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ARTICLE

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Biphenyl-Substituted Oxazolidinones as Cholesteryl Ester Transfer Protein Inhibitors: Modifications of the Oxazolidinone Ring Leading to the Discovery of Anacetrapib

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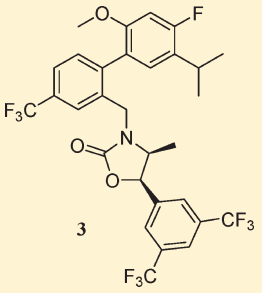
ABSTRACT: The development of the structure−activity studies leading to the discovery of anacetrapib is described. These studies focused on varying the substitution of the oxazolidinone ring of the 5-aryloxazolidinone system. Specifically, it was found that substitution of the 4-position with a methyl group with the *cis*-stereochemistry relative to the 5-aryl group afforded compounds with increased cholesteryl ester transfer protein (CETP) inhibition potency and a robust in vivo effect on increasing HDL-C levels in transgenic mice expressing cynomolgus monkey CETP.



INTRODUCTION

Cardiovascular disease (CVD) is now the leading cause of death worldwide. In 2005, approximately 17.5 million deaths were attributed to CVD, with approximately 7.6 million of those mortalities resulting from coronary heart disease (CHD).[1] Elevated levels of low density lipoprotein-cholesterol (LDL-C) are considered to be a major risk factor for CHD. The development of the statins (3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, e.g. simvastatin and atorvastatin) has significantly helped to reduce LDL-C levels in patients at risk for CHD and to reduce cardiovascular events but only by approximately 30%.[2,3] Therefore, patients on statin therapy can still be at significant risk of CVD. There is now a growing body of epidemiological evidence linking increased levels of high density lipoprotein-cholesterol (HDL-C) with decreased risk of development of CHD.[4−7] Some cholesterol lowering drugs, including niacin, the fibrates, and the statins, have a modest effect on increasing HDL-C levels.[8−11] Niacin is the only therapy currently approved for raising HDL-C levels, despite its modest efficacy (∼20% increase). Consequently, the identification of improved approaches to raising HDL-C remains to be addressed.

Low density lipoproteins (LDL) and high density lipoproteins (HDL) are macromolecular lipoprotein structures that are comprised of a hydrophobic core of cholesteryl esters and triglycerides encased by a hydrophilic layer of phospholipids, free cholesterol, and apolipoproteins. Both LDL and HDL are responsible for the transport of lipids in the plasma. LDL has a well established role in the promotion of atherogenesis, but the mechanism of the protective effect of HDL is more complex.[12] The beneficial antiatherogenic effects of HDL are thought to arise primarily from its participation in reverse cholesterol transport (RCT), although anti-inflammatory and antioxidant properties have also been ascribed to this lipoprotein class. Reverse cholesterol transport is the process by which excess cholesterol is moved from lipid laden macrophages (foam cells) and HDL to the liver for catabolism or excretion into the bile. Cholesteryl ester transfer protein (CETP) is a 476-residue hydrophobic glycoprotein that mediates the exchange of cholesteryl ester (CE) from HDL with triglycerides from the apolipoprotein B (apoB)-containing lipoproteins, primarily very low density lipoprotein (VLDL).[13,14] Hence, CETP acts to decrease HDL-C levels and increase LDL-C levels and so could be considered to be a pro-atherogenic factor.[15] On the other hand CETP also enhances the rate of RCT, suggesting a possible antiatherogenic role.[16] Studies to investigate the therapeutic potential of CETP inhibition in animal models have been inconclusive. In mice, a species that lacks natural CETP expression, results have been mixed and in rabbits, a species where CETP is expressed in high levels, inhibition appears to reduce atherogenesis.[15,16] A population of CETP deficient humans has been identified in Japan.[17,18] These individuals displayed high levels of HDL-C and low levels of LDL-C and apoB.[18] Although the effect of CETP deficiency on atherosclerosis was not clear,

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the observed lipid profiles for these individuals highlights the potential of CETP as a therapeutic target for raising HDL.[16]

Torcetrapib and dalcetrapib were the first CETP inhibitors to be developed and tested in humans with phase III data only available for torcetrapib.[19−26] These clinical studies established that pharmacological inhibition of CETP leads to significant increases in plasma HDL-C concentrations.[27] Despite this observation, the RADIANCE 1 and 2 imaging studies showed torcetrapib had no effect on the progression of atherosclerosis.[28−30] The ILLUSTRATE imaging study was consistent with the RADIANCE studies, but a small group of patients that presented the highest increases in HDL-C levels did show some regression in atheroma plaque volume.[31,32] Consistent with earlier clinical studies, the ILLUMINATE phase III outcomes trial showed significant increases in HDL-C levels, but the study was halted prematurely due to increased mortality in patients receiving torcetrapib relative to the atorvastatin-only arm. There was also an increase in mean systolic blood pressure as well as changes in blood electrolytes levels in the torcetrapib-treated arm. Post hoc analysis indicated increased aldosterone levels in these patients, which was consistent with the observed changes in electroytes. Studies in preclinical species have recapitulated both the blood pressure and aldosterone-releasing effects of torcetrapib and have shown that they occur independently of CETP inhibition.[33−36] Thus, it has been established that torcetrapib possesses off-target activities affecting blood pressure and aldosterone levels, although the underlying causative mechanism has not yet been elucidated. There is currently a significant debate regarding the off-target activities of torcetrapib, and whether they can account for the increased mortality observed in the ILLUMINATE trial and/or whether they were a contributing factor to the lack of efficacy observed in the imaging studies.[37−41] Given the potential cardiovascular benefits that may be realized by pharmacologic increase in HDL-C, however, there remains continued interest in the development of CETP inhibitors. To determine whether CETP inhibition will be beneficial, large scale clinical studies on a compound or compounds lacking both the blood pressure and aldosterone effects will be required.

A chemistry program was initiated at Merck in order to identify a suitable CETP inhibitor for development as a treatment for atherosclerosis, and this program led to the discovery of anacetrapib. The ability of anacetrapib to inhibit CETP-mediated transfer of both cholesteryl ester and triglycerides and its mechanism of action has been characterized.[42] Anacetrapib has been extensively profiled in phase I and II clinical trials and was shown to elicit a dose-dependent increase in HDL-C levels and decrease in LDL-C levels.[43−48] It was also found that HDL isolated from humans treated with anacetrapib had increased potential to promote cholesterol efflux and retained anti-inflammatory effects.[49] Preclinical and clinical studies with anacetrapib, including recent results from the phase III safety study DEFINE, have thus far given no evidence of blood pressure or aldosterone increases and so development of the compound continues.[33,50,51] Herein we describe the medicinal chemistry that led to the discovery of anacetrapib.

Early development of CETP inhibitors at Merck led to the discovery of the first benchmark compound **1**.[52] This compound was a moderately potent inhibitor of CETP-mediated CE transfer and only elicited an modest increase in HDL-C levels in the B6-Tg(CETP) mouse in vivo model. The SAR was subsequently advanced by introduction of a conformational constraint that restricted the conformation of the methyl

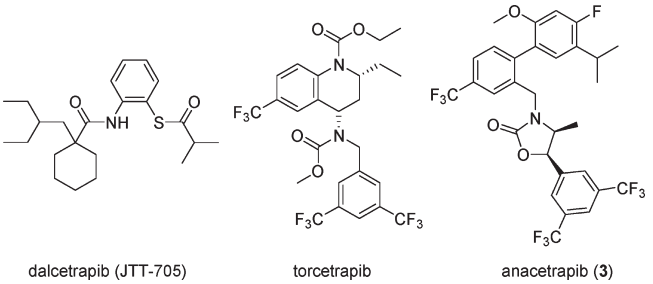
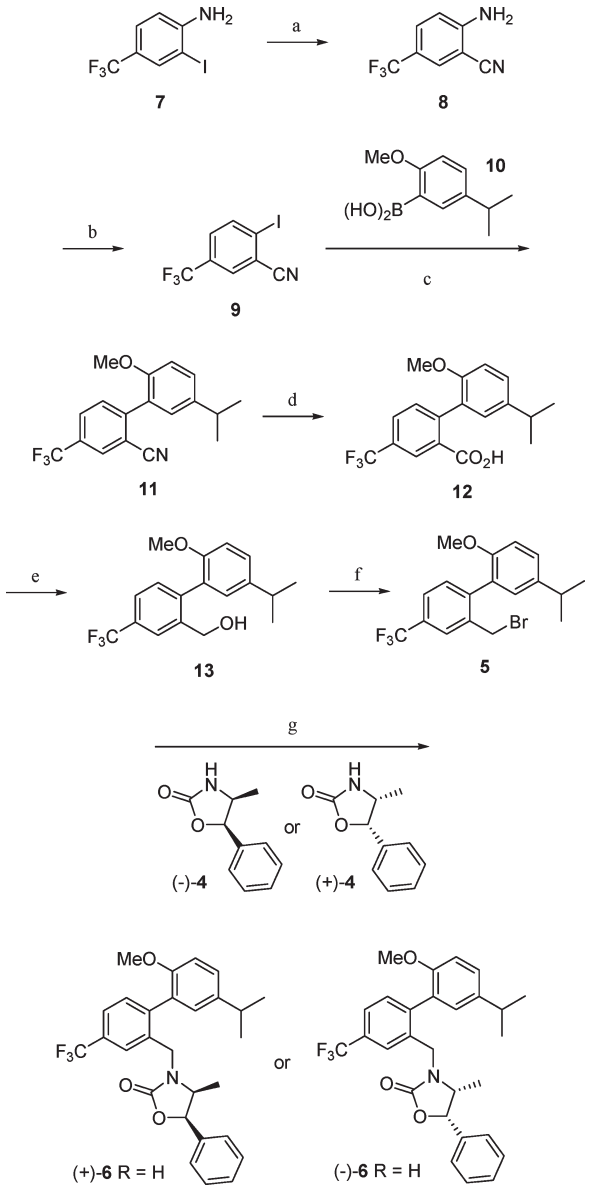


Figure 1

Scheme 1[a]



[a] Reagents: (a) CuCN, DMF, Δ, 1 h, 90%; (b) *t*-BuONO, CH_2I_2, 60 °C, 30 min, 83%; (c) **10**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, EtOH, H_2O, $\mu\lambda$, 150 °C, 10 min, 98%; (d) KOH, *i*-PrOH, H_2O, $\mu\lambda$, 130 °C, 4 h, 43%; (e) borane, THF, reflux, 3 h, 61%; (f) Br_4C, Ph_3P, CH_2Cl_2, 0−25 °C, 1 h, quant; (g) (−)-**4** or (+)-**4**, NaHMDS, THF, 25 °C, 15 h, 63% and 55%.

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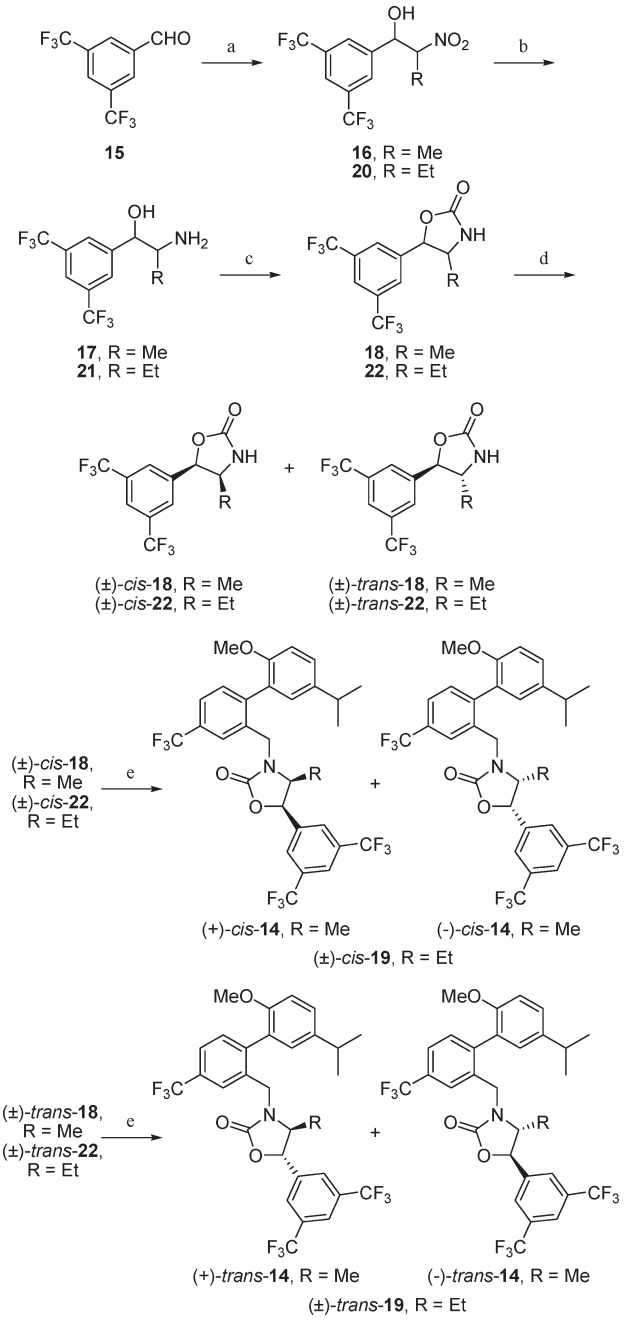
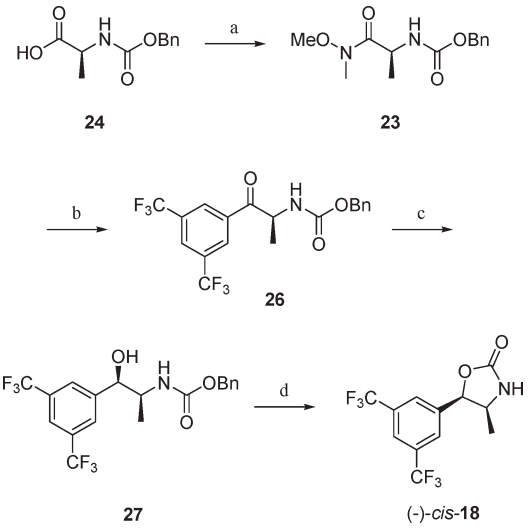
Scheme 2[a]



[a] Reagents: (a) (i) $EtNO_2$,or *n*-$PrNO_2$, 10% aq NaOH, EtOH, 0 °C, 1 h; (ii) 2% aq AcOH, 25 °C, 1 h, 97−99%; (b) H_2, RaNi, 30% aq HCO_2H, MeOH, 25 °C, 15 h, 86−94%; (c) *i*-Pr_2NEt, $(Cl_3CO)_2CO$, CH_2Cl_2, 0 °C, 1 h, 75−78%; (d) separation of diastereoisomers by flash chromatography; (e) **5**, NaHMDS, THF, 25 °C, 15 h, 51−96%.

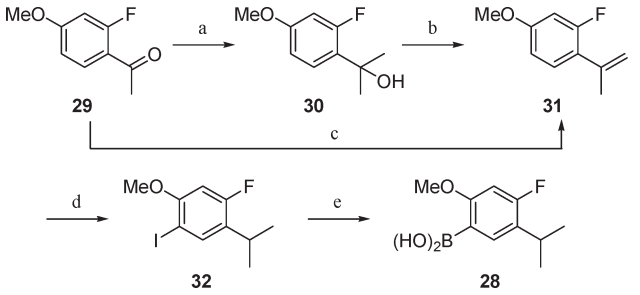
carbamate to afford oxazolidinone **2**.[53] This compound, though slightly more potent in CE transfer inhibition, did not have any effect on HDL-C levels in vivo at 10 mpk, possibly due to the poor pharmacokinetic profile observed. We therefore investigated further modifications of the lead series in an effort to afford compounds with potent CETP inhibition and improved pharmacokinetic profiles that would be effective in increasing HDL-C levels in our in vivo model. Herein we detail the investigation of

Scheme 3[a]



[a] Reagents: (a) (i) *N*-methylmorpholine, *t*-BuOCOCl, CH_2Cl_2; (ii) $Me(MeO)NH_2Cl$, 99%; (b) (i) *i*-PrMgCl, THF, −15 °C, 15 min; (ii) [3,5-bis(trifluoromethyl)phenyl]magnesium bromide (**25**), THF, −15 to 25 °C, 2 h, 83%; (c) $PhMe_2SiH$, TFA, 0 °C, 15 h; (d) KOH, MeOH, THF, 25 °C, 3 h, 68% over 2 steps.

