147 kg) and MTBE (423 kg). The solution was cooled to −70 to −75 °C, and then *sec*-butyllithium (468 kg of a 1.4 M solution in hexane) was added to the reaction mixture, keeping the reaction temperature below −70 °C. The solution was agitated for 3 h at −70 to −75 °C; then CO_2 (52.5 kg) was added, keeping the reaction temperature below −70 °C. The mixture was agitated at −70 to −75 °C for 1 h and then sampled for reaction completion (3.3% **7** remaining, HPLC method 1). The mixture was warmed to 0−10 °C, and water (927 kg) was charged, followed by $NaHSO_4$ (272 kg). The batch was warmed to 22−25 °C and agitated for 30 min. The batch was allowed to stand for 30 min. The aqueous lower phase was removed, water (420 kg) was added, and the batch was agitated for 30 min and then allowed to stand for 30 min. The lower aqueous phase was removed, and the batch was filtered. The batch was concentrated to approximately 284 L under vacuum. Ethyl acetate (527 kg) was added, and the batch was concentrated to approximately 284 L under vacuum. Again, ethyl acetate (518 kg) was added, and the solution was concentrated to approximately 420 L under vacuum to give a solution of **rac-8** (200 kg of 8 as a 25.5% solution in ethyl acetate). To the solution of rac-8 was charged ethyl acetate (720 kg) and IPA (960 kg). The batch was cooled to −10 to 5 °C, and (*S*)-1,2,3,4-tetrahydro-1-naphthylamine (80 kg) was added. The batch was agitated for 5 h at −10 to 5 °C, and the resultant slurry was filtered, rinsing the wet cake with ethyl acetate. A sample of the wet cake was analyzed (HPLC method 1 and Chiral HPLC Method 1) to give crude **8 (*S*)-THNA**, 98.7% diastereomeric purity, 94% enantiomeric purity. To crude **8 (*S*)-THNA** wet cake was charged ethyl acetate (840 kg) and IPA (640 kg). The batch was warmed to reflux (70−75 °C) to give a clear solution, then cooled to −15 to −5 °C over 5 h and then stirred for 4 h. The batch was filtered, rinsing the solids with EtOAc. A sample of the wet cake was analyzed (HPLC method 1 and Chiral HPLC Method 1) to give **8 (*S*)-THNA**, 99.8% diastereomeric purity, 99.9% enantiomeric purity. The wet cake was dried at 30−40 °C for 25 h to give 105.4 kg of **8 (*S*)-THNA** (33.5% yield based on the total molar charge of **7**). ^{1}H NMR (400 MHz, CD_3OD) δ 7.45−7.37 (m, 1H), 7.34−7.14 (m, 3H), 4.92 (br. s, 3H), 4.49 (t, J = 5.5 Hz, 1H), 3.86 (d, J = 2.5 Hz, 1H), 3.69 (ddd, J = 10.0, 7.9, 2.2 Hz, 1H), 3.19 (dt, J = 10.7, 5.0 Hz, 1H), 2.99−2.73 (m, 2H), 2.63 (tt, J = 7.5, 3.6 Hz, 2H), 2.25−2.09 (m, 1H), 2.08−1.67 (m, 6H), 1.59 (dddd, J = 14.7, 10.6, 6.9, 3.9 Hz, 2H), 1.43 (d, J = 5.9 Hz, 10H). ^{13}C NMR (101 MHz, CD_3OD) δ 180.67, 156.82, 139.08, 133.44, 130.87, 129.81, 129.48, 127.67, 80.71, 80.42, 69.98, 69.55, 54.26, 53.87, 51.24, 43.57, 42.81, 34.48, 34.32, 33.42, 29.79, 29.27, 28.89, 28.81, 26.47, 19.68. IR (cm^{-1}, neat): 1683.98, 1559.86, 1405.28, 1180.68, 1124.34. ESI-HRMS (m/z) calcd for

dx.doi.org/10.1021/op500040j | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

$C_{13}H_{21}NNaO_4$ $[M + Na]^+$ 278.1363, found 278.1368; calcd for $C_{10}H_{14}N$ $[M + H]^+$148.1121, found 148.1126.

