

New Phenylglycine-Derived Primary Amine Organocatalysts for the Preparation of Optically Active Warfarin

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In this work we present new, fully synthetic phenylglycine-derived primary amine organocatalysts useful for the one-step preparation of optically active warfarin, an important anticoagulant. Both enantiomeric forms of the catalysts are equally available and can be prepared by robust procedures without recourse to chromatographic purification. Together with a co-catalyst, particularly acetic acid or 2,4-dinitrophen-

ol, they can furnish warfarin in approximately 80 % *ee* and represent inexpensive alternatives to other primary amine organocatalysts such as the chiral diamines and Cinchona-derived primary amines.

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Introduction

Warfarin is a Vitamin K antagonist, inhibiting Vitamin K epoxide reductase and thereby decreasing blood coagulation by preventing the Vitamin K-dependent synthesis of blood-clotting proteins. In the form of its sodium salt (Coumadin[®], Marevan[®]) it is one of the most widely prescribed anticoagulants for prevention of thrombosis and embolism. Although currently prescribed as the racemate, activity and metabolism are markedly dissimilar for the two enantiomers, the (*S*) enantiomer being more active than the (*R*) enantiomer by a factor of 2–5.^[1] Efficient asymmetric syntheses of warfarin are therefore of great interest, and organocatalysis in particular has proven itself a valuable instrument in the preparation of enantiomerically enriched warfarin.^[2]

The two key building blocks for virtually all preparations of warfarin are benzylideneacetone and 4-hydroxycoumarin. They are inexpensive industrial products, benzylideneacetone being simply the aldol condensation product of acetone and benzaldehyde, whereas 4-hydroxycoumarin is readily available from, among others, acetylsalicylic acid or *o*-hydroxyacetophenone.^[3] Through organocatalysis, these two simple building blocks can be forged directly into optically active warfarin.^[2] The asymmetric Michael addition of 4-hydroxycoumarin to benzylideneacetone is of special interest within organocatalytic reactions since it not only provides a product of crucial medical importance, but also because it mechanistically favours primary amine organocatalysts.^[2] Primary amine organocatalysis,^[4] either

alone or in conjunction with other functionalities,^[4f,4g] is a rapidly expanding field within organocatalysis with (among others) primary amino acids, Cinchona-derived amines and chiral diamines being the preferred catalysts.^[4] Unlike secondary amine organocatalysts, which can react with aldehydes, ketones and α,β -unsaturated aldehydes, the primary amine catalysts can also easily convert the less active α,β -unsaturated ketones.

Herein we wish to report our studies on the asymmetric organocatalytic preparation of warfarin, its preference for primary amine organocatalysts over the standard pyrrolidine-derived secondary amines and the development of new phenylglycine-derived organocatalysts that are cheaper and more large-scale-adaptable than previous primary amine organocatalysts, as well as nearly equally affordable in both enantiomeric forms.

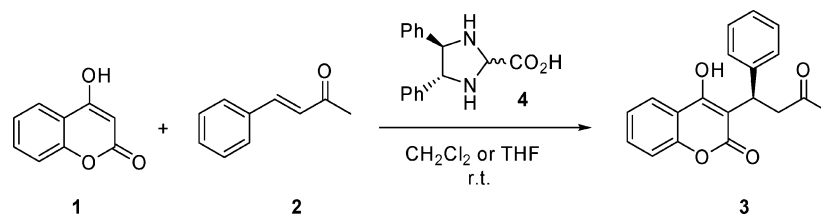
Results and Discussion

The research group of Jørgensen in Denmark reported in 2003 that the imidazolidine catalyst **4** was an efficient asymmetric catalyst for the formation of warfarin (**3**) from 4-hydroxycoumarin (**1**) and benzylideneacetone (**2**), as depicted in Scheme 1.^[2a]

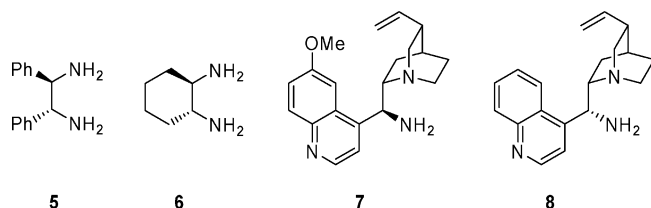
In 2006, a report argued convincingly that the efficiency of imidazolidine catalyst **4** in the preparation of warfarin originated in its decomposition into chiral diamine **5** (Figure 1) and that this chiral diamine was the genuine catalyst for the transformation.^[2b] The authors then employed this diamine directly, using acetic acid as co-catalyst, and obtained similar or better results.^[2b] Importantly, the authors postulated a diimine intermediate as essential for the high degree of asymmetric induction.^[2b] Interestingly, replacing diaryldiamine **5** with alkylldiamine **6** gave reduced stereose-

