Stereocontrolled Preparation of a Nonpeptidal (−)-Spirobicyclic NK-1 Receptor Antagonist

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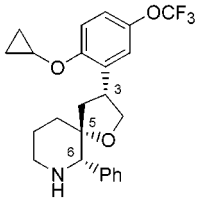
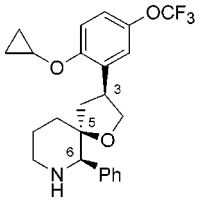
The synthesis of a spirobicyclic NK-1 receptor (Substance-P) antagonist **1** antipode is described. Retrosynthetic analysis reveals an allylic halide **A** bearing the cyclopropoxy-substituted aryl group and a 2-phenyl-3-piperidone **B**. The stereochemistry in the spirobicyclic system bearing three chiral centers is initially set via a highly diastereoselective zinc-mediated coupling of the allylic bromide **23** to the optically active ketopiperidine **3**. The remaining benzylic asymmetric center is set by a diastereoselective hydroboration followed by cyclization to the spirobicyclic system.

Introduction

The neurokinin NK-1 receptor antagonists are an area of continued interest in the pharmaceutical field.[1] The observation of antidepressant activity exhibited by a neuropeptide antagonist developed by Merck has motivated further interest in these Substance-P antagonists.[2] The spirobicyclic NK-1 receptor antagonist (+)-**1** has been identified as a candidate required for our clinical program.[3]



(3*R*,5*R*,6*S*)-(+)-1
NK-1 Receptor Antagonist

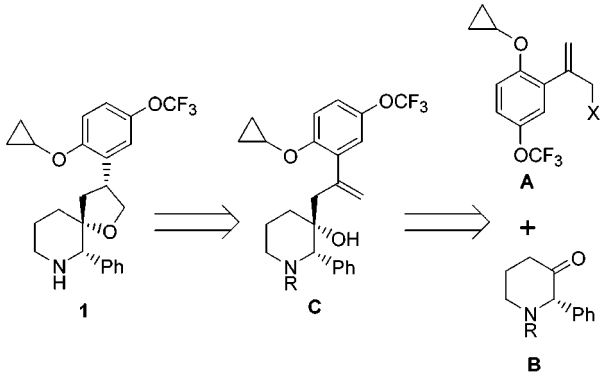


(3*S*,5*S*,6*R*)-(-)-1

Results and Discussion

This novel 6-phenyl-1-oxa-7-azaspiro[4,5]decane structure poses several synthetic challenges including the installation of three chiral centers embedded within the spirobicyclic system and the unusual cyclopropoxy and trifluoromethoxy substituents. We were primarily interested in developing a convergent route that would unite

Scheme 1



the key intermediate piperidinone **B** with an aryl three-carbon fragment **A** already bearing the cyclopropoxy function (Scheme 1).[4] The resulting homoallylic alcohol **C** would essentially be an isomer of the spirobicyclic system. Attainment of this goal was initially hampered by the sensitivity of the cyclopropoxy group to palladium catalysts and other aggressive Lewis acids.[5]

To rapidly explore the feasibility of conversion of a homoallylic alcohol with structure **C** to the spirobicyclic

(1) (a) Swain, C. J. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Oxford, A. W., Eds.; Elsevier Science BV: Amsterdam, 1998; Vol. 35, pp 57−81. (b) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545−2550. (c) Snider, R. M.; Constantine, J. W.; Lowe, J. A., III; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E.; Desai, M. C.; Vinick, F. J.; Spencer, R. W.; Hess, H.-J. *Science* **1991**, *251*, 435−437.

(2) Kramer, M. S.; Cutler, N.; Feighner, J.; Shrivastava, R.; Carman, J.; Sramek, J. J.; Reines, S. A.; Liu, G.; Snavely, D.; Wyatt-Knowles, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Swain, C. J.; Harrison, T.; Hill, R. G.; Hefti, F.; Scolnick, E. M.; Cascieri, M. A.; Chicchi, G. G.; Sadowski, S.; Williams, A. R.; Hewson, L.; Smith, D.; Carlson, E. J.; Hargreaves, R. J.; Rupniak, N. M. J. *Science* **1998**, *281*, 1640−1645.

(3) (a) Elliott, J. M.; Cascieri, M. A.; Chicchi, G. G.; Curtis, N. R.; Hargreaves, R.; Harrison, T.; Hollingworth, G. J.; Kulagowski, J.; Kurtz, M. M.; Owen, S.; Rupniak, N. M. J.; Rycroft, W.; Sadowski, S.; Seward, E.; Swain, C. J.; Tattersall, F. D.; Williams, B.; Williams, A. R. A New Class of Spirocyclic NK1 Antagonists. *Book of Abstracts*, Tachykinins 2000; Physiology, Drug Discovery and Clinical Applications, La Grande Motte, France, 2000; poster P84. (b) Baker, R.; Curtis, N. R.; Elliott, J. M.; Harrison, T.; Hollingworth, G. J.; Jackson, P. S.; Kulagowski, J. J.; Seward, E. M.; Swain, C. J.; Williams, B. J. WO 97/49710, 1997; *Chem Abstr.* **1998**, *128*, 88921.

(4) (a) Wallace, D. J.; Goodman, J. M.; Kennedy, D. J.; Davies, A. J.; Cameron, J.; Cowden, C. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H.; Reider, P. J. *J. Org. Lett.* **2001**, *3*, 671−674. (b) Kulagowski, J. J.; Curtis, N. R.; Swain, C. J.; Williams, B. *J. Org. Lett.* **2001**, *3*, 667−670. (c) Wallace, D. J.; Cowden, C. J.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Tetrahedron Lett.* **2000**, *41*, 2027−2029. (d) Wallace, D. J.; Bulger, P. G.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Synlett*, in press.

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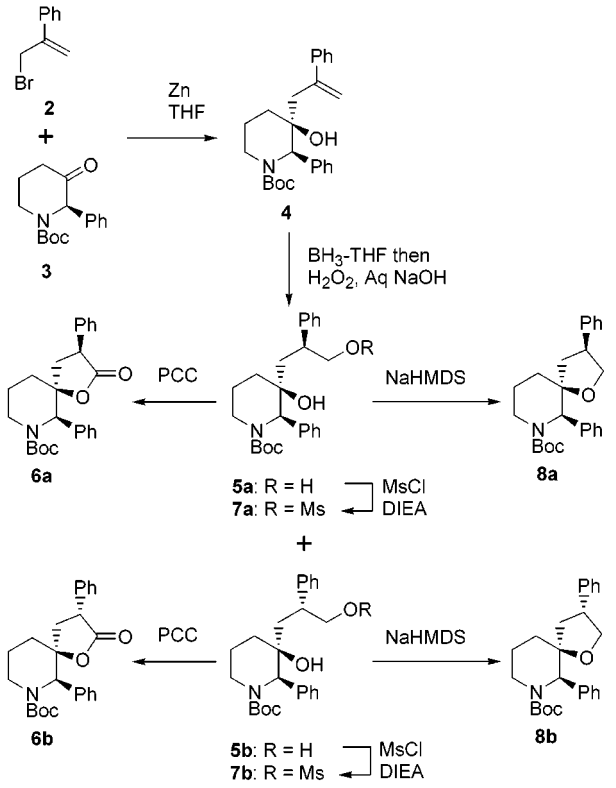
Scheme 2



system, a simpler model system was prepared. Condensation of 2-phenylallyl bromide (**2**)[6] as its organozinc derivative with (2*R*)-ketone **3**[7,1b] in Scheme 2 gave homoallylic alcohol **4** in low yields. Alternatively, addition of **2** to a mixture of **3** and zinc dust in THF furnished **4** in 74% yield.[8] As expected, attack of the ketone **3** proceeded with virtually complete anti selectivity with respect to the 2-phenyl group as shown by NOE interactions.[9]

Attempts at direct isomerization of **4** to the spirobicyclic system gave complex mixtures and were hampered by the acid lability of **4**.[10] Hydroboration/oxidation of **4** with BH_3·THF or BH_3·Me_2S gave a 2:1 diastereomeric mixture of diols which was separated by silica gel chromatography to provide **5a** (42%) and **5b** (20%). Oxidation (PCC, CH_2Cl_2) of each diastereomer **5a** and **5b** provided lactones **6a** and **6b**, respectively.[11] Treatment of either pure lactone **6a** or **6b** with DBU gave a mixture of **6a** and **6b** in a 60:40 ratio, respectively, in both cases as judged by HPLC analysis.[12] Both diols **5a** and **5b** were converted to their corresponding methanesulfonates **7a** and **7b** which were cyclized to the spirobicyclic ethers **8a** and **8b**, respectively.[13] The relative stereochemistry of **8a** and **8b** was ascertained by observation of NOE interactions within their spirobicyclic frameworks as was done in the case of **6a** and **6b**.[14]

A substantial improvement of hydroboration stereoselectivity could open the path to an efficient and convergent route to the desired spirobicyclic product. Such a sequence involving the coupling of **2** with (*R*)-**3** followed by diastereoselective hydroboration of **4** would allow the asymmetry to be transferred from (*R*)-**3** ulti-

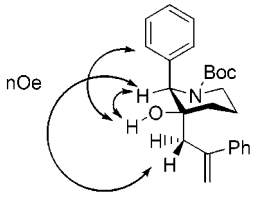
(5) The cyclopropoxy moiety is isomerized to the allyloxy group in the presence of palladium or strong acid. The resulting aryl allyl ether undergoes cyclization to the dihydropyran. Hollingworth, G. J.; Dinnell, K.; Dickinson, L. C.; Elliott, J. M.; Kulagowski, J. J.; Swain, C. J.; Thomson, G. *Tetrahedron Lett.* **1999**, *40*, 2633−2636.

