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Improved Asymmetric Synthesis of 3,4-Dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]-5-[3-(trifluoromethoxy)phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol, a Potent Cholesteryl Ester Transfer Protein Inhibitor

Thomas A. Rano* and Gee-Hong Kuo

Johnson & Johnson Pharmaceutical Research & Development, L.L.C., 1000 Route 202, P.O. Box 300, Raritan, New Jersey 08869

trano@its.jnj.com

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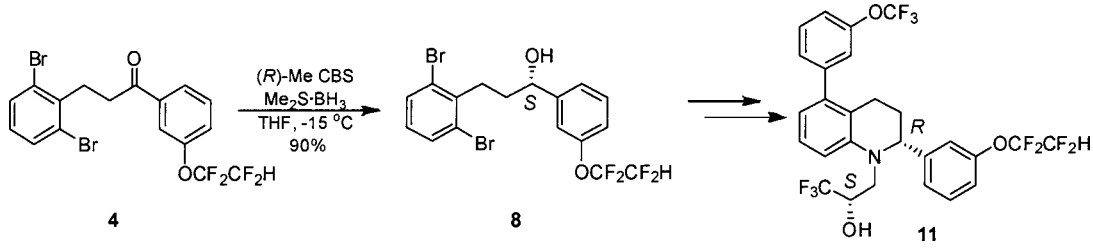
ABSTRACT



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The asymmetric synthesis of 3,4-dihydro-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-[3-(trifluoromethoxy)phenyl]-α-(trifluoromethyl)-1(2*H*)-quinolineethanol (compound 11), a cholesteryl ester transfer protein inhibitor, is accomplished. The asymmetric center is established via the chiral reduction of ketone 4 employing Corey's (*R*)-Me CBS oxazaborolidine reagent. The tetrahydroquinoline core of the molecule is established via a Cu-mediated intramolecular amination reaction. The preparation of the prochiral ketone 4 has also been improved by eliminating the use of a hazardous aryltin reagent.

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that facilitates the movement of cholesteryl esters and triglycerides between the various lipoproteins in the blood by mediating the transfer of cholesteryl esters from the cardioprotective high density lipoprotein cholesterol (HDL-C) to the proatherogenic low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein (VLDL-C). HDL cholesterol (the "good" cholesterol) plays a major role in the transfer of excess cholesterol from the peripheral tissues to the liver (reverse cholesterol transport), where it can be cleared from the body. Thus, the movement of cholesteryl esters from HDL-C to LDL-C by CETP has the overall undesirable effect of lowering HDL cholesterol. It therefore follows that inhibition of CETP should lead to elevation of plasma HDL cholesterol and lowering of plasma LDL cholesterol, thereby providing a therapeutically beneficial plasma lipid profile.[1,2] Currently, there are no marketed CETP inhibitors, although there were two compounds in clinical trials[3] through late 2006. Pfizer's torcetrapib[4] is a potent CETP inhibitor which was recently withdrawn from phase III trials due to risks associated with blood pressure increase. Japan Tobacco's JTT-705[5](an

(1) Tall, A. R. *J. Lipid Res.* **1993**, *34*, 1255–1274.
(2) McCarthy, P. A. *Med. Res. Rev.* **1993**, *13*, 139–159.
(3) For an excellent review of CETP inhibitors, see: Sikorski, J. A. *J. Med. Chem.* **2006**, *49*, 1–21.

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irreversible inhibitor), which recently completed phase II trials, is of lower potency (Figure 1).

