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Articles

Optimization and Scale-Up of an Asymmetric Route to the LTB_4 Inhibitor Ontazolast

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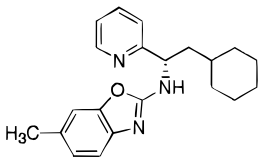
Abstract:

An efficient asymmetric synthesis of the LTB_4 inhibitor Ontazolast is described. Commercially available (*S*)-α-pinene, which contains a 93.5% enantiomeric excess (ee) of the desired isomer, can be oxidized using phase-transfer conditions to the corresponding (*R*)-hydroxy ketone. Condensation of this keto alcohol with 2-(aminomethyl)pyridine provides an intermediate imine that can be alkylated with cyclohexylmethyl bromide or iodide. The alkylation proceeds with nearly complete transfer of chirality under mild conditions. Cleavage of the chiral auxiliary and isolation of the resulting (*S*)-pyridylamine by crystallization with L-tartaric acid furnishes the key amine building block in >99% ee and in excellent overall yield. The tartrate salt is then directly converted to the final product. The reaction sequence is described on a multigram scale.

Introduction

For at least two decades considerable research has been centered on the discovery of compounds that inhibit the arachidonic acid cascade. One particular strategy involves the inhibition of leukotriene biosynthesis, and this area has been well reviewed in the literature.[1] Several years ago our inflammatory disease group discovered a series of potent benzoxazolamines that inhibit this biosynthetic pathway, specifically the synthesis of leukotriene B_4. After considerable optimization a potential clinical candidate emerged, Ontazolast (**1**, BIRM-270).[2]



Ontazolast (**1**, BIRM-270)

In order for preclinical studies to proceed, sufficient quantities of enantiomerically pure material were required. The route provided by the discovery effort centered on a racemic synthesis that required a resolution step. This protocol involved addition of a Grignard reagent to 2-cyanopyridine, followed by reduction of the resultant imine with borohydride. Resolution was effected using chiral preparative HPLC. Subsequent coupling with the chlorobenzoxazole furnished moderate quantities of **1**. The initial scale-up campaign followed a similar route except that the resolution was accomplished using a chiral acid (Scheme 1).

Although this method of synthesis could provide sufficient quantities of bulk drug product for preliminary toxicology and pharmacology studies, it was not efficient enough to ultimately produce the multikilogram quantities necessary for full clinical development. In order to gain efficiency, a

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(1) Recent reviews: Musser, J. H.; Kreft, A. F. *J. Med. Chem.* **1992**, *35*, 2501−2513. Summers, J. B. *Drug News Perspect.* **1990**, *3*, 3517−3526.

(2) Lazer, E. S.; Miao, C. K.; Wong, H. C.; Sorcek, R.; Spero, D. M.; Gilman, A.; Pal, K.; Behnke, M.; Graham, A. G.; Watrous, J. M.; Homon, C. A.; Nagel, J.; Shah, A.; Guindon, Y.; Farina, P.; Adams, J. *J. Med. Chem.* **1994**, *37*, 913−923. Lazer, E. S.; Adams, J.; Miao, C. K.; Farina, P. U.S. Patent 5,296,486, 1994.

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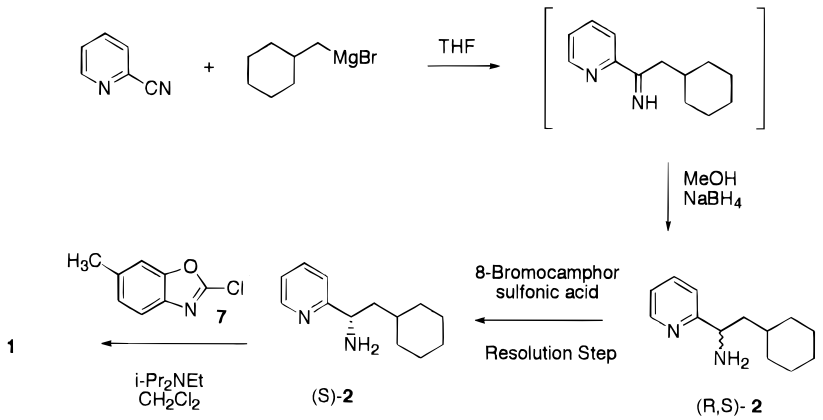
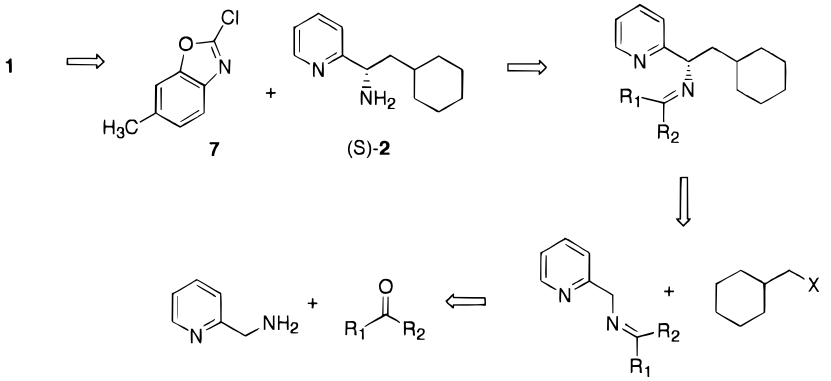
Scheme 1. **Initial synthesis of 1**



