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Development of an Efficient Process for the Preparation of Sch 39166: Aziridinium Chemistry on Scale

Dinesh Gala,* Vilas H. Dahanukar,* Jeffery M. Eckert, Brian S. Lucas, Doris P. Schumacher, and Ilia A. Zavialov

Schering-Plough Research Institute, Department of Synthetic Chemistry, 1011 Morris Avenue, Union, New Jersey 07083, U.S.A.

Patrik Buholzer, Peter Kubisch, Ingrid Mergelsberg, and Dominik Scherer

Chemical Development Department, Werthenstein Chemie AG, 6105 Schachen, Switzerland

Abstract:

A large-scale synthesis of a tricyclic D1/D5 dopamine antagonist based on regio- and stereoselective ring opening of an aziridinium ion with a Grignard reagent was optimized and scaled up.

Introduction

Sch 39166 (**1**) is a potent dopamine D-1 antagonist that was initially developed to treat schizophrenia.[1] Subsequent in vivo animal autoradiography studies[2] demonstrated that **1** was a highly selective D1/D5 antagonist. Since the neurotransmitter dopamine is involved in the reward mechanism that induces craving, **1** was shown in animal models to reduce cravings for addictive substances (cocaine, nicotine, alcohol, etc.) and food.[3] New phase II trials showed that **1** reduced the euphoric effects of cocaine,[4] but was not effective in completely treating the addiction.[5] Additional clinical studies were planned to evaluate **1** in reducing cravings for food (to treat obesity) and nicotine. With renewed interest in conducting phase II and phase III clinical trials of **1**, a commercial synthesis was urgently required to support these activities and future marketing needs.

Several different syntheses of **1** were explored,[6,7] and the approach based on aziridinium chemistry[7] proved to be the most attractive. This report deals with the chemistry aspects of process development and optimization of the aziridinium route (Scheme 1) that enabled us to manufacture several hundred kilograms of Sch 39166. The aziridinium route was demonstrated in the laboratory to provide a quick access to **1**. However, the following challenges were identified with this approach which required additional work to make it a robust, plant-suitable process capable of making large quantities of Sch 39166 needed to support clinical trials: (1) An efficient and cheap synthesis of key starting material **2** was necessary. (2) N-Alkylation of **2** to **3** was slow and required very long reaction times. (3) The yields obtained in the aziridinium formation and opening step were highly variable (45−60%), and an excess (2.1 equiv) of the expensive Grignard reagent **4** was required to obtain these moderate yields. The purity of isolated product varied from 85 to 95%, requiring a chromatographic purification of **5**.[17] Overall, the mechanistic aspects of the chemistry involved in this transformation were poorly understood. (4) The cyclization/reduction protocol for the conversion of **5** to **6**

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(12) Other sulfonyl choride reagents investigated as activating reagents (benzenesulfonyl chloride, 4-chlorobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, and MsCl) showed no advantage over *p*-TsCl. Other reagents (methanesulfonic anhydride, *p*-toluenesulfonyl imidazole, carbonyldimidazole, thionyl chloride, trifluoroacetic anhydride, and oxalyl chloride) also proved to be inferior to *p*-TsCl.
(13) ^{31}P NMR (THF-d_8, 161.98 MHz) spectra were recorded using H_3PO_4 as an external reference standard.
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(15) Several copper salts other than CuCl and CuCN were screened in catalytic amounts (10 mol %): CuBr, CuI, CuSCN, CuSPh, Cu(OtBu), $CuCl_2$, $Cu(OAc)_2$, $Cu(BF_4)_2$, $Cu(OTf)_2$, copper (II) naphthenate, copper (II) acetylacetonate, copper (II) tifluoroacetylacetonate, copper (II) benzoylacetonate, lithium 2-thienylcyanocuprate, and Cu(I) phenylacetylide. Other metal salts (Cr, Fe, Mn, and Ni) failed to show any improvement in the reaction of **16** with **4**.
(16) In the laboratory, after forming **15b** at −20 °C, it was mixed with **4** at various temperatures and held for several hours. Aliquots were taken and analyzed periodically by HPLC to quantitate the amount of product **5**. This work showed that the reaction of **4** with **16** was sluggish below 0 °C and proceeded faster at 25−35 °C.
(17) This would be a large waste burden for a commercial process; hence, it was to be avoided at any cost.

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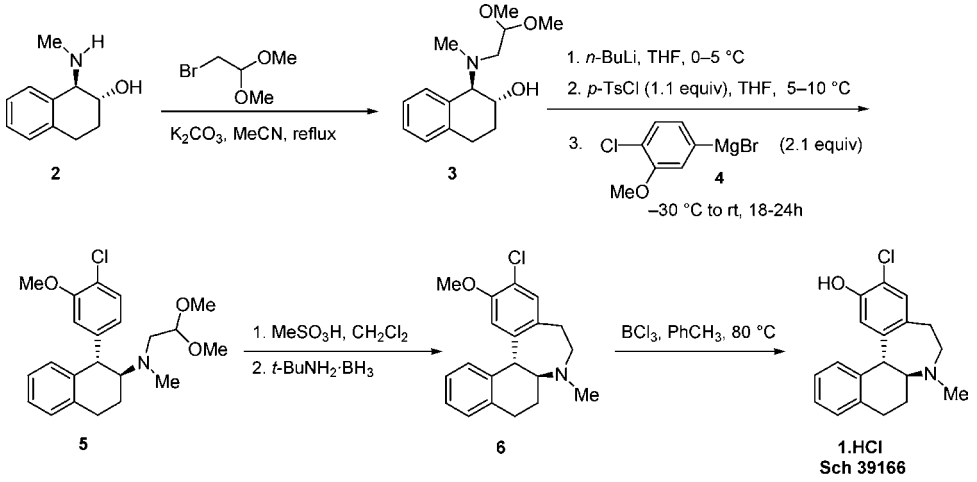
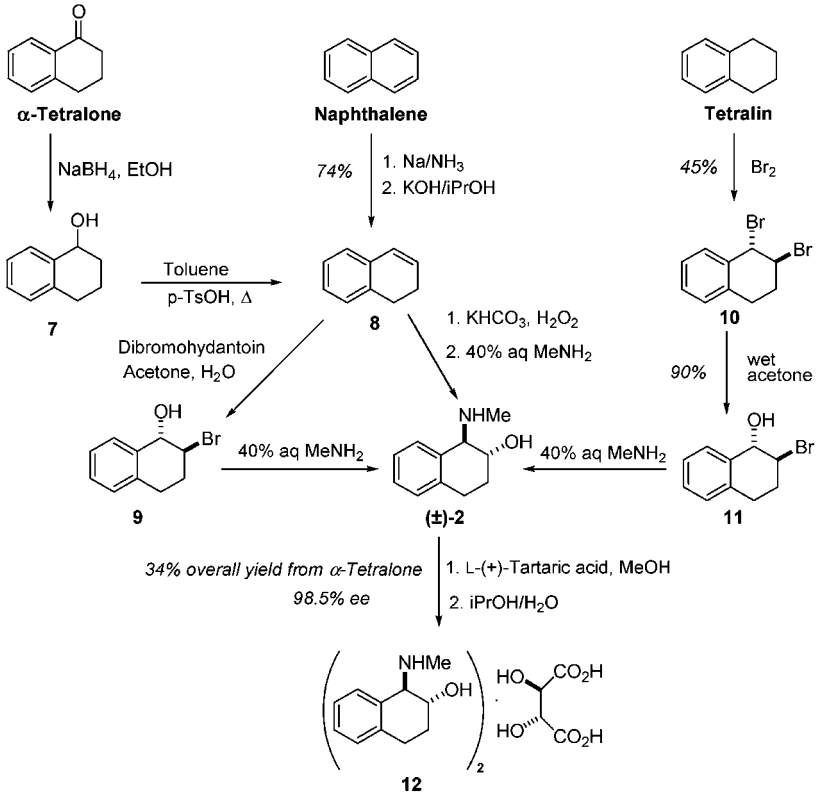
Scheme 1. **Laboratory synthesis of Sch 39166**



Scheme 2. **Commercial synthesis of 12**



used methylene chloride as a solvent and then $NaHCO_3$ neutralization (the literature[7] does not have this procedure; this is based on the optimized supply route chemistry described in ref 6) of methanesulfonic acid before reduction with *tert*-butylamine borane (TBAB). The cyclization time was about 2−3 days, and neutralization of acid was difficult on scale due to excessive foaming with CO_2. Isolation and purification of free base **6** was known only via crystallization as a 1:1 mixture of (+)-di-*p*-toluoyl-D-tartaric acid (DTTA) salt. The use of this expensive chiral acid in salt formation of enantiopure **6** was undesirable. (5) Finally, the impurity profile of Sch 39166 prepared via this route must meet or exceed the specifications set by supply route as per ICH guidelines. The last criterion was critical for this aziridinium-route synthesis to be a viable option for providing drug substance required for clinical studies. With these difficulties and potential issues in mind, we embarked on the process development of this route.

