Pure Appl. Chem., Vol. 74, No. 8, pp. 1359–1368, 2002.

Development of a practical synthesis of sumanirole*

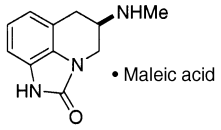
Peter G. M. Wuts[1,‡], Rui Lin Gu[1], Jill M. Northuis[1], Tricia A. Kwan[1], Doris M. Beck[2], and Michael J. White[2]

[1]Chemical Process Research and Development and [2]Bioprocess and Formulation Technology, Pharmacia, Kalamazoo, MI 49001, USA

Abstract: A new synthesis of sumanirole that is being developed to treat Parkinson's disease is described. The basic skeleton is constructed from 8-hydroxyquinoline and elaborated to the key tricylic intermediate 14. Further elaboration affords a 1,2-amino alcohol, which is converted to an aziridine by a new process. Finally, dissolving metal reduction to open the aziridine and protecting group removal affords sumanirole.

INTRODUCTION

Parkinson's disease is a neurodegenerative disease characterized by increasing loss of motor function resulting from a loss of brain cells that are responsible for the synthesis of the neurotransmitter dopamine, formed from *L*-DOPA by *L*-DOPA decarboxylase. The prevailing hypothesis is that stimulation of D_2 receptors assists in the restoration of motor function [1–2]. Thus, in order to minimize side effects, it is highly desirable to have a very selective D_2 agonist and, as such, sumanirole **1** represents an excellent clinical candidate for the treatment of this debilitating disease. It has a K_i of 9 nM for the D_2 receptor subtype, whereas the affinity for the D_1, D_3, D_4, and α_1 receptors is >2300 nM [3]. Sumanirole is currently in phase II clinical trials. It is typically at this stage that the demand for bulk drug starts to increase dramatically, and it soon became clear that the existing technology would not be able to meet the increasing bulk drug requirements. It was also desirable to have final process material for the start of the phase III clinical trials. With the increasing demand for bulk drugs and the desire to have final process material before phase III trials, a simple and robust process was required. This report will describe the work that led to a practical synthesis of sumanirole.



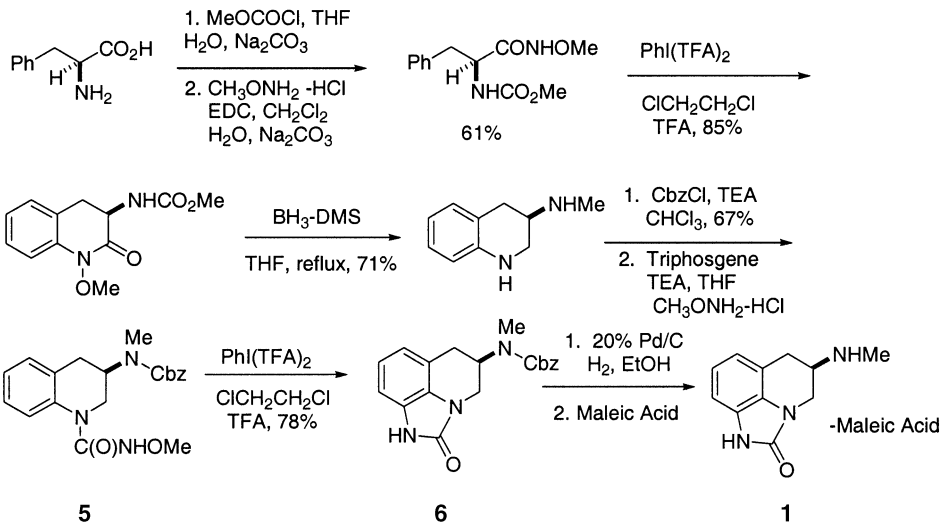
Sumanirole (PNU-95666e) **1**

*Plenary lecture presented at the 3rd Florida Conference on Heterocyclic Chemistry (FloHet-III), Gainesville, Florida, USA, 6–8 March 2002. Other lectures are published in this issue, pp. 1317–1368.