(1*S*,3a*R*,6a*S*)-*tert*-Butyl Octahydrocyclopenta[*c*]-pyrrole-1-carboxylate Oxalic Acid Salt (2). To **8** (*S*)-**THNA** (160 kg, 397 mol) was added MTBE (592 kg) and a 5% aqueous $NaHSO_4$ solution (prepared by the dissolution of 85.0 kg of $NaHSO_4$ in 1700 kg of water). The mixture was agitated for 3 h and then allowed to stand for 30 min. The lower aqueous phase was collected (Aq-1). The batch was washed with water (800 kg) and the aqueous phase was collected (Aq-2). The organic phase was filtered, and the solution was concentrated again to about 440 L. MTBE (322 kg) was charged, and the solution was concentrated to approximately 650 L. The dilution/concentration cycle was repeated two more times, and then the batch was finally concentrated to approximately 440 L. *t*-BuOH (222 kg) and DMAP (9.1 kg) were added. A solution of Boc_2O (120.2 kg, 0.31 mol) in MTBE (94 kg) was added over 1 h, keeping the batch temperature at 22−27 °C (CO_2 gas evolution occurred). The batch was stirred for 5 h. A sample removed for HPLC analysis (HPLC method 2) showed 0.0% **8** remaining. A solution of $NaHSO_4$ (24.5 kg) in water (490 kg) was added to the reaction mixture, the batch was agitated for 30 min and then allowed to stand for 30 min. The lower aqueous phase was removed. A solution of sodium chloride (24.4 kg) in water (493 kg) was added, and the batch was agitated for 30 min and then allowed to stand for 30 min. The lower aqueous phase was removed. The aqueous NaCl wash was repeated. Na_2SO_4 (30 kg) was added, and the batch was agitated for 2 h and then filtered. The batch was concentrated to 440 L under vacuum, then THF (520 kg) was added. The batch was concentrated again to 440 L. This step was repeated, and the batch was cooled to 20−30 °C to give crude **24**.

Methanesulfonic acid (106 kg) was added over 1 h, keeping the temperature at 22−27 °C (CO_2 gas evolution), and the batch was stirred at 22−27 °C for 11 h. HPLC analysis of an aliquot for reaction completion showed undetectable amounts of **24**. The reaction mixture was charged to a solution of K_2CO_3 (208 kg) in water (520 kg). The batch was agitated for 30 min and then allowed to stand for 30 min. The phases were separated. The aqueous phase was extracted with IPAc (2 × 436 kg), and the organic phases were combined. The organic phase was concentrated under vacuum to approximately 440 L. IPAc (340 kg) was charged, and the batch was concentrated under vacuum to approximately 600 L. IPAc (180 kg) was charged, and the batch was washed with water (580 kg). Na_2SO_4 (30.8 kg) was added, and the batch was filtered. The batch was concentrated under vacuum to approximately 440 L. IPAc (162 kg) was charged, the batch was concentrated under vacuum to 440 L, and then IPAc (408 kg) was charged again. A solution of oxalic acid (42.4 kg) in MTBE (257 kg) was added, and the mixture was agitated for 2.5 h. The resultant slurry was filtered, and the wet cake was dried at 35−40 °C for 24 h to yield 82.0 kg (68.5% yield) of **2 oxalate salt**. Chemical purity (HPLC Method 2): 99.1%. Chiral purity (Chiral GC Method 1): 100.0%. ^{1}H NMR (d_6-DMSO, 400 MHz,) δ 10.70 (s, 3H), 3.84 (d, J = 8.0 Hz, 1H), 3.47 (dd, J = 10.7, 7.5 Hz, 1H), 2.79−2.67 (m, 3H), 1.74−1.56 (m, 5H), 1.45 (s, 10H). ^{13}C NMR (d_6-DMSO, 101 MHz) δ 167.81, 164.72, 82.68, 64.07, 49.92, 46.46, 41.18, 30.72, 30.69, 27.48, 24.21. IR (cm^{-1}, neat): 1719.94, 1611.41, 1230.06, 1201.20, 1153.52. Elem. Anal.: Found: C 55.88, H 7.79, N 4.60; Calcd for $C_{14}H_{23}NO_6$: C 55.80, H 7.69, N 4.65.

Recovery of (*S*)-THNA. The aqueous phases Aq-1 and Aq-2 were combined and washed twice with EtOAc (2 × 149 kg). NaOH (111 kg) was charged to the aqueous phase, and the solution was agitated for 30 min, and analyzed to ensure pH ≥ 12 (analysis gave pH = 13). The aqueous phase was extracted with ethyl acetate (2 × 154 kg). NaOH (75.0 kg) was charged to adjust the pH to 13, and the solution was extracted with ethyl acetate (2 × 154 kg). The combined organic phases were concentrated to 54 L under vacuum. Ethyl acetate (166 kg) was added, and the batch was concentrated to 57 L to give 57 kg of a 93.2 wt % solution of (*S*)-THNA (92% recovery) in ethyl acetate. HPLC analysis (HPLC Method 1) showed 99.6% purity.

