# Articles

## Asymmetric Synthesis of MK-0499

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*Received March 17, 1995*®

Described herein is an efficient asymmetric synthesis of the potent antiarrhthymia agent MK-0499. The route is convergent and is highlighted by two stereoselective reactions. A ruthenium-catalyzed, enantioselective hydrogenation of an enamide was developed for the preparation of the key amine intermediate. Oxazaborolidine-mediated ketone reduction was utilized to establish the alcohol stereochemistry. Optimization of this chemistry led to an IPA modified reduction method which provides enhanced stereoselectivity.

### Introduction

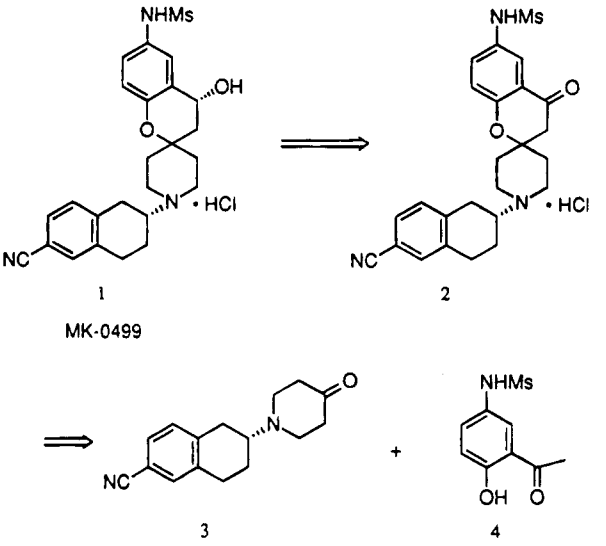
MK-0499 (**1**) is a potent potassium channel blocker which mediates repolarization of cardiac tissue.[1,2] This compound is under investigation for treatment of ventricular arrhythmias and the prevention of sudden cardiac death. Described herein is an efficient asymmetric synthesis of this drug candidate. The structure of MK-0499 offers several challenges from a synthetic perspective. Most notable are the two remote chiral centers and the spirofused ring system. Our approach is highly convergent as indicated by the retrosynthetic analysis shown in Scheme 1.

In this route, MK-0499 is derived from ketone **2** by an asymmetric reduction. Interestingly, **2** also has potent antiarrhythmic properties. Ketone **2** arises in one step by spirocondensation of **3** and **4**.

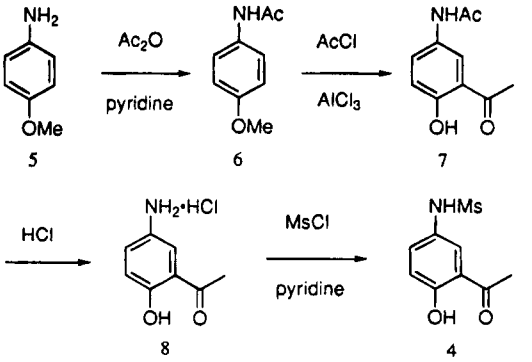
**Synthesis of 2-Hydroxy-5-sulfonamido Acetophenone 4.** The synthesis of **4** is straightforward as shown in Scheme 2. *p*-Anisidine is acylated with acetic anhydride and the resulting N-acylated anisidine **6** is treated with acetyl chloride and aluminum chloride to effect Friedel–Crafts acylation, as well as demethylation, resulting in the formation of **7**. Acid catalyzed hydrolysis of the acetamide followed by mesylation produces the desired sulfonamide **4** in 58% overall yield from *p*-anisidine.

**Racemic Synthesis of Intermediate 3.** Since **3** is a key intermediate in our approach, we desired a highly efficient synthesis of this fragment. A racemic route was initially developed as shown in Scheme 3. Starting with bromotetralone **10**,[3] reductive amination using piperidone ethylene ketal and sodium triacetoxyborohydride[4] provided the racemic amine **12** in 85% yield.

**Scheme 1**




**Scheme 2**




® Abstract published in *Advance ACS Abstracts,* June 15, 1995.

(1) (a) Presented in part at the 206th ACS National Meeting, Chicago, IL, August 1993. (b) Presented in part at the 208th American Chemical Society National Meeting, Washington, D.C. August 1994, Orgn. #280.

(2) For a discussion on the medicinal aspects of these compounds see: (a) Lynch, J. J.; Wallace, A. A.; Supienski, R. F.; Baskin, E. P.; Bear, C. M.; Appleby, S. D.; Salata, J. J.; Jurkiewicz, N. K.; Sanguinetti, M. C.; Stein, R. B.; Gehret, J. R.; Kothstein, T.; Claremon, D. A.; Elliot, J. M.; Butcher, J. W.; Remy, D. C.; Baldwin, J. J. *J. Pharmacol. Exp. Ther.* **1994**, *269*, 541. (b) Claremon, D. A.; Baldwin, J. J.; Elliot, J. M.; Ponticello, G.S.; Selnick, H. G.; Lynch, J. J.; Sanguinetti, M. C. *Perspectives in Medicinal Chemistry*; Testa, Bernard, Ed.; Verlag Helvetica Chim. Acta: Basel, Switz. (Engl.) **1993**, pp 383–404.

(3) Burkhalter, J. H.; Campbell, J. R. *J. Org. Chem.* **1961**, *26*, 4232.

(4) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. *Tetrahedron Lett.* **1990**, *31*, 5595.

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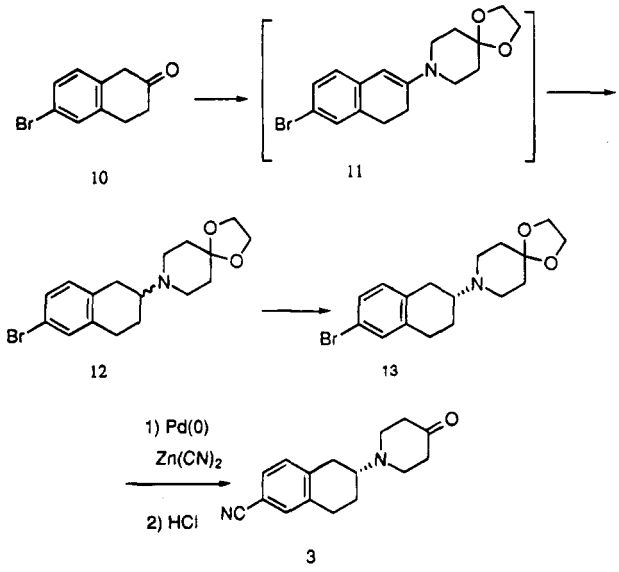
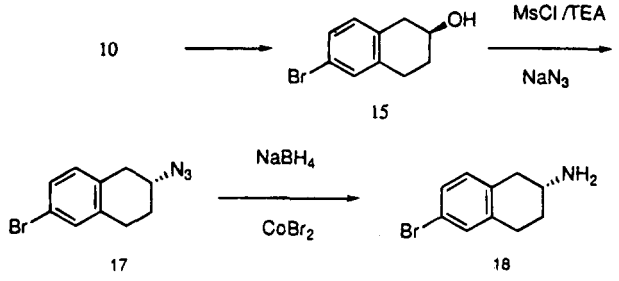
**Scheme 3**




