# Synthesis of Optically Active 2-Benzyldihydrobenzopyrans for the Hypoglycemic Agent Englitazone



Frank J. Urban* and Bernard S. Moore

Process Research and Development Department,
Central Research Division, Pfizer Inc.,
Groton, CT 06340

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Two syntheses of some optically active 2-benzyl-2,3-dihydro-4*H*-benzopyrans and benzopyran-4-ones are presented. An asymmetric synthesis starting from D- and L-phenylalanine was used to provide both enantiomers of 2-benzyl-6-(methoxycarbonyl)-2,3-dihydro-4*H*-benzopyran-4-one **19**. Phenylalanine was diazotized in aqueous sulfuric acid to 2-hydroxy-3-phenylpropionic acid **6** which was converted in four steps to 1-bromo-2-(4-methoxycarbonylphenoxy)-3-phenylpropane **11**. (4*R,S*)-Benzamido-2-benzyl-2,3-dihydro-6-(methoxycarbonyl)-4*H*-1-benzopyran-4-carboxylic acid **16** was prepared from **11** by amidoalkylation with α-hydroxyhippuric acid in methanesulfonic acid solution followed by spiroalkylation to (4*R,S*)-2-benzyl-2,3-dihydro-6-(methoxycarbonyl)spiro[4*H*-benzopyran-4,4'-2'-phenyloxazolidin]-5'-one **15**. After the phenyloxazolidin-5-one **15** was hydrolyzed to the spirobenzamido carboxylic acid **16**, oxidative decarboxylation with sodium hypochlorite yielded optically active 2-benzyl-6-(methoxycarbonyl)-2,3-dihydro-4*H*-benzopyran-4-one **19**. The ketone in **19** was reduced by hydrogenation over palladium on carbon to a methylene group and the ester was converted to the aldehyde to give both isomers of the desired intermediate 2-benzyl-6-(formyl)-2,3-dihydro-4*H*-benzopyran **25**. The second synthesis relied on an enzymatic hydrolysis of ethyl 2,3-dihydrobenzopyran-2-carboxylate **27** with the lipase from *P. fluorescens* to provide the desired 2*R*-ester. The ester group in (*R*)-**27** was converted to the triflate (*R*)-**29**. Displacement of the triflate group with phenylmagnesium bromide and cuprous bromide as catalyst gave 2*R*-benzyl-2,3-dihydro-4*H*-benzopyran (*R*)-**30**. Formylation of (*R*)-**30** provided 2*R*-benzyl-6-(formyl)-2,3-dihydro-4*H*-benzopyran (*R*)-**25** identical with that from the first synthesis. These optically active intermediates are used in the preparation of the hypoglycemic agent englitazone.

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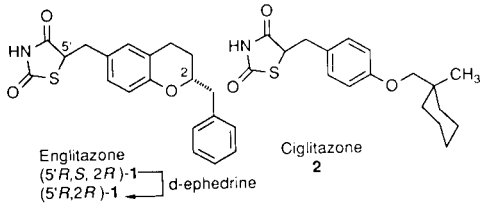
Englitazone [1], 5-[(2*R*-benzyl-3,4-dihydro-2*H*-1-benzopyran-6-yl)methyl]thiazolidine-2,4-dione **1**, a conformationally restricted analogue of ciglitazone **2**, [2] is of potential therapeutic interest as a hypoglycemic agent for the treatment of non-insulin-dependent diabetes mellitus [3]. It is currently in clinical trials.



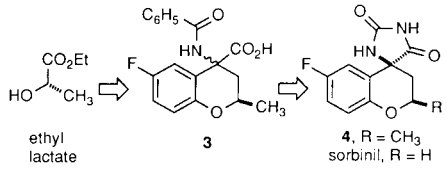

Orginally, the racemic mixture of four diastereomers of **1** was evaluated for biological activity before the (2*R*)-benzylbenzopyran pair of diastereomers were selected for further development. The other asymmetric center on the thiazolidine-2,4-dione was found to undergo a kinetic resolution, similar to that reported for ciglitazone [4], but only when the benzylic center was homochiral. Thus, treatment of the (5'*R,S*,2*R*)-pair with d-(+)-ephedrine in toluene gave an 85% yield of a single diastereomeric salt which was assigned as (5'*R*,2*R*)-**1** (see Experimental). While the resolved free acid (5'*R*,2*R*)-**1** could be recovered by acid treatment and was found to be configurationally stable in methanol solution, the salt itself underwent mutarotation in solution to return to a 1:1 mixture. Based on these experiments as well as the observation of rapid deuterium exchange at the 5' center by Clark *et al.* [1], we focused on the synthesis of optically active 2-benzylbenzopyran precursors to englitazone.

Although the pair of diastereomers resolved at the 2-position of the benzopyran ring were prepared originally through the resolution of 2-benzyl-3,4-dihydro-2*H*-1-benzopyran-6-carboxylic acid [5], this procedure was not suitable for producing large quantities of material of high optical purity. In this paper, we describe two processes for the preparation of optically pure dihydrobenzopyran intermediates used for the large scale synthesis of englitazone.

While there is a large body of literature related to the synthesis of benzopyrans [6], most of the syntheses of benzopyrans with chirality at the 2-carbon have been directed to the preparation of vitamin E [7]. Benzopyrans can be prepared from the corresponding dihydrobenzopyran-4-ones [8]. A synthesis of optically active 2-alkyl benzopyran-4-one has been reported by Wallace [9]; however, it gave material with 90% ee and was not suitable for our needs. Recently, we published a synthesis of (4*R,S*)-benzamido-(2*R*)-methyl-6-fluorobenzopyran 4-carboxylic acid **3** as part of a study on the preparation of spiro amino acid dihydrobenzopyrans related to the spirohydantoin sorbinil [10] (Scheme 1). Assuming that an oxidative decarboxylation of

an intermediate like **3** would provide the 2-alkylbenzopyran-4-one with defined stereochemistry at C2, we explored this approach. This also would allow the assignment of the absolute stereochemistry of englitazone diastereomers.

