A Practical Asymmetric Synthesis of a Novel Topically Active Carbonic Anhydrase Inhibitor

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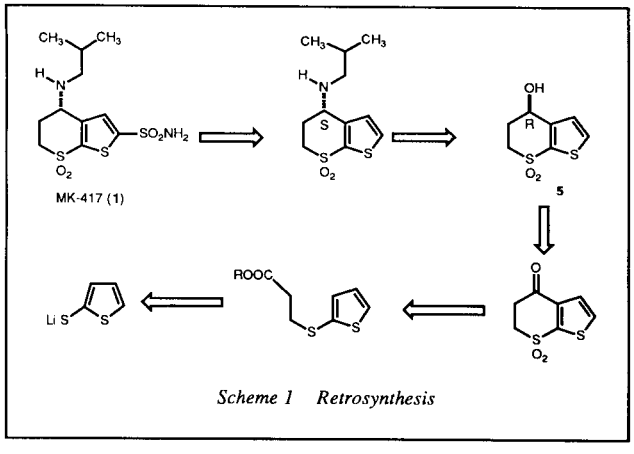
Introduction

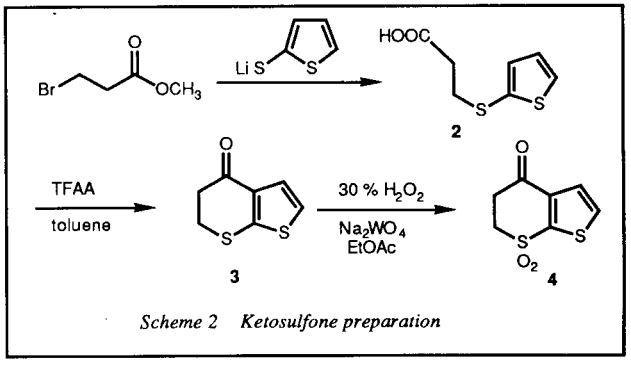
Carbonic anhydrase inhibitors (CAI's) have been used as an oral or intravenous preparations to lower interocular pressure (IOP) in patients with glaucoma.[1] Although the carbonic anhydrase inhibitors are very effective in reducing aqueous humor formation, systemic side effects limit their use in some patients. A topical CAI with an efficacy profile similar to that of oral agents would constitute a major advance in the medical treatment of glaucoma and ocular hypertension.[2] It could well represent the treatment of choice if it were well tolerated, long acting, and devoid of systemic side effects. We chose a novel CAI, the thieno-thiopyran-2-sulfonamide derivative, MK-417[3] as a clinical development candidate. To support ongoing chemical and safety assesment studies for MK-417, we required a practical asymmetric synthesis of this compound. Our retrosynthesis of MK-417 (**1**) is shown in Scheme 1. The key step of this approach is the introduction of chiralty at C-4: an asymmetric reduction of a ketone followed by suitable activation and S_N2 displacement with amine. Due to an inherent solubility problem, we introduced the sulfonamide functionality late stage in synthesis.[4]

Ketosulfone Preparation

The synthesis of ketosulfone is shown in Scheme 2. Lithiation of thiophene, followed by addition of sulfur resulted in formation of lithiated 2-mercaptothiophene, which was alkylated with 3-bromopropionic acid to afford carboxylic acid (**2**). Cyclization was originally carried out by the treatment of the acid chloride with tin tetrachloride; however an improved cyclization process was developed using trifluoroacetic anhydride. This process provided ketosulfide (**3**) in good yield and in excellent purity. Oxidation of **3** with hydrogen peroxide/sodium tungstate afforded the ketosuflone (**4**) in 89% yield.