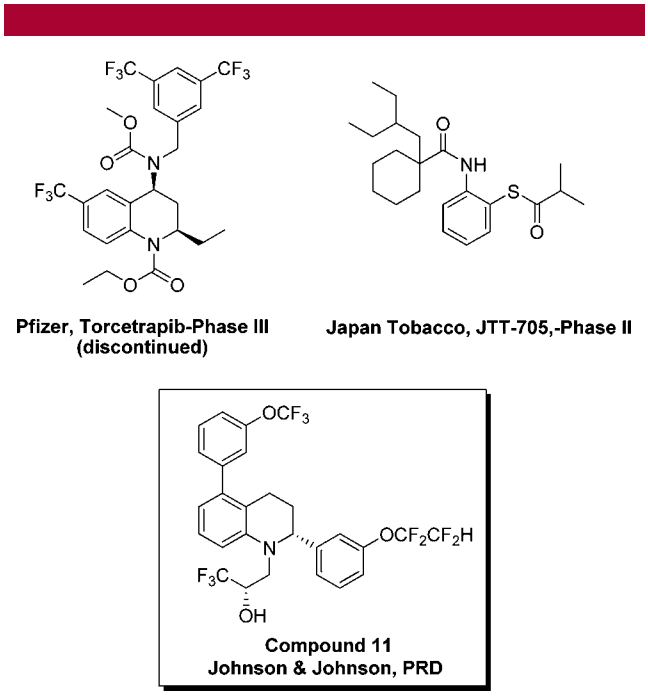


Figure 1. Structures of CETP inhibitors.

The discovery and preparation of potent CETP inhibitors from our laboratories has recently been reported.[6] However, the initial synthesis of these CETP inhibitors provided material in racemic form, which necessitated chiral HPLC separation of advanced intermediate racemates. Furthermore, the absolute configuration of the chiral centers of the biologically active target molecules remained unknown. Herein, we report the asymmetric synthesis of the tetrahydroquinoline core structure of our target compounds as well as the determination of the absolute configuration of each chiral center.

The synthetic route commences with the preparation of aryl ketone **4** (Scheme 1). Exposure of 2,6-dibromobenzyl bromide **1**[7] to the sodium salt of diethyl malonate[8] provided the geminal diester which was decarbalkoxylated under modified Krapcho[9] conditions to cleanly afford the monoester in quantitative yield. Saponification of the resultant ethyl ester with NaOH followed by acidification with HCl cleanly provided the crude acid, which was smoothly converted to acid chloride **2** in 75% overall yield for the four steps. Coupling of arylstannane **3**[10] with **2** afforded requisite ketone **4** in 66% yield.[11] Sodium borohydride reduction was followed by mesylation of the resultant racemic alcohol. Displacement with sodium azide, subsequent reduction of the azide under Brown's[12] conditions, and sulfonamide formation provided nosylate **5** in very good yield. The stage was now set for the copper-mediated intramolecular cyclization. Employing conditions reported by Fukuyama[13] (copper iodide and cesium carbonate in hot DMSO), the tetrahydroquinoline core template was obtained in nearly quantitative yield.[14,15] Removal of the *o*-nitrobenzene sulfonate protecting group[16] provided advanced intermediate **6**, which when subjected to Suzuki coupling conditions employing a wide variety of readily available aryl boronic acids allowed a diverse set of biphenyl analogues to be prepared.[6] Alkylation with 1,1,1-trifluoroepoxypropane (which was sold as a "racemic reagent" from commercial sources) provided the target CETP inhibitor **7** as a mixture of four compounds. The mixture could be easily separated by SiO_2 flash chromatography, affording a higher R_f diastereomer and a lower R_f diastereomer. Assay results consistently determined that the higher R_f diastereomer was superior in activity as opposed to the lower R_f diastereomer. It should be noted that each diastereomeric compound also contained its respective racemate.

In order to determine the absolute configuration of the chiral center contained within the tetrahydroquinoline platform of the more active higher R_f compound, investigation into the asymmetric reduction of prochiral ketone **4** was initiated (Scheme 2). Corey's methyl CBS oxazaborolidine reagents[17] in combination with borane−dimethyl sulfide complex provided the optimal reaction conditions for the asymmetric reduction of **4**. Employing the *R*-Me CBS oxazaborolidine reagent, the *S* alcohol **8** could be obtained

(4) Barter, P. J.; Caulfield, M.; Eriksson, M.; Grundy, S M.; Kastelein, J. J. P.; Komajda, M.; Lopez-Sendon, J.; Mosca, L.; Tardif, J. C.; Walters, D. D.; Shear, C. L.; Revkin, J. H.; Buhr, K.; Fisher, M. R.; Tall, A. R.; Brewer, B. *N. Engl. J. Med.* **2007**, *357*, 2109–2122.

(5) Shinkai, H.; Maida, K.; Yamasaki, T.; Okamoto, H.; Uchida, I. *J. Med. Chem.* **2000**, *43*, 3566–3572.

(6) Rano, T. A.; Sieber-McMaster, E.; Pelton, P. D.; Yang, M.; Demarest, K. T.; Kuo, G.-H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2456–2460.