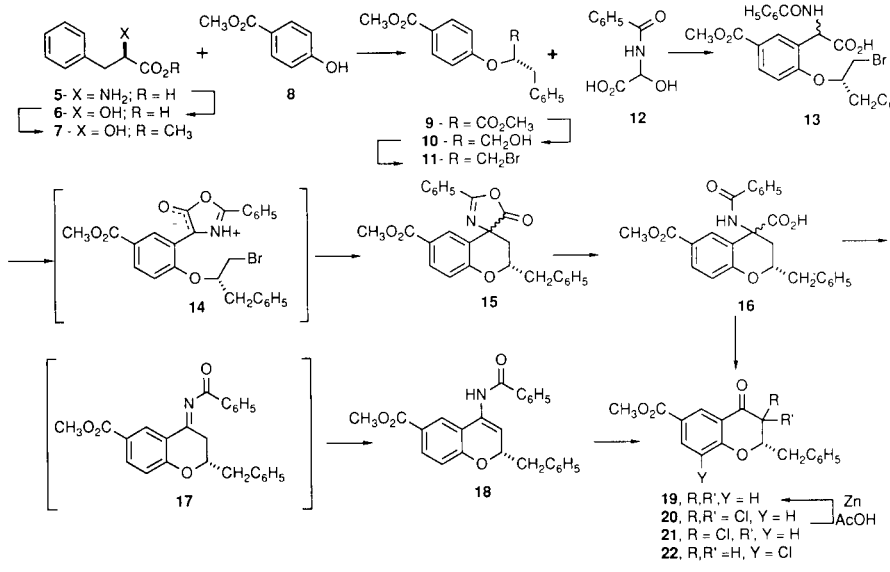
Scheme 1




The asymmetry at the (2*R*)-methylbenzopyran in **3** had been derived from ethyl lactate. The synthesis of (2*R*)-benzyldihydrobenzopyran-4-one **19** is shown in Scheme 2. For the 2-benzyl moiety, phenylalanine **5** was diazotized in aqueous sulfuric acid to provide 2-hydroxy-3-phenylpropionic acid **6** with retention of configuration [11] [12]. After esterification to the methyl ester **7**, Mitsunobu conditions [13] were used to form phenyl ether **9** with methyl 4-hydroxybenzoate **8** with inversion of configuration. Often, one drawback to scale up of Mitsunobu reactions is the need to remove large quantities of the side products, triphenylphosphine oxide and hydrazine dicarboxylate. In the current example, after removal of a large amount of the undesired material by precipitation from a methylene chloride/hexanes solution, the optically active phenyl ether **9** was isolated by a simple recrystallization from 2-propanol to give analytically pure material in *ca.* 75% yield on multikilogram scale. From the racemic alcohol *rac*-**7**, simple replacement of the tetrahydrofuran reaction solvent with isopropyl alcohol gave pure racemic ester *rac*-**9** directly from the reaction mixture.

Coversion of the aliphatic ester in **9** to the primary bromide **11** was carried out in two steps and 88% yield. Selective reduction of the desired ester with sodium borohydride in 10% aqueous tetrahydrofuran gave the alcohol **10** without any reaction at the benzoate ester. The crude alcohol **10** was treated with triphenylphosphine dibromide in methylene chloride to provide the bromide **11**. Bromide **11** was amidoalkylated with *alpha*-hydroxyhippuric acid **12** [14] in methanesulfonic acid solution to afford the phenylglycine derivative **13** as a mixture of diastereomers; both of which have the desired (2*R*)-stereochemistry. This mixture was used in the next reaction without purification since crystallization caused loss of the more soluble diastereomer. Whereas 2-(2-bromoethoxy or propoxy)benzamidophenylglycines previously reported by us [10] could be isolated by dilution of the reaction mixture with water, followed by filtration and drying *in vacuo*, **13** was found to be unstable to heating >40°. Therefore, **13** was isolated by extraction into methylene chloride solution after the amidoalkylation reaction and used directly in the spiroalkylation after workup. The key transformation in the process was the formation and spiroalkylation of the azlactone intermediate **14** which occurred under very mild conditions. Benzamide **13** in dimethyl formamide or acetone solution with 1.5 equivalents of acetic anhydride was treated at room temperature with two equivalents of triethylamine or potassium carbonate, respectively. The reaction occurred in a stepwise fashion with formation of the azlactone **14**, followed by cyclization with bromide displacement. The facile nature of anion formation as well as the stoichiome-

Scheme 2

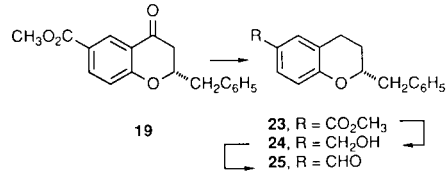


try requiring only two equivalents of weak base suggests that the intermediate which alkylates is the ylide **14**. These dipolar intermediates have been suggested previously by Huisgen and co-workers [15] as the reactive tautomer of azlactones. Since no purification had been done since the isolation of bromide **11**, the spiroazlactone **15** was filtered through a pad of silica gel to remove polar impurities before acid hydrolysis to the spirobenzamido amino acid **16**. Again **16** consisted of a mixture of diastereomers and was used in the following step directly without further purification. The yield was estimated to be *ca.* 85-90% for the spiroalkylation sequence based on hplc analysis.

The lowest yielding step for the process was the oxidative decarboxylation of benzamide **16** to provide the optically active dihydrobenzopyran-4-one **19**. Although lead tetraacetate gave this conversion in *ca.* 30% yield, we focused on sodium hypochlorite as the oxidant most convenient for scale up. Treatment of crude spirobenzamido acid **16** in methylene chloride solution with a large excess of 15% sodium hypochlorite at room temperature for several hours were the standard conditions. The initial product from this reaction was presumably the acyl imine **17**, which could not be isolated but tautomerized to the enamide **18** along with some **19** upon workup. The nmr analysis of the crude product mixture showed it to contain the enamide **18** as the major product as well as dihydrobenzopyran-4-one **19**. At longer reaction times at pilot plant scale, $\alpha$-chlorodihydrobenzopyran-4-ones **20** and **21** were also observed. Aqueous acid hydrolysis of **17**/**18** provided the desired dihydrobenzopyran-4-one **19** in up to 50% yield from the spirobenzamido acid **16**. After purification of **19** by crystallization, any $\alpha$-chlorodihydrobenzopyran-4-ones **20** and **21** present in the filtrate were reduced with zinc in acetic acid to afford more **19** without loss of optical activity.

The *p*H of the 15% sodium hypochlorite solution was >12. When a 1*M* sodium hypochlorite solution of *p*H 9.5 was used in a two phase system with ethyl acetate according to Lee and Freedman [16], a good yield of $\alpha,\alpha$-dichlorodihydrobenzopyran-4-one **20** with a minor amount of $\alpha$-chlorodihydrobenzopyran-4-one **21** was isolated. We believe that the lower *p*H of the reaction allowed the *in situ* hydrolysis of the acylimine **17** to **19** which was subsequently chlorinated. One other set of conditions based on the work of Stevens *et al.* [17], involved treatment of **16** in a mixture of methylene chloride or acetonitrile and acetic acid with sodium hypochlorite. The oxidant in this case was hypochlorous acid formed *in situ* which did not cause *alpha*-chlorination; however, the extent of conversion was low (>10%) and 8-chloro-(2*R*)-benzyldihydrobenzopyran-4-one **22** was isolated.