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Scheme 1. First organocatalytic preparation of warfarine.^[2a]

lectivity and a different reaction pattern, an effect that was attributed to the greater basicity of **6** vs. **5**.^[2b] More recently, the combination of chiral diamine **5** (or its enantiomer) and acid co-catalyst has also proven successful in the archetypical aldol reactions of substituted benzaldehydes with ketones, a manifestation of the growing utility of primary amine organocatalysts.^[5]

Figure 1. Organocatalysts for the asymmetric preparation of warfarin.^[2]

In 2007, a third report on the organocatalytic preparation of warfarin was published,^[2c] this time by using the Cinchona-derived amines 9-amino-9-deoxyepiquinine (**7**) and 9-amino-9-deoxyepicinchonine (**8**), iminium catalysts previously developed by the same research group.^[6] More than 90% *ee* was obtained by reaction in CH_2Cl_2 with $\text{CF}_3\text{CO}_2\text{H}$ as co-catalyst, although still at 20 mol-% of catalyst loading.^[2c] Interestingly, in the original report for these Cinchona-derived amines, the authors also described a diarylamino alcohol derived from L-valine as a useful, but less selective catalyst for Michael addition to α,β -unsaturated ketones.^[6] Such Cinchona-derived primary amines have recently also proven useful for the Michael addition of 1,3-diaryl-1,3-propanedione to nitro olefins.^[7]

Although chiral diamines such as **5** and Cinchona-derived amines such as **7** and **8** are effective iminium catalysts, their preparations are unfortunately adversely ineffective. A racemic mixture of (1*R*,2*R*)-1,2-diamino-1,2-diphenylethane (**5**) and (1*S*,2*S*)-1,2-diamino-1,2-diphenylethane (*ent*-**5**) can be resolved by diastereomeric salt formation with tartaric^[8] or mandelic^[9] acids. However, the synthesis of the racemate starting material is surprisingly cumbersome, a fact only rarely mentioned in the literature.^[10] An efficient synthesis was a long-standing problem,^[10] and better procedures are still needed. On the other hand, the use of Cinchona-derived amines on a preparative scale, although originating from relatively cheap Cinchona alkaloids, is also severely hampered by the costly and/or hazardous azodicarboxylates and azide reagents, such as $\text{HN}_3/\text{benzene}$,^[11a] or

$\text{HN}_3/\text{CHCl}_3$,^[11c] used in their preparation through the Mitsunobu inversion/Staudinger reduction, as well as the need for chromatographic purification.^[11]

We reasoned that the most convenient starting material for primary amine organocatalysts would be a natural or readily available synthetic amino acid, just as is the case for the more common secondary amine organocatalysts **9–12** (Figure 2).

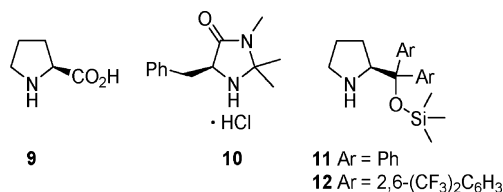


Figure 2. Traditional secondary amine organocatalysts.

As for secondary amines, proline is reported to give excellent conversion in the preparation of warfarin, but racemic product.^[2a] We tested all the four most common secondary amine organocatalysts in the preparation of warfarin from **1** and **2**, namely L-proline (**9**), the typical MacMillan-type imidazolidinone **10** and the Jørgensen/Hayashi diarylprolinols **11** and **12**. As can be clearly seen from Table 1, these standard organocatalysts show negligible conversion (even after more than 9 d of reaction) and give racemic or near racemic products. As mentioned, conversion is good for proline, but enantioselectivity is non-existent. Given the extremely poor results of the secondary amines in terms of stereoselectivity, it is tempting to speculate whether an organocatalytic asymmetric enamine/iminium ion pathway does in fact operate at all (or only to a very small extent), or whether these transformations may simply be general acid/base catalysed (probably depending on co-catalysts), as is the case in the classical preparation of racemic warfarin with bases such as Et_3N , Na_3PO_4 or alkali fluorides.^[12] This has very important implications for the more active primary amine organocatalysts as well, because alongside the asymmetric organocatalytic pathway a racemic pathway may operate, albeit slowly. With very long reaction times, the racemic mechanism may start to dominate, lowering the stereoselectivity, even though overall yields are improving.

