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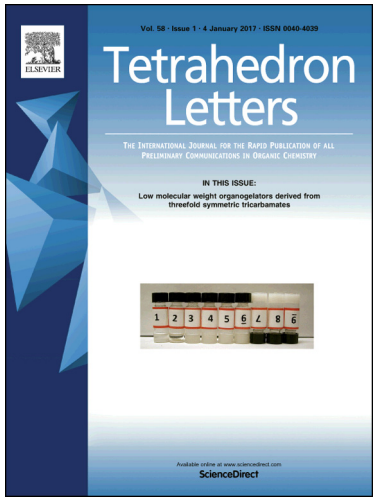

Enantioselective rhodium-catalyzed hydroacylation to access the four stereoisomers of anti-rodent difenacoum

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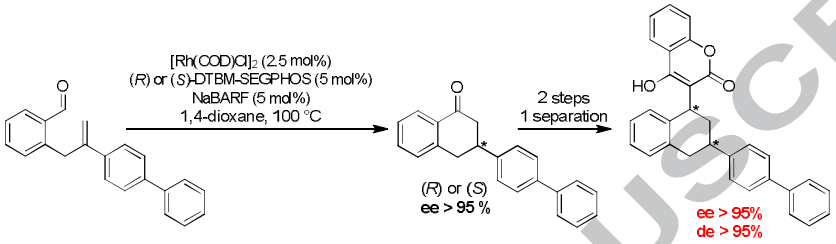

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Enantioselective rhodium-catalyzed hydroacylation to access the four stereoisomers of anti-rodent difenacoum

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ABSTRACT

An efficient asymmetric synthesis of the four stereoisomers of difenacoum, an anticoagulant currently used as a rodenticide in racemic form, is performed using a key step of rhodium catalyzed enantioselective intramolecular hydroacylation. Optimization of the last step, condensation of 4-hydroxycoumarin with chiral 3-([1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydronaphthalen-1-ol, is also discussed. After chromatographic separation of the *cis* and *trans* diastereoisomers, the four stereoisomers were all obtained with excellent enantioselective and diastereoselective ratios (ee ≈ 96% and de > 96%).

Following the development of warfarin discovered in the early fifties for preventing thrombosis, a second generation of anticoagulant has emerged in the middle of the seventies due to the intensification of resistance observed with the first generation. Consequently, brodifacoum and difenacoum (Figure 1), also called super-warfarins, were synthesized with significant structural modification on the lateral chain -introduction of substituted tetralinyl fragment-. Especially, difenacoum **1** has attracted considerable interest for its anticoagulant properties by inhibiting vitamin K epoxide reductase due to its greater potency in comparison to warfarin ($K_i \approx 0.07$ µM *vs* $K_i \approx 0.72 \pm 0.1$ µM on susceptible rats and $K_i \approx 1.6$ µM *vs* $K_i \approx 29$ µM on resistant rats).[1]

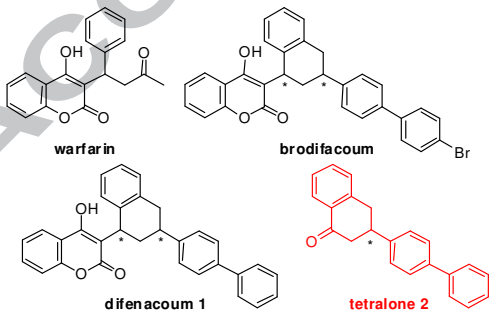


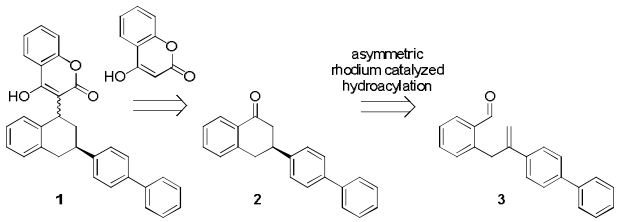
Figure 1 Examples of 1st -2nd generation anticoagulants and targeted tetralone

Unfortunately, due to their increased activity in comparison with 1st generation of anti-coagulants, these compounds are less eco-compatible, threatening the food chain of rodents, especially their predators.