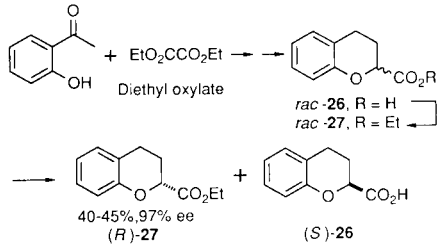
While the yield for the oxidative decarboxylation was only moderate, the process was simple to operate in the lab or pilot plant and the reagents were inexpensive. For the evaluation of the englitazone diastereomer pairs >15 kilograms of optically active benzopyranones were prepared by this process and the absolute stereochemistry of the englitazone diastereomers assigned.




For the adjustment of the oxidation state of the molecule, **19** was hydrogenated to the dihydrobenzopyran **23** in methanol solution with concentrated hydrochloric acid and Pd/C under hydrogen. This reduction had to be monitored carefully since the reduction of the (2*R*)-benzyl moiety to a cyclohexylmethyl group was always seen to some extent and could be formed in >30% yield if the hydrogenation was continued too long. The conversion of the benzoate **23** to the aldehyde **25** was done in very high yield in two steps; reduction to the alcohol **24** with sodium bis(2-methoxyethoxy)aluminum hydride in toluene, followed by oxidation with manganese dioxide. The optically active aldehyde **25** was used in the process previously reported to afford englitazone [1].

While the route described above provided material for the start of development efforts with optically active englitazone, the process was long and the overall yield was low. In seeking a shorter route to the key optically active aldehyde **25**, we examined syntheses from the readily available dihydrobenzopyran-2-carboxylic acid *rac*-**26**. (Scheme 3). This was prepared in two steps from 2-hydroxyacetophenone and ethyl oxalate in the presence of sodium methoxide followed by hydrogenation over Pd/C in acetic acid [18].

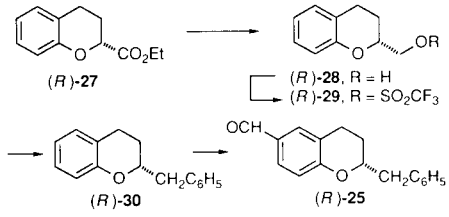
Scheme 3




While a classical resolution of **26** had been described in the literature, it was not very efficient and used amphetamine as the resolving agent [19]. Instead we turned to the use of a bacterial lipase from *Pseudomonas fluorescens* [20] for the hydrolysis of the ethyl ester **27**. This hydrolysis was done as a two phase reaction without any organic solvent to dilute the water immiscible ester **27** and provided the desired (2*R*)-ester (*R*)-**27** in high chemical and optical yield.

The conversion of the ethyl ester (*R*)-**27** to a benzyl group (*R*)-**30** was accomplished in high yield over three steps (Scheme 4). The ester (*R*)-**27** was reduced to the alcohol (*R*)-**28** with sodium borohydride in aqueous tetrahydrofuran and alcohol (*R*)-**28** was activated as its trifluoromethane sulfonate. The triflate group in (*R*)-**29** was displaced with phenyl grignard in the presence of a catalytic amount of cuprous bromide dimethylsulfide complex [21] to provide 2*R*-benzyldihydrobenzopyran (*R*)-**30** in >90% yield along with small amounts of biphenyl as a contaminant. Crude (*R*)-**30** was used without purification in a Vilsmeier-Haack formylation [22] to introduce the required aldehyde group. The reaction produced the desired aldehyde (*R*)-**25** plus a small amount (<10%) of the regioisomeric aldehyde at the C8 position. Treatment of the crude mixture with aqueous ethanolic sodium bisulfite precipitated the pure bisulfite complex of aldehyde (*R*)-**25** which was isolated by filtration while the regioisomer aldehyde and the biphenyl impurities remained in the filtrate. Regeneration of the chemically pure aldehyde and simple crystallization from 2-propanol/hexanes afforded the optically pure benzaldehyde (*R*)-**25**. This second process allowed the synthesis of the key intermediate (*R*)-**25** in fewer steps from inexpensive starting materials and provided a suitable, high yield replacement for the original asymmetric synthesis.

Scheme 4




## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. The nmr spectra were determined on a Bruker WM300 spectrometer in deuteriochloroform or DMSO-$d_6$. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer. Mass spectra were determined with a Finnigan 4510 mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Analytical Chemistry Department, Pfizer.

(2*S*)-Hydroxy-3-phenylpropionic Acid (*S*)-**6**.

L-Phenylalanine (*S*)-**5** (1 kg, 6.05 moles) in 1*M* sulfuric acid (12 *l*) was treated at 0° with sodium nitrite (1.66 kg, 24 moles) in portions over a 5 hour period. The reaction was allowed to warm slowly to room temperature and stirred overnight. The aqueous reaction was extracted with ethyl acetate (3 x 4 *l*) and the combined organic layers were washed with brine (2 *l*) and then dried over magnesium sulfate. The filtered organic solution was concentrated to 1 *l* and diluted with hexanes (3 *l*). The desired acid was collected by filtration and dried *in vacuo*, yield 500 g, 50%, mp 120-123°, $[\alpha]_D$ −20.6° (c = 1, water), lit mp 126-127°, $[\alpha]_D$ −20.0° (water) [11].

(2*R*)-Hydroxy-3-phenylpropionic Acid (*R*)-**6**.

D-Phenylalanine (*R*)-**5** was treated as described above to give (2*R*)-hydroxy-3-phenylpropionic acid in 51% yield, mp 122-125°, $[\alpha]_D$ +21.1° (c = 1, water), lit mp 126-127°, $[\alpha]_D$ +20.4° (water) [11].

Methyl (2*S*)-Hydroxy-3-phenylpropionate (*S*)-**7**.

The *S*-acid (*S*)-**6** (826 g, 4.97 moles) from above was dissolved in dichloromethane (6 *l*) with methanol (481 g, 15 moles), 98% sulfuric acid (15 ml) was added and the mixture was heated at reflux for 18 hours. The reaction mixture was washed with water (2 *l*), with saturated sodium bicarbonate (2 *l*) and with brine. The organic layer was dried over magnesium sulfate and evaporated *in vacuo* to yield the title compound as a low melting solid, 840 g, 94%, mp 47-49°, $[\alpha]_D$ +4.5° (c = 1, methanol).