Scheme 2. **Retrosynthetic strategy**

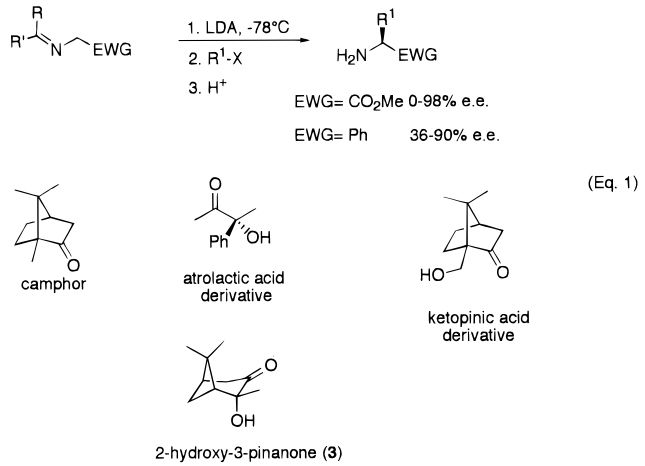


racemization strategy was added to recycle (*R*)-**2**. In addition, the 8-bromocamphorsulfonic acid was commercially available as the ammonium salt, and liberation of the free acid required the use of an ion-exchange resin. The preclinical batches, using this route, involved over 35 separate operations in the pilot plant including five recrystallization steps.

The chiral synthesis of α-substituted amines is an area of significant interest in modern organic synthesis. Strategies include the asymmetric or enantioselective reduction of imines either by borane reagents or through catalytic hydrogenation and the reduction of enamines in a similar manner.[3] Although several other potential routes towards **1** were under exploration, it was felt that optimal efficiency could be obtained if an asymmetric synthesis could be devised for the preparation of the key intermediate, the (*S*)-pyridyl amine **2**. The retrosynthetic analysis is shown in Scheme 2.

In recent years there have been a number of reports describing the asymmetric alkylation of chiral Schiff base anions to furnish amino acid derivatives as well as substituted benzylamines. Several naturally derived chiral ketones have been investigated such as atrolactic acid derivatives,[4] camphor,[5] ketopinic acid derivatives,[6] and 2-hydroxy-3-pinanone (**3**)[7] (eq 1).

It was felt that such an alkylation strategy could be applied to the synthesis of the key pyridyl amine building block of Ontazolast, especially if an inexpensive chiral ketone could



(Eq. 1)

be identified. Also, it was felt that the development of several different routes towards **1** would give us a choice of processes based on best overall cost analysis, impurity profile, and labor factors should the compound reach the manufacturing stage.

Results and Discussion

After a survey of economical, commercially available auxiliaries, camphor was chosen for initial evaluation due

(3) Brunner, H.; Reiter, B.; Riepl, G. *Chem. Ber.* **1984**, *117*, 1330−1354. Sakito, Y.; Yoneyoshi, Y.; Suzukamo, G. *Tetrahedron Lett.* **1987**, 223−223. Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1992**, *3*, 1583−1590.

(4) Nakatsuka, T.; Miwa, T.; Mukaiyama, T. *Chem. Lett.* **1981**, 279−282.

(5) Yaozhong, J.; Guilan, L.; Changyou, Z. *Synth. Commun.* **1987**, *17*, 1545−1548. McIntosh, J. M.; Mishra, P. *Can. J. Chem.* **1986**, *64*, 726−731.

(6) Ikota, N.; Sakai, H,; Shibata, H.; Koga, K. *Chem. Pharm. Bull.* **1986**, *34*, 1050−1055.

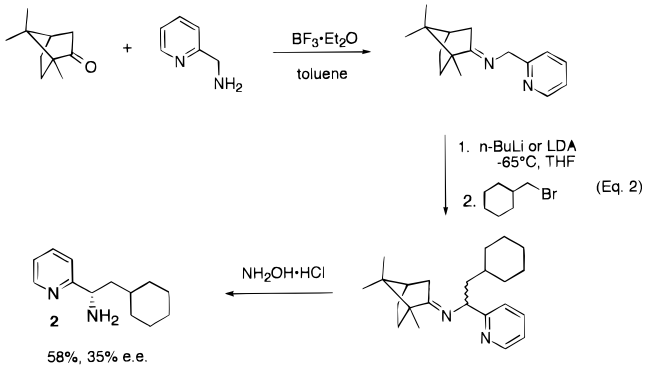
(7) Yuanwei, C.; Aiqiao, M.; Xun, X.; Yaozhong, J. *Synth. Commun.* **1989**, *19*, 1423−1430. Aiqiao, M.; Xun, X.; Lanjun, W.; Yaozhong, J. *Synth. Commun.* **1991**, *21*, 2207−2212. El Achqar, A.; Boumzebra, M.; Roumestant, M. L.; Viallefont, P. *Tetrahedron* **1988**, *44*, 5319−5332. Solladie-Cavallo, A.; Simon, M. C. *Tetrahedron Lett.* **1989**, *30*, 6011−6014.

Table 1. **Optimization of the alkylation of imine 4 (1.0 mmol scale) (R = cyclohexylmethyl)**

base	equiv	temp (°C)	T_1[a]	RX	RX equiv	T_2[b] (h)	% conv[c]
LDA	2.1	−60	3 h	RBr	2.2	2 h (rt)	56
n-BuLi	3.0	0	3 h	RBr	1.1	4	70
n-BuLi	3.0	0	3 h	RBr	2.1	4	100
n-BuLi	2.1	0	3 h	RBr	1.1	4	70
n-BuLi	2.1	0	3 h	RBr	2.1	4	90
n-BuLi	2.1	0	10 min	RBr	2.1	16	100
n-BuLi	2.1	0	10 min	RBr	1.5	16	73−81
n-BuLi	2.1	0	10 min	RBr	1.0	16	40
n-BuLi	2.1	0	10 min	ROMs	2.1	16	50
n-BuLi/TMEDA[d]	2.1	0	10 min	RBr	2.1	3	60−80
n-BuLi/TMEDA	2.1	0	10 min	RBr	2.1	16	100
n-BuLi	2.1	−10[e]	10 min	RI	1.0	16	70−95
n-BuLi	2.1	−10	10 min	RI	1.15	7	100
***n*-BuLi**	**2.1**	**−10**	**10 min**	**RI**	**1.15**	**16**[f]	**100**
n-BuLi[g]	2.1	−10	10 min	RI	1.15	16	100
t-BuOK	2.1	−10	10 min	RI	1.15	16	100 (2:1)

[a] Time allowed for anion formation after addition of *n*-BuLi. [b] Time allowed for quenching after addition of RX. [c] % conversion as determined by ^{1}H NMR ratio of benzylic protons. [d] 1:1 ratio. [e] −10 °C was used instead of 0 °C for 40 mmol scale and larger reactions to control exothermic reaction on *n*-BuLi addition. [f] Reaction was complete after 7 h but left to stir overnight for convenience. [g] Reaction run in MTBE dried over 4 Å molecular sieves.