**Scheme 4**

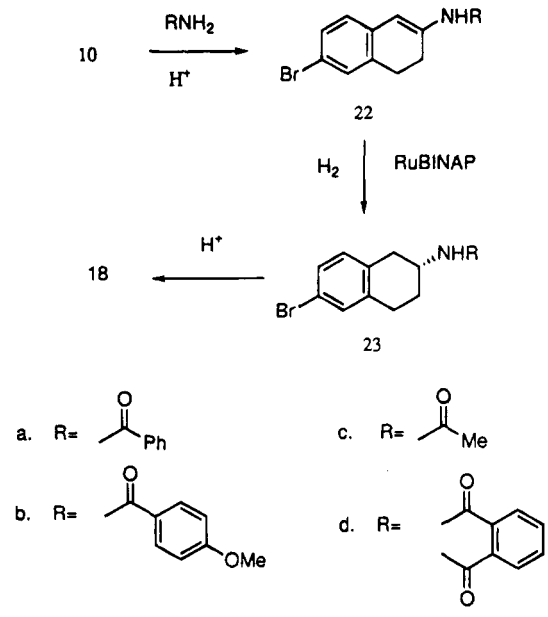



Resolution was carried out by recrystallization of **12** as the di-*p*-toluoyl tartrate salt to provide optically pure **13** in 35% yield. The synthesis of intermediate **3** was then completed using a cyanation procedure which was developed in our lab.[5] Treating bromide **13** with catalytic Pd(0) and zinc cyanide followed by deketalization using aqueous HCl generated **3** in 85% yield. Although this route is attractive due to its simplicity, it suffers from the obvious need for resolution of intermediate **12**.

**Asymmetric Synthesis of Intermediate 3.** With a workable racemic synthesis in hand, we turned our attention toward development of an asymmetric approach to intermediate **3.** Unfortunately, there is very little literature precedence for asymmetric synthesis of 2-amino tetralin derivatives. We have studied several alternative strategies for the asymmetric synthesis of **3** and have developed two efficient routes which are described below. Both approaches target chiral amine **18** as a key intermediate. One of the chiral approaches which we have pursued is outlined in Scheme 4.

Since chemical methods for chiral reduction of $\beta$-tetralone **10** to alcohol **15** were inefficient, we opted for microbial reduction. Exposing $\beta$-tetralone **10** to yeast (trichosporon capitatum) for 24 h produced the desired alcohol **15** in good yield with high enantioselectivity (>98%).[6] For comparison, oxazaborolidine (OAB·$BH_3$) reduction of **10** provided **15** in only 20% ee. The alcohol was then converted to the corresponding mesylate and displaced using sodium azide in DMSO. Complete inversion of stereochemistry is observed with no erosion of the ee. On the other hand, attempts to displace the mesylate with piperidone ethylene ketal to provide **13** directly, was unfortunately accompanied by substantial amounts of olefin byproduct (~50%).

**Scheme 5**




Reduction of the azide **17** to the amine **18** can be conducted under a variety of conditions.[7] We have found sodium borohydride in the presence of catalytic cobalt bromide to be the method of choice.[7a] This procedure provides highly pure amine in good yield (90%) with only trace amounts of concomitant debromination. Loss of the aryl bromide is significant under catalytic hydrogenation conditions. The use of triphenylphosphine to convert **17** to **18** is complicated by the formation of triphenylphosphine oxide which is difficult to separate.

As an alternative route to chiral amine **18**, we studied asymmetric reductive amination. Unfortunately, all efforts to effect an asymmetric reductive amination to form chiral **13** directly, failed. The hydrogenation of enamine **11** was conducted with several chiral BINAP catalysts. All the rhodium based catalysts gave racemic products. Hydrogenation with Ru−(*S*)-BINAP(cymene)-Cl at 1500 psi and ambient temperature showed modest enantioselectivity (30% ee) and low conversion (15%). When the temperature was increased to 50 °C, the conversion improved to 70%, however, the product was racemic. This was not too surprising in light of literature reports which indicate that a secondary binding site on the enamine is required in order to achieve good enantioselectivity.[8] We therefore pursued asymmetric hydrogenation of enamide derivatives (Scheme 5). Since there are only a few known examples of simple enamides which have been reduced with high enantioselectivity, we were cautiously optimistic about chances for success. Conversion of the 6-bromo-2-tetralone **10** to the enamides **22**, by condensation with the corresponding amides, was carried out with an acid catalyst and azeotropic removal of water. Using Amberlyst-15 resin as catalyst and 100%

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(6) This work was done with the asisstance of our colleages in the BioProcess R&D group at Merck: J. Reddy, L. Katz, M. Chartrain. The details of this work will be described in a separate article.

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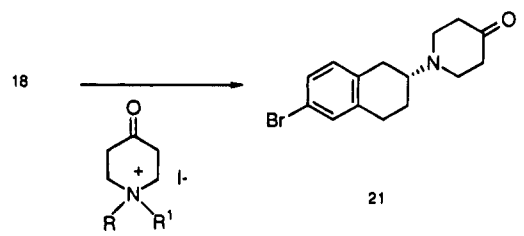
(8) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

**Table 1. Hydrogenation of 22a in Methanol.**

| entry | catalyst | wt % relative to **22a** | conditions | % ee (% yield) |
|---|---|---|---|---|
| 1 | Rh(R)BINAP $ClO_4$ | 10 | 20 °C/1500 psi + HCl | *S*, 95 (100) |
| 2 | Ru(R) BINAP(Cym)Cl | 10 | 20 °C/1500 psi + HCl | *S*, 90 (92) |
| 3 | Ru(S) BINAP(Cym)Cl | 10 | 20 °C/1500 psi + HCl | *R*, 95 (92) |
| 4 | Ru(S) BINAP(Ph)Cl | 10 | 20 °C/200 psi | *R*, 98 (95) |
| 5 | Ru(S) BINAP(Ph)Cl | 2 | 35 °C/150 psi | *R*, 97 (92) |

**Scheme 6**




19 R= Me, $R^1$= Me
20 R= Me, $R^1$= Et

excess of benzamide to drive the reaction to completion, **22a** was prepared in 95% yield. None of the regioisomeric enamide was observed.

Several commercially available chiral catalysts were tested for the reduction of enamides **22**. The best results were obtained with benzamide **22a.** Summarized in Table 1 are the results of the successful reductions.