Results and Discussion

1. Synthesis of 12 (and 2). Naphthalene, tetralin, and α-tetralone were identified as three readily available inexpensive potential starting materials to obtain (±)-**2** (Scheme 2). Due to scale-up issues related to handling liquid ammonia and sodium metal in our facility, the Birch reduction of naphthalene was not pursued. In the tetralin route, dibromination followed by substitution resulted in formation of bromohydrin **11**, which was converted to (±)-**2**. Although this synthesis was demonstrated to work in the laboratory,[7] removal of other brominated impurities as well as constraints

Scheme 3. **Asymmetric epoxidation route**

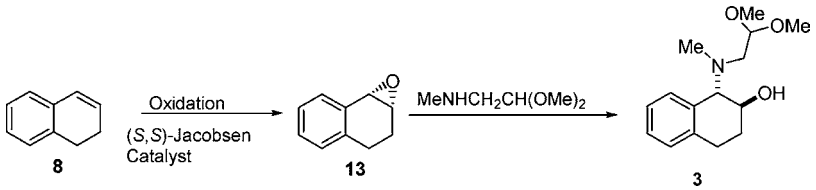


Table 1. **N-Alkylation of the amino alcohol 2 with BADMA**

entry	conditions	% yield
1	K_2CO_3 (2.0 equiv), acetal (1.5 equiv), MeCN, reflux, 48 h	55
2	NaI (0.1 equiv), K_2CO_3 (2.0 equiv), BADMA (1.5), acetone, reflux, 18 h	NR[a]
3	KI (0.1 equiv), K_2CO_3 (1.5), BADMA (1.5 equiv), MeCN, reflux, 48 h	50
4	50% NaOH, $^nBu_4NHSO_4$ (0.1 equiv), BADMA (1.1 equiv), $PhCH_3$, rt, 48 h	NR[a]
5	NaOH (2.0 equiv), K_2CO_3 (1.0 equiv), BADMA(1.1 equiv), $PhCH_3$, reflux 6 h	Decomp[b]
6	K_2CO_3 (1.5 equiv), BADMA (1.2 equiv), DMF, reflux, 14 h	80
7	K_2CO_3 (1.5 equiv), BADMA (1.2 equiv), NMP, 100 °C, 14 h	52
8	K_2CO_3 (1.5 equiv), BADMA (1.2 equiv), diglyme, 130 °C 18 h	90[c]
9	Na_2CO_3 (0.8 equiv), BADM (1.2 equiv), diglyme, 130 °C 18 h	80[d]

[a] NR = no reaction. [b] Decomp = decomposition. [c] Yield corrected for HPLC purity vs standard. [d] Reaction showed other side products (5−10 area %, HPLC).

associated with handling bromine were significant; hence, this process was not scaled up. The first three steps in the α-tetralone route, reduction to **7** followed by dehydration to **8** and bromohydrin formation, could be telescoped in 85% overall yield. Since purification of **8** was difficult, procedures were developed to partially purify **8** and react it with dibromohydantoin in wet acetone to form the desired bromohydrin **9** which can be isolated. Treatment of **9** with an excess of 40% aqueous methylamine solution resulted in formation of (±)-**2**. This reaction proceeds via an epoxide intermediate (±)-**13**. Compared to direct epoxidation of **8**, the bromohydrin sequence gave higher yields of (±)-**2**. Since (±)-**2** has high water solubility, saturated NaCl solution use before extraction with MTBE was incorporated in the workup (see the Experimental Section). L-Tartaric acid proved to be the best among other chiral acids (camphorsulfonic acid, malic acid, mandelic acid, glutamic acid, and aspartic acid) screened for the resolution of (±)-**2**. The addition of small amounts (0.05 equiv) of achiral acids such as HCl, HOAc, and H_2SO_4 in tartaric acid crystallization failed to improve the yield or ee of **12**. In the early stages of this work the addition of L-(+)-tartaric acid (0.25 equiv) to a solution of (±)-**2** in MeOH was used to obtain **12** in 78−85% de, which was upgraded to 98−99% de by two additional crystallizations from MeOH. Additional development led to an even more efficient purification by slurrying the crude product in ^{i}PrOH−H_2O (95:5) to afford **12** of the desired chemical and chiral (98−99% de) purity. Thus, the α-tetralone-based route was scaleable, and several hundred kilograms of **12** was prepared in an overall yield of 32%.

An alternate more direct approach to **3** involved the opening of chiral epoxide **13** with *N*-methylaminoacetaldehyde dimethylacetal (Scheme 3). This approach was investigated as well. Although the feasibility of this approach had been established earlier, low and irreproducible enantioselectivity (55−88%), poor yields (20−40%) of chiral epoxidation and over-oxidation to naphthalene in our hands were major problems that could not be overcome even after extensive screening of reaction conditions.

2. N-Alkylation of 2 (Derived from 12). The original reaction conditions for the conversion of **12** to **3** involved the removal of tartaric acid from **12** to form **2** followed by N-alkylation with bromoacetaldehyde dimethyl acetal (BADMA) in acetonitrile as a solvent [MeCN/K_2CO_3 (2 equiv)/BADMA (1.5 equiv)]. [7] Under these conditions, the reaction required 6 days for completion and afforded 78% isolated yield after workup. Thus, further development of this chemistry was required to improve the step yield as well as shorten the reaction time. Some of this work is summarized in Table 1.

Conversion of **12** to its free base form **2** was a necessary operation as direct N-alkylation of **12** with BADMA in the presence of a base afforded low yields under a variety of conditions. Our initial conditions for preparing **2** were addition of 30% NH_4OH to a suspension of **12** in MTBE. Due to significant loss of **2** to the aqueous layers under these conditions, the aqueous layer had to be saturated with NaCl for an efficient extraction of **2**. To avoid use of NaCl, MTBE, and NH_4OH an improved procedure was developed, wherein a limited amount of water and 25% NaOH were added to a suspension of **12** in toluene. Sodium tartrate formed during neutralization, saturated the water layer, and after extraction with toluene, less than 2% of **2** was lost in the aqueous phase. Atmospheric distillation of the batch provided low levels of residual water which was necessary (see below) before the start of N-alkylation step.

Lowering the reaction time of the conditions described above to 2 days resulted in a 55% yield (Table 1, entry 1), with unreacted **2** washed out in the aqueous layer during the original workup. An alternate reaction condition that was also included in the earlier report[7] that involved the use of KF adsorbed over alumina (3.3 equiv) provided a higher yield (94%) with a relatively short reaction time (2 days). This option was unattractive because of the unavailability of KF

adsorbed over alumina on large scale and the waste-handling issues.

Addition of KI to induce in situ generation of the more reactive iodo acetal from the BADMA failed to improve the conversion (entries 2,3). Phase transfer conditions reported for the alkylation of amides and anilines[8] were also ineffective (entries 4 and 5). Screening experiments revealed that anhydrous K_2CO_3 was the best base compared to other inorganic bases such as Na_2CO_3, $NaHCO_3$, and $KHCO_3$. Use of organic bases led to complex reaction mixtures and the bases proved difficult to remove from the product (compound **3** is a viscous liquid). It was thought that the cause of slow reaction was the reaction temperature, which was limited by the boiling point of the solvent. Hence, alternate polar solvents and bases were screened. Although, polar aprotic solvents such as DMF and NMP (entries 6,7) appeared promising in the screening experiments, they were avoided as compound **3** could not be isolated free of these solvents and these solvents are incompatible with organometallic reagents used in the subsequent aziridinium chemistry step. Diglyme provided an excellent conversion (97−99%) in 18−20 h at 130−135 °C (entries 8,9). Use of these reaction conditions for N-alkylation of secondary amines has been reported.[9] After further optimization the amount of BADMA required was lowered to 1.2 equiv.

Alkylation of **2** in diglyme is a heterogeneous reaction. Laboratory studies on this reaction indicated that the type of K_2CO_3 used, the amount of water, the agitation rate, and the rate of heating of the reaction mixture were important factors influencing the reaction outcome. In general, small particles of anhydrous grade K_2CO_3 were more preferable than large, spherical hydrated K_2CO_3. The former allowed for rapid trapping of HBr and did not add water burden to the reaction mixture. Laboratory studies also showed that presence of 5% (v/v compared to diglyme) water led to a slower and inefficient reaction (50−60% conversion vs 98% conversion without the added water). A slow, programmed heating of the reaction mixture over a period of 3 h from room temperature to 128 °C was recommended so that the rate of HBr generation would not exceed the rate of its neutralization by K_2CO_3 under these heterogeneous conditions. Control experiments showed that rapid heating and/or inefficient trapping of the HBr formed during the reaction led to the cyclic acetal byproducts.[18] Other expected side products such as tetra-N-alkylated **2**, O-alkylation product, and N-demethylation impurities were not detected under these stressed conditions. Finally, a rapid agitation of the reaction mixture allowed for improved suspension of the K_2CO_3, resulting in efficient removal of HBr.

The above laboratory findings led to the following plant recommendations for efficient scale-up of this reaction. Commercially available milled anhydrous K_2CO_3 (screened through a #23 or #28 screen) was used in the plant. The rate of heating was limited to about 0.5−1 °C/min to avoid the rapid heat up. The rate of reaction under these conditions was rapid during the first 5 h and then slowed. The last 10% of reaction required about 10 h for completion (see Figure 1). On the basis of reaction calorimetery studies, the addition of BADMA to the diglyme solution of **2** was shown to be mildly exothermic (adiabatic temperature rise of 2.9 °C, and heat of reaction −1.1cal/g) and in the subsequent heat up an adiabatic temperature rise of 75 °C was detected. The water content of **2** was controlled (0.1% by Karl-Fisher), and water formed during the reaction via neutralization of HBr with potassium carbonate was absorbed by anhydrous potassium carbonate. It is worth noting that under these conditions, distillation of a water−diglyme azeotrope (literature bp 100 °C at 760 mm, 78% water) was not seen. The agitation rate was equipment dependent and a minimum agitation was determined prior to the use of equipment as this reaction was scaled up in three plants with about 10-fold variation in the batch size.

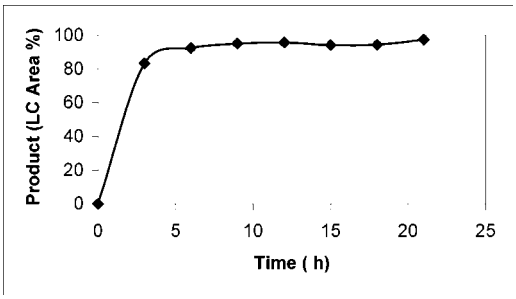


Figure 1. **Progress of reaction of 2 with BADMA in the presence of milled K_2CO_3.**

Since compound **3** is a viscous liquid, we decided to use it in solution for the subsequent steps. Purification via vacuum distillation was avoidable, and we chose that path. In the workup step, inorganic solids were filtered and washed with toluene. Then **3** was extracted with dilute sulfuric acid. The aqueous acidic layer was saturated with sodium chloride, neutralized with NH_4OH to pH 9−10 (use of NaOH in this step resulted in emulsion and pH control proved difficult) and extracted with toluene. Because of complete water miscibility of diglyme, saturation of the aqueous layers with NaCl was necessary to minimize product loss to the aqueous layer. Removal of toluene from the organic layer via distillation provided **3** as a 45−50% w/w solution in diglyme, suitable for the next reactions and which could be stored under nitrogen atmosphere for about 12 months without any decomposition or color change. This process was scaled up to 160 kg to produce product of consistent quality in about 90−95% molar yield.

