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An asymmetric approach to coumarin anticoagulants via hetero-Diels–Alder cycloaddition

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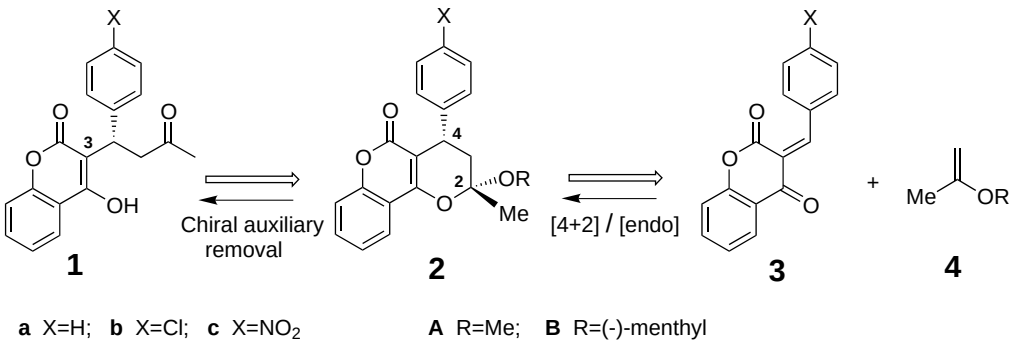
Abstract—We have developed a general, two-step protocol for the synthesis of chiral non-racemic coumarin anticoagulants (e.g. warfarin, coumachlor and acenocoumarol). This approach features a one-pot three-component tandem Knoevenagel–hetero-Diels–Alder reaction between in situ generated 3-arylidene-2,4-chromanediones and *iso*-propenyl ether derived from (−)-menthol.

A number of coumarin compounds possessing anticoagulant activity (like their prototype, dicoumarol) have been synthesised as potential drugs for the management of myocardial infarction. Starting from dicoumarol, a number of modifications (→**1a**–**1c**) of the 4-hydroxycoumarin moiety have been performed,[1] including the introduction of a (het)arylmethyl group at the 3-position and the stereochemical control of the newly created stereocentre.

Warfarin **1a** is today the dominant coumarin anticoagulant owing to its excellent potency and good pharmacokinetic profile. While its marketed form is the racemic sodium salt (Coumadin®), the anticoagulant activity of the (*S*)-(−) enantiomer is known to be six times higher than that of the (+)-enantiomer.[2] Access to both enantiopure warfarin enantiomers[3] is feasible through 'classical' racemate resolution, by crystallising the quinidine/quinine salts, as well as by direct chromatographic separation on a chiral stationary phase.

Our interest in this area was stimulated by the prospect of designing an enantioselective entry to this class of oral anticoagulants, which includes compounds such as **1a**–**1c**, based on chiral auxiliary-directed π-facial discrimination in an intermolecular hetero-Diels–Alder (HDA) reaction (Scheme 1). At the outset of our investigations there were no published reports of any asymmetric synthesis of **1a**. However, since 1996 Li et al. reported enantioselective hydrogenation in the presence of Duphos–Rh(I) catalyst as the key step in the synthesis of (−)-**1a**.[4]



Scheme 1. Asymmetric synthesis of chiral non-racemic coumarin anticoagulants **1a**–**1c**.

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3-Arylidene-2,4-chromanediones **3**, deriving from the Knoevenagel condensation of 4-hydroxycoumarin with aldehydes, undergo an easy HDA cycloaddition with suitable *iso*-propenyl ethers **4**. Heterodienes **3** are electron-deficient 4π-systems that may undergo inverse-electron-demand Diels–Alder reactions (which are favoured by a dominant interaction between the LUMO of 1-oxo-1,3-butadiene and the HOMO of electron-rich 2π-systems such as enol ethers, strained unsubstituted olefinic and acetylenic dienophiles). These are usually concerted non-synchronous transformations that preserve the configuration of the dienophile and usually exhibit high regioselectivity.[5]

In a preliminary attempt to synthesise (±)-**1a**–**1c**, the isolation of the requisite 3-arylidene-2,4-chromanediones **3a**–**3c** under classical Knoevenagel conditions, even at low temperature, proved unsuccessful, being uniformly frustrated by the formation of 2:1 adducts as the sole products.[6]

Therefore, we needed to develop different conditions so that Knoevenagel adducts **3** would not react further. Pilot studies disclosed that the one-pot three-component reaction of 4-hydroxycoumarin, benzaldehyde (1.1 equiv.) and 2-methoxypropene (2.2 equiv.) in dry dioxane (90°C, 4 hours, screw cap pressure tube) in the presence of catalytic ethylenediammonium diacetate (Tietze base) and powdered oven-dried 5 Å molecular sieves proved to be the most convenient and satisfactory, giving a mixture of *endo*- and *exo*-adducts **2Aa** in a 3:1 ratio (83% yield). These isomers correspond to the *cis*- and *trans*-products, respectively, regarding the 2-OMe and 4-Ph groups.