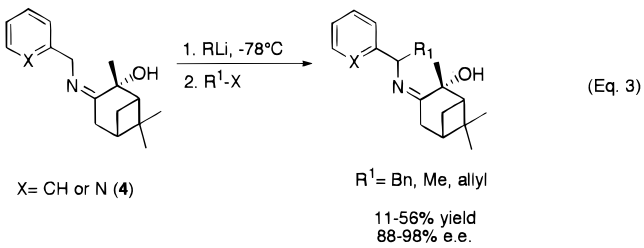
to its wide availability. Condensation of 2-(aminomethyl)-pyridine with either (*R*)-(+)- or (*S*)-(−)-camphor in toluene, using a catalytic amount of BF_3•Et_2O, furnished the desired ketimine in excellent yield (eq 2).



In our initial studies we found that deprotonation of imine **4** with either *n*-BuLi or lithium diisopropylamide at low temperature, followed by quenching of the azaallyl anion with a 2-fold excess of cyclohexylmethyl bromide, afforded the intermediate alkylated product. Chiral HPLC analysis indicated that the crude alkylation product was formed in a 35% diastereomeric excess, and this value was further verified by similar HPLC analysis of pure **2** obtained after hydrolysis of the camphor imine. A variety of conditions were explored without yielding a further improvement in stereoselectivity. It is interesting to note that the few literature references[5] describing the asymmetric alkylation of benzylimines derived from (*R*)- or (*S*)-camphor illustrate that the diastereoselectivity of the alkylation step depends on the electronic nature of the electrophile. Yaozhong[7] and co-workers report that alkylation of imines derived from the (*R*)-2-hydroxy-3-pinanone is not dependent on the nature of the alkylating agent.

Therefore, next surveyed was this commercially available, albeit expensive, chiral auxiliary. At the time of this study, there appeared to be little commercial market for (1(*R*)-(+)-2-hydroxy-3-pinanone ((*R*)-hydroxy ketone, **3**) and catalog suppliers quoted high prices for >98% enantiomerically pure kilogram lots.[8]

Several methods are available for direct oxidation of the inexpensive α-pinene; therefore, it was felt that it would be cost effective to develop our own oxidation procedure should the auxiliary offer good transfer of chirality on alkylation.



Initial experiments, following Yaozhong's protocol, indicated that alkylation could be achieved with complete chirality transfer from the auxiliary but the isolated yield of product was low due to incomplete alkylation (eq 3). Starting imine could also be recovered from the reaction mixture. The experimental conditions shown above were clearly not suitable for an industrial process, and although the stereoselectivity was high, yields were poor. In light of this, effort was focused on optimization of this step. Parameters that were optimized during the course of the study were time, temperature, stoichiometry, and electrophile. A brief summary is shown in Table 1.

Examination of the results from the optimization study revealed the following information. Initial experiments using lithium diisopropylamine as the base were abandoned due to potential downstream problems of separating the residual diisopropylamine from the desired (*S*)-pyridyl amine **2**, as well as for cost reasons. It was discovered that the reported reaction temperature of −78 °C was not necessary for efficient stereocontrol of the alkylation and that a range of −10 to 0 °C was sufficient. A slight excess of butyllithium

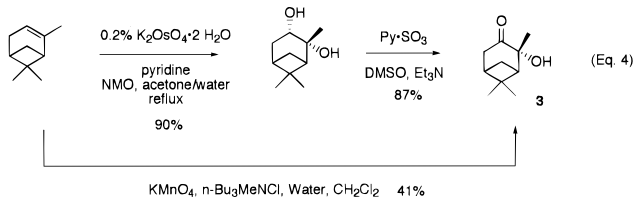
(8) Catalog prices proved to be quite high (ca. $10,000/kg based on gram quantity prices) for material of high enantiomeric excess, and significant bulk quantities (>1 kg) of this material were not available from the vendor.

is necessary to quench any adventitious water present in the reaction since technical grade solvents were evaluated without further drying. The desired dianion is formed immediately on addition of the alkyllithium, and extended aging periods are not necessary. Additives such as TMEDA have no beneficial effect, and the reaction can be run in THF or MTBE with similar results. Potassium *tert*-butoxide was basic enough to deprotonate the imine; however, the alkylated product was obtained as a 2:1 mixture of diastereomers.

Choice of leaving group on the electrophilic component appears to be critical to the success of the alkylation. If less than 2 equiv of alkyl bromide is used, incomplete conversion is seen. The use of a mesylate as a leaving group does not give complete conversion even in the presence of excess reagent. The alkyl iodide is the reagent of choice, with only a slight excess being necessary for complete reaction.

With proven stereoselectivity in the crucial alkylation step, we next turned our attention towards developing this into a scalable process. The remaining steps to be examined were economic generation of the auxiliary, imine formation, imine hydrolysis, and final bulk product formation and isolation.