Scheme 4[a]



[a] Reagents: (a) MeMgBr, THF, 0 °C, 4 h, 80%; (b) MsCl, Et_3N, CH_2Cl_2, 0−25 °C, 2 h, 56%; (c) NaHMDS, $MePh_3PBr$, THF, −78 °C, 1.5 h, 63%; (d) (i) H_2, 10% Pd/C, MeOH, 25 °C, 1 h; (ii) Ag_2SO_4, I_2, MeOH, 25 °C, 4 h, 75%; (e) *n*-BuLi, $(MeO)_3B$, −78 °C, 3 h, 60%.

further substitution of oxazolidinone ring system of compound **2**, ultimately leading to identification of the clinical candidate anacetrapib **3** (Figure 1).

CHEMISTRY

The first two 4-substituted oxazolidinone derivatives investigated, (+)-**6** and (−)-**6**, were synthesized by coupling benzyl bromide **5** with commercially available norephedrine derived oxazolidinones (−)-**4** and (+)-**4**, respectively, as in Scheme 1. Benzyl bromide **5** was derived from aryl iodide **7**. Cyanation to give aryl cyanide **8** was followed by Sandmeyer reaction to afford aryl iodide **9**. Palladium catalyzed coupling of **9** with boronic acid **10** afforded nitrile **11**. Nitrile hydrolysis to afford carboxylic acid **12** was followed by reduction with borane to give benzyl alcohol **13**. This was efficiently transformed into benzyl bromide **5** with triphenylphosphine and carbon tetrabromide. Deprotonation of oxazolidinones (−)-**4** and (+)-**4** with NaHMDS followed by

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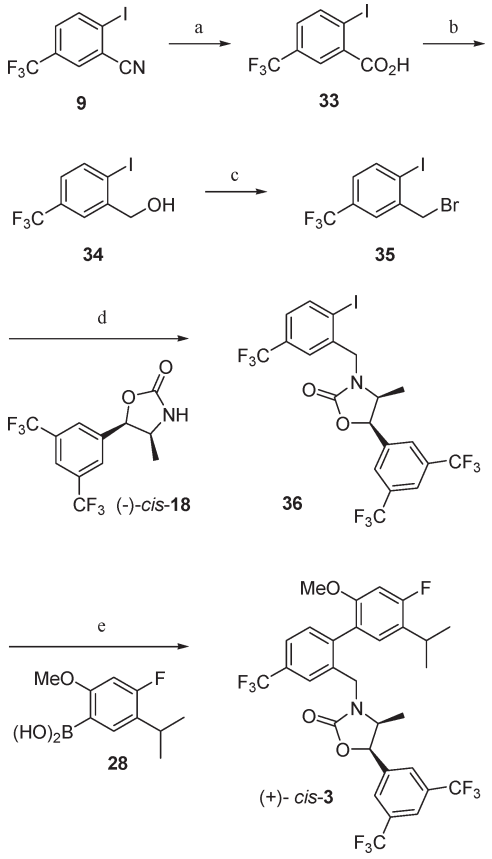
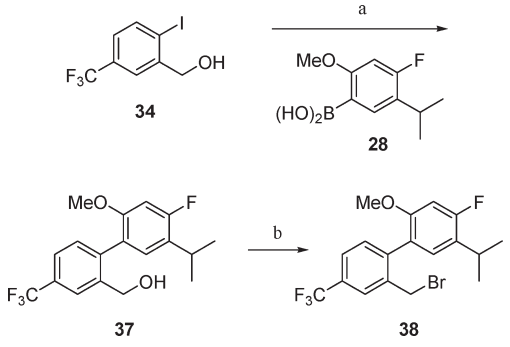
Scheme 5[a]



[a] Reagents: (a) KOH, H_2O, *i*-PrOH, Δ, 14 h, 66%; (b) borane, THF, Δ, 1.5 h, 88%; (c) Br_4C, Ph_3P, CH_2Cl_2, 0−25 °C, 48 h, 96%; (d) (−)-*cis*-**18**, NaH, THF, 25 °C, 14 h, 83%; (e) **28**, $(Ph_3P)_4Pd$, Na_2CO_3, C_6H_6, EtOH, H_2O, Δ, 14 h, 76%.

Scheme 6[a]

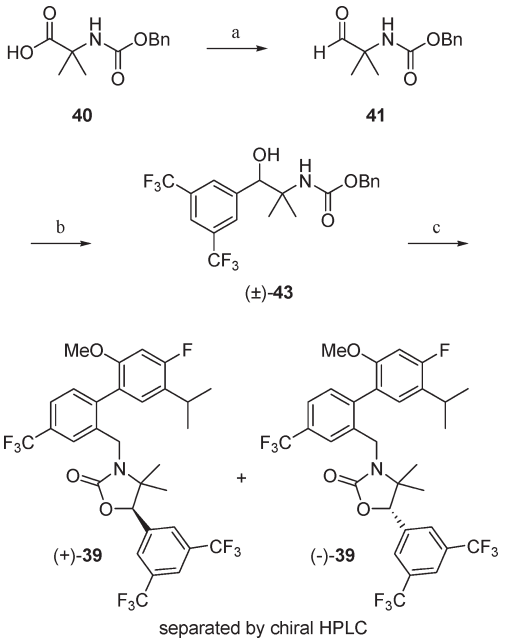


[a] Reagents: (a) **28**, $(Ph_3P)_4Pd$, Na_2CO_3, EtOH, H_2O, Δ, 24 h, 97%; (b) Br_4C, Ph_3P, CH_2Cl_2, 0−25 °C, 2 h, 93%.

coupling with benzyl bromide **5** gave biphenyl oxazolidinones (+)-**6** and (−)-**6**.

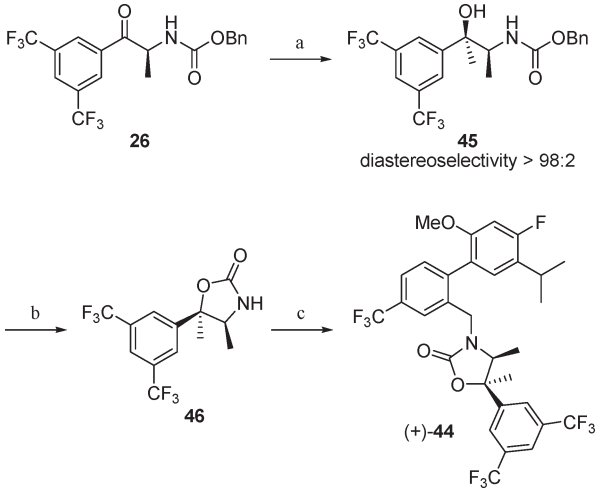
Initially, the synthesis of oxazolidinone **14** was conducted in racemic fashion as shown in Scheme 2. Nitro-aldol reaction of benzaldehyde **15** with nitroethanol gave alcohol **16**. Reduction with Raney nickel afforded amine **17**. Reaction with triphosgene gave oxazolidinone **18**, which was separated into racemic *cis*- and

Scheme 7[a]



[a] Reagents: (a) (i) *N*-methylmorpholine, *t*-BuOCOCl, CH_2Cl_2, 0 °C, 1.5 h; (ii) Me(MeO)NH_2Cl, 3 h, 41%; (iii) DIBALH, THF, −78 °C, 4 h, 98%; (b) [3,5-bis(trifluoromethyl)phenyl]magnesium bromide (**25**), THF, −20 to 25 °C, 4 h, 49%; (c) **38**, NaH, DMF, 25 °C, 15 h, 40%.

Scheme 8[a]



[a] Reagents: (a) MeMgBr, Et_2O, 25 °C, 2 h, 94%; (b) KOH, MeOH, THF, 25 °C, 3 h, 92%; (c) **38**, NaH, DMF, 25 °C, 2 h, 65%.

trans-diastereoisomers *cis*-**18** and *trans*-**18**. Coupling of *cis*-**18** and *trans*-**18** with benzyl bromide **5** afforded racemic biphenyl oxazolidinones (±)-*cis*-**14** and (±)-*trans*-**14**, which were each separated into the corresponding pure enantiomers (+)-*cis*-**14**, (−)-*cis*-**14**, (+)-*trans*-**14**, and (−)-*trans*-**14** by chiral HPLC.

The synthesis of racemic *cis*- and *trans*-ethyl derivatives **19** was achieved by a method analogous to that for **14** starting with nitropropane (Scheme 2).

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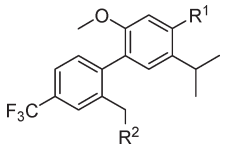
Table 1. SAR of Biphenyl-Substituted Oxazolidinones



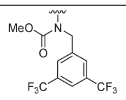
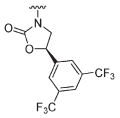
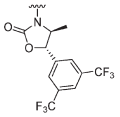
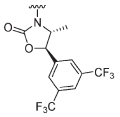
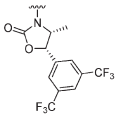
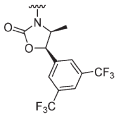
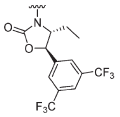
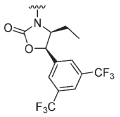
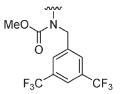
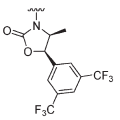
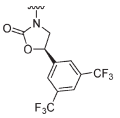
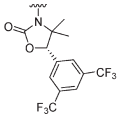
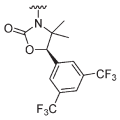
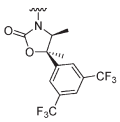
Cmpd	R^1	R^2	CE		ΔHDL-C
			IC_{50} (nM)[a]	% inhib.@ 100 μM	(mg/mL @ 10 mg/kg)[b]
1	H		126	87	15[c]
(-)-**2**	H		93.0	93	no effect
(+)-*cis*-**6**	H		39.3	94	6.3[c]
(-)-*cis*-**6**	H		5.67×10^3	90	n.m.[d]
(+)-*trans*-**14**	H		n.d.[e]	20	n.m.[d]
(-)-*trans*-**14**	H		266	90	n.m.[d]
(-)-*cis*-**14**	H		n.d.[e]	8	n.m.[d]
(+)-*cis*-**14**	H		15.2	94	22[c]
(±)-*trans*-**19**	H		n.d.[e]	49	n.m.[d]
(±)-*cis*-**19**	H		268	87	n.m.[d]
51	F		117	88	15[c]
(+)-*cis*-**3**	F		17.2	94	35[f]
(-)-**52**[g]	F		25.6	97	6.3[c]

Table 1. Continued

Cmpd	R^1	R^2	CE		ΔHDL-C
			IC_{50} (nM)[a]	% inhib.@ 100 μM	(mg/mL @ 10 mg/kg)[b]
(-)-**39**	F		n.d.[e]	21	n.m.[d]
(+)-**39**	F		17.8	94	17[c]
(+)-**44**	F		n.d.[e]	46	n.m.[d]

[a] Average of one or more 10-point titrations. [b] Transgenic mouse pharmacodynamic assay: C57BL/6 male mice 12−16 weeks of age expressing cynomolgus monkey CETP were used.[58] Predose blood samples were collected by retro-orbital bleed. Compounds were formulated in DMSO/cremophor/saline at a 4:4:92 ratio and screened at 10 mg/kg PO BID. Twenty-four hours after the first dose, the mice were euthanized and blood was collected by cardiac puncture. HDL-C was measured on the pre- and postbleed samples using a HDL-E biochemical assay kit from Wako Chemicals USA (catalogue no. 431-52501), following manufacturer's instructions. The Δ*H*DL-C reported is relative to the baseline. A change in HDL-C of 5 mg/dL or less was generally considered not significant. [c] Mean increase in HDL cholesterol in B6-Tg(CETP) mice (mean of 5 mice per dose). [d] n.m.: not measured. [e] n.d.: not determined; indicates <50% inhibition of CETP at a concentration of 100 μM. [f] Mean increase in HDL cholesterol in B6-Tg(CETP) mice (mean of 9 mice per dose). [g] This compound was synthesized using the same procedure as for compound (−)-**2**[53] by substituting boronic acid **10** for boronic acid **28**.

A more efficient synthesis of the required oxazolidinone enantiomer (−)-*cis*-**18** was developed as shown in Scheme 3. Amide **23**, conveniently accessed from carboxylic acid **24**, was initially deprotonated with an equivalent of isopropylmagnesium chloride and then treated with Grignard reagent **25** (generated by treatment of 1-iodo-3,5-bis(trifluoromethyl)benzene with ethylmagnesium bromide) to give ketone **26**.[54] Diastereoselective reduction of ketone **26** with triethylsilane in TFA afforded *syn*-alcohol **27**.[55] Treatment of this alcohol with aqueous sodium hydroxide gave oxazolidinone (−)-*cis*-**18** in enantiopure form.

Parallel SAR studies had shown that incorporation of fluorine into the anisole ring was beneficial for improving potency and pharmacokinetics. The requisite fluorine atom was incorporated at the 4-position of the biphenyl moiety as shown in Schemes 4, 5, and 6. The required boronic acid **28** was synthesized as shown in Scheme 4. Acetophenone **29** was treated with methylmagnesium bromide to afford alcohol **30**. Elimination of **30** to afford the styrene derivative **31** was effected by treatment with mesyl chloride. Alternatively, acetophenone **29** was reacted with methyltriphenylphosphonium bromide to directly afford **31**. Reduction of alkene **31** was facilitated by hydrogenation with palladium on carbon, and then iodination of the resulting product with iodine and silver sulfate afforded aryl iodide **32**. Iodide **32** was converted to boronic acid **28** by treatment with

butyllithium and trimethyl borate. Boronic acid **28** was subsequently incorporated into derivatives by one of two methods. As shown in Scheme 5, nitrile **9** was hydrolyzed to carboxylic acid **33** with KOH. This was then reduced to benzyl alcohol **34** with borane. **34** was converted to benzyl bromide **35** with triphenylphosphine and carbon tetrabromide. Benzyl bromide **35** was then coupled with oxazolidinone (−)-*cis*-**18** to afford **36**. Finally, aryl iodide **36** was coupled with boronic acid **28** to afford derivative (+)-*cis*-**3**. Alternatively, as in Scheme 6, palladium catalyzed coupling of boronic acid **28** with **34** afforded alcohol **37**, which was further converted to benzyl bromide **38** using triphenylphosphine and carbon tetrabromide. Benzyl bromide **38** was incorporated into final derivatives in a manner analogous to Scheme 1 and in the following description.

Multiple substitution of the oxazolidinone 4-position was investigated by synthesizing *gem*-dimethyl derivative **39**. This compound was synthesized by a route analogous to that shown in Scheme 3 starting with **40**, followed by separation of enantiomers by chiral HPLC (Scheme 7). Carboxylic acid **40** was first converted to aldehyde **41** via reduction of the corresponding Weinreb amide **42** with DIBAL-H. Treatment of aldehyde **41** with [3,5-bis(trifluoromethyl)phenyl]magnesium bromide (**25**) afforded racemic alcohol **43**. In situ cyclization and coupling of **43** with benzyl bromide **38** using two equivalents of NaH afforded derivatives (+)-**39** and (−)-**39**.

