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Enzymatic resolution for an improved enantioselective synthesis of benzofuranyl derivatives: precursors to a class of vitamin E related antioxidants

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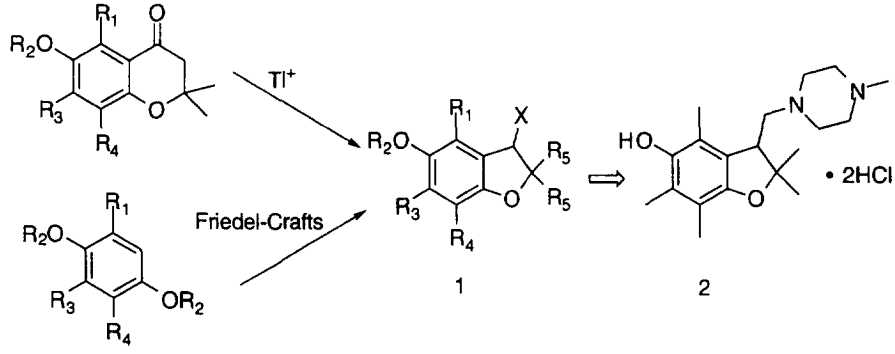
Abstract: Enzymatic resolution of 3-hydroxymethylbenzofurans using *Candida rugosa* lipase provides an enantioselective synthesis of vitamin E related antioxidants. © 1997 Published by Elsevier Science Ltd. All rights reserved.

Introduction

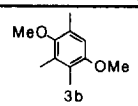
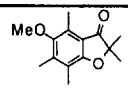
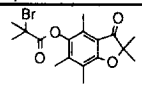
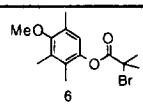
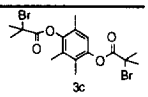
Currently, there is tremendous interest in the synthesis of antioxidants for the treatment of head trauma and stroke.[1,2] One class of compounds related to vitamin E are the benzofuranyl compounds of general formula **1**. Previously, we synthesized the skeleton of these compounds by using a Tl-based ring contraction,[1,3] and more recently we developed a Friedel–Crafts approach that avoids the use and disposal of toxic thallium reagents (Scheme 1).[1,4] In addition to the challenge of constructing the benzofuranyl system, we also needed to develop a method for the preparation of the enantiomers of **1**. After screening a number of compounds of type **1**, it was shown that piperazine **2** was one of the most effective for *in vitro* inhibition of lipid autooxidation of rat brain homogenate. In order to establish clearly the relative efficacy and toxicology of the enantiomers of **2** in a timely fashion, we required an efficient enantioselective synthesis.[1,4,5] We now describe our work on the improvement of the overall synthesis of the optical isomers of **2**.[6]



Scheme 1.

* Corresponding author.

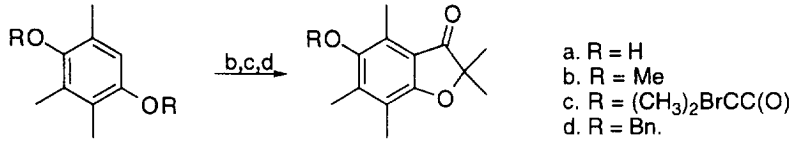
Table 1. GC–MS study of Friedel–Crafts reaction[a]

Time (h)	Reaction Mixture (%)				
	 3b	 4b	 4c	 6	 3c
24	52	30	<1	16	<1
48	<1	50	31	15	4
72	<1	13	71	5	11
96	<1	3	80	7	10

[a] 0.2 eq. of $FeCl_3$ was added at time 0, 24, and 48 h following removal of an aliquot.

Results and discussion

In our process work, we chose to use the Friedel–Crafts reaction for the construction of the benzofuranyl skeleton because of the ready availability of the trimethylhydroquinone **3a** and bromo-*iso*-butyryl bromide. Transformation of the hydroquinone into the dimethyl analog **3b** was required for the Friedel–Crafts reaction to proceed. All attempts to transform the hydroquinone **3a** into the desired benzofuranone *via* a Fries rearrangement failed.[4,7] Nevertheless, when the protected hydroquinone **3b** and 2-bromo-*iso*-butyryl bromide were reacted with $FeCl_3$, reasonable yields of the intermediate ester **4c** along with a substantial amount of diester **3c** were obtained.