(7) Soloshonok, V. A.; Tang, X.; Hruby, V. J. *Tetrahedron* **2001**, *57*, 6375–6382.

(8) The sodium salt of dimethyl malonate or di-*tert*-butyl malonate could also be used with equal efficiency. In the latter case, the monocarboxylic acid could be obtained via the two-step process of *tert*-butyl ester removal with TFA followed by 6 N HCl heated to reflux.

(9) Markgraf, J. H.; Ibsen, M. S.; Kinney, J. B.; Kuper, J. W.; Lurie, J. B.; Marrs, D. R.; McCarthy, C. A.; Pile, J. M.; Pritchard, T. J. *J. Org. Chem.* **1977**, *42*, 2631–2632.

(10) Stannane **3** was prepared from the corresponding commercially available aryl bromide under standard conditions employing $Me_3SnSnMe_3$ and $Pd(PPh_3)_4$ in approximately 65% yield.

(11) Several synthetic routes to **4** were attempted without success. For example, direct alkylation of the lithium, potassium, or sodium enolate of *m*-tetrafluoroethoxy acetophenone with **1** led to complex mixtures of ketone **4** along with bis-alkylation, starting material, and decomposition products. Halogen−metal exchange of *m*-tetrafluoroethoxybromobenzene followed by addition to 3-(2,6-dibromopheny)propionaldehyde provided no desired product. It was subsequently determined that the hydrogen atom of the tetrafluoroethoxy moiety was sufficiently acidic to be deprotonated by strong base, resulting in the splitting out of tetrafluoroethylene and the corresponding phenol.

(12) Salunkhe, A. M.; Brown, H. C. *Tetrahedron Lett.* **1995**, *36*, 7987. Interestingly, several other commonly employed methods of azide reduction resulted in intractable mixtures, the exception being PPh_3/H_2O, which afforded the desired amine in 28% yield.

(13) Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, *2*, 231.

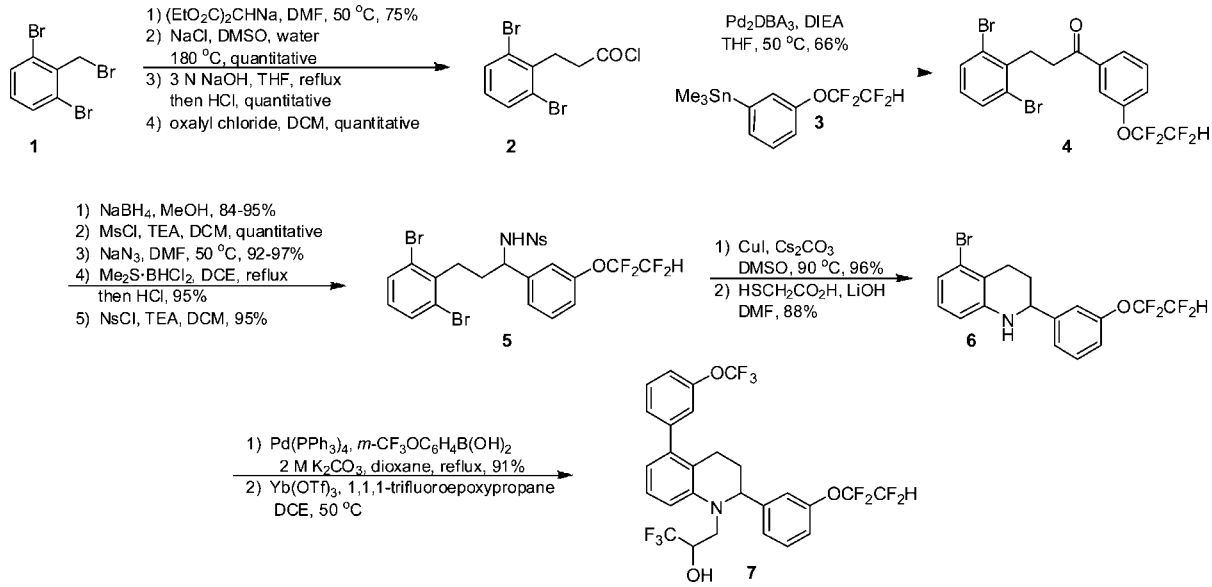
(14) Intramolecular Fukuyama cyclization under identical conditions on the free amine did not produce any desired product.