Compound (+)-**44** was synthesized as shown in Scheme 8. Ketone **26** was treated with methylmagnesium bromide to afford alcohol **45** with a diastereoselectivity of >98:2. Treatment of **45** with potassium hydroxide afforded oxazolidinone **46**, which was coupled with benzyl bromide **38** to afford compound (+)-**44**.

RESULTS AND DISCUSSION

The inhibition of CETP mediated CE transfer for compounds synthesized was characterized in vitro using a fluorescence transfer assay with human recombinant CETP.[56] The assay uses synthetic HDL donor particles that contain self-quenching BODIPY labeled CE along with an additional fluorescence quencher. As the BODIPY labeled CE is transferred from the donor particle to an acceptor lipoprotein by CETP, fluorescence is observed and quantified. Inhibition of CETP mediated CE transfer is characterized by a decrease in levels of fluorescence observed relative to control.

Test compounds were characterized in an in vivo pharmacodynamic assay using C57BL/6 mice that were transgenic for Cynomolgus monkey CETP (B6-Tg(CETP)UCTP20Pnu mice). Mice were prebled and HDL-C levels were measured for each mouse prior to compound dosing. Compounds were dosed at 10 mg/kg po BID at t = 0 and 7 h, and a terminal bleed was performed at t = 24 h. HDL-C levels were again measured, and a change in HDL-C levels was characterized for each animal. Five mice were dosed with each compound and a mean change in HDL-C was calculated.

The reason for the lack of efficacy of oxazolidinone **2** in vivo was not known positively, but it was postulated to be because of a poor pharmacokinetic profile. It was hypothesized that potency and pharmacokinetics could be enhanced by further conformational restriction of the compound. Substitution of the oxazolidinone core with small alkyl groups was one such idea to test this hypothesis. The first such derivatives investigated were the two methyl substituted *cis*-oxazolidinone enantiomers, (+)-*cis*-**6** and (−)-*cis*-**6**. Gratifyingly, the CE transfer inhibition potency for isomer (+)-*cis*-**6** was found to be 39 nM (isomer (−)-*cis*-**6** was inactive), and it elicited a modest increase in HDL-C levels in vivo of 6.3 mg/dL (Table 1).

Table 2. Dose Titration of Anacetrapib ((+)-*cis*-3) in B6-Tg(CETP) Mice

oral dose BID (mg/kg)	Δ*H*DL-C (mg/dL)[a]
10	35.3 ± 1.17
3	21.7 ± 1.26
1	16.4 ± 1.56
0.3	14.0 ± 1.06

[a] Transgenic mouse pharmacodynamic assay: C57BL/6 male mice 12−16 weeks of age expressing cynomolgus monkey CETP were used.[58] Predose blood samples were collected by retro-orbital bleed. Compounds were formulated in DMSO/cremophor/saline at a 4:4:92 ratio and screened at 10 mg/kg PO BID. Twenty-four hours after the first dose, the mice were euthanized and blood was collected by cardiac puncture. HDL-C was measured on the pre- and postbleed samples using a HDL-E biochemical assay kit from Wako Chemicals USA (catalogue no. 431-52501), following manufacturer's instructions. The Δ*H*DL-C reported is relative to the baseline. A change in HDL-C of 5 mg/dL or less was generally considered not significant. Mean increase in HDL cholesterol ± SEM in B6-Tg(CETP) mice (mean of 9 mice per dose).

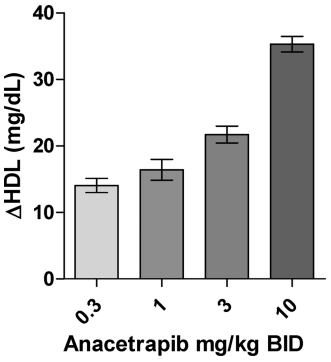


Figure 2

Incorporation of the bis-3,5-trifluoromethyl substitution pattern into the oxazolidinone phenyl ring as found in lead compound **2** was investigated next. All four possible *cis*- and *trans*-diastereoisomers **14** were synthesized, and the biological properties of these compounds are shown in Table 1. Consistent with previous compounds, the majority of the biological activity was found with *cis*-enantiomer (+)-*cis*-**14**, which had a CE transfer inhibition IC_{50} of 15 nM and increased HDL-C levels in vivo by 22 mg/dL. The active *trans*-enantiomer (−)-*trans*-**14** had the same stereoconfiguration at the oxazolidinone aryl stereocenter as that found in (+)-*cis*-**14** and was found to be approximately 10-fold less active (Table 1). Thus, it was shown that the (*S*)- and (*R*)-stereochemistries at the 4-and 5-positions respectively were very important for potent CETP inhibition.

The substitution of the oxazolidinone at the 4-position was further investigated by the synthesis of racemic ethyl derivatives **19**. This compound was found to be 10-fold less potent, indicating a low tolerance for steric bulk in this portion of the structure (Table 1).

Incorporation of a fluorine atom at the 4-position of the biphenyl moiety seemed to enhance both potency (compare

Table 3. Mean Pharmacokinetic Parameters of Anacetrapib ((+)-*cis*-3) in Mouse[a]

Cl_b[b] (mL/min/kg)	V_d[b] (L/kg)	$T_{1/2}$[b] (h)	$AUCN_{IV}$[b] (μM·h·kg/mg)	$AUCN_{PO}$[b] (μM·h·kg/mg)	C_{max}[b] (μM)	T_{max}[b] (h)	F_{oral}[b] (%)
11	2.0	3.6	2.40	0.356	0.28	1.0	15

[a] The IV doses were formulated in DMSO:PEG400:water (10:55:35. v/v/v) and injected at 0.6 mg/kg to male C57BL/6 mice. The oral doses were formulated in DMSO:cremophor:saline (2:4:94, v/v/v) and given at 2 mg/kg to mice. [b] Cl_b, blood clearance; V_d, volume of distribution; $T_{1/2}$, terminal half-life; $AUCN_{IV}$, IV normalized area under curve; $AUCN_{PO}$, PO normalized area under curve; C_{max}, observed maximal plasma concentration following oral dosing; T_{max}, time to reach the C_{max}; F_{oral}, oral bioavailability.

compounds **1** to **51** and (−)-**2** to (−)-**52**) and pharmacokinetic profile (data not shown). Incorporation of this feature into (+)-*cis*-**14** gave compound (+)-*cis*-**3**. This compound was found to inhibit CE transfer with an IC_{50} of 17 nM and elicit an increase in HDL-C levels of 28 mg/dL in the B6-Tg(CETP) mouse in vivo model.

The SAR of the 4-position of the oxazolidinone was further investigated by the synthesis of *gem*-dimethyl derivative (+)-**39**. This compound was found to have an identical IC_{50} to that of (+)-*cis*-**3** but did not elicit as great an increase in HDL-C in vivo. Further substitution of the oxazolidinone 5-position with a methyl group, affording compound (+)-**44**, completely suppressed activity.

After further investigation of the substitution of the oxazolidinone failed to yield any further enhancements in biological properties, compound (+)-*cis*-**3** was further characterized by a dose-titration in the B6-Tg(CETP) mouse in vivo model (Table 2 and Figure 2). The compound consistently increased HDL-C levels in a dose dependent manner at doses of 0.3, 1, 3, and 10 mg/kg, respectively. The pharmacokinetics of (+)-*cis*-**3** was characterized in mice (Table 3), rats and rhesus monkeys.[57] Across species, the compound was found to have a pharmacokinetic profile with moderate oral bioavailabilities, and clearances and half-lives appropriate for QD dosing. On the basis of its favorable in vitro and in vivo properties, compound (+)-*cis*-**3** was selected as a candidate for further development.

CONCLUSIONS

Further substitution of the phenyl oxazolidinone moiety of the CETP inhibitor scaffold (−)-**2**[53] was investigated. Substitution of the oxazolidinone 4-position in particular provided compounds that were potent orally active inhibitors of CETP. These compounds inhibited CETP with excellent potency and good in vivo efficacy in the B6-Tg(CETP) mouse in vivo model. Small alkyl groups were preferred as substituents at the oxazolidinone 4-position. 4-Methyl and 5-[3,5-bis(trifluoromethyl)phenyl] were the best substitutions on the oxazolidinone moiety. It was also shown that the (*S*)- and (*R*)-stereochemistries at the 4-and 5-positions respectively were very important for potent CETP inhibition. Compound (+)-*cis*-**3** was identified as the compound with the best overall profile. This compound had excellent CETP inhibition potency and good preclinical pharmacokinetic parameters and in vivo efficacy. Compound (+)-*cis*-**3** was selected for clinical study in man and was ultimately designated as anacetrapib.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were recorded on a Varian InNova 600 or 500 MHz instrument. Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel 60 F_{254} plates. All compounds were visualized as single spots using short wave UV light and/or cerium ammonium molybdate stain. Low resolution mass spectra were obtained using a liquid chromatography mass spectrometer (LCMS) that consisted of an Agilent 1100 series LC coupled to a Waters Micromass ZQ mass spectrometer (electrospray positive ionization). The LC used an Xterra C18 3.5 μM column, and compounds were analyzed using a gradient of 10% MeCN/90% water to 98% MeCN/2% water over 3.75 min and then 98% MeCN/2% water for 1 min; LC solvents contained 0.05% TFA. High-resolution mass spectra were obtained using a LTQ-Orbitrap (Thermo Fisher Scientific) with a electrospray ionization coupled with Waters Acquity UPLC. Approximately 3 μL of 10 μM samples were introduced to the mass spectrometer by an external loop using 50% MeCN/0.1% HCO_2H in water at a flow rate of 400 μL/min. Preparative chiral HPLC was performed using 20 mm × 250 mm Chiralpak columns manufactured by Daicel Chemical Industries, Ltd. Optical purity was characterized by analytical chiral HPLC with 4.6 mm × 250 mm Chiralpak or Chiralcel columns manufactured by Daicel Chemical Industries, Ltd. using a Shimadzu analytical HPLC system equipped with a Jasco CD-1595 detector. The sign of rotation was characterized as the sign observed in the CD spectrum at 235 nm. Reagents were purchased commercially and used without further purification unless otherwise stated. Final compounds were judged to be ≥95% analytically pure based on their LCMS and ^{1}H NMR spectra. Compounds gave a single LCMS peak with desired MW, and the only signals detected in the NMR corresponded to the final compound.

2-Amino-5-(trifluoromethyl)benzonitrile (8). A 2 L flask was charged with 4-amino-3-iodobenzotrifluoride (**7**) (100 g, 0.348 mol), CuCN (40 g, 0.447 mol), and DMF (750 mL). The mixture was heated at reflux for 1 h. The reaction was cooled and poured into water (3 L) containing concentrated ammonium hydroxide (300 mL). To the mixture was added CH_2Cl_2 (1 L). The mixture was then filtered through Celite. The layers were separated, and the aqueous layer was back extracted with CH_2Cl_2. The organic extracts were combined and the solvent removed under reduced pressure. The residue was dissolved in Et_2O (1.5 L), and the resulting solution was washed with 1 N ammonium hydroxide, aq sodium bisulfite, 1 N aq HCl, and brine. The solution was dried ($MgSO_4$) and filtered through a silica gel plug containing a layer of $MgSO_4$ on top. The plug was washed with Et_2O (5 L). The Et_2O solutions were combined and concentrated to 750 mL and let stand at room temperature. After 2 days, the resulting solids were collected, washed with hexanes, and dried under reduced pressure to afford 2-amino-5-(trifluoromethyl)benzonitrile (**8**) (64.8 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.58 (d, J = 8.5 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 4.80 (br s, 2H).

2-Iodo-5-(trifluoromethyl)benzonitrile (9). 2-Amino-5-(trifluoromethyl)benzonitrile (**8**) (3.06 g, 16.45 mmol) was suspended in CH_2I_2 (36 mL), and *t*-butyl nitrite (3.9 mL, 32.9 mmol) was added dropwise by syringe. The reaction was heated slowly to 100 °C and was maintained at this temperature for 30 min. The reaction mixture was cooled to room temperature, diluted with hexanes (200 mL), loaded on a silica gel column, and eluted with 100% hexanes to 15% EtOAc in hexanes gradient. The resulting product was further purified by flash chromatography (Si, 5% CH_2Cl_2 in hexanes) to afford 2-iodo-5-(trifluoromethyl)benzonitrile (**9**) (3.11 g, 64%), as a colorless solid. R_f = 0.44 (15% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz)

δ 8.10 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 1.8 Hz, 1H), 7.52 (dd, J = 8.5, 1.8 Hz, 1H).

2′-Methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-carbonitrile (11). To a solution of 2-iodo-5-(trifluoromethyl)-benzonitrile (**9**) (2.0 g, 6.7 mmol) and (5-isopropyl-2-methoxyphenyl)-boronic acid (**10**) (1.6 g, 8.4 mmol) in dimethyl ethylene glycol (30.4 mL) was added 2 M aq Na_2CO_3 (6.8 mL), ethanol (9.6 mL), and water (10 mL). The solution was degassed with nitrogen for 2 min. $(PPh_3)_4Pd$ (774 mg, 0.67 mmol) was added, and the solution was degassed with nitrogen again for 2 min. The solution was divided equally into two 40 mL microwave tubes. Each tube was degassed with nitrogen for 1 min, sealed, and placed in a microwave reactor. The wattage was set for 200 W until the temperature reached 150 °C, and then the temperature was held at 150 °C for 10 min. The tubes were then cooled to room temperature, combined, poured into water (50 mL), and extracted with EtOAc (100 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 15% CH_2Cl_2 in hexanes) to afford 2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-carbonitrile (**11**) (2.14 g, 98%), as a light-yellow oil. R_f = 0.65 (25% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.31 (dd, J = 8.5, 2.0 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 3.82 (s, 3H), 2.93 (m, 1H), 1.27 (d, J = 7.0 Hz, 6H).

2′-Methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-carboxylic acid (12). A solution of 2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-carbonitrile (**11**) (727 mg, 2.28 mmol) and KOH (767 mg, 13.7 mmol) in water (7.70 mL) and *i*-PrOH (11.55 mL) was subjected to microwave irradiation (300 W, 130 °C, 4 h) in a sealed tube. The reaction mixture was concentrated in vacuo to remove the *i*-PrOH. The aqueous slurry obtained was diluted with water (50 mL) and extracted with EtOAc (50 mL). The organic extract was dried (Na_2SO_4) and concentrated in vacuo to afford byproduct 5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-carboxamide. The aqueous layer was acidified with concentrated HCl and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give 2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-carboxylic acid (**12**) (335.2 mg, 43%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.04 (s, 1H), 6.77 (d, J = 8.1 Hz, 1H), 3.68 (s, 3H), 2.84 (septet, J = 6.7 Hz, 1H), 1.19 (d, J = 6.7 Hz, 6H).

[2′-Methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methanol (13). A solution of borane in THF (1 M, 2.98 mL, 2.98 mmol) was added dropwise to a stirred solution of 2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-carboxylic acid (**12**) (335.2 mg, 0.992 mmol) in dry THF (10.5 mL) at room temperature under N_2. The reaction was stirred overnight at room temperature and carefully quenched with water (10 mL). The mixture was extracted with EtOAc (3 × 20 mL), and the combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 25 mm × 160 mm, 0−30% EtOAc in hexanes gradient) to afford [2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methanol (**13**) (268.5 mg, 83%), as a colorless oil. R_f = 0.27 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.62 (dd, J = 8.0, 1.3 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.29 (dd, J = 8.5, 2.3 Hz, 1H), 7.03 (d, J = 2.3 Hz, 1H), 6.96 (d, J = 8.5, 1H), 4.51 (m, 2H), 3.74 (s, 3H), 2.93 (septet, J = 7.0 Hz, 1H), 2.51 (s, 1H), 1.29 (d, J = 7.0 Hz, 6H).