‡Corresponding author

AN EARLY APPROACH

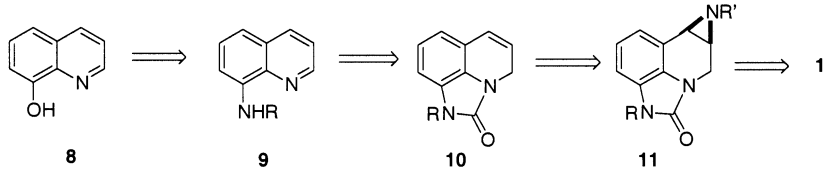
A number of routes for the synthesis of sumanirole have been explored [4], and the most promising of these was one that was developed by Romero (Scheme 1) [5]. The synthesis is outlined in Scheme 1. In this approach, the chirality is secured from *d*-phenylalanine, and the remaining part of the skeleton is elaborated by the use of 2 oxidative cyclizations. The issues faced with this chemistry are that the reagents are rather costly and that the chemistry did not scale well. One other issue in this synthesis is that the methyl group is introduced by reduction of a carbamate with diborane. Although the reaction works reasonably well, there were occasions where cleavage occurred to a minor extent, which led to material lacking the *N*-methyl group. This proved rather serious because it could not be removed by crystallization. This also places a severe constraint on how the methyl group is introduced in any new synthesis. Perfect efficiency is required.



Scheme 1

A NEW APPROACH

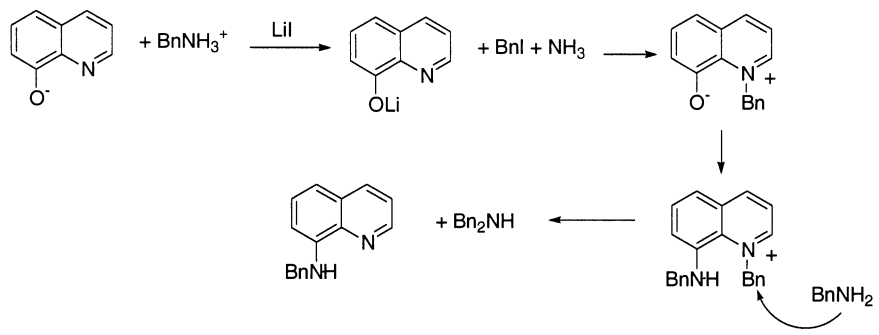
In designing a new approach to sumanirole, we considered the plan illustrated in Scheme 2. 8-Hydroxyquinoline **8** is a very low-cost material that incorporates the majority of the carbon framework, and we felt that it could be elaborated to the olefin **10**. Aziridination using the Jacobsen or Evans protocol could provide the chiral aziridine **11** that, upon reduction and deprotection, would give **1** as its free base.



Scheme 2

In 1904, Bucherer had shown that 8-hydroxyquinoline could be converted to 8-aminoquinoline with $(NH_4)_2(SO_3)NH_3/H_2O$ [6]. Since the overall synthetic plan necessitated protection of the nitrogen, we examined the possibility of carrying out a Bucherer-like process with the benzyl amine bisul-

fite salt. Unfortunately, this failed, and we were forced to find an alternative method for the direct displacement of the hydroxyl with benzylamine. A number of screening experiments established that heating 8-hydroxyquinoline and benzylamine with catalytic halide ion to 185 °C would effect the desired transformation. Of the various salts examined, it was found that LiI has the best catalytic properties. Scheme 3 provides a mechanistic rational. The reaction probably occurs by ammonia displacement with iodide ion, and the resulting benzyl iodide then alkylates 8-hydroxyquinoline on nitrogen. Alkylation on oxygen is reversible since 8-benzyloxyquinoline reacts similarly. Tautaumerization and Shiff base formation introduces the benzylamine. Dealkylation of the quinoline nitrogen with benzylamine affords the product. This is also consistent with the formation of di- and tribenzylamine and ammonia. It should be noted that if the reaction is performed on the benzyl ether of 8-hydroxyquinoline, the first thing that occurs is dealkylation of the benzyl group. The reaction then proceeds normally. The product was readily isolated by a pH-controlled extraction. At pH = 4, benzylaminoquinoline is not protonated.