All the purchased catalysts gave minimal reduction at 1500 psi hydrogen pressure. Addition of a drop of 2 N HCl to the methanol solution accelerated the reduction dramatically, and **23a** was produced in high yield and enantiomeric excess (entries 1−3).[9] At lower pressure and higher temperature the solvolytic destruction of the enamide reduced the yield significantly. Freshly prepared Ru−(S)-BINAP(Ph)Cl was a more active catalyst, and the rate of hydrogenation was not affected by acid. With as little as 2 wt % catalyst, the product was obtained with high enantioselectivity and excellent yield (entry 5). After recrystallization, **23a** was obtained in 87% yield and 99% ee. Several preparative scale runs were carried out in a stirred autoclave with similar results.

The anisoyl enamide **22b**, was hydrogenated with similar rate and selectivity as **22a**. Enamide **22c** reacted much slower and the phthaloyl derivative **22d** could not be reduced at 1500 psi.

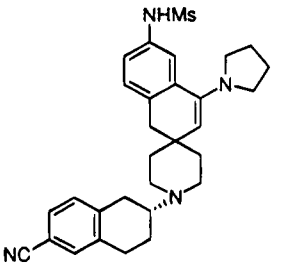
Hydrolysis of the benzamide group required rather harsh acidic conditions. Treatment of **23a** with methanesulfonic acid and acetic acid at 160 °C for 24 h was necessary in order to effect hydrolysis. No epimerization of the chiral center is observed under these conditions.

Having demonstrated two efficient routes to chiral amine **18**, we then focused on the development of an efficient method for the formation of the piperidone ring.

**Formation of the Piperidone Ring.** Construction of the piperidone ring was achieved by modification of Kuehne's procedure (Scheme 6).[10,11] When the amine **18** was treated with 1-methyl-4-piperidone methiodide **19** (R, $R^1$ = Me) under Kuehne's conditions, the desired piperidone was obtained in only 69% yield. The ratio of **21** to **18** was 73/27. Attempts to drive the reaction to completion by distilling out dimethylamine were unsuccessful. We decided to alter the amine substituents (R, $R^1$) in order to shift the equilibrium in a favorable direction. Interestingly, we observed that subtle changes in the nitrogen substituents do indeed alter the reaction. Replacing the *N*,*N*-dimethylpiperidone with the *N*-methyl-*N*-ethylpiperidone shifts the equilibrium to a 98:2 ratio of **21** to **18** and the yield increased to 87%. Likewise, the *N*-methyl *N*-benzyl and the *N*,*N*-diethyl analogs also shift the equilibrium toward the product **21**.

**Palladium Catalyzed Cyanation.** Completion of the synthesis of fragment **3** required an efficient method for cyanation of aryl bromide **21**. Under our previously described conditions[5] of zinc cyanide and Pd(0) the unprotected piperidone ketone is somewhat unstable (80 °C for 4 h). This instability resulted in decomposition and led to lower yields. However, we found that modifying the ligand from triphenylphosphine to tri-*o*-tolylphosphine accelerated the rate of reaction significantly. Using this ligand, we observed complete reaction within 1.5 h at 60 °C and yields as high as 90% have been achieved with as little as 3 mol % catalyst. After extractive workup to remove zinc salts, the reaction product is typically highly pure and can be used in the subsequent steps without purification. It is important to note that careful deoxygenation of the reaction solvents is crucial to the success of these reactions. Since the reaction mixture is heterogeneous, the particle size of the zinc cyanide can influence the rate of reaction. The reaction is accelerated by using zinc cyanide with small particle size (<20 $\mu$m).

**Spirocyclization.** Spirocyclization of **3** and **4** to form **2** was conducted in one step under conditions similar to those described by Kabbe for the synthesis of 4-chromanones.[12] Thus, reacting **3** with **4** in the presence of pyrrolidine, followed by acidic workup, produces **2** in 85% isolated yield. As previously indicated,[12] the initial product of this reaction is the enamine **24** which is hydrolyzed back to the ketone **2** upon acidic workup.




24

Pyrrolidine is the amine of choice for carrying out this spirocondensation. In fact, attempts to replace pyrrolidine with other amines such as diethylamine, piperidine, and morpholine have provided little or no product.

**Chiral Reduction of Ketone 2.** One of the key

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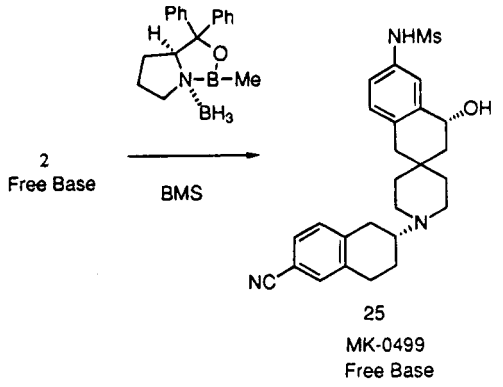
(10) Kuehne, M. E.; Muth, R. S. *J. Org. Chem.* **1991**, *56*, 2701.
(11) Mistryukov, E. A.; Aronova, N. L.; Kucherov, V. F. *Izv. Aka. Nauk SSSR, Ser. Khim.* **1961**, 932.
(12) (a) Kabbe, H. J. *Synthesis* **1978**, 886. (b) Kabbe, H. J.; Widdig, A. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 247.

**Scheme 7**



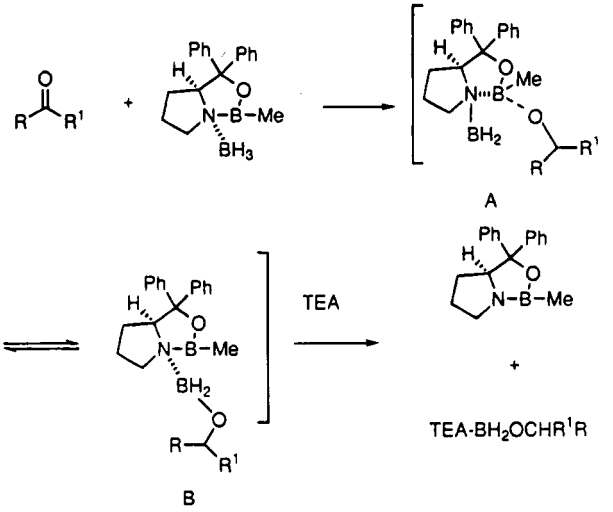

transformations in this synthesis is the asymmetric reduction of ketone **2** to MK-0499 free base **25** (Scheme 7).

It is important to note that the existing chiral center in **2** is relatively far removed from the ketone carbonyl and therefore has little effect on the stereoselectivity of the reduction. As previously reported, we have found OAB·$BH_3$ to be a useful reagent for this reduction.[13-16] Stoichiometric amounts of oxazaborolidine–borane complex (OAB·$BH_3$) reduce ketone **2** to alcohol **25** with >99% de. However, early attempts to carry out this reduction with a catalytic amount (10 mol %) of OAB·$BH_3$ led to lower diastereoselectivity (90% de). Even with slow addition (2 h) of ketone to OAB·$BH_3$, and borane–methyl sulfide (BMS) or simultaneous addition of ketone and BMS to catalyst led to 93% de at best. Ketone **2** is only slowly reduced by BMS (<1%/h at 0 °C), and therefore the lower diastereoselectivity is not the result of this competing racemic reduction. Since we required final product which was >98% de, we studied this reduction more closely.

