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Stereoselective Preparation of a Cyclopentane-Based NK1 Receptor Antagonist Bearing an Unsymmetrically Substituted Sec−Sec Ether

Jeffrey T. Kuethe,* Jean-Francois Marcoux, Audrey Wong, Jimmy Wu, Michael C. Hillier, Peter G. Dormer, Ian W. Davies, and David L. Hughes

Department of Process Research, Merck & Company, Incorporated, P.O. Box 2000, Rahway, New Jersey 07065

Jeffrey_Kuethe@Merck.com

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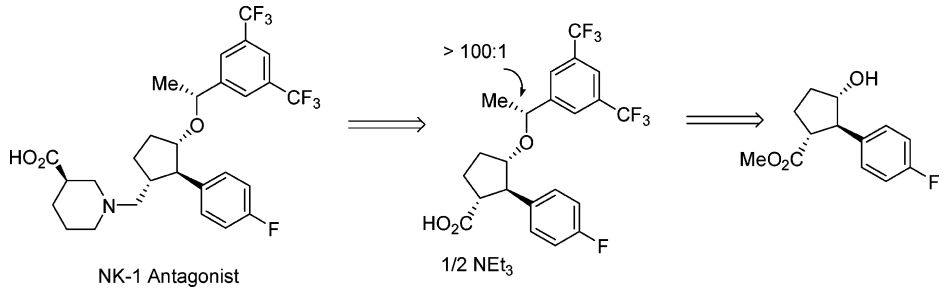

A highly efficient synthesis of the potent and selective NK-1 receptor antagonist **1** is described. The key transformation involved the etherification reaction between cyclopentanol **12** and chiral imidate **30** which was catalyzed by HBF_4 to initially give ether **14** as a 17:1 mixture of diastereomers and in 75% combined yield. The diastereoselectivity was upgraded to 109:1 by crystallization of the triethylamine solvate **44** which was isolated in 54% yield from **12**. Mechanistic studies confirmed that the etherification reaction proceeds through an unprecedented S_N2 reaction pathway under typical S_N1 reaction conditions.

Introduction

Located in specific areas of the central nervous system (CNS) and primarily associated with sensory neurons, neurokinin-1 (NK-1) is a member of the seven-transmembrane G-protein-coupled receptor family. The natural ligand for NK-1 is the tachykinin peptide substance P and has been implicated in the pathophysiology of a wide range of conditions including anxiety, asthma, cystitis, emesis, inflammatory bowel disease, migraine, movement disorders, pain, and psoriasis.[1] The search for potent, nonpeptide antagonists of the human neurokinin-1 (hNK-1) receptor has been an intensive area of investigation.[2,3] The prevention of chemotherapy-induced emesis has been established with Merck's aprepitant (Emend), the only approved drug in this class.[4,5] Efforts to target other potent, orally active hNK-1 antagonists has led to the discovery of a series of cyclopentane-based compounds such as **1** which have significant binding affinity (subnanomolar) for the hNK-1 receptor.[6,7] Compound **1** contains five stereocenters: a central core possessing three contiguous all-trans stereocenters, a pendent bis(trifluoromethyl)-

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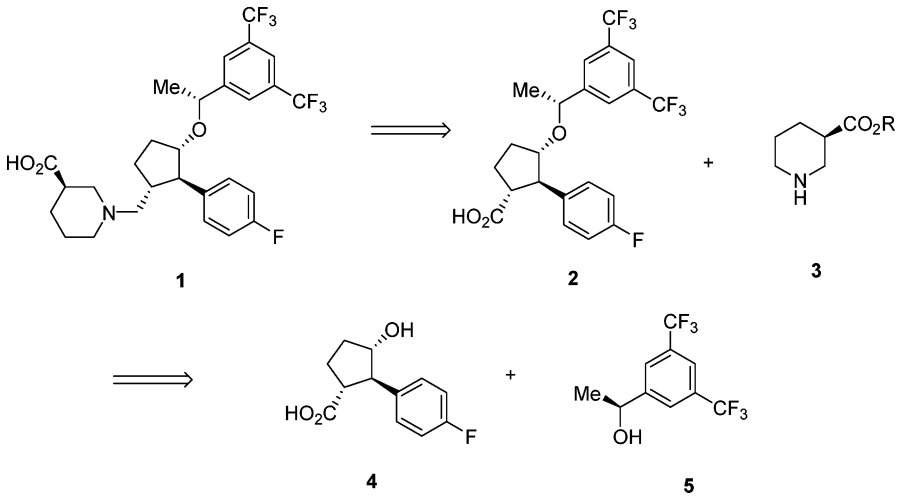
SCHEME 1



benzylic ether, and a nipecotic acid moiety. To fully evaluate this compound, an efficient and practical synthesis was required which would allow for the preparation of kilogram quantities. We have previously described the enantioselective synthesis of the core 1,2,3-trisubstituted cyclopentane carboxylic acid **4**.[8] The most challenging aspect for the preparation of **1** was construction of the unsymmetrically substituted sec−sec chiral bis(trifluoromethyl)benzylic ether functionality which posed formidable synthetic challenges and required careful control of the relative and absolute stereochemistry. In this paper we disclose the preparation of **1** including a detailed account of the issues and mechanistic details associated with the formation of the sec−sec ether bond of this challenging substrate Scheme 1).

Results and Discussion

Preparation of Ether (2). Ether bond formation is one of the most important and frequently utilized transformations in organic synthesis.[9] The formation of carbon−oxygen single bonds via the attack of an alkoxide on an alkyl halide, first reported in 1850 (Williamson ether synthesis), is still extensively used at industrial scale. Carbon−oxygen single bond forming reactions which lead directly to chiral acyclic *secondary*−*secondary* (sec−sec) ethers of subclass **6** are particularly rare (Scheme 2). Reactions leading to sec−sec ethers are typically nonstereospecific, and mixtures of ethers **6a** and **6b** are formed. Notable exceptions have surfaced, including palladium-, iridium-, and zinc-catalyzed allylic etherifications,[10] asymmetric aldol additions,[11] diastereoselective additions to α-acetoxy ethers using α-(trimethylsilyl)benzyl auxiliaries,[12] oxa-Michael additions of alkoxides to Michael acceptors,[13] and addition of silyl enol ethers to 1,3-butadienes in the presence of SO_2.[14] However, each of these methods give ethers with particular substitution patterns which are not broadly applicable. The preparation of **7** was envisioned to arise from two possible disconnections as shown in Scheme 2. Disconnection A would involve formation