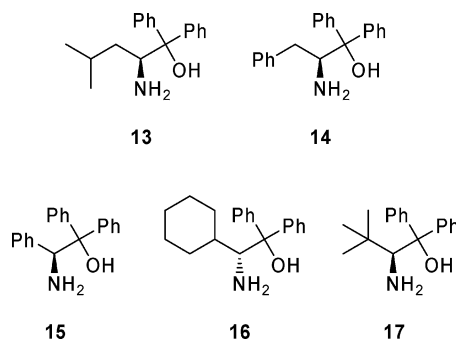
By taking readily available primary amino acids as the natural starting point for the preparation of new primary amine organocatalysts, we prepared a series of bulky amino alcohols (**13–17**) (Figure 3). They are easily prepared on a

Table 1. Traditional secondary amine organocatalysts in the preparation of optically active warfarin from **1** and **2**.

| Catalyst ^[a] | Reaction time [h] | Yield [%] ^[b] | ee [%] ^[c] |
|-------------------------|-------------------|--------------------------|-----------------------|
| 9 ^[d] | 24 | 88 | racemic |
| 10 | 235 | 5 | racemic |
| 11 | 235 | 19 | 14 |
| 12 | 235 | 34 | racemic |

[a] All reactions, except with **9**, were undertaken with 20 mol-% catalyst at room temperature in THF with 1 equiv. of CH₃CO₂H as co-catalyst. [b] Isolated yield. [c] Determined by chiral HPLC. [d] In DMSO with 50 mol-% catalyst.

large scale, with no chromatographic purification involved, by treating the appropriate methyl or ethyl ester hydrochloride salt of the amino acid with a five- to tenfold excess of PhMgBr in Et₂O or THF. In this way, naturally occurring L-leucine and L-phenylalanine gave **13** and **14**,^[13] whereas synthetic or semisynthetic L-phenylglycine, D-cyclohexylglycine and L-*tert*-leucine gave increasingly bulky amino alcohols **15–17**, respectively.^[14–16] D-Cyclohexylglycine is available by simple hydrogenation of D-phenylglycine,^[15] and L-*tert*-leucine is produced on a ton scale by Evonik Degussa GmbH through an enzymatic process.^[17] We tested these five bulky amino alcohols in the preparation of warfarin using acetic acid as co-catalyst, and the results are presented in Table 2.

Figure 3. Bulky amino alcohols **13–17**.Table 2. Bulky amino alcohols **13–17** in the preparation of optically active warfarin from **1** and **2**.

| Catalyst ^[a] | Reaction time [h] | Yield [%] ^[b] | ee [%] ^[c] |
|-------------------------|-------------------|--------------------------|-----------------------|
| 13 | 24 | 11 | 4 |
| 14 | 24 | 18 | 11 |
| 15 | 24 | 76 | 81 |
| 16 | 24 | 12 | –8 |
| 16 | 192 | 65 | –6 |
| 17 | 24 | 2 | racemic |
| 17 | 192 | 10 | racemic |

[a] All reactions were undertaken with 20 mol-% catalyst at room temperature in THF with 1 equiv. of CH₃CO₂H as co-catalyst. [b] Isolated yield. [c] Determined by chiral HPLC.

As can be clearly seen from Table 2, most of these amino alcohols, like the traditional secondary amine organocatalysts, show no promise for the preparation of warfarin. However, the phenylglycine-derived amino alcohol **15** is remarkably effective in this transformation, giving good yield

and approximately 80% ee in only 24 h, almost identical to the previous reports on diamine **5**.^[2b] It was originally anticipated by us that introducing sterically more demanding side chains through cyclohexylglycine or *tert*-leucine (amino alcohols **16–17**) would enhance the enantioselectivity even further, a hypothesis obviously invalidated by experiment. Clearly, the presence of an aromatic moiety is crucial. Among the amino acids, phenylglycine is in an especially fortunate position. D-Phenylglycine is a side-chain moiety in several important penicillins (e.g. ampicillin) and cephalosporins (e.g. cephalixin), and several thousand tons of this compound are prepared every year by DSM and others, primarily for this very purpose.^[18] In the traditional industrial synthesis, racemic phenylglycine is prepared by a Strecker reaction of benzaldehyde, followed by hydrolysis of the nitrile. This racemate is then resolved by diastereomeric salt formation,^[18a] with (+)-(1*S*)-camphor-10-sulfonic acid being a very effective resolving agent for this compound.^[19] Therefore, phenylglycine is particularly useful as a starting material for primary amine organocatalysts since both enantiomers are nearly equally inexpensive.