Careful consideration of the mechanism of this reaction in conjunction with model studies indicated that competing reduction by the 1:1 adducts A or B and/or monoalkoxyborane might be responsible for lower enantioselectivity (Scheme 8). Our previous studies using stoichiometric amounts of OAB·$BH_3$ had shown that adding tertiary amines to the reaction mixture improves the enantioselectivity. We conducted extensive NMR studies which indicate that 1:1 OAB–monoalkoxyborane complexes such as A and B are formed in these reactions. We also demonstrated that triethylamine reacts rapidly with these species leading to the formation of $Et_3N$–$BH_2$-$OCHR^1R$. However, tertiary amines form tight complexes with boron and therefore inhibit the catalytic cycle.

Therefore, we searched for an alternative additive which would suppress competing side reactions without interfering with the catalytic cycle. We ultimately found that addition of 1 mol of IPA to the reaction improves the diastereoselectivity in the reduction of **2** to **25**. Treatment of **2** (free base) with 2.2 mol of BMS, 1 mol of IPA, and 10 mol % OAB·$BH_3$ provides the alcohol in 98% de (without IPA 90% de). We have observed similar enhancement in the enantioselectivity of the OAB reductions of other ketones as well.[13]

**Scheme 8**




Initially we speculated that IPA enhanced the enantioselectivity by trapping the intermediate 1:1 OAB borane complex. To support this finding we generated the 1:1 complex A at low temperature (~50 °C) in an NMR tube and treated it with 1 equiv of IPA. The result was rapid consumption of the 1:1 complex and generation of free OAB and dialkoxyborane. More recently, we have discovered similar enhancement in enantioselectivity even when all the IPA has been converted to the corresponding dialkoxyborane. In fact, we have observed the same enhanced ee's when acetone is used in place of IPA, thus indicating that diisopropoxyborane may in fact be the species which is enhancing the enantioselectivity. We postulate that the added dialkoxyborane serves to accelerate the recycle of the 1:1 OAB–monoalkoxyborane intermediates back to the active OAB–$BH_3$, thus precluding the reaction of these intermediates with the ketone.

A more detailed discussion of the mechanistic pathway for these reductions is the subject of another paper.[17]

**HCl Salt Formation.** Conversion of MK-0499 free base to the HCl salt initially appeared to be straightforward. However, this step is complicated by the fact that the final product has numerous crystal types.[18] Several (12) different solvates, hydrates, and polymorphs have been isolated and characterized. We identified a dihydrated form (type A) to be the most desirable crystal type due to its stability. Interestingly however, while this crystal type is the most stable form in the solid state, it is metastable at temperatures below 37 °C when in contact with solvent. In addition, MK-0499 is chemically unstable under acidic conditions at elevated temperatures. Racemization and dehydration of the benzylic OH are observed under acid conditions at temperatures >50 °C. Therefore, the challenge was to carefully design an HCl salt formation procedure which would generate the desired crystal form in high yield without decomposing the product. We ultimately developed a salt formation which reproducibly provides the desired type A form in

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(16) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Sing, V. K. *J. Am Chem Soc.* **1987**, *109*, 7925. (c) Itsuno, S.; Ito, K.; Hirao, A. *J. Org. Chem.* **1984**, *49*, 555.
(17) Douglas, A. W.; Reamer, R. A. Submitted to *J. Am.Chem. Soc.*
(18) McCauley, J. A.; Varsolona, R. J.; Levorse, D. A. *J. Phys. D: Appl. Phys.* **1993**, *26*, B85.

>90% yield. The details of the procedure are described in the Experimental Section.

## Conclusion

We have demonstrated an efficient asymmetric synthesis of MK-0499. In the course of this work, we have developed some synthetic methodology which will undoubtedly have applications elsewhere. Some of the highlights of this chemistry include (1) a Ru catalyzed asymmetric enamide hydrogenation which is highly enantioselective (2) an improved method for the formation of piperidone rings; (3) a new procedure for Pd catalyzed cyanation; (4) an IPA modified, OAB catalyzed, chiral reduction.

## Experimental Section

**N-Acetylanisidine (6).** To a stirred suspension of *p*-anisidine (6.02 g, 49 mmol) in methylene chloride (20 mL) was added acetic anhydride (4.6 mL, 49 mmol) over 1 h while maintaining the temperature 25−30 °C using a cold water bath. The mixture was then stirred for an additional 1.5 h at 25 °C. Hexane (60 mL) was added to the mixture over 1 h, and the slurry was aged for 1 h. The product was collected by filtration and dried *in vacuo* at 40 °C to provide 7.7 g (95%) of the desired product. IR ($CHCl_3$) 3450, 3340, 3005, 1680, 1515, 1240, 1035 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.39 (m, 2H, 7.28 (bs, NH), 6.86 (m, 2H), 3.79 (s, 3H), 2.16 (s, 3H). $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 168.7, 156.4, 131.1, 128.0, 122.1, 114.1, 55.5, 24.2. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.32; H, 6.62; N, 8.46.

**5-Acetamido-2-hydroxyacetophenone (7).** To a stirred suspension of *N*-acetylanisidine (3.8 g, 23 mmol) in methylene chloride (23 mL) at 25 °C was added acetyl chloride (4.7 mL, 66 mmol). Aluminum chloride (10 g, 75 mmole) was carefully added in several portions over 1.5 h while maintaining the temperature 30−35 °C using intermittent ice bath cooling. The mixture was heated to reflux for 4.5 h and then cooled to 30 °C prior to careful quenching into ice water. **Caution!** The quench was exothermic and HCl gas evolved. The resulting slurry was stirred for 30 min, and the product was collected by filtration and dried *in vacuo* at 40 °C to yield 4.2 g (88%). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 12.11 (s, 1H), 8.16 (d, $J$ = 2.44 Hz, 1H), 7.33 (dd $J$ = 8.79 Hz, 1H), 7.30 (bs, 1H), 6.92 (d, $J$ = 8.79 Hz, 1H), 2.63 (s, 3H), 2.18 (s, 3H). $^{13}C$ NMR (75.5 MHz, DMSO-$d_6$) $\delta$ 203.5, 167.9, 156.3, 131.0, 127.9, 120.9, 119.9, 117.6, 27.8, 23.7. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.06; H, 5.70; N, 7.20.

