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The First Practical Asymmetric Synthesis of *R* and *S* -Warfarin

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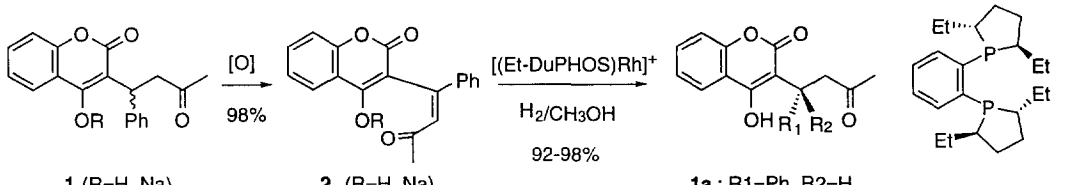
Abstract: A highly efficient synthesis of both enantiomers of warfarin **Ia** and **Ib** has been developed by using a novel two step "chiral switch" strategy and a DuPHOS-Rh(I) catalyzed asymmetric hydrogenation.

There has been increasing interest in the pharmaceutical industry to replace existing racemic drugs by their pure enantiomeric form due to the fact that one of the enantiomers often has a pharmacological profile superior to the racemate.[1] Asymmetric synthesis is one of the most attractive ways to produce these chiral drugs,[2] but it can be costly if multistep operations and/or stoichiometric amounts of chiral reagents are required. Conceptually, one of the most economic approaches for the preparation of these chiral drugs is the "*chiral switch*": conversion of a racemate into its pure enantiomer directly. This can be achieved by an asymmetric transformation, such as selective inversion of the "wrong" enantiomer into the desired "right" enantiomer, or conversion of the racemate into a prochiral molecule in which a chiral center can be restored via asymmetric synthesis to provide the pure enantiomer. Sodium warfarin (**1** R=Na), Coumadin®, is the most widely prescribed orally-active anticoagulant in North America.[4] Clinically, warfarin is administered as a racemic mixture. Both **1a** and **1b** are potent inhibitors of vitamin K epoxide reductase, but they possess dissimilar pharmacological profiles. The major metabolites of S-warfarin are S-6-hydroxyl and S-7-hydroxyl



1 (R=H, Na) **2** (R=H, Na) **1a** : R1=Ph, R2=H **1b**: R1=H, R2=Ph (R,R)-Et-DuPHOS

warfarin, which both are derived by 2C9 P_{450} isoenzyme.[5] The 2C9 isoenzyme is also critical for the metabolism of many other common drugs, so one of the problems associated with warfarin is drug-drug interactions. On the other hand, R-warfarin can be metabolized by several pathways, which did not cause the metabolic drug interactions observed in the clinical use of racemic sodium warfarin **1**.[6] Until now, preparation

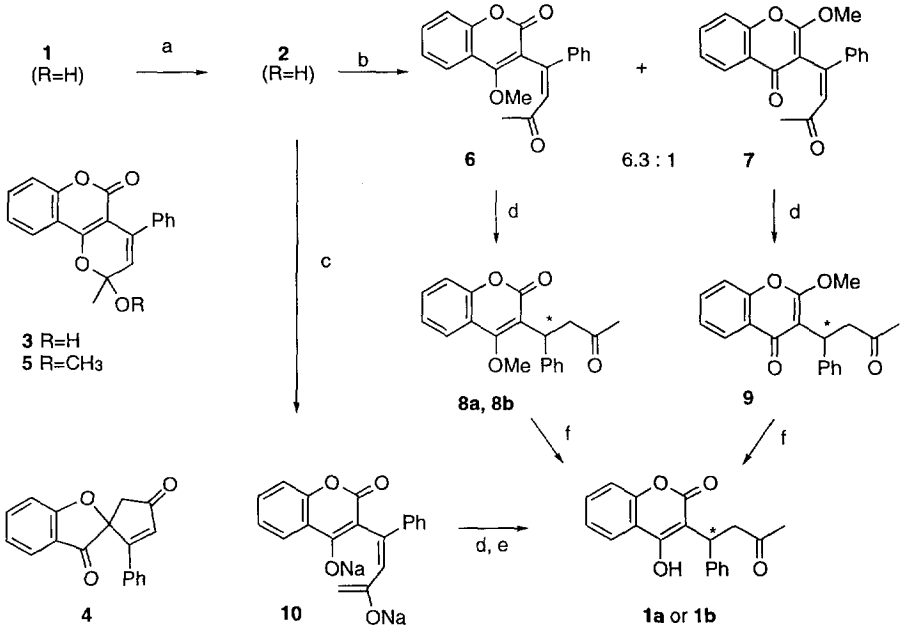
of enantiomeric pure warfarin has involved resolution of racemic warfarin via repeated recrystallization of quinidine/quinine salts,[7] or chromatographic separation.[8] These methods are limited to small scale preparation. We report here a highly efficient two step process by using our chiral switch strategy for the preparation of either R or S-warfarin via a highly efficient DuPHOS - Rh catalyzed asymmetric hydrogenation of an α,β-unsaturated ketone as the key step. To our knowledge, this is the first report that a racemic ketone can be "switched" to its pure enantiomers via a prochiral enone, and the first asymmetric hydrogenation of a prochiral α,β-unsaturated ketone in high enantiomeric excess.[3]