All efficient catalysts for the preparation of warfarin [diamine **5**, cinchona amines **7/8** and diphenylphenylglycinol (**15**)] then seem to have a common structural motif where the primary amine has an aromatic moiety in α -position, preferably together with a somewhat bulky group. Diimine formation does not seem to be a prerequisite for good enantioselectivity. To probe the importance of the bulky side group, we tried amine **18**, amino alcohol **19**, and silyl ether **20**, in the preparation warfarin (Table 3). α -Methylbenzylamine (**18**) is commercially available in both enantiomeric forms at very low cost, the racemate being efficiently resolved with malic or tartaric acid.^[20] Phenylglycinol (**19**) is conveniently prepared by direct reduction of phenylglycine with NaBH₄/I₂ or NaBH₄/H₂SO₄.^[21–23] The silyl ether **20** has to the best of our knowledge not been previously reported, but is prepared from amino alcohol **15** in one non-chromatographic step by using the iodine-catalysed silylation with hexamethyldisilazane.^[24] This excellent method eliminated any need for TMS triflate. The complete synthesis of the new primary amine organocatalyst **20**, with amino alcohol **15** as an intermediate, is shown in Scheme 2. Because of the synthetic nature of phenylglycine, the enantiomeric form of catalyst **20** is equally available by starting with D-phenylglycine (syntheses of both amino alcohols are provided in the Experimental Section) (Figure 4).

The results in Table 3 provide interesting insights. First, by comparing catalysts **18**, **19**, **15** and **20** (in the standard system of THF with 1 equiv. CH₃CO₂H), we found the enantioselectivity to increase from 33% ee for the simple α -methylbenzylamine (**18**), through 51% for phenylglycinol (**19**) to 81% for diphenylphenylglycinol (**15**) (after 24 h of reaction time), all of them with fairly high yields (Entries 1–3). Then, for silyl ether **20**, the enantioselectivity reaches 86% ee under the same conditions, but only with a modest 23% isolated yield (Entry 5). This seems to fit nicely in a pattern where introduction of increasingly bulky groups in-

Table 3. Primary amine organocatalysts **15** and **18–20** in the preparation of optically active warfarin from **1** and **2**.

| Entry | Catalyst ^[a] | Co-catalyst (1 equiv.) | Reaction time [h] | Yield [%] ^[b] | ee [%] ^[c] |
|-------|-------------------------|--|-------------------|--------------------------|-----------------------|
| 1 | 18 | CH ₃ CO ₂ H | 24 | 90 | –33 |
| 2 | 19 | CH ₃ CO ₂ H | 24 | 73 | –51 |
| 3 | 15 | CH ₃ CO ₂ H | 24 | 76 | 81 |
| 4 | 15 | CH ₃ CO ₂ H | 48 | 90 | 65 |
| 5 | 20 | CH ₃ CO ₂ H | 24 | 23 | 86 |
| 6 | 20 | CH ₃ CO ₂ H | 48 | 68 | 70 |
| 7 | 20 | CH ₃ CO ₂ H | 72 | 80 | 68 |
| 8 | 20 | CH ₃ CO ₂ H ^[d] | 96 | 93 | 70 |
| 9 | 15 | none | 24 | 67 | 66 |
| 10 | 15 | CH ₃ CO ₂ H ^[e] | 24 | 62 | 79 |
| 11 | 15 | CH ₃ CO ₂ H ^[f] | 24 | 80 | 79 |
| 12 | 15 | HFP ^[g] | 24 | 37 | 50 |
| 13 | 15 | 2,4-DNP ^[h] | 24 | 64 | 69 |
| 14 | 20 | none | 24 | 54 | 80 |
| 15 | 20 | 2,4-DNP | 24 | 40 | 80 |
| 16 | 20 | 2,4-DNP ^[h] | 48 | 46 | 83 |
| 17 | 20 | 2,4-DNP ^[h] | 72 | 72 | 67 |
| 18 | 20 | 2,4-DNP ^[h] | 96 | 70 | 63 |
| 19 | 20 | 2,4-DNP ^[i] | 96 | 54 | 79 |
| 20 | 20 | 2,4-DNP ^[j] | 336 | 76 | 40 |
| 21 | 20 | CF ₃ CO ₂ H | 24 | 11 | 84 |
| 22 | 20 | CF ₃ CO ₂ H ^[k] | 96 | 18 | 81 |
| 23 | 20 | CCl ₃ CO ₂ H | 24 | – | – |
| 24 | 20 | CSA ^[l] | 24 | – | – |
| 25 | 20 | HCO ₂ H | 24 | 38 | 68 |
| 26 | 20 | PhCO ₂ H | 24 | 47 | 70 |
| 27 | 20 | PCP ^[m] | 24 | 44 | 73 |

[a] All reactions were undertaken with 20 mol-% catalyst at room temperature in THF (unless other solvents are noted) together with 1 equiv. of co-catalyst (unless otherwise noted). [b] Isolated yield. [c] Determined by chiral HPLC. [d] 10 equiv. of CH₃CO₂H. [e] Reaction in THF/CH₂Cl₂ (1:1). [f] Reaction in THF/PhF (7:5). [g] HFP = Hexafluoroisopropanol. [h] 2,4-DNP = 2,4-dinitrophenol (20 mol-%). [i] 4 equiv. of DNP. [j] 20 mol-% DNP, reaction in CH₂Cl₂. [k] 2 equiv. of CF₃CO₂H. [l] CSA = (+)-(1*S*)-camphor-10-sulfonic acid. [m] PCP = 2,3,4,5,6-pentachlorophenol.