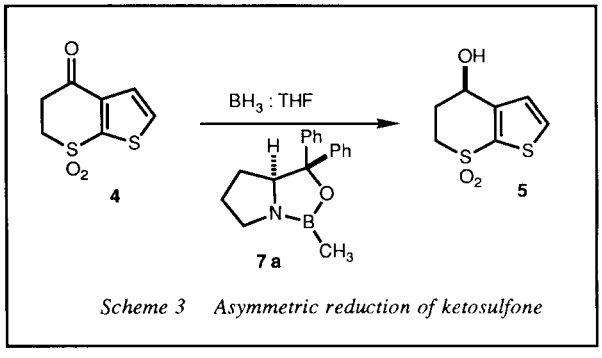
Scheme 1 Retrosynthesis



Scheme 2 Ketosulfone preparation

Asymmetric Reduction

To obtain the 4-(R)-hydroxy thienothiopyran derivative, we tried three common asymmetric reducing reagents for the reduction of ketosulfone (**4**) to alcohol (**5**): (-)-B-chlorodiisopinocampheylborane[5] (IPC_2BCl; 12:88, *R:S*), yeast reduction (11:89, *R:S*), and 1,3,2-oxazaborolidine catalyzed borane reduction[6] (90:10, *R:S*). Since work up of IPC_2BCl reduction on a large scale would be difficult and yeast gave the undesired enantiomer, we chose to develop the process based on borane reduction. This process would be suitable for large scale operation due to its catalytic nature, and the R-stereochemistry is provided using natural proline (Scheme 3).



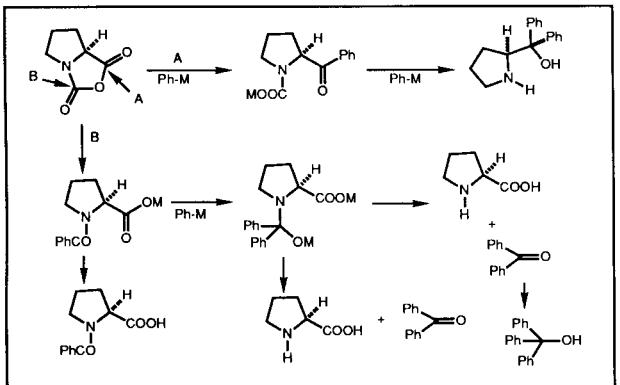
Scheme 3 Asymmetric reduction of ketosulfone

Synthesis of Pyrrolidinemethanol

To support our development of a practical asymmetric synthesis of alcohol (**5**), we required a reproducible procedure for the large-scale preparation of (*S*)-α,α-diaryl-2-pyrrolidinemethanol (**6**) and the corresponding B-methyloxazaborolidine [(*S*)-**7a**]. Diaryl-2-pyrrolidinomethanols are utilized in the preparation of several 1,3,2-oxazaborolidines.[7] Although many routes to (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (**6a**) have been reported[8], none were deemed suitable for our needs. We developed a practical two-step synthesis of (*S*)-**6a** by the reaction of phenylmagnesium chloride with proline-*N*-carboxyanhydride [(*S*)-Pro-NCA, (*S*)-**8**]. Treatment of (*S*)-

proline with phosgene in THF afforded (*S*)-Pro-NCA, (*S*)-**8** in >95% yield. It is preferable that the filtered THF solution be used immediately. This process is also applicable for the preparation of (*R*)-**8**.

Addition of (*S*)-**8** to phenyllithium gave **6a** in 93% yield with 92% ee, determined by capillary GC analysis after a standard derivatization with (*R*)-MTPA[(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid]. In order to minimize observed racemization, we have developed the process by reacting purified (*S*)-**8** with phenylmagnesium chloride at -20°C. The major byproducts of the reaction were identified to be proline, the *N*-benzamide derivative of proline, benzophenone and triphenylmethanol (Scheme 4).

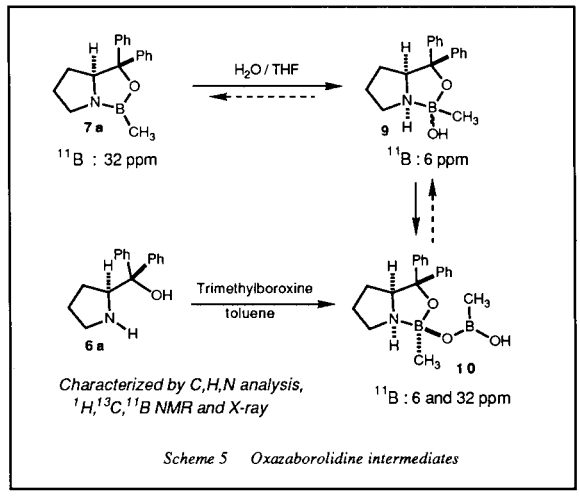


Scheme 4 Reaction of (S)-Pro-NCA with phenylmagnesium chloride

We developed a convenient work-up for isolation of the amino alcohol from the excess magnesium salts. The reaction was quenched into aqueous H_2SO_4, affording an easily stirred precipitate of $MgSO_4$, which was removed from the aqueous THF solution by filtration. Removal of THF gave an insoluble precipitate of (*S*)-**6a** sulfate which was isolated. After washing of crude **6a** sulfate with water followed by ethyl acetate, the purity of **6a** sulfate was >99 wt%. This process was successfully applied to several other substituted phenyl Grignard reagents such as 4-fluoro, 4-chloro, 4-methyl,4-trifluoromehtyl, 3,4-dimethyl, etc to afford α,α-diaryl-2-pyrrolidinemethanols in excellent ee (>99%).