(6) Bromide **2** was generated in 95% yield by treatment of 2-phenylallyl alcohol with PPh_3Br_2 in CH_2Cl_2 followed by dilution with pentane, filtration through a plug of silica gel, and isolation of **2** by vacuum distillation. Allylic bromide **2** has been prepared mixed with isomeric 1-bromo-2-phenylpropene by bromination of commercially available α-methylstyrene with NBS: (a) Vaccher, C.; Berthelot, P.; Flouquet, N.; Vaccher, M.-P.; Debaert, M. *Synth. Commun.* **1993**, *23*, 671−679. (b) Mulzer, J.; Bruntrup, G.; Kuhl, U.; Hartz, G. *Chem. Ber.* **1982**, *115*, 3453. 2-Phenylallyl alcohol can be obtained by treatment of PhCOCl with $ClCH_2I$ and MeLi·LiBr: (c) Barluenga, J.; Concellon, J. M.; Fernandezsimon, J. L.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1988**, *8*, 536−537; or from oxidation of α-methylstyrene with *t*-BuOOH in the presence of SeO_2 (0.2 mol %).

(7) (2*R*)-Ketone **3** was employed for the synthesis of (3*S*,5*S*,6*R*)-(−)-**1**. (2*R*)-Ketone **3** was prepared from a sample of enantiomerically enriched intermediate (2*R*,3*R*)-*cis*-3-hydroxy-2-phenylpiperidine kindly provided by Dr. R. D. Wilson by recrystallization as the dibenzoyl D-tartrate salt followed by protection as the *N*-Boc derivative and Swern oxidation to (2*R*)-**3**. (2*S*)-Ketone **3** is the material required for the NK-1 receptor antagonist (3*R*,5*R*,6*S*)-(+)-**1** and (2*R*)-**3** was the byproduct available from the resolution of racemic **3** to prepare (2*S*)-**3**. For an asymmetric synthesis of **3**, see: Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6223−6225.

(8) Competitive allylic homocoupling was responsible for low yields observed when the **2** was first converted to its organozinc derivative. Addition of **2** to zinc in the presence of **3** alleviated this problem, but reaction proceeded only to ca. 80% completion. Separation of **4** from the crude product containing unreacted **3** was not possible by silica gel chromatography but treatment of the crude product with $NaBH_4$ in MeOH converted **3** to the more polar corresponding alcohol which was easily removed from the product by chromatography. **4**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44−7.23 (m, 10 H), 5.44 (d, *J* = 1.6, 1 H), 5.26 (d, *J* = 1.6, 1 H), 5.14 (s, 1 H), 4.06 (m, 1 H), 3.10 (m, 1 H), 3.06 (d, *J* = 14.0, 1 H), 2.97 (d, *J* = 14.0, 1 H), 1.93−1.64 (m, 4 H), 1.39 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.4, 145.0, 142.5, 139.2, 129.4, 129.0, 128.5, 128.0, 127.7, 127.1, 126.6, 125.4, 118.6, 79.9, 72.8, 63.0, 44.1, 38.8, 31.3, 28.4, 21.8.

(9) The relative stereochemistry of a similar addition product derived from **3** (ref 4a−c) was proven by the NOE interactions. Similar NOE interactions were observed for **4** as shown.



(10) Treatment of **4** with HCl, TsOH, $ZnCl_2$, $AlCl_3$, $TiCl_4$, $ZrCl_4$, Cp_2ZrCl_2, Cp_2ZrHCl, BF_3·OEt_2, $PdCl_2$, $Pd(OAc)_2$, $NiBr_2$, $CuCl_2$, CuCl, Cu(OTf)$_2$, KO*t*-Bu, KO*t*-Bu/CuI, or BuLi lead to complex mixtures or to no reaction.

(11) Oxidation of **5a** and **5b** was performed with 2 equiv of PCC in CH_2Cl_2 in the presence of 3 Å molecular sieves to provide lactones **6a** (71%) and **6b** (52%), respectively. Swern oxidation (DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N) gave similar results, and none of the corresponding lactols were observed in either oxidation.

(12) Both lactones were equilibrated to the diastereomeric mixtures by treatment of each pure lactone **6a** and **6b** (2 mg) with DBU (2 mg) in MeCN (0.05 mL) for 30 min at 20 °C. The mixtures were directly analyzed by HPLC.

(13) Diols **5a** and **5b** were separately converted to **7a** and **7b** with 1.2 equiv of MsCl and 1.5 equiv of DIEA in CH_2Cl_2 at −20 °C followed by aq $NaHSO_4$ workup. Crude **7a** and **7b** were treated with 1.5 equiv of NaHMDS in THF at 0 °C which afforded **8a** (70%) and **8b** (60%) after aq $NaHSO_4$ workup and silica gel chromatography. **8a**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.64 (m, 2 H), 7.34−7.23 (m, 8 H), 5.35 (s, 1 H), 4.32 (t, *J* = 8.1, 1 H), 3.98 (m, 1 H), 3.91 (t, *J* = 9.0, 1 H), 3.58 (m, 1 H), 2.76 (m, 1 H), 2.69 (dd, *J* = 12.7, 7.6, 1 H), 2.26 (td, *J* = 12.7, 5.3, 1 H), 1.90 (dd, *J* = 12.7, 10.7, 1 H), 1.84−1.63 (m, 4 H), 1.48 (s, 9 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.4, 141.3, 138.9, 129.0, 128.7, 128.1, 127.3, 126.8, 126.7, 84.9, 80.0, 74.1, 60.3, 45.8, 445, 38.9, 32.8, 28.5, 23.8.

(14) NOE interaction was observed between the 6-piperidine benzylic proton and the 3-tetrahydrofuran benzylic proton.

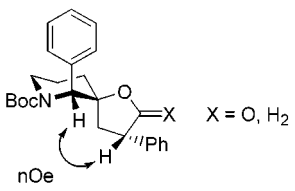
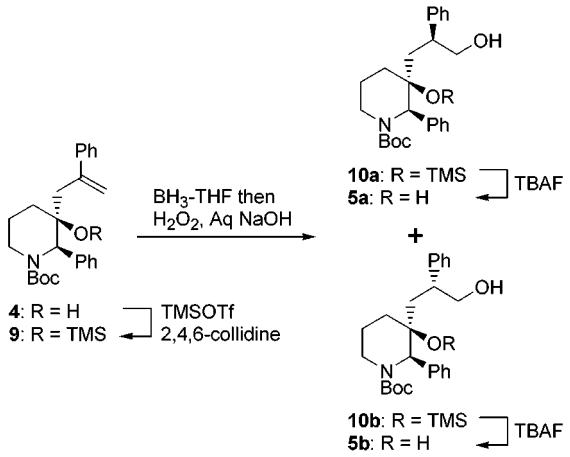


Table 1. Hydroboration of 4 and 9

substrate	conditions[a]	ratio **5a**/**5b**[b]
4	BH_3·THF, 0 °C	62/38
4	BH_3·Me_2S/THF, 0 °C	61/39
4	catecholborane/THF, 60 °C	55/45
4	9-BBN/THF, 60 °C	66/33
4	9-BBN/toluene, 60 °C	60/40
9	BH_3·THF, 0 °C	83/17
9	9-BBN/THF, 60 °C	70/30

[a] The borane (3 equiv) was added to the substrate (0.1 mmol) in the specified solvent (0.3 mL) at 0 °C, and the mixture was raised to the specified temperature for 1 h. [b] Ratios were determined by HPLC analysis after quenching with 0.3 mL 2:1 5 M aq NaOH/30% H_2O_2. In the case of **9** the quenched reaction mixtures were treated with 0.3 mL of 1 M TBAF in THF.

Scheme 3

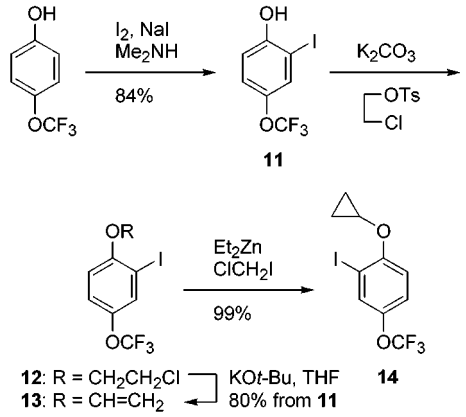


mately to the C-5-spirocenter of the spirobicyclic system and then in turn to the tetrahydrofuran C-3 center. The exploration of several borane reagents revealed BH_3·THF gave the highest stereoselectivity (2:1) for the desired diol **5a** (Table 1).