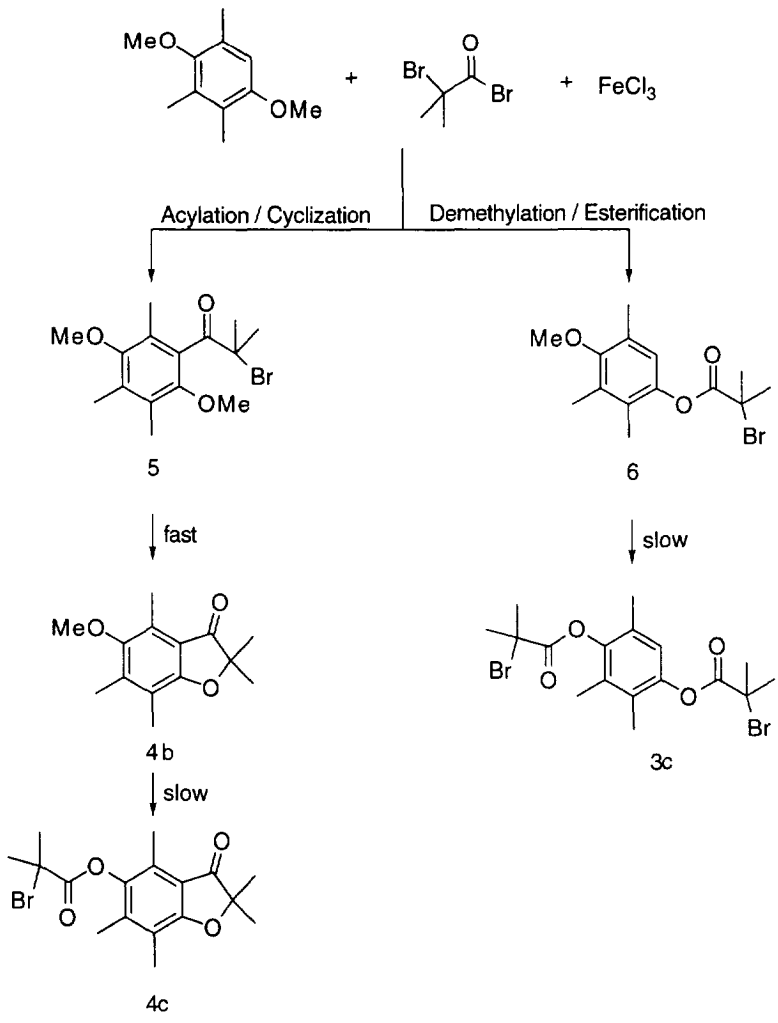
3 4

(a) 3a→3b: Me_2SO_4, KOH, MeOH (b) $(CH_3)_2BrCC(O)Br$, $FeCl_3$, $ClCH_2CH_2Cl$
(c) NaOH, MeOH, THF, H_2O (d) BnBr, K_2CO_3, acetone

In order to establish a better understanding of the Friedel–Crafts reaction, an experiment was conducted in which $FeCl_3$ was added portionwise to a slurry of dimethoxybenzene **3b** and acid bromide. Aliquots were removed, hydrolyzed, and analyzed by GC–MS. As the data in Table 1 indicate, the acylation/cyclization pathway *via* intermediate **5** predominates until the methoxybenzofuranone **4b** reaches a maximum of 50% of the product mixture (Scheme 2). A slower demethylation/esterification process ultimately provides ester **4c** as the major product. However, the alternative pathway involving demethylation/esterification of the starting dimethoxybenzene **3b** provides intermediate monoester **6** which is converted into diester **3c**, the major byproduct.[1] Thus, the rate of acylation must be faster than the rate of demethylation so that a reasonable yield of ester **4c** is obtained.[8] In addition, a key feature of the work-up of this reaction is to add 1 eq of Na, K tartrate (saturated aqueous solution) to precipitate the iron salts which are now readily removed by filtration. Saponification of the crude ester **4c** with NaOH in THF/MeOH/water provides the phenol **4a** in 45% overall yield.

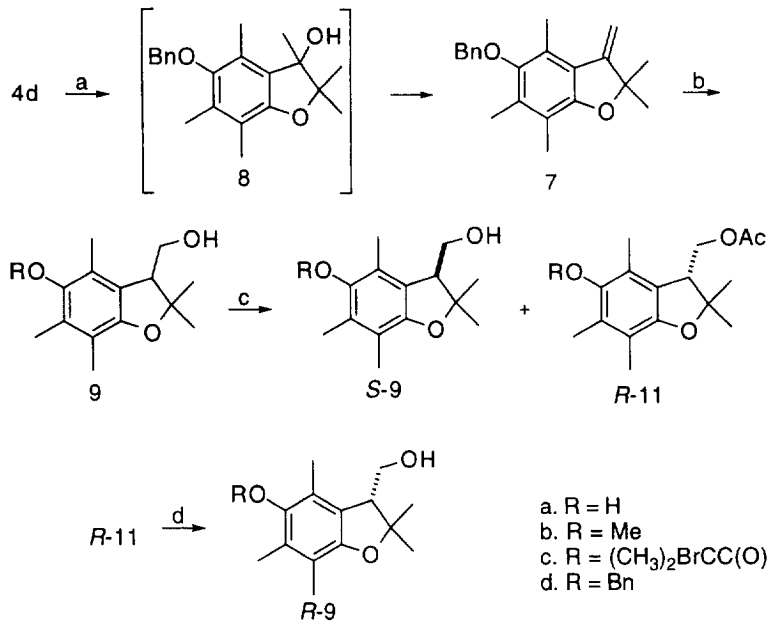
Owing to the ease of removal of the benzyl group, the phenol **4a** was protected as the benzyl ether **4d**. Previously, one carbon homologation to the exomethylene compound **7** was accomplished using standard Wittig chemistry.[4] We found that this homologation is more efficiently achieved by a one-pot reaction of **4d** with MeMgCl followed by elimination of the tertiary alcohol **8** with H_2SO_4 Scheme 3. This alternative procedure is a significant improvement over the former method as less waste is generated and no chromatography is required for purification.

Conversion of olefin **7** into the corresponding hydroxymethyl compound **9d** was performed as before using the standard hydroboration/oxidation protocol.[4] Having prepared a racemic mixture, we



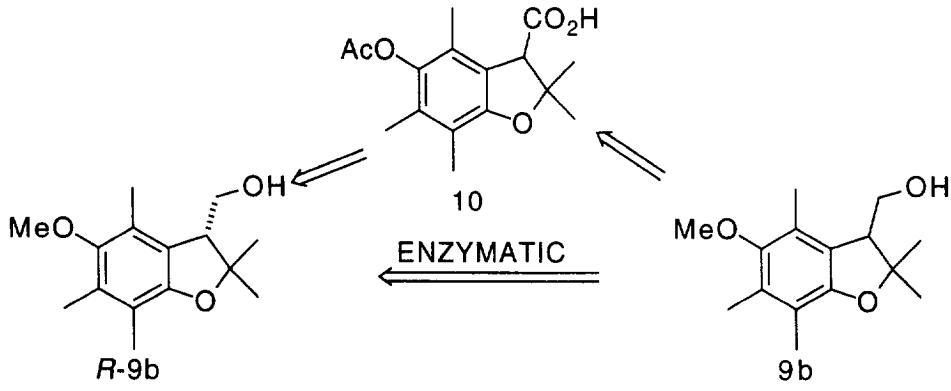
Scheme 2.