Synthesis of 1,3,2-Oxazaborolidine

Several reported methods[7] for the preparation of 1,3,2-oxazaborolidine (**7**) are not acceptable for large scale operation and, in addition, these processes are not reproducible. In our hands, enantioselective reductions using **7a** prepared by these methods showed erratic results; therefore we investigated the chemistry of **7**.[9] Careful examination of **7a** prepared by the reported methods indicated that it is contaminated with 2-13% of unreacted amino alcohol and "dimeric" impurity. Our initial method to drive formation of **7a** to completion was the sequential addition of methylboronic acid and azeotropic removal of both water and excess methylboronic acid. The oxazaborolidine catalyst prepared *via* this process, with purification by molecular distillation (140°C/0.01 mBar), reproducibly afforded high levels of enantioselectivity. Addition of 1 equivalent of H_2O or D_2O to the solution of (*S*)-**7a** resulted in the appearance of a single major resonance (^{11}B NMR 8.9 ppm) that quickly changed to two resonances (7.8 and 30.4 ppm). When we attempted to prepare **9** by addition of trimethylboroxine (0.33 mole) to diphenyl-2-pyrrolidinemethanol (**6a**), we obtained a different white crystalline solid (**10**). Spectroscopic examination indicated that **10** has two B-CH_3 groups per molecule. Therefore it was more efficiently prepared by adding 0.67 mole of trimethylboroxine to (*S*)-**6a** (Scheme 5).



Scheme 5 Oxazaborolidine intermediates

The structure of "dimer" (**10**) was established by single-crystal X-ray analysis on a crystal grown in benzene. The crystal structure of **10** is shown in Figure 1 and represents the absolute configuration of this molecule. There are no unusual bond distances and angles present in this structure.

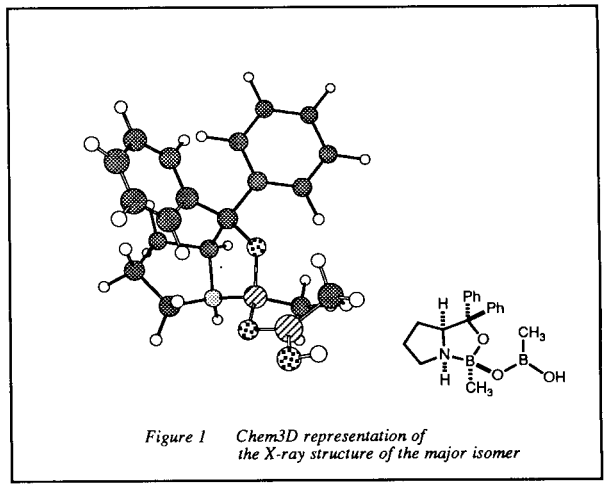


Figure 1 Chem3D representation of the X-ray structure of the major isomer

Variable-temperature 'H NMR studies were employed to characterize the solution behavior of **10**. At ambient temperature, **10** exists as two isomers in dynamic equilibrium, the major isomer having the structure identified by single-crystal X-ray analysis. NOE difference studies at ambient temperature clearly show saturation transfer between the two species. Diagnostic NOE's obtained at -10°C in $CDCl_3$ are shown in Figure 2.

Based on these data we concluded that **7a** prepared by the reported method was contaminated with **9** and **10**. Thus our prefered method for the preparation of (*S*)-**7a** is as follows (Scheme 6): to a toluene solution of (*S*)-**6a** is added trimethylboroxine (0.67 mole). The solution is stirred at 20° for 30 min and then heated to reflux with removal of toluene and methylboronic acid (as trimethylboroxine). This is followed by three subsequent toluene flushes to insure complete removal of water and excess methylboronic acid. This process provides 2,1,3-oxazaborolidine **7a** in 99% yield with 99% purity. Similarly, we prepared a series of phenyl-substituted oxazaborolidine catalysts in quantitative yield in most cases.