Attempts to remove the *N*-Boc group from the piperidine ring of **4** in order to alter the conformation of the system prior to hydroboration lead only to complex mixtures due to the apparent acid lability of **4**.[10] Conversion of the tertiary alcohol in **4** to various alkyl, acyl, and silyl derivatives was investigated with the intent of changing the steric environment in the vicinity of the olefin and the ability of the tertiary alcohol to complex with the borane. The best results were obtained with the trimethylsilyl ether derivative; thus, **4** was converted to the trimethylsilyl ether **9** (Scheme 3).[15] Exposure of **9** to excess BH_3·THF provided a 5:1 ratio of **5a** and **5b** after silyl ether cleavage with TBAF (Table 1). The use of less than 3 equiv of borane gave variable results (2:1 ratio of **5a** and **5b** and incomplete conversion). It was also found that the silyl ether cleavage was faster with **5a** than with **5b**.[16]

Encouraged by these results, we turned our attention to the preparation of the fully functionalized 2-aryl-

Scheme 4



substituted allylic halide **A**. A synthetic route to aryl iodide **14** starting from commercially available 4-trifluoromethoxyphenol in Scheme 4 has been developed during initial explorations toward installation of the cyclopropoxy functionality early in the synthetic sequence. The development of milder conditions for the formation of the spirobicyclic system now could allow such a convergent synthesis. Optimization of the route to **14** allowed the rapid preparation of large quantities of **14** in 67% overall yield from 4-trifluoromethoxyphenol.[17]

The aryl iodide **14** could be smoothly converted to its Grignard reagent **15** by treatment with Mg in methyl *tert*-butyl ether (MTBE) or diethyl ether (complete conversion by HPLC after quenching an aliquot in water). Interestingly, the Grignard reagent formation did not occur in THF or DME; it was found that the Grignard reagent prepared in MTBE was completely precipitated from solution by both THF and DME.[18] Low yields of the allylic alcohol **16** could be isolated by transition metal catalyzed additions of **15** to the alkoxides of propargyl alcohol and 2-chloropropenol (Scheme 5) while addition to their THP ethers only gave complex mixtures.[19]

The addition of **15** to chloroacetone and dichloroacetone in Scheme 6 proceeded in nearly quantitative yield to furnish the chlorohydrins **17** and **18**, respectively. Acid-catalyzed elimination of tertiary alcohol **17** led to a 2:1 mixture of **19b** and **19a** in favor of the undesired vinyl halide **19b**.[20] Conversion of **18** to the methanesulfonate **20a**, acetate **20b**, and trichloride **20c** followed by reduc-

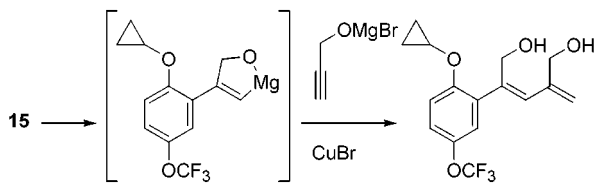
(15) The steric congestion in the vicinity of the tertiary alcohol in **4** made derivatization difficult. Acetylation of **4** (Ac_2O, DMAP) provided the corresponding acetate only as a minor product which gave complex mixtures upon hydroboration with BH_3·THF. Alkylation of **4** with MeI, Me_2SO_4, or BnBr in the presence of NaH or NaOH was sluggish. Milder silylation protocols with TMSCl and various amine bases did not convert **4** to **9**. Treatment of **4** with TMSOTf and 2,4,6-collidine in THF at 0 °C provided **9** in 75% yield.

(16) It was important to effect complete cleavage of the silyl ether prior to determining the hydroboration selectivity, but this desilylation rate difference could be taken advantage of to enrich the product mixtures in **5a**.

(17) An improved protocol in which Et_2Zn is slowly added to a mixture containing ClH_2I and **13** generates the more reactive $ClCH_2$-$ZnCH_2Cl$ rather than $ClCH_2ZnEt$ and generates the unstable carbenoid slowly to allow it to react with **13**, providing cyclopropane **14** in virtually quantitative yield. Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974−6981.

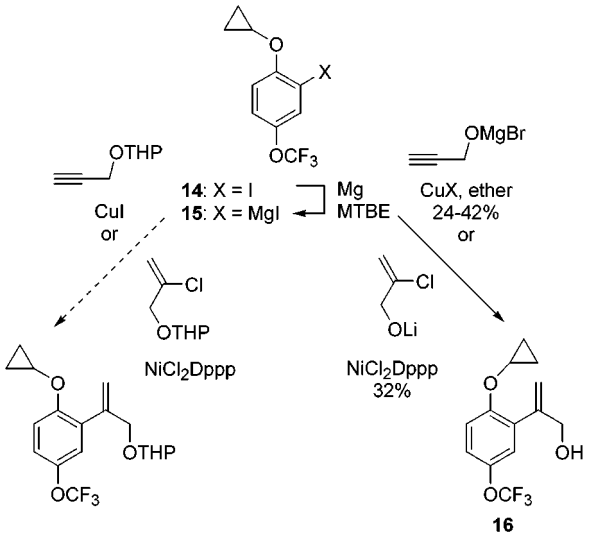
(18) The Grignard reagent precipitated by THF was found to react very sluggishly with ketones.

(19) (a) Organ, M. G.; Murray, A. P. *J. Org. Chem.* **1997**, *62*, 1523−1526. (b) Negishi, E.-I.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B. *J. Org. Chem.* **1986**, *51*, 4080−4082. Dppp = 1,3-Bis(diphenylphosphino)-propane. The copper catalyzed addition of HC∞CCH_2OMgBr to **15** gave up to 8% of the product resulting from a second addition of HC≡CCH_2-OMgBr.

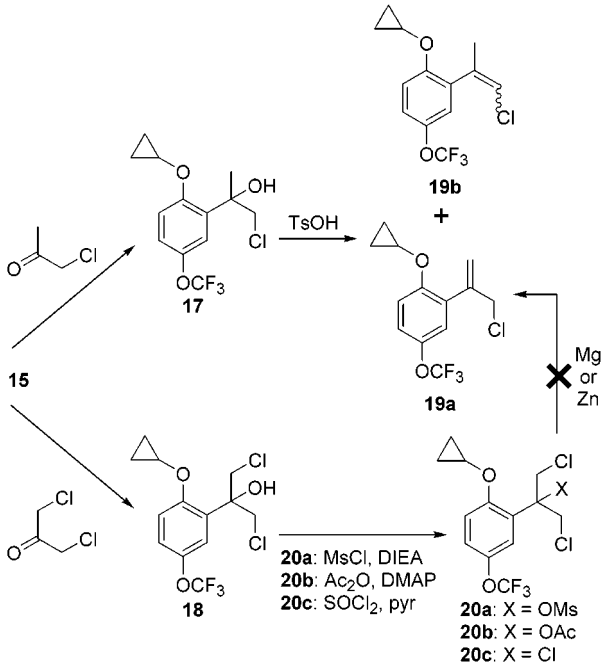


(20) Kuo, S.-C.; Hou, D.; Zhan, Z.-Y. US Pat. 5349099, 1994.

Scheme 5



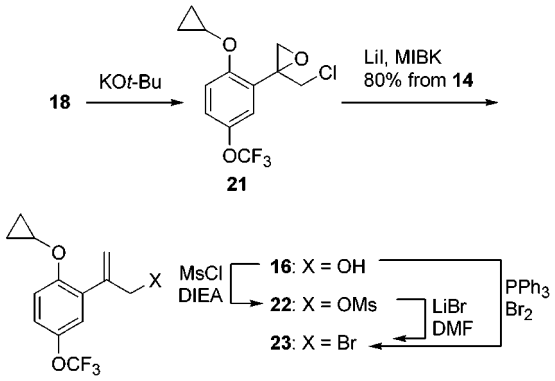
Scheme 6



tive elimination with zinc or magnesium resulted in dark complex reaction mixtures.[21]

A much more efficient conversion of **14** to **16** was realized in the sequence of steps shown in Scheme 7.[22] The dichlorohydrin **18** was converted to the epichlorohydrin **21** with KO*t*-Bu and **21** was converted to **16** (80% overall from **14**) by treatment with LiI in an enolizable ketone such as methyl isobutyl ketone (MIBK), diethyl ketone, or cyclohexanone at 100 °C.[23] Allylic bromide **23** was obtained from **16** in 95% yield either by treatment with PPh_3/Br_2 or more conveniently in multigram quantities by conversion of **16** to its methanesulfonate **22** followed by nucleophilic displacement with bromide.

Scheme 7



With the key retrosynthetic fragment **23** in hand, the coupling was probed. Since (2*R*)-ketone **3** was available in large quantities from a resolution[7] of the racemate while the (2*S*)-ketone was in short supply at the time of this study, we opted to use the 2*R* antipode in our investigations to ultimately prepare the antipodal NK-1 receptor antagonist (−)-**1**. Furthermore, only (+)-**1** had been synthesized thus far, and our work could provide the yet to be prepared (−)-**1** antipode while at the same time potentially resulting in a new route to optically active **1**. Addition of the preformed organozinc derivative of **23** to (2*R*)-**3**[7] gave the desired homoallylic alcohol **24a** albeit in moderate yields (allylic homocoupling) after flash column chromatography.[24] Addition of **23** to a mixture of Rieke zinc and (*R*)-**3** in THF gave somewhat better results, but in all these cases HPLC analysis of **24a** (Chiralpak AD, supercritical CO_2/MeOH) indicated extensive racemization (10−50%). Superior results were obtained by gradual addition of **23** to a mixture of ordinary zinc dust and (*R*)-**3** (98%ee) in DMF at 10−15 °C (Scheme 8). This procedure gave a 99% yield of pure **24a** (no detectable allylic homocoupling by HPLC analysis) without the need of chromatographic purification and <2% racemization. The mild conditions of the zinc-mediated coupling had no effect on the cyclopropoxy group. An X-ray diffraction study of **24a** confirmed the structure, and the absolute configuration of **24a** was confirmed by conversion to its *p*-bromobenzoate **24b** followed by an X-ray diffraction study.[25] Furthermore, the X-ray structure of **24a** shown in Scheme 8 clearly illustrates the axial orientation of the phenyl and allylic substituents on the piperidine ring due to the steric bulk of the *N*-Boc group.

Hydroboration of **24a** with BH_3·THF or BH_3·Me_2S gave a 2:1 diastereomeric mixture of diols **25a** and **25b** as in

(21) Hosokawa, A.; Tanaka, K. Jpn. Pat. 09188637, 1997.