now decided to pursue an enzymatic resolution of the enantiomers of **9d** which would shorten the synthesis and increase the overall yield. Previously, resolution of acid **10** was achieved by selective crystallization with (+)- or (−)-α-methylbenzylamine.[4] In this case, oxidation of alcohol **9b** (Swern then $NaClO_2$) and subsequent adjustment of the phenol protecting group to an acetate was necessary to generate the resolvable acid **10**. After resolution, the optically pure isomer of **10** was reduced back to alcohol **9b** for conversion to the final product. Thus, we envisioned that an enzymatic resolution would shorten the synthesis and improve the overall process.



(a) MeMgCl, THF; then H_2SO_4 (b) BH_3•DMS, THF; then NaOH, H_2O_2
(c) CH_2=CH-OAc, *Candida rugosa* lipase, TBME (d) Na_2CO_3, MeOH.

Scheme 3.



We chose to examine the selective acylation of one of the enantiomers of alcohol **9** with a variety of enzymes.[9] Initially, we had planned to use the methyl protected phenol **9b** in the synthesis, but we later changed to the benzyl derivative **9d** which was more amenable to the overall synthetic scheme. After screening several enzymes for the selective acylation of **9b** using vinyl acetate (see Table 2), the use of *Candida rugosa* lipase was found to provide both high ee and a good reaction rate. We were delighted to find that changing to the benzyl derivative **9d** did not alter the enzymatic resolution. Thus, we chose to optimize further the enzymatic resolution using the *Candida rugosa* lipase for the preparation of alcohol *R*-**9d**.[6,10] The best conditions for the conversion to acetate *R*-**11d** involved the use of 3–4 eq of vinyl acetate with *tert*-butyl methyl ether (TBME) as the solvent and running the reaction to 43% conversion. This procedure produced acetate *R*-**11d** with 84–87% ee in 24 h. A simple plug filtration through silica gel followed by basic methanolysis of the acetate gave the *R*-enantiomer of alcohol **9d** with 84–87% ee. One recrystallization of this material from hexane provided *R*-**9d** with >98% ee in

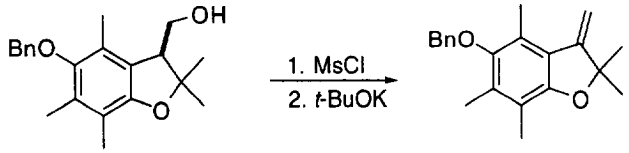
Table 2. Enzymatic acylation of hydroxymethylbenzofuran **9**[a]

Entry	Substrate	Enzyme (Lipase)	Time (h)	% Conv[b]	% ee (*R*-**11**)[b]
1	**9b**	*Pseudomonas cepecia*	12	3	>95
2	**9b**	Porcine pancreatic	12	No Rxn	
3	**9b**	*Aspergillus niger*	12	9	>95
4	**9b**	*Mucor meihei*	12	2	50
5	**9b**	*Candida rugosa*	12	59	92
6	**9b**	*Burkholdia species* (L-1)[c]	24	No Rxn	
7	**9b**	*Candida antartica*, fraction B (L-2)[c]	24	No Rxn	
8	**9b**	*Candida rugosa* (L-3)[c]	24	70	85
9	**9b**	*Pseudominas* species (L-4)[c]	24	6	nd
10	**9b**	*Candida antartica*, fraction A (L-5)[c]	24	18	87
11	**9b**	*Pseudominas* species (L-6)[c]	24	9	nd
12	**9b**	Porcine pancreatic (L-7)[c]	24	2	nd
13	**9d**	*Candida rugosa* (Sigma Lot 115F-024)[d]	24	42	95
14	**9d**	*Candida rugosa* (Sigma Lot 36C-0113)[d]	24	24	90
15	**9d**	*Candida rugosa* (L-3)[c]	24	50	96
16	**9d**	*Candida antartica*, Fraction A (L-5)[c]	24	7	nd
17	**9d**	Celluzyme 0.7T (Novo)	24	No Rxn	
18	**9d**	N-lipase-100T (Novo)	24	No Rxn	
19	**9d**	Ter-60-T (Novo)	24	No Rxn	

[a] Typical Scouting Procedure: 10 mg of **9**, 2-3 eq CH_2=CH-OAc, 20-50 mg of lipase in 2 mL of TBME. [b] % conversion and ee's determined by HPLC (Chiralpak AD®, 25 cm, 5% EtOH / pentane as eluant, 1.5 mL / min, 210 nm). [c] Chirazyme® lipase kit (Boehringer Mannheim). [d] In some cases, different lots showed different rates.