Methyl (2*R*)-Hydroxy-3-phenylpropionate (*R*)-**7**.

The *R*-acid was reacted similarly, 94% yield, mp 47-49°, $[\alpha]_D$ −4.3° (c = 1, methanol).

Methyl (2*R*)-(4-Methoxycarbonylphenoxy)-3-phenylpropionate (*R*)-**9**.

A solution of methyl (2*S*)-hydroxy-3-phenylpropionate (*S*)-**7** (827 g, 4.58 moles), methyl 4-hydroxybenzoate **8** (696 g, 4.58 moles) and triphenylphosphine (1262 g, 4.81 moles) in tetrahydrofuran (9 *l*) was stirred at 10° under nitrogen while diisopropyl azodicarboxylate (1016 g, 5.02 moles) was added dropwise over 90 minutes with the temperature <20°. After stirring overnight at room temperature, water (180 ml) was added and the reaction was concentrated *in vacuo*. Methylene chloride (1400 ml) was added to the residual material and the mixture was mechanically stirred while hexanes (4 *l*) was added in a slow stream. The mixture was filtered and the filtrate was washed with 1*N* sodium hydroxide, water, and brine. The solution was dried with magnesium sulfate and then evaporated to a solid. Crystallization of the solid from isopropyl alcohol afforded the desired product, 1098 g, 70% yield, mp 77.5-79°, $[\alpha]_D$ +24.0° (c = 1, methanol); $^1$H nmr (deuteriochloroform): δ 7.94 (d, 2), 7.29 (m, 5), 6.84 (d, 2), 4.90 (t, 1), 3.85 (s, 3), 3.70 (s, 3), 3.28 (d, 2).

*Anal.* Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.92; H, 5.61.

Methyl (2*S*)-(4-Methoxycarbonylphenoxy)-3-phenylpropionate (*S*)-**9**.

Under the same conditions (*R*)-**7** was reacted in 70% yield, mp 77.5-78°, $[\alpha]_D$ −23.3° (c = 1, methanol).

*Anal.* Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 69.0; H, 5.77.

(2*R*)-(4-Methoxycarbonylphenoxy)-3-phenyl-1-propanol (*R*)-**10**.

The (2*R*)-ester (*R*)-**9** (1.092 kg, 3.47 moles) was dissolved in tetrahydrofuran (10.9 *l*) and water (1.09 *l*) and stirred at room temperature under nitrogen while sodium borohydride (181.5 g, 4.8 moles, pellets from Aldrich) was added over 5 minutes. The reaction was stirred for 30 hours at which time tlc showed the reaction was complete. Methylene chloride (3 *l*) was added to the reaction followed by sodium chloride solution (3 *l*). The organic layer was washed with sodium chloride solution (4 x 3 *l*) and dried

over magnesium sulfate. Evaporation of the filtered organic layer gave the pure, chiral alcohol as a low melting, colorless solid; 979 g, 98% yield; mp 51.5-57°, $[\alpha]_D$ +37.8° (c = 1, methanol); $^1$H nmr (deuteriochloroform): δ 7.95 (d, 2), 7.26 (m, 5), 6.92 (d, 2), 4.62 (m, 1), 3.87 (s, 3), 3.76 (m, 2), 3.00 (m, 2).

(2*S*)-(4-Methoxycarbonylphenoxy)-3-phenyl-1-propanol (*S*)-**10**.

The 2*S*-ester was reduced as above in 98% yield, mp 51.5-58°, $[\alpha]_D$ −38.1° (c = 1, methanol).

*Anal.* Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.27; H, 6.41.

1-Bromo-(2*R*)-(4-methoxycarbonylphenoxy)-3-phenylpropane (*R*)-**11**.

Bromine (591 g, 3.7 moles) was added dropwise over 7 hours to a solution of triphenylphosphine (954 g, 3.64 moles) in methylene chloride (7 ℓ). The chiral alcohol (*R*)-**10** (950 g, 3.32 moles) in methylene chloride (1 ℓ) was added dropwise to the solution of triphenylphosphine dibromide with the temperature maintained at <28°. After several hours, the tlc showed the reaction to be complete. Methanol (16 g, 0.5 mole) was added to decompose the excess reagent. The reaction was concentrated under vacuum to a slurry and then diluted with hexanes and stirred at 25°. The mixture was filtered to removed triphenylphosphine oxide and concentrated to give the bromide (1037 g) as a low melting, lachrymatory solid in 90% yield over two crops, $[\alpha]_D$ +13.1° (c = 1, methanol); $^1$H nmr (deuteriochloroform): δ 7.99 (d, 2), 7.28 (m, 5), 6.92 (d, 2), 4.70 (m, 1), 3.89 (s, 3), 3.50 (dd, 2), 3.15 (m, 2).

1-Bromo-(2*S*)-(4-methoxycarbonylphenoxy)-3-phenylpropane (*S*)-**11**.

Treatment of alcohol (*S*)-**10** as above afforded the bromide in 99% yield as a viscous oil, $[\alpha]_D$ −13.0° (c = 1, methanol).

*N*-Benzoyl 2-(1-bromo-3-phenyl-(2*R*)-propoxy)-5-(methoxycarbonyl)-(*R,S*)-phenylglycine (*R*)-**13**.

To a solution of 1-bromo-(2*R*)-(4-methoxycarbonylphenoxy)-3-phenylpropane (*R*)-**11** (1124 g, 3.22 moles) in methanesulfonic acid (4.5 ℓ) at 20° was added α-hydroxyhippuric acid (716 g, 3.67 moles) in portions over 5 minutes. The reaction was stirred overnight. The reaction mixture was carefully and slowly poured into a mixture of methylene chloride (7 ℓ) and water (20 ℓ) with the temperature <10°. The organic solution was washed with water ( 3 x 4 ℓ) and then was dried over magnesium sulfate. After filtering off the drying agent, the solution was concentrated to an oil which contains a few percent of the bromide as well as some more polar material. This was sufficiently pure for use in the next step. Alternatively, the reaction can be quenched into ice water with stirring to produce a solid which can be filtered. However, this crude, wet solid has been found to decompose upon drying if the temperature was >45°. Since the product was a mixture of diastereomers, attempted recrystallization caused the loss of material. The main diagnostic peaks in the nmr were at δ 6.06 and 6.0 (doublets for the protons alpha to the amino acid), δ 4.78 (m, methine) and δ 3.82 (2s, methyl esters). The (*S*)-isomer (*S*)-**11** gave a similar result.