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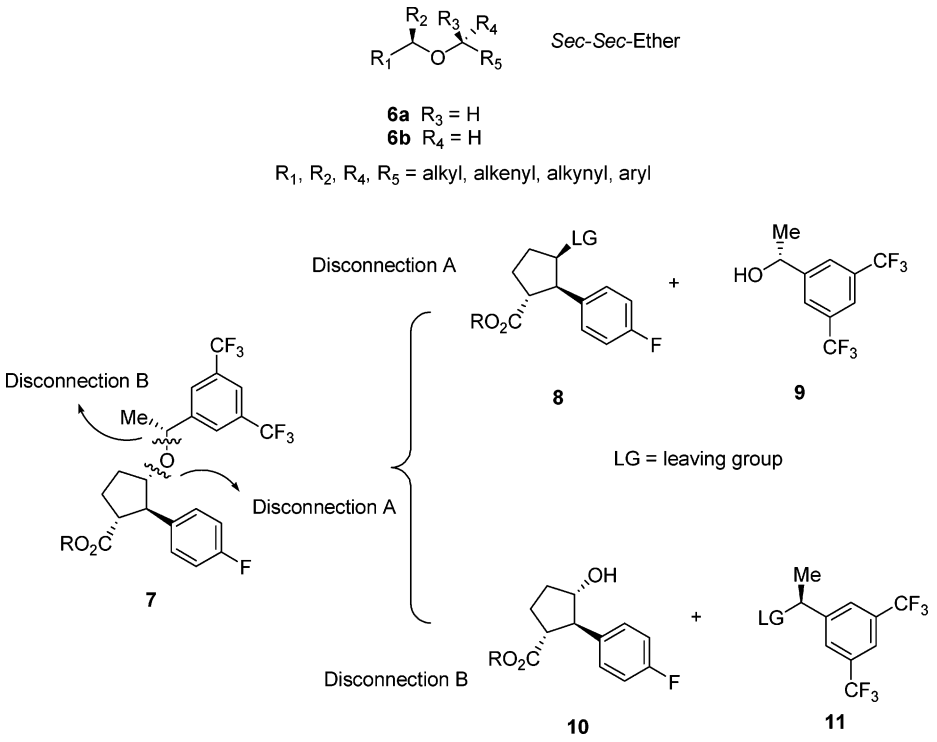
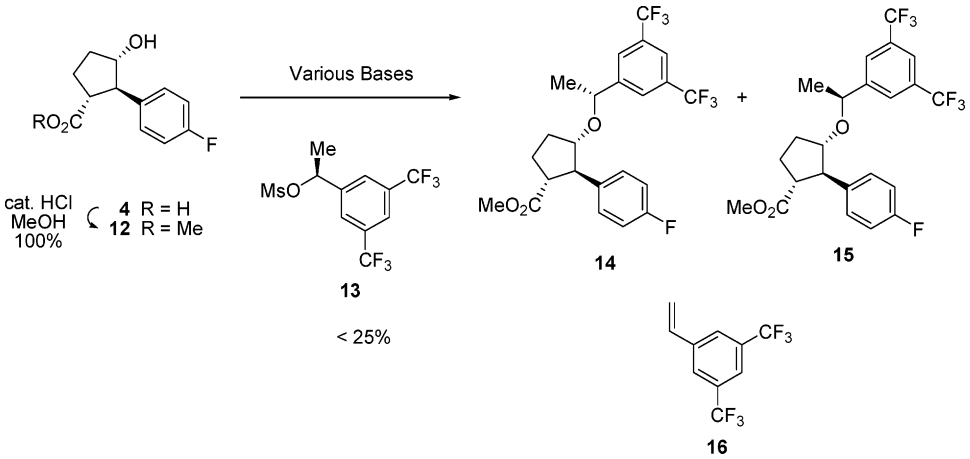
SCHEME 2



SCHEME 3

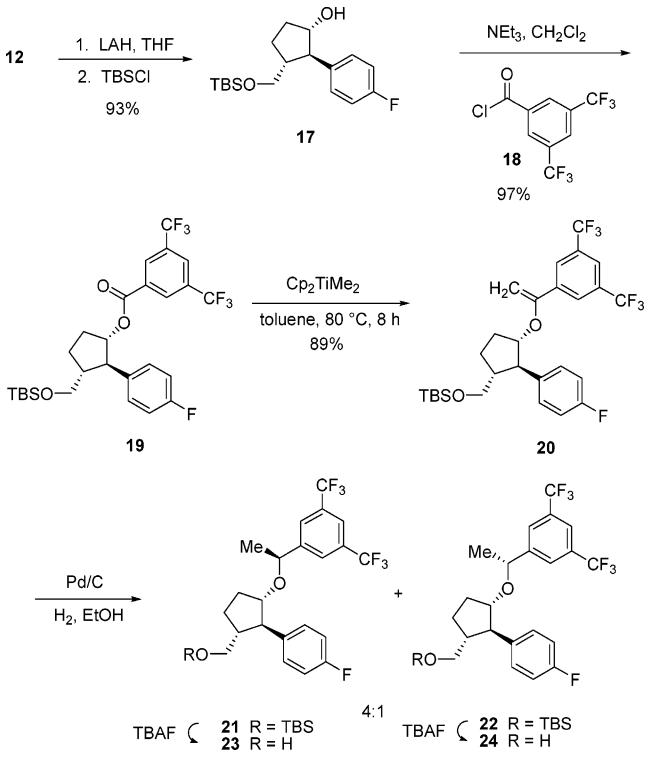


of the ether bond by displacement of a suitable leaving group on the cyclopentane core **8** with chiral benzylic alcohol **9**. Disconnection B would involve formation of the ether bond by displacement of a suitable benzylic leaving group on the bis-(trifluoromethyl)phenyl moiety **11** with alcohol **10**. Each of these disconnections posed concerns including low substrate reactivity, stereocenter scrambling, and elimination. From a synthetic standpoint, only disconnection B appeared to offer significant advantages, since both **10** and **11** would be available in a limited number of steps and would not suffer from diminished reactivity of alcohol **9**.

Our investigations began by examining the direct displacement of **11** bearing various leaving groups with alcohol **12** under strictly S_N2 reaction conditions analogous to the Williamson ether synthesis (Scheme 3). Conversion of **4** to **12** was accomplished by treatment of **4** with a catalytic amount of HCl in MeOH and gave **12** in quantitative yield. Treatment of a mixture of **12** with 10 equiv of mesylate **13** in the presence of various bases (NaO*t*-Bu, KO*t*-Bu, BuLi, NEt_3, pyridine, NaH) led to extremely low conversions (<10%) to the desired ether **14**; however, the observed diastereoselectivity was >20:1 for **14**:**15**. In the presence of 30 equiv of **13** the yield of **14** improved to 22%. Under essentially all conditions examined, elimination of the mesylate and the formation of styrene **16** was the major reaction pathway. The use of other leaving groups such as OTs, $OSO_3C_6H_4$-4OMe, OTf, and Br did not improve the reaction profile and resulted in extensive formation of **16** and led to only to minor amounts (<30%) of **14**, and this approach was quickly abandoned.

Substrate-controlled diastereoselective hydrogenation of vinyl ethers has been utilized in the preparation of chiral secondary ethers and often can proceed with complete control of absolute stereochemistry.[15] A diastereoselective hydrogenation approach was successfully utilized on large scale for the preparation of kilograms of Merck's aprepitant (Emend) where a similar bis-(trifluoromethyl)benzylic ether was required.[4] With a great deal

SCHEME 4



of in-house experience, we examined the preparation and catalytic hydrogenation of vinyl ether **20** (Scheme 4). Reduction of **12** with LAH in THF gave the intermediate diol in quantitative yield. Subsequent protection of the primary alcohol was accomplished with TBDMSCl/imidazole in DMF and furnished the monoprotected alcohol **17** in 74% unoptimized yield. Reaction of **17** with bis(trifluoromethyl)benzoyl chloride **18** in the presence of NEt_3 afforded ester **19** in 97% yield. Conversion of **19** to vinyl ether **20** was conducted with 2.3 equiv of dimethyltitanocene (DMT)[16] in toluene at 80 °C for 8 h and gave **20** in 89% yield. Catalytic hydrogenation over 5% Pd/C under an atmosphere of 20 psi hydrogen for 8 h afforded a 1:4 mixture of **21**:**22** in 93% combined yield. Desilyation of this mixture with TBAF gave **23**:**24** which unequivocally established the absolute stereochemistry (vida infra). This result confirmed that hydrogenation of **20** was not completely diastereoselective and that preferential formation of the undesired diastereomer **21**, most likely due to approach of the catalyst from the α face, would be a difficult hurdle to overcome. This approach was also abandoned due to more promising routes under parallel investigation (vida infra).

The reductive etherification of carbonyl compounds with alkoxytrimethylsilanes in the presence of TMSOTf and a trialkylsilane has been reported to be a promising method for the preparation of ethers under nonbasic conditions.[17,18] In certain cases acceptable levels of diastereoselectivity have been achieved although the use of this methodology for the preparation of acyclic sec−sec ethers has not been realized. It was envisioned that construction of the ether bond of **1** via the TMSOTf-mediated reductive etherification of **25** with acetophenone **26** in the presence of Et_3SiH would provide an attractive method for the preparation of **1** (Scheme 5). Trimethylsilyl ether **25** was prepared in 94% yield by reaction of **12** with TMSCl and NEt_3 in CH_2Cl_2 at 0 °C. Treatment of a mixture of **25** and **26** with substoichiometric amounts (0.1−0.5 equiv) of TMSOTf and Et_3SiH (1.2 equiv) in CH_2Cl_2 at −78 °C and allowing the mixture to warm to −20 °C afforded a 2.3:1 mixture of **14** and **15** in 37% HPLC assay yield.[19] The remaining mass balance was identified as alcohol **12**, acetophenone **26**, and racemic alcohol **5** arising from competitive reduction of **26**. Despite the low conversion to products, it was encouraging that the major product was the desired diastereomer. In an attempt to improve the ratio of **14**:**15** the reaction parameters were varied with respect to TMSOTf, reaction temperature, and reducing agent. The optimal reaction conditions involved reaction of **25** with **26** in the presence of 5 equiv of TMSOTf and 1.2 equiv of Et_3SiH for 18 h and gave **14** and **15** in 65% combined HPLC assay yield and as a 3.2:1 mixture of diastereomers. To rationalize the observed diastereoselectivities, molecular modeling calculations were conducted on the proposed oxonium ion intermediates.[20] The oxonium ion can form in either the *E* (shown) or *Z* conformations. Since the *Z* oxonium ion conformers were approximately 3 kcal/mol higher in energy, these conformers most likely do not contribute to the stereochemical outcome of the reaction.[21] The *E* conformation had two prevalent conformers **27** and **28** where the steric bulk of the 4-fluorophenyl group blocks the *β*-face of the oxonium ions. Reduction occurs from the α-face on each conformer leading to the dias-tereomeric mixture of products. Since there was only a 0.6 kcal/mol energy difference in these lowest energy conformers leading to **14** and **15** this nicely supports the observed product distribution of ∼3:1 of **14**:**15** under the best reaction conditions. Thus, the observed diastereoselectivity of the reaction may be attributed to the energetic difference between rotamers **27** and **28**.