Recovery of 6. The pH of aqueous solution of **6** (147 kg) was adjusted to NLT 12 by charging NaOH. Heptane (319 kg) was added, and the mixture was agitated for 35 min at 30−35 °C. The mixture was filtered, and then the lower aqueous layer was removed. Na_2SO_4 (16.0 kg) was added, and the mixture was agitated for 2 h. The mixture was filtered, and then the solution was concentrated under vacuum to about 210 L. MTBE (365 kg) was added, and the solution was concentrated under vacuum to about 210 L. The solution was analyzed to give 74.1 wt % **6** (136 kg as a 74.1 wt % solution in MTBE, 94.3% recovery).

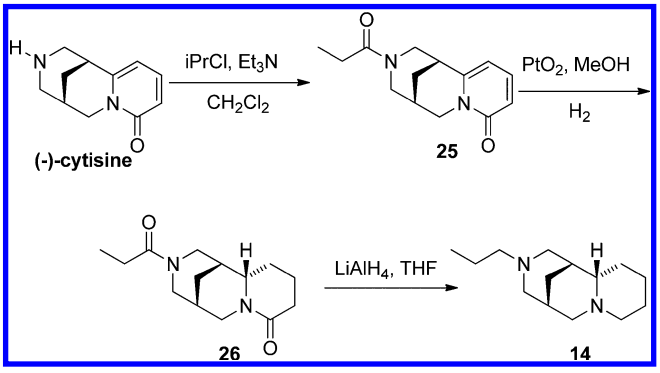
Preparation of Chiral Diamine Ligands 6 and 14−17. Chiral diamine ligands **6**, **15**, **17** were prepared using the method of O'Brien, et al.[9] for ligands **6**, **15**, and **17**. A modification of the O'Brien method was used for ligands **14** and **16**.

(1*R*,5*S*,11a*S*)-3-Methyldecahydro-1*H*-1,5-methanopyrido-[1,2-*a*][1,5]diazocine (6). Prepared in 40% overall yield, after Kugelrohr distillation, starting from cytisine (10.0 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (d, J = 7.7 Hz, 2H), 2.89 (m, 2H), 2.24 (d, J = 7.2 Hz, 1H), 2.16 (s, 3H), 1.97 (d, J = 6.8 Hz, 1H), 1.91 (d, J = 6.8 Hz, 1H), 1.81 (br. s, 1H), 1.78−1.63 (m, 4H), 1.62−1.43 (m, 5H), 1.36−1.21 (m, 2H).

(1*R*,5*S*,11a*S*)-3-Isopropyldecahydro-1*H*-1,5-methano-pyrido[1,2-*a*][1,5]diazocine (15). Prepared in 40% overall yield, after Kugelrohr distillation, starting from cytisine (10 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01−2.54 (m, 6H), 2.32−2.09 (m, 2H), 1.97−1.66 (m, 4H), 1.66−1.33 (m, 6H), 1.33−1.18 (m, 2H), 1.05 (d, J = 6.7 Hz, 3H), 0.93−0.83 (m, 3H).

(1*R*,5*S*,11a*S*)-3-Neopentyldecahydro-1*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocine (17). Prepared in 29% overall yield, after Kugelrohr distillation, starting from cytisine (10 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10−2.92 (d, J = 15.1 Hz, 1H), 2.86 (d, J = 10.5 Hz, 1H), 2.79 (t, J = 15.3 Hz, 1H), 2.71 (t, J = 13.9 Hz, 1H), 2.52 (br s, 1H), 2.38 (br s, 1H), 2.29 (br s, 1H), 2.10−1.89 (m, 3H), 1.89−1.41 (m, 9H), 1.40−1.18 (m, 2H), 0.89 (t, J = 7.6 Hz, 9H).