(4*R,S*)-Benzamido-(2*R*)-benzyl-2,3-dihydro-6-(methoxycarbonyl)-4*H*-1-benzopyran-4-carboxylic Acid (*R*)-**16**.

*N*-Benzoyl 2-(1-bromo-3-phenyl-(2*R*)-propoxy)-5-(methoxycarbonyl)-(*R,S*)-phenylglycine (*R*)-**13** (an estimated 3.22 moles of crude product from above) was dissolved in dimethylformamide (1 ℓ) with acetic anhydride (657 g, 6.44 moles). This solution was stirred while triethylamine was added dropwise over 20 minutes with a cooling bath to keep the temperature below 37°. The spiroalkylation reaction was complete after 1 hour. The solution was diluted with methylene chloride (8 ℓ) and washed with water (4 x 4 ℓ). The organic layer was dried over magnesium sulfate and then filtered through a pad of silica gel (63-200 mesh) using dichloromethane/hexanes (1:1) as eluant. This removed most of the more polar impurities from the two steps and provides a solution of (4*R,S*)-(2*R*)-benzyl-2,3-dihydro-6-(methoxycarbonyl)spiro[4*H*-benzopyran-4,4′-2′-phenyloxazolidin]-5′-one (*R*)-**15** which was concentrated *in vacuo* to an oil. The oil was dissolved in acetone (4 ℓ), treated with 4*N* hydrochloric acid (300 ml) and stirred at room temperature overnight to hydrolyze the azlactone. The acetone was evaporated *in vacuo* and the residual oil was dissolved in methylene chloride (8 ℓ). This solution was washed with water (3 x 3 ℓ). During the washing the methylene chloride layer became a slurry as one of the diastereomers partially precipitated. An aliquot of the slurry was evaporated to dryness to provide a sample for nmr. The diagnostic absorptions were at δ 4.92 and 4.46 (m, OC*H*), 3.80 (2s, $CO_2CH_3$), 3.06 (m), 2.62 and 2.14 (2t, ring protons). The slurry of crude *N*-benzamidodihydrobenzopyrancarboxylic acid (*R*)-**16** was used directly in the oxidative decarboxylation.

Starting with (*S*)-**13** gave similar results with identical crude materials as determined by tlc and nmr.

(2*R*)-Benzyl-6-(methoxycarbonyl)-2,3-dihydro-4*H*-benzopyran-4-one (*R*)-**19**.

The slurry of crude *N*-benzamidobenzopyran-4-carboxylic acid (*R*)-**16** in methylene chloride (12 ℓ) was added with cooling to a stirred solution of 15% sodium hypochlorite (75 ℓ) with the temperature held below 30°. After 4 hours the reaction was judged by tlc to be complete. The layers were separated and the aqueous was extracted 3 times with methylene chloride. The combined organic layers were washed with water, sodium bisulfite solution, water and finally with brine. After drying over magnesium sulfate, the solution was evaporated to an oil. An aliquot of the crude oil was chromatographed over silica gel with methylene chloride to provide the major product. This was identified by its nmr and mass spectrum as 4-(*N*-benzamido)-(2*R*)-benzyl-6-(methoxycarbonyl)-2*H*-benzopyran (*R*)-**18**; mp 121-122°; $^1$H nmr (deuterichloroform): δ 7.85 (m, 4), 7.55 (m, 4), 7.25 (m, 5), 6.9 (d, 1), 6.6 (d, 1), 5.25 (m, 1), 3.9 (s, 3), 3.1 (abx, 2); hrms: m/z Calcd. for $C_{25}H_{21}NO_4$: 399.1465. Found: 399.1484. The remaining crude oil was dissolved in methanol (3 ℓ) with 6*N* hydrochloric acid (600 ml) and warmed to 50° for 2 hours. The methanol was removed *in vacuo* and the resulting aqueous solution was extracted with methylene chloride to provide the crude product. The purified dihydrobenzopyran-4-one (*R*)-**19** was recovered by crystallization from isopropyl alcohol, 252 g, 26% yield from the bromide, mp 95.5-98°, $[\alpha]_D$ +66.3° (c = 1, methanol); $^1$H nmr (deuteriochloroform) δ 8.53 (d, 1), 8.11 (dd, 1), 7.25 (m, 5), 7.0 (d, 1), 4.71 (m, 1), 3.88 (s, 3), 3.20 (q, B of ABX, 1), 3.03 (q, A of ABX, 1), 2.69 (q, 2).

*Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.78; H, 5.38.

(2*S*)-Benzyl-6-(methoxycarbonyl)-2,3-dihydro-4*H*-benzopyran-4-one (*S*)-**19**.

The (2*S*)-isomer (*S*)-**16** was treated as described above to afford the (2*S*)-dihydrobenzopyran-4-one in 30% yield from the bromide, mp 93-96°, $[\alpha]_D$ −66.5° (c = 1, methanol).

*Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.93; H, 5.26.

Alternate Oxidative Decarboxylation Studies: (2*S*)-Benzyl-3,3-dichloro-6-(methoxycarbonyl)-2,3-dihydro-4*H*-benzopyran-4-one (*S*)-**20**.

The *N*-benzamide amino acid (*S*)-**16** (1 g, 2.25 mmoles) in ethyl acetate (25 ml) was treated with 1*M* sodium hypochlorite solution (40 ml, *p*H 9.7) at room temperature for 4 days. The colorless organic layer was washed with sodium bisulfite solution, 1*N* hydrochloric acid and brine. After evaporation to an oil (0.78 g), a portion was chromatographed over silica gel with methylene chloride to provide the title compound (*S*)-**20**; $^1$H nmr (deuteriochloroform): δ 8.67 (d, 1), 8.18 (dd, 1), 7.35 (m, 5), 7.0 (d, 1), 4.63 (dd, 1), 3.90 (s, 3), 3.55 (dd, 1), 3.35 (dd, 1); ms: m/z 364 ($M^+$). The remainder of the sample was treated with an excess of zinc metal in acetic acid acid to provide the optically active dihydrobenzopyran-4-one (*S*)-**19** identical to that described above.

(2*S*)-Benzyl-8-chloro-6-(methoxycarbonyl)-2,3-dihydro-4*H*-benzopyran-4-one (*S*)-**22**.

