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Convergent Synthesis of Both Enantiomers of 4-Hydroxypent-2-ynoic Acid Diphenylamide for a Thrombin Receptor Antagonist Sch 530348 and Himbacine Analogues

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Abstract: Sch 530348 and many himbacine analogues were prepared by using 4-hydroxypent-2-ynoic acid diphenylamide as the only chiral material. We developed deracemization methods to prepare both enantiomers of this propargyl alcohol. These methods involved a resolution followed by inversion. The objective for the resolution step was to obtain the desired enantiomer as an ester, and undesired enantiomer as an alcohol. With (*R*)-selective lipase, this was achieved by transesterifcation for (*R*)-alcohol, and ester hydrolysis for (*S*)-alcohol. The undesired enantiomer was inverted through the corresponding tosylate to yield the desired enantiomer as the ester. Deprotection of the ester gave enantiopure alcohol as the product. These methods not only overcame the 50% yield limit in resolution, but also eliminated the need to remove the undesired enantiomer.

Keywords: deracemization; enzyme catalysis; kinetic resolution; preparative scale synthesis; propargylic alcohols; S_N2 inversion

Introduction

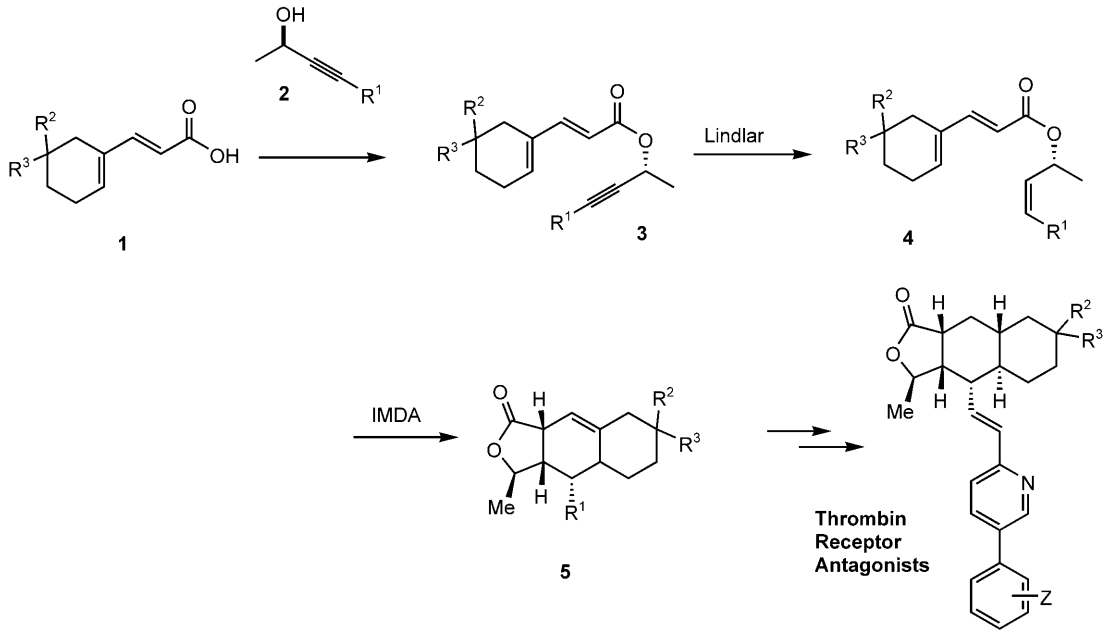
Sch 530348 is an investigational candidate for the prevention of arterial thrombosis in patients with acute coronary syndrome and peripheral arterial disease.[1] Currently the candidate is in phase III clinical development for secondary prevention of cardiovascular morbidity and mortality in at-risk patients.

The structure of Sch 530348 was derived from a natural product, himbacine, a tetracyclic piperidine alkaloid isolated from the Australian magnolia tree, *Galbulimima baccatta*.[2] Himbacine itself showed strong antagonistic activity for muscarinic receptors, and has been used as a lead for drugs in Alzheimer's disease treatment.[2,3] Its *ent*-derivatives including Sch 530348, however, exhibited a potent inhibition of platelet aggregation, a key process in clot formation.[1a,b,4] These *ent*-derivatives appeared to be excellent candidates for treatment of arterial thrombosis.[1a,c,d,5]

Chackalamannil et al. invented a highly efficient method to prepare *ent*-himbacine analogues including Sch 530348 (Scheme 1).[1f,6] Briefly, the chiral perhydronaphthofuranone **5** and the heterocycle were prepared separately, and then tethered together in the final steps. The construction of the chiral perhydronaphthofuranone was based on an intramolecular Diels–Alder (IMDA) cyclization of a chiral triene **4**. Remarkably, the single chiral center and a proper choice of R^1 in propargyl alcohol **2** were sufficient for installing all the other chiral centers stereoselectively.[7] There was no need for additional chiral auxiliaries or catalysts.