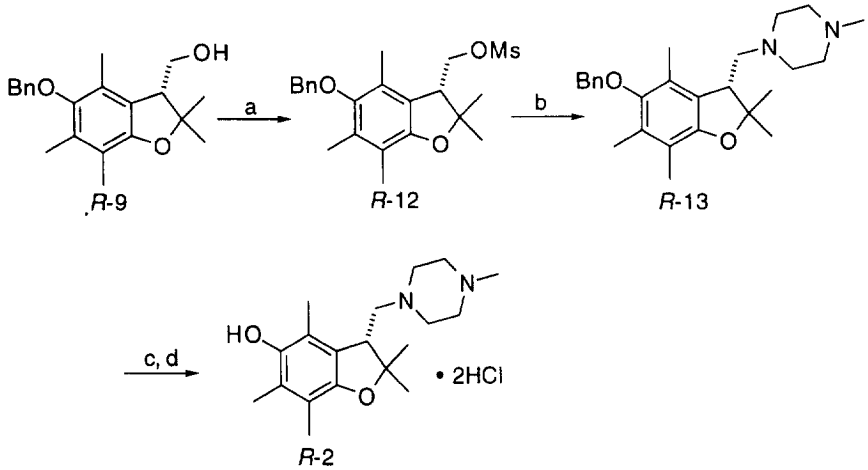
26% yield. Recycle of the mother liquor through the enzymatic resolution provides an additional 7% of *R*-**9d** (>98% ee). Alternatively, if the *S*-isomer of **9d** is desired, the enzymatic acylation is run for 3 days to drive the reaction to 48% conversion to provide *S*-**9d** with 92% ee. Recrystallization from hexane provided *S*-**9d** with >98% ee in 35% yield. Because the *R*-isomer of alcohol **9d** was needed, the larger scale enzymatic resolutions were performed using the former reaction parameters.

In addition to developing the enzymatic resolution of alcohol **9**, we also devised a process to recycle the undesired isomer which increases the overall yield. On this accord, treatment of enriched *S*-**9d** with MsCl to generate the *S*-enriched mesylate **12** followed by the addition of KO*t*-Bu provided olefin **7** in a one-pot process in 98% yield. This recycle now increases the yield of the enzymatic resolution step to 65% with 3 recycles.



S-9 7

With the enantiomerically pure alcohol in hand, we then completed the synthesis of the desired antioxidants. Formation of mesylate *R*-**12** followed by nucleophilic displacement of the mesyl group with *N*-methylpiperazine gave *R*-**13**. Additives such as NaI or KI promoted elimination to provide 5–15% of olefin **7**.[11] However, when mesylate *R*-**12** was used with no additives, clean conversion to *R*-**13** occurred with none (<1%) of olefin **7** being observed and no purification of this intermediate was required. Finally, catalytic hydrogenation with Pd/C removed the benzyl group to provide the unprotected phenol *R*-**2**. Formation of the dihydrochloride salt gave the pharmacologically acceptable form of the antioxidant. The 3-step transformation of *R*-**9d** to *R*-**2** was achieved in 74% overall yield.



R-9 *R*-12 *R*-13

R-2

(a) MsCl, Et_3N, THF (b) methylpiperazine, K_2CO_3, MeCN
(c) H_2, Pd / carbon, EtOH / AcOH (d) HCl, H_2O / water

Synthesis of *S*-**2** was conducted in a similar fashion, except the *S*-isomer of alcohol **9d** was used. Thus, conversion of *S*-**9d** to the mesylate followed by displacement with methylpiperazine and deprotection provided *S*-**2**.

In conclusion, we have developed a new route to the synthesis of optically active benzofuranyl compounds **1** involving the enzymatic resolution of alcohols **9**. This new process has provided an excellent enantioselective synthesis for the multigram production of an important class of antioxidants.

Experimental

General

^1H and ^{13}C NMR spectra were recorded using a Varian XL 300 or Gemini 300 spectrometer operating at 300 and 75 MHz, respectively. IR spectra were recorded on a Mattson Galaxy 500 FTIR. Mass Spectra (MS) were obtained on a Finnigan MAT4600 spectrometer. Melting points were obtained on a Thomas–Hoover melting point apparatus. Chromatography was conducted using 60–200 mesh silica gel (grade 62).

*1,4-Dimethoxy-2,3,5-trimethylbenzene (**3b**)*[12]

To a solution of 250 g (1.6 mol) of 2,3,5-trimethylhydroquinone (**3a**) in 1.6 L of MeOH was slowly added 621 mL (6.6 mol) of Me_2SO_4. The temperature dropped to 15°C with the addition. After cooling with an ice bath, a solution of 552 g of KOH in 1.4 L of MeOH was added very slowly (exothermic

reaction) to maintain the temperature of the solution below 35°C. After 18 h at room temperature, 100 mL of water was added. The mixture was filtered and concentrated. The residue was dissolved in 2 L of EtOAc, washed with 2 L of water, 1 L of sat'd $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated to give 292 g (99%) of **3b** as thick reddish oil: ^1H NMR ($CDCl_3$) δ 6.52 (s, 1) 3.79 (s, 3), 3.65 (s, 3), 2.27 (s, 3), 2.20 (s, 3), 2.1 (s, 3); ^{13}C NMR ($CDCl_3$) δ 153.4, 150.5, 130.5, 127.6, 123.7, 110.3, 60.1, 55.7, 16.2, 12.6, 11.8; MS (EI) m/z (relative intensity) 180 (65), 165 (100), 40 (20).