α-Pinene is commercially available in bulk lots of different enantiomeric purities, and since several methods are available for direct oxidation it was felt that it would be cost effective to optimize this oxidation, procedure. Initial studies involving a two-step sequence employing Sharpless dihydroxylation with secondary oxidation to **3** (eq 4) proved fruitful and offered high yields. This was not explored on larger than a 500 g scale due to the cost of $K_2Os_4 \cdot H_2O$ and disposal issues concerning the use of a toxic heavy metal reagent. The details of this study have been reported elsewhere.[9]



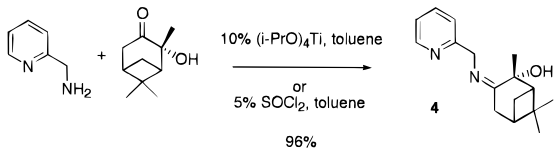
(Eq. 4)

The published procedure by Carson and Pierce[10] calls for direct oxidation using $KMnO_4$ in acetone and provides the desired product in a reproducible manner. In addition, although the catalog prices for high-ee α-pinene were quite high, we were able to locate a source of 93.5% ee α-pinene, and the cost proved reasonable.[11]

During the safety evaluation for this step, a report was found describing an explosion hazard when an alkylamine was oxidized to the corresponding nitroalkane in an identical permanganate/acetone system.[12] Although no problems were encountered during the initial 500 g run, it was felt that an alternate procedure should be devised.

Since conventional methods for using permanganate as an oxidant for organic substrates are severely limited by the lack of solvents that can dissolve permanganate without co-oxidation of the solvent, it was felt that use of phase-transfer catalysis might be applicable to our situation. It was found that α-pinene could be safely and effectively oxidized with permanganate in the presence of a catalytic amount of a quaternary ammonium salt using a water/dichloromethane solvent mixture (eq 4). Using chiral GC, we were ultimately able to demonstrate this reaction with no loss of stereochemistry (as determined by chiral GC analysis) on an 11 kg scale.

As illustrated in eq 5, the process unfolded as follows. The best laboratory procedure for the formation of the chiral imine **4** involved condensation of 2-(aminomethyl)pyridine with the (*R*)-hydroxy ketone **3** in refluxing benzene using 10 mol % of $BF_3 \cdot Et_2O$ as the catalyst. Toluene was found to be an acceptable substitute for benzene. Reproducible yields of 98% were obtained. Since BF_3 was not compatible for use in glass-lined equipment, an alternate procedure was devised. Initial studies showed that acetic acid would catalyze the reaction in refluxing benzene. However, when toluene was used the results were erratic. *p*-Toluenesulfonic acid was not an effective substitute. It was found that titanium isopropoxide was an effective catalyst if at least 10 mol % was used. Lesser amounts (1−5%) increased reaction time and decreased the quality of **4**. The resulting titanium solids had a tendency to form gels, so addition of silica gel was found to be necessary to aid filtration. The crude filtrate and washes were then concentrated to completely remove the toluene, and the crude ketimine could be used directly in the next step. Although this protocol was effective for laboratory scale synthesis, the filtration of the fine solids proved problematic on scale-up, and ultimately, thionyl chloride (5 mol %) was evaluated and chosen as the catalyst of choice. It was presumed that the small amount of thionyl chloride was hydrolyzed by moisture in the solvent to furnish HCl which acted as the dehydration catalyst.



(Eq. 5)

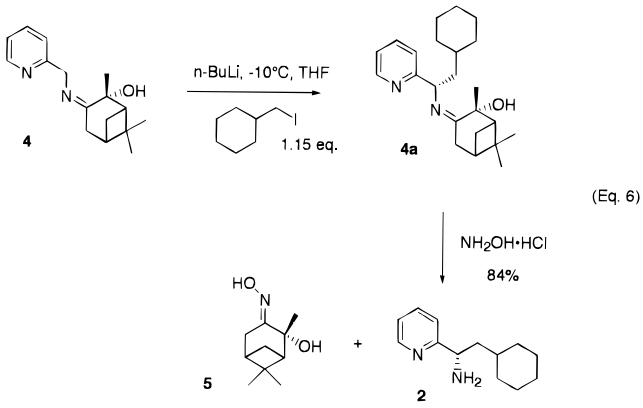
The critical alkylation step proved uneventful, on scale-up, using the optimized conditions highlighted in bold in Table 1. Although cyclohexylmethyl iodide was the preferred electrophile, the process was also demonstrated on large scale using 2 equiv of the corresponding bromide since multikilogram quantities were on hand. The alkylation reaction was complete after 7 h, but the reaction mixture could be stirred for 16 h without degradation.

With regard to the hydrolysis step, some problems were encountered. Ketimines, in general, can be hydrolyzed by either acids or bases. Acidic hydrolysis, the method of choice for amino acid synthesis using this auxiliary, was not suitable for our application. Attempts at hydrolysis using 1−4 M citric acid solutions were unsuccessful, with less than 5% cleavage seen after several days. Hydrochloric acid solutions (1−2 M) proved to be too harsh and led to decomposition as well as racemization of the imine.

Imine exchange is also useful for cleavage of ketimines, and the literature reports that hydroxylamine acetate is an

(9) Krishnamurthy, V.; Landi, J. J.; Roth, G. P. *Synth. Commun.* **1997**, *27*, 853−860.
(10) Carlson, R. G.; Pierce, J. K. *J. Org. Chem.* **1971**, *36*, 2319−2321.
(11) A total of 2316 lb of 93.5% ee α-pinene was purchased from SCM-Glidco Organics, Jacksonville, FL for about $5.50/kg.
(12) *Bretherick's Handbook of Reactive Chemical Hazards*, 5th ed.; Urben, P. G., Ed.; Butterworth-Heinemann: London, 1995; Vol. 1, p 1627.