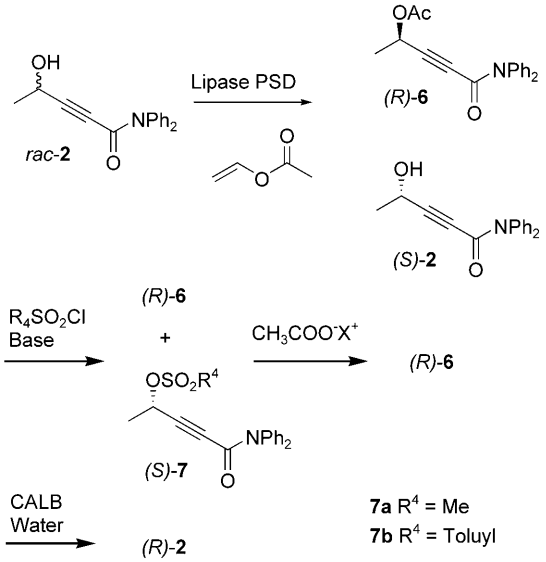
For chiral propargyl alcohol preparation on a large scale, hydrolase-catalyzed resolution of a racemic mixture is more straightforward and easier to scale up when compared with other approaches.[8] Since the theoretical yield of a resolution is 50%, a deracemization strategy of combining resolution with stereo-inversion has been used not only to break this limit, but also to eliminate the need to remove the undesired enantiomer.[9] In the resolution step, the racemate is converted *via* hydrolysis or transesterication to give products with the desired enantiomer as the ester, and the undesired enantiomer as the alcohol. In the following inversion step, the alcohol is transformed into the desired enantiomer by an S_N2 displacement of the corresponding activated ester. Both enantiomers can be prepared in 100% theoretical yield without employing enzymes with opposite selectivities. The practicality of this strategy was successfully demonstrated by Chirotech Technology Ltd in the preparation of an (*R*)-propargyl alcohol on a kilogram-scale.[9c]

Herein, we describe the preparation of either enantiomer of 4-hydroxypent-2-ynoic acid diphenylamide based on the deracemization strategy. The resolution

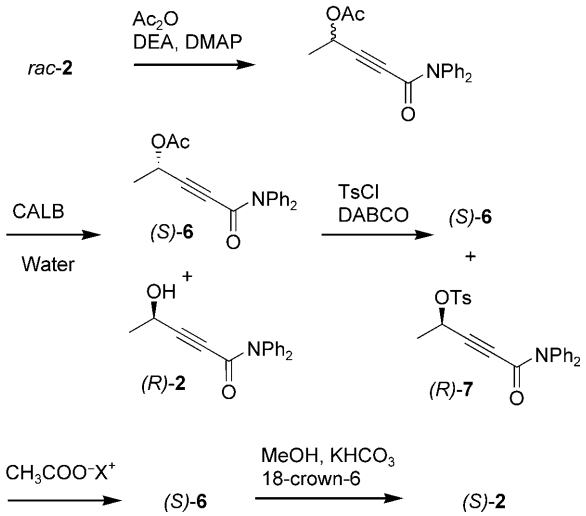


Scheme 1. Synthesis of *ent*-himbacine-based thrombine receptor antagonists based on IMDA strategy.

steps were both catalyzed by (*R*)-selective lipases. The synthesis of (*R*)-**2** enantiomer began with the resolution of *rac*-**2** *via* lipase-catalyzed transesterification (Scheme 2). The (*R*)-enantiomer was esterified to give (*R*)-**6**. The undesired (*S*)-**2** was converted to tosylate (*S*)-**7**, and then inverted *in situ* to converge with the desired enantiomer at (*R*)-**6**. In the last step, (*R*)-**6** was hydrolyzed with a lipase to give product (*R*)-**2**. All the steps were carried out in one stream. The product was isolated by crystallization. In the preparation of (*S*)-**2** (Scheme 3), hydrolytic resolution gave (*R*)-**2**, and (*S*)-**6** as products. The undesired (*R*)-**2** was



Scheme 2. Convergent synthesis of (*R*)-4-hydroxy-pent-2-ynoic acid diphenylamide.



Scheme 3. Convergent synthesis of (*S*)-4-hydroxy-pent-2-ynoic acid diphenylamide.

inverted to give (*S*)-**6** in two steps through tosylate (*R*)-**7**. Deprotection of (*S*)-**6** *via* methanolysis gave (*S*)-**2** as the final product. The (*R*)-enantiomer was used in the preparation of Sch 530348, while the (*S*)-enantiomer was used in the synthesis of himbacine analogues.[7,10]

Results and Discussion

Enzyme Identification in Transesterification

In all, 212 commercially available hydrolases (85 lipases, 95 proteases, 10 amidases, and 22 esterases)

were screened for the acylation of **2** with vinyl acetate in MTBE or in MeCN (see Experimental Section for conditions). Most lipases, acylases and proteases demonstrated moderate to high (*R*)-selectivity. Among them 13 lipases exhibited excellent selectivity ($E>200$, Table 1). In these cases, the conversions were all close to 50%, and the *ee* for (*R*)-**6** and (*S*)-**2** were both >95%. A few proteases exhibited preference for the (*S*)-enantiomer, albeit with poor enantioselectivity ($7<E<10$).