*5-Hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-3-one (**4a**)*

A 12-L flask equipped with a stirrer, ice/water bath, and an internal thermometer was charged with 576 g (3.1 mol) of **3b** and 3 L of dichloroethane. After blanketing with N_2, 1.2 L (9.7 mol) of 2-bromoisobutyryl bromide was added at once and stirring commenced. When the internal temperature reached 15°C, 600 g (3.7 mol) of $FeCl_3$ was added all at once (slightly exothermic). After stirring vigorously for 3 h, the mixture was allowed to warm to room temperature. After 5 days, 950 mL of a saturated K, Na tartrate solution in water was added dropwise followed by 2 L of water and 2 L of EtOAc. After 1 h, the slurry was allowed to settle for 2 h. The mixture was filtered and the resulting solids were washed with 6 L of EtOAc. The filtrate was separated and the aqueous phase was extracted twice with 500 mL of EtOAc. The combined organic layers were concentrated to give a dark red–brown oil. This oil was placed in a 12-L flask and 2 L of THF, 1.4 L of MeOH, and 2 L of water were added. To this mixture was added 700 g of NaOH pellets in 50 g portions (CAUTION: Strong exotherm). The solution was refluxed for 6 h and then stirred overnight at ambient temperature. After concentrating to remove most of the THF and MeOH, excess dry ice was carefully added. The resulting solid was collected. The aqueous filtrate was treated with HCl to a pH of about 4 and extracted with 1 L of EtOAc. This extract was added to the solid filtered off and 1 L of EtOAc was added to effect dissolution. After adding 2 L of hexane, the resulting solution was filtered through 3 L of dry silica gel (60–200 mesh) using 1:1 EtOAc/hexane as eluant (TLC — 10% EtOAC/90% hexane, silica gel, R_f of product is 0.35) to give a brown solid after concentration. The solid was suspended in 200 mL of EtOAc and collected. The solid was washed with a solution of 20 mL of cold EtOAc and 500 mL of hexane. After air drying, 295 g of **4a** was collected. Hexane was added to the filtrate until cloudy. This solution was poured onto 2 L of silica gel and eluted with 10% EtOAc/90% hexane to give an additional 22 g of **4a**. Total amount of **4a** collected was 317 g (45%): ^1H NMR ($CDCl_3$) δ 4.82 (br s, 1), 2.50 (s, 3), 2.28 (s, 3), 2.21 (s, 3), 1.64 (s, 6).

*5-Benzyloxy-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-3-one (**4d**)*

To a solution of 453 g (2.1 mol) of **4a** in 2 L of acetone was added 720 g of K_2CO_3. A solution of 423 g (2.5 mol) of benzyl bromide in 200 mL of acetone was added portionwise over 10 min. A slight exotherm was observed. The pot temperature increased from 20°C to 22°C after 15 min, to 23°C after 30 min, to 30°C after 1 h, and to 36°C after 2 h. The temperature remained at 36°C for 1 h. The mixture was heated to reflux. After 39 h, TLC showed complete conversion to product. The mixture was cooled to 50°C and filtered using 1.5 L of EtOAc to remove the solids from the flask. The solids were washed with 1.5 L of EtOAc. The fitrate was concentrated. The resulting solids were dissolved in 7 L of EtOAc. The solution was washed with water, dried ($MgSO_4$) and concentrated. The resulting solids were placed on a tray for air-drying. After 2 days, 638 g of **4d** (99%) was collected: mp 114–115°C, R_f=0.65 (20% EtOAc/hexane), ^1H NMR ($CDCl_3$) δ 7.50–7.30 (m, 5), 4.75 (s, 2), 2.57 (s, 3), 2.28 (s, 3), 2.09 (s, 3), 1.43 (s, 6); ^{13}C NMR ($CDCl_3$) δ 205.5, 166.5, 150.0, 141.2, 137.2, 128.6 (2), 128.1, 127.9, 127.8 (2), 119.6, 115.1, 87.2, 74.9, 23.4, 13.9 (2), 11.2, 11.1; IR (KBr) 1695 cm^{-1}; MS (EI) m/z (relative intensity) 310 (12), 219 (78), 191 (22), 91 (100); Anal. calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.06; H, 7.21.

5-Benzyloxy-3-methylene-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran (7)

To a solution of 500 g (1.6 mol) of **4d** in 1.8 L of THF at 0°C was added 800 mL (2.4 mol) of 3.0 M MeMgCl in THF over 1 h. The mixture was allowed to warm to room temperature. After 15

h, TLC and GC showed complete conversion to alcohol **8**. The mixture was cooled to 0°C and 350 mL of a saturated NH_4Cl solution was added VERY CAREFULLY. Concentrated H_2SO_4 (300 mL) was added dropwise over 1 h. TLC showed conversion to **7**. Water (1.5 L), EtOAc (1.5 L), and 1 L of saturated NH_4Cl solution were added to dissolve the salts. The organic phase was dried ($MgSO_4$) and concentrated. The crude oil was transferred to a crystallization dish using minimal EtOAc and seeded. Complete crystallization was obtained in ca. 30 min. The solid was placed on a tray and allowed to air-dry. After 2 days 492 g (99%) of **7** was collected: mp 55–57°C; ^{1}H NMR ($CDCl_3$) δ 7.50–7.30 (m, 5), 5.33 (s, 1), 4.81 (s, 1), 4.66 (s, 2), 2.40 (s, 3), 2.24 (s, 3), 2.14 (s, 3), 1.44 (s, 6); ^{13}C NMR ($CDCl_3$) δ 155.9, 155.2, 149.2, 137.7, 132.2, 128.5 (2), 127.9, 127.8 (2), 124.9, 120.0, 117.0, 101.5, 87.8, 75.1, 28.8 (2), 13.2, 12.9, 11.9; IR (KBr) 1630 cm^{-1}; MS (EI) m/z (relative intensity) 308 (22), 217 (100); Anal. calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 80.76; H, 7.90.

*5-Benzyloxy-2,2,3,4,6,7-hexamethyl-2,3-dihydro-1-benzofuran-3-ol (**8**)*

To a solution of 5.0 g (16.1 mmol) of **4d** in 30 mL of THF at 0°C was added 17.3 mL (24.2 mmol) of 1.4 M MeMgBr in THF over 10 min. The mixture was allowed to warm to room temperature. After 18 h, 50 mL of sat. NH_4Cl solution was carefully added dropwise. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated to give 5.16 g (98%) of **8**: mp 111–112 °C; ^{1}H NMR ($CDCl_3$) δ 7.57–37 (m, 5), 4.74 (s, 2), 2.43 (s, 3), 2.26 (s, 3), 2.15 (s, 3), 1.78 (s, 1), 1.62 (s, 3), 1.48 (s, 3), 1.37 (s, 3); ^{13}C NMR ($CDCl_3$) δ 155.9, 155.1, 149.1, 137.7, 132.1, 128.5 (2), 127.9, 127.8 (2), 124.9, 120.0, 117.0, 101.5, 87.8, 75.1, 28.8 (2), 13.1, 12.9, 11.9; IR (KBr) 3501; MS (EI) m/z (relative intensity) 326 (18), 308 (8), 235 (100), 217 (83), 91 (53); Anal. calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.45; H, 8.04.