(22) (a) Blundell, P.; Ganguly, A. K.; Girijavallabhan, V. M. *Synlett* **1994**, *4*, 263−265. (b) Attempted reductive elimination of **21** with Te, Na_2Te, Na_2Se, or Na_2S resulted in sluggish reactions. Polson, G.; Dittmer, D. C. *Tetrahedron Lett.* **1986**, *27*, 5579−5582.

(23) Reaction is sluggish below 90 °C, i.e., when methyl ethyl ketone at reflux is used. The use of other iodine scavengers such as phenol, zinc dust, or magnesium powder instead of a ketone gave no detectable product **16**.

(24) Reactions in which **23** was first converted to the organozinc derivative did not proceed to completion (ca 50%). No reaction between **23** and magnesium in THF to form the Grignard reagent was observed.

(25) *p*-Bromobenzoate ester **24b** was prepared by reaction of **24a** (0.20 mmol) with *p*-bromobenzoyl chloride (0.22 mmol) and Et_3N (0.25 mmol) in CH_2Cl_2 (0.5 mL) at 20 °C for 15 min followed by aqueous workup and purification by flash column chromatography (silica, 5% MTBE in hexanes) to provide **24b** (94%). Crystals suitable for X-ray crystallography were obtained by crystallization of **24b** from 2:1 MeOH−$CHCl_3$. The X-ray structure of **24b** shows the trifluoromethyl group to be disordered. Thermal ellipsoids are drawn at the 30% probability level in Scheme 8, and only selected hydrogen atoms are shown for clarity. X-ray data was obtained on a Bruker AXS instrument with data collection using a Bruker SMART program and data reduction using a Bruker SHELXTL program. Structure solution and refinement were performed with SHELXS-97 and SHELXL-97, respectively.

Scheme 8

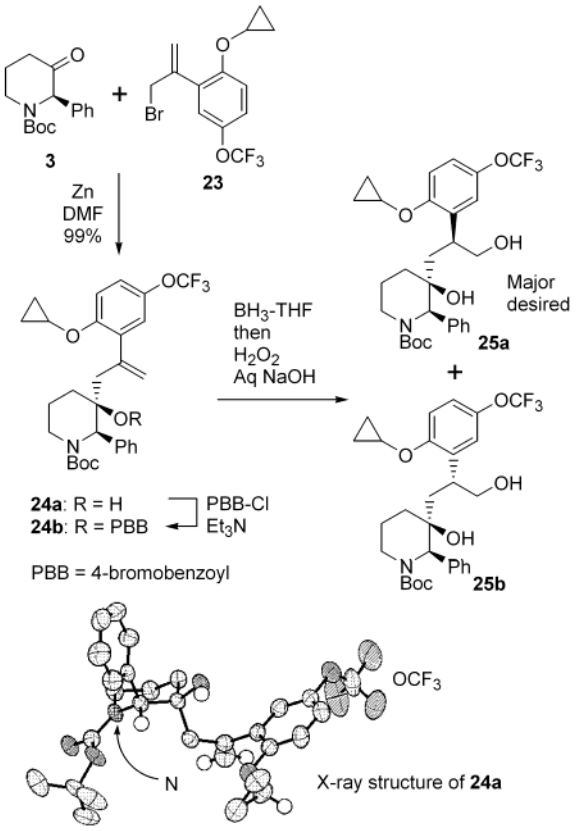


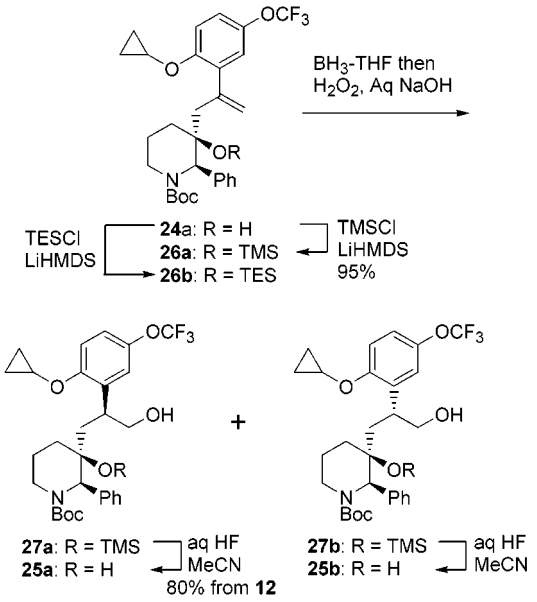
Table 2. Hydroboration of 24a, 24b, 26a, and 26b

substrate	conditions[a]	ratio **5a**/**5b**[b]
24a	BH_3·THF, 25 °C	67/33
24a	BH_3·THF, −10 °C	76/24
24a	9-BBN/THF, 25 °C	71/29
24a	9-BBN/THF, 0 °C	78/22
24b	BH_3·THF, 25 °C	62/38[c]
26a	BH_3·THF, 25 °C	80/20
26a	BH_3·THF, −10 °C	90/10
26a	BH_3·Me_2S/THF, 0 °C	87/13
26a	1.5 equiv of BH_3·Me_2S/THF, 0 °C	64/36
26a	9-BBN/THF, 25 °C	72/28
26a	(+)-IPC_2BH/THF, 20 °C	60/40
26a	(−)-IPC_2BH/THF, 20 °C	70/30
26b	BH_3·THF, 20 °C	67/33

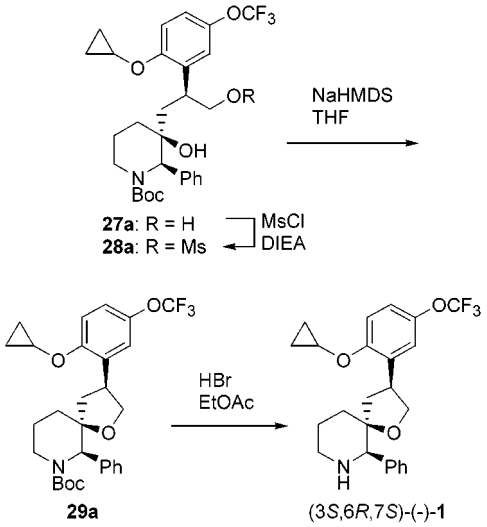
[a] The borane (5 equiv) was added to the substrate (0.1 mmol) in the specified solvent (0.3 mL) at −10 °C, and the mixture was raised to the specified temperature for 18 h unless otherwise stated. [b]Ratios were determined by HPLC analysis after quenching with 0.3 mL 2:1 5 M aq NaOH/30% H_2O_2. In the case of **26a** and **26b** the quenched reaction mixtures were treated with 0.3 mL of 1 M TBAF in THF. [c]The PBB ester was partly cleaved (ca. 25%, HPLC) during the hydroboration (reduction of ester to 4-bromobenzyl alcohol) and completely cleaved by the aq NaOH/H_2O_2 quench.

the model system. The use of other boranes and solvents did not appreciably affect the diastereoselectivity of the hydroboration (Table 2). Silylation of **24a** proved to be more difficult than with the unsubstituted model **4**. Treatment of **24a** with silyl triflates in the presence of bases such as 2,4,6-collidine, DIEA, and LiHMDS gave mixtures of products, but treatment with TMSCl in the presence of LiHMDS provided a high yield of the sterically congested silyl ether **26a** (Scheme 9). The triethylsilyl ether **26b** could also be prepared by this method but in somewhat lower yield (70%) due to a lower conversion rate. The most favorable results were obtained from the

Scheme 9



Scheme 10



hydroboration of **26a** with BH_3·THF at −10 °C which gave a 9:1 diastereomeric mixture of diols **25a** and **25b** after desilylation. Interestingly, the use of excess borane was critical to maintaining a high diastereoselectivity in the hydroboration of **26a** as was observed with the hydroboration of model **9**. The desilylation of the major diastereomer **27a** was faster than **27b** as observed in the model case. Consequently, cautious silyl ether cleavage with HF in aqueous MeCN provided diol **25a** in 80% yield containing <1% of the minor diastereomer **25b** after simple chromatographic purification.

Conversion to the spirobicyclic system **29a** was accomplished in 88% yield (Scheme 10) via cyclization of the methanesulfonate derivative **28a** with NaHMDS in THF at −20 °C. A moderate diastereoselectivity was observed for the cyclization, favoring the cyclization of **28a** over **28b**, thus affording a further opportunity for rejection of the undesired diol **25b**. The major diastereomer **29a** was found to be identical to an authentic sample of **29a** (NMR and HPLC analysis) except it had the opposite optical configuration (chiral HPLC and optical rotation).[3b] Cleavage of the *N*-Boc protecting group provided **1** in 95% yield which was also found to be

identical to an authentic sample but with the expected opposite optical configuration.[3b] The optical purity of (−)-**1** generated by this synthetic route was found to be 97% ee by HPLC analysis after derivatization with Marfey's reagent.[26]

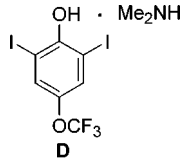
Conclusion

In conclusion, a new convergent synthesis of **1** has been identified allowing its rapid preparation from readily available raw materials. This route provides **1** in 40% overall yield from commercially available 4-trifluoromethoxyphenol and requires only three chromatographic purifications. The asymmetry of ketopiperidine **3** is transmitted to the adjacent asymmetric center via a highly diastereoselective zinc mediated coupling of an allylic bromide **23** to **3**. This asymmetry is in turn transmitted to the C-3 center via a diastereoselective hydroboration followed by cyclization to the spirobicyclic system. The diastereoselectivity of the hydroboration and the selective reactivity for the desired diastereomers observed in the subsequent conversions allow the enrichment of the final product to >99% diastereomeric purity with minimal effort in purification. Finally, this environmentally friendly synthesis requires no heavy metal compounds or cryogenic temperatures, produces little waste, and requires few isolations.