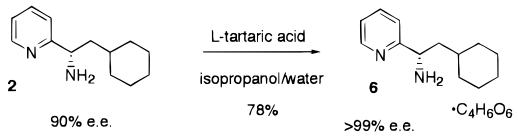
effective reagent for this cleavage.[13] Treatment of chromatographically pure alkylated imine with a slight excess of commercially available hydroxylamine hydrochloride in ethanol/water led to smooth cleavage resulting in liberation of the (*S*)-pyridyl amine without detectable racemization. Further optimization showed that the imine from the crude reaction mixture could also be cleanly cleaved in this manner and that isolation was not necessary. The washed THF fraction from the alkylation could be directly treated with a slight excess of hydroxylamine hydrochloride with the addition of a small amount of ethanol and water to enhance solubility. Stirring at ambient temperature overnight allowed for smooth cleavage without any racemization detectable within experimental error. Acid/base extraction allowed for effective removal of hydrolyzed auxiliary (as the corresponding oxime **5**) as well as aliphatic impurities (eq 6).



(Eq. 6)

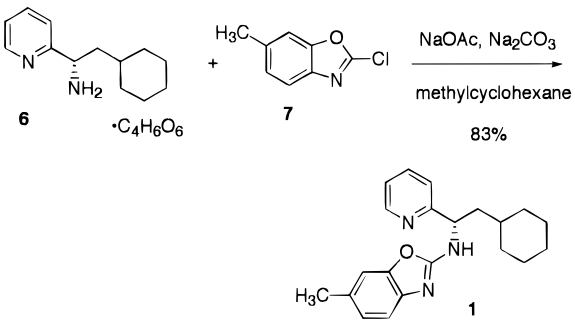
Scaling the reaction from millimole up to a 30 mol scale proceeded smoothly, and this step was ultimately streamlined into an imine formation, alkylation, then hydrolysis sequence to provide **2** without the need for isolation of any intermediates. Again, the ee of isolated **2** can be directly correlated to the ee of the α-pinene used for the preparation of **3**. Larger scale runs (>0.5 kg of imine) have indicated that the ee may vary slightly, but not more than 2−3%.

Since the α-pinene was available in 93.5% ee, the resulting (*S*)-pyridyl amine required an enantiomeric enrichment step. In addition, with an effective enrichment step, α-pinene of lower optical purity can also be used in this process. Several commercially available chiral acids were surveyed, and it was found that L-tartaric acid worked the best. As shown in eq 7, treatment of a wet 2-propanol solution of crude **2** with 1 equiv of L-tartaric acid, with slow stirring overnight, furnished the corresponding salt, which could be isolated as a stable white solid. This convenient method for precipitation of **2** not only allowed for the isolation of the salt **6** as a free-flowing solid but also increased the ee to >99%. It is interesting to note that on laboratory scale reactions the hemi-tartrate salt (1:0.5 amine/tartrate) was routinely isolated. When the process was demonstrated in the pilot plant, we were only able to obtain the stoichiometric salt (1:1 amine/tartrate). A study of the salt crystal morphology and interconversion between forms was not conducted due to time constraints. Each salt form gave identical resolution results.



(Eq. 7)

The final step of this process involves the coupling of the chiral fragment with the substitued benzoxazole building block **7** to give the target drug candidate. The goals for the final synthesis step, from a technical point of view, were to omit methylene chloride and substitute Hünig's base with an inorganic base. A variety of solvents such as acetonitrile, toluene, and DMF along with the bases sodium or potassium carbonate, bicarbonate, or acetate had not been satisfactory with respect to yield or quality of the isolated material. Several initial procedures involving regeneration of the free base **2**, with subsequent isolation before coupling, were evaluated. Ultimately, the most efficient route involved the *in situ* breaking of the tartrate salt **6** to furnish **2**, then coupling by addition of the chlorobenzoxazole **7** (eq 8).



(Eq. 8)

Since the final bulk drug product is produced at the end of this sequence of steps, several issues become critical. They include water content, residual solvent content, final enantiomeric excess, and overall percent purity. Accordingly, two recrystallizations were found to be necessary, the first using methylcyclohexane, and the second, ethanol/water. This was necessary because it was not possible to completely remove the methylcyclohexane from crude Ontazolast by drying because the wet crystals easily "melted" at about 30 °C in the vacuum drying oven. Therefore the wet crude crystals were dissolved in a mixture of ethanol/water and refluxed on a Dean−Stark apparatus. The ternary mixture has the lowest boiling point (methylcyclohexane, 61%; ethanol, 32%; water, 7%; bp 69.6 °C).[14] This protocol removed the residual hydrocarbon solvent and allowed for isolation of bulk drug product with the correct water and residual ethanol content to meet specifications.

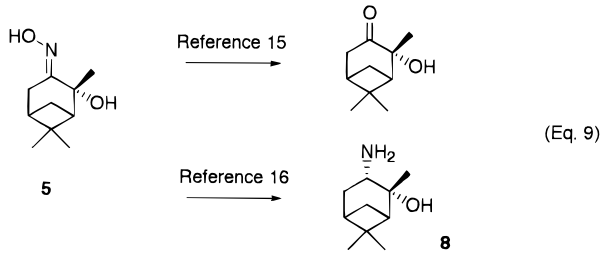
In conclusion, we have demonstrated a potential manufacturing process involving a telescoped series of operations including imine formation, an asymmetric alkylation, auxiliary removal, and intermediate isolation to furnish a stable diastereomeric salt. Isolation of intermediate **2** as a diastereomeric salt (**6**) served two purposes: allowing for the convenient isolation of oily **2** in solid form and also enhancing the ee of the product through a partial resolution. In addition we did not have to be concerned on sourcing consistantly high ee α-pinene on a continuous basis since a

(13) Yamada, S. I.; Oguri, T.; Shiori, T. *J. Chem. Soc., Chem. Commun.* **1976**, 136−137.