The *N*-benzamide amino acid (*S*)-**16** (2.23 g, 0.005 mole) was suspended in methylene chloride (30 ml) with acetic acid (3 ml, 0.052 mole). This thin slurry was treated with 2*M* sodium hypochlorite solution (10 ml, 0.02 mole) dropwise over 15 minutes at room temperature. After an additional 1.5 hours stirring, the reaction was diluted with water and the organic layer was washed with sodium bisulfite solution, water, 1*N* hydrochloric acid, saturated sodium bicarbonate and brine. The crude oil was treated with methanolic hydrogen chloride and diluted with 2-isopropanol to provide a sample of (*S*)-**22**, 0.1 g, 7% yield; $^1$H nmr (deuteriochloroform): δ 8.46 (d, 1), 8.20 (d, 1), 7.38 and 7.22 (m, 5), 4.87 (m, 1), 3.90 (s, 3), 3.34 (m, 2), 2.81 (m, 2); hrms: m/z Calcd. for $C_{18}H_{15}O_4Cl$: 330.0655. Found: 330.0693. The remainder of the material in the filtrate was unconverted *N*-benzamide amino acid (*S*)-**16**.

(2*R*)-Benzyl-6-(methoxycarbonyl)-2,3-dihydro-4*H*-benzopyran (*R*)-**23**.

The (2*S*)-benzyldihydrobenzopyran-4-one (*S*)-**19** (1.16 kg, 3.9 moles) was dissolved in THF (11.5 ℓ) with concentrated hydrochloric acid (2.3 ℓ). Palladium on carbon (10%) (50% water wet) was added and the mixture stirred under hydrogen atmosphere (50 psi) for 18 hours. At this point additional catalyst was added (290 g) and the reaction continued for another 12 hours. The reaction mixture was filtered and the catalyst washed with THF (11 ℓ). The combined filtrates were evaporated and the resulting solid taken up in methylene chloride and washed with water and brine. The solution was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a low volume. The residual methylene chloride was replaced with hexanes by distillation at atmospheric pressure to a final volume of 4.5 ℓ. Cooling of the hexane solution gave the desired product as a white solid, 840 g, over two crops, 74% yield, mp 63-65°, $[\alpha]_D$ −134.5° (c = 1, methanol); $^1$H nmr (deuteriochloroform): δ 7.78 (m, 2), 7.28 (m, 5), 6.82 (d, 1), 4.29 (m, 1), 3.88 (s, 3), 3.15 (q, 3), 2.90 (q, 1), 2.80 (m, 2), 2.04 (m, 1), 1.72 (m, 1).

*Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.66; H, 6.55.

(2*S*)-Benzyl-6-(methoxycarbonyl)-2,3-dihydro-4*H*-benzopyran (*S*)-**23**.

In a similar manner, the (2*S*)-isomer was prepared in 70% yield, mp 65.5-67°; $[\alpha]_D$ +135.6° (c = 1, methanol).

*Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.68; H, 6.49.

(2*R*)-Benzyl-6-(hydroxymethyl)-2,3-dihydro-4*H*-benzopyran (*R*)-**24**.

A solution of (*R*)-**19** (800 g, 2.82 moles) in toluene (14.3 ℓ) was stirred while a solution of sodium bis-(2-methoxyethoxy)aluminum hydride (1.8 ℓ, 6.5 moles of a 3.4 molar solution) was added over 1 hour with the temperature held under 20°. The reaction was stirred for 1 hour after the addition at which time tlc showed the reduction was complete. A solution of Rochelle salt (1.6 kg) in water (4.8 ℓ) was added carefully. The layers were separated and the organics were washed with water (3 times), with brine and dried over magnesium sulfate. After the solution was filtered an aliquot was evaporated to provide a sample of alcohol (*R*)-**24**, mp 41-43°, $[\alpha]_D$ −112.6° (c = 1, methanol); $^1$H nmr (deuteriochloroform): δ 7.31 (m, 5), 7.08 (m, 2), 6.83 (d, 1), 4.58 (s, 2), 4.25 (m, 1), 3.19 (q, 1), 2.90 (q, 1), 2.78 (m, 2), 2.10 (s, 1), 2.01 (m, 1), 1.7 (m, 1).

*Anal.* Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.22; H, 7.13.

(2*R*)-Benzyl-6-(formyl)-2,3-dihydro-4*H*-benzopyran (*R*)-**25**.

The toluene solution from the previous preparation was stirred under nitrogen while manganese dioxide (3.7 kg, Type M) was added in portions over 1.5 hours. After an additional 2 hours of stirring, the solution was filtered and evaporated to 4 ℓ. Hexanes (4 ℓ) were added and the mixture stirred for 1 hour and then filtered to give pure aldehyde (*R*)-**25**, 570 g, 80% yield, mp 68-70°, $[\alpha]_D$ −164.4° (c = 1, methanol); $^1$H nmr (deuteriochloroform): δ 9.82 (s, 1), 7.61 (m, 2), 7.30 (m, 5), 6.90 (d, 1), 4.31 (m, 1), 3.17 (q, 1), 2.93 (q, 1), 2.82 (m, 2), 2.05 (m, 1), 1.75 (m, 1).

*Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.86; H, 6.25.

(2*S*)-Benzyl-6-(hydroxymethyl)-2,3-dihydro-4*H*-benzopyran (*S*)-**24** and (2*S*)-Benzyl-6-(formyl)-2,3-dihydro-4*H*-benzopyran (*S*)-**25**.

In a similar manner (*S*)-**23** was converted to the aldehyde (*S*)-**25** in 85% overall yield. Alcohol (*S*)-**24** had mp 40-45°, $[\alpha]_D$ +114.8° (c = 1, methanol).

*Anal.* Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.22; H, 7.09.

Oxidation of (*S*)-**24** yielded the aldehyde (*S*)-**25**, mp 70-71.5°, $[\alpha]_D$ +164.0° (c = 1, methanol).

*Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.88; H, 6.52.

Ethyl 2,3-Dihydrobenzopyran-2-carboxylate *Rac*-**27**.

2,3-Dihydrobenzopyran 2-carboxylic acid *rac*-**26** (35.6 g, 0.2 mole) (prepared according to the method of Augstein *et al.* [18]) and absolute ethanol (24.3 g, 0.6 mole) were combined in methylene chloride (300 ml) and sulfuric acid (96%, 0.6 ml) was added. The mixture was refluxed for 21 hours, then cooled and diluted with water (500 ml). The organic layer was separated, washed with saturated sodium bicarbonate and then water, dried over

magnesium sulfate and evaporated to provide the ester as a colorless liquid, 38.6 g, 93% yield; $^1$H nmr (deuteriochlorofrom): δ 7.12 (t, 1), 7.02 (d, 1), 6.92 (d, 1), 6.85 (t, 1), 4.71 (q, 1), 4.25 (q, 2), 2.80 (m, 2), 2.22 (m, 2), 1.29 (t, 3).