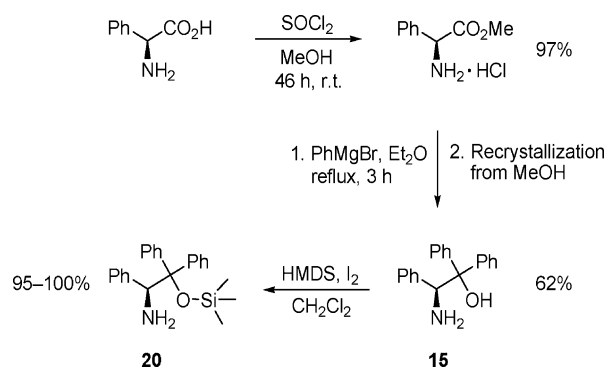
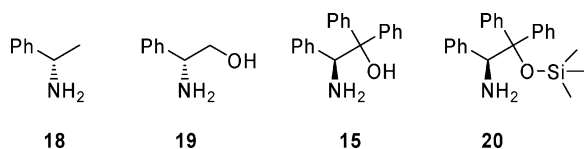
Scheme 2. Preparation of primary amine organocatalyst **20**.

Figure 4. Structurally similar primary amine organocatalysts.

creases the selectivity, but at the cost of catalytic efficiency, and then especially for silyl ether **20**. However, if the reaction time is lengthened to improve overall conversion, the enantioselectivity drops from 81% *ee* to 65% for diphenylphenylglycinol (**15**) after 48 h of reaction time (Entries 3–4) and from 86% *ee* to 68% for silyl ether **20** after 72 h of

reaction time. It is important to note that 4-hydroxycoumarin has an unusually selective solubility, making THF one of extremely few possible solvents for this reaction. Modified solvent systems, prepared by adding CH₂Cl₂ or PhF (Entries 10–11), do not seem to offer any added benefits. The use of CH₂Cl₂ as the reaction medium is interesting because 4-hydroxycoumarin has a poor solubility in this solvent. Nevertheless, previous disclosures have reported the successful preparation of warfarin in CH₂Cl₂.^[2a,2c] Especially the Cinchona derivatives **7** and **8** work remarkably well in this solvent,^[2c] whereas the silyl ether **20** shows only very modest results in CH₂Cl₂ (Entry 20). We hypothesized that phase-transfer effects could be at play, but addition of the phase-transfer catalyst benzyltriethylammonium chloride to our reaction mixtures in CH₂Cl₂ was of no use.

As for additives, strongly acidic ones, such as CCl₃CO₂H, CF₃CO₂H and camphorsulfonic acid (Entries 21–24) drastically reduced the conversion for silyl ether **20**, but can give good selectivity (84% *ee* for CF₃CO₂H, the only one of them to give an isolable yield). Additives of medium acidity, such as HCO₂H, PhCO₂H and pentachlorophenol (Entries 25–27) gave higher conversions, but showed no added benefits over standard CH₃CO₂H, and hexafluoro-2-propanol (Entry 12) seemed entirely uninteresting. On the other hand, 2,4-dinitrophenol is an additive that has been recently reported to be unusually effective for primary amine organocatalysts in aldol reactions,^[25] with interesting results also being obtained in this work, although more so for the silyl

ether **20** (Entries 15–20) than for the more reactive diphenylphenylglycinol **15** (Entry 13). However, also in this case, reductions in enantioselectivity occurred at prolonged reaction times (Entries 16–18), and large excesses of the additive lowered the yields (Entries 15 and 19) but seemed to preserve the enantioselectivity somewhat better at long reaction times. Nevertheless, 2,4-dinitrophenol cannot be considered a practical additive. It has explosive properties (particularly in the form of its metal salts), as well as a considerable toxicity associated with it, and a strong yellow discolouration that is easily carried over to the reaction products.^[26]