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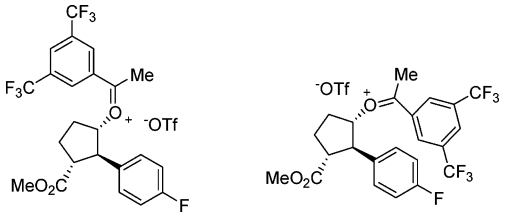
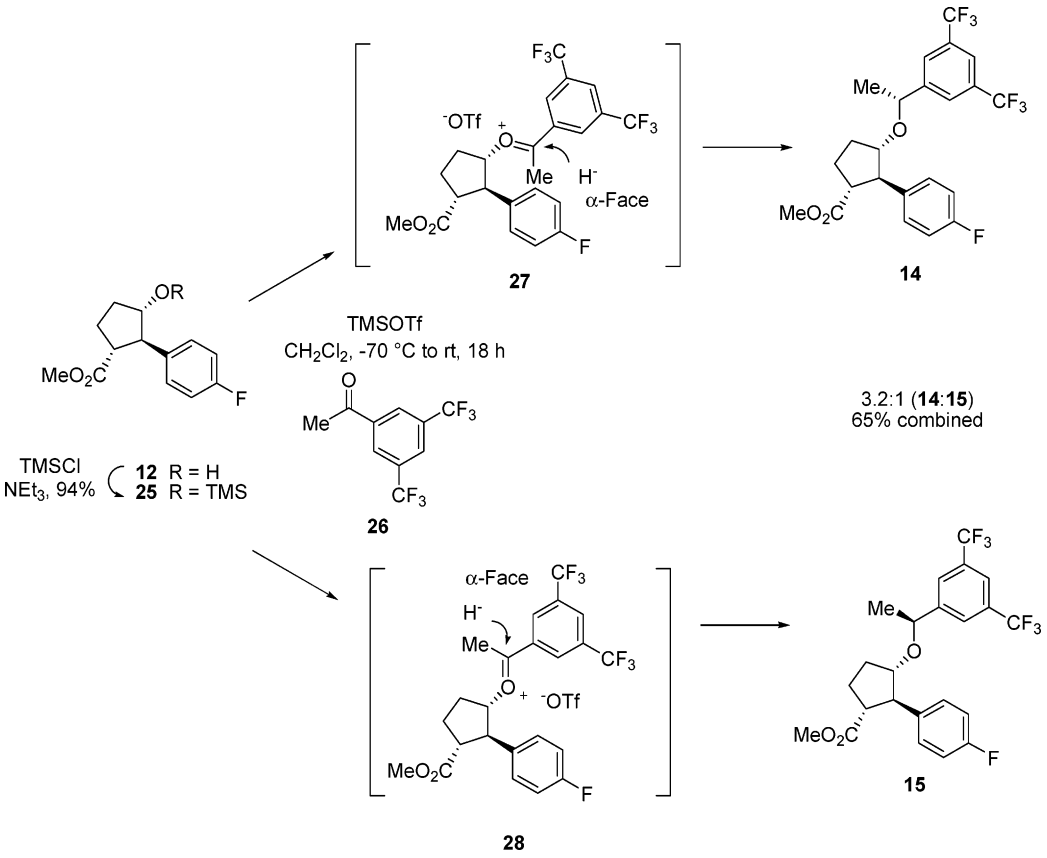
(19) HPLC assay yield refers to quantitative HPLC analysis of the crude reaction mixtures using an analytically pure standard.

(20) The Titan software package was used to perform the analysis. The "Conformer Study" option was selected as a computation type, and PM3 was selected as the method, the results in conformations being generated using the included MMFF94 molecular mechanics force field and the resulting structures being minimized with the PM3 semiempirical method. Calculations were performed in the gas phase.

(21) The following *Z* conformations were ∼3 kcal/mol higher in energy and most likely do not contribute to the stereochemical outcome of the reaction:



SCHEME 5



The use of trichloroimidates for the preparation of ethers is an effective method for O-alkylation of alcohols.[22] This method has found widespread use in the protection of alcohols as benzyl ethers since the corresponding trichlorobenzylimidate is inexpensive and commercially available.[23] The mechanism involves activation of the imidate with a catalytic amount of a strong acid (typically TfOH) which leads to ionization of the electrophile and the formation of carbocation which is trapped by the alcohol. To achieve high conversions to the ether products, a large excess of the imidate is often required. This also generates large amounts of trichloroacetamide as the reaction byproduct. For the preparation of sec−sec ethers, this protocol has been limited to glycosidation reactions due to the S_N1 nature of the reaction which leads to diastereomeric mixtures of products.[22]

The original synthesis of ether **14** involved reaction of alcohol **12** with racemic imidate **29** in the presence of a catalytic amount of TfOH and furnished an ~1.2:1 mixture of **14**:**15** and required careful chromatographic separation (Scheme 6).[6b−e,7] We thought it worthwhile to reinvestigate this reaction with chiral imidate **30** in an effort to improve the selectivity of the reaction. Imidate **30** was prepared in 95% yield and in 99.5% ee by reaction of **5** with 1.05 equiv of trichloroacetonitrile in the presence of catalytic (0.1 equiv) DBU. Treatment of a mixture of alcohol **12** and chiral imidate **30** with catalytic TfOH only afforded a 1.2 to 1.3:1 mixture of **14**:**15** in a combined 91% HPLC assay yield. The use of other acid catalysts (TMSOTf, HCl, H_2SO_4, TFA, MsOH) in a number of solvent systems and under a variety of reaction conditions did not improve the diastereomeric ratio of the products (~1.2:1 **14**:**15**) or simply resulted in no reaction. These results suggested that reaction of **12** with imidate **20** was occurring under S_N1 conditions when these catalysts were employed. Typical HPLC assay yields for reactions giving a 1.2:1 mixture of **14**:**15** were >85%.