Preparation of 14. *(1R,5S)-3-Propionyl-3,4,5,6-tetrahydro-1H-1,5-methanopyrido[1,2-a][1,5]diazocin-8(2H)-one (**25**).* To (−)-cytisine (10 g, 52.56 mmol) was added CH_2Cl_2 (100.0 mL) and triethylamine (10.64 g, 14.66 mL, 105.1 mmol). The reaction mixture was cooled to 0−5 °C, and then propionyl chloride (5.96 g, 5.59 mL, 63.07 mmol) was added, keeping the



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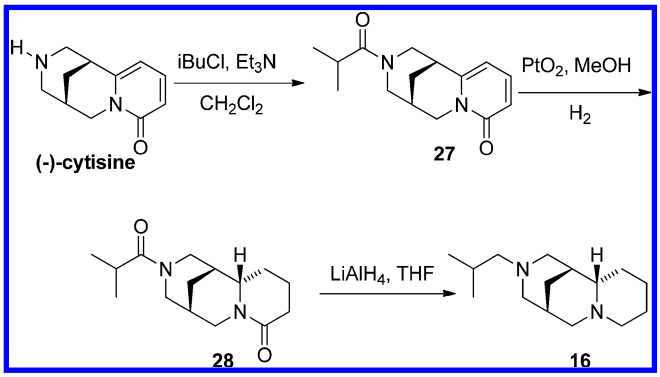
reaction temperature below 15 °C. The mixture was warmed to 20−22 °C and stirred for 3 h. The slurry was concentrated on the rotovap, then EtOAc (10 vol) was added, and the mixture was filtered. The filtrate was concentrated to dryness to give 12.30 g of crude **25**. Compound **25** was taken to the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dt, J = 6.5, 4.5 Hz, 3H), 6.41 (dd, J = 9.1, 3.1 Hz, 3H), 6.05 (dd, J = 7.2, 2.9 Hz, 3H), 4.75 (d, J = 13.4 Hz, 2H), 4.06 (dd, J = 20.8, 15.7 Hz, 3H), 3.98−3.76 (m, 6H), 3.38−3.25 (m, 3H), 3.09−3.03 (m, 3H), 2.85−2.72 (m, 3H), 2.53−2.46 (m, 3H), 2.22 (dd, J = 7.3, 3.3 Hz, 2H), 2.06−1.94 (m, 7H), 1.87 (d, J = 7.5 Hz, 1H), 0.96 (t, J = 7.4 Hz, 4H), 0.83 (t, J = 7.4 Hz, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.99, 163.14, 148.73, 148.65, 139.23, 138.57, 117.58, 117.08, 106.07, 105.07, 52.69, 51.48, 48.97, 48.63, 47.63, 34.94, 34.38, 27.53, 27.34, 26.17, 26.09, 25.85, 9.20, 9.17. IR (cm^{-1}, neat solid): 1630.34, 1574.69, 1539.82, 1450.90, 1427.80, 1360.16, 121825, 1145.07. ESI-HRMS (m/z) calcd for $C_{14}H_{19}N_2O_2^+$ $[M + H]^+$ 247.1441, found 247.1448.

*(1R,5S,11aS)-3-Propionyloctahydro-1H-1,5-methanopyrido-[1,2-a][1,5]diazocin-8(2H)-one (**26**).* To **25** (12.30 g, 49.94 mmol) was added EtOH (246 mL) and then PtO_2 (567 mg, 2.50 mmol). The reaction vessel was evacuated and pressurized to 50 psig with H_2 (3×). The mixture was stirred at 20−22 °C for 22 h. (GC analysis showed 90% reaction completion). H_2 gas was recharged, and the mixture was stirred for 3 h. (GC analysis showed 100% reaction completion.) The mixture was filtered through a pad of Celite, which was rinsed with EtOH. The filtrate was concentrated in vacuo to give 12.73 g of the crude **26** as a thick oil which solidified upon standing. Compound **26** was taken to the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (dt, J = 13.9, 2.2 Hz, 1H), 4.76 (dt, J = 13.8, 2.3 Hz, 1H), 3.92−3.83 (m, 1H), 3.44−3.31 (m, 1H), 3.21 (dt, J = 13.2, 2.5 Hz, 1H), 2.72 (ddd, J = 13.9, 3.3, 1.9 Hz, 1H), 2.60−2.50 (m, 1H), 2.33−2.06 (m, 4H), 2.05−1.67 (m, 6H), 1.66−1.58 (m, 1H), 1.54−1.44 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.51, 169.85, 59.28, 50.18, 45.79, 41.94, 33.52, 32.78, 32.56, 27.91, 27.65, 26.17, 19.81, 9.27. IR (cm^{-1}, neat solid): 1621.30, 1459.84, 1414.23, 1417.02, 1345.90, 1309.71, 1247.32, 1217.15. ESI-HRMS (m/z) calcd for $C_{14}H_{23}N_2O_2^+$ $[M + H]^+$ 251.1754, found 251.1759.