(14) Swietoslawski, W.; Zieborak, K.; Galska-Krejewsks, A. *Bull. Acad. Pol. Sci., Ser. Sci., Chim., Geol. Geogr.* **1959**, *7*, 43−49.

diastereomeric enhancement did occur during the isolation. The end game of the route involved coupling of the chiral intermediate **6** with a chlorobenzoxazole subunit. This sequence provided the final crystalline product in an isolated 83% yield (52% overall for the process; based on formation of imine as the first step) with >99.5% purity and >99% ee Earlier campaigns, following the racemic/resolution route, afforded product in 25−35% overall yield and involved additional steps to regenerate the 8-bromocamphorsulfonic acid resolution agent. This proved labor intensive.

During the course of this work a safe and effective phase-transfer oxidation procedure for the preparation of the chiral auxiliary **3** was developed allowing for its preparation and the ultimate preparation of **1** on a 20 kg scale in the pilot plant using 20 and 50 gal glass-lined reactors. It was felt that the oxidation procedure to generate **3** could also be contracted to an outside manufacturer should the need arise. Although a true hallmark for an asymmetric synthesis is the recovery of the auxiliary at the end of the synthesis, it was found not to be cost effective.[15] Conversion of the oxime cleavage product **5** to the novel amino alcohol **8** (eq 9) proved to be more valuable from a synthetic standpoint.[16]



5 **8** (Eq. 9)

Experimental Section

General Conditions. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC-270 MHz instrument using an inverse detection proton/broad band 5 mm probe. All spectra were run using $CDCl_3$ as solvent. Chiral HPLC analysis was done using a Rainin Dynamax system with a UV detector set at 254 nm. The Chiralpak AD column (Daicel Chemical Ind. Ltd, 0.46 × 25 cm), used for the (*S*)-pyridyl amine **2** analysis, was purchased from Chiral Technologies Inc., 730 Springdale Dr., P.O. Box 564, Exton, PA. The mobile phase for chiral analysis consisted of hexanes containing 5% anhydrous ethanol and 0.5% of diethylamine. This was used at a flow rate of 1.5 mL/min. The retention times are as follows: *R* isomer, 6.51 min; *S* isomer, 5.43 min.

The chiral analysis of Ontazolast (**1**) was accomplished using a Chiracel OD-H column and a mobile phase containing hexanes/2-propanol/diethylamine (992:8:1) at a flow rate of 1.0 mL/min. The retention times are as follows: *R* isomer, 16.90 min; *S* isomer, 21.99 min.

A total of six 55 gal drums of (−)-α-pinene were received and analyzed using chiral gas chromatography to verify enantiomeric purity. The analysis was carried out using a Perkin-Elmer Sigma 2000 capillary GC with a flame ionization detector. A 0.5 μL sample was injected on a Supelco β-cyclodextrin 110 column (0.25 × 30 m) at 60 °C (isothermal) with a flow rate of 1 mL/min. All other reagents and solvents were purchased from Aldrich and used as received.

Synthesis of (1*R*,2*R*,5*R*)-(+)-2-Hydroxy-3-pinanone (3). Oxidation of α-Pinene with Potassium Permanganate in Acetone. A 12 L flask equipped with an overhead mechanical stirrer, a nitrogen inlet, a thermocouple, and an ethanol bath cooled by a circulating glycol/water coil was charged with (*S*)-(−)-α-pinene (750.0 g, 5.50 mol, 93.5% ee) and a volume of 10% water in acetone (6.62 kg). The resulting mixture was cooled to 0 °C, and over a 9 h period, $KMnO_4$ (1.50 kg, 9.49 mol) was added in small portions (ca. 100.0−150.0 g each). Note: On addition of early portions, an immediate exotherm is seen; as the reaction progresses and the slurry becomes thick, there is a slight induction period before an exotherm. At no time was the reaction unmanageable. The reaction temperature was maintained at 2−3 °C during the addition period and then held for an additional 40 h. The resulting solids were then removed by filtration and washed with 10% water in acetone (4.0 L). The combined filtrates were concentrated on a rotary evaporator (35 °C bath, 50 mmHg). The resulting residue was partitioned between water (750 mL) and diethyl ether (1.5 L). The aqueous layer was extracted with diethyl ether (750 mL). The combined organics were washed with water (750 mL), followed by saturated aqueous $NaHCO_3$ (750 mL). The organic fraction was dried over $MgSO_4$ (50.0 g) and concentrated to dryness. The crude product was distilled through a 30 cm Vigreux column (90−100 °C, 2 mmHg) to furnish the desired product as a colorless oil (385.4 g, 41.7% yield; basis: α-pinene).

Alternate Preparation of 3: Phase-Transfer Oxidation. A 12 L jacketed flask equipped with an overhead mechanical stirrer, a thermocouple, and a recirculating chiller was charged with water (2.5 L), dichloromethane (2.5 L), 75% aqueous methyltributylammonium chloride (34.0 g, 5 wt %), and (*S*)-(−)-α-pinene (500.0 g, 3.67 mol, 93.5% ee). The mixture was cooled to 0 °C, and over a 7 h period, $KMnO_4$ (1.0 kg, 6.3 mol) was added in portions (ca. 75.0−125.0 g each) while the reaction temperature was kept at or below 5 °C. Note: On addition of early portions, an immediate exotherm is seen; as the reaction progresses and the slurry becomes thick, there is a slight induction period before an exotherm. At no time was the reaction unmanageable. After addition was complete, the slurry was allowed to warm to room temperature and stirred for 20 h. To this was then added toluene (2.5 L), and the reaction mixture was stirred for 15 min. The liquid phase was decanted through filter paper, and the remaining solids were washed with toluene (2 × 2.5 L). The combined organics were washed with water (2.5 L) and then concentrated on a rotary evaporator to furnish the crude product as a light brown oil. Purification by distillation (as above) furnished the desired product as a colorless oil (251.30 g, 40.6%).