**5-Amino-2-hydroxyacetophenone Hydrochloride (8).** To a stirred suspension of 5-*N*-acetamido-2-hydroxyacetophenone (4.2 g, 20.2 mmol) in ethanol (38 mL) at 25 °C was added 6 N aqueous hydrochloric acid (14 mL). The mixture was heated to reflux for 14 h. The mixture was concentrated *in vacuo* to a volume of 19 mL. Additional ethanol (19 mL) was added and concentration was continued to a final volume of 19 mL. After cooling to 0−5 °C for 1 h the crystallized product was collected by filtration and dried *in vacuo* to afford 3.25 g (83% yield). $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.66 (s, 1H), 10.32 (bs, 2H), 7.82 (d, $J$ = 2.70 Hz, 1H), 7.50 (dd, $J$ = 2.70, 8.81 Hz, 1H), 2.61 (s 3H). $^{13}C$ NMR (75.5 MHz, DMSO-$d_6$) $\delta$ 206.5, 164.3, 135.4, 130.3, 128.2, 127.3, 124.1, 34.3. Anal. Calcd for $C_8H_{10}NO_2Cl$: C, 51.21; H, 5.37; N, 7.46. Found: C, 51.15; H, 5.29; N, 7.46.

**5-Methansulfonamido-2-hydroxyacetophenone (4).** Pyridine (3.5 mL, 43.1 mmol) was added to a stirred suspension of 5-amino-2-hydroxyacetophenone hydrochloride (3.4 g, 18 mmol) in methylene chloride (40 mL) at 0−5 °C. Methanesulfonyl chloride (1.45 mL, 18.9 mmol) was added to the mixture over 45 min while maintaining the temperature 0−5 °C. The batch was then warmed to 25 °C and stirred for an additional 1 h. The mixture was washed with 1 N aqueous HCl (2 × 20 mL), and the organic layer was concentrated *in vacuo* to a volume of 20 mL. Hexanes (20 mL) was added to the stirred mixture over 2 h and the slurry was aged for 4 h at 20−25 °C. The crystalline product was filtered and washed with hexanes (4 mL). The product was dried *in vacuo* for 24 h at 40 °C to provide 3.4 g (83%). mp = 121 °C. IR ($CHCl_3$) 3080, 3330, 1660, 1500, 1330, 1155 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 12.21 (s, 1H), 7.73 (d, $J$ = 2.4 Hz, 1H), 7.36 (dd, $J$ = 2.4, 8.8 Hz, 1H), 6.99 (d, $J$ = 8.8 Hz, 1H), 6.74, (bs, NH), 2.99 (s, 3H), 2.65 (s, 3H). $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 202.9, 157.6, 130.4, 129.3, 123.9, 120.9, 118.3, 38.7, 28.1.

**6-Bromo-2-tetralone (10).** To a solution of 4-bromophenylacetic acid (48.0 g, 0.223 mol) in methylene chloride (480 mL) was added DMF (0.355 mL, 0.005 mol). Oxalyl chloride (22.0 mL, 0.252 mol) was added dropwise over 6 h at 20−25 °C. The mixture was stirred for an additional 18 h and then cooled to 0−5 °C. Aluminum chloride (32.74 g, 0.246 mol) was added in portions while maintaining the temperature 0−5 °C. Ethylene was added to the mixture via a subsurface tube as a slow stream over 1 h. The mixture was then carefully quenched into cold water (500 mL). The layers were cut and the methylene chloride solution of 6-bromo-2-tetralone was taken into the next step without purification. HPLC assay: Zorbax Rx C8, acetonitrile:water (0.1% $H_3PO_4$) 50:50; flow rate = 1.25 mL/min, UV detection at 220 nm, $t_R$ (product) = 7.6 min, $t_R$ (bromophenylacetic acid) = 4.3 min.

A sample was crystallized from methylene chloride/hexane. IR ($CHCl_3$) 3005, 1720, 1600, 1485, 1415, 1335, 1220, 1175, 1075 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.38 (s, 1H), 7.32 (dd, $J$ = 2.0, 8.1 Hz, 1H), 6.99 (d, $J$ = 8.1, 1H), 3.52 (s, 3H), 3.03 (t, 3H), 2.52 (t, 3H). $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 209.5, 138.9, 132.3, 130.6, 129.9, 129.8, 120.5, 44.6, 37.7, 28.1.

**Racemic Reduction of 6-Bromo-2-tetralone.** 6-Bromo-2-tetralone (20.2 g, 90 mmol) was mixed with MeOH (70 mL) at 0 °C. Sodium borohydride (6.8 g, 180 mmol) was added at such a rate as to maintain the internal reaction temperature below 5 °C. Within 30 min, HPLC showed complete consumption of the starting material. The reaction mixture was diluted with 300 mL of $CH_2Cl_2$ and washed twice with 300 mL of aqueous $NaHCO_3$ and once with 300 mL of saturated brine. The solution was dried with sodium sulfate and filtered. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (eluted with 5:1 hexanes:EtOAc) to afford 18.4 g of 6-bromo-2-tetralol (90%). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.22 (s, 1H), 7.19 (s, 1H), 6.90 (d, $J$ = 7.8 Hz, 1 H), 4.08 (m, 1H), 3.13 (s, 1H), 2.80 (m, 4H), 1.98 (m, 1H), 1.77 (m, 1H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 138.1, 133.4, 131.3, 131.1, 128.9, 119.6, 66.6, 37.7, 31.0, 26.7. Anal. Calcd for $C_{10}H_{11}BrO$: C, 52.88; H, 4.89. Found: C, 52.89; H, 4.90.

**Mesylation of 15.** To a solution of the alcohol **15** (30.6 g, 135 mmol) in methylene chloride (140 mL) at 0 °C was added mesyl chloride (12.5 mL, 162 mmol) and triethylamine (28.2 mL, 203 mmol). After 1.25 h NMR indicated complete consumption of the alcohol. The mixture was diluted with methylene chloride (60 mL) and washed twice with aqueous sodium bicarbonate (200 mL) and once with brine. The organic layer was dried over sodium sulfate and chromatographed on silica gel (hexane:ethyl acetate 4:1) to afford 37.0 g (90%) of the mesylate. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.26 (s, 1H), 7.24 (s, 1H), 6.96 (d, $J$ = 8.7 Hz, 1H), 5.16 (m, 1H), 2.97 (m, 7H), 2.15 (m, 1H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 137.1, 131.5, 131.3, 130.9, 129.4, 120.1, 77.5, 77.1, 76.9, 76.7, 38.8, 35.0, 28.4, 25.6. Anal. Calcd for $C_{11}H_{13}BrO_3S$: C, 43.28; H, 4.30; S, 10.51. Found: C, 43.29; H, 4.26; S, 10.78.

**Azide 17.** A solution of the mesylate (3.0 g, 9.84 mmol) and sodium azide (6.4 g, 98.4 mmol) in DMSO (200 mL) was heated at 50 °C for 3.5 h. HPLC assay shows complete consumption of the starting material. The reaction was quenched with brine and extracted with methylene chloride (250 mL). The organic layer was washed three times with aqueous bicarbonate (250 mL) and once with brine. After drying over sodium sulfate the product was chromatographed on silica gel (eluting with hexanes) to afford 2.21 g of the azide (89%). $^1H$ NMR ($CDCl_3$) $\delta$ 7.26 (s, 1H), 7.24 (s, 1H), 6.96 (d, $J$ = 8.7 Hz, 1H), 3.89 (m, 1H), 2.89 (m, 4H), 2.10 (m, 1H), 1.88 (m, 1H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 137.5, 132.3, 131.5, 130.9, 129.2, 120.0, 56.6, 34.2, 27.6, 26.7. Anal. Calcd for $C_{10}H_{10}BrN_3$: C, 47.63; H, 4.01; N, 16.67. Found: C, 47.69; H, 4.01; N, 16.80.