To avoid lengthy acid−base workup an alternate distillative procedure was also developed, wherein after reaction completion the solids were filtered and washed with toluene as above. Unreacted BADMA was removed by vacuum distillation (20 mm, 120 °C). The reaction mixture was cooled to room temperature and filtered to remove any precipitated solids. Although the yield was comparable, this approach was abandoned because pilot-plant isolated **3** had an intense dark-brown color (light-colored solutions of **3** facilitate the observation of color change during the formation of lithium alkoxide **14** upon treatment with *n*-HexLi in the subsequent steps). Also, higher levels of impurities were

(18) During stress studies, this cyclic acetal was isolated and fully characterized (NMR, MS, IR).

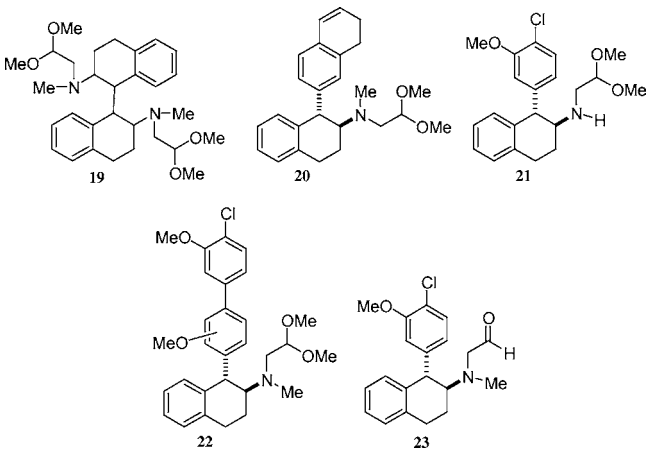


Figure 2. **Impurities isolated in aziridinium ring-opening reaction.**

observed due to the prolonged vacuum distillation operation in the pilot plant.

3. Synthesis of 5. This is a critical multistep conversion with minimal prior mechanistic understanding. The laboratory procedure identified earlier gave variable yields (45−60%) in the key reaction sequence from **3** to **5**. Our initial efforts to improve the reaction yield by varying standard reaction parameters (concentration, mode of addition, reaction time/temperature) led to only minimal improvement in the outcome. During this initial laboratory work some major byproducts identified (LC−MS, or via isolation) from this reaction sequence were α-tetralone and compounds **19**−**23** (Figure 2). Additionally, the presence of piperazinium salts[10,11] resulting from the dimerization of aziridinium ion were also confirmed by LC−MS. Compound **22** originated from reaction of dimeric Grignard reagent (up to 15% by HPLC area, formed especially in the presence of *p*-toluenesulfonyl chloride) with **16**, whereas **23** probably resulted from hydrolysis of **5**. Lab work also indicated that a large excess of **4** typically resulted in higher amounts of **21**. The mechanism for formation of **19** and **20** is unclear. In earlier studies it was proposed that aziridinium chloride **16** was the reactive intermediate. However, we subsequently identified that chloroamines **17** and **18** are formed during the preparation of **16** and influenced the course of reaction. A detailed mechanistic investigation of this reaction has been published recently.[11]

Thus, though small discrete pieces of the conversion of **3** to **5** were understood, the overall understanding remained inadequate after the initial work. Hence, more detailed studies were undertaken. The conversion of **3** to **5** involves several major distinct steps as depicted in Scheme 4: (a) deprotonation of **3** to form the lithium alkoxide **14**, (b) reaction of the alkoxide with an activating reagent to form intermediate **15a**, (c) in situ generation of aziridinium ion **16**, which exists in equilibrium with chloroamines **17** and **18**, and (d) opening of the aziridinium ion with Grignard reagent **4** to form product **5**. The discussion herein is focused on the salient aspects of process development, optimization, and scale-up of the above steps of this reaction.

A. Deprotonation of 3. Of several different bases screened for deprotonation, initially ^{n}BuLi (2.5 M solution in hexanes) was the reagent of choice in the alkoxide-generation step because of quantitative conversion of **3** to **14** at low temperature and formation of a homogeneous reaction mixture. Butane gas formed at low temperature (−10 to −30 °C) remained dissolved in the reaction solvents and was liberated during subsequent reaction steps, which

Scheme 4. **Aziridinium ion formation**

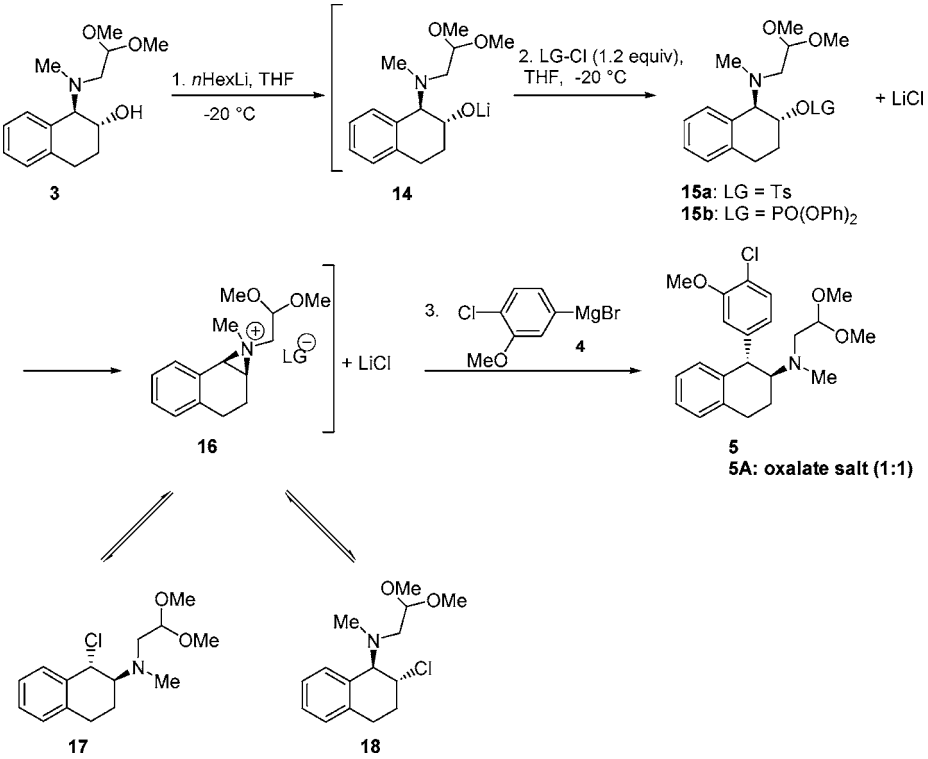
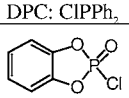


Table 2. **In-solution yields for conversion of 3 to 5 with phosphorus activating reagents**[a]

Activating Reagents	LC In Solution Yield (%)
DECP: $ClPO(OEt)_2$	80
DPCP: $ClPO(OPh)_2$	84
DPPC: $ClPO(Ph)_2$	82
DPC: $ClPPh_2$	0
	20
$POCl_3$	2.6

[a] Experiments were conducted in the presence of CuCl·2LiCl (5 mol %) for reasons discussed later in this manuscript.

necessitated appropriate controls throughout this procedure. Due to safety concerns on large scale, and due to the precautions required in the usage of this reagent, ^{n}BuLi was substituted with *n*-hexyllithium (*n*-HexLi, 2.5 M in hexanes) as the byproduct hexane from this reagent posed significantly reduced safety concerns. 1,10-Phenanthroline was added as an indicator to the reaction mixture to facilitate observation of the endpoint of *n*-HexLi addition to a solution of **3** in THF (reaction mixture color change from pale yellow to deep red). On-scale appropriate equipment modifications were put in place for a facile monitoring of this change (site glass with a recycling loop). Laboratory stress studies had established that addition of up to 10% of excess *n*-hexyllithium did not affect the reaction yield and purity. However, an undercharge of *n*-hexyllithium led to unreacted **3**, which interfered with the isolation of **5**. Thus, slight overcharging was practiced for this reaction.

B. Activating Reagents. In published work *p*-TsCl was used as an activating reagent. Among other sulfonyl chloride activating reagents[12] screened in our laboratory, *p*-TsCl remained the reagent of choice. However, variable yields and higher amounts of dimer **25** were obtained, especially in the presence of the copper catalyst used to improve the reactivity of the Grignard reagent (vide infra). A variety of other (nonsulfonyl chloride) activating reagents were investigated of which phosphorus-based activating reagents gave the most promising results (Table 2). From commercially available phosphorus reagents diphenyl chlorophosphate (DPCP) was selected for scale-up for the following reasons: (a) a complete consumption of **3** (unlike with *p*-TsCl, where about 2−4% of unreacted **3** was always detected); (b) overall highest in-solution yield; (c) about 33% less dichloro dimer **25** formed (more details later) as the side product from **4** which lowered the usage of expensive **4**; (d) a minimal formation of **22**.

Although other chlorophosphates were equally effective as activating reagents, DPCP was preferred due to its lower toxicity and moderate cost. Diethyl chlorophoshate (DECP) is highly neurotoxic, and hence it was not explored further despite obvious advantages of atom economy and the absence of phenol in waste streams. DPPC was found to be comparable to DPCP, whereas DPC and $POCl_3$ were less effective. DPC failed to provide any product, presumably reflecting the poor leaving-group ability of the trivalent verses a pentavalent phosphorus. $POCl_3$ on the other hand has "three" leaving groups, and this probably led to other reactions resulting in very low yield. In the DPPC reaction, an insoluble precipitate of diphenyl phosphinic acid formed at the end of reaction, which could be conveniently removed by filtration. This, however, did not lower the workup burden for this process. Because of the higher cost of the reagent and the need for disposal of diphenyl phosphinic acid solid waste, the use of DPPC was not pursued further. Potential recycling of this reagent offered only minimal cost savings.