Scheme 3

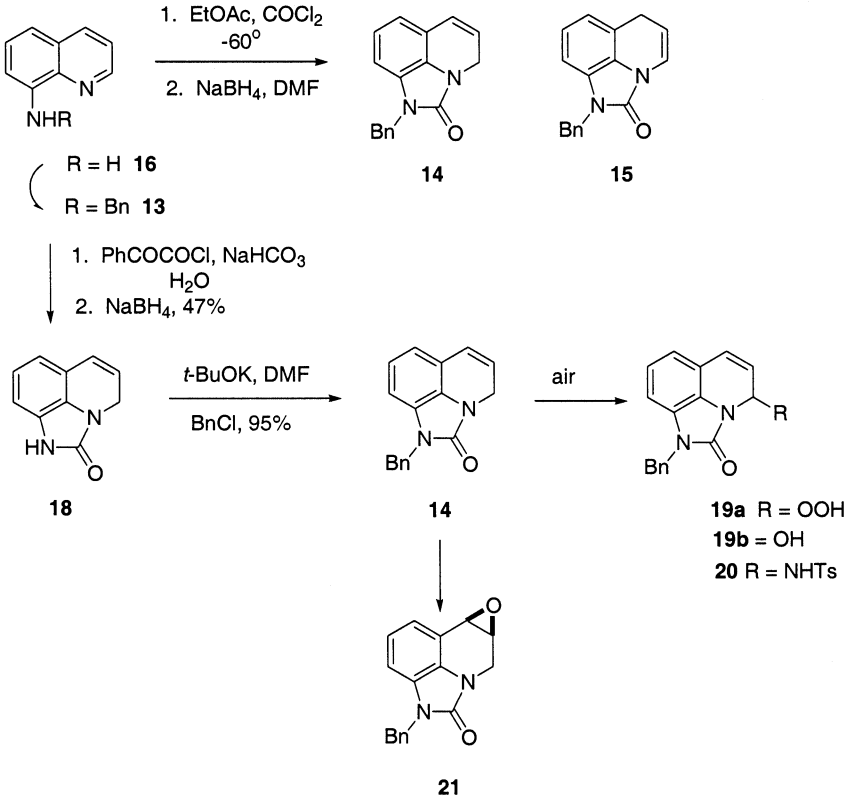
The plan was to carry out the 1,2-reduction through a Reissert-type salt, a methodology that has been extensively used by Commins with substituted pyridines [7]. Thus, treatment of the quinoline **13** with phosgene and reduction with borohydride forms the isomeric tricyclic olefins **14** and **15**. Purification of **14** is achieved by recrystallization from IPA. A number of experiments were conducted in an effort to improve the ratio. Table 1 highlights some of the results. Adding $NaBH_4$ as a solid gave the best results. Solids addition is required because dimethylformamide (DMF) solutions of borohydride are unstable [8]. Switching to dimethylacetamide (DMAC) gave reduced ratios, which may be the result of having to work at a higher temperature owing to DMAC's increased freezing point. Without the cosolvent, $NaBH_4$ does

Table 1 Reissert salt reductions with different reducing agents.

Reducing agent	Solvent for reducing agent	Reduction temp.	LC area %	Ratio **14**:**15**
$NaBH_4$	DMAC	–30 °C	73	2:1
$NaBH_4$ (solid)	DMF prior to $NaBH_4$	–60 °C	80	2.5:1
DIBAH	Toluene	–60 °C	63	1:3.2
Super-hydride	THF	–60 °C	35.92	2.53:1
Morpholine–BH_3	THF	–60 °C	83.64	1.76:1
NH_3–BH_3	THF	–60 °C	88.12	1.14:1
Diispropylamine–BH_3	THF	–60 °C	82.22	1.39:1
Me_2NH–BH_3	THF	–60 °C	86.91	1.25:1
Dabco–BH_3	THF	–60 °C	75.22	1:1.10
BH_3–Me_2S	THF	–60 °C	92.68	1.23:1
Me_3N–BH_3	EtOAc	–60 °C	84.91	1.40:1

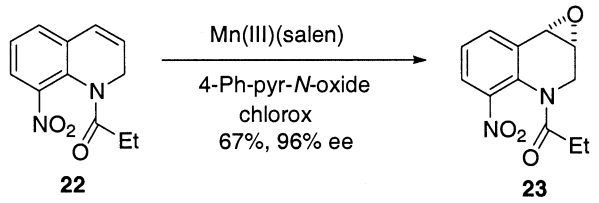
not have sufficient solubility to react. A number of amine boranes were also examined as reducing agents, but failed to give improved ratios. It is also interesting to note that the use of Dibal reverses the ratio in favor of **15**. To improve the safety of the process, triphosgene could be used in place of phosgene, but the initial reaction temperature had to be raised to –40 °C owing to its reduced reactivity.