(15) A variety of copper-mediated Buchwald conditions were also attempted with limited success, affording the tetrahydroquinoline core in approximately 25% yield.

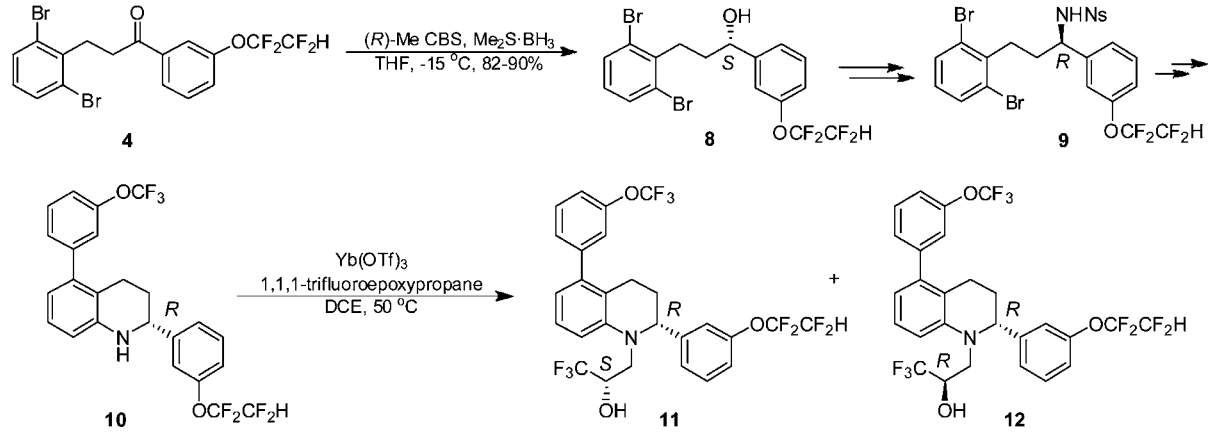
(16) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.

(17) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.

Scheme 1. Preparation of Racemic CETP Inhibitor



Scheme 2. Asymmetric Synthesis of CETP Inhibitor



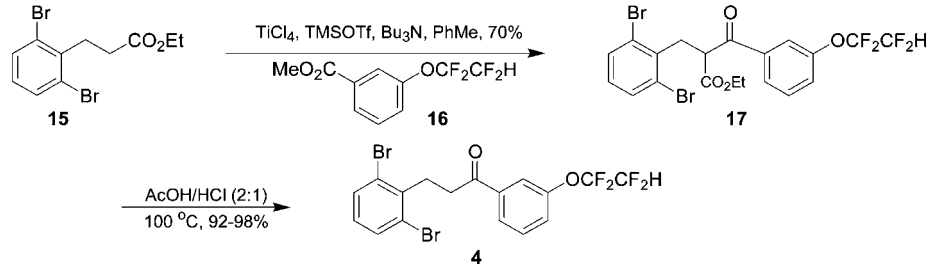
in 82−90% yield and approximately 91% enantiomeric excess.[18] The assignment of the *S* configuration to alcohol **8** was based upon the precedent sent forth in the Corey paper.[17] The optical rotation of *S* alcohol **8** was determined to be −12.1 (*c* 1; $CHCl_3$). The *S* alcohol **8** was then processed through to the penultimate intermediate **10** as illustrated in Scheme 1. Note that azide displacement of the mesylated benzylic alcohol inverts the chiral center as illustrated in compound **9**, ultimately affording the *R* configuration at the 2 position of the tetrahydroquinoline ring of **10**. Concomitantly, the *S*-Me CBS oxazaborolidine reagent was employed to procure the corresponding *R* antipode of alcohol **8**, and the absolute configuration was determined once again by precedent sent forth in the Corey paper[17] and also confirmed by the method of Ohtani.[19]

Interestingly, when enantiomerically enriched **10*R*** was alkylated with commercially available "racemic" 1,1,1-trifluoroepoxypropane, a 1:1 mixture of diastereomeric alcohols **11** and **12** was not obtained. Instead, higher R_f diastereomer **11** was obtained in approximately 73% yield, and lower R_f diastereomer **12** was obtained in approximately 18% yield. This result prompted further examination of the 1,1,1-trifluoroepoxypropane reagent, as it was suspected that the epoxide was not racemic. Examination of the rotation of the commercial "racemic" epoxide revealed a rotation of −9.2 (*c* 5; $CHCl_3$). The rotation of the known (*S*)-(−)-1,1,1-

(18) Enantiomeric excess determined by chiral HPLC (Chiralcel AS; isocratic elution 90/10 Hexane/IPA) by area integration at 210 nm). The structure assigned to each new compound is in accord with its 400 MHz NMR spectrum as well as appropriate ion identification by mass spectrometry.