C. Generation and Stability of 16. The formation of **16** was extensively studied by ^{1}H, ^{13}C, ^{15}N (with ^{15}N-labeled **3**), and ^{31}P NMR (for DPCP) as well as by ReactIR. Due to scant literature information on ^{15}N NMR chemical shifts and IR wavenumbers for aziridinium ions, an indisputable interpretation of experimental data from these experiments alone was difficult. These data will be published elsewhere. However, on the basis of the combination of all spectroscopic data above, HPLC chromatograms (of in-process and isolated materials) and isolated yield the following conclusions were drawn. These allowed for an identification of the preferred process conditions described in the Experimental Section. The conversion of **14** to **15a**/**15b** was rapid at −20 °C, and no byproducts from unreacted alkoxide **14** with **15a/15b** were observed in the reaction mixture. In the case of DPCP, ^{31}P NMR showed that **15b** (δ −7.6 ppm, doublet, $J = 6.5$ Hz)[13] formed and stored at −20 °C was stable for 6-8 h. Only upon warming to room temperature was the formation of lithium diphenyl phosphate (δ −6.8 ppm) observed. On the basis of ^{1}H NMR and ^{13}C NMR studies it was established that **16** in the reaction mixture existed in equilibrium with chloroamines **17** and **18**. Compound **18** was isolated and characterized. In contrast, **15a** was stable at −25 °C for about 1 h, and upon warming to −5 °C, **16**, **17**, and **18** were formed. Compounds **17** and **18** are converted in situ to aziridinium ion **16**, which reacts with **4** to form **5**. Between **17** and **18**, the latter is about an order of magnitude less reactive than the former towards formation of **5**.[11] In fact, the existence of such a "chloramine sink" was beneficial as it prevented the buildup of aziridinium ion in solution and helped to reduce the formation of dimeric piperazinium byproducts.

Finally, proof that the conversion of **3** to **16** was near quantitative was obtained via the following control experiments (in triplicate). Reaction of deschloro-**4**, i.e., 4-methoxyphenylmagnesium bromide with **16** formed under the optimum conditions described in the Experimental Section afforded the corresponding product (deschloro-**5**) in overall 95% isolated yield. These results assured us that with DPCP the yield for the aziridinium formation step (**3** to **16**) was 95% or higher.

D. Grignard Reagent (4). This was prepared from 5-bromo-2-chloroanisole (**26**) using the standard procedure (addition of 5-bromo-2-chloroanisole to a well-agitated suspension of magnesium metal turnings in THF). A flat-bottom reactor with efficient agitation provided a large surface area for this heterogeneous reaction. With conical-bottom reactors Mg turnings accumulated at the bottom

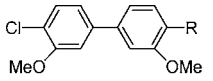
Table 3. **Role of Cu(I) catalyst in the formation of 5 from 3**

Grignard reagent	catalyst[a]	product (% yield)[b]
4	none	**5** (60)
deschloro-**4**	none	deschloro-**5** (95)
4	CuCl·2LiCl	**5** (80)
deschloro-**4**	CuCl·2LiCl	deschloro-**5** (94)

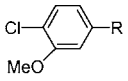
Grignard reagent	catalyst[a]	ratio **5**:deschloro-**5**
4 + deschloro-**4** (1:1)	none	1:5.4
4 + deschloro-**4** (1:1)	CuCl·2LiCl	1:1.7

[a] 5 mol % catalyst. [b] Solution yields via HPLC.

valve, resulting in a slow or an incomplete reaction. The presence of air during the reaction led to the formation of phenol **29** and other dimeric biphenyl impurities (**24** and **25**). Hence, before charging **26** the reactor was evacuated and flushed with nitrogen. The reaction was reliably initiated by adding about 7% of the total charge of **26** (as a solution in THF) to a suspension of Mg chips in THF. To check for reaction completion, a portion of the reaction mixture was quenched in methanol and assayed for 2-chloroanisole (**27**) content by GC versus unreacted **26**. Cooling this solution to 0−5 °C resulted in a gel that dissolved upon warming to 30−35 °C. Once formed, the reagent (ca, 1.2 M in THF) could be stored at room temperature under nitrogen atmosphere for 4 months without loss of titer.



24: R = H
25: R = Cl

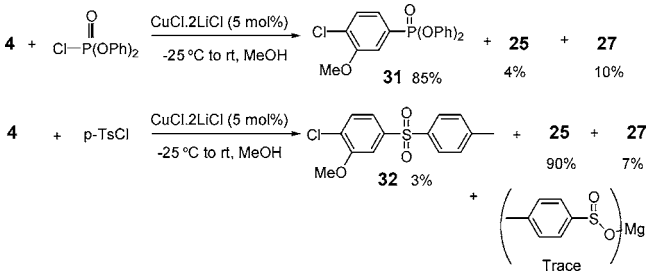


26: R = Br
27: R = H
28: R = Me
29: R = OH
30: R = OMe

E. Effect of Copper Salts on the Reactivity of 4 with 16.[19] Even under the optimized aziridinium formation conditions the yield for the conversion of **3** to **5** remained around 60−65% with the remaining mass in many byproducts. The control experiments reported above clearly indicated that the formation of **3** to **16** was high yielding (>95%). Thus, the loss of yield was in the conversion of **16** to **5**. The control experiments also suggested that with a more reactive nucleophile (i.e., deschloro-**4**) overall conversion of **3** to the corresponding product (deschloro-**5**) can be high (95%). Thus, it was concluded that enhancement of the reactivity of **4** was needed, and research efforts were directed towards that end. Copper is known to influence the reactivity of Grignard reagents with different electrophiles.[14] Of the several copper salts screened,[15] addition of a catalytic amount (5 mol %) of CuCN and CuCl (either to **4** or to a solution of **16**, or to a mixture of both) increased the nucleophilicity of the Grignard reagent and improved the solution yields of the aziridinium ring-opening reaction by 20−25% (Table 3). It is plausible that a more reactive cuprate might be generated in situ by transmetalation of **4** with Cu(I) salts. Competitive kinetic experiments (last two entries in Table 3) clearly demonstrated that Cu significantly enhances the nucleophilicity of **4** and hence favors the formation of **5** compared to that of deschloro-**5**.

Other observations of interest are the following: Cu(II) salts gave about 5−10% lower yield than Cu(I) salts. Compared to CuCl alone, a soluble form of copper reagent in THF formed by the addition of LiCl to CuCl gave reproducible yields and was more amenable to scale-up. Hence, this was used for the production process. Although CuCN·2LiCl gave about 3−5% more in-solution yield than CuCl·2LiCl, the use of CuCN on scale was avoided due to toxicity and waste disposal issues. Addition of more than 5 mol % CuCl·2LiCl did not further improve the yield and also made workup difficult due to emulsion formation.

When the Grignard reagent was mixed with activating reagents to simulate stressed conditions in the absence of air and in the presence of copper salts (CuCl and its THF soluble LiCl complex), only small amounts of phenol **29** and dichlorodimer **25** formed when DPCP was used as the activating reagent. However, when *p*-TsCl was used as the activating reagent under similar conditions, dichlorodimer **25** was formed as the major product along with magnesium *p*-toluene sulfinate as a byproduct. A very small amount of tosylated product **32** was obtained. In contrast, DPCP did not enhance reductive dimerization, but it slowly reacted with **4** to form the corresponding phosphate adduct **31**. This difference in reactivity of DPCP and *p*-TsCl towards **4** was one more factor that led us to select DPCP on scale. Thus, with DPCP the amount of **4** was reduced to 1.2 equiv from approximately 2 equiv needed with *p*-TsCl for an optimum yield of **5**. Under the optimum conditions, the former offered higher yields of **5**.



F. Order of Mixing. Once the aziridinium intermediate was generated, it could be reacted with **4** in three different ways: (a) direct addition of solution of **4** to a solution of **16**; (b) inverse addition of **16** to **4**; and (c) mixing streams of **4** and **16** in a continuous mixing reactor. All three of these modes of addition were studied for improving the yields and processability of this reaction. These studies also showed that the copper catalyst could be added to a solution of **4** or **16** before mixing the solutions of **4** and **16** with practically no impact on the outcome.

(a) Direct Addition. For the first-generation *p*-TsCl process, the direct-addition mode gave better yields. To avoid formation of the relatively less reactive chloroamine **18**,[11] the solution of **15a** was held at −20 °C, and the copper catalyst was added prior to adding **4**. Since the reaction of **4** with **16** and chloroamines was relatively slow at −20 °C, the reaction mixture was rapidly warmed to 30−35 °C to

(19) Organolithium and organozinc reagents were evaluated in place of Grignard reagents. The former two gave poor yields and/or many byproducts; hence, the decision was made to optimize the Grignard reagent process.

speed up the desired reaction.[16] If the reaction mixture was not warmed promptly after the addition of **4**, higher amounts of **19**, **20**, **25**, and piperazinium dimers were formed. Under ideal conditions about 65−75% solution yield of **5** was obtained via the direct-addition process. The adiabatic temperature rise for the reaction of **4** with **16** was 50 °C. On-large-scale heat-transfer manipulations were tedious and demanding due to the initial need of keeping the reaction mixture cooler during addition of **4** and then the need to heat to 30−35 °C. When **15a** was subjected to inverse addition in the lab, about 10% lower solution yield of **5** was obtained. Here, large amounts of byproducts from **4** were generated, necessitating an excess of **4** for consumption of **16**. This in turn led to workup difficulties, leading to lower isolated yields.

(b) Inverse Addition. This mode proved to be best when DPCP was used as an activating reagent. The conversion of phosphate **15b** to **16** and further to chlooramines (**17**,**18**) was very slow at −20 °C. Thus, the undesired formation of chloramine **18** was minimized when cold **15b** was added to a solution of **4** (containing the catalyst) maintained at 20−25 °C. Unlike the direct addition mode, an excess of **4** is available for reaction with **15b** in the initial phase of the reaction. Typical solution yields of **5** obtained in this procedure were 80−85%. Heat exchange in the inverse addition mode was well controlled, resulting in reproducible yields. This process was readily scaled up in three plants without any significant heat transfer issues.

(c) Continuous Mixing. Mixing streams of the Grignard reagent containing the catalyst and the aziridinium reaction mixture in a static mixer equipped with a heat exchanger also gave 80−85% yield. The proof of principle was demonstrated on a 200-g-scale reaction in the laboratory. This process was not scaled up in the pilot plant as the inverse addition process described above allowed for a rapid scale-up with the available plant equipment and utilities. Note that this continuous mixing procedure worked well for *p*-TsCl as well as for DPCP processes.

G. Workup. This is a multistep transformation with several reagents, byproducts, and side products. An immense cost of raw materials as well as processing is involved at this stage of the process. Thus, it was very important to identify a sleek and reproducible isolation procedure for good-quality **5**. After completion of reaction, aqueous ammonium chloride solution was added to quench the unreacted Grignard reagent. Mg and Cu salts did not precipitate with the NH_4Cl workup (aqueous layer, pH 8). Copper chloride formed the blue $[Cu(NH_3)_4]^{+2}$ complex with ammonium chloride that remained in the aqueous layer, thus efficiently removing it from **5** in the organic layer. Other quenching reagents such as phosphate buffer, sodium acetate, acetic or dilute sulfuric acid were unsatisfactory due to precipitation of salts and emulsion formation.