Table 1. Highly selective lipases [$E>200$ for (*R*)-**2**] in the resolution of *rac*-**2**.

Enzyme	Vendor	Source	Solvent
Lipase PS	Amano	*P. cepacia*	TBME or MeCN
Lipase AK	Amano	*P. fluorescens*	TBME or MeCN
Lipase PSC	Amano	*P. cepacia*	MeCN
Lipase PSD	Amano	*P. cepacia*	MeCN
Lipase AH	Amano	*P. cepacia*	TBME
Lipase BC	BioCatalytics	n/a	TBME
Lipase ICR-107	BioCatalytics	n/a	TBME
Lipase ICR-108	BioCatalytics	n/a	TBME or MeCN
Lipase 20	Europa Bio-products	*Alcaligenes* sp.	MeCN
Lipase 4	Europa Bio-products	*P. cepacia*	TBME or MeCN
Lipase 3	Europa Bio-products	*P. glumea*	MeCN
Lipase 21	Europa Bio-products	*Pseudomonas*	MeCN
Lipase LIP-300	Toyobo	*Pseudomonas* sp.	MeCN

All 13 highly selective lipases were further examined to identify the most efficient one at high substrate loading. The reactions were carried out at 100 g/L of *rac*-**2** in MTBE, MeCN, and *t*-BuOAc with 10% (w/w) enzyme. Lipase PSD in MeCN exhibited the highest conversion and excellent selectivity: in 40 h the reaction reached 49% conversion, giving (*R*)-**6** and (*S*)-**2** both in >98% *ee*. This enzyme was selected for further development for (*R*)-**2** preparation.

Transesterification Resolution Optimization

The optimization was carried out in terms of temperature, substrate loading, and the amount of vinyl acetate. Interestingly, lipase PSD was most active when *rac*-**2** reached saturation in MeCN: at 200 g/L the reaction rate was 10 times faster than that at 10 g/L. This increase suggested a very high K_m value for (*R*)-**2**, and the absence of inhibition by (*S*)-**2** in MeCN. For preparative resolution, we used 500 g *rac*-**2**/L in MeCN to maximize lipase activity as well as volumetric productivity. Under optimal condition, the temperature was 35 °C, and 4 molar equivalents of vinyl acetate were used. Lipase PSD remained highly selective throughout the course of the reaction. In a typical example, 3 g (6% w/w) of lipase PSD was used to resolve 50 g *rac*-**2** in 100 mL of MeCN. The conversion reached 49% in 30 h, giving (*R*)-**6** and (*S*)-**2** in 99.8% and 95.1% *ee*, respectively.

We also tested the recycling of lipase PSD to further reduce the cost. At the end of a resolution, lipase PSD was recovered by filtration and used in the next run. This enzyme could be reused for at least three times without compromising the conversion and enantioselectivity, although longer time was needed in each successive round (Table 2).

Table 2. Re-using lipase PSD in the resolution of *rac*-**2**.[a]

Repeats	Conversion [%]	*ee* for (*R*)-**6** [%]	*ee* for (*S*)-**2** [%]	Time [h]
1	50.1	99.5	99.8	<20
2	49.7	99.2	98.2	26
3	49.2	99.3	96.2	44

[a] *Conditions:* the reaction was carried out by mixing *rac*-**2** (25 g, 94 mmol), vinyl acetate (32.4 g, 4 equiv.), and lipase PSD (1.75 g) in 50 mL of MeCN, and agitating at 35 °C.

Inversion of (*R*)-2

In the deracemization of secondary alcohols, inverting the undesired enantiomer was accomplished by a number of methods, including those through sulfonates or under Mitsunobu conditions.[9] Since the Mitsunobu reaction was tedious to scale up, we focused on the inversions through either mesylate or tosylate. Representative results are summarized in Table 3.

The inversion of (*R*)-**2** was carried out through either tosylate or mesylate with acetate anion as the nucleophile. Although enantiopurity was well preserved in all cases, their yields varied significantly; and several by-products formed in quantities proportional to the losses in yield. The selectivity was dependent not only on the nature of the sulfonate, but also on the selection of acetate salts, reaction medium, and reaction conditions. With tetrabutylammonium acetate as the nucleophile, the reaction could be carried out homogeneously in toluene. The reaction was fast, but only gave (*S*)-**6** in moderate yield (Method A). Reaction selectivity was improved under heterogeneous condition with K^+AcO^- as the nucleophile. With DMSO as the solvent, the yield was improved

Table 3. The inversion of (*R*)-**2** (99% *ee*) *via* sulfonates.