2-(Bromomethyl)-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl (5). CBr_4 (112 mg, 0.211 mmol) and Ph_3P (55 mg, 0.211 mmol) were added successively to a stirred solution of [2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methanol (**13**) (57.1 mg, 0.176 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C under N_2. The solution was stirred at room temperature for 1 h, and the reaction mixture was concentrated in vacuo to afford the crude product. This was purified by flash chromatography (Si, 12 mm × 160 mm, 0−20% EtOAc in hexanes gradient) to give 2-(bromomethyl)-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl (**5**) (68.6 mg, quantitative yield) as a colorless oil. R_f = 0.95 (20% EtOAc/hexanes). LCMS calcd = 387.05; found = 387.0 $(M + H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.60 (dd, J = 8.0, 1.3 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.29 (dd, J = 8.5, 2.3 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.95 (d, J = 8.5, 1H), 4.45 (d, J = 10.6 Hz, 1H), 4.33 (d, J = 10.6 Hz, 1H), 3.76 (s, 3H), 2.94 (septet, J = 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H).

(+)-(4*S*,5*R*)-3-{[2′-Methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-5-phenyl-1,3-oxazolidin-2-one ((+)-6). Sodium bis(trimethylsilyl)amide (115 μL of a 1 M solution in THF, 0.115 mmol) was added to a stirred solution of (4*S*,5*R*)-4-methyl-5-phenyl-1,3-oxazolidin-2-one ((−)-**4**) (18.5 mg, 0.104 mmol) in dry THF (1 mL) at room temperature under N_2. The reaction was stirred for 15 min and a solution of 2-(bromomethyl)-5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl (**5**) (20.2 mg, 0.0522 mmol) in dry THF (2 mL) was added via cannula. The reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 mm × 160 mm, 0−40% EtOAc in hexanes gradient) to afford (+)-(4*S*,5*R*)-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-5-phenyl-1,3-oxazolidin-2-one ((+)-**6**) (16.1 mg, 63%) as a colorless oil. R_f = 0.45 (20% EtOAc/hexanes). LCMS calcd = 484.21; found = 484.2 $(M + H)^+$. ^{1}H NMR (500 MHz, benzene-d_6, 1:1 mixture of atropisomers) δ 7.99 (s, 0.5H), 7.77 (s, 0.5H), 7.35 (d, J = 7.7 Hz, 1H), 7.12−6.95 (m, 5H), 6.94−6.86 (m, 3H), 6.64 (d, J = 8.5 Hz, 0.5H), 6.55 (d, J = 8.5 Hz, 0.5H), 4.97−4.75 (m, 2H), 4.06 (d, J = 15.8 Hz, 0.5H), 3.95 (d, J = 15.9 Hz, 0.5H), 3.36 (s, 1.5H), 3.23−3.16 (m, 2H), 3.15−3.06 (m, 0.5H), 2.79−2.68 (m, 1H), 1.20−1.14 (m, 6H), 0.09 (d, J = 6.5 Hz, 1.5H), 0.03 (d, J = 6.5 Hz, 1.5H). HRMS (ES^+) calcd for $C_{28}H_{29}F_3NO_3$ $(M + H)^+$ *m*/*e*, 484.2094; found, 484.2081.

(−)-(4*R*,5*S*)-3-{[2′-Methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-5-phenyl-1,3-oxazolidin-2-one ((−)-6). Sodium bis(trimethylsilyl)amide (105 μL of a 1 M solution in THF, 0.105 mmol) was added to a stirred solution of (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidin-2-one ((+)-**4**) (16.8 mg, 0.0950 mmol) in dry THF (1 mL) at room temperature under N_2. The reaction was stirred for 15 min, and a solution of 2-(bromomethyl)-5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl (**5**) (18.4 mg, 0.0475 mmol) in dry THF (2 mL) was added via cannula. The reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 mm × 160 mm, 0−40% EtOAc in hexanes gradient) to afford (−)-(4*R*,5*S*)-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-5-phenyl-1,3-oxazolidin-2-one ((−)-**6**) (12.7 mg, 55%) as a colorless oil. R_f = 0.45 (20% EtOAc/hexanes). LCMS calcd = 484.21; found = 484.2 $(M + H)^+$. ^{1}H NMR (500 MHz, benzene-d_6, 1:1 mixture of atropisomers) δ 7.99 (s, 0.5H), 7.77 (s, 0.5H), 7.35 (d, J = 7.6 Hz, 1H), 7.12−6.95 (m, 5H), 6.94−6.86 (m, 3H), 6.64 (d, J = 8.5 Hz, 0.5H), 6.55 (d, J = 8.5 Hz, 0.5H), 4.96−4.75 (m, 2H), 4.06 (d, J = 15.8 Hz, 0.5H), 3.95 (d, J = 15.9 Hz, 0.5H), 3.36 (s, 1.5H), 3.34−3.03 (m, 2H), 3.16−3.07 (m, 0.5H), 2.79−2.68 (m, 1H), 1.20−1.14 (m, 6H), 0.09 (d, J = 6.5 Hz, 1.5H), 0.03 (d, J = 6.5 Hz, 1.5H). HRMS (ES^+) calcd for $C_{28}H_{29}F_3NO_3$ $(M + H)^+$ *m*/*e*, 484.2094; found, 484.2083.

1-[3,5-Bis(trifluoromethyl)phenyl]-2-nitropropan-1-ol (16). A stirred solution of 3,5-bis(trifluoromethyl)benzaldehyde (**15**) (1.00 g, 4.13 mmol) and nitroethane (1.13 g, 1.08 mL, 15.1 mmol) in absolute EtOH (20 mL) at 0 °C was treated with 10% (m/v) aq NaOH (1.73 mL, 4.34 mmol), stirred for 1 h, and treated with 2% (m/v) aq acetic acid (13.0 mL, 4.34 mmol). The reaction was stirred for 1 h at room temperature and then partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with saturated aq $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a 1.5:1 mixture of *trans*- and *cis*-1-[3,5-bis(trifluoromethyl)-phenyl]-2-nitropropan-1-ol (**16**) (1.30 g, 99%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) *trans*-diastereoisomer: δ 7.88 (br s, 1H), 7.86 (br s, 2H), 5.22 (d, J = 8.4 Hz, 1H), 4.77 (dq, J = 8.4, 6.9 Hz, 1H), 3.03 (br s 1H), 1.42 (d, J = 6.9 Hz, 3H); *cis*-diastereoisomer: δ 7.90 (br s, 1H), 7.86 (br s, 2H), 5.59 (d, J = 3.2 Hz, 1H), 4.72 (dq, J = 3.2, 6.9 Hz, 1H), 3.03 (br s 1H), 1.50 (d, J = 6.9 Hz, 3H).

2-Amino-1-[3,5-bis(trifluoromethyl)phenyl]propan-1-ol (17). A suspension of Raney nickel (50 mg) in a solution of a 1.5:1 mixture of *trans*- and *cis*-1-[3,5-bis(trifluoromethyl)phenyl]-2-nitropropan-1-ol (**16**) (50 mg, 0.158 mmol) in 30% (v/v) aq HCO_2H (0.75 mL) and MeOH (10 mL) was stirred overnight at room temperature under H_2 (15 psi). The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to remove the MeOH. The aqueous slurry was adjusted to pH 9−10 with 28% aq NH_4OH, diluted with water (20 mL), and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a 1.5:1 mixture of *trans*- and *cis*-2-amino-1-[3,5-bis(trifluoromethyl)phenyl]propan-1-ol (**17**) (39.1 mg, 86%) as a colorless solid. LCMS calcd = 288.08; found = 288.1 $(M + H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) *trans*-diastereoisomer: δ 7.79 (br s, 3H), 4.35 (br s, 1H), 3.25 (br s, 1H), 2.59 (br s, 3H), 0.86 (d, J = 6.1 Hz, 3H); *cis*-diastereoisomer: δ 7.79 (br s, 3H), 4.71 (br s, 1H), 3.00 (br s, 1H), 2.59 (br s, 3H), 1.06 (d, J = 5.0 Hz, 3H).

5-[3,5-Bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (18). Diisopropylethylamine (106 mg, 142 μL, 0.817 mmol) and triphosgene (20.2 mg, 0.068 mmol) were added successively to a stirred solution of a 1.5:1 mixture of *trans*- and *cis*-2-amino-1-[3,5-bis(trifluoromethyl)phenyl]propan-1-ol (**17**) (39.1 mg, 0.136 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C under N_2. The reaction was stirred at 0 °C for 1 h and then concentrated in vacuo to a volume of about 5 mL. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 mm × 160 mm, 0−70% EtOAc in hexanes gradient) to afford *trans*-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one ((±)-*trans*-**18**) (17.5 mg) and *cis*-5-[3,5-bis-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one ((±)-*cis*-**18**) (14.4 mg) (overall yield 75%), as colorless solids. *trans*-Diastereoisomer: R_f = 0.63 (50% EtOAc/hexanes). LCMS calcd = 314.06; found = 314.1 $(M + H)^+$. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.83 (br s, 2H), 6.71 (br s, 1H), 5.17 (d, J = 7.0 Hz, 1H), 3.86 (br pentet, J = 6.2 Hz, 1H), 1.48 (d, J = 6.2 Hz, 1H). *cis*-diastereoisomer: R_f = 0.38 (50% EtOAc/hexanes). LCMS calcd = 314.06; found =314.1 $(M + H)^+$. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.79 (br s, 2H), 5.83 (d, J = 8.0 Hz, 1H), 5.34 (br s, 1H), 4.31 (br pentet, J = 7.0 Hz, 1H), 0.84 (d, J = 6.6 Hz, 1H). This compound was separated into its enantiomers (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one ((−)-*cis*-**18**) and (4*R*,5*S*)-5-[3,5-bistrifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one ((+)-*cis*-**18**) using chiral HPLC (AS column, 20 mm × 250 mm, 15% *i*-PrOH in heptane).

(−)-(4*R*,5*S*)-5-[3,5-Bis(trifluoromethyl)phenyl]-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((−)-*cis*-14) and (+)-(4*S*,5*R*)-5-[3,5-Bis(trifluoromethyl)phenyl]-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((+)-*cis*-14). Sodium bis(trimethylsilyl)amide (172 μL of a 1 M solution in THF, 0.172 mmol) was added to a stirred solution of *cis*-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one ((±)-*cis*-**18**) (50 mg, 0.129 mmol) in dry THF (1 mL) at room temperature under N_2. The reaction was stirred for 15 min, and a solution of 2-(bromomethyl)-5′-isopropyl-2′-methoxy-4-(trifluoromethyl)-biphenyl (**5**) (27.0 mg, 0.0861 mmol) in dry THF (2 mL) was added via cannula. The reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 mm × 160 mm, 0−40% EtOAc in hexanes gradient) to afford *cis*-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((±)-*cis*-**14**) (40.8 mg, 76%) as a colorless oil. R_f = 0.64 (20% EtOAc/hexanes). LCMS calcd = 620.18; found = 620.2 $(M + H)^+$. ^{1}H NMR (600 MHz, benzene-d_6, 1:1 mixture of atropisomers) δ 7.94 (s, 0.5H), 7.72 (s, 0.5H), 7.64 (s, 0.5H), 7.63 (s, 0.5H), 7.39−7.34 (m, 3H), 7.12−7.04 (m, 2H), 6.95 (d, J = 2.1 Hz, 0.5H), 6.86 (d, J = 1.7 Hz, 0.5H), 6.64 (d, J = 8.5 Hz, 0.5H), 6.56 (d, J = 8.5 Hz, 0.5H), 4.99 (d, J = 15.9 Hz, 0.5H), 4.93 (d, J = 15.9 Hz, 0.5H), 4.73 (d, J = 7.9 Hz, 0.5H), 4.61 (d, J = 7.9 Hz, 0.5H), 3.88 (d, J = 15.9 Hz, 0.5H), 3.82 (d, J = 15.9 Hz, 0.5H), 3.35 (s, 1.5H), 3.24 (s, 1.5H), 3.05 (septet, J = 6.9 Hz, 0.5H), 3.01 (septet, J = 6.9 Hz, 0.5H), 2.75 (m, 1H), 1.19 (dd, J = 6.9, 2.7 Hz, 3H), 1.17 (dd, J = 10.9, 6.9 Hz, 3H), −0.18 (d, J = 6.4 Hz, 1.5H), −0.33 (t, J = 6.4 Hz, 1.5H). This compound was separated into its enantiomers (−)-(4*R*,5*S*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((−)-*cis*-**14**) (HRMS (ES^+) calcd for $C_{30}H_{27}F_9NO_3$ $(M + H)^+$ m/e, 620.1842; found, 620.1823) and (+)-(4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((+)-*cis*-**14**) (HRMS (ES^+) calcd for $C_{30}H_{27}F_9NO_3$ $(M + H)^+$ m/e, 620.1842; found, 620.1826) using chiral HPLC (AD column, 20 mm × 250 mm, 3% *i*-PrOH in heptane).

(+)-(4*S*,5*S*)-5-[3,5-Bis(trifluoromethyl)phenyl]-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((+)-*trans*-14) and (−)-(4*R*,5*R*)-5-[3,5-Bis(trifluoromethyl)phenyl]-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((−)-*trans*-14). Sodium bis(trimethylsilyl)amide (112 μL of a 1 M solution in THF, 0.112 mmol) was added to a stirred solution of *trans*-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one ((±)-*trans*-**18**) (17.5 mg, 0.0559 mmol) in dry THF (1 mL) at room temperature under N_2. The reaction was stirred for 15 min, and a solution of 2-(bromomethyl)-5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl (**5**) (32.0 mg, 0.0838 mmol) in dry THF (2 mL) was added via cannula. The reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 mm × 160 mm, 0−50% EtOAc in hexanes gradient) to afford *trans*-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((±)-*trans*-**14**) (30.2 mg, 87%) as a colorless oil. R_f = 0.46 (20% EtOAc/hexanes). LCMS calcd = 620.18; found = 620.2 $(M + H)^+$. ^{1}H NMR (600 MHz, benzene-d_6, 1:1 mixture of atropisomers) δ 7.83 (s, 0.5H), 7.80 (s, 0.5H), 7.70 (s, 1H), 7.52 (s, 1H), 7.49 (s, 1H), 7.31−7.24 (m, 1H), 7.12−7.07 (m, 1H), 7.04 (d, J = 8.0 Hz, 0.5H), 7.00 (d, J = 7.9 Hz, 0.5H), 6.88−6.87 (m, 1H), 6.61 (d, J = 8.5 Hz, 0.5H), 6.58 (d, J = 8.5 Hz,

0.5H), 4.72 (d, J = 16.3 Hz, 0.5H), 4.44 (d, J = 16.3 Hz, 0.5H), 4.30−4.22 (m, 1.5H), 4.05 (d, J = 16.3 Hz, 0.5H), 3.23 (s, 1.5H), 3.20 (s, 1.5H), 2.79−2.72 (m, 1.5H), 2.74−2.67 (m, 0.5H), 1.20−1.17 (m, 6H), 0.42−0.37 (m, 3H). This compound was separated into its enantiomers (+)-(4*S*,5*S*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((+)-*trans*-**14**) (HRMS (ES^+) calcd for $C_{30}H_{27}F_9NO_3$ $(M + H)^+$ *m/e*, 620.1842; found, 620.1824) and (−)-(4*R*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((−)-*trans*-**14**) (HRMS (ES^+) calcd for $C_{30}H_{27}F_9NO_3$ $(M + H)^+$ *m/e*, 620.1842; found, 620.1825) using chiral HPLC (AD column, 20 mm × 250 mm, 3% *i*-PrOH in heptane).