For the *p*-TsCl process an acid−base workup was needed to isolate **5**. The organic extract was treated with 1 N H_2SO_4, and then the acidic extract was neutralized with 10% NH_4OH to pH 5.0−5.5. Since **5** is less basic (pK_a of **5** was determined to be about 6.0), other more basic impurities remained dissolved in the water, and the pure product was extracted into MTBE. This tedious acid−base workup was unnecessary with DPCP because the solution yield of **5** was high and the amount of neutral dimeric and other side products was low. This was another criterion that further supported the selection of the DPCP process for the commercial process. The procedure used for large-scale work is available in the Experimental Section.

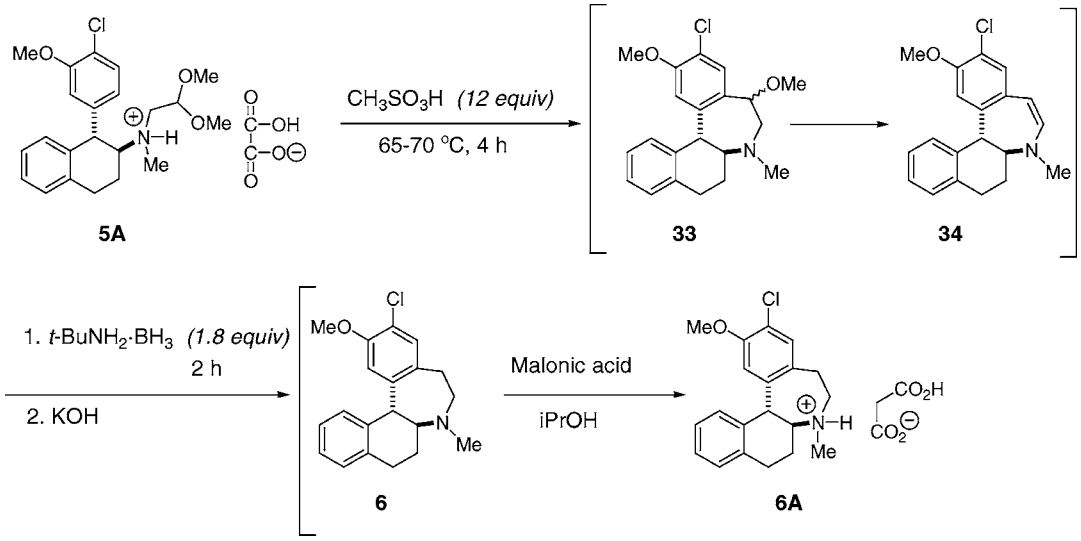
Environmental aspects can play in important role in the commercial development of a process. For the DPCP process the amount of phenol generated during the workup was closely monitored as the plan was to remedy the aqueous waste by treating it with microorganisms. These organisms are affected by the antimicrobial phenol generated in the process via hydrolysis of DPCP. The amount of phenol in the aqueous waste streams was <0.5%, which was an important consideration for waste management.

Aqueous sodium hydroxide could be used to remove the small amount of phenol present in organic extracts, but emulsions were formed and the color of organic extracts darkened under basic conditions. This was avoided by a controlled NH_4Cl quench that minimized their formation. Also, residual inorganic salts were sometimes carried into the isolation of **5** as a salt and gave product with acceptable impurities but lower wt % purity. To overcome this, an aqueous NH_4Cl quench followed by aqueous sodium acetate washing of the organic extract was developed that prevented emulsions and facilitated the removal of inorganic salts. A final 5% aqueous sodium chloride wash of the organic extract gave a stream suitable for direct crystallization of **5**.

H. Salt Formation of 5. In the early phase of this work **5** obtained as an oil was used for further reactions. However, this practice left only one isolation via crystallization throughout the process, i.e. the isolation of penultimate intermediate **6**. Although this was practiced for the initial amounts of API, in the long range it was desirable to have a process that would allow isolation of **5** as a solid of known quality. This would also allow for purification as well as extended storage. Thus, a tremendous amount of effort was exerted in identifying an efficient purification/isolation of **5**. Of dozens of organic and inorganic acids screened in a number of solvents, only oxalic acid gave a crystalline salt in high yield and purity.

Isolation of the oxalic acid salt of **5** was unique. For example, various combinations of alcoholic solvents (MeOH, EtOH, ^{i}PrOH, ^{n}BuOH, ^{i}BuOH, ^{t}BuOH) or etheral solvents (THF, MTBE, DME, diglyme) or esters (MeOAc, EtOAc, ^{i}PrOAc) and hydrocarbons (hexanes, heptane, toluene) were unsuitable for direct crystallization of **5A**. Precipitation of oxalic acid salt from ethers and hydrocarbon solvents was also difficult. On the other hand, a combination of MTBE and ^{i}PrOH (1:1) was found to be the best system for crystallization. Via this process neutral dimeric impurities as well as polar impurities were purged efficiently. Seeding of the crystallization mixture at room temperature and then gradual cooling to 0−5 °C and a hold time of about 18 h were critical to get the maximum isolated yield of quality product. The presence of excess water and inadequate

Scheme 5. **Cyclization and reduction of 5A and 6A**



crystallization time led to lower recovery of the product. Use of anhydrous oxalic acid improved the yield by 2−3% at the expense of purity. The amount of water present in oxalic acid dihydrate was optimal and gave **5A** in consistently good yield (85−90% recovery of **5**) and purity. On average, about 8−12% product was lost in the mother liquor.

Residual isopropyl alcohol in **5A** forms an isopropylated impurity (**37**) in the cyclization/elimination reduction sequence, which is difficult to purge and which contaminates the final product. Hence, the amount of residual isopropyl alcohol trapped in **5A** was controlled to less than 0.5% w/w by vacuum-drying at 50−60 °C.

Finally, isolation of **5** as an oxalate salt (**5A**) led to an unexpected result. It was found that starting with **12** of 94% ee, **5A** with 98−99% ee was isolated after crystallization. Thus, formation of **5A** not only removed other chemical impurities but also purged diastereomeric impurities and significantly improved the enantiomeric purity of **5A** without the use of an expensive resolving reagent. Since **12** was always obtained in high ees, this finding was not put to use for commercial purposes.

I. Scale-Up of Aziridinium Chemistry Experience. Our first-generation process involved ^{n}BuLi/*p*-TsCl (1.2 equiv)/**4** (1.3 equiv)/CuCN·2LiCl (10 mol %) and a direct addition mode that gave an average solution yield of about 65%. Upon acid−base workup followed by oxalate salt formation, **5A** was isolated in about 50−60% yield. This process was scaled up to 50 kg. A robust second-generation process was sought because of irreproducible yields, scale-up difficulties resulting from rapid warming requirements, acid−base workup, and issues with cyanide waste from CuCN.

In our second-generation process, *n*-HexLi/DPCP (1.1 equiv)/**4** (1.2 equiv)/CuCl·2LiCl (5mol %), with inverse addition mode gave solution yields of about 85%. After NH_4Cl quench, followed by MTBE extraction and 5% NaOAc and NaCl washes, the product was directly crystallized from MTBE−IPA (1:1) in ∼70% yield. This process was scaled up to 100+ kg of **3** per batch.

4. Formation of 6A. The laboratory conditions for the cyclization/elimination steps, i.e., conversion of free base **5** to **34**, derived from the supply-route plant conditions where racemic **6** was made via an alternate route, used CH_2Cl_2 as the solvent with $MeSO_3H$ or sulfuric acid as the reagents that caused cyclization/elimination. The reaction sequence for Friedel−Crafts cyclization of **5** proceeded via intermediate **33** (structure confirmed by LC−MS) which eliminated methanol to form enamine **34**. The reaction mixture was partially neutralized by adding a slurry of $NaHCO_3$ in CH_2Cl_2, and then **34** was reduced in situ with *tert*-butylamine borane complex (TBAB) to amine **6** (Scheme 5).

The reaction of free base **5** with methanesulfonic acid to give enamine **34** in CH_2Cl_2 took about 3 days for completion (<2% **33**) and required 16 volumes of CH_2Cl_2. The higher dilution was needed to minimize the dimeric/polymeric byproducts. Also the neutralization of the acidic reaction mixture with $NaHCO_3$ before the addition of TBAB led to severe frothing which was difficult to control on scale. The controlled addition of $NaHCO_3$ as a CH_2Cl_2 slurry was time consuming and equipment constraining. The prolonged reaction and processing times seriously limited the throughput for this step. Finally, due to environmental concerns with the use of CH_2Cl_2 on scale, an alternate nonhalogenated solvent was required for the reaction sequence. In fact this provided an opportunity to arrive at a better process that eliminated all these restraints.

Several acids such as sulfuric acid, BF_3·AcOH, AcOH, formic acid (which in principle can serve as a Brønsted acid as well as a hydride source), P_2O_5-methanesulfonic acid (Eaton's reagent), *p*-toluenesulfonic acid, and camphorsulfonic acid were evaluated for the cyclization/elimination reaction sequence in a variety of solvents such as sulfolane, diglyme, toluene, NMP, MeCN, and ^{i}PrOAc. Interesting results from these screening experiments are summarized in Table 4. Although Eaton's reagent, and the sulfuric acid/sulfolane system provided desirable conversions of the free base **5** to **34**, they were not pursued as more efficient conditions were discovered with neat methanesulfonic acid (entry 6). Sulfolane with about 12 equiv of sulfuric acid at 70−75 °C for 3 h gave a clean conversion of **5** to **34**. This reaction mixture was then subjected to typical transfer

Table 4. **Friedel−Crafts cyclization/elimination and reduction of 5 or 5a to 6**

entry	conditions	results/comments
	A. Cyclization/Elimination	% Conversion to **34**
1	camphorsulfonic acid (1.8 equiv)/$PhCH_3$, reflux, 24 h	5
2	formic acid (excess), reflux, 24 h	0
3	Eaton's reagent (excess), rt, 5 h	95
4	diglyme/ H_2SO_4 (12 equiv), rt, 4 h	46
5	sulfolane/H_2SO_4 (12 equiv), 70−75 °C, 3 h	98
6	$MeSO_3H$ (12 equiv), 65−70 °C, 4 h[a]	99
	B. Reduction[b]	% Conversion to **6**
7	polymethylhydrosilane, rt, 24 h	0
8	Et_3SiH, rt, 24 h	0
9	HCO_2NH_4/Pd/C, H_2O, rt, 12 h	60
10	$Na_2HPO_4/NaBH_4$ (5 equiv)/^{i}PrOH−H_2O, rt, 6 h	53
11	$NH_4OH/NaBH_4$ (5 equiv)/^{i}PrOH−H_2O, rt, 6 h	80
12	TBAB (2.0 equiv)/MTBE, 5−10 °C, 2 h	99

[a] **5A** was used instead of free base **5**. [b] Reaction conducted with mixture from entry **5**.