Experimental Section

General. Reagents were used as received unless otherwise stated; 3 Å molecular sieves were used to dry solvents for anhydrous reactions. Unless otherwise noted, all manipulations were carried out under an inert atmosphere of nitrogen gas. In general, glassware was not specially dried prior to use. High-pressure liquid chromatography (HPLC) analysis was performed with a Hewlett-Packard series 1100 HPLC system. Analytical TLC was performed using Merck Kieselgel G60 F_{254} precoated plates (0.25 mm) followed by visualization with UV light (254 nm), staining with iodine vapor or staining with a solution of 14% ammonium molybdate and 0.5% ceric sulfate in 10% aqueous sulfuric acid and then heat. Flash column chromatography was performed using silica gel (Merck, 70−230 mesh ASTM). Optical rotations were obtained with a Perkin-Elmer 241 polarimeter. Melting points were obtained with a Barnstead/Thermolyne MEL-TEMP apparatus and are uncorrected. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm; coupling constants are reported in hertz. ^{1}H and ^{13}C spectra were recorded on Bruker AM and AMX systems. IR spectra were recorded on a Nicolet Magna-IR 550 spectrophotometer. Elemental analyses were obtained from Quantitative Technologies Inc, Whitehouse, NJ.

2-Iodo-4-trifluoromethoxyphenol (11). A homogeneous solution of iodine (175.1 g, 0.690 mol) and NaI (269.8 g, 1.80 mol) in water (600 mL) was added to a solution of 4-trifluoromethoxyphenol (106.9 g, 0.600 mol) and 40% aq Me_2NH (412 mL, 3.30 mol) over 45 min maintaining the temperature below 0 °C. The mixture was aged for 64 h at −5 to 0 °C.



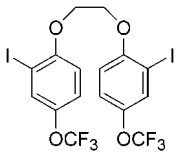
D

The mixture was filtered at 5 °C, and the filter cake containing **D**·Me_2NH salt was washed with 100 mL water at 5 °C. The filtrate was acidified to pH = 5−6 by the addition of concd HCl (45 mL) over 10 min with cooling to maintain the temperature below 30 °C. The resulting two-phase mixture was extracted with MTBE (500 mL). The organic phase (upper layer) was washed with water (500 mL), 3% aq Na_2SO_3 (500 mL), and saturated aq NaCl (200 mL). A single portion of MTBE (100 mL) was used to sequentially extract the aqueous phases from the acidified reaction, water wash, 3% Na_2SO_3 wash, and saturated NaCl wash from the aforementioned extractions, respectively. The combined organic extracts were dried over $MgSO_4$, treated with Darco G-60 (1 g) for 30 min at 20 °C, and filtered through a pad composed of silica (5 g) layered over neutral alumina (5 g), using MTBE (60 mL) to wash the pad. The filtrate was concentrated via distillation through a Snyder fractioning column (100 °C bath, 760 → 10 Torr). The residue was fractionally vacuum distilled at 1 Torr and three fractions were collected: 6.6 g (bp 70−80 °C, 4-trifluoromethoxyphenol 14.9 area%, **11** 84.2 area%, **D** <0.1 area%, 4% yield) and 146.2 g (bp 80−85 °C, 4-trifluoromethoxyphenol 0.6 area%, **11** 99.1 area%, **D** <0.1 area%, 80% yield). The main fraction #2 was obtained as a yellow oil which solidified at 15−20 °C. *Caution: persistent stench.* HPLC retention times: 4-trifluoromethoxyphenol = 2.7 min, **11** = 3.7 min, 2,6-diiodo-4-trifluoromethoxyphenol **D** = 5.0 min. HPLC conditions: 150 × 4.6 mm HP Eclipse XDB−C8 5 μm column, gradient elution with 60 to 80% MeCN in 0.025% aq H_3PO_4 over 7 min then isocratic elution with 80% MeCN in 0.025% aq H_3PO_4 for 5 min at 1 mL/min, 25 °C with detection at 220 nm. **11**: R_f = 0.25 (4:1 hexane−MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 2.8, 0.8, 1 H), 7.16 (ddd, J = 8.9, 2.8, 0.8, 1 H), 7.00 (d, J = 8.9, 1 H), 5.34 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 142.6, 130.9, 123.3, 120.5 (q, J = 258, O*C*F_3), 115.2, 84.6; FTIR (thin film) ν_{max} 3492, 1482, 1259, 1218, 1194, 1173. Anal. Calcd for $C_7H_4F_3IO_2$: C, 27.66; H, 1.33; F, 18.75; I, 41.74. Found: C, 27.39; H, 1.18; F, 18.78; I, 41.87.

1-(2-Chloroethoxy)-2-iodo-4-trifluoromethoxybenzene (12). A mixture of phenol **11** (136.8 g, 0.450 mol), 2-chloroethyl *p*-toluenesulfonate (107.7 g, 0.459 mol), DMF (450 mL), and K_2CO_3 (124.4 g, 0.900 mol) was aged for 16 h at 50 °C. Water (900 mL), MTBE (300 mL), and hexanes (150 mL) were added, and the mixture was stirred for 5 min and was allowed to settle for 5 min. The organic phase was washed with water (900 mL). The aqueous phase was back-extracted with a mixture of MTBE (100 mL) and hexanes (50 mL). The organic back-extract was washed with the 900 mL water that was used to wash the first organic extract. The two organic phases were combined, washed with saturated aq NaCl, dried over $MgSO_4$, and filtered through a pad of silica (20 g), washing the pad with a mixture of MTBE (40 mL) and hexanes (20 mL). The combined filtrates were evaporated on the rotary evaporator to give crude chloroethyl ether **12** as a pale yellow oil (165 g) which solidified after several days to a pale yellow crystalline solid. HPLC profile of crude **12**: 3.3 area% 2-chloroethyl *p*-toluenesulfonate, 82.3 area% **12**, 12.6 area% dimeric byproduct **E**. Retention times: **11** = 3.7 min, **12** = 6.5 min, 2-chloroethyl *p*-toluenesulfonate = 3.1 min, dimeric byproduct **E** = 12.6 min. HPLC conditions: 150 × 4.6 mm HP Eclipse XDB−C8 5 μm column, gradient elution with 60 → 80% MeCN in 0.025% aq H_3PO_4 over 7 min then isocratic elution with 80% MeCN in 0.025% aq H_3PO_4 for 5 min at 1 mL/min, 25 °C with detection at 220 nm. **12**: mp = 41−42 °C; R_f = 0.36 (4:1 hexane−MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 2.7, 0.8, 1 H), 7.20 (ddd, J = 9.0, 2.7, 0.8, 1 H), 6.81 (d, J = 9.0, 1 H), 4.27 (t, J = 6.0, 2 H), 3.87 (t, J = 6.0, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 143.4, 132.2, 122.2, 120.5 (q, J = 258, O*C*F_3), 112.6, 86.4, 70.0, 41.4; FTIR (thin film) ν_{max} 1485, 1251, 1218, 1192, 1170 cm^{-1}. **E** (isolated below in the preparation of **13**): mp 95−97 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.66 (d, J = 2.6, 2 H), 7.21 (dd, J = 9.0, 2.6, 2 H),

(26) Derivatization of **1** with Marfey's reagent (*N*-α-(2,4-dinitro-5-fluorophenyl)-L-alaninamide) was performed by heating a mixture of 1 mg of **1**, 2 mg of Marfey's reagent, 0.1 mL of 5% aq $NaHCO_3$, and 1 mL of MeCN at 55 °C for 5 min. The resulting mixture was then analyzed directly by HPLC. (a) Marfey, P. *Carlsberg Res. Commun.* **1984**, *49*, 591. (b) Brückner, H.; Keller-Hoehl, C. *Chromatographia* **1990**, *30*, 621. (c) Petér, A.; Olajos, E.; Casimir, R.; Tourwé, D.; Broxterman, G. B.; Kaptein, B.; Armstrong, D. W. *J. Chromatogr. A* **2000**, *871*, 105−113.

6.95 (d, J = 9.0, 2 H), 4.43 (s, 4 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.3, 143.2, 132.5, 122.3, 120.4 (q, J = 257, OCF_3), 112.9 86.4, 68.5; FTIR (thin film) ν_{max} 1492, 1256, 1213, 1178 cm^{-1}. Anal. Calcd for $C_{16}H_{10}F_6I_2O_4$: C, 30.31; H, 1.59; F, 17.98; I, 40.03. Found: C, 30.45; H, 1.44; F, 17.80; I, 40.14.