Method	Sulfonate	Nucleophile	Conditions and time to complete	Yield, *ee* for (*S*)-**6**
A	**7b**	1.5 equiv. $Bu_4N^+AcO^-$	4× toluene, 2× MeCN, 10 °C for 7 h	73% in 98% *ee*
B	**7b**	3 equiv. K^+AcO^-	5× DMSO, 25 °C for 40 h	87% in 98% *ee*
C	**7b**	3 equiv. K^+AcO^- 0.2 equiv. $Bu_4N^+HSO_4^-$	6× toluene, 0.15% water and 0.1% acetic acid; 55 °C for 22 h	93% in 98% *ee*
D	**7a**	3 equiv K^+AcO^-, 0.1 equiv. $Bu_4N^+HSO_4^-$	14× toluene 0.25% water, 40 °C for 20 h	77% in 98% *ee*

to 87% although the reaction took 40 h to complete (Method B). A phase-transfer catalyst (PTC) not only facilitated the mass transfer of AcO^- in toluene, but also improved reaction selectivity. Under optimal conditions (Method C), the reaction completed in 22 h, giving (*S*)-**6** in 93% yield. Inversion of mesylate (*R*)-**7a** under PTC conditions gave a much lower yield (Method D).

Deprotection of 6

Either enantiomer of ester **6** was converted to **2** *via* methanolysis in the presence of $KHCO_3$ at 10 °C. The reaction was facilitated by 18-crown-6. The solution yield of **2** was typically 85%.

Lipase-mediated hydrolysis was much more efficient for (*R*)-**6** deprotection. The reaction conditions were mild; there was also further improvement in product *ee*. Novozym CALB (*Candida antarctica*) was found to be highly selective ($E > 500$) for (*R*)-**6**. Product (*R*)-**2** was typically isolated in >95% solution yield with >99% *ee*. The resolution was carried out in a toluene-water mixture at 35 °C. There was essentially no side reaction under these conditions.

Preparation of (*R*)-2

The scalability of the developed approach was then demonstrated with a preparation on a 50 g scale.

Rac-**2** (50 g) was resolved by lipase PSD-catalyzed transesterification as described in the Experimental Section. The reaction came to a halt at about 50% conversion, giving (*R*)-**6** and (*S*)-**2** both in >95% *ee*. The lipase was removed by filtration, and MeCN was replaced by toluene. Tosylation of (*S*)-**2** with TsCl at 0 °C was completed in 1 h, giving (*S*)-**7b** quantitatively. Treatment of this mixture with K^+AcO^-, and $Bu_4N^+AcO^-$ under the PTC conditions offered (*R*)-**6** in 80% overall yield and >95% *ee*. In the final step, (*R*)-**6** was converted to (*R*)-**2** by CALB hydrolysis. The product was isolated by crystallization. After drying, (*R*)-**2** was obtained in 73% yield and >99% *ee*.

Preparation of (*S*)-2

The resolution of *rac*-**6** was carried out by CALB-catalyzed hydrolysis under the conditions described in the Experimental Section. At about 50% conversion, the enantiopurity for (*R*)-**2** and (*S*)-**6** both reached >96% *ee*. In the same stream, (*R*)-**2** was inverted *via* tosylate (*R*)-**7b** to give (*S*)-**6**. Deprotection of (*S*)-**6** was carried out by methanolysis to give (*S*)-**2** as the major product. After crystallization, (*S*)-**2** was isolated in 64.2% yield and 99.5% *ee*.

Conclusions

Deracemization methods were developed for both enantiomers of 4-hydroxypent-2-ynoic acid diphenylamide by using (*R*)-selective lipases in the resolution. The yields in resolution were close to 100% at remarkably high substrate concentrations. The undesired enantiomer was converted to the corresponding tosylate and then inverted to the desired enantiomer in the same stream. Inversion under optimal PTC conditions reached >90% yield. After deprotection and crystallization, the (*R*)-enantiomer was isolated in 73% yield with >99% *ee*. The (*S*)-enantiomer was prepared in 64% isolation yield with 99.5% *ee*.

Both enantiomers were used to prepare either himbacine analogues or *ent*-himbacine derivatives including Sch 530348.