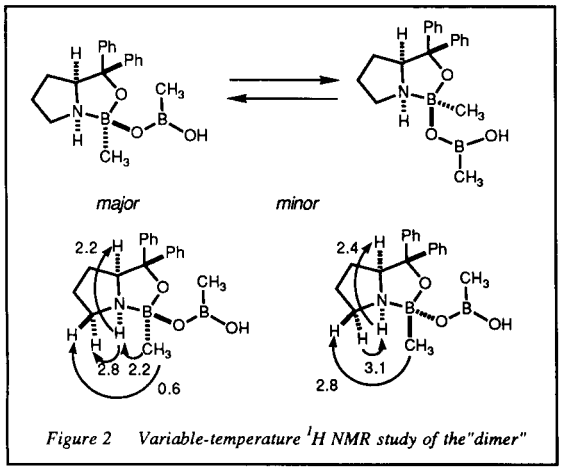
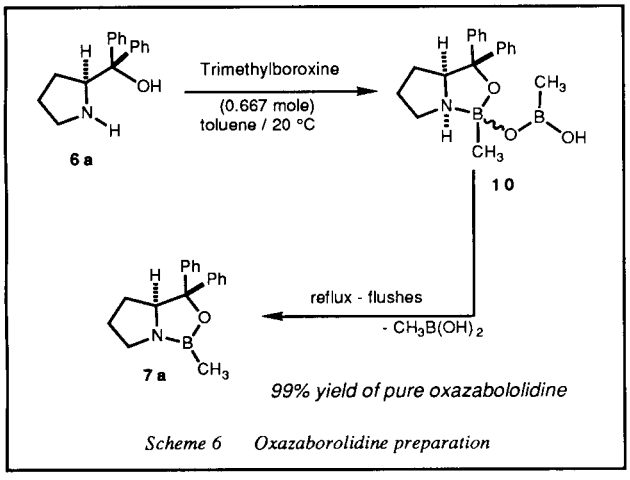


Figure 2 Variable-temperature ^1H NMR study of the "dimer"



Scheme 6 Oxazaborolidine preparation

Asymmetric Reduction of Ketosulfone Catalyzed by 1,3,2-Oxazaborolidines

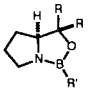
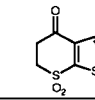
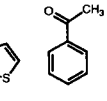
Initially, we obtained erratic results from the oxazaborolidine catalyzed reduction: from 3:1 to 50:1 selectivity. Neat borane-methyl sulfide complex (BMS) was employed instead of borane-THF complex or commercial solution of BMS because we found commercial samples gave widely variable results with the same sample of ketone **4**. After several investigations, we settled on adding the catalyst (solid or toluene solution) to the ketone in THF, coooling to -15°C, and then adding BMS at a rate to maintain the temperature below -10°C. This protocol generally provided >93% of the desired enatiomer. As shown in Table 1, intentional addition of water to the reaction with pure ketone **4** proved deleterious.

Table 1. Effect of water on the oxazaborolidine-catalyzed reduction of **4**

H_2O (µg / ml THF)	*R* : *S*
41	98 : 2
103	78 : 22
396	75 : 25

The amount of water required to lower the enantioselective excess from 95% to 50% is approximately 1 mg of water per 1 g of **4**. With this information in hand, we routinely dried the ketone (**4**) in THF over 4- or 5-Å molecular sieves prior to reduction until Karl-Fisher titration showed the water content to be less than 40 µg/ml. This drying procedure reproducibly provided ≥95:5 selectivity. Further, we were concerned that methylboronic acid, trimethylboroxine, diphenylprolinol, benzophenone, **9** or **10** could be in the catalyst we were using. Separate addition of 2 mol% diphenylprolinol, 2 mol% methylboronic acid, 1 mol% triphenylboroxine, or 1 mol% benzophenone to reaction mixtures prior to the addition of BMS resulted in diminished enantioselectivity: 85:15 for the first two reactions, 92:8 for the third and 96:4 for the fourth. Compounds **9** and **10** were screened as catalysts (10 mol%) and provided enantioselectivities of 79:21 and 86:14, respectively, with ketone **4**. With a good catalyst and ketone there was limited variability in enantioselectivity (95-99% *R*-isomer), and that has been attributed to the quality of the catalyst employed. The generality of our reaction conditions and catalyst was demonstrated by the reduction of several pro-chiral ketones as shown in Table 2.

Table 2. The enantioselective reduction of prochiral ketones

R	R'				
Ph	Me	98/2	99/1	98/2	97/3
Ph	Ph	98/2	86/14	91/9	97/3
4-$CF_3C_6H_4$	Me	98/2	95/5	96/4	96/4
3,5-$Me_2C_6H_3$	Me	96/4	97/3	96/4	97/3
Ph	4-FC_6H_4	99/1	94/6	88/12	97/3
Ph	4-MeC_6H_4	99/1	94/6	92/8	97/3
Ph	4-$MeOC_6H_4$	97/3	85/1	92/8	95/5

Contrary to the hypothesis of the Harvard group,[7] our data indicate that the postulated transition-state assembly does not fully explain the observed results (Table 2). Upon inspection of models of the proposed transition-state assembly, one would not predict that the larger B-phenyl group would fit endo to the 3,3,0 ring system as well as a B-methyl (1,3 interactions are encountered). Since the B-alkyl substituent can be as bulky as phenyl and still be an effective catalyst, one could argue that contact between the ketone and the weakly Lewis basic boron is minimized. Unfortunately, the studies required to thoroughly understand the nature of the asymmetric induction are beyond the scope of our investigation.

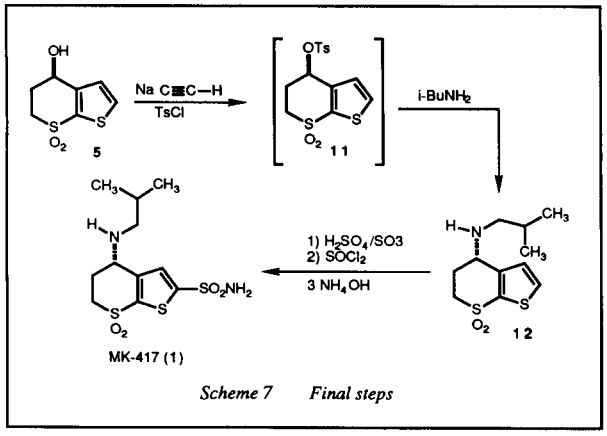
Separation of Alcohol 5 from Diphenylprolinol

Commonly used procedures such as simple aqueous acid extraction failed. We developed an alternate non aqueous isolation protocol. After the reduction, the excess borane was quenched with methanol and the volatile boron compounds were removed by distillation. Filtration through SuperCel removed the remaining boron species. Eluting the alcohol (**5**)/diphenylprolinol (**6a**) mixture in methanol through a column packed with the ammonium form of Amberlyst 15 resulted in clean separation with **6a** being retained. Diphenylprolinol (**6a**) was easily recovered by regenerating column with 6% aqueous ammonia in methanol. Employing this process we have separated reaction mixtures on a kilogram scale and recovered 99% of alcohol (**5**) and 95% of diphenyl-prolinol (**6a**).

Final Steps

Tosylation of alcohol (**5**) under standard conditions formed large amounts of chloride. The sodium salts of **5** generated with sodium hydride, provided the derived tosylate free from chloride, albeit with low conversion. The sodium salt prepared under these conditions

formed an unstirrable gummy solid in THF and/or dimethoxyethane. After several other sodium bases were examined, we concluded that commercially available sodium acetylide (a slurry in xylene/light mineral oil) is the base of choice. The combination of sodium acetylide and toluenesulfonyl chloride (TsCl) cleanly provided tosylate (**11**) in high yield. The displacement with isobutylamine gave desired amine (**12**) with insignificant loss in stereochemical integrity. The overall tosylation/displacement sequence afforded a 73% yield of >99:1 (*S:R*) amine (**12**) after recrystallization. The thiophene ring of amine (**12**) is sufficiently deactivated that forcing conditions are required for electrophilic substitution. Fuming sulfuric acid (oleum) produced regioisomers (a 90:10 = C_2:C_3) at 5-8°C. Treatment with a large excess of thionyl chloride followed by aqueous ammonia quench gave MK-417 in overall 65% yield from amine (**12**). This process provided MK-417 (isolated as its hydrochloride salt hemihydrate) in nine steps, 30% overall yield from bromopropionic acid, with >95% enantioselectivity.



Scheme 7 *Final steps*

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