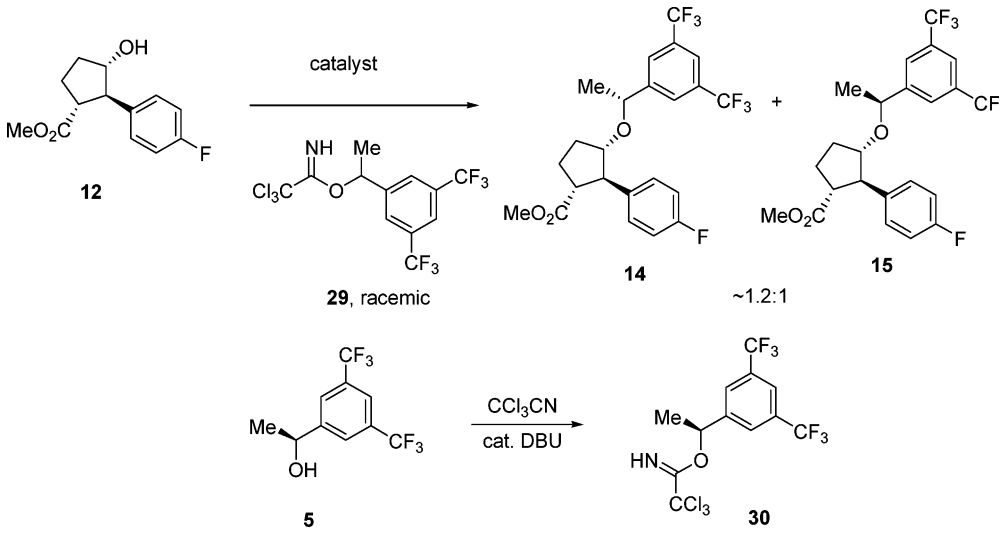
Interesting reactivity was observed when a mixture of **12** and two equiv of imidate **30** was treated with 20 mol % of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −15 °C (Scheme 7). While HPLC analysis of the crude reaction mixture after 3 h indicated low conversion to products (<10%), the diastereomeric ratio of **14**:**15** was 8:1. Upon warming the reaction mixture to room temperature and stirring for an additional 15 h this ratio dropped to 1.6:1. This indicated that the initial reaction between **12** and **30** may be proceeding through an unprecedented S_N2 reaction pathway. Warming the reaction mixture appeared to divert into a conventional S_N1 pathway. Unfortunately, prolonged reaction at −15 °C did not improve the overall conversion to **14** and **15** (36% combined). After considerable optimization of the reaction parameters including similar catalysts and catalyst loading, temperature, and solvent combinations, it was discovered that reaction of a mixture of alcohol **12** and imidate **30** (1.5 equiv) with 10 mol % HBF_4[24] in a solvent system of 1,2-dichloroethane

(22) For leading references, see: (a) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240. (b) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731. (c) Schmidt, R. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 406. (d) Wessel, H. P.; Iversen, T.; Bundel, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247. (e) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139. (f) Nakajima, N.; Saito, M.; Ubukata, M. *Tetrahedron Lett.* **1998**, *39*, 5565. (g) Eichler, E.; Yan, F.; Sealy, J.; Whitfield, D. M. *Tetrahedron* **2001**, *57*, 6679. (h) Kusumoto, T.; Hanamoto, T.; Sato, K.; Hiyama, T.; Takehara, T.; Shoji, T.; Osawa, M.; Kuiyama, T.; Nakamura, K.; Fujisawa, T. *Tetrahedron Lett.* **1990**, *31*, 5343.

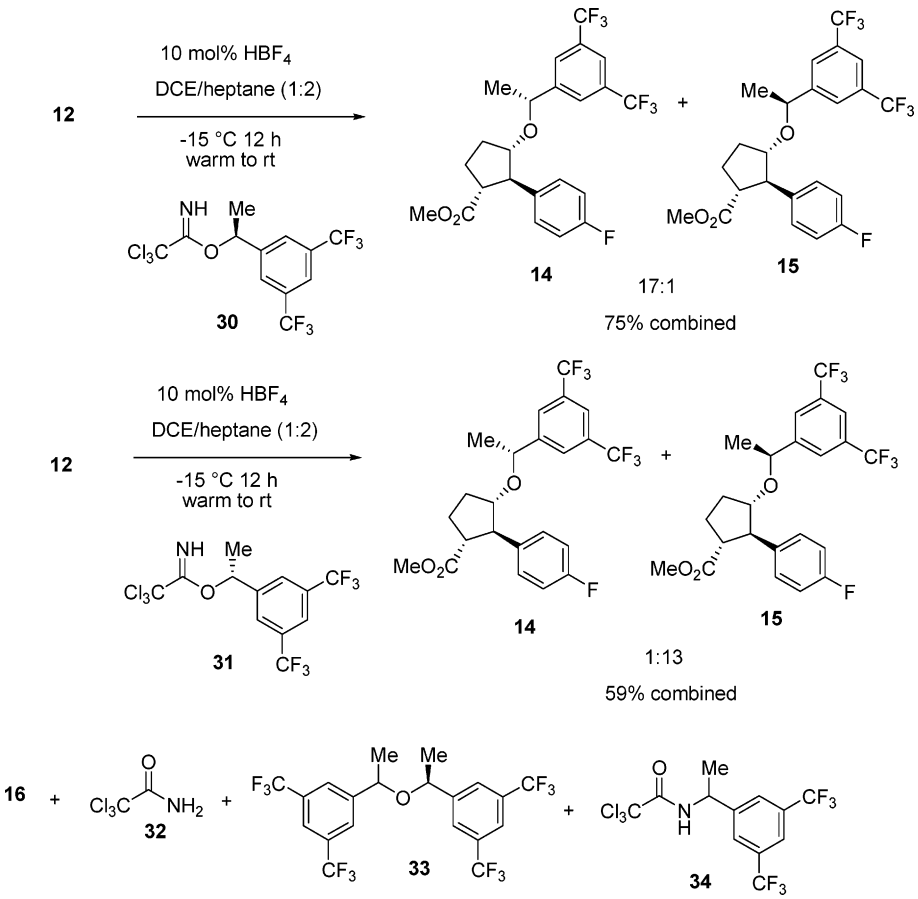
(23) Available from Aldrich Chemical Co.

(24) Commercially available 54 wt % tetrafluoroboric acid solution in diethyl ether was used in all transformations.

SCHEME 6



SCHEME 7

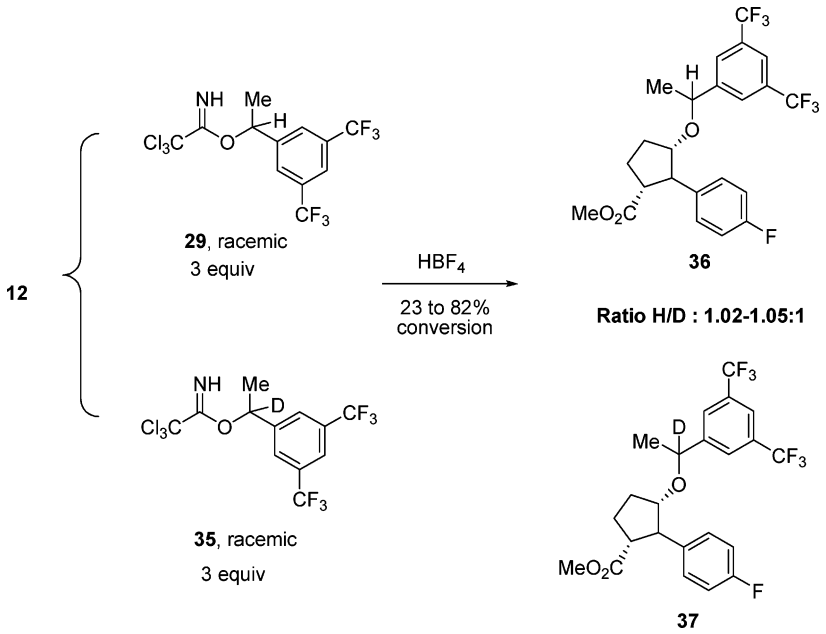


(DCE)/heptane (1:2) at −15 °C for 12 h and warming to room temperature gave **14** and **15** as a 17:1 mixture of diastereomers and in a combined 75% HPLC assay yield. The remaining mass balance was predominantly unreacted starting material **12** (10−13%). Also identified as minor reaction products in the crude reaction mixture were styrene **16**, trichloroacetamide **32**, bisether **33**, and the racemic amide **34** arising from rearrangement of imidate **30** (vida infra).[25] Since ether **14** was the major reaction product, the etherification reaction was occurring with nearly complete inversion of configuration of the imidate reaction center. Further evidence was obtained by repeating the experiment with imidate **31**. Treatment of a mixture of **12** and **31** with 10 mol % HBF_4 under identical reaction conditions afforded a 13:1 mixture of **15** and **14** in an unoptimized 59% assay yield.[26]

(25) The individual components of the crude reaction mixture were identified by analysis of the crude NMR and were not separated from one another.

(26) We cannot completely rule out a matched−mismatched interaction between chiral alcohol **4** and imidates **30** and **31**.