*(1R,5S,11aS)-3-propyldecahydro-1H-1,5-methanopyrido-[1,2-a][1,5]diazocine (**14**).* To **26** (12.50 g, 49.93 mmol) was added THF (50.0 mL), then LiAlH4 (1.89 g, 49.93 mmol) . The mixture was warmed to reflux for 16 h, after which GC analysis showed the starting material consumed. The mixture was cooled to 5−10 °C, and EtOAc (25 mL) was added. The mixture was carefully quenched with saturated Na_2SO_4 solution. (The reaction temperature rose to 44−45 °C during the quench.) The slurry was filtered through a pad of Celite, and rinsed with 9:1 CH_2Cl_2/MeOH (1 L). The solution was concentrated in vacuo, and the residue was suspended in EtOAc. The mixture was filtered through Celite again, and the filtrate was concentrated in vacuo to give a light-brown oil. The crude product was purified by Kugelrohr distillation (130−170 °C) to give 4.29 g of **14** (37% overall yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (dt, J = 11.3, 2.3 Hz, 1H), 2.96−2.62 (m, 3H), 2.39 (ddd, J = 11.7, 10.5, 5.3 Hz, 1H), 2.21 (dddd, J = 13.8, 11.1, 3.8, 1.6 Hz, 2H), 2.07−1.29 (m, 15H), 1.33−1.09 (m, 2H), 0.80 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 66.33, 61.91, 60.68, 59.27, 57.51, 52.94, 34.92, 34.07, 30.69, 30.63, 25.73, 25.23, 19.97, 11.99. IR (cm^{-1}, neat): 2928.92, 2756.12, 2720.98. ESI-HRMS (m/z) calcd for $C_{14}H_{27}N_2^+$ $[M + H]^+$ 223.2169, found 223.2169.

Preparation of 16. *(1R,5S)-3-Isobutyryl-3,4,5,6-tetrahydro-1H-1,5-methanopyrido[1,2-a][1,5]diazocin-8(2H)-one*



*(**27**).* To (−)-cytisine (10 g, 52.56 mmol) was added CH_2Cl_2 (100 mL) and triethylamine (10.64 g, 14.7 mL, 105 mmol). The reaction mixture was cooled to 0−5 °C, then isobutyryl chloride (6.86 g, 6.80 mL, 63.07 mmol) was added keeping the reaction temperature below 15 °C. The mixture was warmed to 20−22 °C and stirred for 3 h. (GC analysis showed consumption of (−)-cytisine.) The slurry was concentrated by rotary evaporation, then EtOAc (10 vol) was added, and the mixture was filtered. The filtrate was concentrated to dryness to give crude **28**. Compound **28** was used directly in the next step. ^{1}H NMR (400 MHz, d_6-DMSO) δ 4.83 (dq, J = 13.7, 2.2 Hz, 1H), 4.58 (dt, J = 13.6, 2.2 Hz, 1H), 3.97 (dt, J = 13.3, 2.0 Hz, 1H), 3.38−3.23 (m, 1H), 2.82−2.63 (m, 2H), 2.58 (dd, J = 13.6, 2.7 Hz, 1H), 2.27−1.42 (m, 11H), 0.95 (dd, J = 6.7, 3.8 Hz, 1H), 0.90 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.23, 167.90, 58.37, 49.69, 45.20, 41.46, 32.68, 32.51, 32.33, 28.86, 27.49, 27.31, 19.51, 19.36, 19.14. IR (cm^{-1}, neat solid): 1649.80, 1620.68, 1573.43, 1543.11, 1462.35, 1435.75. ESI-HRMS (m/z) calcd for $C_{15}H_{20}N_2NaO_2^+$ $[M + Na]^+$ 283.1417, found 283.1420.