*5-Benzyloxy-3-hydroxymethyl-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran (**9d**)*

To a solution of 492 g (1.6 mol) of **7** in 1.6 L of THF cooled with an ice bath was added 950 mL (1.9 mol) of a 2.0 M solution of BH_3·DMS in THF over 2 h. The pot temperature was maintained between 0 and 5°C. The solution was allowed to warm to room temperature. After 15 h, the solution was cooled with an ice bath and 900 mL of water WAS CAREFULLY ADDED (hydrogen evolution ceased after ca. 30 mL of water had been introduced.) A 3.0 M NaOH solution (530 mL) was added over 30 min maintaining the pot temperature below 10°C. A 30% H_2O_2 solution (530 mL) was introduced keeping the pot temperature below 20°C. After 3 h, 1 L of water and 1 L of EtOAc were added. The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated. The oily residue was poured into 2 L of hexane causing crystallization. The solid was collected and air dried to give 371 g of **9d**. The mother liquor was concentrated to 700 mL and charcoal was added. After filtering through diatomaceous earth, seed crystals were added. An oily solid mixture was obtained upon concentration. The solid was collected and washed thoroughly with hexane to provide 28 g of **9d**. The mother liquor was concentrated and chromatography through silica gel using an EtOAc / hexane gradient provided 52 g of additional **9d**. Total **9d** collected was 451 g (87%): ^{1}H NMR ($CDCl_3$) δ 7.52–7.32 (m, 5), 4.73 (s, 2), 3.81 (m, 2), 3.03 (m, 1), 2.22 (s, 3), 2.21 (s, 3), 2.08 (s, 3), 1.62 (s, 3), 1.40 (m, 1), 1.33 (s, 3); ^{13}C NMR ($CDCl_3$) δ 153.3, 149.1, 137.8, 130.0, 128.5 (2), 127.8, 127.7 (2), 125.1, 123.0, 116.7, 87.0, 74.5, 61.7, 53.0, 29.2, 22.5, 13.0, 12.8, 12.2; IR (KBr) 3397 cm^{-1}; MS (EI) m/z (relative intensity) 326 (14), 235 (100), 217 (20), 205 (41), 91 (41); Anal. calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.28; H, 7.99.

*(3R)-5-Benzyloxy-3-hydroxymethyl-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran (R-**9d**)*

A mixture of 40.1 g (120 mmol) of **9d**, 132 g of lipase/*Candida rugosa* lipase and 35 g (410 mmol) of vinyl acetate in 1.8 L of TBME were combined at room temperature. After 24 h, the mixture was filtered and concentrated. Chromatography gave 19.7 g of *R*-**11** (87% ee, HPLC) and 24 g of *S*-**9d** (64% ee). Compound *R*-**11** (87% ee) showed: $[\alpha]_D$=+22.2 (c=1.1, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.5–7.2 (m, 5), 4.7 (m, 2), 4.2 (m, 2), 3.2 (m, 1), 2.3 (s, 3), 2.2 (s, 3), 2.1 (s, 3), 2.0 (s, 3), 1.5 (s, 3), 1.3 (s, 3); MS (EI) m/z (relative intensity) 368 (20), 277(100), 217(90).

To a solution of 19.7 g (53 mmol) *R*-**11** (87% ee) in 0.4 L of MeOH was added 2.0 g (14 mmol) of anhydrous K_2CO_3. After 5 h, the mixture was concentrated. The residue was dissolved in 300 mL of Et_2O, washed with water, dried ($MgSO_4$) and concentrated. The oily residue (17 g) was dissolved in 800 mL of hot hexane. After 48 h, the solvent was decanted from the crystal mass. The solid was collected and air dried to give 10.9 g of *R*-**9d** (98.4% ee). The mother liquor was concentrated to give 5.9 g of enriched *R*-**9d** (62% ee).

A solution of 5.9 g of enriched *R*-**9d** (62% ee) in 265 mL of TBME was treated at room temperature with 5.2 g (60 mmol) of vinyl acetate and 20 g of *Candida rugosa* lipase. After 6 days, the mixture was filtered and and concentrated. Chromatography of the residue using an EtOAc/hexane gradient gave 4.9 g *R*-**11d** (91.5% ee). A solution of 4.9 g *R*-**11d** (91.5% ee, HPLC) in 200 mL of MeOH was treated with 2.0 g of K_2CO_3. After 15 h, the mixture was concentrated. The residue was dissolved in 150 mL of Et_2O, washed with water, dried ($MgSO_4$), and concentrated. The residue was dissolved in 200 mL of hot hexane. Crystallization occurred over a 48 h period. The solvent was decanted and the crystalline mass was suspended in 200 mL of cold hexane and collected. After air-drying 2.4 g of *R*-**9d** (99.4% ee, HPLC). In total, 13.4 g (33%) of *R*-**9d** (99.2% ee, HPLC) was prepared from racemic **9d**. Compound *R*-**9d** showed: $[\alpha]_D$=+8.0 (c=1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.51–7.31 (m, 5), 4.70 (m, 2), 3.80 (m, 2), 3.10 (m, 1), 2.22 (s, 3), 2.20 (s, 3), 2.10 (s, 3), 1.6 (s, 3), 1.4 (s, 3); MS (CI) m/z (relative intensity) 327 (100), 309 (40), 235 (60). Anal. calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.35; H, 7.96.