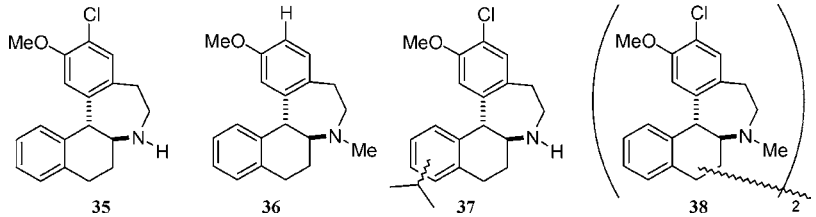


Figure 3. **Impurities identified in 6.**

hydrogenation and hydride reduction conditions. The main challenge associated with using hydride reagents was the high acidity of the reaction medium which had to be moderated by addition of a base prior to the addition of the hydride reagent to avoid a violent reaction with hydrogen evolution. Although sodium borohydride showed good results, a complete conversion of **34** to **6** could not be accomplished by adding excess reagent. With TBAB a complete conversion was obtained (<1.0% of **32**).

Finally, we discovered that when **5A** itself was added directly to $MeSO_3H$ (12 equiv) and heated to 55−65 °C for 2 h, a near quantitative conversion to **34** was observed. Since $MeSO_3H$ is a stronger acid than oxalic acid, **5A** is converted to the $MeSO_3H$ salt which then undergoes cyclization. This procedure precluded the need of any solvent and the necessity of converting solid **5A** into a free base. Furthermore, the reaction time was shortened to a few hours. As dissolution of solid **5A** in methanesulfonic acid was rather slow, efficient agitation and warming of the reaction mixture was necessary for complete reaction. The viscous reaction mixture was cooled to 0−5 °C and diluted with MTBE. A suspension of TBAB (1.1 equiv) in MTBE was added slowly to the reaction mixture to reduce **34** to **6**. Here too, of various reducing agents evaluated, TBAB provided a fast and complete reduction. The acidity moderation of the reaction mixture by the *tert*-butylamine in the TBAB complex, and its solubility in organic solvent made it an ideal reagent for the reduction step. After dilution with water (exothermic) the reaction mixture was quenched with 25% aqueous KOH solution. Use of NaOH led to formation of less soluble sodium oxalate and emulsions. As potassium oxalate has higher water solubility, KOH was the base of choice which enabled an efficient removal of oxalic acid.

Some impurities formed in trace amounts were identified on the basis of LC−MS studies and are shown in Figure 3. Their genesis was traced to the following. When lumps formed during the charge of **5A** to $MeSO_3H$ (e.g., inefficient agitation, rapid addition, cooler temperature), unreacted **5** was carried over in isolated **6**. Analyses of several samples of isolated **6** showed that the des methyl impurity **35** and the des-chloro impurity **36** originated in the aziridinium chemistry step as well as in the cyclization/reduction sequence. Typically impurities **35**−**37** formed in small (<0.5% amounts) and were removed during the purification of **6** and/or **1**. The isopropyl derivative of **6** (**37**) was correlated with residual ^{i}PrOH content in **5A**. Impurity **37** when formed in >0.5% could not be easily purged from **6** or **1**; hence, it was controlled by limiting the ^{i}PrOH content to ≤0.5% in **5A**. Dimeric impurities **38** were also identified, and their formation could be lowered by using a higher temperature (70−80 °C) during the conversion of **5A** to **34**, but the higher temperature led to more **37**. Since **38** could be purged more easily than **37** in the subsequent purifications, the higher temperature conditions were not used.

Crystallization of 6. Since penultimate intermediate amine **6** is an oil, a crystalline salt was desirable to aid its purification. Of several inorganic and organic acids screened for salt formation with **6** under a variety of conditions, (+)-DTTA and malonic acid gave the best yield and purity. Since compound **6** was of high chiral purity to begin with, the use of expensive chiral (+)-DTTA was undesirable for a non-chiral purification. Hence, readily available, inexpensive malonic acid was chosen for optimization/scale-up. Our criteria for salt selection were yield and quality (to meet or exceed **6** made via the supply route where it was isolated as (+)-DTTA salt). Specific optimization was needed to ef-

Table 5. **Salt formation Screening of 6[a]**

salt/conditions	% recovery	LC area % purity	**35** %
(+)-DTTA (^{n}BuOH:H_2O, 9:1)	80	99.5	0.16
HCl (MeCN)	56	98.4	0.11
HCl ($PhCH_3$)	89	93.8	0.38
malonate (^{i}PrOH:H_2O, 95:5)	76	99.6	0.10

[a] Compound **6** used for these experiments had LC area % purity of 93.0% and 0.67% of **35**.

ficiently purge desmethyl impurity **35** (Table 5) via the malonate salt process. Among several solvents evaluated, aqueous ^{i}PrOH was the solvent of choice. A higher amount of water (>5%) led to high-quality product with a corresponding increased loss of product to the mother liquor. Impurities resulting from dimerization of **5A** were removed by crystallization in ^{i}PrOH−H_2O (95:5). However, since these impurities were controlled by process conditions, the efficiency for their removal during the salt-formation step was not critical. For purging impurities for a typical **6** generated via the chosen process ∼97:3 ^{i}PrOH:H_2O was ideal. Via this procedure (described in the Experimental Section) the yield for the isolation of **6A** was 90%. It is interesting that the stressed conditions in the laboratory showed that the isopropylated impurities in >0.5% could not be removed by IPA−water crystallization. They could be removed only after treating isolated **6A** in THF, albeit with a large loss of yield. These isopropylated impurities **37** cannot be purged from **1**, even after recrystallization, whereas dimeric impurities **38**, if present, were purged out in the final recrystallization step. Both the reaction and the isolation were successfully implemented in three plants where the overall yields for the conversion of **5A** to **6A** were 80−85%.

Final Demethylation Step. Conversion of 6 to 1. The chemistry used in this step, BCl_3-mediated selective O-demethylation of **6**, was kept the same as in the supply route to maintain the process lock and match the purity as well as the polymorphic profile of the drug substance. Advantages of BCl_3 were a clean reaction and direct isolation of the desired hydrochloride salt in high yield. Salt **6A** was converted to **6** by treatment with 25% NaOH at 40−50 °C in toluene. and the toluene extract was distilled to remove water as an azeotrope. The reactor used for the BCl_3 reaction was equipped with a condenser maintained at −20 °C to condense BCl_3 (bp 12 °C) but not MeCl (bp −24 °C). BCl_3 was charged as a liquid above the batch surface, and as the addition was exothermic, the batch temperature was maintained below 50 °C. The reaction mixture was heated at 60−70 °C for 18 h to obtain ≥99.5% conversion. The batch was cooled to room temperature, and excess BCl_3 as well as the borate complex was quenched by adding in portions to excess MeOH. After distillation of $B(OMe)_3$, MTBE was added to precipitate **1**. A final crystallization of **1** from a MeOH/MTBE mixture gave Sch 39166 in 99+% chemical and >99% chiral purity.

Summary

The process for the key starting material **12** from readily available α-tetralone was developed and optimized to obtain an overall 34% via a commercially feasible route. Next, the N-alkylation step was optimized wherein the reaction time was reduced and 90% yield was realized. The aziridinium ion based synthesis was successfully scaled in three different plants to produce several hundred kilograms of Sch 39166. This synthesis highlights the formation and regio- and stereoselective opening of an aziridinium ion with a Grignard reagent. The stability and reactivity of the aziridinium ion was studied to improve the reaction yield. A catalytic amount (5 mol %) of CuCl·2LiCl complex improved the nucleophilicity of the Grignard reagent. In this sequence of four reactions, an overall isolated yield of 70% was achieved without any need of chromatographic purification. Another key step where two reactions were telescoped was the conversion of **5A** to **6A**. Here, by careful selection of reaction parameters the processing time was lowered to 2 days from 7 days, throughput was improved 4-fold, and the reaction yield was improved by 20%. Furthermore, the use of environmentally unacceptable CH_2Cl_2 and expensive (+)-DTTA was eliminated. After final demethylation followed by recrystallization, the hydrochloride salt was isolated from α-tetralone in an overall yield of about 20%.

Experimental Section

Melting points are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded in $CDCl_3$ or $(CD_3)_2SO$ solutions. Unless specified otherwise, all reagents and solvents were used as supplied by the manufacturer. All reactions were conducted under an inert N_2 atmosphere.

***trans*-(±)-2-Bromo-1-hydroxytetralin (9).** To a glass-lined reactor were charged ethanol (400L) and sodium borohydride (7.20 kg, 190 mol) at ambient temperature. The reactor was evacuated and purged twice with nitrogen to reduce the oxygen concentration. Slowly, α-tetralone (80.4 kg, 550 mol) was added to the $NaBH_4$ suspension over a period of about 30 min (**Caution! Hydrogen evolution!**) without cooling. The batch temperature increased to about 45 °C. After the completion of addition, the solution was heated to 50−55 °C for 3 h and sampled for reaction completion. Another reactor was charged with water (240 L), evacuated and purged twice with nitrogen. The reduction reaction mixture (precooled to 20−25 °C) was added over a period of about 20 min to water without cooling. Ethanol was distilled under reduced pressure (45−50 °C at 120−160 mbar pressure) to a residual volume of about 120 L. The batch was cooled to 20−25° C, diluted with toluene (240 L) and agitated, and the water layer was separated. The aqueous layer was extracted twice with toluene (2 × 80 L), and the combined toluene phases were washed with water (80 L). This solution of **7** (98−100% in-solution yield) was used directly for the next stage.