(19) Ohtani, I. Kusumi, T. Kashman, Y. Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096. Both the *R* and *S* Mosher esters of the *R* antipode of alcohol **8** were prepared for use in this study. The 400 MHz NMR spectra of these compounds are included in the Supporting Information.

Scheme 3. Improved Route to Ketone **4**



trifluoroepoxypropane epoxide is reported to be −10.9 (*c* 5; $CHCl_3$),[20] confirming that the commercial epoxide was not racemic, but instead enriched in the *S* isomer. Therefore, the stereochemical assignment of the alcohol chiral center of the major higher R_f diastereomer **11** may be assigned as the *S* configuration. The optical rotation of **11** was determined to be −117.3 (*c* 1; $CHCl_3$).

Table 1. Stereospecificity of CETP Inhibition

compd	configuration	CETP inhibition
11	*R*,*S*	85% at 1 μM IC_{50} = 39 nM[a]
12	*R*,*R*	62% at 1 μM IC_{50} > 3 μM
13[22]	*S*,*R*	46% at 1 μM
14[22]	*S*,*S*	20% at 1 μM

[a] Compounds possessing IC_{50}'s < 250 nM were typically assayed at least twice, while those with IC_{50}'s > 250 nM were assayed only once.

The stereospecificity for CETP inhibition of all four diastereomers is illustrated in Table 1. Compound **11** inhibits partially purified CETP with an IC_{50} of 39 nM as well as CETP in human plasma with an IC_{50} of 190 nM. There was also an increase in HDL-C in hCETP transgenic mice treated with **11**.[21]

As interest in **11** gathered momentum, requests for ancillary studies necessitated the preparation of multigram quantities of drug substance. Reassessment of the synthetic route revealed that the Stille reaction employed in the union of compounds **2** and **3** proved to be the least efficient step at 66% yield. Furthermore, elimination of the hazardous aryl tin reagent would be beneficial from both a safety as well as an environmental point of view. Therefore, efforts were directed toward improving this synthetic step. To our delight, the mixed Claisen condensation of ethyl ester **15** (an intermediate in the preparation of acid chloride **2**) and methyl benzoate **16** (itself easily prepared from the commercially available benzoic acid) in the presence of $TiCl_4$ and catalytic amounts of TMSOTf afforded a reproducible 70% yield of the desired β-keto ester **17**. When **17** was subjected to the Krapcho conditions previously employed (NaCl, H_2O, DMSO, 180 °C) decarbalkoxylation did occur, but with concomitant splitting out of tetrafluoroethylene, due to the base-sensitive nature of the tetrafluoroethoxy side chain.[11] Fortunately, acid-catalyzed Krapcho reaction occurred smoothly by simply heating **17** in a 2:1 mixture of AcOH/HCl for 1 h at 100 °C. The desired prochiral ketone **4** was obtained in excellent yield, thus avoiding the use of aryl stannane reagent **3** as well as shortening the synthetic sequence by one step (Scheme 3).

In summary, an asymmetric synthesis of the tetrahydroquinoline core structure of our CETP inhibitor **11** has been established, as well as the determination of the absolute configuration of the chiral centers in question. A more efficient alternative synthetic sequence to the prochiral ketone **4** has also been worked out, eliminating the use of a hazardous aryl tin reagent. Multigram quantities of **11** in high enantiomeric excess were prepared. Further studies on **11** are ongoing and will be reported in due course.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900639J

(20) Ramachandran, P. V.; Gong, B.; Brown, H. C. *J. Org. Chem.* **1995**, *60*, 41–46.

(21) For a detailed report of the biological evaluation of compound 11, please see: Kuo, G. H.; Rano, T.; Pelton, P.; Demarest, K. T.; Gibbs, A. C.; Murray, W. V.; Damiano, B. P.; Connelly, M. A. *J. Med. Chem.* **2009**, *52*, 1768−1772.

(22) The structures of compound **13** and **14** are as follows: