A Convenient Route for the Synthesis of *S,S*- and *R,R*-Warfarin Alcohols

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S,S- and *R,R*-warfarin alcohols **3** are prepared in good yield and in 99% d.e. (diastereomeric excess) by the reaction of *S*- or *R*-warfarin **1** with *S* or *R*-Alpine-Hidride **2**.

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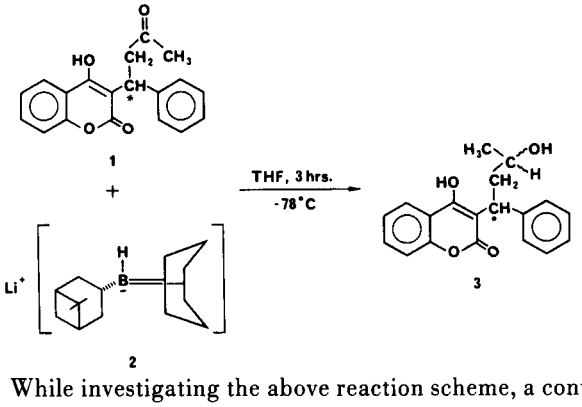
Fractional crystallization of diastereomeric salts with quinidine and quinine has been the most widely used method for the resolution of racemic warfarin [1]. This method is slow and gives poor yield. To overcome these disadvantages, we investigated a new approach which involves the reduction of racemic warfarin to diastereoisomeric alsohols with chiral borohydride reagents followed by oxidation of chromatographically separated alcohols. Lithium *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride (Alpine Hydride) made from (+)-α-pinene is used for the selective reduction of ketones to *R*-enriched alcohols [2]. Likewise, *S*-Alpine-Hydride made from (-)-α-pinene reduces ketones to their *S*-enriched alcohols. It was thought that racemic warfarin would react with *S*- or *R*-Alpine-Hydride to yield a mixture of warfarin alcohols (*S,S*- and *R,S*- or *S,R*- and *R,R*,-warfarin alcohols) which can be resolved by both tlc and LC.



1 + 2 → 3

While investigating the above reaction scheme, a convenient route for the synthesis of *S,S*- or *R,R*-warfarin alcohol was found. Experimental results showed that irrespective of the chirality of Alpine-Hydride reagents, the reduction products of racemic warfarin were always a mixture of unresolvable *S,S*- and *R,R*-warfarin alcohols. Reduction of *S*-warfarin with *S*- or *R*-Alpine-Hydride gave *S,S*-warfarin alcohol in 99.8% d.e. Similarly, *R,R*-warfarin alcohol was obtained by the reduction of *R*-warfarin with *S*- or *R*-Alpine-Hydride. The reason for not getting the chiral induction products in these reactions could be due to the large steric hinderance in both warfarin and the borohydride reagents.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The proton nmr spectra were recorded on a Brucker 200 MHz instrument using TMS as the internal reference. Mass Spectra were recorded at 70 eV on a Finnigan Model 4000 Mass Spectrometer with Model 6000 Data System. Optical rotations were measured on a Perkin-Elmer Model 241 Polarimeter.

THF was distilled under nitrogen from benzophenone ketyl and stored under a positive nitrogen pressure. Alpine-Hydride solutions (0.5 *M* in THF) were obtained from Aldrich Chemical Co.

S,S- or *R,R* Warfarin Alchohol **3a**.

A dry 100 ml three-necked flask equipped with a side arm covered with a rubber stopper, a dropping funnel, a reflux condenser connected to a purge valve and a magnetic stirring bar was flushed with nitrogen. The flask was charged with 2.47 g (8.2 mmoles) of *S*-warfarin and flushed again with nitrogen. A syringe was used to add 25 ml of dry THF to the flask and the contents of the flask were cooled to -78°C. Then 45 ml (16.6 mmoles) of a 0.5 *M* solution of *R*-Alpine-Hydride (or *S*-Alpine-Hydride) in THF (cooled to -78°) was introduced slowly (~ 15-20 minutes). The resulting mixture was stirred at -78° for 3 hours. Then it was brought to 0° and excess hydride was destroyed by the addition of water. Glacial acetic acid (3 ml) was added to the reaction mixture and refluxed for 2 hours. After adding 20 ml of 0.1 *N* sodium hydroxide solution, THF was removed in a rotary evaporator and then the aqueous solution was extracted with 3 × 25 ml ethyl ether. The aqueous extract was diluted to 250 ml with distilled water and acidified to *p*H 4 with 0.5 *N* hydrochloric acid solution. The resulting milky solution on standing overnight gave a crystalline product. Crystallization of the product from acetone/water gave colorless crystals of *S,S*-warfarin alcohol, yield 1.79 g (72%), mp 171-172° (uncorrected), lit [3] mp 171-172.5°; $[\alpha]_D^{25}$ = -85.6° ± 0.4° (C = 0.84, 95% ethanol); the mass spectrum of the product has molecular ion peak at m/z 310 with abundant fragments at m/z 265, 251, 249, 187, 121, and 93; nmr (perdeuterioacetone): δ 1.41 (d, 3H), 2.42-2.59 (m, 1H), 2.66-2.83 (m, 1H), 3.88-4.05 (m, 1H), 4.91 (t, 1H).

R,R-Warfarin Alcohol (**3b**).

This product was prepared in a manner similar to that described for **3a** starting with *R*-warfarin and *R*- or *S*-Alpine Hydride. The product, *R,R*-warfarin alcohol, was crystallized from acetone/water, yield 71%, mp 171.5-173°, lit [3] mp 172-173.5°; $[\alpha]_D^{25}$ = +82.5° ± 0.6° (C = 0.79, 95% ethanol); the mass spectrum of the product has molecular ion peaks at m/z 310 with abundant fragments peaks at m/z 265, 251, 249, 187, 121 and 93; nmr (perdeuterioacetone): δ 1.40 (d, 3H), 2.41-2.57 (m, 1H), 2.65-2.83 (m, 1H), 3.87-4.05 (m, 1H), 4.90 (t, 1H).

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REFERENCES AND NOTES

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