(1R,5S,11aS)-3-Isobutyryloctahydro-1H-1,5-methanopyrido-[1,2-a][1,5]diazocin-8(2H)-one. To **27** (13.68 g, 52.55 mmol) was added MeOH (274 mL), then PtO_2 (597 mg, 2.63 mmol) . The reaction vessel was evacuated and pressurized to 50 psig with H_2 (3×). The mixture was stirred at 20−22 °C for 16 h. (GC analysis showed 90% reaction completion). H_2 was recharged and the mixture was stirred for 4 h. (GC analysis showed 99% reaction completion). The mixture was filtered through a pad of Celite, which was rinsed with MeOH. The filtrate was concentrated in vacuo to give 11.00 g of the crude product as a brown thick oil. The crude product **28** was taken to the next step without purification. ^{1}H NMR (d_6-DMSO, 400 MHz): δ4.82 (d, 1H); 4.59 (d, 1H); 3.99 (d, 1H); 3.46 (m, 1H); 3.27 (d, 1H); 2.70 (m, 2H); 2.59 (d, 1H); 2.18−1.41 (m, 10H); 0.90 (d, 3H); 0.85 (d, 3H). ^{13}C NMR (d_6-DMSO, 101 MHz): δ 174.27, 167.95, 58.62, 49.71, 41.48, 40.02, 32.70, 32.53, 32.34, 29.07, 27.69, 27.32, 19.53, 19.38, 19.16. IR (cm^{-1}, neat solid): 1621.23, 1436.35, 1424.44, 1227.71, 1219.06, 1162.93, 1059.95. ESI-HRMS (m/z) calcd for $C_{15}H_{25}N_2O_2^+$ $[M + H]^+$ 265.1911, found 265.1923.

*(1R,5S,11aS)-3-Isobutyldecahydro-1H-1,5-methanopyrido-[1,2-a][1,5]diazocine (**16**).* To crude **28** (11.00 g, 41.61 mmol) was added THF (198 mL), then $LiAlH_4$ (9.48 g, 10.33 mL, 250 mmol) . The mixture was warmed to reflux for 21 h. (GC analysis showed starting material consumed.) The mixture was cooled to 5−10 °C, and MTBE (100 mL) was added. The mixture was carefully quenched with saturated Na_2SO_4 solution. (The reaction temperature rose to 44−45 °C during the quench.) The slurry was filtered through a pad of Celite, and rinsed with 9:1 CH_2Cl_2/MeOH (1 L). The solution was concentrated in vacuo, and the residue was suspended in EtOAc. The mixture was filtered through Celite

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again, and the filtrate was concentrated in vacuo to give a light-brown oil. The crude product was purified by Kugelrohr distillation (140−180 °C) to give 7.56 g of **16** (77% overall yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (dt, J = 11.2, 2.0 Hz, 1H), 2.82−2.62 (m, 3H), 2.32−2.11 (m, 2H), 2.08−1.92 (m, 2H), 1.91−1.61 (m, 6H), 1.62−1.33 (m, 6H), 1.35−1.11 (m, 2H), 0.87 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.35, 65.91, 61.00, 58.93, 57.10, 53.52, 35.12, 34.00, 30.71, 30.61, 26.11, 25.60, 25.33, 21.04, 20.60. IR (cm^{-1}, neat): 2929.46, 2755.57, 2721.32. ESI-HRMS (m/z) calcd for $C_{15}H_{29}N_2^+$ $[M + H]^+$ 237.2325 found 237.2329.

■ ENANTIOSELECTIVE LITHIATION/CARBOXYLATION

General Experimental Procedure. To **16** (5.68 g, 24.03 mmol), was added MTBE (39.05 mL) and **7** (3.905 g, 18.48 mmol). The solution was cooled to −75 to −70 °C. *s*-BuLi (15.25 g, 20.33 mL of 1.0 M, 20.33 mmol) was added, keeping reaction temp below −65 °C. The mixture was stirred for 5.5 h at −75 to −70 °C. CO_2 gas was bubbled into the reaction mixture, keeping the temperature below −65 °C. The solution was warmed to 22−25 °C and quenched with saturated $NaHSO_4$. The phases were separated, and the organic phase was washed with saturated $NaHSO_4$. The aqueous phase was extracted with MTBE (1 × 40 mL).

The organic phase was extracted with 2 N NaOH soln (2 × 40 mL). The pH of the combined aq phases was adjusted to 2−3, and the aq phase was extracted with MTBE (2 × 40 mL). The MTBE solution was dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The remaining oil (3.63 g) was dissolved into 11 mL of MTBE (3 vol), 11 mL of heptane was added, and the solution was stirred for 1 h to give a white slurry. The mixture was cooled to 5−10 °C and stirred for 1 h. Heptane (11 mL) was added, and the mixture was stirred for another 2 h. The slurry was filtered, and the solids were rinsed with heptane. The white solid was dried to give 1.19 g of desired product **8** (25% yield). Enantiomeric ratio of exo isomer (Chiral HPLC Method 1): 100:0; diastereomeric ratio (HPLC Method 1): 97.6:2.4. Matched ^{1}H NMR and HPLC of authentic sample.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Table 1 contained errors in the version published ASAP May 22, 2014; the correct version reposted May 28, 2014.