Conclusions

In essence, we have screened a number of amino acid derived primary amines for the preparation of warfarin by asymmetric Michael addition of 4-hydroxycoumarin to benzylideneacetone and identified potentially highly useful phenylglycine-derived structural motifs that offer a useful starting point for the preparation of new primary amine organocatalysts. We found diphenylphenylglycinol, especially in combination with co-catalysts such as acetic acid or 2,4-dinitrophenol, to be a surprisingly effective organocatalyst for this transformation, far better than other amino alcohols. This may be an indication that not only steric, but also more subtle electronic perturbations most probably influence the performances of primary amine organocatalysts substantially. From this, we prepared a new primary amine organocatalyst from diphenylphenylglycinol by straightforward silylation. This catalyst may be perceived as representing a type of primary amine analogue of the Jørgensen/Hayashi diarylprolinols **11/12**. This catalyst is conveniently available in both enantiomeric forms by a non-chromatographic procedure and together with its parent alcohol represents affordable alternatives to chiral diamines and Cinchona-derived primary amines for the preparation of optically active warfarin. This is potentially very useful, as the optical purity of warfarin can be further enhanced by simple recrystallization^[2a] and as preparation of optically active warfarin by classical resolution is very cumbersome.^[27] Optically active warfarin is therefore by now one of the relatively few medicinal compounds for whose preparation a catalytic asymmetric synthesis may actually be the preferred route, even on a large scale.

Experimental Section

General: All commercially available reagents were used as received, and all solvents were used without further purification. *L*-tert-Leucine and D-cyclohexylglycine were generously donated by Evonik Degussa GmbH. All other reagents were obtained from Sigma–Aldrich or VWR. The heating mantles used in this work were of the type Heat-On[®] from Radleys, either fluoropolymer-coated or with anodized finish. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F₂₅₄ TLC plates, either on aluminium sheets or glass. They were visualized by UV light, or by immersion in a solution of either (NH₄)₆Mo₇O₂₄·4H₂O and Ce(SO₄)₂·

4H₂O in aqueous H₂SO₄, a solution of *p*-anisaldehyde, concd. H₂SO₄ and glacial CH₃CO₂H in 96% EtOH or a solution of KMnO₄, K₂CO₃ and NaOH in water, all followed by heating. Merck silica gel (60, 40–63 μm) was used for flash chromatography, either manually or with a Teledyne Isco CombiFlash[®] Companion[®] with PeakTrak[™] software (v. 1.4.10), by using EtOAc/hexanes of technical quality. ¹H and ¹³C NMR spectra were recorded with a Bruker Avance[™] DPX-300 or -200 spectrometer operating at 300/200 MHz (¹H) or 75/50 MHz (¹³C). Chemical shifts are reported in parts per million (δ) and are, unless otherwise noted, reported relative to the internal references of the solvent: δ = 2.49/39.7 ppm for [D₆]DMSO and δ = 7.26/77.0 for CDCl₃. Electrospray ionisation mass spectra were recorded with a Micromass Q-ToF-2[™] mass spectrometer. Infrared spectra were recorded with a Perkin–Elmer Spectrum[™] One FTIR spectrometer. Melting points were determined with a Büchi Melting Point B-545 apparatus. Optical rotation was recorded by using a Perkin–Elmer Instruments 341 Polarimeter at room temperature. The enantiomeric excess was determined by using a Thermo Scientific SpectraSYSTEM[®] P2000 pump with a SpectraSYSTEM[®] UV3000 UV/Vis detector and a Chiralcel[®] AD-H column from Daicel Chemical Industries.

(R)-Diphenylphenylglycinol (Enantiomer of 15): (–)-D-α-Phenylglycine (36.26 g, 240 mmol) was suspended in MeOH (350 mL), and the reaction flask was cooled in an ice/water bath. Dropwise, SOCl₂ (26.0 mL, 358 mmol) was added over a period of 20 min. The reaction flask was removed from the ice/water bath, and the solution was stirred at room temperature for 46 h. The volatiles were evaporated in vacuo, and the residual crystals were slurried in Et₂O (200 mL), vacuum-filtered and dried at room temperature for 28 h to give D-phenylglycine methyl ester hydrochloride (48.12 g, 99%) as colourless, fibrous crystals.

A three-necked 1000 mL round-bottomed flask, equipped with an addition funnel, reflux condenser and glass stopper, was charged with magnesium turnings (34.37 g, 1414 mmol) and an egg-shaped stirring bar (1.5 × 0.625 in). Dry Et₂O (80 mL) was added, followed by a small portion of a solution of bromobenzene (222.51 g, 1417 mmol) in dry Et₂O (430 mL). When the reaction had initiated, the rest of the PhBr solution was added over a period of 1 h 20 min, keeping the mixture at reflux. The mixture was stirred an additional 1 h at reflux to dissolve most of the Mg and then diluted with dry Et₂O (300 mL). The reaction flask was cooled in an ice/water bath, while D-phenylglycine methyl ester hydrochloride (47.98 g, 238 mmol) was added carefully in small portions over a period of 10 min. The mixture was refluxed in a heating mantle for 3 h, the reaction flask cooled in an ice/water bath, and its contents were carefully poured onto crushed ice (1250 mL) in a 3000 mL beaker. Saturated aqueous NH₄Cl (300 mL), EtOAc (300 mL) and water (200 mL) were added. The mixture was stirred for 1 h and separated in a large separation funnel. The aqueous phase was extracted with EtOAc (2 × 300 mL), and the combined organic extracts were washed with brine (200 mL), dried with anhydrous MgSO₄, filtered, and the solvents were evaporated in vacuo to give a yellow solid.