**2-Amino-6-bromo tetralin (18).** At ambient temperature, $CoBr_2$ (42.4 mg, 0.19 mmol) was added to EtOH (60 mL), making a light blue solution. 2,2'-Dipyridyl (90.9 mg, 0.58 mmol) was added, and the solution became orange and then yellow. After adding $NaBH_4$ (0.48 g, 12.7 mmol), the solution was dark blue. The azide (2.44 g, 9.70 mmol) was added slowly (exothermic). After 2 h, the reaction was quenched with HOAc until no bubbling was observed with addition of acid. After concentrating in vacuo, the crude product was chromatographed on silica gel (95:5:0.5 $CH_2Cl_2$:MeOH:$NH_4OH$) to afford 2.03 g of the amine as an oil (92.5% yield). $^1H$ NMR ($CDCl_3$) $\delta$ 7.17 (s, 1H), 7.14 (s, 1H), 6.88 (d, $J$ = 7.9, 1H), 3.10 (m, 1H), 2.82 (m, 3H), 2.41 (m, 1H), 1.92 (m, 1H), 1.50 (m, 1H), 1.38 (s, 2H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 138.2, 134.3, 131.4, 130.9, 128.7, 119.3, 47.0, 38.9, 32.5, 27.9. Anal. Calcd for $C_{10}H_{12}BrN$: C, 53.11; H, 5.36; N, 6.20. Found: C, 52.92; H, 5.31; N, 6.01.

**Enamide 22a.** A solution of **10** (50 g, 0.18 mol), benzamide (54.7 g, 0.45 mol), and Amberlyst 15 (25 g) in 250 mL of toluene was heated to reflux for 24 h with continuous removal of water using a Dean–Stark trap. The hot mixture was filtered, and the resin was washed with 2 × 200 mL of toluene. The combined solution was heated to 60 °C and extracted with 1% sodium bicarbonate solution (500 mL) followed by water (400 mL). The solution was concentrated *in vacuo* to 250 mL, and the product was allowed to crystallize at 20 °C. The slurry was cooled to 0–5 °C for 1 h, filtered, and washed with toluene (3 × 25 mL at 0 °C) followed by hexane (2 × 25 mL). After drying at 50 °C *in vacuo*, 42.7 g of the enamide was obtained as a tan solid.

Filtering a methylene chloride solution of **22a** through a short column of silica gel, followed by crystallization from toluene, yielded a pure sample, as colorless crystals, mp 156–157 °C. $^1H$ NMR ($CDCl_3$) $\delta$ 2.54 (t, 2H, $J$ = 8.5 Hz), 2.89 (t, 2H, $J$ = 8.5 Hz), 6.9 (d, 1H, $J$ = 7 Hz), 7.15-7.30 (m, 3H), 7.35 (m, 3H), 7.8 (d, 2H, $J$ = 6 Hz). $^{13}C$ NMR ($CDCl_3$) $\delta$ 165.9, 135.4, 134.8, 134.7, 133.6, 131.9, 129.9, 129.6, 128.8, 127.5, 126.9, 119.0, 111.1, 27.7, 27.4. Anal. Calcd for $C_{17}H_{14}NOBr$: C, 62.22; H, 4.88; N, 4.24. Found: C, 62.11; H, 4.20; N, 4.20.

**Asymmetric Hydrogenation.** A solution of enamide **22a** (20 g) in methanol (400 mL) was deoxygenated using $N_2$ and charged into a stirred autoclave. A deoxygenated solution of Ru–(*S*)–BINAP(Ph)Cl (100 mg) in 50 mL of methanol was added. The autoclave was pressurized with 150 psi $H_2$ at 35 °C and agitation continued for 24 h. The solution was concentrated to 200 mL, and the product was crystallized at 0–5 °C for 2 h. After filtration, washing with 3 × 10 mL of cold methanol and drying at 50 °C *in vacuo*, 18.3 g (87%) of product was obtained as colorless crystals, mp 188–190 °C. $^1H$ NMR ($CDCl_3$) $\delta$ 1.75–195 (m, 1H), 2.05–2.25 (m, 1H), 2.68 (dd, 1H, $J$ = 9 and 16 Hz), 2.77–2.95 (m, 2H ), 3.15 (dd, 1H, $J$ = 4.8 and 17 Hz), 4.35–4.55 (m, 1H), 6.34 (d, 1H, $J$ =7.5 Hz), 6.91 (d, 1H, $J$ = 8 Hz), 7.2–7.3 (m, 2H), 7.40–7.55 (m, 3H), 7.75 (dm, 2H, $J$ = 10 Hz). $^{13}C$ NMR ($CDCl_3$ ) $\delta$ 27.2, 28.4, 35.2, 45.5, 119.8, 126.9, 128.5, 129.0, 131.0, 131.6, 133.1, 134.6,, 137.7, 167.2. $(\alpha)_D$ 38.2° ($c$ = 1, $CHCl_3$). Anal. Calcd for $C_{17}H_{16}NOBr$: C, 61.82; H, 4.88; N, 4.24. Found: C, 61.74; H,4.78; N, 4.17. Chiral HPLC assay: 99.6% ee (Chiracel OD-R; $CH_3CN$ : $H_2O$: $NaClO_4$, 60:40:0.1., 1.5 mL/min. UV detection at 254 nm; $t_R$ (*S* isomer) = 13 min, $t_R$ (*R* isomer) = 15.5 min.

**Benzamide Hydrolysis.** A mixture of benzamide **23a** (13.8 g), methanesulfonic acid (28 mL), acetic acid (21 mL), and water (21 mL) was placed in a heavy walled glass tube, sealed, and heated in a rocking autoclave to 160 °C for 24 h. The mixture was cooled and diluted with water (100 mL) and the pH adjusted to 12 using 50% aqueous sodium hydroxide. The product was extracted with *tert*-butyl methyl ether (150 mL) and washed with 0.4 N NaOH (100 mL) and brine (100 mL). Quantitative HPLC assay of the extracts indicated 8.6 g (93%) of the aminotetralin **18**. HPLC assay: Zorbax Rx-C8 column. Acetonitrile:water (0.1% $H_3PO_4$). Gradient from 20: 80 to 90:10 over 25 min. Flow rate 1.5 mL/min. UV detection at 254 nm; $t_R$ (aminotetralin **18** ) = 6.4 min, $t_R$ (benzamide **23**) = 25 min.