Given the poor ratios obtained in the reduction and thus the relatively low yield, an alternative method was developed that used the more expensive 8-aminoquinoline (Scheme 4). Saari [9] had reported that the phenyl carbamate of 8-aminoquinoline could be reduced with borohydride to give olefin **18** in 47 % yield. Alkylation with benzyl chloride gives a 95 % yield of **14**. It should be noted that the olefin **14** is very susceptible to air oxidation, especially in solution, at the allylic position to give a hydroperoxide **19a**.



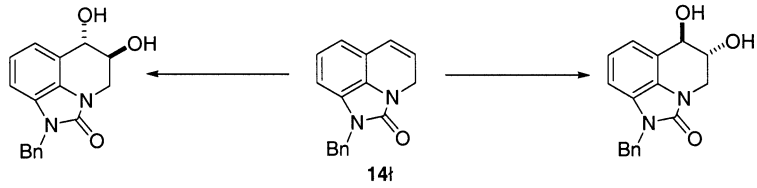
Scheme 4

We planned to introduce the nitrogen by a direct aziridination using either the Evans [10] technology or the Jacobson [11] approach. In the event, after an assiduous effort with the Evans protocol, we were unable to effect this transformation using a variety of iodosyl derivatives (PhI=NTs, PhI=NNs, $PhINSO_2An$) [12]. Only the allylic oxidation product **20** could be isolated in variable yields (20–74 %). The Jacobsen method resulted in gross mixtures that we believe to be a result of oxidation of the electron-rich aromatic ring with the hypochlorite used in the process. The related Jacobsen epoxidation [13] failed to give the epoxide **21**, and only the allylic alcohol **19b** could be isolated in 10 % yield. Here, again, the electron-rich aromatic seems to interfere with the reaction. This is corroborated by the fact that the electron-deficient nitro derivative **22** does give epoxide **23** (Scheme 5) [14]. With the Shi epoxidation [15], we achieved only a 30 % conversion with a 13 % ee, and this required a substantial excess of the chiral ketone. The Sharpless aminohydroxylation [16] seemed an attractive alternative, but the regiochemistry of the reaction and the yield both proved unacceptable.



Scheme 5

Since chemical methods failed, we turned to a microbiological approach wherein the olefin **14** was screened against 130 fungi and 39 bacterial strains in several media in hopes of obtaining the chiral epoxide (Scheme 6) [17]. Although several strains of fungi were found that would react with the olefin, none of them accumulated the epoxide. The only products isolated were each of the enantiomeric diols, depending on the strain and medium (Table 2). We believe the diols were accumulated in preference to the epoxides due to in situ hydrolysis through low-fermentation pH and/or an endogenous epoxidase. Attempts to chemically differentiate the alcohols in a fashion that would allow for introduction of the *N*-methyl group were also not very successful. Another problem with this approach was that the fungi appeared to use the starting material as a metabolic carbon source. The absolute stereochemistry of the diols was not determined.