The solid was dissolved in boiling MeOH (500 mL). Crystallisation at room temperature for 2 h gave a first crop of crystals, while subsequent crystallisation in an ice/water bath for 2 h gave a second crop. The two isolated crops were combined and dried at room temperature to give (R)-diphenylphenylglycinol (45.55 g, 66%).

High-purity product was obtained by recrystallisation of this product from MeOH (500 mL) with crystallisation at room temperature for 2 h and in an ice/water bath for 2 h, followed by isolation by filtration and drying at room temperature to give (R)-diphenylphenylglycinol as beautiful needle-shaped crystals. M.p. 131–

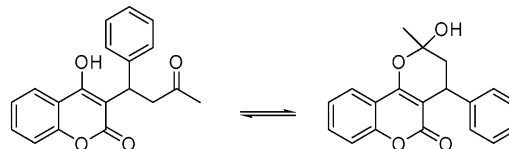
132 °C (dec.). $[\alpha]_D^{20} = +240$ ($c = 1.030$, CHCl_3). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 1.81$ (s, 2 H, NH_2), 4.99 (s, 1 H, 2-H), 5.60 (s, 1 H, OH), 6.93–7.34 (m, 13 H, Ph-H), 7.71–7.75 (m, 2 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 61.1$, 80.0, 125.5, 125.8, 126.1, 126.3, 126.6, 126.7, 127.1, 127.9, 129.0, 142.2, 145.7, 147.4 ppm. This is a known compound with spectroscopic properties in accordance with those reported.^[14]

(S)-Diphenylphenylglycinol (15): In a completely analogous procedure to the one above, (+)-L- α -phenylglycine (37.24 g, 246 mmol) and SOCl_2 (27.0 mL, 372 mmol) in MeOH (350 mL) gave L-phenylglycine methyl ester hydrochloride (48.35 g, 97%) as colourless, fibrous crystals. A portion of this ester hydrochloride (48.17 g, 239 mmol) was treated with the Grignard reagent prepared from Mg (35.53 g, 1462 mmol) and bromobenzene (229.94 g, 1464 mmol), by using the same amounts of Et_2O as above, in the same manner to give (S)-diphenylphenylglycinol (**15**; 43.18 g, 62%) after recrystallisation from MeOH (500 mL). Very pure material of needle-shaped crystals was likewise obtained by an additional recrystallisation from MeOH (500 mL), as was done for the other enantiomer. M.p. 132–133 °C (dec.), $[\alpha]_D^{20} = -241$ ($c = 1.036$, CHCl_3). ^1H NMR (300 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 1.81$ (s, 2 H, NH_2), 4.99 (s, 1 H, 2-H), 5.60 (s, 1 H, OH), 6.93–7.34 (m, 13 H, Ph-H), 7.71–7.75 (m, 2 H, Ph-H) ppm. ^{13}C NMR (75 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 61.1$, 80.0, 125.5, 125.8, 126.1, 126.3, 126.6, 126.7, 127.1, 127.9, 129.0, 142.2, 145.7, 147.4 ppm. This is a known compound with spectroscopic properties in accordance with those reported.^[14]