4-(4-Chlorophenyl)- **2Ab** and 4-(4-nitrophenyl)-pyranocoumarin **2Ac** were similarly obtained from the corresponding aldehydes in 78–84% range yield, with good diastereoselectivity favouring the *cis*(*endo*)-isomer (*cis*/*trans* ratio from 1.3:1 to 2.1:1). For all cycloadducts chemical shifts of H-(4) for the major isomers were consistently 0.1–0.3 ppm higher than those for minor isomers. The OMe group is ψ-equatorial in a half-chair conformation ($^3H_2$) for *cis* adducts and ψ-axial for *trans* adducts, considering the 4-aryl substituent to be ψ-equatorial in all cases.[7]

With the cycloaddition step under control, unmasking of the carbonyl function in **2Aa**–**2Ac** was next addressed. As expected, exposure of ketals to 3N HCl in the presence of SiO_2 as a promoter[8] or 19:1 TFA/H_2O (overnight, rt) furnished the targeted compounds **1a** (warfarin), **1b** (coumachlor) and **1c** (acenocoumarol) in near to quantitative yields. It should be noted that compounds **1a**–**1c** exist in solution as equilibrium mixtures of open-chain keto and cyclic hemiketal forms (as a diastereomeric mixture) as observed previously.[9]

From this finding we recognised the potential of the two-step cycloaddition/hydrolysis protocol for the general and enantioselective synthesis of coumarin anticoagulants. A few examples of chiral non-racemic 2-alkoxy-3,4-dihydro-2*H*-pyran synthesis via HDA reaction have been described, with the chiral auxiliary attached to the heterodiene[10,11] or to the dienophile.[12,13]

A survey of chiral auxiliaries was undertaken in order to optimise product diastereoselectivities and to increase yields such that this process might become synthetically useful. Specifically, *iso*-propenyl ether **4B**, derived from (−)-(1*R*,2*S*,5*R*)-menthol, has thus far given the best results among all of the chiral non-racemic vinyl ethers tested. A key advantage of using the menthyl group as a chiral auxiliary is that both enantiomers are available commercially, the auxiliary is cheap and is recyclable if required.

Since the methods previously reported for the preparation of these compounds [i.e. Hg(II)-promoted transetherification reaction with *n*-butyl vinyl ether][14] were not applicable, the required dienophile **4B** was prepared in an unoptimised yield of 51% with e.e. of 96% by modification of a literature method [(i) *iso*-propenyl methyl ether, dichloroacetic acid, rt; (ii) TMSOTf, TEA, DCM, 0°C→rt].[15]

The reaction of **4B** (1.1 equiv.) with benzaldehyde (1.2 equiv.) and 4-hydroxycoumarin in dry dioxane in the presence of Tietze base and 5 Å molecular sieves at 80°C was complete in 10 hours (TLC). Prior to chromatographic separation, analysis of the crude reaction mixture by ^{1}H NMR and HPLC analysis (Waters, μ-Porasil 7.8×300 mm, column) revealed that the reaction proceeded with *endo*-selectivity (with an *endo*/*exo* ratio of 4.1:1).

After release of the chiral auxiliary (19:1 TFA/H_2O), the enantioselectivity (76% e.e.) of the HDA reaction was determined by chiral HPLC of the crude product (on an *R*,*R* Whelk-O type column). In chromatographic separation of the crude product on a neutral alumina column (hexane/EtOAc 19:1) *cis*(*endo*)-adducts (2*R**,4*S**)-**2Ba** eluted first, followed by *trans*(*exo*)-adducts (2*R**,4*R**)-**2Ba**. It was found that the early eluted cycloadducts as a rule can be efficiently upgraded to diastereomeric purity by recrystallisation. Accordingly, the *endo*-mixture was dissolved in the minimum volume of EtOAc and diluted with twice the volume of di-*iso*-propyl ether. The resulting suspension was warmed to 40°C until a clear solution was obtained and allowed to stand at rt until crystals were formed. Two crystallisations and acid hydrolysis of enriched (2*R*,4*S*)-**2Ba** provided (*S*)-warfarin **1a** with e.e. of 95% by chiral HPLC in 61% overall yield referred to 4-hydroxycoumarin. The cleaved chiral auxiliary can easily be recovered at this stage if required.

Although the C-(2) stereochemistry is irrelevant to the present work, the (2*R*,4*S*)-absolute configuration in upgraded **2Ba** was evident from: (i) comparison of CD spectra (which showed the presence of an inherently dissymmetric chromophore with $[\theta] \approx 1.2\times10^5$ observed at ca. 220 nm) with those of the (2*R*,4*S*)-cyclocoumarol **2Aa** and (*S*)-warfarin;[16] (ii) the elution order in chiral HPLC of the hydrolysis products; (iii) NMR studies (^{1}H NMR, COSY and NOESY) and our previous

results on other related cycloadducts.[7b] Under our optimised conditions, 4-chloro- and 4-nitrobenzaldehyde reacted with **4B** to give (*S*)-coumachlor **1b** in 56% overall yield with 93% e.e. and (*S*)-acenocoumarol **1c** with 95% e.e. in 59% overall yield.

The reaction of **4B** with the in situ generated **3a**–**3c** in the presence of Lewis acids at rt was attempted with little success: either the products were obtained without any enantiomeric enrichment, or the Lewis acid was not an effective promoter. This is presumably due to the lability of electron-deficient olefin dienophiles, e.g. **3**, in the presence of many Lewis acids.

The major reaction products probably arise from an intramolecular HDA through an *s-trans* conformation of **4B**. This reaction exposes the C(α) *Re*-face of the double bond to intermolecular attack by (*Z*)-heterodiene, while positioning the C(α) *Si*-face so as to be shielded by the *i*-Pr group of the chiral auxiliary.

In summary, our strategy based on a thermal intermolecular HDA reaction represents a novel method for an enantiocontrolled installation of the stereogenic centre in coumarin anticoagulants. Furthermore, the successful incorporation of different substituents at C-(4) (cyclocoumarol numbering) makes it suitable for generating a library of enantiomerically enriched warfarin-like analogues.

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