1-[3,5-Bis(trifluoromethyl)phenyl]-2-nitrobutan-1-ol (20). A stirred solution of 3,5-bis(trifluoromethyl)benzaldehyde (**15**) (1.00 g, 4.13 mmol) and nitropropane (1.34 g, 1.08 mL, 15.1 mmol) in absolute EtOH (20 mL) at 0 °C was treated with 10% aq NaOH (m/v) (1.73 mL, 4.34 mmol), stirred for 1 h, and treated with 2% (m/v) aq acetic acid (13.0 mL, 4.34 mmol). The reaction was stirred for 1 h at room temperature and then partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with saturated aq $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a 2:1 mixture of *trans*- and *cis*-1-[3,5-bis(trifluoromethyl)-phenyl]-2-nitrobutan-1-ol (**20**) (1.33 g, 97%), as a colorless oil. ^1H NMR (600 MHz, $CDCl_3$) *trans*-diastereoisomer: δ 7.89 (br s, 1H), 7.86 (br s, 2H), 5.20 (d, J = 8.5 Hz, 1H), 4.63−4.56 (m, 1H), 3.14 (br s 1H), 1.98−1.87 (m, 1 H), 1.51−1.43 (m, 1 H), 0.92 (t, J = 7.3 Hz, 3H); *cis*-diastereoisomer: δ 7.89 (br s, 1H), 7.86 (br s, 2H), 5.36 (d, J = 4.3 Hz, 1H), 4.63−4.56 (m, 1H), 3.14 (br s 1H), 2.22−2.13 (m, 1 H), 1.83−1.75 (m, 1 H), 0.94 (t, J = 7.3 Hz, 3H).

2-Amino-1-[3,5-bis(trifluoromethyl)phenyl]butan-1-ol (21). A suspension of Raney nickel (500 mg) in a solution of a 2:1 mixture of *trans*- and *cis*-1-[3,5-bis(trifluoromethyl)phenyl]-2-nitrobutan-1-ol (**20**) (1,22 g, 3.68 mmol) in 30% (v/v) aq HCO_2H (3.75 mL) and MeOH (50 mL) was stirred overnight at room temperature under H_2 (15 psi). The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to remove the MeOH. The aqueous slurry was adjusted to pH 9−10 with 28% aq NH_4OH, diluted with water (50 mL), and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a 2:1 mixture of *trans*- and *cis*-2-amino-1-[3,5-bis(trifluoromethyl)-phenyl]butan-1-ol (**21**) (1.04 g, 94%) as a colorless solid. LCMS calcd = 302.10; found = 302.1 $(M + H)^+$. ^1H NMR (600 MHz, $CDCl_3$) *trans*-diastereoisomer: δ 7.80 (br s, 3H), 4.43 (d, J = 5.8 Hz, 1H), 2.75−2.71 (m, 1H), 1.57−1.49 (m, 1 H), 1.37−1.24 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H); *cis*-diastereoisomer: δ 7.80 (br s, 3H), 4.74 (d, J = 4.3 Hz, 1H), 3.02−2.98 (m, 1H), 1.37−1.24 (m, 1H), 1.07 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H).

5-[3,5-Bis(trifluoromethyl)phenyl]-4-ethyl-1,3-oxazolidin-2-one (22). Diisopropylethylamine (2.68 g, 3.61 mL, 20.7 mmol) and triphosgene (513 mg, 1.73 mmol) were added successively to a stirred solution of 2:1 mixture of *trans*- and *cis*-2−2-amino-1-[3,5-bis(trifluoromethyl)phenyl]butan-1-ol (**21**) (1.04 g, 3.46 mmol) in dry CH_2Cl_2 (220 mL) at 0 °C under N_2. The reaction was stirred at 0 °C for 2 h then concentrated in vacuo to a volume of about 5 mL. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 40 mm × 160 mm, 0−70% EtOAc in hexanes gradient) to afford *trans*-5-[3,5-bis(trifluoromethyl)phenyl]-4-ethyl-1,3-oxazolidin-2-one ((±)-*trans*-**22**) (561 mg) and *cis*-5-[3,5-bis(trifluoromethyl)-phenyl]-4-ethyl-1,3-oxazolidin-2-one ((±)-*cis*-**22**) (315.7 mg) (overall yield 78%) as colorless solids. *trans*-diastereoisomer: R_f = 0.80 (50% EtOAc/hexanes). LCMS calcd = 328.08; found = 328.1 $(M + H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.81 (s, 2H), 7.16 (s, 1H), 5.25 (d, J = 6.1 Hz, 1H), 3.69 (q, J = 6.2 Hz, 1H), 1.90−1.70 (m, 2H), 1.09−1.02 (m, 3H). *cis*-diastereoisomer: R_f = 0.49 (50% EtOAc/hexanes). LCMS calcd = 328.08; found = 328.1 $(M + H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.78 (s, 2H), 7.14 (s, 1H), 5.84 (d, J = 8.3 Hz, 1H), 4.11−4.05 (m, 1H), 1.08−0.94 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H).

(±)-*cis*-5-[3,5-Bis(trifluoromethyl)phenyl]-4-ethyl-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]-methyl}-1,3-oxazolidin-2-one (19). Sodium bis(trimethylsilyl)amide (138 μL of a 1 M solution in THF, 0.138 mmol) was added to a stirred solution of (±)-*cis*-5-[3,5-bis(trifluoromethyl)phenyl]-4-ethyl-1,3-oxazolidin-2-one ((±)-*cis*-**22**) (23.0 mg, 0.0689 mmol) in dry THF (1 mL) at room temperature under N_2. The reaction was stirred for 15 min, and a solution of 2-(bromomethyl)-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl (**5**) (40.0 mg, 0.0838 mmol) in dry THF (2 mL) was added via cannula. The reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 mm × 160 mm, 0−40% EtOAc in hexanes gradient) to afford (±)-*cis*-5-[3,5-bis(trifluoromethyl)phenyl]-4-ethyl-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-1,3-oxazolidin-2-one ((±)-*cis*-**19**) (22.6 mg, 51%) as a colorless oil. R_f = 0.53 (20% EtOAc/hexanes). LCMS calcd = 634.20; found = 634.2 $(M + H)^+$. ^1H NMR (500 MHz, benzene-d_6, 1:1 mixture of atropisomers) δ 7.95 (s, 0.5H), 7.69 (s, 0.5H), 7.61 (s, 1H), 7.44 (s, 1H), 7.42 (s, 1H), 7.38 (s, 0.5H), 7.36 (s, 0.5H), 7.13−7.05 (m, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 2.4 Hz, 0.5H), 6.87 (d, J = 2.3 Hz, 0.5H), 6.62 (d, J = 8.5 Hz, 0.5H), 6.52 (d, J = 8.5 Hz, 0.5H), 5.00 (d, J = 8.3 Hz, 0.5H), 4.97 (d, J = 8.1 Hz, 0.5H), 4.70 (d, J = 7.9 Hz, 0.5H), 4.57 (d, J = 7.8 Hz, 0.5H), 3.94 (d, J = 15.8 Hz, 0.5H), 3.90 (d, J = 15.7 Hz, 0.5H), 3.38 (s, 1.5H), 3.18 (s, 1.5H), 2.99−2.88 (m, 1H), 2.78−2.68 (m, 1H), 1.19−1.14 (m, 6H), 0.62−0.30 (m, 2H), −0.04 (t, J = 7.4 Hz, 1.5H), −0.12 (t, J = 7.4 Hz, 1.5H). HRMS (ES^+) calcd for $C_{31}H_{29}F_9NO_3$ $(M + H)^+$ *m/e*, 634.1998; found, 634.1974.

(±)-*trans*-5-[3,5-Bis(trifluoromethyl)phenyl]-4-ethyl-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]-methyl}-1,3-oxazolidin-2-one (19). Sodium bis(trimethylsilyl)-amide (138 μL of a 1 M solution in THF, 0.138 mmol) was added to a stirred solution of (±)-*trans*-5-[3,5-bis(trifluoromethyl)phenyl]-4-ethyl-1,3-oxazolidin-2-one ((±)-*trans*-**19**) (23.0 mg, 0.0689 mmol) in dry THF (1 mL) at room temperature under N_2. The reaction was stirred for 15 min, and a solution of 2-(bromomethyl)-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl (**5**) (40.0 mg, 0.0838 mmol) in dry THF (2 mL) was added via cannula. The reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 mm × 160 mm, 0−40% EtOAc in hexanes gradient) to afford (±)-*trans*-5-[3,5-bis(trifluoromethyl)phenyl]-4-ethyl-3-{[2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]-methyl}-1,3-oxazolidin-2-one ((±)-*trans*-**19**) (41.4 mg, 93%) as a colorless oil. R_f = 0.41 (20% EtOAc/hexanes). LCMS calcd = 634.20; found = 634.2 $(M + H)^+$. ^1H NMR (500 MHz, benzene-d_6, 1:1 mixture of atropisomers) δ 7.75 (s, 0.5H), 7.70 (s, 1.5H), 7.55−7.51 (m, 2H), 7.27−7.20 (m, 1H), 7.09−7.05 (m, 1H), 7.00 (d, J = 8.0 Hz, 0.5H), 6.97 (d, J = 8.0 Hz, 0.5H), 6.90−6.78 (m, 1H), 6.56 (d, J = 8.5 Hz, 0.5H), 6.53 (d, J = 8.5 Hz, 0.5H), 4.97 (d, J = 16.2 Hz, 0.5H), 4.54−4.44 (m, 1.5H), 4.24 (d, J = 16.2 Hz, 0.5H), 3.94 (d, J = 16.2 Hz, 0.5H), 3.18 (s, 1.5H), 3.15 (s, 1.5H), 2.92−2.81 (m, 1H), 2.77−2.69 (m, 1H), 1.19−1.15 (m, 6 H), 0.92−0.78 (m, 2H), 0.29−0.24 (m, 3H). HRMS (ES^+) calcd for $C_{31}H_{29}F_9NO_3$ $(M + H)^+$ *m/e*, 634.1998; found, 634.1995.

Benzyl {(2*S*)-1-[Methoxy(methyl)amino]-1-oxopropan-2-yl}carbamate (23). *N*-Methylmorpholine (5.66 g, 6.16 mL, 56.0 mmol) and isobutyl chloroformate (3.82 g, 3.66 mL, 28.0 mmol) were added successively to a stirred solution of *N*-[(benzyloxy)carbonyl]-L-alanine (**24**) (5.00 g, 22.4 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C under N_2. The resulting cloudy mixture was stirred for 15 min at 0 °C. *N*,*O*-Dimethylhydroxylamine hydrochloride (2.62 g, 26.9 mmol) was added portionwise, and the reaction was warmed to room temperature and stirred for 3 h. The reaction was poured into 1 N aq HCl (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 40 mm × 160 mm, 0−70% EtOAc in hexanes gradient) to afford benzyl {(2*S*)-1-[methoxy(methyl)-amino]-1-oxopropan-2-yl}carbamate (**23**) (5.80 g, 99%) as a colorless solid. R_f = 0.53 (50% EtOAc/hexanes). LCMS calcd = 267.13; found = 267.3 $(M + H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 5.59 (d, *J* = 8.5 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 5.07 (d, *J* = 12.3 Hz, 1H), 4.74 (t, *J* = 7.8 Hz, 1H), 3.77 (s, 3H), 3.20 (s, 3H), 1.34 (d, *J* = 6.9 Hz, 3H).

Benzyl {(2*S*)-1-[3,5-Bis(trifluoromethyl)phenyl]-1-oxopropan-2-yl}carbamate (26). A solution of isopropyl magnesium chloride (1.84 mL of a 2 M solution in THF, 3.68 mmol) was added dropwise to a stirred solution of benzyl {(2*S*)-1-[methoxy(methyl)-amino]-1-oxopropan-2-yl}carbamate (**23**) (1.00 g, 3.76 mmol) in dry THF (4.8 mL) at −15 °C under N_2. The reaction was stirred at −15 °C for 15 min, and then a solution of 3,5-bis(trifluoromethyl)phenyl magnesium bromide (**25**) (prepared by added ethyl magnesium bromide (5.63 mL of a 1 M soln in THF, 5.63 mmol) to a stirred solution of 1-iodo-3,5-bis(trifluoromethyl)benzene (2.11 g, 1.10 mL, 6.20 mmol) in dry THF (3 mL) at room temperature under N_2 and stirring for 25 min) in dry THF was added dropwise via cannula. The reaction was allowed to warm to room temperature and was stirred for 45 min. After this time, additional 3,5-bis(trifluoromethyl)phenyl magnesium bromide (**25**) (prepared by added ethyl magnesium bromide (2.82 mL of a 1 M solution in THF, 2.82 mmol) to a stirred solution of 1-iodo-3,5-bis(trifluoromethyl)benzene (1.05 g, 0.55 mL, 3.10 mmol) in dry THF (1.5 mL) at room temperature under N_2 and stirring for 25 min) in THF was generated and added at 0 °C. After stirring for 2 h at room temperature, the reaction was quenched with 1 N aq HCl (20 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 40 mm × 160 mm, 0−20% EtOAc in hexanes gradient) to afford benzyl {(2*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-1-oxopropan-2-yl}carbamate (**26**) (1.30 g, 83%) as a colorless solid. R_f = 0.27 (10% EtOAc/hexanes). LCMS calcd = 420.10; found = 420.2 $(M + H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 2H), 8.12 (s, 1H), 7.38−7.30 (m, 5H), 5.79 (d, *J* = 7.6 Hz, 1H), 5.42−5.33 (m, 1H), 5.15 (s, 2H), 1.48 (d, *J* = 7.2 Hz, 3H).

(4*S*,5*R*)-5-[3,5-Bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one ((−)-*cis*-18). A solution of benzyl {(2*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-1-oxopropan-2-yl}carbamate (**26**) (1.30 g, 3.10 mmol) and dimethylphenylsilane (507 mg, 570 μL, 3.72 mmol) in trifluororoacetic acid (5 mL) was stirred at 0 °C under N_2 for 5 h. The reaction was quenched with saturated aq $NaHCO_3$ (~50 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to afford benzyl {(1*R*,2*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-1-hydroxypropan-2-yl}carbamate (**27**) as a colorless oil. LCMS calcd = 422.12; found = 422.1 $(M + H)^+$. A solution of this compound in 7.5 N aq KOH (22 mL), MeOH (45 mL), and THF (89 mL) was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo to remove the majority of organic solvents, and the resulting aqueous slurry was acidified with 1 N aq HCl and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 40 mm × 160 mm, 0−100% EtOAc in hexanes gradient) to afford (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one ((−)-*cis*-**18**) (660 mg, 68%) as a colorless solid. R_f = 0.33 (50% EtOAc/hexanes). LCMS calcd = 314.06; found = 314.2 $(M + H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.78 (s, 2H), 6.33 (s, 1H), 5.82 (d, *J* = 8.0 Hz, 1H), 4.36−4.27 (m, 1H), 0.83 (d, *J* = 6.6 Hz, 3H).

2-(2-Fluoro-4-methoxyphenyl)propan-2-ol (30). A solution of MeMgBr (2.4 M in THF, 11.6 mmol, 27.8 mmol) was added to a solution of 2′-fluoro-4′-methoxyacetophenone (**29**) (4.45 g, 26.5 mmol) in dry THF (50 mL) at 0 °C under N_2. The mixture was stirred at 0 °C and then at room temperature for 4 h. The reaction was quenched with saturated aq NH_4Cl. The resulting mixture was extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 20% EtOAc in hexanes) to afford 2-(2-fluoro-4-methoxyphenyl)propan-2-ol (**30**) (3.89 g, 80%), as an oil.