Experimental Section

General Methods

NMR data were collected with a Bruker 400 MHz instrument. Mass spectrometry was carried out either by electron spray MS with a Waters Micromass ZQ instrument or by

FAB-MS with a JEOL MStation. The reaction was monitored with reverse phase HPLC chromatography on a C-18 column. Optical rotation was measured with Perkin–Elmer 243B polarimeter. All the solvents and enzymes were used as purchased. *Rac*-**2** was prepared by in-house methods.[7]

Rac-**6** was prepared by esterifying **2** under standard conditions. *Rac*-**2** was a white crystalline powder. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.12$ (3H, d, $J = 6.7$ Hz), 4.31 (1H, q, $J = 6.7$ Hz), 7.13–7.33 (10H, m); ^{13}C NMR: $\delta = 23.2$, 56.1, 78.3, 94.8, 125.9, 126.8, 128.5, 129.2, 129.4, 141.2, 142.3, 153.4; HR-FAB-MS: $m/z = 266.1182$, corresponding to $C_{17}H_{16}NO_2$ $(M+H)^+$. *Rac*-**6** was a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$ (3H, d, $J = 6.8$ Hz), 1.96 (3H, s), 5.29 (1H, q, $J = 6.8$), 7.18–7.48 (10H, m); ^{13}C NMR $\delta = 20.3$, 21.0, 59.6, 78.6, 91.1, 125.9,126.8, 128.3, 129.2, 129.4, 141.2, 142.1, 152.9, 169.5; HR-FAB-MS: $m/z = 308.1276$, corresponding to $C_{19}H_{18}NO_3$ $(M+H)^+$.

Chiral Methods

The *ee* determination of **2** and **6** was carried out by HPLC with Chiracel OJ-H at 23–25 °C (0.46×15 cm, Chiral Technologies Inc.). The detection was by UV at 260 nm. The elution was isocratic with 40% *i*-PrOH in hexanes as the mobile phase, and a flow rate at 1 mL min^{-1}. The retention times were: (*R*)-**2**, 8.2 min; (*S*)-**2**, 6.9 min; (*R*)-**6**, 21.7 min; and (*S*)-**6**, 14.3 min.

Enzyme Screen for the Kinetic Resolution of *rac*-2

A screen reaction mixture contained 10 mg *rac*-**2** (3.7 μmol), 17 mg of vinyl acetate (19.7 mmol), and 10 mg of an enzyme in 1 mL solvent (MeCN or TBME). After 24 h agitation at 25 °C, the product was analyzed for yield and *ee* after enzyme removal by filtration.

Enzyme Screen for Hydrolytic Resolution of *rac*-6

A screen reaction mixture included 20 mg of *rac*-**6** (6.5 μmol) in 0.2 mL toluene, 20 mg of a solid enzyme or 100 μL of a liquid enzyme, and 0.8 mL of 0.2 M phosphate buffer, pH 7.0. The reaction was agitated at 35 °C for 1.5 h. The product in organic phase was analyzed for conversion and *ee*.

(*R*)-7b [Tosylation of (*R*)-2]

In a flask, 23 g of (*R*)-**2** (87 mmol) were dissolved in 180 mL of toluene. The solution was chilled to 0 °C, and then 13.6 g DABCO (1,4-diazabicyclo[2,2,2]octane, 121 mmol) and 0.52 g DMAP (4.3 mmol) were added. To this mixture, a tosyl chloride solution (21.5 g in 40 mL MeCN) was added over 30 min. The reaction was agitated for additional 30 min to complete the conversion. The reaction was quenched with 150 mL 5% sulfuric acid. After aqueous work-up and solvent removal, an off-white solid was obtained; yield: 36.0 g. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.32$ (3H, d, $J = 6.7$ Hz), 2.47 (3H, s), 5.02 (1H, q, $J = 6.7$ Hz), 7.18–7.42 (12H, m), 7.71–7.74 (2H, m); ^{13}C NMR $\delta = 21.8$, 21.9, 66.7, 80.6, 88.4, 125.8, 126.9, 128.2, 128.6, 128.9, 129.2, 129.5, 130.1, 133.5, 141.0, 141.7, 145.4, 152.3; HR-FAB-MS: $m/z = 420.1252$, corresponding to $C_{24}H_{22}NO_4S$ $(M+H)^+$; $[\alpha]_D$: +104.8 (*c* 1.0, CH_2Cl_2, 18 °C).

(*S*)-6, Method A

(*R*)-**7b** (36 g, 86 mmol) was dissolved in 150 mL toluene. The reaction mixture was chilled to 10 °C and $Bu_4N^+AcO^-$ (39.2 g, 130 mmol in 80 mL MeCN) was added over 30 min. The mixture was agitated for 7 h at 10 °C, and then quenched with 5% sulfuric acid. After work-up and solvent removal (*S*)-**6** was obtained; yield: 21.5 g (89%); purity: 89% *ee*: 98%.

(*S*)-6, Method B

In a flask, 1 g of (*R*)-**7b** (2.4 mmol) and 0.7 g of K^+AcO^- (7.1 mmol) were mixed together in 5 mL DMSO. The reaction was agitated at 25 °C. After 40 h, 20 mL of EtOAc were added to the reaction mixture. The solution was washed with 5% sulfuric acid, 5% $NaHCO_3$, and brine. After solvent removal (*S*)-**6** was obtained; yield: 0.82 g; purity: 79%, *ee*: 98%.