^{1}H NMR ($CDCl_3$, 270 MHz): δ 2.60−2.58 (m, 2H); 2.48−2.41 (m, 2H, 1 H is exchangeable); 2.12−2.09 (m, 2H); 1.66 (d, 1H, J = 10.8 Hz); 1.36 (s, 3H); 1.34 (s, 3H);

(15) A variety of oxime reduction/hydrolysis protocols were evaluated; for example: Negi, S.; Matsukura, M.; Mizuno, M.; Miyake, K.; Minami, N. *Synthesis* **1996**, 991−996. Kim, J. N.; Ryu, E. K. *Bull. Korean Chem. Soc.* **1990**, *11*, 479−481. Hershberg, E. B. *J. Org. Chem.* **1948**, *13*, 542. Kamal, A.; Rao, M. V.; Meshram, H. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, *8*, 2056−2057.

(16) Roth, G. P.; Leonard, S. F.; Tong, L. *J. Org. Chem.* **1996**, *61*, 5710−5711.

0.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 213.96; 49.48; 42.76; 39.00; 38.05; 28.17; 27.07; 24.95; 22.63.

Condensation of 2-(Aminomethyl)pyridine with (*R*)-Hydroxypinanone. Imine 4. A 5 L flask fitted with an overhead mechanical stirrer, a nitrogen inlet, a Dean−Stark trap, and a heating mantle was charged with 2-(aminomethyl)pyridine (241.0 g, 2.23 mol), (*R*)-hydroxypinanone (**3**) (375.0 g, 2.23 mol), and 1.6 L of toluene. To this was added $Ti(O\text{-}i\text{-}Pr)_4$ (52.4 mL, 10 mol %). The resulting mixture was heated to reflux for 3 h and then cooled to 30 °C, and the suspension was filtered through a pad of silica gel (375 g). The filter cake was then washed with toluene (2.2 L). The combined filtrate and wash were evaporated to dryness on a rotary evaporator, and the resulting residue was dissolved in THF (500 mL) and evaporated again. This procedure was repeated, and the residue was evaporated to dryness on a rotary evaporator, to give the desired imine as an orange oil (555.39 g, 96.4% yield; based on (*R*)-hydroxypinanone).

Alternate Method. A 5 L flask fitted with an overhead mechanical stirrer, a nitrogen inlet, a Dean−Stark trap, and a heating mantle was charged with 2-(aminomethyl)pyridine (241.0 g, 2.23 mol), (*R*)-hydroxypinanone (**3**) (375.0 g, 2.23 mol), and 1.6 L of toluene. To this was slowly added a solution of $SOCl_2$ (8.1 mL, 0.11 mol) in 50 mL of toluene. The resulting mixture was heated to reflux for 5 h, at which time the reaction was shown complete by TLC (10% CH_3OH in CH_2Cl_2). The resulting brown solution was then evaporated to dryness on a rotary evaporator. To the residue was added THF (500 mL), and the solution was evaporated as above. This procedure was again repeated to give the desired imine as an orange oil (555.3 g, 96% yield).

^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.51−8.48 (m, 1H); 7.63 (dt, 1H, J = 1.8, 7.7 Hz); 7.49 (d, 1H, J = 8.1 Hz); 7.14−7.09 (m, 1H); 4.60 (apparent t, 2H); 2.86 (broad s, 1H, exchangeable); 2.57 (broad s, 2H); 2.33−2.29 (m, 1H); 2.08−2.00 (m, 2H); 1.55 (d, 1H, J = 10.8 Hz); 1.53 (s, 3H); 1.29 (s, 3H); 0.82 (s, 3H).

^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 177.62; 160.15; 148.96; 136.59; 121.71; 56.26; 50.22; 38.52; 38.30; 33.94; 28.39; 28.17; 22.81.

(*S*)-α-(Cyclohexylmethyl)-2-pyridinemethanamine (2). A jacketed 12 L flask equipped with an overhead mechanical stirrer, a nitrogen inlet, an addition funnel, a thermocouple, and a recirculating chiller was charged with imine **4** (538.9 g, 2.08 mol) and THF (5.5 L). The solution was cooled to −10 °C and to it, over a 2.5 h period, was added 2.5 M *n*-BuLi in hexanes (1.67 L, 4.16 mol) while the reaction temperature was maintained at or below −5 °C. The resulting deep red solution was stirred at −10 to −5 °C for 1 h, and then cyclohexylmethyl iodide was added (536.1 g, 2.39 mol) over a 1 h period while the reaction temperature was maintained at or below −5 °C. The reaction mixture was stirred between −10 and 5 °C for 16 h. To the mixture was then added, over 2 h, saturated aqueous NH_4Cl solution (1.5 L) while the reaction temperature was maintained at or below −3 °C. After addition was complete, the reaction mixture was warmed to room temperature. The organic fraction was isolated and charged back to the reaction flask. To this were added 95% ethanol (386 mL), water (193 mL), and hydroxylamine hydrochloride (173.9 g, 2.5 mol). The resulting solution was stirred at room temperature for 20 h. To this was then added 1 N HCl (5.5 L), and the mixture was extracted with ethyl acetate (3 × 2.0 L). The aqueous fraction was then made basic by addition of concentrated NH_4OH (600 mL, pH = 11) and then extracted with CH_2Cl_2 (3 × 2.0 L). The organic fraction was dried over $MgSO_4$ (130 g) and concentrated to dryness on a rotary evaporator to furnish **2** as a light brown oil (358.2 g, 84% crude yield; basis: imine). Chiral HPLC shows the material to be of 90% ee. This material was used directly in the next step. A small sample was purified by flash chromatography (silica gel, hexanes/ethyl acetate, 1:1) to furnish pure product as a pale yellow oil.