(3S)-5-Benzyloxy-3-hydroxymethyl-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran (S-***9d***)

Method A (racemic alcohol)

A mixture of 2.0 g (6.2 mmol) of racemic alcohol **9d**, 3.6 g of *Candida rugosa* lipase, and 1.6 g (18.5 mmol) of vinyl acetate in 60 mL of TBME was prepared. After 72 h, the mixture was filtered and concentrated. HPLC analysis showed an 83.5% ee for acetate *R*-**11d** and a 93% ee for alcohol *S*-**6d**. Chromatography on silica gel using 80:20 hexane:EtOAc provided 1.2 g of acetate *R*-**11d** and 0.9 g of alcohol *S*-**9d**. Recrystallization of *R*-**9d** from 50 mL of hexane gave 0.7 g (35%) of *R*-**9d** with >98%ee.

Method B (enriched alcohol)

A mixture 51.5 g (0.16 mol) of enriched *S*-**9d** (65% ee), 170 g of Lipase Type IV from *Candida rugosa* lipase and vinyl acetate (45.3 g, 0.53 mol) in TBME (2.3 L) was stirred at room temperature for 24 h. The mixture was filtered and concentrated. Chromatography using an EtOAc/hexane gradient gave 38.8 g of *S*-**9d** (99.8% ee): $[\alpha]_D$=−8.0 (c=1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.50–7.30 (m, 5), 4.74 (s, 2), 3.80 (m, 2), 3.04 (m, 1), 2.22 (s, 3), 2.20 (s, 3), 2.10 (s, 3), 1.64 (s, 3),1.34 (s, 3), 1.2 (m, 1); ^{13}C NMR ($CDCl_3$) δ 153.4, 149.1, 137.9, 130.0, 128.5 (2), 127.8, 127.7 (2), 125.1, 123.0, 116.9, 87.0, 77.2, 74.5, 61.7, 53.0, 29.2, 22.5, 13.0, 12.8, 12.2; IR (KBr) 3425 cm^{-1}; MS (CI) (relative intensity) 327 (100), 309 (40), 297 (100), 235 (80).

(3R)-5-Benzyloxy-3-(methanesulfonato)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran (R-***12***)

To a solution of 80 g (0.25 mol) of *R*-**9d** (>98% ee) and 30 g (0.29 mol) of Et_3N in 800 mL of THF at 0°C was added 34 g (0.29 mol) of MsCl portionwise over 30 min. After 30 min, the mixture was allowed to warm to room temperature. After 3 h, 500 mL of water and 1 L of EtOAc were added. The organic phase was dried ($MgSO_4$) and concentrated to give 99 g (99%) of *R*-**12** as a white solid: mp 122–123°C; ^{1}H NMR ($CDCl_3$) δ 7.50–7.30 (m, 5), 4.72 (s, 2), 4.27 (m, 2), 3.24 (m, 1), 2.90 (s, 3), 2.24 (s, 3), 2.21 (s, 3), 2.08 (s, 3), 1.62 (s, 3), 1.38 (s, 3); ^{13}C NMR ($CDCl_3$) δ 153.1, 149.4, 137.7, 130.8, 128.5 (2), 127.9, 127.7 (2), 125.3, 121.7, 117.1, 86.5, 74.6, 67.7, 50.3, 37.4, 28.6, 22.7, 13.0, 12.8, 12.1; IR (KBr) 1352, 1171 cm^{-1}; MS (CI) m/z (relative intensity) 405 (82), 404 (86), 314 (30), 313 (64), 309 (100); $[\alpha]_D$=+10.5 (c=0.99, MeOH); Anal. calcd for $C_{22}H_{28}O_5S$: C, 65.32; H, 6.98. Found: C, 65.26; H, 6.88.

*(3S)-5-Benzyloxy-3-(methanesulfonato)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran (S-**12**)*

In a similar fashion 31 g (99%) of *S*-12 was prepared from 25 g (77 mmol) of *S*-**9d** (>98%) and 9.3 g (92 mmol) of Et_3N in 250 mL of THF. Compound *S*-**12** showed: ^1H NMR ($CDCl_3$) δ 7.50–7.30 (m, 5), 4.72 (s, 2), 4.27 (m, 2), 3.24 (m, 1), 2.90 (s, 3), 2.24 (s, 3), 2.21 (s, 3), 2.08 (s, 3), 1.62 (s, 3), 1.38 (s, 3); ^{13}C NMR ($CDCl_3$) δ 153.1, 149.4, 137.7, 130.8, 128.5 (2), 127.9, 127.7 (2), 125.3, 121.7, 117.1, 86.5, 74.6, 67.7, 50.3, 37.4, 28.6, 22.7, 13.0, 12.8, 12.1; IR (KBr) 1352, 1171 cm^{-1}; MS (CI) m/z (relative intensity) 405 (40), 404 (837), 314 (24), 313 (50), 309 (100); $[\alpha]_D$=−10.8 (c=0.94, MeOH); Anal. calcd for $C_{22}H_{28}O_5S$: C, 65.32; H, 6.98. Found: C, 64.66; H, 6.75.