2-Fluoro-1-isopropenyl-4-methoxybenzene (31). MsCl (1.95 mL, 25.4 mmol) and Et_3N (6.52 mL, 46.5 mmol) were added successively to a solution of 2-(2-fluoro-4-methoxyphenyl)propan-2-ol (**30**) (3.89 g, 21.14 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C under N_2. The resulting solution was stirred at 0 °C and then at room temperature for 2 h. The solution was diluted with CH_2Cl_2 (100 mL), washed with water, dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 10% EtOAc in hexanes) to afford 2-fluoro-1-isopropenyl-4-methoxybenzene (**31**) (1.96 g, 56%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, *J* = 9.0 Hz, 1H), 6.68 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.63 (dd, *J* = 13, 2.5 Hz,1H), 5.20 (d, *J* = 17.0 Hz, 2H), 3.82 (s, 3H), 2.18 (s, 3H). Alternate method: A solution of sodium bis(trimethylsilyl)-amide (1.0 M in THF, 714 mL, 0.714 mmol) was added to a suspension of methyltriphenylphosphonium bromide (255 g, 0.714 mmol) in dry THF (2.50 L) cooled with an ice bath. The resultant yellow-colored suspension was stirred for 30 min at ice bath temperature and then cooled to −78 °C. A solution of 2-fluoro-4-methoxyacetophenone (**29**) (100 g, 0.595 mmol) in THF (200 mL) was added dropwise, and the resulting mixture was stirred at −78 °C for 1.5 h. The reaction mixture was allowed to warm to room temperature over 1 h and then quenched with AcOH (~80 mL, pH ~7). The mixture was stirred for 30 min, concentrated to a slush, diluted with hexane/EtOAc (7:2), and allowed to stand overnight. Solids were removed by filtration, and the filtrate was concentrated in vacuo to give yellow oil. This was purified by flash chromatography (Si, 10% EtOAc in hexanes) to afford 2-fluoro-1-isopropenyl-4-methoxybenzene (**31**) (62.30 g, 63%) as an oil.

1-Fluoro-4-iodo-2-isopropyl-5-methoxybenzene (32). A solution of 2-fluoro-1-isopropenyl-4-methoxybenzene (**31**) (1.96 g, 11.81 mmol) in MeOH (30 mL) was charged with hydrogen at 1 atm with catalytic amount of 10% Pd/C. The mixture was stirred at room temperature for 1 h. The mixture was filtered through a plug of Celite. The filtrate obtained was added to a mixture of Ag_2SO_4 (3.68 g, 11.81 mmol) and I_2 (3.00 g, 11.81 mmol) in MeOH (10 mL), and the resulting mixture was stirred at room temperature for 3 h until the color of the solution became light yellow. The mixture was filtered, and the filtrate was concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 5% EtOAc in hexanes) to afford 1-fluoro-4-iodo-2-isopropyl-5-methoxybenzene (**32**) (2.60 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 12.5 Hz, 1H), 3.90 (s, 3H), 3.18 (m, 1H), 1.28 (m, 6H).

(4-Fluoro-5-isopropyl-2-methoxyphenyl)boronic Acid (28). *n*-BuLi (4.26 mL of a 2.5 M solution in hexanes, 10.65 mmol) was added dropwise to a solution of 1-fluoro-4-iodo-2-isopropyl-5-methoxybenzene (**32**) (2.61 g, 8.88 mmol) in dry THF at −78 °C

under N_2. The resulting solution was stirred at −78 °C for 30 min. $(MeO)_3B$ (2.98 mL, 26.6 mmol) was added, and the solution was stirred at −78 °C for 3 h. The reaction was quenched at −78 °C with saturated aq NH_4Cl, and the mixture was warmed to room temperature. The mixture was extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (**28**) (1.13 g, 60%) as a colorless solid pure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 10.0 Hz, 1H), 6.62 (d, J = 12.5 Hz, 1H), 5.65 (br s, 2H), 3.92 (s, 3H), 3.20 (m, 1H), 1.22 (m, 6H).

2-Iodo-5-(trifluoromethyl)benzoic Acid (33). Potassium hydroxide (3.78 g, 0.0673 mol) was added to a stirred solution of 2-iodo-5-(trifluoromethyl)benzonitrile (**9**) (4 g, 0.0135 mol) in a 1:1 2-propanol:water solution (60 mL). The reaction was heated at reflux for 14 h and then partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (50 mL) and acidified to pH 5 with 6 N HCl. The aqueous layer was further extracted with EtOAc (4 × 50 mL), and the combined extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 2-iodo-5-(trifluoromethyl)benzoic acid (**33**) (2.81 g, 66%), as a yellow solid. LCMS calcd = 316.93; found = 317.0 $(M + H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 1.6 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.47 (dd, J = 8.2, 1.8 Hz, 1H).

[2-Iodo-5-(trifluoromethyl)phenyl]methanol (34). Borane−THF (1.0 M solution in THF, 94 mL, 94 mmol) was added to a stirred solution of 2-iodo-5-(trifluoromethyl)benzoic acid (**33**) (2.97 g, 9.4 mmol) in THF (300 mL) at 0 °C under N_2. The reaction was heated at reflux for 90 min and then carefully quenched with 6 N HCl until no further gas evolution. The reaction was diluted with water (250 mL) and extracted with EtOAc (3 × 250 mL). The combined extracts were washed with brine (300 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (Si, 0−25% EtOAc in hexanes gradient) to afford [2-iodo-5-(trifluoromethyl)-phenyl]methanol (**34**) (2.29 g, 88%) as a white solid. LCMS calcd = 284.94; found = 285.0 $(M-17)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.3 Hz, 1H), 7.79 (s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 4.75 (s, 2H).

2-(Bromomethyl)-1-iodo-4-(trifluoromethyl)benzene (35). Carbon tetrabromide (1.86 g, 5.6 mmol) and triphenylphosphine (1.47 g, 5.6 mmol) were added successively to a stirred solution of [2-iodo-5-(trifluoromethyl)phenyl]methanol (**34**) (1.13 g, 3.74 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C under N_2. The reaction was stirred at room temperature for 48 h. A second equivalent of carbon tetrabromide (1.2 g, 3.74 mmol) and triphenylphosphine (0.98 g, 3.74 mmol) was added, and the reaction was stirred an additional 14 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (Si, 0−25% EtOAc in hexanes gradient) to afford 2-(bromoethyl)-1-iodo-4-(trifluoromethyl)benzene (**35**) (1.30 g, 96%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 1.8 Hz, 1H), 7.26 (dd, J = 8.3, 1.8 Hz, 1H), 4.64 (s, 2H).

(4*S*,5*R*)-5-[3,5-Bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (36). To a stirred suspension of NaH (60% dispersion in mineral oil; 1.30 g, 0.0325 mol) in THF (60 mL) at 0 °C under N_2 was added dropwise a solution of (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one ((−)-*cis*-**18**)) (4.077 g, 0.013 mol) in THF (50 mL). Gas evolution was observed. The resultant mixture stirred at 0 °C for 30 min prior to addition of a solution of 2-(bromomethyl)-1-iodo-4-(trifluoromethyl)-benzene (**35**) (4.754 g, 0.013 mol) in THF (20 mL). The reaction was allowed to warm to room temperature and stirred for 14 h. The reaction was carefully quenched with water (15 mL) and partitioned between EtOAc (250 mL) and water (75 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (Si, 0−20% EtOAc/hexanes gradient) to afford (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (**36**) (6.4 g, 83%) as a white solid. LCMS calcd = 597.99; found = 598.1 $(M + H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.2 Hz, 1H), 7.90 (s, 1H), 7.79 (s, 2H), 7.58 (s, 1H), 7.30 (dd, J = 8.2 Hz, J = 2.0 Hz, 1H), 5.76 (d, J = 8 Hz, 1H), 4.88 (d, J = 15.8 Hz, 1H), 4.37 (d, J = 15.8 Hz, 1H), 4.09−4.02 (m, 1H), 0.80 (d, J = 6.6 Hz, 3H).

(+)-(4*S*,5*R*)-5-[3,5-Bis(trifluoromethyl)phenyl]-3-{[4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]-methyl}-4-methyl-1,3-oxazolidin-2-one ((+)-*cis*-3). A stirred mixture of (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (**36**) (4.29 g, 7.19 mmol), [4-fluoro-2-methoxy-5-(propan-2-yl)phenyl]boronic acid (**28**) (4.57 g, 21.57 mmol), $(Ph_3P)_4Pd$ (1.0 g, 0.86 mmol), and sodium carbonate (6.35 g) in C_6H_6/EtOH/water (120 mL/17 mL/51 mL) was heated at reflux (100 °C) under N_2 for 14 h. The reaction was partitioned between EtOAc (200 mL) and water (100 mL). The aqueous phase was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by silica-gel flash chromatography (Si, 0−25% EtOAc/hexanes gradient) to afford (+)-(4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((+)-*cis*-**3**), (3.50 g, 76%), as a colorless solid. LCMS calcd = 638.18; found = 638.3 $(M + H)^+$. ^{1}H NMR (500 MHz, benzene-d_6, 1:1 mixture of atropisomers) δ 7.82 (s, 0.5H), 7.60 (s, 0.5H), 7.57 (s, 1H), 7.33 (d, J = 8 Hz, 1H), 7.27 (d, J = 9.9 Hz, 2H), 7.02−6.98 (m, 1H), 6.89 (d, J = 8.5 Hz, 0.5H), 6.82 (d, J = 8.5 Hz, 0.5H), 6.45 (d, J = 12.1 Hz, 0.5H), 6.35 (d, J = 11.9 Hz, 0.5H), 4.94 (d, J = 16.0 Hz, 0.5H), 4.87 (d, J = 15.8 Hz, 0.5H), 4.54 (d, J = 8.0 Hz, 0.5H), 4.50 (d, J = 7.8 Hz, 0.5H), 3.74−3.66 (m, 1H), 3.23−3.15 (m, 1H), 3.12 (s, 1.5H), 2.99 (s, 1.5H), 2.97−2.92 (m, 0.5H), 2.89−2.84 (m, 0.5H), 1.21−1.09 (m, 6H), −0.27 (d, J = 6.7 Hz, 1.5H), −0.40 (d, J = 6.7 Hz, 1.5H). HRMS (ES^+) calcd for $C_{30}H_{26}F_{10}NO_3$ $(M + H)^+$ m/e, 638.1748; found, 638.1731.

Alternate Procedure for Synthesizing (4*S*,5*R*)-5-[3,5-Bis-(trifluoromethyl)phenyl]-3-{[4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((+)-*cis*-3). A mixture of (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (**36**) (50 mg, 0.084 mmol), [4-fluoro-2-methoxy-5-(propan-2-yl)phenyl]boronic acid (**28**) (22 mg, 0.105 mmol), palladium acetate (6 mg, 0.0103 mmol), and potassium carbonate (29 mg, 0.257 mmol) in 5:1 acetone/water (6 mL) was heated at reflux for 1 h. The acetone was removed in vacuo, and the residue was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (Si, 0−25% EtOAc/hexanes gradient) to afford (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one ((+)-*cis*-**3**) (23 mg, 44%) as a clear glass.

[4′-Fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)-biphenyl-2-yl]methanol (37). A mixture of [2-iodo-5-(trifluoromethyl)phenyl]methanol (**34**) (3.09 g, 10.2 mmol), (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (**28**) (4.34 g, 20.5 mmol), $(Ph_3P)_4Pd$ (1.42 g, 1.23 mmol), and Na_2CO_3 (9.11 g, 85.9 mmol) in benzene/EtOH/water (7:1:3, 250 mL) was heated at reflux for 24 h under N_2. After cooling to room temperature, the aqueous phase was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 65 × 200 mm, 0−20% EtOAc in hexanes gradient) to afford [4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methanol

(**37**) (3.38 g, 97%). R_f = 0.50 (20% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1 H), 7.59 (d, J = 6.7 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 6.68 (d, J = 12.0 Hz, 1H), 4.52 (br s, 1H), 4.46 (br s, 1H), 3.73 (s, 3H), 3.25−3.17 (m, 1H), 1.82 (br s, 1H), 1.24 (d, J = 6.8 Hz, 6H).

2′-(Bromomethyl)-4-fluoro-2-methoxy-5-(propan-2-yl)-4′-(trifluoromethyl)biphenyl (38). A solution of triphenylphosphine (3.11 g, 11.8 mmol) in dry CH_2Cl_2 (7 mL) was added via cannula to a stirred solution of carbon tetrabromide (3.93 g, 11.8 mmol) and [4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]-methanol (**37**) (3.38 g, 9.87 mmol) in dry CH_2Cl_2 (56 mL) at 0 °C under N_2. The reaction was allowed to warm to room temperature. After 2 h, the reaction mixture was concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 65 mm × 200 mm, 0−20% EtOAc in hexanes gradient) to afford 2′-(bromomethyl)-4-fluoro-2-methoxy-5-(propan-2-yl)-4′-(trifluoromethyl)biphenyl (**38**) (3.71 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 6.72 (d, J = 12.0 Hz, 1H), 4.43 (br d, J = 10.0 Hz, 1H), 4.30 (br d, J = 10.2 Hz, 1 H), 3.76 (s, 3H), 3.30−3.22 (m, 1H), 1.29 (d, J = 6.9 Hz, 6H).

Benzyl {2-[Methoxy(methyl)amino]-1,1-dimethyl-2-oxoethyl}carbamate (42). *N*-Methyl morpholine (682 mg, 741 μL, 6.74 mmol) and *iso*-butyl chloroformate (460 mg, 441 μL, 3.37 mmol) were added successively to a stirred solution of *N*-carbobenzyloxy-2-methylalanine (**40**) (0.64 g, 2.69 mmol) in dry CH_2Cl_2 at 0 °C under N_2. The resulting cloudy mixture was stirred at 0 °C for 90 min. *N*,*O*-Dimethylhydroxylamine hydrochloride (316 mg, 3.24 mmol) was added portionwise, and the mixture was warmed to room temperature and stirred for 3 h. The mixture was poured into 1 N HCl (30 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined extracts were washed with 1 N HCl (30 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 40 mm × 160 mm, 0−80% EtOAc in hexanes gradient) to afford benzyl {2-[methoxy(methyl)amino]-1,1-dimethyl-2-oxoethyl}carbamate (**42**) (308.8 mg, 41%). R_f = 0.47 (50% EtOAc in hexanes). LCMS calcd = 303.13; found = 303.2 $(M + Na)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H), 5.82 (s, 1H), 5.09 (s, 2H), 3.60 (s, 3H), 3.18 (s, 3H), 1.60 (s, 6H).

Benzyl (1,1-Dimethyl-2-oxoethyl)carbamate (41). Diisobutylaluminum hydride (1.77 mL, 1 M solution in toluene, 0.708 mmol) was added to a stirred solution of benzyl {2-[methoxy(methyl)amino]-1,1-dimethyl-2-oxoethyl}carbamate (**42**) (198.5 mg, 0.708 mmol) in dry THF (7.1 mL) at −78 °C under N_2. The reaction was stirred at −78 °C for 4 h. MeOH (100 μL) and 1 N HCl (250 μL) were added, and the reaction was allowed to warm to room temperature. The mixture was diluted with Et_2O (50 mL) and washed with 1 N HCl (2 × 50 mL), 50% saturated aq $NaHCO_3$ (50 mL), and water (50 mL) and then dried ($MgSO_4$) and concentrated in vacuo to give benzyl (1,1-dimethyl-2-oxoethyl)carbamate (**41**) (153.5 mg, 98%). R_f = 0.40 (20% EtOAc in hexanes). LCMS calcd = 244.09; found = 244.1 $(M + Na)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.38−7.30 (m, 5H), 5.34 (s, 1H), 5.09 (s, 2H), 1.37 (s, 6H).