Alkylated Cyclohexylmethyl−Ketimine Intermediate (4a). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.49−8.47 (m, 1H); 7.59 (dt, 1H, J = 1.8, 9.1 Hz); 7.32 (d, 1H, J = 8.1 Hz); 7.12−7.07 (m, 1H); 4.78 (dd, 1H, J = 2.1, 8.1 Hz); 2.71−0.86 (complex series of m, 20H; including singlets at 1.52 (3H); 1.28 (3H); 0.88 (3H)).

^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.29; 175.59; 163.44; 148.72; 136.62; 121.75; 121.19; 62.47; 53.38; 49.93; 45.44; 38.24; 34.60; 34.10; 33.49; 32.70; 28.51; 27.93; 27.27; 26.48; 26.38; 26.23; 25.24; 22.78; 20.82.

Anal. Calcd for $C_{23}H_{34}N_2O$: C, 77.92; H, 9.67; N, 7.90 Found: C, 77.88; H, 9.69; N, 7.95

(*S*)-Pyridyl Amine 2. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 8.53 (dd, 1H, J = 2.7, 4.6 Hz); 7.58 (dt, 1H, J = 1.8, 9.7 Hz); 7.24−7.20 (m, 1H); 7.14−7.09 (m, 1H); 5.00 (br s, 2H); 4.01 (apparent dd, 1H, J = 6.4, 8.1 Hz); 1.75−0.86 (complex m, 13H).

^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 165.4; 149.1; 136.8; 121.6; 120.7; 54.4; 46.4; 34.7; 32.6; 31.8; 26.4; 26.1; 26.0.

Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71 Found: C, 76.40; H, 9.87; N, 13.73.

Enantiomeric Enrichment of (*S*)-α-(Cyclohexylmethyl)-2-pyridinemethanamine Using L-Tartaric Acid. Tartrate Salt 6. A 1 L round bottom flask equipped with an overhead mechanical stirrer and an addition funnel was charged with the (*S*)-pyridyl amine **2** (65.3 g, 0.32 mol) and 2-propanol (254 mL). In a separate flask L-tartaric acid (24.0 g 0.5 equiv) was mixed with water (21.8 g). When the solids were completely dissolved, 2-propanol (241 mL) was added and the mixture was transferred to the addition funnel. The tartaric acid solution was added dropwise over a 20 min period. After completion of addition, the resulting thick slurry was stirred at ambient temperature for 18 h. The solids were collected by filtration and washed with 25% 2-propanol/hexanes (3 × 100 mL). The resulting white solid was dried under house vacuum at ambient temperature for 18 h to furnish the desired tartrate salt (69.8 g, 78%; 99.4% ee by chiral HPLC).

Preparation of (*S*)-*N*-[2′-Cyclohexyl-1′-(2″-pyridinyl)-ethyl]-5-methyl-2-benzoxazolamine, Ontazolast (1). A round bottom flask equipped with a Dean−Stark trap was charged with (*S*)-pyridyl amine **2** (83.5 g, 0.236 mol), water (167 mL), 45% aqueous NaOH (82.1 g), and methylcyclohexane (167 mL). The mixture was stirred and heated to 50 °C. The layers were separated, and an additional charge of methylcyclohexane (167 mL) was added. The mixture

was heated at reflux until water separation stopped, and then the mixture was cooled to 60 °C. To the reaction mixture were added sodium carbonate (30.13 g, 0.284 mol) and sodium acetate (1.93 g, 0.024 mol). The benzoxazole **7** (39.7 g, 0.236 mol) was then added over a 10 min period. The mixture was heated for 3 h at 80 °C, then the solids were removed by filtration, and the filter cake was washed with three portions of methylcyclohexane (40 mL each). The filtrate was concentrated by distillation of some solvent (275 mL), then it was cooled to 10 °C, and water (4.2 mL) was added. After cooling at 0 °C for 2 h the crystals were collected by filtration and washed with methylcyclohexane (40 mL). The wet product was suspended in a solution of ethanol (148 mL) and water (35 mL). After refluxing on a Dean−Stark apparatus until no more methylcyclohexane separated, the solution was cooled to 40 °C. Water (113 mL) was added within 30 min, and then the mixture was cooled in an ice/water bath for 1 h. The solids were collected by filtration and washed twice with ethanol/water, 4:1 (30 mL), and once with water (50 mL). The product was dried at reduced pressure (30 °C, 16 h) to furnish pure **1** as a white solid (69.0 g, 83%, >99% ee by chiral HPLC); mp 80−86 °C.

^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.83−1.95 (m, 13H); 2.33 (s, CH_3); 3.20 (broad s, H_2O); 5.13 (m, 1′-H); 6.74 (m, 6-H); 7.01 (d, 7-H); 7.12 (m, 5″-H); 7.13 (d, 4-H); 7.34 (d, 3″-H); 7.52 (d, J = 8.0 Hz, NH); 7.57 (m, 4″-H); 8.52 (d, 6″-H).

^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 21.6 (CH_3); 26.1; 26.3; 26.5; 33.0; 33.7; 34.4; 44.3 (C-2′); 55.9 (C-1′); 108.2; 116.6; 121.2; 121.7; 122.4; 133.4; 136.8; 143.3; 146.8; 149.4; 161.6; 162.3.

IR (Nujol, cm^{-1}): 3270 and 3202 (N−H), 2915 and 2865 (C−H), 1645 (C═N), 1590 (aryl-C═C), 1568 (pyr-C═C), 1255 (C−O).

Anal. Calcd for $C_{21}H_{25}N_3O\cdot H_2O$: C, 71.36; H, 7.70; N, 11.89. Found: C, 71.24; H, 7.73; N, 11.99.

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