Ethyl 2,3-Dihydrobenzopyran-(2*R*)-carboxylate (*R*)-**27**.

Lipase P-30 (5 g) was suspended in water (500 ml) at *p*H 7 and the mixture was heated to 35°. Racemic ethyl ester *rac*-**27** (103 g, 0.5 mole) was added neat in one portion. The mixture stirred at 35° with *p*H maintained at *ca.* *p*H 7 by means of a *p*H controller until 275 ml of 1*N* sodium hydroxide had been added. The reaction was cooled to room temperature and extracted 3 times with hexanes. The hexanes were combined, filtered through celite and then washed twice with water. The organics were dried over magnesium sulfate, filtered and concentrated to afford the resolved ester (*R*)-**27**, 45.4 g, 45% yield as a colorless oil, $[\alpha]_D$ −9.3° (c = 1.24, methanol). This corresponded to 97%ee and was suitable for use in the next reaction.

(2*R*)-(Hydroxymethyl)-2,3-dihydrobenzopyran (*R*)-**28**.

Ester (*R*)-**27** (43.3 g, 0.21 mole) was dissolved in tetrahydrofuran (433 ml) and water (43 ml) under nitrogen. Sodium borohydride (18.91 g, 0.5 mole) was added in portions over 1 hour with the temperature held <20°. After stirring overnight at room temperature, the solution was cooled to 5° and treated dropwise with acetone (40 ml). After 1 hour water (750 ml) was added followed by methylene chloride (30 ml). The aqueous layer was extracted twice with methylene chloride (200 ml). The combined organics were washed with water, dried over magnesium sulfate and evaporated *in vacuo* to give 32.3 g, 94% yield as a colorless oil, $[\alpha]_D$ −113.4° (c = 1.12, methanol); $^1$H nmr (deuteriochloroform): δ 7.05 (m, 2), 6.83 (m, 2), 4.15 (m, 1), 3.8 (m, 2), 2.85 (m, 2), 2.24 (t, 1), 1.79 (m, 2). Analysis of the Mosher's ester of this alcohol confirmed the >97%ee.

(2*R*)-(Trifluorosulfonyloxymethyl)-2,3-dihydrobenzopyran (*R*)-**29**.

A solution of (**R**)-**28** (14.0 g, 0.085 mole) and pyridine (15.8 g, 0.2 mole) in methylene chloride (400 ml) was cooled to −5° and stirred under nitrogen while trifluoromethylsulfonyl anhydride (28.8 g, 0.102 mole) in methylene chloride (50 ml) was added dropwise over 30 minutes. After stirring for an additional 1 hour at 0°, water (200 ml) was added and the layers separated. The organic layer was washed with 1*N* hydrochloric acid, water, sodium bicarbonate solution, and finally water. This solution was dried over magnesium sulfate, filtered, and evaporated *in vacuo* to afford the triflate as an oil, 23.7 g, 94% yield, $[\alpha]_D$ −65.1° (c = 1, methanol); $^1$H nmr (deuteriochloroform): δ 7.10 (m, 2), 6.85 (m, 2), 4.63 (m, 2), 4.30 (m, 1), 2.87 (m, 2), 2.05 (m, 1), 1.87 (m, 1). This was used in the next reaction without further purification.

(2*R*)-Benzyl-2,3-dihydrobenzopyran (*R*)-**30**.

The triflate (*R*)-**29** (23.2 g, 0.783 mole) and cuprous bromide dimethylsulfide complex (2.8 g, 0.0136 mole) in tetrahydrofuran (326 ml) were stirred under nitrogen at −5° while 3*M* phenylmagnesium bromide in ether (71.5 ml, 0.215 mole) was added dropwise over 20 minutes. After stirring for 2.5 hours at 0°, the reaction was poured slowly into a stirred mixture of water (800 ml), ammonium chloride (96 g, 1.8 moles) and methylene chloride (400 ml). The layers were separated and the aqueous extracted twice with methylene chloride. The combined organics were washed with aqueous ammonium chloride and water and dried over magnesium sulfate. Evaporation afforded the desired compound contaminated with some biphenyl. This was suitable for use in the next reaction but could be purified by chromatography over silica gel with hexanes/methylene chloride to yield 14.87 g (85%) of the dihydrobenzopyran as a colorless oil, $[\alpha]_D$ −110° (c = 1, methanol); $^1$H nmr (deuteriochloroform): δ 7.29 (m, 5), 7.08 (m, 2), 6.85 (m, 2), 4.24 (m, 1), 3.08 (q, 1), 2.89 (q, 1), 2.77 (m, 2), 2.00 (m, 1), 1.73 (m, 1).

*Anal.* Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.80; H, 7.16.

(2*R*)-Benzyl-6-(formyl)-2,3-dihydro-4*H*-benzopyran (*R*)-**25**.

Phosphorus oxychloride (31.74 g, 0.207 mole) was added slowly and with stirring to *N*-methylformanilide (27.98 g, 0.207 mole). After stirring for 15 minutes, (*R*)-**30** (28.61 g, 0.138 mole, corrected for biphenyl content) was added in methylene chloride (30 ml) and stirred at room temperature for 15 minutes. The resulting solution was heated to 65° with the distillation of the methylene chloride and held at 65° for 1 hour. The mixture was cooled to room temperature and diluted with methylene chloride (400 ml) and 15% aqueous sodium acetate. The layers were separated and the organics were washed with 15% sodium acetate, 1*N* hydrochloric acid, and water. After drying over magnesium sulfate, the solution was filtered and evaporated to an oil (47.1 g). This crude product was dissolved in ethanol (144 ml) and treated with a solution of sodium bisulfite (57.5 g, 0.552 mole) in water (144 ml) and ethanol (106 ml) at 40°. The resulting mixture was stirred for 1 hour while cooling to room temperature and then the bisulfite adduct of the desired aldehyde (39.8 g) was recovered by filtration. The adduct was added in portions to a stirred mixture of toluene (250 ml), water (400 ml) and sodium carbonate (42.3 g, 0.4 mole). The mixture was diluted with hexanes (250 ml) and stirred for 1.5 hours. The desired aldehyde was recovered from the organic layer as a low melting solid, 27.2 g, 76% yield. This was recrystallized from isopropanol and hexanes to afford 21 g (59%) of analytically pure (*R*)-**25** identical with that described above.