(*S*)-6, Method C

(*R*)-**7b** (11 g, 26.2 mmol) was mixed with 7.7 g of K^+AcO^- (78.4 mmol), 1.8 g of $Bu_4N^+HSO_4^-$, (5.3 mmol) 1 mL water, and 0.66 mL acetic acid in 66 mL toluene. The reaction was agitated at 55 °C. After 22 h, the conversion was complete. The reaction was quenched with 45 mL 8% sulfuric acid. After aqueous work-up and solvent removal, (*S*)-**6** was obtained; yield: 8.4 g; purity: 89%; *ee*: 98%.

(*S*)-6, Method D

(*R*)-**2** (1.4 g, 5.3 mmol) was placed into a jacketed flask containing 30 mL THF, and the solution was chilled to 0 °C. To this solution, 0.35 g of DABCO (3.1 mmol) were added, followed by addition of 0.71 g mesyl chloride (6.2 mmol) over 10 min. (*R*)-**2** was completely converted to (*R*)-**7a** after agitation at 0 °C for 30 min. After aqueous work-up, and THF removal by evaporation, the solution was reconstituted in 20 mL toluene. For inversion, 1.6 g of K^+AcO^- (16.3 mmol), 185 mg of $Bu_4N^+HSO_4^-$ (0.55 mmol), and 50 μL of water were added to the toluene solution. This mixture was agitated at 40 °C for 20 h to complete the conversion. After aqueous work-up and solvent removal, (*S*)-**6** was obtained; yield: 1.5 g; purity: 83%; *ee*: 98%.

(*R*)-2 from *rac*-2

Resolution of *rac*-2 by transesterification: The resolution was carried out by mixing 50 g *rac*-**2** (181 mmol, purity 96%) with 65 g vinyl acetate (755 mmol), and 3 g of lipase PSD in 100 mL MeCN. After 30 h at 35 °C, the conversion reached 48.8%, giving (*R*)-**6** in 99.8% *ee*, and (*S*)-**2** in 95.1% *ee*. The enzyme was removed by filtration and the solvent was replaced with 300 mL toluene.

***In-situ* tosylation of (*S*)-2:** TsCl solution (21.6 g, 113 mmol in 30 mL of MeCN) was added to the toluene solution at 0 °C. Next, a solution of DABCO (13.7 g, 122 mmol) and DMAP (0.6 g, 4.9 mmol in 60 mL MeCN) was added over 30 min while the temperature was maintained below 5 °C. The reaction was agitated at 0 °C for additional 30 min to complete the conversion (> 99%). The reaction was quenched with 200 mL 8% H_2SO_4. The aque-

ous phase was removed, and the organic layer was washed with $NaHCO_3$, and brine.

***In-situ* inversion of (*S*)-7b:** The displacement of tosylate (*S*)-**7b** with K^+AcO^- was conducted under phase transfer condition. To the reaction stream from the previous step, 27.7 g of K^+AcO^- (282 mmol), 6.4 g catalyst $Bu_4N^+AcO^-$ (21.2 mmol), 3.3 mL of AcOH, and 3.3 mL of water were added. The reaction was agitated at 55 °C for 24 h to complete. The reaction was quenched with 200 mL 8% H_2SO_4. The organic layer was washed with 8% $NaHCO_3$. The solution was concentrated to a final volume of 150 mL.

Deprotection of (*R*)-6 and isolation of (*R*)-2: The toluene solution of (*R*)-**6** was mixed with 250 mL of phosphate buffer (0.1 M, pH 7.0) and 10 g CALB (Novozyme, Franklinton, NC). The reaction mixture was agitated at 35 °C, and pH was maintained at 7.0 by titrating 1 N NaOH with a pH stat. After 20 h the conversion reached 96%, giving (*R*)-**2** as the major product. EtOAc (200 mL) was added, and the mixture was filtered through celite. The organic was washed with 8% H_2SO_4, $NaHCO_3$, and brine.

The product was isolated by crystallization with heptane as the anti-solvent. In total, 35.0 g crystalline (*R*)-**2** (purity: >98%, *ee*: >99% by HPLC) was obtained. $[\alpha]_D$: +29.7 (*c* 1.0, CH_2Cl_2, 18 °C).

(*S*)-2 from *rac*-2

***Rac*-6:** To prepare the acetate, 50 g of *rac*-**2** (181 mmol, 96% purity), 26.7 g TEA (263 mmol), 0.5 g DMAP (4.1 mmol), and 28.9 g Ac_2O (283 mmol) were dissolved in 300 mL MTBE. The mixture was agitated for 20 h at 18 °C to complete the reaction. The reaction was quenched with 200 mL 8% sulfuric acid. The organic phase was washed with sodium bicarbonate solution. The solvent was removed, and the remainder was reconstituted in 150 mL of toluene.

Hydrolytic resolution of *rac*-6: The toluene solution of *rac*-**6** was mixed with 300 mL phosphate buffer (0.1 M) and 17 mL CALB. The pH was maintained at 7.0 by titrating 2 N NaOH with a pH stat. After 20 h agitation at 35 °C, the conversion reached 51%, giving (*R*)-**2** and (*S*)-**6** in 97%, and 99% *ee*, respectively. The reaction mixture was filtered through celite and the aqueous phase was removed.

***In-situ* tosylation of (*R*)-2:** The toluene solution was concentrated to 100 mL. Additional toluene (200 mL) was added. This solution was chilled to 0 °C followed by addition of tosyl chloride (21.5 g, 113 mmol in 40 mL MeCN). The solution of bases (13.7 g, 122 mmol of DABCO, and 0.57 g, 4.7 mmol of DMAP in 60 mL MeCN) was added over 30 min while maintaining the temperature between −5 and 0 °C. The solution was agitated for one hour at 0 °C to complete the conversion. The reaction was quenched with 200 mL of 8% sulfuric acid. The organic phase was washed with sodium bicarbonate, and then brine.

Inversion of tosylate (*R*)-**6:** Water (4.8 mL) was added to the toluene solution from the last step. Potassium acetate (27.7 g, 282 mmol), acetic acid (4 mL), and tetrabutylammonium acetate (6.4 g, 19 mmol) were added to the toluene/water mixture. The reaction was agitated at 55 °C. After 40 h, the conversion reached 94%, giving (*S*)-**2** as the only major product.

Deprotection of (*S*)-6: For (*R*)-**2** solution from the previous step, toluene was replaced by 200 mL methanol as the solvent. The methanol solution was chilled to 5 °C, followed by addition of potassium bicarbonate (75 g, 750 mmol), and 18-crown-6 (7.5 g, 28.4 mmol). The reaction reached 98% conversion at 5 °C in 10 h. The reaction mixture was filtered, and MeOH was replaced by 200 mL EtOAc. The solution was washed with 8% sulfuric acid, 5% sodium bicarbonate, and brine.

Isolation of (*S*)-2: Product was isolated from above solution with heptane as the anti-solvent. After drying under vacuum, (*S*)-**2** was obtained; yield: 31.7 g (purity: >98%, *ee*: 99.5% by HPLC). $[\alpha]_D$: −29.3 (*c* 1.0, CH_2Cl_2, 18 °C).

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References

[1] a) S. Chackalamannil, Y. Wang, W. J. Greenlee, Z. Hu, Y. Xia, H. S. Ahn, G. Boykow, Y. Hsieh, J. Palamanda, J. Agans-Fantuzzi, S. Kurowski, M. Graziano, M. Chintala, *J. Med. Chem.* **2008**, *51*, 3061–3064; b) S. Chackalamannil, *J. Med. Chem.* **2006**, *49*, 5389–5403; c) S. Chackalamannil, Y. Xia, W. J. Greenlee, M. Clasby, D. Doller, H. Tsai, T. Asberom, M. Czarniecki, H. S. Ahn, G. Boykow, C. Foster, J. Agans-Fantuzzi, M. Bryant, J. Lau, M. Chintala, *J. Med. Chem.* **2005**. *48*, 5884–5887; d) S. Chackalamannil, H. S. Ahn, Y. Xia, D. Doller, C. Foster, *Curr. Med. Chem.*: *Cardiovascular & Hematological Agents*, **2003**, 1, 37–45; e) S. Chackalamannil, M. V. Chelliah, M. C. Clasby, Y. Xia, (Schering Corporation, USA), World Patent 2003033501, **2003**; f) S. Chackalamannil, T. Asberom, Y. Xia, D. Doller, M. C. Clasby, M. F. Czarniecki, (Schering Corporation, USA), World Patent 9926943, **1999**; g) S. Chackalamannil, M. C. Clasby, W. J. Greenlee, Y. Wang, Y. Xia, E. P. Veltri, M. Chelliah, (Schering Corporation, USA), World Patent 2003089428, **2003**.

[2] A. U. H. Gilani. *Phytotherapy Res.* **1998**, *12*, S66-S69.

[3] a) S. Chackalamannil, D. Doller, R. McQuade, V. Ruperto, *Bioorg. & Med. Chem. Lett.* **2004**. 14, 3967–3970; b) D. Doller, S. Chackalamannil, M. Czarniecki, R. McQuade, V. Ruperto, *Bioorg. & Med. Chem. Lett.* **1999**. *9*, 901–906.

[4] S. R. Coughlin, *Proc. Nat. Acad. Sci. USA*, **1999**, *96*, 11023–11027.

[5] a) M. V. Chelliah, S. Chackalamannil, Y. Xia, K. Eagen, M. C. Clasby, X. Gao, W. Greenlee, H.-S. Ahn, J. Agans-Fantuzzi, G. Boykow, Y. Hsieh, M. Bryant, J. Palamanda, T. M. Chan, D. Hesk, M. Chintala, *J. Med. Chem.* **2007**, *50*, 5147–5160; b) S. Husted, *Eur. Heart J. Suppl.* **2007**. *9*, D20-D27.

[6] a) S. Chackalamannil, R. J. Davies, T. Asberom, D. Doller, D. Leone, *J. Am. Chem. Soc.* **1996**, *118*, 9812–9813; b) S. Chackalamannil, R. J. Davies, Y. Wang, T. Asberom, D. Doller, J. Wong, D. Leone, A. T. McPhail, *J. Org. Chem.* **1999**, *64*, 1932–1940; c) S. Chackalaman-

nil, D. Doller, M. Clasby, Y. Xia, K. Eagen, Y. Lin, H. A. Tsai, A. T. McPhail, *Tetrahedron Lett.* **2000**, *41*, 4043–4047;.

[7] G. G. Wu, A. Sudhakar, T. Wang, J. Xie, F. X. Chen, M. Poirier, M. Huang, V. Sabesan, D. L. Kwok, J. Cui, X. Yang, T. K. Thiruvengadam, J. Liao, I. Zavialov, H. N. Nguyen, N. K. Lim, (Schering Corporation, USA). *World Patent* 2006076415, **2006**.

[8] Methods by terminal alkyne addition to aldehyde: a) L. Pu, *Tetrahedron* **2003**, *59*, 9873–9886; b) G. Gao, R. G. Xie, L. Pu, *Proc. Nat. Acad. Sci. USA*, **2004**, *101*, 5417–5420; c) G. Gao, Q. Wang, X. Q. Yu. R.-G. Xie, L. Pu, *Angew. Chem.* **2006**, *118*, 128–131; *Angew. Chem. Int. Ed.* **2006**, *45*, 122–125; d) D. Boyall, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2002**, *4*, 2605–2606; e) N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688; f) B. M. Trost, A. H. Weiss, A. J. Von Wangelin, *J. Am. Chem. Soc.* **2006**, *128*, 8–9; g) R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13760–13761. Methods by alkynyl ketone reduction: h) C. Alemany, J. Bach, J. Garcia, M. Lopez, A. B. Rodriguez, *Tetrahedron* **2000**, *56*, 9305–9312; i) K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739; j) K. A. Parker, M. W. Ledeboer, *J. Org. Chem.* **1996**, *61*, 3214–3217; k) T. Schubert, W. Hummel, M-R. Kula, M. Muller, *Eur. J. Org. Chem.* **2001**, 4181–4187; l) T. Schubert, W. Hummel, M. Muller, *Angew. Chem.* **2002**, *114*, 656–659; *Angew. Chem. Int. Ed.* **2002**, *41*, 634–637. Methods by enzymatic resolution: m) P. Allevi, M. Anastasia, F. Cajone, P. Ciuffreda, A. M. Sanvito, *Tetrahedron: Asymmetry* **1994**, *5*, 13–16; n) P. Allevi, P. Ciuffreda, M. Anastasia, *Tetrahedron: Asymmetry* **1997**. *8*, 93–99; o) K. Nakamura, K. Takenaka, A. Ohno, *Tetrahedron: Asymmetry* **1998**. *9*, 4429–4439; p) D. Xu, Z. Li, S. Ma, *Tetrahedron Lett.* **2003**, *44*, 6343–6346. Methods by resolution with synthetic catalysts; q) V. B. Birman, L. Guo, *Org. Lett.* **2006**, *8*, 4859–4861. Methods by propargyl hydroxylation: r) S. Hu, L. P. Hager, *J. Am. Chem. Soc.* **1999**. *121*, 872–873.

[9] a) N. Bouzemi, L. Aribi-Zouioueche, J.-C. Fiaud, *Tetrahedron: Asymmetry* **2006**, *17*, 797–800; b) H. Danda, A. Maehara, T. Umemura, *Tetrahedron Lett.* **1991**, *32*, 5119–5122; c) M. E. Fox, M. Jackson, I. C. Lennon, R. McCague, J. S. Parratt, *Adv. Synth. Catal.* **2002**, *344*, 50–56; d) A. Wallner, H. Mang, S. M. Glueck, A. Steinreiber, S. F. Mayer, K. Faber, *Tetrahedron: Asymmetry* **2003**, *14*, 2427–2432; e) M. J. Kim, I. S. Lee, *Synlett* **1993**, 767–768.

[10] S. Chackalamannil, Y. Wang, T. K. Thiruvengadam, I. Zavialov, T. Li, (Schering Corporation, USA), World Patent 2008085923, **2008**.