E

1-(Vinyloxy)-2-iodo-4-trifluoromethoxybenzene (13). Solid KO*t*-Bu (62.7 g, 0.559 mol) was added over 5 min to a solution of **12** (164 g, 0.447 mol crude from above alkylation) in THF (675 mL), maintaining the temperature below 0 °C, and the mixture was aged at 20 °C for 20 h. Water (1.2 L) was added to the mixture which was transferred to a 3 L separatory funnel and was extracted with a mixture of hexanes (600 mL) and MTBE (300 mL). The organic phase was washed with water (1 L). The aqueous phase was back-extracted with 2:1 hexanes−MTBE (180 mL). The organic back-extract was washed with the 1 L water that was used to wash the first organic extract. The two organic phases were combined and washed with saturated aq NaCl (200 mL). The organic phase was dried over K_2CO_3 and filtered through a pad composed of silica (20 g) layered over neutral alumina (10 g), using 2:1 hexanes−MTBE (100 mL) to wash the pad. The filtrate was concentrated via distillation through a Snyder fractioning column (100 °C bath, 760 → 10 Torr). The residue was diluted with 2-methylbutane (100 mL) and aged at −20 °C for 18 h. The precipitated crystalline dimeric byproduct **E** (14 g) was filtered off, and the filtrate was concentrated through a Snyder column as above. The residue was flash vacuum distilled through a vacuum jacketed Vigreux column (0.20−0.25 Torr, 120−130 °C bath, 80−90 °C still head) into an ice-cooled receiver. Vinyl ether **13** was collected as a colorless liquid (117 g, 80% from **2**, >98 area% purity by HPLC analysis). TLC retention factors: **11** = 0.38, **12** = 0.53, **13** = 0.90, **B** = 0.47, 2-chloroethyl toluenesulfonate = 0.18 (2:1 hexanes−CH_2Cl_2, silica). HPLC retention times: **12** = 6.5 min, **13** = 6.8 min, dimeric byproduct **E** = 12.0 min (vide supra). HPLC conditions: 150 × 4.6 mm HP Eclipse XDB−C8 5 μm column, gradient elution with 60 → 80% MeCN in 0.025% aq H_3PO_4 over 7 min then isocratic elution with 80% MeCN in 0.025% aq H_3PO_4 for 5 min at 1 mL/min, 25 °C with detection at 220 nm. **13**: R_f = 0.53 (9:1 hexane−MTBE); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.68 (m, 1 H), 7.20 (m, 1 H), 6.96 (d, J = 8.8, 1 H), 6.54 (dd, J = 13.6, 6.0, 1 H), 4.80 (dd, J = 13.6, 2.0, 1 H), 4.57 (dd, J = 6.0, 2.0, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.6, 147.7, 144.7, 132.3, 122.3, 120.4 (q, J = 258, OCF_3), 117.1, 96.8, 87.0; FTIR (thin film) ν_{max} 1644, 1475, 1252, 1218, 1191, 1167 cm^{-1}. Anal. Calcd for $C_9H_6F_3IO_2$: C, 32.75; H, 1.83; F, 17.27; I, 38.45. Found: C, 32.78; H, 1.70; F, 16.89; I, 38.58.

1-(Cyclopropoxy)-2-iodo-4-trifluoromethoxybenzene (14). Via addition funnel, Et_2Zn (59.3 g, 0.480 mol) was added to a mixture of **13** (99.0 g, 0.300 mol), $ClCH_2I$ (169.3 g, 0.960 mol), and $ClCH_2CH_2Cl$ (450 mL) over 2 h, maintaining the temperature at −5 to 0 °C. The mixture was warmed to 20 °C and aged at 20−25 °C for 15 min. The mixture was cooled back to 0 °C, and saturated aq NH_4Cl (600 mL), concd aq NH_4OH (100 mL), and hexanes (600 mL) were added. The organic phase was washed with saturated aq NH_4Cl (100 mL). The aqueous phase was back-extracted with hexanes (100 mL). The organic back-extract was washed with the 100 mL of saturated aq NH_4Cl that was used to wash the first organic extract. The two organic phases were combined, dried over K_2CO_3, and filtered through a pad composed of silica (20 g) layered over neutral alumina (10 g), using 99:1 hexanes−MTBE (200 mL) to wash the pad. The filtrate was evaporated to a constant weight of 103.2 g (>99% yield, >99 area% purity by HPLC analysis). HPLC retention times: **13** = 6.8 min, **14** = 7.5 min. HPLC conditions: 150 × 4.6 mm HP Eclipse XDB−C8 5 μm column, gradient elution with 60 → 80% MeCN in 0.025% aq H_3PO_4 over 7 min then isocratic elution with 80% MeCN in 0.025% aq H_3PO_4 for 5 min at 1 mL/min, 25 °C with detection at 220 nm. **14**: R_f = 0.43 (9:1 hexane−MTBE); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.62 (d, J = 2.3, 1 H), 7.18 (m, 2 H), 3.78 (m, 1 H), 0.84 (m, 4 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.7, 142.9, 132.2, 122.1, 120.2 (q, J = 270, OCF_3), 112.8, 85.1, 52.5, 6.4; FTIR (thin film) ν_{max} 1481, 1252, 1190, 1036, 810 cm^{-1}. Anal. Calcd for $C_{10}H_8F_3IO_2$: C, 34.91; H, 2.34; F, 16.56; I, 36.88. Found: C, 34.86; H, 2.23; F, 16.51; I, 37.10.

Dichlorohydrin 18. A mixture of **14** (10.32 g, 30.0 mmol), magnesium turnings (0.766 g, 31.5 mmol) and anhydrous MTBE (60 mL) were stirred for 3 h while moderating the exotherm to a gentle reflux with a water bath. The mixture was cooled to −20 °C, and a solution of 1,3-dichloroacetone (4.00 g, 31.5 mmol) in anhydrous MTBE (15 mL) was added over 5 min. The mixture was allowed to warm to 5 °C over 20 min and was quenched with saturated aq NH_4Cl (30 mL) and water (3 mL). The biphasic mixture was filtered from unreacted magnesium through a cotton plug using pentane (50 mL) to complete the transfer. The organic phase was separated from the filtrate, dried ($MgSO_4$), treated with Darco G60 (50 mg, 15 min), and filtered through a plug composed of silica (5 g) layered over neutral alumina (5 g). The plug was washed with 1:1 hexanes−MTBE (80 mL), and the combined filtrates were evaporated to provide the crude dichlorohydrin **18** (10.48 g). HPLC retention times: **18** = 5.5 min, 4-cyclopropoxy-1-trifluoromethoxybenzene **F** = 6.0 min. HPLC conditions: 150 × 4.6 mm HP Eclipse XDB−C8 5 μm column, gradient elution with 60 → 80% MeCN in 0.025% aq H_3PO_4 over 7 min then isocratic elution with 80% MeCN in 0.025% aq H_3PO_4 for 5 min at 1 mL/min, 25 °C with detection at 220 nm. **18**: R_f = 0.39 (4:1 hexane−MTBE); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.52 (d, J = 2.8, 1 H), 7.29 (d, J = 8.9, 1 H), 7.20 (m, 1 H), 4.06 (dd, J = 23.2, 11.3, 4 H), 3.79 (m, 1 H), 3.25 (s, 1 H), 0.83 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 153.5, 143.3, 129.2, 122.2, 122.1, 120.5 (q, J = 257, OCF_3), 113.9, 75.6, 51.7, 49.3, 6.6; FTIR (thin film) ν_{max} 1485, 1260, 1243, 1221, 1185, 1160 cm^{-1}.

Epichlorohydrin 21. A solution of dichlorohydrin **18** (10.13 g, 29.0 mmol) in THF (29 mL) was cooled to −20 °C, and KOtBu (3.58 g, 31.9 mmol) was added as a solid over 2 min. The mixture was allowed to warm to 20 °C over 20 min. MTBE (60 mL), hexanes (60 mL), water (30 mL), and brine (30 mL) were added, and the mixture was extracted. The organic extract was washed with brine (60 mL), dried ($MgSO_4$), treated with Darco G60 (200 mg, 15 min), and filtered through a plug composed of silica (5 g) layered over neutral alumina (5 g). The plug was washed with 1:1 MTBE−hexanes (50 mL) and the combined filtrates were evaporated to provide the crude epichlorohydrin **21** (8.95 g). HPLC retention time: **21** = 6.3 min. HPLC conditions: 150 × 4.6 mm HP Eclipse XDB−C8 5 μm column, gradient elution with 60 → 80% MeCN in 0.025% aq H_3PO_4 over 7 min then isocratic elution with 80% MeCN in 0.025% aq H_3PO_4 for 5 min at 1 mL/min, 25 °C with detection at 220 nm. **21**: R_f = 0.43 (4:1 hexane−MTBE); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28−7.14 (m, 3 H), 4.14 (d, J = 11.8, 1 H), 3.79 (m, 1 H), 3.61 (d, J = 11.8, 1 H), 3.15 (d, J = 5.1, 1 H), 2.81 (d, J = 5.1, 1 H), 0.81 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.9, 142.7, 126.5, 122.2, 122.1, 120.5 (q, J = 257, OCF_3), 113.1, 57.8, 53.8, 51.5, 47.7, 6.5; FTIR (thin film) ν_{max} 1494, 1356, 1247, 1218, 1185, 1162, 972 cm^{-1}.

Allylic Alcohol 16. A mixture of epichlorohydrin **21** (7.72 g, 25.0 mmol), LiI (5.02 g, 37.5 mmol), and 3-pentanone (10 mL) was heated to 100 °C for 30 min. The mixture was cooled to 25 °C diluted with 1:1 MTBE−hexanes (120 mL) and filtered. The filtrate was washed with saturated aq NH_4Cl (60 mL), water (60 mL), 39% aq $NaHSO_3$ (2 × 60 mL), water (60 mL), and brine (60 mL). The organic phase was dried ($MgSO_4$), treated with Darco G60 (200 mg, 15 min), and filtered through a plug composed of silica (5 g) layered over neutral alumina (5 g). The plug was washed with 1:1 MTBE−hexanes (50 mL), and the combined filtrates were evaporated. The residue was purified by flash column chromatography (silica, 30% MTBE in hexanes) to provide allylic alcohol **16** (5.48 g, 80% from **14**). HPLC retention time: **16** = 4.4 min. HPLC conditions: 150

× 4.6 mm HP Eclipse XDB−C8 5 μm column, gradient elution with 60 → 80% MeCN in 0.025% aq H_3PO_4 over 7 min then isocratic elution with 80% MeCN in 0.025% aq H_3PO_4 for 5 min at 1 mL/min, 25 °C with detection at 220 nm. **16**: R_f = 0.53 (1:1 hexane−MTBE); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24 (d, J = 9.9, 1 H), 7.11 (m, 2 H), 5.43 (dd, J = 2.7, 1.3, 1 H), 5.23 (d, J = 1.3, 1 H), 4.36 (s, 2 H), 3.74 (m, 1 H), 2.18 (br s, 1 H), 0.80 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.4, 146.8, 142.9, 130.5, 123.2, 121.2, 120.5 (q, J = 256, O*C*F_3), 116.2, 113.4, 65.2, 51.5, 6.3; FTIR (thin film) ν_{max} 3375, 1492, 1246, 1220, 1185, 1160 cm^{-1}.