SCHEME 8



The use of HBF_4 as the catalyst for the etherification was crucial for obtaining high levels of diastereoselectivity and relatively high conversion to product. The fact that sec−sec ethers have rarely, if ever, been obtained with high levels of diastereocontrol in S_N2 fashion under S_N1 reaction conditions prompted us to investigate the complex mechanistic details of this exceptional reaction. The origin of the inversion of the imidate center was established by kinetic isotope experiments (Scheme 8). For example, reaction of **12** with a mixture of 3 equiv of racemic imidate **29** and 3 equiv of deuterated imidate **35** was conducted under the optimized conditions described above. Examination of the crude NMR at different time intervals clearly indicated a negligible secondary kinetic isotope effect ($K_{H/D} \sim 1.0$) which was consistent with a minimal hybridization change at the reacting center.[27]

After extensive optimization, complete conversion of the starting material to products was never achieved. This observation was only noticed when HBF_4 and $BF_3{\cdot}OEt_2$ were employed as the catalysts. Furthermore, the amount of time the starting material was in contact with HBF_4 had a profound impact in the conversion. For example, when HBF_4 was added in one portion to a mixture of the two starting materials **12** and **30** under the optimized reaction conditions, typical conversion to products was noted (75%). On the other hand, the longer the starting material was aged with the Lewis acid prior to the addition of imidate **30**, the lower the conversion to products (Table 1). In an effort to understand this phenomenon, a series of NMR experiments were devised to determine the nature of the deactivation of the starting material. The course of the deactivation of **12** was conducted by the addition of HBF_4 or $BF_3{\cdot}OEt_2$ to a solution of **12** in CD_2Cl_2 and analyzing the reaction mixture by ^1H, ^{11}B, and ^{19}F NMR. Treatment of **12** with 1.0 equiv of $BF_3{\cdot}OEt_2$ at −10 °C gave a nearly 1:1 mixture of **12**:**38**. Analysis of the ^{11}B NMR was consistent with coordination of BF_3 to the alcohol **38** (Scheme 9).[28] In addition, there were no detectable amounts of **40**−**42** present.[28] Subsequent warming of the sample led to the exclusive formation of **38** which was irreversible under the reaction conditions and does not participate in the etherification reaction with imidate **30**. The nearly complete coordination of BF_3 nicely accounts for the lack of reactivity of alcohol **12** in the etherification reaction.

TABLE 1

age time (h)	Lewis acid	equiv	assay yield **14**:**15** (%)
0	HBF_4	0.15	75
1	HBF_4	0.15	56
3	HBF_4	0.15	20
5	HBF_4	0.15	0
1	$BF_3{\cdot}OEt_2$	0.15	<5
0	$BF_3{\cdot}OEt_2$	1.00	16
0	HBF_4	1.00	42

When **12** was treated with 1.0 equiv of HBF_4 at −10 °C for 1 h, <20% coordination was observed. The ^{11}B NMR spectrum clearly indicated the presence of a different coordinated intermediate, which we speculate was **39**, although there were also detectable amounts of **38** present (Scheme 9). It is hypothesized that a rapid equilibrium between **12** and complex **39** exists. Upon warming to room temperature, both the ^1H and ^{11}B NMR spectrums of the crude reaction mixture became increasingly broad and complex, most likely due to exchange processes. As the etherification reaction progresses, increased amounts of BF_3 and HF are present, since HBF_4 can be considered as an equilibrium mixture of BF_3 and HF. As the concentration of BF_3 in the reaction medium increases, increased amounts of **38** are formed. Since HBF_4 is a more active catalyst than BF_3, activation of **30** and subsequent etherification is the preferred reaction pathway at the early stages of the reaction. When the concentration of BF_3 increases, competitive deactivation and the formation of **38** leads to unreacted starting material at the end of the etherification reaction. Efforts to breakup this coordination and increase the conversion by the addition of certain additives such as water, $NaPF_6$, KPF_6, $LiPF_6$, or Na_2-

(27) Carpenter, B. K. *Determination of Organic Reaction Mechanisms*; John Wiley and Sons: New York, 1984.

(28) Nöth, H.; Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; Springer-Verlag: New York, 1978.

SCHEME 9

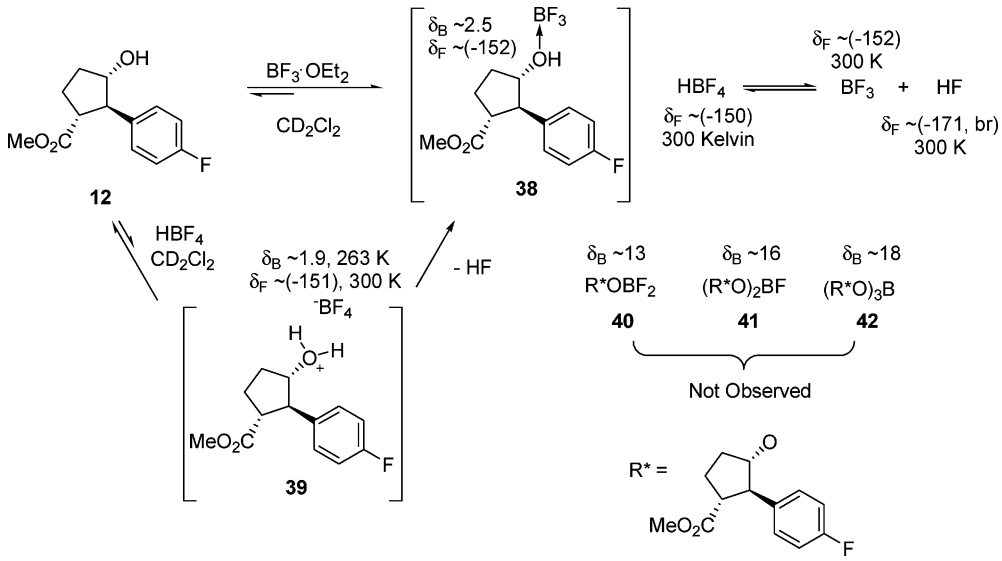


TABLE 2

entry	time	temperature (°C)	ee of **30** %	% conversion (**14**:**15**)
1	0	−15	99.5	0
2	5 min	−15	90	5
3	1 h	−15	90	20
4	6 h	−15	90	35
5	12 h	−15	90	72
6	15 h	20	90	75

SiF_6 either lead to no improvement or a shut down in the S_N2 pathway, and significant erosion in the diastereoselectivity resulted.

In an effort to identify the origin of the formation of the minor diastereomer **15** and understand whether its formation was a function of a breakdown in the S_N2 pathway to an S_N1 pathway, the activation of the imidate (**30**) was investigated. When the etherification reaction was performed under the optimized conditions (1.5 equiv **30**, 10 mol % HBF_4, 1:2 DCE/heptane, −15 °C, 12 h, warm to room temperature) and the ee of the imidate **30** was monitored during the course of the experiment, it was discovered that epimerization of the imidate **30** was occurring (Table 2). The data in Table 2 show that once the HBF_4 was added to the mixture of **12** and **30** at −15 °C a rapid epimerization occurred. No further epimerization of **30** was noted even after the reaction reached room temperature. It is believed that addition of HBF_4 to reaction mixture caused a localized exotherm leading to a small amount of **43** (Scheme 10). Intermediate **43** can either reform the imidate leading to racemization or rearrange to give racemic amide byproduct **34**. Slow addition of HBF_4 to the reaction mixture failed to stop the epimerization and resulted in decreased conversion to product. When HBF_4 was added to a −78 °C solution of **12** and **30**, which effectively minimized any localized exotherm resulting from the addition of HBF_4 to the reaction mixture, the diastereomeric ratio of **14**:**15** jumped to 55:1; however, the overall conversion after warming to room temperature was only ∼55%. We speculate that the formation of the minor diastereomer **15** is a result of the reaction of **12** with the epimerized imidate **31** under S_N2 conditions, although we cannot conclusively rule out the involvement of **43** under S_N1 conditions.

The isolation of the desired ether **14** from the crude reaction mixture was accomplished by conversion of the ester to the corresponding carboxylic acid and crystallization as the triethylamine solvate **44** (Scheme 11). Upon completion of the etherification reaction the insoluble trichloroacetamide **32** was filtered leaving a 17:1 mixture of **14** and **15** as a DCE/heptane solution. The solvent was switched to MeOH, and the ester was saponified with KOH. The carboxylic acid was isolated after neutralization and the addition of NEt_3, which gave the highly crystalline triethylamine solvate **44** as a 40:1 mixture of diastereomers. Recrystallization from MTBE/heptane gave a 109:1 diastereomeric mixture of **44** in 54% overall yield from **12**.

