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A Concise Asymmetric Synthesis of Torcetrapib

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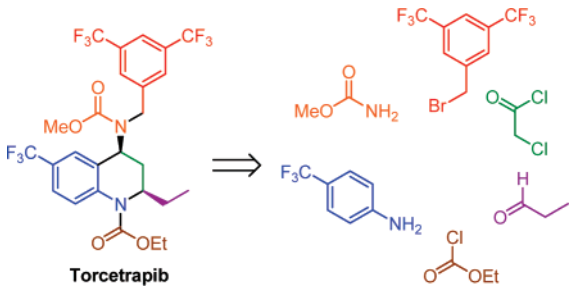


Optically active torcetrapib was synthesized in seven steps from achiral precursors without the need for protecting groups, utilizing an enantioselective aza-Michael reaction to achieve asymmetry.

Coronary heart disease (CHD) is caused by the build up of fatty plaques in the coronary arteries (atherosclerosis), which restricts blood flow to the heart. In the last few decades, it has fast become the leading cause of death in many developed countries, largely as a result of poor diet and lifestyle choices adopted by an increasingly affluent society.

Currently, statins constitute one of the most effective classes of drugs prescribed for the treatment of CHD, by reducing levels of low-density lipoprotein cholesterol (LDL-C, "bad" cholesterol) through the inhibition of an enzyme known as HMG-CoA reductase. However, in recent years, adverse side effects of statins are starting to emerge.[1] Coupled with the expiry of patent protection for several highly commercially successful statins, there is a drive to develop drugs that can inhibit or prevent atherosclerosis via novel mechanisms.[2] In this context, the story of torcetrapib (**1**, Figure 1) has been followed with a great deal of interest, both by the pharmaceutical industry and the media.The core structure of torcetrapib consists of a tetrahydroquinoline with stereogenic centers at C-2 and C-4, occupied by ethyl and *N*-benzylcarbamate substituents, respectively. An inhibitor of the cholesteryl ester transfer protein (CETP), it can boost the level of high-density lipoprotein cholesterol (HDL-C, "good" cholesterol) and lower LDL-C.[3]

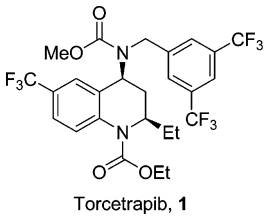
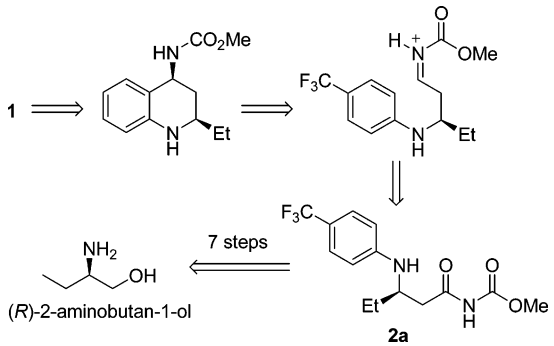


FIGURE 1. Structure of torcetrapib.

SCHEME 1. Published Asymmetric (Retrosynthetic) Route to Torcetrapib



Hailed at one stage as "one of the most important drugs of our generation", it was to be the first CETP inhibitor to be developed commercially, to be used in combination with a statin for the treatment of CHD. However, despite a great deal of optimism and anticipation, drug development was halted during late stages of a Phase III clinical trial in December 2006, due to increased risk of patient death. Clinical trial data subsequently revealed that the combination therapy not only failed to inhibit the onset of atherosclerosis but also appeared to elevate blood pressure, despite significant improvements in lowering LDL-C and increasing HDL-C levels.[4] This unexpected result raised several questions on the role of LDL-C and HDL-C on atherosclerosis and the future of CETP inhibitors as therapeutic drugs. At the time of writing, it is not clear whether the failure of the clinical trial was due to specific toxicity or mechanism of action.[5]

Preparative routes for compound **1** were first disclosed by its inventors in the patent literature[6] and subsequently in two journal articles.[7] In one of these reports, the tetrahydroquinoline ring was constructed by a stereospecific ring cyclization of an acyl immonium ion, generated from the N-arylated amino acid derivative **2a** (Scheme 1). Asymmetric synthesis of this key

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(2) Kidd, J. *Nat. Rev. Drug Discovery* **2006**, *5*, 813.