Allylic Methanesulfonate 22. Methanesulfonyl chloride (2.41 g, 21.0 mmol) was added over 15 min to a mixture of allylic alcohol **16** (5.48 g, 20.0 mmol) and DIEA (2.84 g, 22.0 mmol) in CH_2Cl_2 (20 mL), maintaining the temperature below −40 °C. The mixture was warmed to 0 °C over 15 min, and water (35 mL), pentane (30 mL), and ether (30 mL) were added. The organic phase was washed with 5% aq HBr (2 × 25 mL), water (25 mL), and saturated aq Na_2SO_4 (25 mL). The organic phase was dried ($MgSO_4$), treated with Darco G60 (200 mg, 15 min), and filtered through a plug composed of silica (5 g) layered over neutral alumina (5 g). The plug was washed with 1:1 pentane−ether (50 mL), and the combined filtrates were evaporated to provide the crude allylic methanesulfonate **22** (7.05 g). HPLC retention time: **22** = 5.9 min. HPLC conditions: 150 × 4.6 mm HP Eclipse XDB−C8 5 μm column, gradient elution with 60 → 80% MeCN in 0.025% aq H_3PO_4 over 7 min and then isocratic elution with 80% MeCN in 0.025% aq H_3PO_4 for 5 min at 1 mL/min, 25 °C with detection at 220 nm. **22**: R_f = 0.50 (1:1 hexane−MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.17 (m, 2 H), 7.09 (m, 1 H), 5.55 (d, J = 0.6, 1 H), 5.40 (s, 1 H), 5.06 (s, 2 H), 3.76 (m, 1 H), 2.90 (s, 3 H), 0.82 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 142.9, 140.6, 128.3, 123.5, 122.1, 120.6 (q, J = 256, O*C*F_3), 120.0, 113.6, 71.1, 51.7, 37.9, 6.4; FTIR (thin film) ν_{max} 1492, 1358, 1248, 1218, 1176, 971 cm^{-1}.

Allylic Bromide 23. A mixture of crude allylic methanesulfonate **22** (7.05 g, 20.0 mmol) and LiBr (3.47 g, 40.0 mmol) in DMF (20 mL) was stirred for 16 h at 10 °C and was diluted with water (50 mL), pentane (49 mL), and ether (1 mL). The organic phase was separated and washed with 0.5% aq Na_2SO_4 (2 × 50 mL) and saturated aq Na_2SO_4 (25 mL). The organic phase was dried ($MgSO_4$), treated with Darco G60 (200 mg, 15 min), and filtered through a plug composed of silica (5 g) layered over neutral alumina (5 g). The plug was washed with 29:1 pentane−ether (50 mL), and the combined filtrates were evaporated to provide the crude allylic bromide **23** (6.47 g, 96% from **16**). HPLC retention times: **23** = 7.7 min. HPLC conditions: 150 × 4.6 mm HP Eclipse XDB−C8 5 μm column, gradient elution with 60 → 80% MeCN in 0.025% aq H_3PO_4 over 7 min and then isocratic elution with 80% MeCN in 0.025% aq H_3PO_4 for 5 min at 1 mL/min, 25 °C with detection at 220 nm. **23**: R_f = 0.40 (19:1 hexane−MTBE); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24 (d, J = 9.0, 1 H), 7.16 (m, 2 H), 5.50 (d, J = 1.0, 1 H), 5.24 (d, J = 1.0, 1 H), 4.37 (s, 2 H), 3.75 (m, 1 H), 0.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 143.7, 142.8, 129.4, 123.8, 121.7, 120.6 (q, J = 256, O*C*F_3), 120.1, 113.4, 51.6, 35.2, 6.4; FTIR (thin film) ν_{max} 1492, 1245, 1221, 1190, 1160 cm^{-1}.

Method 2. Bromine (352 mg, 2.20 mmol) was added to a mixture of PPh_3 (629 mg, 2.40 mmol) and CH_2Cl_2 (3 mL) over 10 min, maintaining the temperature below −10 °C. Allylic alcohol **16** (548 mg, 2.00 mmol) in CH_2Cl_2 (1 mL) was added, and the mixture was allowed to warm to 10 °C over 20 min. The mixture was diluted with pentane (25 mL) and filtered through a plug composed of silica (5 g) layered over neutral alumina (5 g). The plug was washed with 29:1 pentane−ether (30 mL), and the combined filtrates were evaporated to provide the crude allylic bromide **23** (641 mg, 95% from **16**).

Homoallylic Alcohol 24a. TMSCl (0.050 mL) was added to a mixture of (*R*)-piperidine **3** (4.08 g, 14.83 mmol), zinc dust (1.16 g, 17.8 mmol), and DMF (13 mL), the mixture was aged for 10 min at 40 °C, dibromoethane (0.050 mL) was added, and the mixture was again aged for 10 min at 40 °C. Allylic bromide **23** (5.10 g, 15.1 mmol) was added to the mixture over 20 min, maintaining the temperature <16 °C and using DMF (2 mL) to complete the transfer. The mixture was aged at 15 °C for 1 h, diluted with water, saturated aq NH_4Cl, MTBE, and hexanes (15 mL each), and filtered from any remaining zinc through a cotton plug. The organic phase was separated from the filtrate and was washed with a mixture of water (15 mL) and saturated aq NH_4Cl (15 mL) and then with water (40 mL). The aqueous phases were extracted with 1:1 MTBE−hexanes (20 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. The residue (97 area% purity by HPLC and NMR analysis) was purified by flash column chromatography (silica, 25% MTBE in hexanes) to provide homoallylic alcohol **24a** as a white crystalline solid (7.84 g, 99%, >99 area% purity by HPLC and NMR analysis). Crystals suitable for X-ray diffraction analysis was prepared by recrystallization of a sample of **24a** from hexane. HPLC retention times: **24a** = 9.7 min, (*R*)-Boc-2-phenyl-3-piperidone (**3**) = 4.7 min. HPLC conditions: 150 × 4.6 mm HP Eclipse XDB−C8 5 μm column, gradient elution with 60 → 80% MeCN in 0.025% aq H_3PO_4 over 7 min then isocratic elution with 80% MeCN in 0.025% aq H_3PO_4 for 5 min at 1 mL/min, 25 °C with detection at 220 nm. Chiral supercritical phase chromatography (SFC) indicated **24a** (after chromatography but not crystallized) to be >96%ee. SFC conditions: Chiralpak AD 250 × 4.6 mm column, isocratic elution, 2% MeOH in supercritical CO_2 for 2 min then gradient elution with 2 → 10% MeOH in supercritical CO_2 over 8 min at 250 bar, 1.5 mL/min flow at 50 °C with detection at 220 nm. SFC Retention times: (2*R*,3*S*)-**24a** = 8.3 min, (2*S*,3*R*)-**24a** = 9.4 min. **24a**: mp 78−80 °C; R_f = 0.23 (4:1 hexane−MTBE); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41−7.07 (m, 8 H), 5.32 (d, J = 1.7, 1 H), 5.24 (d, J = 1.7, 1 H), 4.62 (s, 1 H), 4.03 (dt, J = 12.9, 3.3, 1 H), 3.72 (m, 1 H), 3.08 (m, 1 H), 2.94 (dd, J = 17.5, 14.1, 2 H), 1.81 (m, 1 H), 1.59 (m, 3 H), 1.37 (s, 9 H), 0.74 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.4, 154.1, 142.9, 142.7, 139.3, 133.8, 129.3, 128.1, 127.2, 122.9, 121.6, 120.9, 120.6 (q, J = 254, O*C*F_3), 113.5, 79.9, 72.7, 63.3, 51.5, 45.1, 39.0, 31.2, 28.4, 21.6, 6.4; FTIR (thin film) ν_{max} 3455, 1688, 1492, 1416, 1245, 1214, 1162 cm^{-1}. Anal. Calcd for $C_{29}H_{34}F_3NO_5$: C, 65.28; H, 6.42; N, 2.63. Found: C, 65.11; H, 6.36; N, 2.51.