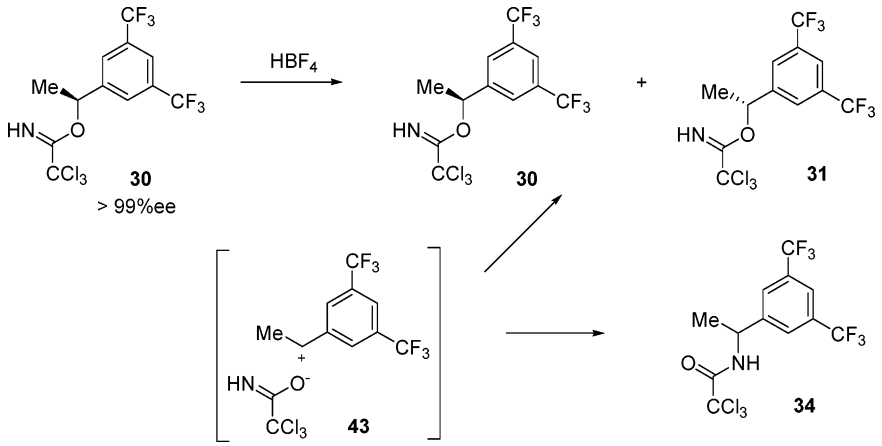
Completion of the Synthesis. The completion of the synthesis of **1** required an effective method for the preparation of the (*R*)-nipecotic moiety (**3**). While (*R*)-ethyl nipecotate L-tartrate is commercially available,[23] the saponification of the ethyl ester moiety at the final stages of the synthesis was accompanied by small amounts of epimerization at the carboxylic acid center resulting in diastereomeric contamination of the final product. To avoid this epimerization under strongly basic conditions, a *tert*-butyl group was selected for its ease in removal under acidic conditions. *tert*-Butyl nipecotate **48** could be prepared via two separate protocols (Scheme 12). For example, reaction of **45**[29] with isobutylene in the presence of a catalytic amount of H_2SO_4 gave *tert*-butyl ester **46** in 97% yield. Catalytic hydrogenation over 10% Pd/C afforded **48** in quantitative yield. Since the preparation of **45** began with (*R*)-nipecotic acid **47**, a more streamlined approach was developed and involved the direct conversion of **47** to **48**. Treatment of **47** with BF_3·OEt_2 in *t*-BuOAc furnished the desired product **48** in 70% yield for the one-pot procedure.[30] While **48** could be isolated in analytically pure form by distillation, the purity of the material from either synthetic route was sufficiently high to allow for its use in subsequent transformations without the need for additional purification.

Conversion of **44** to the final product **1** involved a series of high-yielding transformations where **1** was the only isolated

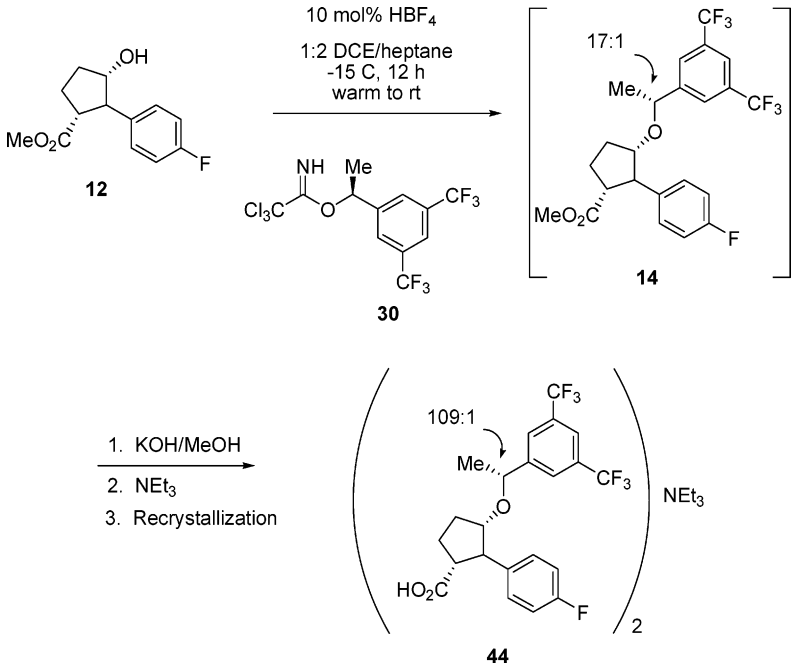
(29) Das, J.; Kimball, S. D.; Reid, J. A.; Wang, T. C.; Lau, W. F.; Roberts, D. G. M.; Seiler, S. M.; Schumacher, W. A.; Ogletree, M. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 41.

(30) Grigan, N.; Musel, D.; Veinberg, G. A.; Lukevics, E. *Synth. Commun.* **1996**, *26*, 1183.

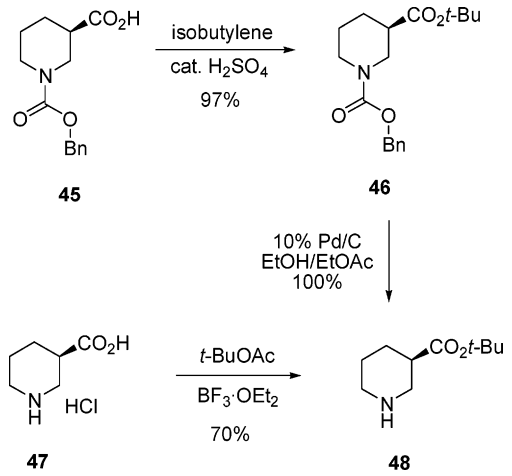
SCHEME 10



SCHEME 11



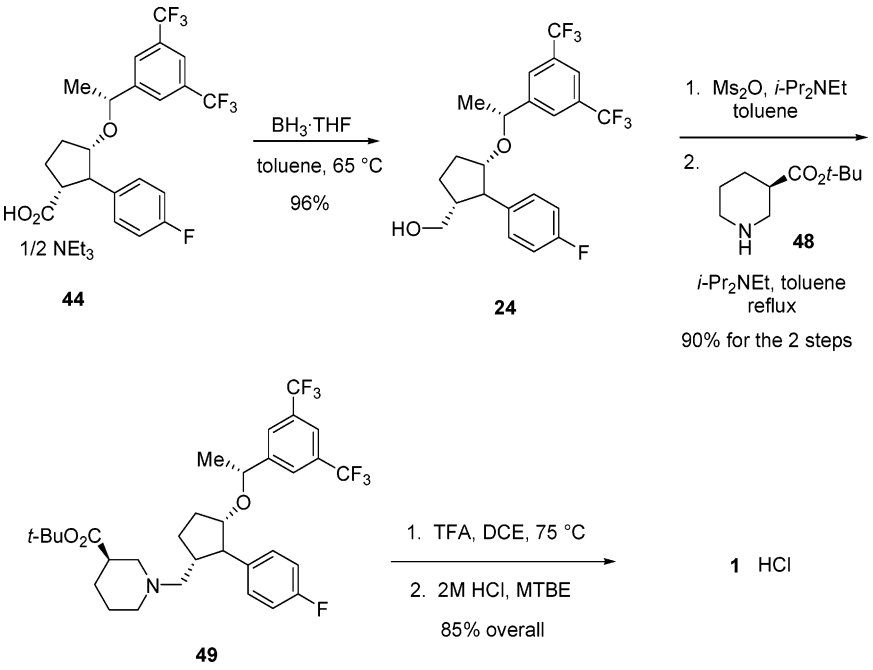
SCHEME 12



product (Scheme 13). Direct reduction of **44** to alcohol **24** was conducted with 2 equiv of BH_3·THF in toluene at 65 °C and furnished **24** in 96% HPLC assay yield. After workup, the crude toluene solution of **24** was treated with 1.2 equiv of Ms_2O in the presence of *i*-Pr_2NEt to give the intermediate mesylate. Addition of **48** to the reaction mixture followed by additional *i*-Pr_2NEt and heating to reflux afforded **49** in 90% HPLC assay yield for the two-step one-pot process. Finally, the *tert*-butyl protecting group was cleaved with TFA in 1,2-dichloroethane (DCE) at 75 °C to give **1** in 95% yield. The free base of compound **1** was not a crystalline solid and was converted to its crystalline HCl salt by treatment with 2 N HCl in ether (85%).