The toluene solution of **7** was atmospherically concentrated to a volume of about 305 L at normal pressure. The water content of the batch was determined by KF titration (0.05%). The solution was cooled to 60−70 °C, and

p-toluenesulfonic acid monohydrate (400 g, 2.1 mol) was added. The solution was heated at reflux (80−110 °C) for about 4 h, and water generated in the reaction was distilled off azeotropically (approximately 9.9 L water separated). When no more water was separated, the batch was sampled for reaction completion by HPLC. The solution of dihydronaphthalene (**8**, about 98−100% in-solution yield) was cooled to 20−25 °C and used directly in the next step.

To a glass-lined reactor were charged 1,3-dibromo-5,5-dimethylhydantoin (78.6 kg, 275 mol, 0.5 equiv), acetone (720 L), and water (80 L). The mixture was agitated at 20−25 °C to get a clear solution and then cooled to 0−5 °C. A solution of **8** in toluene (as obtained above), was added over about 60 min while maintaining the batch temperature between 0 and 10 °C (exothermic reaction). If at the end of addition any solids precipitated, more acetone was added to get a clear solution. The reaction mixture was warmed to 20−25 °C and agitated for 4 h and sampled for reaction completion. After complete reaction, add 320 L of water was added**,** and the reaction mixture was concentrated under vacuum (45−50 °C at 200−300 mbar pressure) to a volume of 400 L. Toluene (80 L) was added to the suspension, and the batch was cooled to 0−5 °C. The precipitated product was filtered, washed well with water (6 × 80 L), and dried in a vacuum tray dryer at 45−50 °C for 12−24 h to obtain 106.4 kg of **9** (overall 84.2% yield from α-tetralone).

***trans*-(1*R*,2*R*)-2-Hydroxy-1-methylaminotetralin, Tartrate (12).** Compound **9** (107.5 kg, 473 mol) was charged to a glass-lined reactor, and then water (215 L) and methylamine (40% solution in water, 424 L, 4 mol, 5.0 equiv) were added. The suspension turned into a solution after stirring for 5 h at 35−40 °C. The reaction mixture was sampled for reaction completion, and sodium chloride (53 kg) was charged to saturate the aqueous layer. The batch was extracted with *tert*-butylmethyl ether (MTBE, 3 × 107 L), and the combined MTBE phases were washed with water (28 L). The MTBE solution was concentrated as much as possible under reduced pressure (40−45°C at 200−400 mbar pressure), methanol (53 L) was added to the residue and distilled again under vacuum at 40−45°C to remove methylamine, MTBE, and water. More methanol (53 L) was charged, and the distillation procedure was repeated. The resulting residue of (±)-**2** was dissolved in methanol (242 L) at 40−45 °C. In a separate reactor, L-(+)-tartaric acid (17.7 kg, 118 mol, 0.25 equiv) was dissolved in methanol (35 L) at 20−40 °C. This solution was added to the racemic solution of (±)-**2** in MeOH over a period of about 20 min, and the temperature was held at 50−55°C for 1 h. The suspension was cooled to 0−5 °C and agitated for 1 h. The precipitated solid was filtered, and the mother liquor was removed as much as possible under vacuum and washed with cold (0−5°C) methanol (41 L). The product was dried in a vacuum tray dryer at 50−55 °C for about 12 h to afford 58.5 kg of **12** (overall 49% yield from **9**, 78−83% ee).

The enantiomeric purity of the product was upgraded by recrystallization from aqueous 2-propanol. Compound **12** (obtained above, 58.5 kg) was charged to a reactor, and 2-propanol (175 L) and water (52 L) were added. The suspension was heated to reflux (80 °C), and at reflux temperature water (10 L) was added to get a clear solution. The batch was held at reflux temperature, and additional 2-propanol (293 L) was added over 40 min without further heating. The temperature dropped to about 50 °C, and the suspension was cooled to 0−5 °C and agitated for 1 h. The product was filtered, washed with cold (0−5°C) 2-propanol (75 L), and dried at 50−55 °C for 18 h in a vacuum tray dryer to provide 43.0 kg of **2** (78% yield, 99.0% ee).

***trans*-(+)-(1*R*,2*R*)-*trans*-1,2,3,4-Tetrahydro-1-[(2,2-dimethoxyethyl)methylamino]-2-naphthalenol (3). A. Acid−Base Workup Procedure.** Methyl *tert*-butyl ether (MTBE, 200 mL) and water (200 mL) were added to a mixture of sodium chloride (70 g) and (+)-(1*R*,2*R*)-*trans*-1,2,3,4-tetrahydro-1-(methylamino)-2-naphthalenol hemitartrate (100 g, 0.198 mol). Ammonium hydroxide (100 mL) was added to the suspension, and the mixture was stirred at room temperature for 30 min to get a clear solution. The aqueous layer was separated and extracted with MTBE (200 mL), and the combined MTBE extracts were distilled atmospherically to a volume of 200 mL. Diglyme (200 mL) was then added to the free base and again distilled atmospherically under nitrogen atmosphere to a remove MTBE. The solution was further heated to 105−115 °C, and vacuum was applied carefully until the temperature dropped to 70−75 °C. This ensured removal of MTBE as well as water (the water content of the batch by Karl-Fisher titration was <0.1%) and cooling of the batch needed for subsequent operation. After cooling to room temperature, freshly powdered anhydrous potassium carbonate (93 g, 0.67 mol) and bromoacetaldehyde dimethyl acetal (57 mL, 0.48 mol) were added to the free base solution in diglyme. The suspension was agitated and heated gradually over a period of 3 h to 125−130 °C and then held at 130 °C for 18 h. HPLC analysis of the reaction mixture indicated less than 2% of starting material. The suspension was cooled to room temperature and filtered to remove the solids. Solids and the reaction flask were washed with two portions of MTBE (200 mL and 100 mL). To the combined filtrate was added 1 N sulfuric acid (2 × 200 mL), and the mixture was stirred at room temperature for 10 min. The lower aqueous layer was separated, and the organic layer was again extracted with 1 N sulfuric acid (200 mL). Sodium chloride (120 g) was added to the acidic aqueous layer and stirred until the solids almost dissolved. MTBE (200 mL) was added to the mixture, and then pH was adjusted to 10 using ammonium hydroxide. The organic layer was separated, and the aqueous layer was extracted again with MTBE (200 mL). The combined organic extracts were distilled atmospherically under nitrogen atmosphere to remove MTBE and concentrated to a volume of 200 mL. By HPLC analysis, the in-solution yield of the product in diglyme and its purity were determined to be 93−97 g (0.351−0.366 mol, 90−92% molar yield) and >95%, respectively. EIMS: 267 (M + 2, 24), 266 (M + 1, 100), 235 (20), 234 (95), 202 (35), 184 (7), 171 (8), 155 (15).

B. Vacuum Distillation Procedure. Toluene (200 mL) and water (81 mL) were added to (+)-(1*R*,2*R*)-*trans*-1,2,3,4-tetrahydro-1-(methylamino)-2-naphthalenol hemitartrate (100

g, 0.198 mol). The suspension was stirred at room temperature, and then 25% aqueous sodium hydroxide (68 mL) was added in one portion. The temperature of the reaction mixture increased to 35 °C, and the suspension upon further stirring for 30 min turned into a clear solution. The lower aqueous layer was separated and discarded. 2-Methoxyethyl ether (diglyme, 220 mL) was added to the pale-yellow toluene extract and then heated under nitrogen atmosphere to 120−125 °C to distill toluene. The solution was cooled to 70−80 °C, and vacuum (10 mmHg) was applied to concentrate the solution to a volume of 250 mL. The water content of the batch by Karl-Fisher titration was found to be 0.1%. Freshly powdered anhydrous potassium carbonate (93 g, 0.67 mol) and bromoacetaldehyde dimethyl acetal (57 mL, 0.48 mol) were added to the free base solution in diglyme. The suspension was agitated with a mechanical stirrer and gradually heated over a period of 3 h to 125−130 °C under a nitrogen atmosphere. The heating was continued for 18 h after which the pale red-brown reaction mixture was cooled to room temperature and filtered. The reaction flask and solids were rinsed with two portions of toluene (200 and 100 mL each), and the filtrate was concentrated under vacuum at 65−70 °C to a volume of 150 mL. By HPLC analysis, the in-solution yield of the product in diglyme and its purity were determined to be 93−96 g (0.351−0.362 mol, 90−91.2% molar yield) and >95%, respectively.

(+)-(1*R*,2*R*)-*trans*-1-(4-Chloro-3-methoxyphenyl)-*N*-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydro-*N*-methyl-2-naphthaleneamine Oxalate (1:1) 5A: 3-Methoxy-4-chlorophenylmagnesium Bromide. Magnesium metal turnings (11.3 g, 0.47 mol) were charged to a nitrogen flushed flask, and then anhydrous THF (100 mL) was added. A solution of 5-bromo-2-chloroanisole (100 g, 0.45 mol) in anhydrous THF (100 mL) was prepared, and 5 mL of this solution was added to a vigorously stirred magnesium suspension in THF. Initiation of the reaction was observed by a temperature increase to 40−45 °C. The reaction mixture was held in a water bath, and the remaining solution of 5-bromo-2-chloroanisole was added at such a rate so as to maintain the reaction temperature between 40 and 50 °C. After completion of addition, the reaction mixture was maintained at 40−45 °C for 3 h. HPLC analysis of a MeOH-quenched sample of the reaction mixture indicated >95% of 2-chloroanisole.