***N*-Methyl-*N*-ethyl-4-oxo-piperidinium Iodide (19).** Methyl iodide (3.67 mL, 58.9 mmol) was slowly added to a solution of *N*-ethylpiperidone (6.62 mL, 49.1 mmol) in acetone (50 mL) while using a water bath to maintain the reaction temperature 20–30 °C. The mixture was stirred at 20–25 °C for 5 h, and the product was collected by filtration and washed with acetone (20 mL). The product was dried *in vacuo* for 2 h to provide 12.4 g (94%). $^1H$ NMR (300 MHz, DMSO-$d_6$), $\delta$ 3.78 (t, $J$ = 6.5, 4H), 3.64 (q, $J$ = 7.3, 2H), 3.23 (s, 3H), 2.71 (m, 4H), 1.31 (t, $J$ = 7.2, 3H). $^{13}C$ NMR (75.5 MHz, DMSO-$d_6$) $\delta$ 201.8, 58.0, 57.6, 46.5, 34.8, 7.6. MS (EI) 142, 141, 128, 127, 82, 72, 55. Anal. Calcd for $C_8H_{18}IN$: C, 35.70; H, 5.99; N, 5.20; I, 47.15. Found: C, 35.71; H, 5.97; N, 5.15; I, 47.29.

**Bromopiperidone 21.** A solution of iodide salt **19** (12.4 g, 46.2 mmol) in water (23 mL) was added over 30 min to a refluxing mixture of amine **18** (6.96 g, 30.8 mmol) and potassium carbonate (0.43 g, 3.1 mmol) in ethanol (53 mL). The reaction mixture was heated to reflux for an additional 45 min. Water (55 mL) was added over 30 min. The slurry was then cooled to 20 °C over 1 h and aged for 1 h. The product was filtered and washed with water (128 mL). The material was dried *in vacuo* at 40 °C to provide 8.25 g (87%) of the desired bromopiperidone **21**. $[\alpha]_D$ +58° ($c$ = 1.0 MeOH), IR ($CHCl_3$) 2940, 2820, 1720, 1600, 1485, 1200 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.23 (s, 1H), 7.21 (s, 1H), 6.95 (d, $J$ = 8.4 Hz, 1H), 2.85 (m, 9H), 2.48 (t, $J$ = 5.9, 4H), 2.09 (m, 1H), 1.68 (m, 1H). $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 209.3, 138.3, 138.5, 134.6, 131.3, 131.0, 128.8, 119.4, 59.6, 48.9, 41.9, 31.5, 29.2, 25.9. MS (EI) 309, 307, 210, 184, 124, 82, 69, 55, 42, 28. Anal. Calcd for $C_{15}H_{18}BrNO$: C, 58.46; H, 5.89; N, 4.54. Found: C, 58.50; H, 5.79; N, 4.39.

**(R)-5,6,7,8-Tetrahydro-6-(4-oxopiperidin-1-yl)-2-naphthalenecarbonitrile (3).** Palladium acetate (116 mg, 0.52 mmole) and tri-*o*-tolylphosphine (632 mg, 2.08 mmol) were charged to a round bottom flask and evacuated and then vented to nitrogen. *N*-Methylpyrrolidinone (12 mL) which had been degassed with $N_2$ was added, and the mixture was heated to 55 °C for 30 min. Diethylzinc in hexane (0.94 mL of 1 M solution) was added, and the mixture was maintained at 55 °C for 30 min.

This mixture was then cannulated to a flask containing bromopiperidone **21** (4.0 g, 13 mmol) and zinc cyanide (0.916 g, 7.8 mmol) in NMP (20 mL). The reaction mixture was heated to 60 °C for 1.5 h and then quenched slowly into a mixture of toluene (54 mL), water (33 mL), and ammonium hydroxide (9 mL) over 30 min. The organic layer was filtered through Celite, washed with dilute ammonium hydroxide (5 mL of concentrated ammonium hydroxide and 15 mL of water), and then concentrated to 30 mL of total volume, and heptane (90 mL) was added. The resulting slurry was stirred for 16 h and the product was collected by filtration. The product was dried *in vacuo* at 40 °C to provide 2.64 g (80%). Mp = 168–169 °C. IR ($CHCl_3$) 2940, 2820, 2230, 1720, 1490, 1380, 1220, 1135 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.34 (s, 1H), 7.33 (s, 1H, 7.14 (d, $J$ = 8.4 Hz, 1H), 2.89 (m, 9H), 2.45 (t, $J$ = 6.0 Hz, 4H), 2.11 (m, 1H). $^{13}C$ NMR (75.5 MHz, $CDCl_3$), $\delta$ 209.1, 141.7, 137.6, 132.2, 130.2, 129.2, 119.1, 109.6, 59.1, 48.8, 41.8, 32.3, 29.0, 25.7. MS (EI) 254, 124, 82, 69, 55, 42, 28. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.0. Found: C, 75.51; H, 7.17; N, 10.97.

***N*-[1'-(6-Cyano-1,2,3,4-tetrahydronapth-2(*R*)-yl)-3,4-dihydro-4-oxospiro[2*H*-1-benzopyran-2,4'-piperidin]-6-yl]-methanesulfonamide Monohydrochloride (2). Caution: This compound is a PB-ECL Level 4 compound and should be handled with extreme caution!** To a solution of pyrrolidine (2.0 mL, 24 mmol) in methanol (60 mL) was added the 5-sulfonamido-2-hydroxyacetophenone **4** (4.0 g, 17.5 mmol) at 20–25 °C. Cyanopiperidone **3** (4.0 g, 15.7 mmol) was added to the solution, and the mixture was stirred for 24 h. A 1 M solution of HCl in IPA (24 mL) was added to the mixture over 10 min and the resulting solution was heated to 40 °C. An additional 24 mL of 1 M HCl in IPA was added, and the mixture was heated to 60 °C for 1 h. The resulting slurry was cooled to 20 °C over 1 h and stirred for an additional 6 h. The product was filtered, washed with methanol (25 mL), and dried *in vacuo* to provide 6.15 g (85%). IR (Nujol) 2725–2400, 2226, 1683, 1610, 1333, 1153, 856 $cm^{-1}$. $^1H$ NMR (300 MHz, $CD_3OD$:$D_2O$, 70:30) $\delta$ 7.70 (d, $J$ = 2.8 Hz, 1H), 7.54 (m,

3H), 7.40 (d, $J$ = 7.9 Hz 1H), 7.24 (d, $J$ = 8.9 Hz, 1H), 4.8 (active), 3.7 (m, 1H), 3.6–3.4 (m, 4H), 3.15 (m, 2H), 3.0 (S, 3H), 2.9 (m, 2H), 2.4 (m, 3H), 2.13 (m, 4H). $^{13}$C NMR (75.5 MHz, $CD_3OD$:$D_2O$, 70:30) $\delta$ 194.0, 157.8, 140.1, 138.0, 133.7, 133.5, 132.9, 131.8, 131.1, 121.8, 121.4, 120.8, 120.4, 110.9, 76.9, 47.5, 46.4, 46.2, 39.6, 32.5, 31.2, 28.9, 24.9. Anal. Calcd for $C_{25}H_{28}N_3O_4SCl$: C, 59.81; H, 5.62; N, 8.37. Found: C, 59.44; H, 5.60; N, 8.20. HRMS calcd for $C_{25}H_{28}N_3O_4S$: 466.1801. Found: 466.1788.