(S)-Diphenylphenylglycinol Trimethylsilyl Ether (20): A portion of (S)-diphenylphenylglycinol (10.096 g, 34.9 mmol) was dissolved in CH_2Cl_2 (120 mL), and iodine (123 mg, 0.48 mmol) and hexamethyldisilazane (5.639 g, 34.9 mmol) were added. The reaction mixture was stirred at room temperature for 4 h, and MeOH (3.0 mL) was added to quench residual HMDS. The mixture was stirred for 5 min, and the volatiles were removed by evaporation in vacuo. The residual oil was redissolved in CH_2Cl_2 (120 mL), a solution of $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ (10.405 g) in H_2O (120 mL) was added, and the mixture was stirred for 5 min and separated. The organic phase was dried with anhydrous MgSO_4 , filtered through a short pad of Celite® 535 by using a Büchner funnel, and the filter cake was washed with CH_2Cl_2 (50 mL). The filtrate was concentrated in vacuo to give (S)-diphenylphenylglycinol trimethylsilyl ether (**20**) in quantitative yield. Light yellow, honey-like oil. $[\alpha]_D^{20} = -11.1$ ($c = 1.198$, CHCl_3). ^1H NMR (300 MHz, CDCl_3): $\delta = -0.15$ (s, 9 H, SiMe_3), 1.69 (s, 2 H, NH_2), 4.95 (s, 1 H, 2-H), 6.79–6.85 (m, 2 H, Ph-H), 7.02–7.14 (m, 3 H, Ph-H), 7.23–7.33 (m, 8 H, Ph-H), 7.35–7.43 (m, 2 H, Ph-H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 1.8$, 62.6, 84.5, 126.5, 126.6, 126.6, 127.4, 127.7, 128.9, 129.1, 129.2, 141.5, 142.3, 143.7 ppm. IR (film): $\tilde{\nu} = 3390$, 3087, 3060, 3032, 2955, 2897, 1602, 1494, 1447, 1251 cm^{-1} . HRMS (ESI): calcd. for $[\text{C}_{23}\text{H}_{27}\text{NOSi} + \text{H}]$ 362.1940; found 362.1949.

General Procedure for the Preparation of Warfarin (3): A small vial was charged with 4-hydroxycoumarin (**1**, 81.1 mg, 0.50 mmol), benzylideneacetone (**2**, 87.7 mg, 0.60 mmol), additive (if appropriate) and the appropriate catalyst (0.10 mmol, 20 mol-%). A small magnetic stirring bar and THF (1 mL) were added, and the reaction mixture was stirred at room temperature for 24 h. The volatiles were removed by flushing with pressurized air. The residue was purified by column chromatography on silica gel with 15% EtOAc in hexanes to give pure warfarin (**3**) as a white solid. The enantiomeric excess was determined by HPLC analysis of the purified product with an AD-H chiral column (20% *i*PrOH in isohexane, 1.0 mL/min, $\lambda = 254$ nm, minor enantiomer $t_R = 6.5$ min and major enantiomer $t_R = 11.6$ min).

Warfarin exists in a rapid equilibrium with a pair of pseudo-diastereomeric hemiketals and therefore gives highly complicated and concentration-dependant NMR spectra. The integrals in the NMR spectroscopic data below are therefore given relative to the species, either the keto form or one of the two pseudo-diastereomeric hemiketal forms, to which it belongs and not absolute relative to the other species.



^1H NMR (300 MHz, CDCl_3): $\delta = 1.66$ (s, 3 H, CH_3 ketal), 1.67 (s, 3 H, CH_3 ketal), 1.92–2.03 (m, 1 H, CH_2 ketal), 2.27 (s, 3 H, CH_3 keto), 2.33–2.55 (m, 3 H, CH_2 ketal), 3.31 (dd, $^3J = 19.3$ and 2.6 Hz, 1 H, CH_2 keto), 3.43 (s, 1 H, OH ketal), 3.83 (dd, $^3J = 19.3$ and 10.0 Hz, 1 H, CH_2 keto), 3.89 (s, 1 H, OH ketal), 4.16 (dd, $^3J = 11.3$ and 6.9 Hz, 1 H, CH ketal), 4.25 (dd, $^3J = 6.9$ and 3.7 Hz, 1 H, CH ketal), 4.71 (dd, $^3J = 10.0$ and 2.6 Hz, 1 H, CH keto), 7.15–7.35 (m, 21 H, 7 H Ar-H ketal, 7 H Ar-H ketal, 7 H Ar-H keto), 7.42–7.60 (m, 3 H, 1 H Ar-H ketal, 1 H Ar-H ketal, 1 H Ar-H keto), 7.79 (dd, $^3J = 8.0$ and 1.4 Hz, 1 H, Ar-H ketal), 7.89 (dd, $^3J = 8.0$ and 1.4 Hz, 1 H, Ar-H keto), 7.93 (dd, $^3J = 8.0$ and 1.4 Hz, 1 H, Ar-H keto), 9.52 (s, 1 H, OH keto) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 27.5$, 28.0, 30.0, 34.3, 34.8, 35.3, 40.0, 42.6, 45.1, 99.0, 100.5, 101.2, 104.1, 107.8, 115.5, 115.9, 116.1, 116.4, 116.6, 122.7, 123.0, 123.5, 123.8, 123.9, 126.4, 126.6, 126.9, 127.0, 127.1, 127.9, 128.1, 128.5, 129.1, 131.4, 131.7, 131.9, 139.6, 141.5, 143.2, 152.7, 152.8, 152.9, 158.9, 159.7, 161.0, 161.4, 162.1, 162.2, 212.5 ppm. This is a known compound with spectroscopic properties in accordance with those reported.^[2]

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for compound **20**.

Acknowledgments

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