Benzyl {2-[3,5-Bis(trifluoromethyl)phenyl]-2-hydroxy-1,1-dimethylethyl}carbamate ((±)-43). Ethyl magnesium bromide (1.63 mL, 1 M in THF, 1.63 mmol) was added dropwise to a stirred solution of 1-iodo-3,5-bis(trifluoromethyl)benzene (608 mg, 317 μL, 1.79 mmol) in dry THF (1 mL) at room temperature under N_2, and the reaction was stirred for 30 min. The resulting solution was added to a stirred solution of benzyl (1,1-dimethyl-2-oxoethyl)carbamate (**41**) (163.5 mg, 0.739 mmol) in dry THF (1 mL) at −20 °C, and the reaction was allowed to warm to room temperature over 3 h. Saturated aq NH_4Cl (10 mL) and water (10 mL) were added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 25 mm × 160 mm, 0−40% EtOAc in hexanes gradient) to afford benzyl {2-[3,5-bis(trifluoromethyl)-phenyl]-2-hydroxy-1,1-dimethylethyl}carbamate ((±)-**43**) (158.7 mg, 49%). R_f = 0.40 (20% EtOAc in hexanes). LCMS calcd = 436.13; found = 436.0 $(M + H)^+$. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.77 (s, 2H), 7.39−7.33 (m, 5H), 5.13 (br s, 1H), 5.12−5.08 (m, 2H), 4.90 (d, J = 4.4 Hz, 1H), 4.81 (s, 1H), 1.36 (s, 3H), 1.23 (s, 3H).

(−)-(5*S*)-5-[3,5-Bis(trifluoromethyl)phenyl]-3-{[4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4,4-dimethyl-1,3-oxazolidin-2-one ((−)-39) and (+)-(5*R*)-5-[3,5-Bis(trifluoromethyl)phenyl]-3-{[4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]-methyl}-4,4-dimethyl-1,3-oxazolidin-2-one ((+)-39). NaH (60% dispersion in mineral oil, 20.6 mg, 0.515 mmol) was added to a stirred solution of benzyl {2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-1,1-dimethylethyl}carbamate ((±)-**43**) (89.7 mg, 0.206 mmol) in dry DMF (1 mL) at room temperature under N_2. The reaction was stirred for 15 min, and a solution of 2′-(bromomethyl)-4-fluoro-2-methoxy-5-(propan-2-yl)-4′-(trifluoromethyl)biphenyl (**38**) (100 mg, 0.247 mmol) in dry DMF (2 mL) was added via cannula. The reaction was stirred at room temperature overnight. The reaction was quenched with saturated aq NH_4Cl (10 mL) and water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 mm × 160 mm, 0−40% EtOAc in hexanes gradient) to afford (±)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4,4-dimethyl-1,3-oxazolidin-2-one ((±)-**39**) (54.2 mg, 40%) as a colorless oil. R_f = 0.44 (20% EtOAc/hexanes). LCMS calcd = 652.19; found = 652.2 $(M + H)^+$. ^{1}H NMR (600 MHz, $CDCl_3$, 1:1 mixture of atropisomers) δ 7.89 (s, 1H), 7.80−7.72 (m, 3H), 7.57 (t, J = 7.5 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 6.99 (dd, J = 10.3, 8.2 Hz, 1H), 6.70 (dd, J = 11.9, 3.0 Hz, 1H), 5.29 (s, 0.5H), 5.25 (s, 0.5H), 4.67 (d, J = 16.5 Hz, 0.5H), 4.36 (d, J = 16.7 Hz, 0.5H), 4.31 (d, J = 16.7 Hz, 0.5H), 3.96 (d, J = 16.5 Hz, 0.5H), 3.75 (s, 3H), 3.27−3.17 (m, 1H), 1.26−1.18 (m, 7.5H), 1.07 (s, 1.5H), 0.54 (s, 1.5H), 0.51 (s, 1.5H). This compound was separated into its enantiomers (−)-(5*S*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4,4-dimethyl-1,3-oxazolidin-2-one ((−)-**39**) (HRMS (ES^+) calcd for $C_{31}H_{28}F_{10}NO_3$ $(M + H)^+$ m/e, 652.1904; found, 652.1885) and (+)-(5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4,4-dimethyl-1,3-oxazolidin-2-one ((+)-**39**) (HRMS (ES^+) calcd for $C_{31}H_{28}F_{10}NO_3$ $(M + H)^+$ m/e, 652.1904; found, 652.1889) using chiral HPLC (IA column, 20 mm × 250 mm, 2% *i*-PrOH in heptane).

Benzyl{(2*S*)-3-[3,5-bis(trifluoromethyl)phenyl]-3-hydroxybutan-2-yl}carbamate (45). To a vigorously stirred solution of benzyl{(2*S*)-1-[3,5-bis(trifluoromethyl)phenyl]-1-oxopropan-2-yl}carbamate (**26**) (150 mg, 0.358 mmol) in dry Et_2O (15 mL) under N_2 was added methylmagnesium bromide (3 M in Et_2O, 418 μL, 1.25 mmol). The resulting mixture was stirred at room temperature for 2 h. Saturated aq NH_4Cl was added to the reaction solution. The mixture was diluted with water, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue yielded benzyl{(2*S*)-3-[3,5-bis(trifluoromethyl)phenyl]-3-hydroxybutan-2-yl}-carbamate (**45**) (146 mg, 94%). LCMS calcd = 436.13; found = 436.1 $(M + H)^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (2H, s), 7.83 (s, 1H), 7.46−7.34 (m, 5H), 5.27−5.11 (m, 2H), 4.99 (d, J = 8.8 Hz, 1H), 4.13−4.02 (m, 1H), 2.82 (s, 1H), 1.67 (s, 3H), 0.96 (d, J = 6.6 Hz, 3H).

(4*S*,5*R*)-5-[3,5-Bis(trifluoromethyl)phenyl]-4,5-dimethyl-1,3-oxazolidin-2-one (46). To a solution of benzyl{(2*S*)-3-[3,5-bis(trifluoromethyl)phenyl]-3-hydroxybutan-2-yl}carbamate (**45**)

(116 mg, 0.266 mmol) in MeOH (8 mL) and THF (16 mL) was added aq KOH (7.5 N, 4 mL). The mixture was stirred at room temperature overnight. The mixture was neutralized with 1 N HCl to pH 7. The mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue yielded (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl) phenyl]-4,5-dimethyl-1,3-oxazolidin-2-one (**46**) (80.3 mg, 92%). LCMS calcd = 328.08; found = 328.1 $(M + H)^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.83 (s, 2H), 6.27 (s, 1H), 4.02−3.95 (m, 1H), 1.91 (s, 3H), 0.82 (d, J = 6.5 Hz, 3H).

(+)-(4*S*,5*R*)-5-[3,5-Bis(trifluoromethyl)phenyl]-3-{[4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4,5-dimethyl-1,3-oxazolidin-2-one ((+)-44). To a solution of (4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-4,5-dimethyl-1, 3-oxazolidin-2-one (**46**) (27.9 mg, 0.085 mmol) in DMF (0.5 mL) was added NaH (60% dispersion in mineral oil) (5.1 mg, 0.128 mmol). The mixture was stirred at room temperature for 15 min. To the above mixture was added a solution of 2′-(bromomethyl)-4-fluoro-2-methoxy-5-(propan-2-yl)-4′-(trifluoromethyl)biphenyl (**38**) (34.4 mg, 0.085 mmol) in DMF (0.5 mL). The mixture was stirred at room temperature for 2 h. Saturated aq NH_4Cl was added to the reaction solution. The mixture was diluted with water, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue yielded (+)-(4*S*,5*R*)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[4′-fluoro-2′-methoxy-5′-(propan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4,5-dimethyl-1,3-oxazolidin-2-one ((+)-**44**) (36.2 mg, 65%). LCMS calcd = 652.19; found = 652.2 $(M + H)^+$. ^1H NMR (500 MHz, $CDCl_3$, 1:1 mixture of atropisomers) δ 7.85 (s, 0.5 H), 7.84 (s, 0.5H), 7.76 (s, 1H), 7.75 (s, 1H), 7.70 (s, 0.5H), 7.68 (s, 0.5H), 7.66−7.58 (m, 1H), 7.41−7.32 (m, 1H), 7.02 (d, J = 8.39 Hz, 0.5H), 6.97 (d, J = 8.4 Hz, 0.5H), 6.74−6.64 (m, 1H), 4.90 (d, J = 15.9 Hz, 0.5H), 4.75 (d, J = 16.0 Hz, 0.5 H), 4.13 (d, J = 16.0 Hz, 0.5H), 3.87 (d, J = 15.9 Hz, 0.5H), 3.76 (s, 1.5H), 3.75 (s, 1.5H), 3.63−3.56 (m, 0.5H), 3.43−3.36 (m, 0.5H), 3.26−3.18 (m, 1H), 1.77 (s, 3H), 1.30−1.13 (m, 6H), 0.51 (d, J = 6.5 Hz, 1.5H), 0.33 (d, J = 6.5 Hz, 1.5H). (HRMS (ES^+) calcd for $C_{31}H_{28}F_{10}NO_3$ $(M + H)^+$ m/e, 652.1904; found, 652.1887).

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ABBREVIATIONS USED

CVD, cardiovascular disease; CHD, coronary heart disease; LDL-C, low density lipoprotein-cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HDL-C, high density lipoprotein-cholesterol; LDL, low density lipoprotein; HDL, high density lipoproteins; CETP, cholesteryl ester transfer protein; RCT, reverse cholesterol transport; apoB, apolipoprotein B; VLDL, very low-density lipoprotein; CE, cholesteryl ester; BODIPY, boron-dipyrromethene; $\mu\lambda$, microwave

REFERENCES

(1) World Health Organization Cardiovascular Diseases—Fact Sheet no. 317. http://www.who.int/en/, February 28, 2007.

(2) Kearney, P. M.; Blackwell, L.; Collins, R.; Keech, A.; Simes, J.; Peto, R.; Armitage, J.; Baigent, C. Efficacy of cholesterol-lowering therapy in 18686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* **2008**, *371*, 117–125.

(3) Baigent, C.; Keech, A.; Kearney, P. M.; Blackwell, L.; Buck, G.; Pollicino, C.; Kirby, A.; Sourjina, T.; Peto, R.; Collins, R.; Simes, J. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90056 participants in 14 randomised trials of statins. *Lancet* **2005**, *366*, 1267–1278.

(4) Rhoads, G.; Gulbrandsen, C.; Kagan, A. Serum lipoproteins and coronary heart disease in a population study of Hawaii Japanese men. *N. Engl. J. Med.* **1976**, *294*, 293–298.

(5) Castelli, W.; Doyle, J.; Gordon, T.; Hames, C.; Hjortland, M.; Hulley, S.; Kagan, A.; Zukel, W. HDL cholesterol and other lipids in coronary heart disease. The cooperative lipoprotein phenotyping study. *Circulation* **1977**, *55*, 767–772.

(6) Gordon, T.; Castelli, W. P.; Hjortland, M. C.; Kannel, W. B.; Dawber, T. R. High density lipoprotein as a protective factor against coronary heart disease: The Framingham study. *Am. J. Med.* **1977**, *62*, 707–714.

(7) Lewington, S.; Whitlock, G.; Clarke, R.; Sherliker, P.; Emberson, J.; Halsey, J.; Qizilbash, N.; Peto, R.; Collins, R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55000 vascular deaths. *Lancet* **2008**, *370*, 1829–1839.

(8) The Lipid Research Clinics Coronary Primary Prevention Trial Results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA, J. Am. Med. Assoc.* **1984**, *251*, 365−374.

(9) Brown, B. G.; Stukovsky, K. H.; Zhao, X.-Q. Simultaneous low-density lipoprotein-C lowering and high-density lipoprotein-C elevation for optimum cardiovascular disease prevention with various drug classes, and their combinations: a meta-analysis of 23 randomized lipid trials. *Curr. Opin. Lipidol.* **2006**, *17*, 631–636.

(10) Otvos, J. D.; Collins, D.; Freedman, D. S.; Shalaurova, I.; Schaefer, E. J.; McNamara, J. R.; Bloomfield, H. E.; Robins, S. J. Low-Density Lipoprotein and High-Density Lipoprotein Particle Subclasses Predict Coronary Events and Are Favorably Changed by Gemfibrozil Therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. *Circulation* **2006**, *113*, 1556–1563.

(11) Pedersen, T. R.; Olsson, A. G.; Færgeman, O.; Kjekshus, J.; Wedel, H.; Berg, K.; Wilhelmsen, L.; Haghfelt, T.; Thorgeirsson, G.; Pyorala, K.; Miettinen, T.; Christophersen, B.; Tobert, J. A.; Musliner, T. A.; Cook, T. J. Lipoprotein Changes and Reduction in the Incidence of Major Coronary Heart Disease Events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* **1998**, *97*, 1453–1460.

(12) Singh, I. M.; Shishehbor, M. H.; Ansell, B. J. High-density lipoprotein as a therapeutic target: a systematic review. *J. Am. Med. Assoc.* **2007**, *298*, 786–798.

(13) Tall, A. R.; Yvan-Charvet, L.; Terasaka, N.; Pagler, T.; Wang, N. HDL, ABC Transporters, and Cholesterol Efflux: Implications for the Treatment of Atherosclerosis. *Cell Metab.* **2008**, *7*, 365–375.

(14) Barkowski, R. S.; Frishman, W. H. HDL metabolism and CETP inhibition. *Cardiol. Rev.* **2008**, *16*, 154–162.

(15) Masson, D.; Jiang, X. C.; Lagrost, L.; Tall, A. R. The role of plasma lipid transfer proteins in lipoprotein metabolism and atherogenesis. *J. Lipid Res.* **2009**, *50* (Suppl S), S201–S206.

(16) Barter, P. J.; Brewer, H. B., Jr; Chapman, M. J.; Hennekens, C. H.; Rader, D. J.; Tall, A. R. Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, 160–167.

(17) Brown, M. L.; Inazu, A.; Hesler, C. B.; Agellon, L. B.; Mann, C.; Whitlock, M. E.; Marcel, Y. L.; Milne, R. W.; Koizumi, J.; Mabuchi, H.; Takeda, R.; Tall, A. R. Molecular basis of lipid transfer protein deficiency in a family with increase high-density lipoproteins. *Nature* **1989**, *342*, 448–451.

(18) Inazu, A.; Brown, M. L.; Hesler, C. B.; Agellon, L. B.; Kolzumi, J.; Takata, K.; Maruhama, Y.; Mabuchi, H.; Tall, A. R. Increased

high-density lipoprotein levels caused by a common cholesteryl-ester transfer protein gene mutation. *N. Engl. J. Med.* **1990**, *323*, 1234–1238.

(19) Clark, R. W.; Sutfin, T. A.; Ruggeri, R. B.; Willauer, A. T.; Sugarman, E. D.; Magnus-Aryitey, G.; Cosgrove, P. G.; Sand, T. M.; Wester, R. T.; Williams, J. A.; Perlman, M. E.; Bamberger, M. J. Raising High-Density Lipoprotein in Humans Through Inhibition of Cholesteryl Ester Transfer Protein: An Initial Multidose Study of Torcetrapib. *Arterioscler. Thromb. Vasc. Biol.* **2004**, *24*, 490–497.

(20) Brousseau, M. E.; Schaefer, E. J.; Wolfe, M. L.; Bloedon, L. T.; Digenio, A. G.; Clark, R. W.; Mancuso, J. P.; Rader, D. J. Effects of an Inhibitor of Cholesteryl Ester Transfer Protein on HDL Cholesterol. *N. Engl. J. Med.* **2004**, *350*, 1505–1515.

(21) Davidson, M. H.; McKenney, J. M.; Shear, C. L.; Revkin, J. H. Efficacy and Safety of Torcetrapib, a Novel Cholesteryl Ester Transfer Protein Inhibitor, in Individuals with Below-Average High-Density Lipoprotein Cholesterol Levels. *J. Am. Coll. Cardiol.* **2006**, *48*, 1774–1781.