TMS Ether 26a. Chlorotrimethylsilane (TMSCl, 1.01 mL, 0.869 g, 8.00 mmol) and a 1 M solution of LiHMDS (8.0 mL, 8.0 mmol) in THF were added simultaneously over 30 min to a solution of **24a** (2.13 g, 4.00 mmol) in THF (8 mL) maintained at 20 °C, and the mixture was aged for 1 h. The mixture was evaporated to half its volume, diluted with water (40 mL), and extracted with hexanes (40 mL). The organic extract was washed with aq NaH_2PO_4 (2 × 40 mL) and filtered through a plug of 2:1 by wt silica gel−$MgSO_4$ (5 g). The plug was washed with 2:1 hexanes−MTBE (20 mL), and the combined filtrates were evaporated to provide TMS ether **26a** (2.30 g, 95%). HPLC retention time: **26a** = 11.3 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 90% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 220 nm. **26a**: R_f = 0.31 (4:1 hexane−MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.11 (m, 8 H), 5.29 (d, J = 2.0, 1 H), 5.25 (d, J = 2.0, 1 H), 5.10 (s, 1 H), 4.13 (dd, J = 13.4, 3.6, 1 H), 3.73 (m, 1 H), 3.39 (m, 1 H), 3.04 (d, J = 13.7, 1 H), 2.80 (d, J = 13.7, 1 H), 1.89−1.74 (m, 3 H), 1.63 (m, 1 H), 1.27 (s, 9 H), 0.80 (m, 4 H), −0.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 154.2, 143.9, 142.8, 141.2, 134.8, 129.4, 127.1, 126.3, 123.1, 121.5, 120.6 (q, J = 256, O*C*F_3), 120.2, 113.1, 79.5, 76.4, 61.4, 51.3, 44.9, 40.0, 32.1, 28.2, 21.4, 6.4, 6.2, 1.7; FTIR (thin film) ν_{max} 1693, 1362, 1245, 1164, 978, 837 cm^{-1}.

Diol 25a. A solution of **26a** (1.82 g, 3.00 mmol) in THF (6 mL) was added over 15 min to a 1 M solution of borane in THF (15.0 mL, 15.0 mmol) maintained at −10 °C. The mixture was allowed to gradually warm to 20 °C over 16 h and evaporated to dryness. The residue was dissolved in THF (6 mL), and a mixture of 2 M aq NaOH (10 mL) and 30% H_2O_2 (5 mL) was added over 10 min, maintaining the temperature at 10 °C. The mixture was aged 1 h at 20 °C and 15 min at 45 °C. The mixture was cooled to 20 °C, diluted with water (15 mL), and extracted with MTBE (2 × 20 mL). The combined organic extracts were washed with water (10 mL), 10% aq Na_2-

SO_3 (10 mL), and brine (10 mL). The organic extract was filtered through a plug of 2:1 by wt silica gel−$MgSO_4$ (5 g). The plug was washed with 2:1 hexanes−MTBE (20 mL), and the combined filtrates were evaporated. HPLC analysis of the residue indicated the residue (1.68 g) to be a 6:1:3 mixture of **27a**, **27b**, and **25a** (**25b** was not detected). HPLC retention times: **27a** = 4.0 min, **27b** = 4.2 min, **25a** = 13.2 min, **25b** = 14.0 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 80% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 220 nm. The crude residue was dissolved in MeCN (10 mL), and 48% aqueous HF (0.20 mL) was added at 20 °C. The mixture was aged at 20 °C for 3 h. MTBE (10 mL) and 3M aq K_2CO_3 (20 mL) were added, the organic phase was separated, and the organic phase was evaporated. HPLC analysis indicated the residue to be a 90:3:7 mixture of **25a**, **25b**, and **27b** (**27a** was not detected). The residue was purified by flash column chromatography (silica, 30% MTBE in hexanes) to provide diol **25a** (1.32 g, 80%, >99 area% by HPLC and NMR analysis). HPLC retention times: **25a** = 6.9 min, **25b** = 7.4 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 70% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 220 nm. Typically crude mixtures resulting from the hydroboration of **26a** could be completely desilylated with excess 48% aq HF or TBAF to provide a 9:1 diastereomeric mixture of **25a** and **25b**.

25a major diastereomer: R_f = 0.35 (1:1 hexane−MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.6, 2 H), 7.34−7.20 (m, 4 H), 7.06 (m, 2 H), 5.15 (s, 1 H), 4.04 (m, 1 H), 3.78−3.66 (m, 3 H), 3.54 (quint, J = 6.2, 1 H), 3.15 (m, 1 H), 2.29 (br s, 2 H), 2.25 (dd, J = 14.7, 5.7, 1 H), 2.07 (dd, J = 14.7, 6.6, 1 H), 1.97 (m, 1 H), 1.76 (m, 3 H), 1.28 (s, 9 H), 0.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 154.9, 143.1, 139.1, 133.5, 129.5, 128.2, 127.4, 121.9, 120.6 (q, J = 255, OCF_3), 119.8, 113.5, 79.9, 72.3, 66.9, 62.1, 51.4, 40.8, 39.3, 37.4, 33.1, 28.2, 21.9, 6.5; FTIR (thin film) ν_{max} 3381, 1688, 1661, 1246, 1163 cm^{-1}.

25b minor diastereomer: R_f = 0.28 (1:1 hexane−MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.1, 2 H), 7.36−7.27 (m, 3 H), 7.23 (d, J = 8.9, 1 H), 7.15 (d, J = 2.7, 1 H), 7.07 (m, 1 H), 5.01 (s, 1 H), 4.05 (m, 1 H), 3.83−3.72 (m, 3 H), 3.18 (m, 1 H), 2.56 (br s, 2 H), 2.24 (dd, J = 15.0, 4.1, 1 H), 2.06 (dd, J = 15.0, 8.3, 1 H), 1.99 (dd, J = 13.4, 3.7, 1 H), 1.88 (m, 1 H), 1.71 (m, 2 H), 1.33 (s, 9 H), 0.85−0.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 154.3, 143.2, 138.8, 134.2, 129.5, 128.4, 127.6, 121.2, 120.6 (q, J = 255, OCF_3), 119.8, 113.2, 80.1, 72.7, 66.3, 64.8, 51.4, 41.9, 39.8, 35.7, 30.3, 28.3, 21.6, 6.4; FTIR (thin film) ν_{max} 3395, 1688, 1662, 1244, 1163 cm^{-1}.

***N*-Boc 6-Phenyl-1-oxa-7-azaspiro[4,5]-decanes 29a and 29b.** Methanesulfonyl chloride (143 mg, 1.25 mmol) was added over 5 min to a mixture of diol **25a** (552 mg, 1.00 mmol) and DIEA (194 mg, 1.50 mmol) in THF (1.5 mL) maintained at −20 °C. The mixture was warmed to 0 °C over 1 h. A solution of 1 M NaHMDS in THF (2.5 mL, 2.5 mmol) was added in three portions over 1 h to the mixture maintained at 20 °C. The mixture was diluted with 2 M aq $NaHSO_4$ (10 mL) and extracted with MTBE (2 × 10 mL). The combined organic extracts were washed with brine (5 mL) and evaporated. The residue was purified by flash column chromatography (silica, 20% MTBE in hexanes) to provide **29a** (470 mg, 88%) and **29b** (15 mg, 3%). HPLC retention times: **29a** = 13.3 min, **29b** = 12.9 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 80% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 220 nm. Samples of **29a** and **29b** exhibited spectral data in agreement to those reported in the literature.[3b]

(3*S*,5*S*,6*R*)-29a major diastereomer: R_f = 0.40 (4:1 hexane−MTBE); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 155.4, 143.0, 139.0, 131.3, 129.1, 128.1, 126.8, 120.6 (q, J = 255, OCF_3), 120.3, 119.9, 113.1, 84.5, 79.9, 72.4, 60.4, 51.3, 43.4, 39.0, 38.3, 32.8, 28.5, 23.8, 6.4; FTIR (thin film) ν_{max} 1689, 1496, 1415, 1366, 1247, 1157 cm^{-1}. Anal. Calcd for $C_{29}H_{34}F_3NO_5$: C, 65.28; H, 6.42; N, 2.63. Found: C, 65.06; H, 6.37; N, 2.50.

(3*R*,5*S*,6*R*)-29b minor diastereomer: R_f = 0.30 (4:1 hexane−MTBE); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 155.3, 143.0, 139.0, 131.0, 129.0, 128.0, 126.9, 120.6 (q, J = 257, OCF_3), 120.2, 119.9, 113.0, 84.2, 79.9, 72.4, 62.7, 51.3, 42.9, 38.4, 37.6, 31.5, 28.4, 23.3, 6.4; FTIR (thin film) ν_{max} 1690, 1496, 1414, 1362, 1246, 1162 cm^{-1}.

(3*S*,5*S*,6*R*)-(−)-6-Phenyl-1-oxa-7-azaspiro[4,5]decane (−)-1. A mixture of **29a** (400 mg, 0.750 mmol), EtOAc (3 mL) and 48% aq HBr (0.40 mL) was aged for 1 h at 25 °C and was evaporated to dryness. The residue was dissolved in $CHCl_3$ (3 mL) and washed with 2 M aq Na_2CO_3 (3 mL). The aqueous phase was extracted with $CHCl_3$ (3 mL), and the combined organic extracts were evaporated to dryness to give (−)-**1** (309 mg, 95%). HPLC analysis of the Marfey's reagent (*N*-α-(2,4-dinitro-5-fluorophenyl)-L-alaninamide) derivative[26] indicated (−)-**1** to be optically pure (97% ee). HPLC retention times: (+)-**1** Marfey's derivative = 9.5 min, (−)-**1** Marfey's derivative = 10.2 min, HPLC conditions: 150 × 4.6 mm ACE 3 C18 column, isocratic elution with 70% MeCN in 0.025% aq H_3PO_4 at 1 mL/min, 25 °C with detection at 360 nm. The spectral data exhibited by (−)-**1** was identical to that reported in the literature[3b] except for the expected opposite optical rotation. (−)-**1**: $[\alpha]^{23}_D$ = −12.8° (c = 3.05, MeOH); authentic sample of (+)-**1**: $[\alpha]^{23}_D$ = +12.7° (c = 3.00, MeOH).

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Supporting Information Available: X-ray crystallographic data for compounds **24a** and **24b**. Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **16**, **25a**, and **25b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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