The two stereogenic centers present in difenacoum **1** resulted in the existence of four stereoisomers, which can be described as *cis* and *trans* couples, relative to the cyclohexyl skeleton. A strategy classically used in medicinal chemistry would be to identify the most active stereoisomer, balancing the biological activity and the eco-toxicity. General growing opposition against the use of racemates as drugs / bioactive compounds is discharged by the treatment with a single enantiomer, exhibiting significant differences in biological activities such as pharmacology, toxicology and pharmacokinetics. US Food and Drug Administration (FDA) even recommends the assessments of each enantiomer activity for racemic drugs and promotes the development of new chiral drugs as single enantiomers.[2]

In the continuity of our projects on 4-hydroxycoumarin nucleus, either about methodological aspects, or towards biological applications, our laboratory was receptive to contribute to the enantioselective synthesis of difenacoum.[3]
The first synthesis of racemic difenacoum in six steps and an overall yield of 4% was reported in 1976 by Woodward and coll starting from 1-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-phenylethan-1-one.[4] In 1997, Ferreira and coll subsequently improved the productivity of the synthesis (54% in six steps starting from bromobiphenyl) in comparison with the seminal work, by changing completely the retrosynthetic approach to tetralone.[5] The same group then adapted the previous methodology using chiral auxiliaries [(4*R*,5*S*)-(−)] or [(4*S*,5*R*)-(+)]-1,5-dimethyl-4-phenyl-2-imidazolidinone.[6] The key step, a 1,4 addition of benzyl-based organocuprate to chiral α,ß-unsaturated imide, was

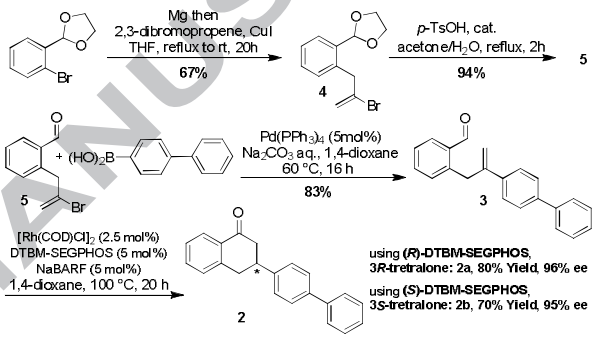
performed with an excellent diastereoselectivity (de up to 97%). The four stereoisomers of difenacoum were obtained in seven steps, but required the used of chiral auxiliaries, adding two supplementary steps of introduction / cleavage of the auxiliary. All the strategies described in literature to access either racemic or enantiopur difenacoum **1** share tetralone **2** as a common intermediate. At last step, difenacoum is formed by condensation of 4-hydroxycoumarin with tetralol, obtained from $NaBH_4$ reduction of tetralone **2**.



Scheme 1 Proposed retrosynthesis of difenacoum

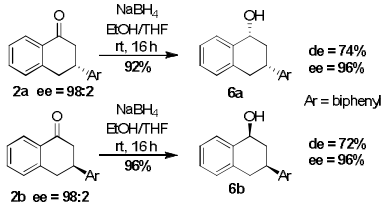
Our objective was to develop an enantioselective synthesis of optically pure (*R*) and (*S*)-3-((1,1'-biphenyl)-4-yl)-3,4-dihydronaphthalen-1(*2H*)-one **2** using a rhodium catalyzed enantioselective intramolecular hydroacylation as a key step (Scheme 1). After a survey of literature, we discarded the direct functionalization by enantioselective 1,4-addition of α,β-unsaturated tetralone, due to its propensity to aromatization into corresponding α-naphthol as reported by Nagasawa.[7] Intramolecular alkene hydroacylation represented thus an appropriate option to provide benzocyclic ketones.[8] Several groups reported the synthesis of indanones and tetralones *via exo-*/*endo*-hydroacylation catalyzed by transition metals, mainly rhodium and copper.[9] Extension to asymmetric olefin hydroacylation has been also covered to 3-substituted indanones, phthalides and other cyclic chiral ketones.[10] In 2015, Stanley developed an enantioselective rhodium-catalyzed *endo*-hydroacylation of unactivated olefin-substituted aldehydes affording chiral tetralones.[11] The optimized conditions required 2.5 mol% of $[Rh(COD)Cl]_2$, 5 mol% of (*R*)-DTBM-SEGPHOS ligand and 5 mol% of NaBARF.[12] Encouraged by this recent work, we exploited these reaction conditions towards the synthesis of the key intermediate tetralone **2**.

The precursor 2-(2-((1,1'-biphenyl)-4-yl)allyl)benzaldehyde **3** was first prepared in 3 steps: commercially available 2-(2-bromophenyl)-1,3-dioxolane reacted in the presence of 3 eq of Mg tunings, CuI (20 mol %) and 2,3-dibromopropene providing olefin **4** in 67% yield. Subsequent hydrolysis of the dioxolane regenerated aldehyde **5** in acidic medium in 94% yield. A Suzuki cross-coupling reaction between bromovinylic derivative **5** and 4-biphenylboronic acid provided *ortho*-allylbenzaldehyde **3**. This key precursor was then subjected to the asymmetric rhodium-catalyzed hydroacylation in the presence of $[Rh(COD)Cl]_2$, (*R*)-DTBM-SEGPHOS and NaBARF in 1,4-dioxane at 100 °C (Scheme 2). We were delighted to observe the formation of the desired tetralone **2** with more than 90% conversion within 20 hours. Handling NaBARF did not require specific attention as the experimentation tolerates the use of commercially available reagent containing 1-5% of water. Indeed, enantiomerically enriched tetralones **2a** and **2b** were independently isolated with 80% yield (96% ee) and 70% yield (95% ee) depending on the use of the bulky ligand, respectively (*R*)-DTBM-SEGPHOS leading to **2a** and (*S*)-DTBM-SEGPHOS leading to **2b** (Scheme 2).



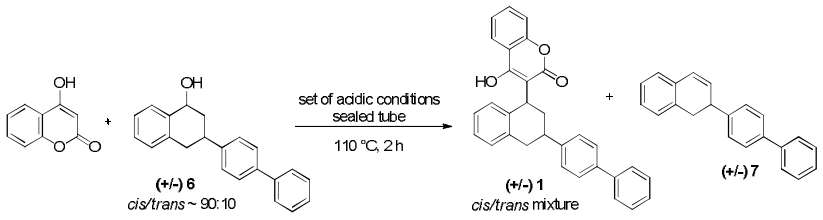
Scheme 2 Synthesis of enantiopure tetralones **2a** and **2b**[13]

Tetralones **2a** and **2b** were subsequently reduced with $NaBH_4$ in EtOH/THF affording predominantly *cis* benzyl alcohols **6a** and **6b** (dr ~ 90:10) in 92-96% yield (Scheme 3).[14,5]



Scheme 3 Reduction of enantiomerically enriched tetralones **2a** and **2b**

Table 1. Condensation of 4-hydroxycoumarin with an excess of racemic tetralol **6**

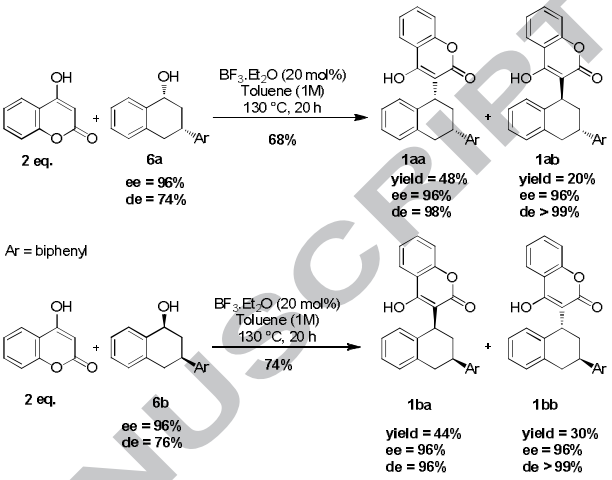


Entry	Coumarin/tetralol	Conditions	Yield % of compound 1
1	**1/1**	$FeCl_3$ (10 mol%), DCE (0.2M)	**42%**
2	**1/1**	BF_3OEt_2 (20 mol%), CH_3CN (0.2M)	**31%**
3	**1/2**	BF_3OEt_2 (20 mol%), CH_3CN (0.2M)	**60%**
4	**1/2**	$FeCl_3$ (10 mol%), DCE (0.2M)	**73%**
5	**1/3**	$FeCl_3$ (10 mol%), DCE (0.2M)	**98%**

In a second part, we investigated the condensation of 4-hydroxycoumarin and tetralol **6** using Brønsted or Lewis acidic catalytic systems.

Several conditions have already been reported in the literature for the condensation of 4-hydroxycoumarin with secondary benzylic alcohol (HCl gas at 160 °C,[5] free[15] or supported[16] *p*-TsOH, iodine,[17] $BF_3.Et_2O$[18] and various metallic catalysts[19]). $BF_3.Et_2O$ and $FeCl_3$, known to be efficient acidic catalysts (Table 1) were first investigated in order to identify the ideal stoichiometric ratio between the two reactants. Condensation of 4-hydroxycoumarin with racemic tetralol **6**, under both conditions, led to the competitive formation of 2-([1,1'-biphenyl]-4-yl)-1,2-dihydronaphthalene **7** (Table 1, entries 1 and 2). To overcome this decrease of yield, 4-HC was used as the limiting reagent. With 20 mol% of $BF_3.Et_2O$ in acetonitrile at 110 °C, difenacoum **1** was obtained in 60% yield using 2 equivalents of tetralol **6** (Table 1, entry 3). With 10 mol% of $FeCl_3$ in 1,2-dichloroethane at 110 °C, the yield increased to 73% (Table 1, entry 4) and even reached 98% with 3 equivalents of tetralol **6** (Table 1, entry 5). Nevertheless, this result should be tempered due to the use of two wasted equivalents of high added-value tetralol **6**. Taking into account this substantial drawback, experiments were resumed, fixing a supplementary parameter: tetralol as the limiting reagent. All the further experiments were performed with 2 equivalents of 4-hydroxycoumarin in comparison with tetralol. Unfortunately, condensation using Brønsted acids (*p*TsOH, CSA, HCl_g) provided 70 to 78% formation of by-product **7** (Table 2, entries 1 to 3). With catalytic amount of iodine in CH_3NO_2 at 50 °C, a selectivity of 52% was observed in favour of difenacoum (Table 2, entry 4).

Under previously reported $FeCl_3$ and $BF_3.Et_2O$ conditions (Table 2, entries 5 and 9),[18,19] modest selectivities of 50% were observed. Selecting again these two catalysts which proved to be efficient in the first part of our study, different solvents and concentrations were screened (Table 2, entries 6-8, 10-11). With 10 mol% of $FeCl_3$, the evaluated ratio of difenacoum could not exceed 57% but with 20 mol% of $BF_3.Et_2O$ in toluene at a concentration of 1M at 130 °C for 20 h, conversion reached 94%. Upon these conditions, racemic difenacoum was isolated in 66% yield (Table 2, entry 11).[20] We applied the identified conditions to the enantiomerically enriched tetralols to allow the isolation of the four stereoisomers of difenacoum (Scheme 4). Tetralol **6a** (ee = 96%; de = 74%) reacted with two equivalents of 4-hydroxycoumarin, in the presence of 20 mol% of $BF_3.Et_2O$, in toluene at 130 °C for 20 hours in sealed tube. After separation by column chromatography, the two diastereoisomers **1aa** and **1ab** were isolated in respectively 48% (ee = 96% and de = 98%) and 20% yield (ee = 96% and de > 99%). The same procedure was repeated from tetralol **6b**, also providing the same range of yields and stereoselectivities.



Scheme 4 Condensation of 4-hydroxycoumarin with chiral tetralols

To conclude we reported the first enantioselective synthesis of the four stereoisomers of difenacoum using a rhodium-catalyzed *endo*-hydroacylation as a determining step for the asymmetric induction. The last step condensation of 4-hydroxycoumarin and enantiopur tetralol in the presence of $BF_3.Et_2O$ afforded separable diastereomers of difenacoum with a high stereoselectivity. This methodology offers the advantage to spare the high added-value tetralol **6** introduced as the limiting reactant.

Table 2. Condensation of tetralol **6** with a one-fold excess of 4-hydroxycoumarin [a]ratio determined by ^{1}H NMR; [b]reaction performed in a sealed tube

Entry	Conditions	Ratio % [a]	
		1	**7**
1	CSA (20 mol%), Na_2SO_4 (1.5 eq.), Toluene (0.2 M), 110°C, 16 h	**30**	**70**
2	APTS (20 mol%), Na_2SO_4 (1.5 eq.), Toluene (0.2 M), 110°C, 16 h	**22**	**78**
3	HCl_g, 160 °C, 30 min	**26**	**74**
4	I_2 (20 mol%), CH_3NO_2 (0.2M), 50 °C, 2 h	**52**	**48**
5	$FeCl_3$ (10 mol%), DCE (0.2M), 110 °C, [b] 20 h	**49**	**51**
6	$FeCl_3$ (10 mol%), DCE (1M), 110 °C, [b] 20 h	**57**	**43**
7	$FeCl_3$ (10 mol%), CH_3CN (1M), 110 °C, [b] 20 h	**33**	**67**
8	$FeCl_3$ (10 mol%), Toluene (1M), 130 °C, [b] 20 h	**54**	**46**
9	BF_3OEt_2 (20 mol%), CH_3CN (0.2M), 110 °C, [b] 2 h	**50**	**50**
10	BF_3OEt_2 (20 mol%), CH_3CN (1M), 110 °C, [b] 20 h	**73**	**27**
		isolated yield : 62%	
11	BF_3OEt_2 (20 mol%), Toluene (1M), 130 °C, [b] 20 h	**94**	**6**
		isolated yield : 66%	

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[12] (*R*)-DTBM-SEGPHOS **:** (*R*)-(−)-5,5′-Bis[di(3,5-di-*tert*butyl-4-methoxyphenyl) phosphino]-4,4′-bi-1,3-benzodioxole; NaBARF: Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

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[20] A blank experiment was made without any catalyst, leading to 48% of difenacoum and 52% of elimination product **7**. Despite these interesting results, the investigations were not carried on due to a significant decrease of the purity of the samples obtained.

Highlights

- The first enantioselective synthesis of the four stereoisomers of difenacoum
- The key step was an asymmetric hydroacylation reaction
- The 4 stereoisomers were obtained with ee ≈ 96% and de > 96%.