Dehydrowarfarin **2** (R=H), first isolated and synthesized by Kaminsky and co-workers by copper (I) - induced oxidation of racemic warfarin **1** (R=H) in pyridine, is a known metabolite of rat hepatic microsomal metabolism of warfarin **1b**.[9] In our hands, the reported procedure was unreliable and at best gave only poor yields of oxidized product **2** (R=H) (<30%). By maintenance a continuous air-stream through the reaction mixture and elevation the reaction temperature (55-60°C), however, dehydrowarfarin **2** (R=H) was obtained in excellent yield (90-98%). Oxidation proceeds in a stereoselective fashion resulting in exclusively *E*- alkene. This geometric isomer is stabilized by formation of hemiketal **3**, as confirmed by the X-ray crystal structure. Careful monitoring of the reaction progress was necessary as prolonged exposure of dehydrowarfarin **2** (R=H) to the oxidation conditions resulted in the formation of a novel spiro benzofuranocyclopentene **4** (Scheme 1). The mechanism of oxidation is analogous to that observed in oxidative decarboxylation of carboxylic acids to the corresponding carbonyl compounds which is believed to involve transient and highly reactive Cu(III) species.[10] Methylation of the coumarin 4-hydroxyl substituent inhibits the reaction, supporting the hypothesis of 4-cupryl intermediates in the oxidative process.

Initial attempts of hydrogenation of dehydrowarfarin **2** (R=H) using a Me-DuPHOS-Rh catalyst system in methanol were unsuccessful. Facile cyclization of **2** (R=H) to the ketal **5** resulted in the generation of an unreactive internalized olefinic bond. By use of tetrahydrofuran as a solvent, this transformation was avoided and hydrogenation proceeded smoothly to afford S-warfarin with a moderate 70% ee (Table 1). Subsequently, the sodium salt of **2** (R=Na), readily prepared by treatment of **2** (R=H) with sodium methoxide or aqueous sodium hydroxide solution, was hydrogenated to afford R or S warfarin with enantioselectivites ranging from 82-86% ee in methanol and 88% ee in 3:2 isopropanol-methanol. No further improvement in enantioselectivity was observed when the countercations were changed to lithium or potassium, or when the reaction temperature was lowered. Acidification and a single recrystallization of the crude hydrogenation products provided *R*- **1a** and *S*-**1b** warfarin in >98% ee.

In contrast to the high enantioselectivities observed in enamide,[11] α-(acylamino)acrylic acid[12] and α,β-unsaturated acid hydrogenations,[13] highly enantioselective hydrogenation of acyclic α,β-unsaturated ketones with conventional chiral catalysts has rarely been achieved.[3] Recently, 2-alkylidene α,β-unsaturated cyclopentanones were hydrogenated in high enantiomeric excess using BINAP-Ru (II) catalyst. Acyclic substrates were not reduced.[14] Substrate chelation through a secondary donor group appeared to be critical, not only for the attainment of high enantioselectivity in catalytic asymmetric reduction but also for reaction progression. Dehydrowarfarin **2** (R=H or Na) has three potential sites, the 4-OH and 2-carbonyl in the coumarin ring, and the sidechain carbonyl, through which chelation to the cationic Rh-center may occur. In order to investigate the role of the coumarin ring in this reaction, hydrogenation of 4-methoxycoumarin **6** and 2-methoxychromone **7** was investigated. Methylation of dehydrowarfarin **2** (R=H) with

Scheme 1



a: Cu(I)Cl, py, 55-60°C, air, 3-5h, 90-98%; b: Me_3SiCHN_2, CH_2Cl_2, 0°C, 95 %; c: 2N NaOH or NaOMe/MeOH, 92%; d: Hydrogenation conditions (see Table 1); e: 2M HCl; f: BBr_3, CH_2Cl_2, -78°C-0°C.

Table 1: Asymmetric Hydrogenation of Dehydrowarfarins[a]

entry	Substrate	Ligand: DuPHOS	Solvnet	Product (Config.)[b]	yield%	ee%[b]
1	**2** (R=H)	(R,R)-Me	MeOH	**5**	92	N/A
2	**2** (R=H)	(R,R)-Me	THF	**1b** (S)	>98	70
3	**2** (R=Na)	(R,R)-Et	MeOH	**1b** (S)	96	83(>98)[c]
3	**2** (R=Na)	(S,S)-Et	MeOH	**1a** (R)	>98	86(>98)[c]
4	**2** (R=Na)	(S,S)-Et	MeOH/IPA[d]	**1a** (R)	>98	88
5	**2** (R=Li)	(R,R)-Et	MeOH	**1b** (S)	>98	82
6	**2** (R=K)	(R,R)-Et	MeOH	**1b** (S)	>98	82
7	**6**	(R,R)-Me	MeOH	**8b** (S)	91	86
8	**6**	(S,S)-Et	MeOH	**8a** (R)	95	89
9	**7**	(S,S)-Et	MeOH	**9** (R)	>98	78

[a] Standard reaction conditions: Methanol, 20-25°C, initial hydrogen pressure of 60psi, reaction time (15-18h), catalyst precursor $[(COD)Rh(P_2)]^+OTf^-$ (0.1 mol %). [b]Determined by chiral HPLC. [c] After one recrystallization from acetone and water. [d] Isopropanol: Methanol 3:2.

trimethylsilyldiazomethane readily afforded a separable 6:1 mixture of the 4-methoxycoumarin **6** and 2-methoxychromone **7**. Under mild hydrogen pressure (60 psi) and at room temperature, 4-methoxycoumarin **6** was hydrogenated to *R*-4-methoxywarfarin (**8a**) in 89% ee and to *S*-4-methoxywarfarin (**8b**) in 86% ee with (S,S)-Et- and (R,R)-Me-DuPHOS-Rh(I) catalysts respectively. Similarly, the 2-methoxy analog **7** was

reduced to *R*-2-methoxywarfarin **9** by the use of (S,S)-Et-DuPHOS as a ligand in 78% ee. Demethylation with boron tribromide then afforded **1a** or **1b**. It is not clear which sites play the key role for stereocontrol in the process of asymmetric hydrogenation of **2**, although we speculate, based on the preliminary result that hydrogenation of the disodium salt of dehydrowarfarin **10** was found to proceed with analogous stereocontrol with (S,S)-Et-DuPHOS (82% ee), that asymmetric hydrogenation is being assisted by ring-carbonyl chelation.

The ready availability of racemic warfarin, the high efficiency of the two step process and the high enantioselectivities of the DuPHOS-Rh hydrogenation to yield either the *R*- **1a** or *S*- **1b** enantiomer make this route to enantiomerically pure warfarin commercially attractive. Initial studies aimed at probing functional group tolerance have revealed that our chiral switch strategy may also provide convenient routes to other important coumarin containing anticoagulants including acenocoumarin[15,16] and coumachlor.[15,17] Further studies of this novel process are currently in progress.

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