(22) McKenney, J. M.; Davidson, M. H.; Shear, C. L.; Revkin, J. H. Efficacy and Safety of Torcetrapib, a Novel Cholesteryl Ester Transfer Protein Inhibitor, in Individuals With Below-Average High-Density Lipoprotein Cholesterol Levels on a Background of Atorvastatin. *J. Am. Coll. Cardiol.* **2006**, *48*, 1782–1790.

(23) de Grooth, G. J.; Kuivenhoven, J. A.; Stalenhoef, A. F. H.; de Graaf, J.; Zwinderman, A. H.; Posma, J. L.; van Tol, A.; Kastelein, J. J. P. Efficacy and Safety of a Novel Cholesteryl Ester Transfer Protein Inhibitor, JTT-705, in Humans: A Randomized Phase II Dose–Response Study. *Circulation* **2002**, *105*, 2159–2165.

(24) Kuivenhoven, J. A.; de Grooth, G. J.; Kawamura, H.; Klerkx, A. H.; Wilhelm, F.; Trip, M. D.; Kastelein, J. J. P. Effectiveness of Inhibition of Cholesteryl Ester Transfer Protein by JTT-705 in Combination With Pravastatin in Type II Dyslipidemia. *Am. J. Cardiol.* **2005**, *95*, 1085–1088.

(25) Stein, E. A.; Stroes, E. S. G.; Steiner, G.; Buckley, B. M.; Capponi, A. M.; Burgess, T.; Niesor, E. J.; Kallend, D.; Kastelein, J. J. P. Safety and Tolerability of Dalcetrapib. *Am. J. Cardiol.* **2009**, *104*, 82–91.

(26) Kastelein, J. J. P.; Duivenvoorden, R.; Deanfield, J.; de Groot, E.; Jukema, J. W.; Kaski, J.-C.; Munzel, T.; Taddei, S.; Lehnert, V.; Burgess, T.; Kallend, D.; Luscher, T. F. Rationale and design of dal-VESSEL: a study to assess the safety and efficacy of dalcetrapib on endothelial function using brachial artery flow-mediated vasodilatation. *Curr. Med. Res. Opin.* **2011**, *27*, 141–150.

(27) Barter, P. J.; Caulfield, M.; Eriksson, M.; Grundy, S. M.; Kastelein, J. J. P.; Komajda, M.; Lopez-Sendon, J.; Mosca, L.; Tardif, J.-C.; Waters, D. D.; Shear, C. L.; Revkin, J. H.; Buhr, K. A.; Fisher, M. R.; Tall, A. R.; Brewer, B. Effects of torcetrapib in patients at high risk for coronary events. *N. Engl. J. Med.* **2007**, *357*, 2109–2122.

(28) Kastelein, J. J. P.; van, L. S. I.; Burgess, L.; Evans, G. W.; Kuivenhoven, J. A.; Barter, P. J.; Revkin, J. H.; Grobbee, D. E.; Riley, W. A.; Shear, C. L.; Duggan, W. T.; Bots, M. L. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N. Engl. J. Med.* **2007**, *356*, 1620–1630.

(29) Bots, M. L.; Visseren, F. L.; Evans, G. W.; Riley, W. A.; Revkin, J. H.; Tegeler, C. H.; Shear, C. L.; Duggan, W. T.; Vicari, R. M.; Grobbee, D. E.; Kastelein, J. J. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial. *Lancet* **2007**, *370*, 153–160.

(30) Vergeer, M.; Bots, M. L.; van Leuven, S. I.; Basart, D. C.; Sijbrands, E. J.; Evans, G. W.; Grobbee, D. E.; Visseren, F. L.; Stalenhoef, A. F.; Stroes, E. S.; Kastelein, J. J. P. Cholesteryl Ester Transfer Protein Inhibitor Torcetrapib and Off-Target Toxicity. *Circulation* **2008**, *118*, 2515–2522.

(31) Nissen, S. E.; Tardif, J.-C.; Nicholls, S. J.; Revkin, J. H.; Shear, C. L.; Duggan, W. T.; Ruzyllo, W.; Bachinsky, W. B.; Lasala, G. P.; Tuzcu, E. M. Effect of torcetrapib on the progression of coronary atherosclerosis. *N. Engl. J. Med.* **2007**, *356*, 1304–1316.

(32) Nicholls, S. J.; Tuzcu, E. M.; Brennan, D. M.; Tardif, J.-C.; Nissen, S. E. Cholesteryl Ester Transfer Protein Inhibition, High-Density Lipoprotein Raising, and Progression of Coronary Atherosclerosis. *Circulation* **2008**, *118*, 2506–2514.

(33) Forrest, M. J.; Bloomfield, D.; Briscoe, R. J.; Brown, P. N.; Cumiskey, A.-M.; Ehrhart, J.; Hershey, J. C.; Keller, W. J.; Ma, X.; McPherson, H. E.; Messina, E.; Peterson, L. B.; Sharif-Rodriguez, W.; Siegl, P. K. S.; Sinclair, P. J.; Sparrow, C. P.; Stevenson, A. S.; Sun, S.-Y.; Tsai, C.; Vargas, H.; Walker, M., III; West, S. H.; White, V.; Woltmann, R. F. Torcetrapib-induced blood pressure elevation is independent of CETP inhibition and is accompanied by increased circulating levels of aldosterone. *Br. J. Pharmacol.* **2008**, *154*, 1465–1473.

(34) Blasi, E.; Bamberger, M.; Knight, D.; Engwall, M.; Wolk, R.; Winter, S.; Betts, A.; John-Baptiste, A.; Keiser, J. Effects of CP-532,623 and Torcetrapib, Cholesteryl Ester Transfer Protein Inhibitors, on Arterial Blood Pressure. *J. Cardiovasc. Pharmacol.* **2009**, *53*, 507–516.

(35) DePasquale, M.; Cadelina, G.; Knight, D.; Loging, W.; Winter, S.; Blasi, E.; Perry, D.; Keiser, J. Mechanistic studies of blood pressure in rats treated with a series of cholesteryl ester transfer protein inhibitors. *Drug Dev. Res.* **2009**, *70*, 35–48.

(36) Hu, X.; Dietz, J. D.; Xia, C.; Knight, D. R.; Loging, W. T.; Smith, A. H.; Yuan, H.; Perry, D. A.; Keiser, J. Torcetrapib induces aldosterone and cortisol production by an intracellular calcium-mediated mechanism independently of cholesteryl ester transfer protein inhibition. *Endocrinology* **2009**, *150*, 2211–2219.

(37) Rader, D. J. Illuminating HDL—is it still a viable therapeutic target? *N Engl. J. Med.* **2007**, *357*, 2180–2183.

(38) Tall, A. R.; Yvan-Charvet, L.; Wang, N. The failure of torcetrapib: was it the molecule or the mechanism? *Arterioscler Thromb. Vasc. Biol.* **2007**, *27*, 257–260.

(39) Tall, A. R. CETP inhibitors to increase HDL cholesterol levels. *N. Engl. J. Med.* **2007**, *356*, 1364–1366.

(40) Barter, P. J. Point: The Relationship between Cholesteryl Ester Transfer Protein and Cardiovascular Risk. *Clin. Chem.* **2010**, *56*, 1547–1549.

(41) Sirtori, C. R.; Mombelli, G. Counterpoint: Cholesteryl Ester Transfer Protein Antagonism by Drugs—A Poor Choice. *Clin. Chem.* **2010**, *56*, 1550–1553.

(42) Ranalletta, M.; Bierilo, K. K.; Chen, Y.; Milot, D.; Chen, Q.; Tung, E.; Houde, C.; Elowe, N. H.; Garcia-Calvo, M.; Porter, G.; Eveland, S.; Frantz-Wattley, B.; Kavana, M.; Addona, G.; Sinclair, P.; Sparrow, C.; O'Neill, E. A.; Koblan, K. S.; Sitlani, A.; Hubbard, B.; Fisher, T. S. Biochemical characterization of cholesteryl ester transfer protein inhibitors. *J. Lipid Res.* **2010**, *51*, 2739–2752.

(43) Krishna, R.; Anderson, M. S.; Bergman, A. J.; Jin, B.; Fallon, M.; Cote, J.; Rosko, K.; Chavez-Eng, C.; Lutz, R.; Bloomfield, D. M.; Gutierrez, M.; Doherty, J.; Bieberdorf, F.; Chodakewitz, J.; Gottesdiener, K. M.; Wagner, J. A. Effect of the cholesteryl ester transfer protein inhibitor, anacetrapib, on lipoproteins in patients with dyslipidaemia and on 24 h ambulatory blood pressure in healthy individuals: two double-blind, randomised placebo-controlled phase I studies. *Lancet* **2007**, *370*, 1907–1914.

(44) Krishna, R.; Bergman, A, J.; Jin, B.; Fallon, M.; Cote, J.; Van Hoydonck, P.; Laethem, T.; Gendrano, I. N., III; Van Dyck, K.; Hilliard, D.; Laterza, O.; Snyder, K.; Chavez-Eng, C.; Lutz, R.; Chen, J.; Bloomfield, D. M.; De Smet, M.; Van Bortel, L. M.; Gutierrez, M.; Al-Huniti, N.; Dykstra, K.; Gottesdiener, K. M.; Wagner, J. A. Multiple-Dose Pharmacodynamics and Pharmacokinetics of Anacetrapib, a Potent Cholesteryl Ester Transfer Protein (CETP) Inhibitor, in Healthy Subjects. *Clin. Pharmacol. Ther.* **2008**, *84*, 679–683.

(45) Krishna, R.; Bergman, A. J.; Jin, B.; Garg, A.; Roadcap, B.; Chiou, R.; Dru, J.; Cote, J.; Laethem, T.; Wang, R. W.; Didolkar, V.; Vets, E.; Gottesdiener, K.; Wagner, J. A. Assessment of the CYP3A-Mediated Drug Interaction Potential of Anacetrapib, a Potent Cholesteryl Ester Transfer Protein (CETP) Inhibitor, in Healthy Volunteers. *J. Clin. Pharmacol.* **2009**, *49*, 80–87.

(46) Krishna, R.; Garg, A.; Panebianco, D.; Cote, J.; Bergman, A. J.; Van, H. P.; Laethem, T.; Van, D. K.; Chen, J.; Chavez-Eng, C.; Archer, L.; Lutz, R.; Hilliard, D.; Snyder, K.; Jin, B.; Van, B. L.; Lasseter, K. C.; Al-Huniti, N.; Dykstra, K.; Gottesdiener, K.; Wagner, J. A. Single-dose

pharmacokinetics and pharmacodynamics of anacetrapib, a potent cholesteryl ester transfer protein (CETP) inhibitor, in healthy subjects. *Br. J. Clin. Pharmacol.* **2009**, *68*, 535–545.

(47) Krishna, R.; Garq, A.; Jin, B.; Keshavarz, S. S.; Bieberdorf, F. A.; Chodakewitz, J.; Wagner, J. A. Assessment of a pharmacokinetic and pharmacodynamic interaction between simvastatin and anacetrapib, a potent cholesteryl ester transfer protein (CETP) inhibitor, in healthy subjects. *Br. J. Clin. Pharmacol.* **2009**, *67*, 520–526.

(48) Bloomfield, D.; Carlson, G. L.; Sapre, A.; Tribble, D.; McKenney, J. M.; Littlejohn, T. W.; Sisk, C. M.; Mitchel, Y.; Pasternak, R. C. Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib as monotherapy and coadministered with atorvastatin in dyslipidemic patients. *Am. Heart J.* **2009**, *157*, 352–360.

(49) Yvan-Charvet, L.; Kling, J.; Pagler, T.; Li, H.; Hubbard, B.; Fisher, T.; Sparrow, C. P.; Taggart, A. K.; Tall, A. R. Cholesterol Efflux Potential and Antiinflammatory Properties of High-Density Lipoprotein After Treatment With Niacin or Anacetrapib. *Arterioscler. Thromb. Vasc. Biol.* **2010**, *30*, 1430–1438.

(50) Cannon, C. P.; Dansky, H. M.; Davidson, M.; Gotto, A. M.; Brinton, E. A.; Gould, A. L.; Stepanavage, M.; Liu, S. X.; Shah, S.; Rubino, J.; Gibbons, P.; Hermanowski-Vosatka, A.; Binkowitz, B.; Mitchel, Y.; Barter, P. J. Design of the DEFINE trial: Determining the EFficacy and Tolerability of CETP INhibition with AnacEtrapib. *Am. Heart J.* **2009**, *158*, 513–519.

(51) Cannon, C. P.; Shah, S.; Dansky, H. M.; Davidson, M.; Brinton, E. A.; Gotto, A. M.; Stepanavage, M.; Liu, S. X.; Gibbons, P.; Ashraf, T. B.; Zafarino, J.; Mitchel, Y.; Barter, P. J. Safety of Anacetrapib in Patients with or at High Risk for Coronary Heart Disease. *N. Engl. J. Med.* **2010**, *363*, 2406–2415.

(52) Lu, Z.; Napolitano, J. B.; Theberge, A.; Ali, A.; Hammond, M. L.; Tan, E.; Tong, X.; Xu, S. S.; Latham, M. J.; Peterson, L. B.; Anderson, M. S.; Eveland, S. S.; Guo, Q.; Hyland, S. A.; Milot, D. P.; Chen, Y.; Sparrow, C. P.; Wright, S. D.; Sinclair, P. J. Design of a novel class of biphenyl CETP inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7469–7472.

(53) Thompson, C. F.; Ali, A.; Quraishi, N.; Lu, Z.; Hammond, M. L.; Sinclair, P. J.; Anderson, M. S.; Eveland, S. S.; Guo, Q.; Hyland, S. A.; Milot, D. P.; Sparrow, C. P.; Wright, S. D. Discovery of substituted biphenyl oxazolidinone inhibitors of cholesteryl ester transfer protein. *ACS Med. Chem. Lett.* **2011**, *2*, DOI: 10.1021/ml100309n.

(54) Liu, J.; Ikemoto, N.; Petrillo, D.; Armstrong, J. D., III. Improved syntheses of α-BOC-aminoketones from α-BOC-amino-Weinreb amides using a pre-deprotonation protocol. *Tetrahedron Lett.* **2002**, *43*, 8223–8226.

(55) Fujita, M.; Hiyama, T. Erythro-directive reduction of alpha-substituted alkanones by means of hydrosilanes in acidic media. *J. Org. Chem.* **1988**, *53*, 5415–5421.

(56) Eveland, S. S.; Milot, D. P.; Guo, Q.; Chen, Y.; Hyland, S. A.; Peterson, L. B.; Jezequel-Sur, S.; O'Donnell, G. T.; Zuck, P. D.; Ferrer, M.; Strulovici, B.; Wagner, J. A.; Tanaka, W. K.; Hilliard, D. A.; Laterza, O.; Wright, S. D.; Sparrow, C. P.; Anderson, M. S. A high-precision fluorogenic cholesteryl ester transfer protein assay compatible with animal serum and 3456-well assay technology. *Anal. Biochem.* **2007**, *368*, 239–249.

(57) Tan, E. Y.; Hartmann, G.; Chen, Q.; Pereira, A.; Bradley, S.; Doss, G.; Zhang, A. S.; Ho, J. Z.; Braun, M. P.; Dean, D. C.; Tang, W.; Kumar, S. Pharmacokinetics, Metabolism, and Excretion of Anacetrapib, a Novel Inhibitor of the Cholesteryl Ester Transfer Protein, in Rats and Rhesus Monkeys. *Drug Metab. Dispos.* **2010**, *38*, 459–473.

(58) Marotti, K. R.; Castle, C. K.; Murray, R. W.; Rehberg, E. F.; Polites, H. G.; Melchior, G. W. The role of cholesteryl ester transfer protein in primate apolipoprotein A-I metabolism. Insights from studies with transgenic mice. *Arterioscler. Thromb. Vasc. Biol.* **1992**, *12*, 736–744.