(3) Brousseau, M. E.; Schaefer, E. J.; Wolfe, M. L.; Bloedon, L. T.; Digenio, A. G.; Clark, R. W.; Mancuso, J. P.; Rader, D. J. *New Engl. J. Med.* **2004**, *350*, 1505.

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(5) Nissen, S. E.; Tardif, J.; Nicholls, S. J.; Revkin, J. H.; Shear, C. L.; Duggan, W. T.; Ruzyllo, W.; Bachinsky, W. B.; Lasala, G. P.; Tuzcu, E. M. *New Engl. J. Med.* **2007**, *356*, 1304.

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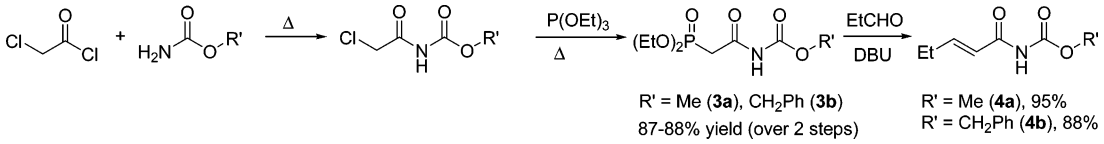
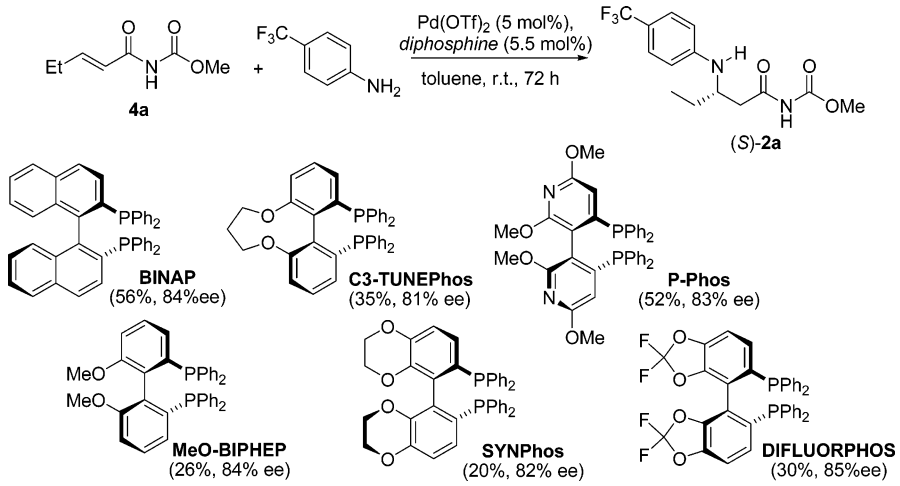
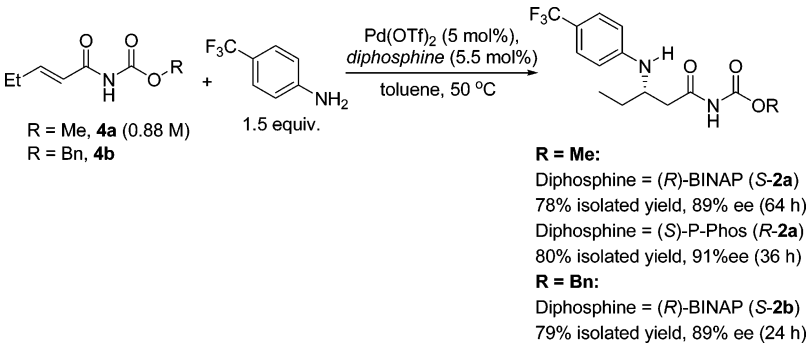
SCHEME 2. Synthesis of Michael Acceptors



SCHEME 3. Chiral Ligand Screening



SCHEME 4. Preparation of Optically Active N-Arylated *β*-Amino Acid Derivatives 2a and 2b under Optimized Reaction Conditions



intermediate was achieved in seven steps from (*R*)-2-aminobutanol, involving the use of protecting groups and substantial functional group conversions.

Herein, we will describe an asymmetric synthesis of the intermediate **2a** in just four steps from achiral precursors, using an enantioselective aza-Michael reaction developed in our laboratory.[8] Following our previously described methodology, Michael acceptors **4a** and **4b** were prepared in high yields in three steps (Scheme 2): a neat mixture of chloroacetyl chloride and the requisite alkyl carbamate was heated to yield the α-chlorocarbamate, which was subjected to an Arbuzov reaction with triethylphosphite to give phosphonate esters **3a** and **3b**. Both of these reactions can be performed without using any solvents in one synthetic operation. Finally, the synthesis of the α,*β*-unsaturated carbamates **4a** and **4b** was accomplished by HWE reactions with propionaldehyde in the presence of DBU. Analytically pure products can be obtained after recrystallization.

The addition of 4-trifluoromethylaniline to **4a**, the direct precursor of the target molecule, was examined in parallel in the presence of different ligands. Six chiral diphosphines were chosen (Scheme 3), which were previously shown to induce high enantioselectivity in analogous aza-Michael reactions.[9] Initially, reactions were conducted using a protocol described before: The palladium catalyst was formed in situ by stirring $Pd(OTf)_2 \cdot 2H_2O$ and a slight excess of the diphosphine ligand for 1 h, whereupon a deeply colored (orange-red) solution was generated. At 5 mol % catalyst loading, 1 equiv of the aniline was exposed to an excess of the alkene substrate (1.5 equiv) at room temperature in toluene. Under these conditions, the addition product (*S*)-**2a** was obtained with high enantioselectivities of between 81 and 85%, even though the reactions were sluggish, achieving no more than 56% conversion in 3 days. Among these, BINAP and P-Phos[10] offered considerably higher yields than the others.

Having identified the best-performing ligands, we optimized the reaction. This included adjustment of reaction temperature, dilution, catalyst loading, solvent, and substrate ratio (Supporting Information). This led us to identify a new set of conditions that afforded substantial improvement in reaction yield, which was subsequently adopted to provide optically active N-arylated *β*-amino acid carbamate esters (Scheme 4). Using (*R*)-BINAP

(8) Hii, K. K. *Pure Appl. Chem.* **2006**, *78*, 341−349.

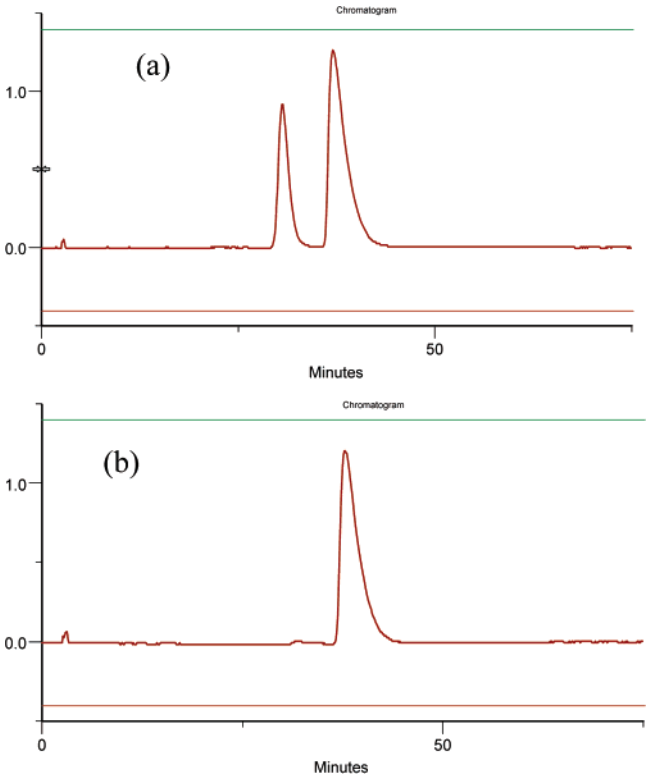


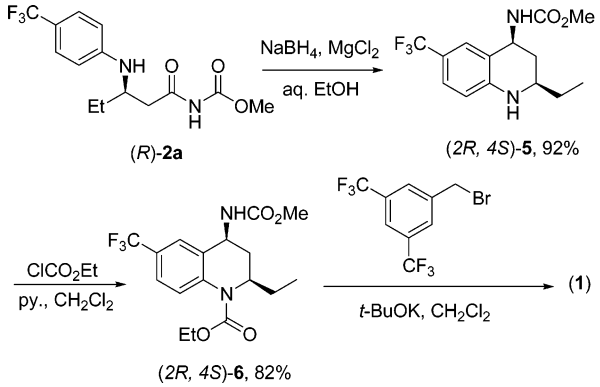
FIGURE 2. Enantiomeric enrichment by recrystallization of optically active **2a** of 60% ee (predominantly (*R*)-isomer) from toluene.cyclohexane: Chiral HPLC chromatograph of (a) deposited crystals (36% ee); (b) mother liquor (>99% ee).

and (*S*)-P-Phos, preparative quantities of (*S*)- and (*R*)-**2a** can be obtained, respectively, in good yields with ca. 90% ee (Scheme 4). The reaction proceeded to completion more rapidly when P-Phos was used, as the catalyst was more soluble under these conditions. Similarly, as the benzyl carbamate **4b** is considerably more soluble than **4a**, the corresponding reaction was complete in 24 h (using the (*R*)-BINAP ligand), affording the addition product (*S*)-**2b** in 79% yield and 89% ee.

Notably, the palladium catalyst appeared to be much more efficacious when it was generated in situ, as the corresponding reaction conducted with the isolated $[(BINAP)Pd(OH_2)_2]^{2+}[TfO]^-_2$ complex (5 mol %) resulted in much lower selectivities (68 and 75% ee for **2a** and **2b**, respectively).[11] This is in accordance with our earlier observation[9] and attributed to the generation of a more stable catalyst, as a slight excess of the chiral diphosphine ligand can be employed.

The Michael product can be purified by column chromatography. Alternatively, the catalyst can be removed from the reaction mixture by filtration through an absorbent (silica gel). The filtrate was then evaporated to give a yellow residue, from which compound **2a** can be separated from the excess aniline by recrystallization from toluene/cyclohexane. During this process, we discovered that the product crystallizes preferentially as a heterochiral conglomerate. Initially, the crude mixture (90% ee) deposited a crop of crystals with low enantiomeric excess (60% ee), while the mother liquor was found to contain a substantial amount of compound **2a** of extremely high optical purity (95% ee), as verified by chiral HPLC. The process can be repeated using the first crop of crystals (60% ee, 250 mg), again by recrystallization from toluene/cyclohexane, to afford a precipitate of reduced enantiopurity (37% ee, 140 mg), while

SCHEME 5. Final Assembly of the Target Molecule



an optically pure sample of (*R*)-**2a** (>99% ee, 100 mg) was obtained from the mother liquor (Figure 2). Indeed, this process of enantiomeric entrainment is highly reproducible and seems to be independent of the initial enantiomeric excess of **2a**.[12] Thus, it will appear that the N-arylated β-amino acid derivative possesses a particularly high eutectic enantiomeric excess value in this mixed-solvent system.[13] The crystallinity of the samples was reflected by the observation of different melting points: optically pure **2a** (72−73 °C, >99% ee) has a much lower value than a less optically active sample (109−111 °C, 37% ee).[14]

Optically pure intermediate (*R*)-**2a** was subsequently converted to torcetrapib using published procedures (Scheme 5):[7] formation of the tetrahydroquinoline heterocycle was effected using the Lewis acid mediated reduction, with the stereochemistry at C-2 directing the cyclization stereospecifically to give (2*R*,4*S*)-**5** as a single diastereomer in an excellent yield. Derivatization at N-1 was then achieved by the reaction with ethyl chloroformate and pyridine, giving (2*R*,4*S*)-**6** in a high yield.

The final alkylation step proved to be tricky, due to considerable steric congestion at N-2. As the reaction is quite slow, the formation of a byproduct becomes competitive.[15] In our hands, the reaction of (2*R*,4*S*)-**6** with 3,5-bis(trifluoromethyl)benzyl bromide using potassium *tert*-butoxide in dichloromethane did not proceed to completion, as the presence of **6** persisted in the final reaction mixture. Hence, this remained the only step in the synthetic sequence where column chromatography was required, giving the product in a moderate yield of 52%.[16]

All the characterization data for the final compound are in good agreement with that previously reported. In contrast to its

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(10) For applications of P-Phos in other asymmetric catalytic reactions, see: Wu, J.; Chan, A. S. C. *Acc. Chem. Res.* **2006**, *39*, 711−720.

(11) In a recent article, 10 mol % of $[(BINAP)Pd(OH_2)_2]^{2+}[TfO]^-_2$ was required to attain a similar ee (89%) in the addition of p-$CF_3C_6H_4NH_2$·HOTf to **4a**: Hamashima, Y. *Chem. Pharm. Bull.* **2006**, *54*, 1351−1364.

(12) The process was replicated three times using various samples of **2** with enantiomeric excesses between 60 and 89%. On every occasion, samples recovered from the mother liquor were found to possess ee values of ≥95%. See Experimental Section for a representative procedure.

(13) (a) For an excellent discussion of phase behavior of chiral compounds, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York; Chapters 6 and 7. (b) For a recent report of the eutectic ee of amino acids, see: Klussmann, M.; White, A. J. P.; Armstrong, A.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7985−7989.

(14) Melting point recorded for a "solvent-free sample" was reported to be 142.3−142.4 °C (ref 7b).

precursors **5** and **6**, torcetrapib exhibits extremely broad NMR resonance signals even at 55 °C, particularly the N-2 substituents. Full assignment of NMR data was eventually achieved by performing COSY, HMQC, TOCSY, and HETCORR ($^{13}C-^{19}F$) correlation experiments.

In summary, a practical asymmetric synthesis of torcetrapib from achiral precursors has been demonstrated. Using a Pd-catalyzed enantioselective aza-Michael reaction as the key bond-forming step, the overall synthesis requires only seven steps from chloroacetyl chloride. The process is highly practical, as it does not require the use of protecting groups. Furthermore, all of the synthetic intermediates are crystalline solids that can be purified by crystallization. As the stereochemistry is established by the aza-Michael reaction, the approach is also more convergent, thus allowing structural modifications to be easily achieved. We envisage that the methodology is applicable for the synthesis of structurally related 4-amino-2-alkyl-1,2,3,4-tetrahydroquinolines, a key structural motif found in many other pharmacologically important molecules.[17]

Experimental Section

Representative aza-Michael Reaction (Preparative Scale): In a three-neck round-bottom flask equipped with a stirrer bar, reflux condenser, and nitrogen inlet, $Pd(OTf)_2 \cdot 2H_2O$ (84 mg, 0.19 mmol, 5 mol %) and (*S*)-P-Phos (135 mg, 0.21 mmol, 5.5 mol %) were mixed in degassed dry toluene (5 mL) at 50 °C for 40 min, whereupon a dark red solution was formed. The catalyst mixture was diluted by the addition of toluene (20 mL), before the addition of substrates methyl carbamate **4a** (600 mg, 3.81 mmol, 1 equiv), (4-trifluoromethyl)aniline (720 μL, 5.7 mmol, 1.5 equiv), and a further portion of toluene (22.5 mL). The reaction mixture was then left to stir at 50 °C for 36 h (complete consumption of **4a** was indicated by TLC). After cooling to room temperature, the reaction mixture was filtered through silica gel and evaporated. The residue can be purified by column chromatography or by recrystallization. The product was obtained (after column chromatography) as predominantly the (*R*)-isomer in 80% yield and 91% ee.

***N*-[3-(4-Trifluoromethylphenylamino)pentanoyl]methyl carbamate, 2a:**[7] White solid; purified either by column chromatography ($R_f = 0.65$, SiO_2, 2% $MeOH/CH_2Cl_2$) or by recrystallization from toluene/cyclohexane; $[\alpha]_D^{22}$ −10.0 ($CHCl_3$, c = 0.02 g/mL, 86% ee, (*S*)-isomer); Daicel Chiralpak AD; hexane/*i*-PrOH 95/5; sample concentration = 1 mg/mL in *i*-PrOH, flow rate = 1.2 mL/min; 254 nm, t_R = 30.5 [*S*-(−)-isomer] and 37.0 [*R*-(+)-isomer] min; δ_H (400 MHz, $CDCl_3$) 7.55 (1H, br s, NH), 7.37 (2H, d, J = 8.6 Hz, Ar−H), 6.61 (2H, d, J = 8.6 Hz, Ar−H), 4.19 (1H, br s, NH), 3.80−3.94 (1H, m, CHN), 3.77 (3H, s, OCH_3), 3.09 (1H, dd, J = 16, 6.5 Hz, CH_2CO), 2.97 (1H, dd, J = 16, 5.6 Hz, CH_2CO), 1.64−1.74 (2H, m, CH_2CH_3), 0.99 (3H, t, J = 7.5 Hz, CH_2CH_3); δ_C (100.6 MHz, $CDCl_3$) 172.6 (C═O), 152.3 (C), 149.8 (C═O), 126.7 (CH), 124.9 (q, J = 270 Hz, CF_3), 118.8 (q, J = 33 Hz, CH), 112.3 (CH), 53.2 (CH), 51.2 (CH_3), 39.8 (CH_2), 27.9 (CH_2), 10.4 (CH_3); m/z (CI+) 319 (MH^+, 100%).

Achieving Enantiopurity by Recrystallization. In a small round-bottom flask equipped with a condenser, a sample of optically active **2a** (250 mg, 60% ee, enriched in the (*R*)-isomer) was suspended in cyclohexane (8 mL) and heated to reflux. Toluene was added dropwise to the boiling suspension via the condenser, until complete dissolution of the solid. The solution was allowed to cool slowly to room temperature. Crystallization was judged to be complete after 3 h, whereupon white needle-like crystals were collected by filtration and dried under vacuum (140 mg, 37% ee, mp 109−111 °C). The filtrate was evaporated, and the resultant pale yellow residue was triturated with cyclohexane to give optically pure (*R*)-**2a** (100 mg, >99% ee, mp 72−73 °C).

Acknowledgment. The work was supported by PPG Fine Chemicals. We are grateful to Professor Alan Armstrong (Imperial College) for discussions on eutectic ee's.

Supporting Information Available: Experimental procedures and characterization data for compounds **3a**, **3b**, **4a**, **4b**, **5**, and **6**. Catalytic reaction optimization, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Resulting from the dimerization of the reactive benzyl bromide, giving a stilbene byproduct (ArCH═CHAr). This was reported previously in ref 7b.

(16) In the original reports (ref 7), the base was added in two portions. Torcetrapib was obtained as a monoethanolate in 73% yield.

(17) Bazin, M.; Kuhn, C. *J. Comb. Chem.* **2005**, *7*, 302−308 and references therein.