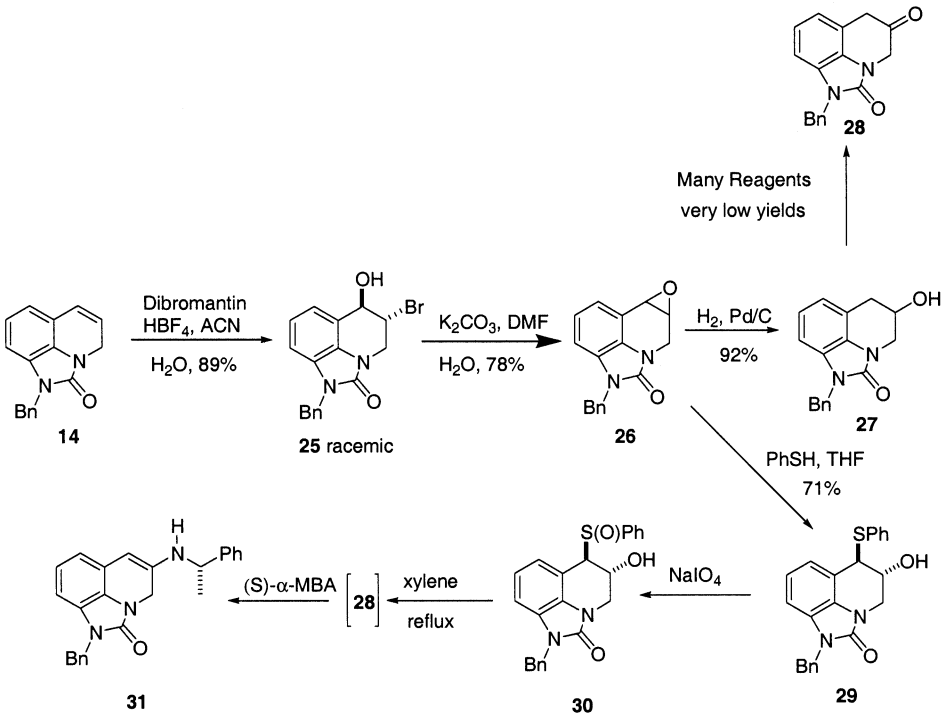
Scheme 6

Table 2 Fungal strains that produce *trans*-diol from alkene, and relative percentages of the enantiomers.

UC #	Strain	Medium [18]	Relative percentages of *trans*-diols [19]
4278	*Aspergillus flavus*	Buffer	88.9:11.1
1978	*Cunninghamella echinulata*	Buffer	13.1:86.9
16617	*C. echinulata*	A	89.4:10.6
		B	94.4:5.6
16636	*C. echinulata*	A	95.7:4.3
		B	95.7:4.3
16640	*C. echinulata*	E	14.5:85.5
16626	*C. elegans*	A	94.4:5.6
		B	91.4:8.6
16645	*C. elegans*	A	30.2:69.8
		B	94.8:5.2
		C	100.0:0
16650	*C. elegans*	C	51.0:49.0
		E	14.2:85.8

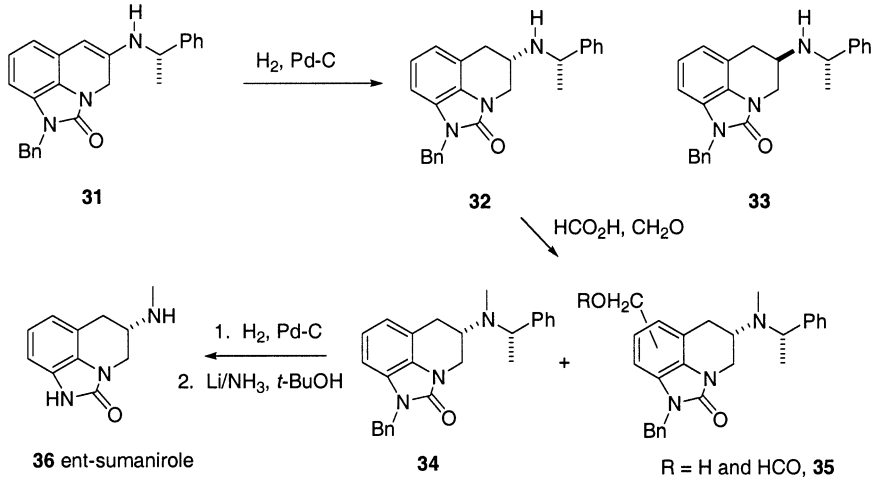
Thwarted by the direct approach, an alternative was envisioned (Scheme 7) that proceeded through reduction of an imine derived from the ketone **28**. We felt that a suitable antecedent to the

ketone was the bromohydrin **25**, which was easily prepared from the olefin with dibromantin. The bromohydrin was converted to the epoxide **26**, but this could not be efficiently converted to the ketone by rearrangement. On a very small scale, some ketone was isolated using BF_3–Et_2O as a catalyst, but the reaction could not be scaled up. We discovered that the ketone was extremely sensitive to oxidative decomposition. This was born out by the fact that an assiduous effort to oxidize the alcohol **27** with a broad spectrum of reagents was very unsuccessful. As a result, a nonoxidative indirect approach was developed that relied on a sulfoxide elimination. Thus, the epoxide was regioselectively opened with thiophenol and oxidized to the sulfoxide **30** with periodate to give the diastereomeric sulfoxides. Thermolysis of the sulfoxide **30** in refluxing xylene gave the long-sought-after ketone **28**, which rapidly reacts with (*S*)-α-methylbenzylamine to give the imine **31** as a highly crystalline solid. This finding was particularly useful, because now the crude pyrolysis mixture, when treated with the amine, resulted in direct precipitation of the enamine, which was now readily isolated in pure form by a simple filtration.