A. *p*-Toluenesulfonyl Chloride/CuCN Procedure. To a solution of (+)-(1*R*,2*R*)-*trans*-1,2,3,4-tetrahydro-1-[(2,2-dimethoxyethyl) methylamino]-2-naphthalenol in diglyme (100 g, 0.377 mol) was added 1,10-phenanthroline (50 mg) and toluene (200 mL). The solution was heated to 120 °C at atmospheric pressure under nitrogen to distill toluene (200 mL). The pale red-brown colored solution was cooled to room temperature, and a Karl Fisher titration of the sample indicated a water content of 0.02%. Anhydrous THF (200 mL) was added to the above obtained solution and then cooled to −30 °C. *n*Butyllithium (160 mL, 2.5 M solution in hexanes, 0.40 mol) was added dropwise so as to maintain the reaction temperature between −15 to −30 °C during the exothermic addition. Towards the end of addition, the red-brown colored reaction mixture turnd dark red in color. After stirring the reaction mixture at −30 °C for 10 min, a solution of *p*-toluenesulfonyl chloride (79 g, 0.414 mol) in THF (200 mL) was added dropwise. During this exothermic addition the reaction temperature was maintained between −20 to −30 °C. The reaction mixture was held at −20 °C for 2 h. Separately, a slurry of copper (I) cyanide (3.37 g, 0.037 mol) in THF (50 mL) was cannulated to the aziridinium solution held at −25 °C. The mixture was stirred for 5 min, and then the Grignard solution was added to the aziridinium ion solution held at −25 °C via a cannula. The addition took about 25 min, and during the addition the temperature of the reaction mixture solution was allowed to rise from −25 to −5 °C. After the addition, the reaction mixture was quickly heated to 40−45 °C and held at that temperature for 1.5 h. The reaction mixture was cooled to 0 °C and quenched with 7% aqueous ammonium chloride solution (500 mL). The reaction mixture was warmed to room temperature and stirred for 30 min. The organic layer was separated and stirred with 7% aqueous ammonium chloride solution (700 mL) for 15 min, and the aqueous layer was separated. The aqueous layers were extracted with MTBE (200 mL). The combined organic layers were stirred with 1 N sulfuric acid (220 mL) for 15 min, the lower aqueous layer was separated, and then the organic layer was stirred with 1 N sulfuric acid (220 mL) for 15 min. MTBE (200 mL) was added to the combined aqueous layer, and the pH was adjusted to 5.5−6.0 using ammonium hydroxide. The organic layer was separated, and to the aqueous layer was added MTBE (200 mL). The pH was again adjusted to 5.5−6.0 with ammonium hydroxide, and the organic layer was separated. The organic layer was distilled atmospherically to a volume of 200 mL. 2-Propanol (200 mL) was added to the dark-brown viscous solution, and the solution was filtered through a sintered glass funnel. The funnel was rinsed with 2-propanol (100 mL), and the combined filtrate was warmed to 40 °C. Separately, a solution of oxalic acid dihydrate (47 g, 0.37 mol) in 2-propanol (200 mL) was prepared by warming to 45 °C and added to the free base solution. The mixture was stirred, gradually cooled to room temperature, and seeded with a slurry of product (0.5 g) in 2-propanol (5 mL). After 2−4 h the product crystallized out, and the slurry was stirred at room temperature for an additional 8 h. The slurry was cooled and held at 0 °C for 4 h and then filtered. The cake was washed with ice-cold 2-propanol (200 mL), then with ice-cold MTBE (200 mL), and finally again with ice-cold MTBE (100 mL). The solid was dried under vacuum for 4 h and then in a vacuum oven at 45 °C for 12 h to give an off-white solid (109−118 g, 60−65% molar yield). FABMS: 235, 271, 314, 358, 390.

B. Diphenyl Chlorophosphate/CuCl·2LiCl Procedure. To a solution of (+)-(1*R*,2*R*)-*trans*-1,2,3,4-tetrahydro-1-[(2,2-dimethoxyethyl) methylamino]-2-naphthalenol in diglyme (100 g, 0.377 mol) was added 1,10-phenanthroline (50 mg) and toluene (200 mL). The solution was heated to 120 °C at atmospheric pressure under nitrogen to distill toluene (200 mL). The pale red-brown solution was cooled to room temperature, and a Karl Fisher titration of the sample indicated a water content of 0.02%. Anhydrous THF (300

mL) was added to the above solution and then cooled to −30 °C. *n*-Hexyllithium (160 mL, 2.5 M solution in hexanes, 0.40 mol) was added dropwise so as to maintain the reaction temperature between −15 to −30 °C during the exothermic addition. Towards the end of addition, the red-brown reaction mixture turned dark red in color. After stirring the reaction mixture at −30 °C for 10 min, diphenyl chlorophosphate (86 mL, 0.415 mol) was added dropwise. During this exothermic addition the reaction temperature was maintained between −20 to −30 °C. The reaction mixture was held at −20 °C for 2 h. Separately, a solution of CuCl·2LiCl was prepared by adding anhydrous THF (50 mL) to a mixture of copper (I) chloride (1.9 g, 0.019 mol) and lithium chloride (1.6 g, 0.038 mol). The mixture was stirred for 15 min at room temperature to give a golden-yellow solution. This solution was cannulated to the Grignard solution held at 25 °C. The mixture was stirred for 5 min, and then the aziridinium ion solution held at −20 °C was added to the Grignard solution via a cannula. The addition took about 45 min, and during the addition the temperature of the Grignard solution was in the range of 30−35 °C. After the addition, the reaction mixture was heated to 40−45 °C and held at that temperature for 1.5 h. The reaction mixture was cooled to 0 °C and quenched with 7% aqueous ammonium chloride solution (500 mL). The reaction mixture was warmed to room temperature and stirred for 30 min. The organic layer was separated and stirred with 7% aqueous ammonium chloride solution (500 mL) for 15 min, and the aqueous layer was separated. The combined aqueous layers were extracted with MTBE (200 mL). The combined organic layers were stirred with 5% NaOH (200 mL), and the organic layer was separated and then stirred with 5% brine solution. The organic layer was separated and then distilled atmospherically to a volume of 200 mL. MTBE (300 mL) was added to the dark-brown viscous solution and filtered through a sintered glass funnel. The funnel was rinsed with 2-propanol (100 mL), and the combined filtrate was warmed to 40 °C. Separately, a solution of oxalic acid dihydrate (47 g, 0.37 mol) in 2-propanol (200 mL) was prepared by warming to 45 °C and added to the free base solution. The mixture was stirred and gradually cooled to room temperature. After 12−14 h the product crystallized out, and the suspension was cooled to 0 °C. The suspension was held at 0 °C for 4 h and then filtered. The cake was washed with ice-cold 2-propanol (200 mL), then with ice-cold MTBE (200 mL), and finally again with ice-cold MTBE (100 mL). The solid was dried under vacuum for 4 h and then in a vacuum oven at 45 °C for 12 h to give an off-white solid (125−135 g, 69−75% molar yield). FABMS: 235, 271, 314, 358, 390.

***trans*-(−)-(6a*S*,13b*R*)-11-Chloro-6,6a,7,8,9,13b-hexahydro-12-methoxy-7-methyl-5H-benzo[*d*]naphth[2,1-*b*]azepine, Malonate (1:1) 6A. 5A** (100 g, 0.208 mol) was charged in portions to stirred methanesulfonic acid (160 mL, 2.47 mol) at room-temperature maintaining a 45−50 °C reaction temperature. After the exothermic addition the suspension was heated to 55−60 °C for 2 h. The dark red-brown reaction mixture was cooled to 0 °C and diluted with MTBE (160 mL). A slurry of *tert*-butylamine borane complex (16 g, 0.813 mol) in MTBE (80 mL) was prepared and added slowly to the reaction mixture at such a rate that the temperature was maintained between 10 and 15 °C. The reaction mixture was cooled to 0 °C, and water (320 mL) was added slowly, followed by 25% potassium hydroxide (640 mL) solution. The organic layer was separated, and the basic aqueous layer was extracted with MTBE (200 mL). The combined MTBE extracts were washed with water (160 mL), and the organic layer was distilled atmospherically under a nitrogen atmosphere to a volume of 200 mL. 2-Propanol (320 mL) was charged, and the batch was concentrated to 300 mL. Separately, a solution of malonic acid (23 g, 0.22 mol) in 2-propanol (200 mL) was prepared, warmed to 45 °C, and added to the stirred free base solution. In a few minutes the product crashed out of solution, and the slurry was cooled gradually to room temperature and then held at 0 °C for 1 h. The slurry was filtered, and the cake was washed with ice-cold 2-propanol (120 mL) and then with ice-cold MTBE (160 mL). The cake was dried under vacuum and then in a vacuum oven at 50 °C for 12 h to give an off white solid (83 g, 0.192 mol, 92% molar yield). FABMS: 331, 330, 329, 328, 327, 289, 232, 181. Anal. Calcd for $C_{23}H_{25}ClO_5N$: C, 63.96; H, 6.07%; N, 3.24. Found: C, 64.30; H, 6.04; N, 3.38.

***trans*-(−)-(6a*S*,13b*R*)-11-Chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5H-benzo[*d*]naphth[2,1-*b*]azepine-12-ol, Hydrochloride (1:1): 1·HCl.** To **6A** (100 g, 0.232 mol) was added toluene (300 mL) and water (300 mL) followed by 25% NaOH (80 mL) solution. The suspension was stirred at 40−50 °C for 30 min to give a biphasic solution which was cooled to room temperature. The toluene layer was separated, and the remaining aqueous layer was extracted with toluene (200 mL). The combined toluene layers were washed with water (50 mL), and the water layer was discarded. The pale-yellow organic layer was concentrated atmospherically to a volume of 270 mL. The water content of the free base in toluene was found to be <0.1%. Boron trichloride (68 g, 0.58 mol) was charged to the stirred free base solution at room temperature, and then the mixture was heated to about 70 °C for 18 h. The reaction mixture was dropped carefully into stirred methanol (180 mL) held in a 25 °C water bath. After the exothermic quench, the reaction mixture was concentrated to about 180 mL. The suspension was cooled to room temperature, MTBE (90 mL) was added, and the mixture was cooled to 0−5 °C for 1 h. The product was filtered and washed with an ice-cold MeOH−MTBE (1:2, 75 mL) mixture and then with ice-cold MTBE (50 mL). The product was dried in a vacuum oven at 50−60 °C for 12 h to afford a colorless to pale-yellow solid (75 g, 0.214 mol, 92% molar yield).

The product was recrystallized as follows: 100 g of **1·HCl** was heated to reflux in MeOH (1.2 L), and then the solution was cooled to room temperature and filtered through a 1-μ filter. The solution was concentrated by atmospheric distillation to 200 mL and then cooled to room temperature. MTBE (300 mL) was added to the suspension and cooled

to 0−5 °C for 1 h. The product was filtered and washed with an ice-cold MeOH−MTBE (1:2, 120 mL) mixture and then with ice-cold MTBE (200 mL). The product was dried in a vacuum oven at 50−60 °C for 12 h to give a colorless solid (87 g, 87% recovery).

Alternatively, addition of MTBE (700 mL) to the concentrated solution obtained after distillation (200 mL) followed by cooling to −20 to −30 °C led to 95% recovery after washing the cake with only ice-cold MTBE (2 × 200 mL).

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