*(3R)-5-Hydroxy-3-[(4-methylpiperazino)-methyl]-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran dihydrochloride hydrate (R-**2**)*

A mixture of 98.9 g (0.25 mol) of *R*-**12**, 49 g (0.49 mol) of 4-methylpiperazine, and 137 g (0.98 mol) of K_2CO_3 in 1.6 L of MeCN was heated to reflux. After 20 h, TLC (10% MeOH/$CHCl_3$: compound *R*-**12**, R_f=0.95; MDL 74722 benzyl ether, R_f=0.38) showed complete conversion. The mixture was cooled to room temperature, filtered and concentrated. The residue was dissolved in 500 mL of water and 2 L of $CHCl_3$. The aqueous phase was extracted with $CHCl_3$. The combined organic phases were dried ($MgSO_4$) and concentrated. EtOH (500 mL) was added and the solution was concentrated to give crude *R*-**13**. Compound *R*-**13** showed: ^1H NMR ($CDCl_3$) δ 7.52–7.30 (m, 5), 4.70 (m, 2), 3.04 (m, 2), 2.67–2.20 (m, 9), 2.27 (s, 3), 2.22 (s, 3), 2.18 (s, 3), 2.07 (s, 3), 1.55 (s, 3), 1.32 (s, 3).

The crude product was dissolved in 250 mL of EtOH and 250 mL of AcOH and added to 11.0 g of 10% Pd/carbon in a Parr bottle. This mixture was placed on a Parr shaker under 50 psi of H_2 for 18 h. After filtration through diatomaceous earth, the solution was concentrated. ^1H NMR of the crude product showed complete debenzylation to give *R*-**2**: ^1H NMR ($CDCl_3$) δ 8.74 (bs, 1), 3.03–2.00 (m, 11), 2.68 (s, 3), 2.14 (s, 3), 2.12 (s, 3), 2.07 (s, 3), 1.52 (s, 3), 1.29 (s, 3).

The above process of mesylation, piperazine displacement, and debenzylation was repeated using 0.15 mol of alcohol (*R*-**9d**). This crude product was combined with the above so that a total of 0.4 mol of *R*-**9d** was converted to *R*-**2**.

To a slurry of 0.4 mol from above of *R*-**2** in 350 mL of EtOH was added 350 mL of a dilute HCl solution (100 mL of concentrated HCl in 250 mL of water). When complete homogeneity had been established, the solution was concentrated to dryness. The residue was dissolved in 1.2 L of hot *i*-PrOH and ca. 2 g of charcoal was added. After filtering through diatomaceous earth, the solution was seeded and allowed to stand for 3 days. A white solid was collected, washed with 200 mL of *i*-PrOH, and allowed to air-dry for 2 days. After 24 h in a vacuum oven at 45°C, 122 g (74%) of the dihydrochloride salt of *R*-**2** was collected as a monohydrate: ^1H NMR (D_2O) δ 3.87–3.5 (m, 10), 3.17 (AB, 1), 3.05 (s, 3), 2.23 (s, 3), 2.14 (s, 3), 2.07 (s, 3), 1.69 (s, 3), 1.38 (s, 3); ^{13}C NMR (D_2O) δ 152.5, 148.3, 129.5, 126.0, 123.7, 120.0, 90.4, 60.6, 53.1, 53.0, 52.7, 48.7, 45.6, 29.9, 26.5, 24.4, 15.2, 14.6, 14.4; IR (KBr) 3408, 3283 cm^{-1}; MS (CI, CH_4) m/z (relative intensity) 319 (100), 318 (44), 317 (40), 113 (54); $[\alpha]_D$=+20.9 (c=0.98, H_2O). Karl–Fisher analysis showed 4.9% or 1.1 eq. of water. Anal. calcd for $C_{19}H_{32}N_2O_2 \cdot 2HCl \cdot 1.1H_2O$: C, 55.3; H, 8.39; N, 6.79. Found: C, 55.35; H, 8.24; N, 6.65.

*(3S)-5-Hydroxy-3-[(4-methylpiperazino)-methyl]-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran dihydrochloride hydrate (S-**2**)*

In a similar fashion 19 g (60%) of the dihydrochloride salt of *S*-**2** was prepared from 31 g (77 mmol) of *S*-**12**. Compound *S*-**2** showed: ^1H NMR (D_2O) δ 3.87–3.5 (m, 10), 3.17 (AB, 1), 3.05 (s, 3), 2.23 (s, 3), 2.14 (s, 3), 2.07 (s, 3), 1.69 (s, 3), 1.38 (s, 3); ^{13}C NMR (D_2O) δ 152.5, 148.3, 129.5, 126.0, 123.7, 120.0, 90.4, 60.6, 53.1, 53.0, 52.7, 48.7, 45.6, 29.9, 26.5, 24.4, 15.2, 14.6, 14.4; IR (KBr) 3408, 3283 cm^{-1}; MS (CI, CH_4) m/z (relative intensity) 319 (78), 318 (37), 317 (38), 113 (100); $[\alpha]_D$=−20.9 (c=1.0, H_2O); Karl–Fisher analysis showed 4.8% or 1.1 eq. of water. TGA was inconclusive. Anal. calcd for $C_{19}H_{32}N_2O_2 \cdot 2HCl \cdot 1.1H_2O$: C, 55.52; H, 8.38; N, 6.81. Found: C, 55.62; H, 8.40; N, 6.79.

Procedure for recycle of S-**9d** *from enzymatic resolution*

To a solution of 31.6 g (97 mmol) of recovered *S*-**9d** (ca. 60% ee) and 11.8 g (116 mmol) of Et_3N in 300 mL of THF at 0°C was added 13.3 g (116 mmol) of MsCl portionwise over 30 min. The mixture was allowed to warm to room temperature. After 3 h, 39 g (348 mmol) of *t*-BuO^- K^+ in 200 mL of THF was added over 30 min. The solution was allowed to warm to room temperature. After 1 h, water and EtOAc were added. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The oil was transferred to a crystallization dish using minimal hexane and seeded. Complete crystallization occurred after 30 min. After air drying overnight, 32 g (98%) of **7** was collected.

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