(5′*R*)-[(2*R*-Benzyl-3,4-dihydro-2*H*-1-benzopyran-6-yl)methyl]thiazolidine-2,4-dione (5′*R*,2*R*)-**1**.

(5*R*,*S*)-[(2*R*-Benzyl-3,4-dihydro-2*H*-1-benzopyran-6-yl)methyl]-thiazolidine-2,4-dione (5′*R*,*S*,2*R*)-**1** (1.767 g, 0.005 mole) was added as a solid to a solution of *d*-(+)-ephedrine (0.827 g, 0.005 mole) in toluene (25 ml) at room temperature. After several minutes crystallization began and the mixture was stirred for 48 hours. The salt was collected and washed with toluene and hexanes, 2.2 g, 85% yield, $[\alpha]_D$ +35.4° (c = 1, methanol). This reading was taken immediately upon dissolution of the salt; after 1 hour the rotation was +4.0°. The salt (2.1 g) was added to a stirred mixture of methylene chloride (50 ml) and 1*N* hydrochloric acid (50 ml). The organic solution was washed with 1*N* hydrochloric acid, with water and was dried over magnesium sulfate. The free acid was recovered by evaporation, 1.33 g, 93% yield, mp 57-61°, $[\alpha]_D$ +36.94° (c = 1, methanol). This did not change with time. The nmr spectrum was identical to that for the (5′*R*,*S*,2*R*)-**1** diastereomers. The hplc analysis showed this to be the (5′*R*,2*R*)-diastereomer. The hplc assay utilized a Resolvosil (serum albumin) column with water:acetonitrile:tetrahydrofuran:-triethylamine:acetic acid (725:275:4:4:2, v/v) as the mobile phase, a 1.5 ml/m flow rate and 229 nm wavelength detection. The assignment of the four diastereomer peaks was based on the asym-

metric synthesis of the optically active 2-benzylbenzopyran pairs of diastereomers synthesized from phenylalanine and a single crystal X-ray analysis of (*R,S/S,R*)-**1** which was obtained by fractional crystallization of **1** as a racemic mixture.

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## REFERENCES AND NOTES

[1] D. A. Clark, S. W. Goldstein, R. A. Volkmann, J. F. Eggler, G. F. Holland, B. Hulin, R. W. Stevenson, D. K. Kreutter, E. M. Gibbs, M. N. Krupp, P. Merrigan, P. L. Kelbaugh, E. G. Andrews, D. L. Tickner, R. T. Suleske, C. H. Lamphere, F. J. Rajeckas, W. H. Kappeler, R. E. McDermott, N. J. Hutson and M. R. Johnson, *J. Med. Chem.*, **34**, 319 (1991).

[2] T. Sohda, K. Mizuno, E. Imamiya, Y. Sugiyama, T. Fujita and Y. Kawamatsu, *Chem. Pharm. Bull.*, **30**, 3580 (1982).

[3] R. A. Stevenson, N. J. Hutson, M. N. Krupp, R. A. Volkmann, G. F. Holland, J. F. Eggler, D. A. Clark, R. K. McPherson, K. L. Hall, B. H. Danbury, E. M. Gibbs and D. K. Kreutter, *Diabetes*, **39**, 1218 (1990).

[4] T. Sohda, K. Mizuno and Y. Kawamatsu, *Chem. Pharm. Bull.*, **32**, 4460 (1984).

[5] J. F. Eggler, G. F. Holland, M. R. Johnson and R. A. Volkmann, U. S. Patent 4,703,052 (1987).

[6] G. P. Ellis and I. M. Lockhart, Chromans and Tocopherols, John Wiley and Sons, New York, NY, 1981.

[7] S. Takano, Y. Shimazaki and K. Ogasawara, *Heterocycles*, **31**, 917 (1990) and references therein.

[8] H.-J. Kabbe and A. Widdig, *Angew. Chem., Int. Ed. Engl.*, **21**, 247 (1982).

[9] S. T. Saengchantara and T. W. Wallace, *Tetrahedron*, **46**, 6553 (1990).

[10] N. L. Dirlam, B. S. Moore and F. J. Urban, *J. Org. Chem.*, **52**, 3587 (1987).

[11] M. Winitz, L. Bloch-Frankenthal, N. Izumiya, S. M. Birnbaum, C. G. Baker and J. P. Greenstein, *J. Am. Chem. Soc.*, **78**, 2423 (1956); [b] S. G. Cohn and S. Y. Weinstein, *J. Am. Chem. Soc.*, **86**, 5326 (1964).

[12] While both D- and L-phenylalanine have been used in this sequence, only the D-phenylalanine intermediates which lead to englitazone are shown for the first process.

[13] O. Mitsunobu, *Synthesis*, 1 (1981).

[14] U. Zoller and D. Ben-Ishai, *Tetrahedron*, **31**, 863 (1975).

[15] H. Gotthardt, R. Huisgen and H. O. Bayer, *J. Am. Chem. Soc.*, **92**, 4340 (1970).

[16] G. A. Lee and H. H. Freedman, *Tetrahedron Letters*, 1641 (1976).

[17] R. V. Stevens, K. T. Chapman and H. N. Weller, *J. Org. Chem.*, **45**, 2030 (1980).

[18] J. Augstein, M. Monro, G. W. H. Potter and P. Scholfield, *J. Med. Chem.*, **11**, 844 (1968); D. T. Witiak, E. S. Stratford, R. Nazareth, G. Wagner and D. R. Feller, *J. Med. Chem.*, **14**, 758 (1971).

[19] T. K. Schaaf, M. R. Johnson, J. W. Constantine, J. S. Bindra, H.-J. Hess and W. Elger, *J. Med. Chem.*, **26**, 328 (1983).

[20] Lipase P-30, Amano International Enzyme Co., Inc., Troy, VA. The resolution of ethyl 3,4-dihydro-7-hydroxy-2*H*-1-benzopyran-2-carboxylate with this same enzyme was described recently; P. Kalaritis, R. W. Regenye, J. J. Partridge and D. L. Coffen, *J. Org. Chem.*, **55**, 812 (1990).

[21] Kotsuki has coupled racemic 2-(trifluoromethylsulfonyloxy)methyltetrahydropyran and phenyl grignard with cuprous bromide. H. Kotsuki, I. Kadota and M. Ochi, *Tetrahedron Letters*, **30**, 1281 (1989).

[22] A. Vilsmeier and A. Haack, *Chem. Ber.*, **60B**, 119 (1927).