Scheme 7

Hydrogenation of the enamine (Scheme 8) resulted in a 6:1 ratio of diastereomers with MeOH as the solvent and a 2:1 ratio with tetrahydrofuran (THF) as the solvent. These were separated by chromatography, and the major isomer was subjected to the Eschweiler–Clark modification of the Leuckart reaction [20] to give the methylated derivative **34** in 59 % yield after chromatography. The majority of the remaining material was determined to be the hydroxymethyl derivative and its formate (23 %) **35**. Clearly, another method must be found for the methylation. Deprotection with $Li/NH_3/t$-BuOH affords *ent*-sumanirole **36**, thus indicating that (*R*)-α-methylbenzylamine should be used in further work. At this point, work on this approach was discontinued because advances in a modified route were more in line with the strict timeline for this development project.

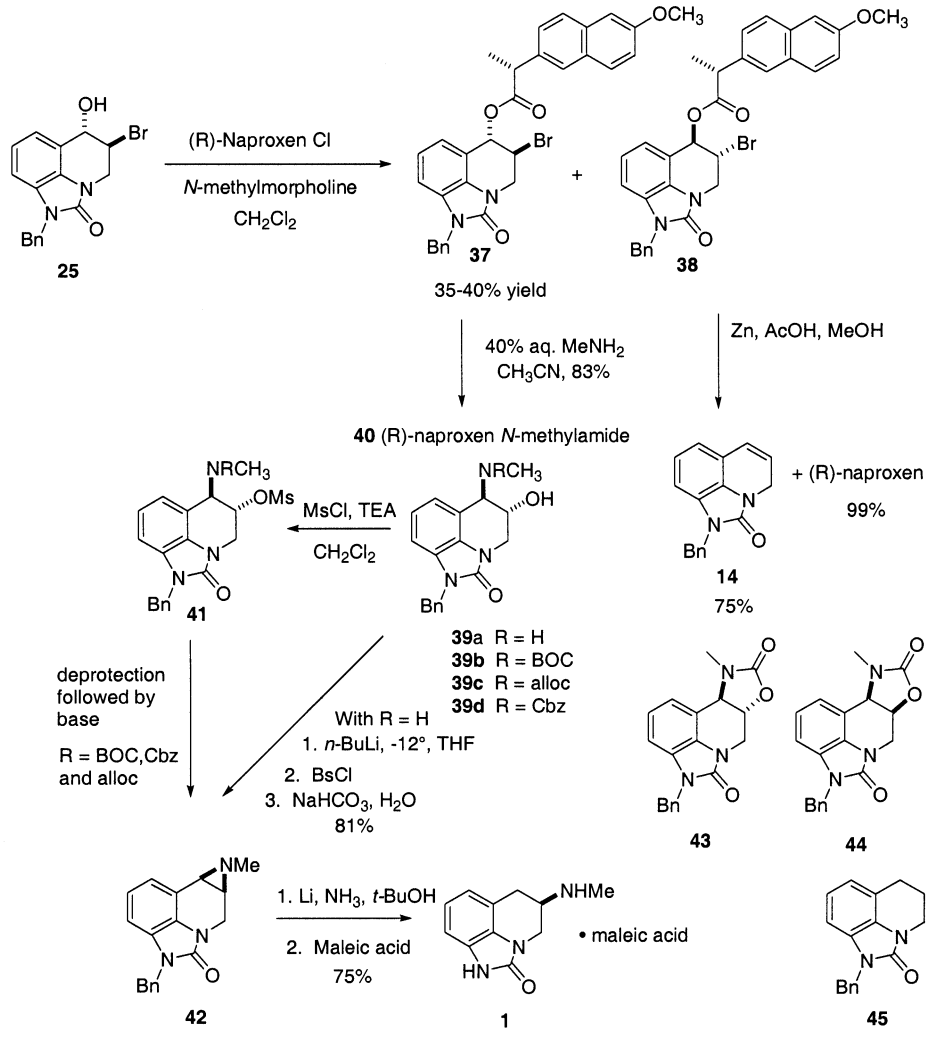


Scheme 8

While examining the asymmetric approach, we also examined a resolution approach to the synthesis. Thus, the racemic bromohydrin was derivatized with (*R*)-naproxen chloride in CH_2Cl_2/*N*-methylmorpholine. The weaker base was required to prevent racemization of the α-methyl group during the esterification. The desired isomer **37** could be crystallized in 35–40 % yield. The other isomer **38** could be recycled back to the olefin **14** with Zn/AcOH/MeOH in 75 % yield. The (*R*)-naproxen could also be recovered in this process. With the chirality secured, the ester was treated with aqueous methylamine in CH_3CN to give the amino alcohol **39a**, along with the *N*-methylamide of (*R*)-naproxen **40**. These were easily separated by an acid/base extraction. This approach has the advantage that the restrictions placed on the methyl introduction have been met, but now the issue of regiochemistry must be addressed.

Although amino alcohols can be converted to aziridines using the Mitsunobu method, this method is not industrially practical owing to the large amount of waste that is generated in the process. In keeping with our vision of simplicity and efficiency, a number of direct approaches to the aziridine were examined, all of which were unsuccessful owing to competitive reactivity of the hydroxyl and the relatively unhindered nitrogen. Clearly, nitrogen protection would be required in order to activate the hydroxyl. The BOC, Alloc, and Cbz derivatives **39b**, **39c**, **39d** (Scheme 9) were examined for this purpose. In general, the protection proceeded cleanly as long as a weak base such as $NaHCO_3$ was used to scavenge the liberated acid. Stronger bases such as K_2CO_3 often lead to the formation of considerable quantities of the trans