**(+)-*N*-[1′-(6-Cyano-1,2,3,4-tetrahydro-2(*R*)-naphthalenyl)-3,4-dihydro-4(*R*)-hydroxyspiro[2*H*-1-benzopyran-2,4′-piperidin]-6-yl]methanesulfonamide (25). Caution: This compound is a PB-ECL Level 4 compound and should be handled with extreme caution!** To a slurry of **2** (16.86 g, 0.032 mol) in methylene chloride (300 mL) was added 5% aqueous sodium bicarbonate (163 mL) at 20–25 °C. The mixture was stirred for 1 h and allowed to settle. The layers were separated, and the organic layer was washed with brine (164 mL). The methylene chloride solution was then treated with Darco KB (5.0 g) at 20 °C for 3 h. The carbon was filtered off and the cake was washed with methylene chloride (300 mL). The methylene chloride solution of free base was concentrated by atmospheric distillation to a final volume of 278 mL which contained 13.9 g (0.030 mol) of **2** free base. 2-Propanol (2.2 mL, 0.031 mol) was added, and the mixture was cooled to −18 °C. Borane–methyl sulfide (7.64 mL of 10 M) was added dropwise over 5 min, and the resulting solution was stirred for 1 h at −18 °C. The oxazaborolidine·$BH_3$ complex (0.89 g, 0.0031 mol) was added as a solid in one portion, and the mixture was stirred at −18 °C for 30 min. The mixture was warmed to 15 °C over 45 min. After 45 min at 15 °C methanol (245 mL) was added and the mixture was stirred for 30 min at 15–20 °C. The mixture was then heated to distill off methyl sulfide, methylene chloride, and trimethyl borate (bp 53–58 °C). Additional methanol (250 mL) was added, and the batch was heated to 65 °C for 30 min to break the amine borane complex. Acetonitrile (250 mL) was added and distilled *in vacuo* to a final volume of 110 mL. Water (150 mL) was added over 1.5 h at 20 °C, and the slurry was stirred for 6 h. The product was filtered, washed with water (25 mL), and dried to provide 14.5 g (92%) as a white crystalline solid. HPLC assay: Zorbax Rx C8. Acetonitrile:water (0.1% $H_3PO_4$). Gradient 15:85 to 50:50 over 25 min. Flow rate = 1.0 mL/min. UV detection at 220 nm. $t_R$ (product) = 20.8 min. $t_R$ (ketone) = 22.7 min. Chiral assay of the Mosher ester's on Water's $\mu$-Bondapak C18 column. Methanol:water (0.1% $H_3PO_4$). Flow rate = 1.25 mL/min, UV detection at 220 nm, $t_R$ (minor *S*-ester) = 20.3 min, $t_R$ (major *R*-ester) = 23.8 min. $^1$H NMR (300 MHz, DMSO-$d_6$), $\delta$ 9.32 (bs, 1H), 7.50 (m, 2H), 7.30 (bm, 2H), 6.99 (m, 1H), 6.74 (d, $J$ = 8.6 Hz, 1H), 5.40 (bs, 1H), 4.64 (m, 1H), 2.91 (m, 1H), 2.89 (s, 3H), 2.8–2.6 (m, 8H), 2.05 (m, 2H), 1.7–1.5 (m, 6H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$), $\delta$ 149.6, 142.5, 137.9, 131.9, 130.3, 130.1, 128.9, 126.9, 122.7, 121.8, 119.1, 116.9, 108.2, 74.2, 60.7, 58.7, 44.2, 40.7, 36.6, 33.4, 31.5, 28.0, 24.8.

***N*-[1′-(6-Cyano-1,2,3,4-tetrahydro-2(*R*)-naphthalenyl)-3,4-dihydro-(4(*R*)-hydroxyspiro[2*H*-1-benzopyran-2,4′-piperidin}-6-yl]methanesulfonamide Monohydrochloride Dihydrate (1). Caution: This compound is a PB-ECL Level 4 compound and should be handled with extreme caution!** Free base **25** (28.0 g, 0.053 moles (contains 12 wt % $H_2O$) was dissolved in acetone (42 mL) and heated to 43 °C. Aqueous HCl (18.76 mL of 3.0 M) was added, and the solution was stirred for 5 min at 45 °C. Water (196 mL) was added over 5 min while acetone was distilled out under reduced pressure. The temperature was maintained between 40–50 °C throughout the addition and distillation. The slurry was then cooled to 20 °C, stirred for 1 h, and filtered. The product was washed with water (25 mL) and dried under an air sweep to provide 26.0 g of the salt as a dihydrate. $[\alpha]^{25}_{365}$ = +113°. IR (Nujol) 3339, 2225, 1320, 1150 cm$^{-1}$. $^1$H NMR (400 MHz, $CD_3OD$:$D_2O$, 70:30) $\delta$ 7.55 (s, 1H), 7.52 (dd, $J$ = 7.9, 1.6 Hz, 1H), 7.39 (d, $J$ = 7.9 Hz, 1H), 7.36 (d, $J$ = 2.4 Hz, 1H), 7.14 (dd, $J$ = 8.7, 2.4 Hz, 1H), 6.96 (d, $J$ = 8.7 Hz, 1H), 4.88 (t, $J$ = 6.7 Hz, 1H), 4.73 (broad actives), 3.69 (m, 1H), 3.58–3.35 (m, 4H), 3.40 (dd, $J$ = 15.9, 3.2 Hz, 1H), 3.18 (dd, $J$ = 15.9, 11.1 Hz, 1H), 3.11 (m, 1H), 3.03–2.92 (m, 1H), 2.98 (S, 3H), 2.46 (m, 1H), 2.35 (bd, $J$ = 15.1, 1H). $^{13}$C NMR (100.6 MHz $CD_3OD$:$D_2O$, 70:30) $\delta$ 150.9, 139.8, 137.7, 133.4, 131.5, 130.8, 126.5, 126.0, 124.6, 120.1, 119.2, 110.6, 72.5, 63.1, 62.6, 46.3, 46.1, 40.9, 39.0, 33.9, 32.5, 30.8, 28.6, 24.6. Anal. Calcd for $C_{25}H_{30}N_3OSCl$: C, 59.55; H, 6.00; N, 8.37; S, 6.36. Found: C, 59.29; H, 5.91; N, 8.35; S, 6.33.

**Acknowledgment.** We thank Alan Douglas and Robert Reamer for their assistance with the NMR aspects of this work.

JO950519R