In conclusion, we have outlined a highly efficient method for the preparation of sec−sec ether found in the potent and selective NK-1 receptor antagonist **1**. The key reaction involved the displacement of alcohol **12** with chiral imidate **30** in the presence of 10 mol % HBF_4 giving the desired ether product **14** as a 17:1 mixture of diastereomers where the diastereomeric ratio could be further increased to >100:1 by crystallization of the triethylamine solvate **44**. The mechanistic details of the reaction support the observation that the reaction was proceeding through an unprecedented S_N2 reaction pathway under standard S_N1 reaction conditions. Finally, the conversion of **44** to **1** was accomplished in four additional steps giving **1** in 57% overall

SCHEME 13



yield from **4**. The overall sequence requires no chromatographic separations and is amenable to multikilogram scale.

Experimental Section

Melting points are uncorrected. All solvents and reagents were used as received from commercial sources. Analytical samples were obtained by chromatography on silica gel using an ethyl acetate−hexane mixture as the eluent unless specified otherwise. The water content (KF) was determined by Karl Fisher titration.

Preparation of Methyl (1*R*,2*R*,3*S*)-2-(4-Fluorophenyl)-3-hydroxycyclopentane-1-carboxylate (12). To a solution of 1.24 kg (5.53 mmol) of **4** in 11 L of MeOH was added 230 mL (2.77 mol) of concentrated HCl. The resulting mixture was heated to reflux for 1 h and cooled to room temperature. To the mixture was added 6 L of 1,2-dichloroethane, and the resulting solution was neutralized to pH 8 with saturated $NaHCO_3$. The layers were separated, and the aqueous layer was back-extracted (2×) with 4 L of 1,2-dichloroethane. The combined extracts were washed with 2 L of water and concentrated under reduced pressure to a final volume of 3.5 L and KF < 100 and used in the next step without further purification. HPLC assay yield of **12** was 1.32 kg (100%). An analytical sample was obtained by silica gel chromatography as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85 (m, 1H), 1.93 (br s, 1H), 2.13 (m, 3H), 2.91 (q, 1H, J = 8.6 Hz), 3.22 (dd, 1H, J = 9.8 and 7.7 Hz), 3.62 (s, 3H), 4.18 (m, 1H), 7.02 (m, 2H), 7.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 33.1, 49.3, 51.9, 56.7, 79.6, 115.5 (d, J = 20 Hz), 129.0 (d, J = 10 Hz), 136.6, 162.4 (d, J = 240 Hz), 175.6; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −114.0. Anal. Calcd for $C_{13}H_{15}FO_3$: C, 65.53; H, 6.35. Found: 65.15; H, 6.05.

Preparation of Methanesulfonic Acid (*S*)-1-(3,5-Bistrifluoromethyl-phenyl)-ethyl Ether (13). To a stirred solution of 1.35 g (5.23 mmol) of (*S*)-1-(3,5-bis-triflurormethyl phenyl)-ethanol in 15 mL of CH_2Cl_2 at 0 °C was added 794 mg (7.84 mmol) of NEt_3 followed by 779 mg (6.80 mmol) of methanesulfonyl chloride. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The slurry was diluted with 15 mL of MTBE and washed with saturated $NaHCO_3$ (2 × 15 mL), 15 mL of 2 N HCl, and 15 mL of brine and then dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by passing through a plug of silica gel to afford 1.70 g (97%) of **13** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.74 (d, 3H, J = 6.5 Hz), 2.97 (s, 3H), 5.85 (q, 1H, J = 6.5 Hz), 7.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4, 38.9, 77.9, 122.7 (d, J = 30 Hz), 122.8 (q, J = 271 Hz), 124.4, 132.3 (q, J = 34 Hz), 142.6; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −63.6. Anal. Calcd for $C_{11}H_{10}F_6O_3S$: C, 39.29; H, 3.00. Found: C, 39.42; H, 2.99.

Preparation of (1*S*,2*R*,3*R*)-3-(*tert*-Butyl-dimethylsilanyloxymethyl)-2-(4-fluorophenyl)-cyclopentanol (17). To a solution of 1.24 g (5.20 mmol) of **12** in 25 mL of THF was added 220 mg (5.70 mmol) of solid $LiAlH_4$. The resulting mixture was stirred at room temperature for 2 h and was cooled to 0 °C and carefully quenched with 1 N HCl. The solution was extracted (2×) with 25 mL of CH_2Cl_2, and the combined extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to afford 1.09 g (100%) of (1*S*,2*R*,3*R*)-2-(4-fluorophenyl)-3-hydroxymethyl-cyclopentanol as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.69 (m, 2H), 1.95 (m, 1H), 2.07 (m, 1H), 2.19 (m, 1H), 2.38 (m, 2H), 2.63 (dd, 1H, J = 10.1 and 8.1 Hz), 3.45 (dd, 1H, J = 9.9 and 8.1 Hz), 3.52 (dd, 1H, J = 10.1 and 5.3 Hz), 4.09 (q, 1H, J = 6.9 Hz), 6.91 (m, 2H), 7.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 33.2, 47.2, 56.5, 65.2, 80.5, 115.2 (d, J = 20 Hz), 129.1 (d, J = 10 Hz), 138.1, 162.3 (d, J = 240 Hz); ^{19}F NMR ($CDCl_3$, 75 MHz) δ −116.4.

To a solution of 3.64 g (17.3 mmol) of the above diol in 3 mL of DMF was added 1.53 g (22.5 mmol) of imidazole followed by 2.87 g (19.0 mmol) of *tert*-butyldimethylsilyl chloride. The resulting mixture was stirred at room temperature for 18 h, diluted with 20 mL of water, and extracted with 25 mL of EtOAc. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography to afford 4.18 g (74%) of **17** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 6H), 0.87 (s, 9H), 1.73 (m, 2H), 1.88 (m, 1H), 2.09 (m, 1H), 2.19 (m, 1H), 2.34 (br s, 1H), 2.71 (dd, 1H, J = 10.1 and 8.1 Hz), 3.57 (m, 2H), 4.12 (q, 1H, J = 6.9 Hz), 6.99 (m, 2H), 7.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.4, 18.3, 25.0, 25.7, 25.9, 33.2, 47.0, 56.2, 64.9, 80.5, 115.3 (d, J = 20 Hz), 129.0.2 (d, J = 10 Hz), 138.4, 162.4 (d, J = 240 Hz); ^{19}F NMR ($CDCl_3$, 75 MHz) δ −117.5. Anal. Calcd for $C_{18}H_{29}FO_2Si$: C, 66.62; H, 9.01. Found: C, 67.01; H, 9.22.

Preparation of 3,5-Bistrifluoromethyl Benzoic Acid (1*S*,2*R*,3*R*)-3-(*tert*-Butyl-dimethylsilanyloxymethyl)-2-(4-fluorophenyl)-cyclopentyl Ester (19). To a stirred solution of 354 mg (1.09 mmol)

of **17** in 7.5 mL of CH_2Cl_2 was added 143 mg (1.42 mmol) of NEt_3 followed by 332 mg (1.20 mmol) of bistrifluoromethyl benzoyl chloride (**18**). The resulting mixture was stirred at room temperature for 30 min and quenched with 20 mL of water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 616 mg (100%) of **19** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 6H), 0.89 (s, 9H), 1.94 (m, 3H), 2.25 (m, 1H), 2.37 (m, 1H), 3.19 (dd, 1H, J = 10.0 and 7.2 Hz), 3.54 (dd, 1H, J = 10.0 and 5.3 Hz), 3.64 (dd, 1H, J = 10.0 and 4.2 Hz), 5.42 (m, 1H), 7.03 (m, 2H), 7.23 (m, 2H), 8.05 (s, 1H), 8.42 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.3, 18.5, 25.9, 26.0, 31.5, 48.3, 52.8, 63.9, 84.4, 115.7 (d, J = 20 Hz), 125.9 (q, J = 190 Hz), 126.4, 129.3 (d, J 10 Hz), 129.8, 132.4, (q, J = 30 Hz), 132.8, 137.5, 162.4 (d, J = 240 Hz), 163.8. Anal. Calcd for $C_{27}H_{31}F_7O_3Si$: C, 57.44; H, 5.53. Found: C, 57.75; H, 5.66.