oxazolidone **43**. Hydroxyl activation as the mesylate followed by deprotection releases the amine, which closes to the aziridine **42** with base. Protection as the BOC derivative was not completely satisfactory, because upon storage solvolysis of the mesylate occurs to give the cis oxazolidone **44**. At this point, we expected that hydrogenolysis would result in deprotection and aziridine opening to give the sumanirole-free base. When the aziridine was subjected to Pd/C in MeOH, the aziridine opens to give the expected amine, but it is also accompanied by substantial amounts of complete hydrogenolysis of the nitrogen to give **45**. The benzyl group on the imidazolone ring was inert to hydrogenolysis even at 1000 psi and 100 °C. The desired transformation was achieved using Na or Li/NH_3, and the maleic acid salt was isolated in 75 % overall yield from the aziridine.

Although it was possible to prepare the aziridine through the sequence described, there were sufficient problems that we explored an alternative approach, which does not require protection and would save 2 steps. The issue in forming the aziridine is that the nitrogen is more nucleophilic than the oxygen. Taking advantage of the pKa differences can reverse the nucleophilicity. Thus, the amino alcohol was treated with 1 equiv of BuLi followed by benzenesulfonyl chloride, which now selectively sul-



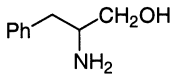
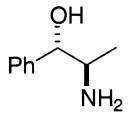
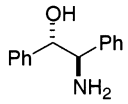
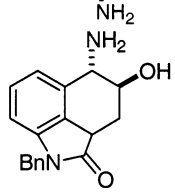
Scheme 9

fonates the hydroxyl and, upon base treatment, causes ring closure to the aziridine in 81 % yield. This latter approach was a considerable improvement over dealing with protection-deprotection strategy. The sequence (**14-25-37-39a-42-1**) has now been used to prepare hundreds of kilos of sumanirole **1**.

This work, and the fact that there are no good ways to make aziridines from unhindered amino alcohols in a single step other than the Mitsunobu reaction, leads us to examine the use of this method on some simple amino alcohols, the results of which are presented in Table 3. These preliminary experiments indicate that the method has potential, but will require additional work to define the most appropriate conditions.

In conclusion, we have developed an efficient and scalable process for the preparation of sumanirole and discovered a new method for the conversion of 8-hydroxyquinoline to 8-benzylaminoquinoline, a new method for the preparation of aziridines of unhindered amino alcohols, and found that the alkene **14** could be converted by fermentation to either of the enantiomeric diols.

Table 3 Formation of aziridines.

Substrate	SM remaining	% Aziridine
	*	49
	*	53
	3	51[a]
	44	37

[a]44 % of the *N*-tosyl aziridine was obtained.
*not determined

ACKNOWLEDGMENTS

We thank Dilip Joshi, Jim Sutton, Vet Carver, Scott Pratt, and Mark Lyster for showing that this chemistry could be scaled to make kilo amounts of material.

REFERENCES

1. P. Seeman and H. B. Niznik. *FASEB J.* 2737 (1990).
2. R. J. Coleman. *Drugs Aging* **2**, 112 (1992).
3. R. F. Heier, L. A. Dolak, J. N. Duncan, D. K. Hyslop, M. F. Lipton, I. J. Martin, M. A. Mauragis, M. F. Piercey, N. F. Nichols, P. J. K. D. Schreur, M. W. Smith, M. W. Moon. *J. Med. Chem.* **40**, 639 (1997).
4. For a review of some of the early approaches, see: P. G. M. Wuts. *Curr Opin. Drug Discov. Devel.* **2**, 557 (1999).
5. A. G. Romero, W. H. Darlington, M. W. McMillan. *J. Org. Chem.* **63**, 6582 (1997).
6. Bucherer reviews: M. S. Gibson. "Introduction of the Amino Group", in Chemistry of the Amino Group, pp. 37–77 (1968); N. L. Drake. *Org. React.* **1**, 105 (1942).
7. D. L. J. Comins and P. Sajan. *Adv. Nitrogen Heterocycl.* **2***,* 251 (1996).
8. ARC data show that the TMR at 90 °C is 4 h for a solution of 0.15 g of $NaBH_4$ in 2.5 mL of DMF.
9. W. S. Saari, W. Halczenko, M. B. Freedman, B. H. Arison. *J. Heterocycl. Chem.* **19** (4), 837 (1982).
10. D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes. *J. Am. Chem. Soc*. **115**, 5328 (1993).
11. Z. Li, K. R. Conser, E. N. Jacobsen. *J. Am. Chem. Soc*. **115**, 5326 (1993).
12. It should be noted that the original Evans work was restricted to *trans* olefins.
13. W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen. *J. Am. Chem. Soc.* **112**, 2801 (1990).
14. R. F. Heier M. W. Moon W. T. Stolle J. A. Easter R. S. P. His. *J. Labelled Compd. Radiopharm.* **38**, 1087 (1996).

15. Y. Tu, Z.-X. Wang, Y. Shi. *J. Am. Chem. Soc*. **118**, 9806 (1996).
16. G. Li, H.-T. Chang, K. B. Sharpless. *Angew. Chem. Int. Ed. Engl*. **35** (4), 451 (1996).
17. C. E. Cerniglia. *J. Ind. Microbiol. Biotechnol.* **19**, 324 (1997); R. N. Patel, A. Banerjee, C. McNamee, D. Brzozowski, L. J. Szarka. "Method of chiral epoxidation of benzopyran or pyranopyridine derivatives using microorganisms", U.S. Patent 5,478,734 (1995); T. A. Crabb, P. J. Dawson, R. O. Williams. *J. Chem. Soc. Perkin Trans. I* (11), 2535 (1980).
18. Media A = pH 3.0, B = pH 6.5; glucose: 20g/L; soy flour: 20 g/L; soybean oil: 30 mL/L; Tween 20-2 mL/L; $MgSO_4 \cdot 7H_2O$: 1 g/L; KH_2PO_4: 0.74 g/L; riboflavin: 10 mg/L. RO water to 1 LMedia C = pH 4.0; D = pH 6.5; cerelose: 120 g/L; soy grits: 33 g/L; EWS lard oil: 5 mL/L; $MgSO_4 \cdot 7H_2O$: 1 g/L; KH_2PO_4: 0.74 g/L; tap water to 1 L. Media E = pH 6.8, cerelose: 22 g/L; yeast extract: 10 g/L; malt peptone: 1 g/L; RO water to one litre.
19. A Daicel Chiralpak AD column, 100 × 2.5 mm, (Chiral Technologies Inc.) was used for chiral analysis. The mobile phase was heptane:isopropanol (75:25, v/v) isocratic 0–35 min, flow rate, 0.5 mL/min, ambient temperature, and detection, 224 nm.
20. M. L. Moore. *Org. React.* **7**, 301 (1949).