Preparation of [(1*R*,2*R*,3*S*)-3-{1-(3,5-Bistrifluoromethylphenyl)-vinyloxy}-2-(4-fluorophenyl)-cyclopentylmethoxy]-*tert*-butyldimethylsilane (20). To a solution of 730 mg (2.93 mmol) of dichlorotitanocene in 25 mL of toluene at −5 °C was added 4.6 mL (7.33 mmol) of a 1.6 M solution of MeLi. The resulting mixture was stirred at 0 °C for 1 h and was quenched with 10 mL of 6% NH_4Cl. The layers were separated, and the organic layer was dried over $MgSO_4$ and concentrated to a final volume of 7 mL. To the solution of dimethyltitanocene was added 550 mg (0.974 mmol) of **19** in 1 mL of toluene, and the mixture was heated to 80 °C for 4 h and cooled to room temperature. The reaction mixture was quenched with 3 mL of 5% MeOH in water, stirred at room temperature for 15 min, and diluted with 10 mL of water and 15 mL of EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford 486 mg (89%) of **20** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.01 (s, 6H), 0.88 (s, 9H), 2.01 (m, 2H), 2.19 (m, 3H), 3.12 (dd, 1H, J = 10.0 and 5.8 Hz), 3.53 (dd, 1H, J = 10.0 and 5.8 Hz), 3.63 (dd, 1H, J = 10.0 and 4.4 Hz), 4.19 (d, 1H, J = 3.3 Hz), 4.54 (m, 1H), 4.74 (d, 1H, J = 3.3 Hz), 7.03 (m, 2H), 7.22 (m, 2H), 7.80 (s, 1H), 7.97 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.3, 18.4, 26.0, 27.5, 31.7, 49.1, 53.9, 64.4, 86.9, 115.6 (d, J = 20 Hz), 122.1, 122.3 (q, J = 190.0 Hz), 125.7, 129.3, 129.4, 131.7 (q, J = 30 Hz), 138.9, 139.0, 156.3, 162.4 (d, J = 240 Hz). Anal. Calcd for $C_{28}H_{33}F_7O_2Si$: C, 59.77; H, 5.91. Found: C, 60.10; H, 6.01.

Palladium-Catalyzed Hydrogenation of Vinyl Ether 20. To a solution of 263 mg (0.467 mmol) of **20** in 8 mL of EtOAc was added 25 mg of 5% Pd/C. The resulting mixture was stirred under an atmosphere of 40 psi hydrogen for 5 h, filtered through a pad of Celite, and concentrated under reduced pressure to afford 245 mg (93%) of a 1:4 mixture of **21**:**22** which could not be separated.

The above crude product was redissolved in 10 mL of THF, and 0.51 mL of a 1 M solution of TBAF in THF was added. The mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. The residue was purified by silica gel chromatography using a 25% solution of EtOAc in hexane. The first product to elute from the column (158 mg, 75%) was identified as [(1*R*,2*R*,3*S*)-3-{(*S*)-1-(3,5-bis-trifluoromethyl-phenyl)-ethoxy}-2-(4-fluorophenyl)-cyclopentyl]-methanol (**23**) and was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, 3H, J = 6.5 Hz), 1.69 (m, 2H), 1.85 (m, 3H), 2.10 (m, 1H), 2.81 (dd, 1H, J = 9.9 and 7.2 Hz), 3.48 (dd, 1H, J = 10.7 and 6.7 Hz), 3.58 (dd, 1H, J = 10.7 and 4.8 Hz), 3.78 (q, 1H, J = 7.2 Hz), 4.32 (q, 1H, J = 6.5 Hz), 7.01 (m, 2H), 7.16 (m, 2H), 7.52 (s, 2H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 25.9, 31.7, 48.3, 54.9, 65.1, 75.5, 86.1, 115.5 (d, J = 21 Hz), 121.4, 123.1 (d, J = 190 Hz), 126.3, 128.9 (d, J = 10 Hz), 131.5 (q, J = 30 Hz), 138.9, 147.0, 161.4 (d, J = 240 Hz); ^{19}F NMR ($CDCl_3$, 75 MHz) δ −63.5, −116.9. Anal. Calcd for $C_{22}H_{21}F_7O_2$: C, 58.67; H, 4.70. Found: C, 58.54; H, 4.66.

The second product to elute from the column (32 mg, 15%) was identified as [(1*R*,2*R*,3*S*)-3-{(*R*)-1-(3,5-bistrifluoromethylphenyl)-ethoxy}-2-(4-fluorophenyl)-cyclopentyl]-methanol (**24**) and was obtained as a colorless solid: mp 39−40 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (d, 3H, J = 6.5 Hz), 1.49 (br s, 1H), 1.77 (m, 2H), 1.95 (m, 1H), 2.10 (m, 2H), 2.76 (dd, 1H, J = 10.1 and 8.1 Hz), 3.48 (m, 1H), 3.58 (m, 1H), 3.73 (q, 1H, J = 7.0 Hz), 4.50 (q, 1H, J = 6.5 Hz), 6.92 (m, 2H), 7.04 (m, 2H), 7.44 (s, 2H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8, 25.8, 30.3, 47.3, 54.6, 65.3, 75.3, 85.6, 115.4 (d, J = 20 Hz), 121.3, 122.3 (q, J = 190 Hz), 126.1, 128.8 (d, J = 10 Hz), 131.4 (q, J = 30 Hz), 137.7, 146.9, 162.3 (d, J = 240 Hz); ^{19}F NMR ($CDCl_3$, 75 MHz) δ −63.4, −117.2. Anal. Calcd for $C_{22}H_{21}F_7O_2$: C, 58.67; H, 4.70. Found: C, 59.01; H, 4.69.

Reductive Etherification of 25. To a 0 °C solution of 180 mg (0.756 mmol) of **12** in 6.5 mL of CH_2Cl_2 was added 115 mg (1.13 mmol) of NEt_3 followed by 285 mg (1.28 mmol) of TMSOTf. The reaction mixture containing **25** was cooled to −78 °C, and 840 mg (3.78 mmol) of TMSOTf, 213 mg (0.832 mmol) of 3′,5′-bis-(trifluoromethyl)acetophenone **26**, and 105.5 mg (0.910 mmol) of triethylsilane were added. The cooling bath was removed, and the reaction mixture allowed to slowly warm to room temperature and was stirred an additional 18 h. HPLC analysis of the crude reaction mixture indicated 80% conversion to **14** and **15** and 65% combined assay yield. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography employing 15% EtOAc in hexanes. The first product to elute from the column (56 mg, 16%) was identified as (1*R*,2*R*,3*S*)-3-[(*S*)-1-(3,5-bistrifluoromethylphenyl)-ethoxy]-2-(4-fluorophenyl)-cyclopentanecarboxylic acid methyl ester (**15**) and was obtained as a colorless oil:: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (d, 3H, J = 6.5 Hz), 1.92 (m, 1H), 2.12 (m, 3H), 2.79 (m, 1H), 3.36 (dd, 1H, J = 10.7 and 8.2 Hz), 3.58 (s, 3H), 3.75 (m, 1H), 4.52 (q, 1H, J = 6.5 Hz), 6.93 (m, 2H), 7.05 (m, 2H), 7.46 (s, 2H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6, 26.8, 30.5, 49.5, 51.7, 54.9, 75.6, 84.6, 115.3 (d, J = 20 Hz), 121.3, 125.1 (q, J = 190 Hz), 126.1, 128.9 (d, J = 10 Hz), 131.6 (q, J = 30 Hz), 136.4, 146.8, 162.4 (d, J = 240 Hz), 174.9; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −62.9, −116.7. Anal. Calcd for $C_{23}H_{21}F_7O_3$: C, 57.74; H, 4.42. Found: C, 57.54; H, 4.29.

The second product to elute from the column (178 mg, 49%) was identified as (1*R*,2*R*,3*S*)-3-[(*R*)-1-(3,5-bistrifluoromethylphenyl)-ethoxy]-2-(4-fluorophenyl)-cyclopentanecarboxylic acid methyl ester (**14**) and was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, 3H, J = 6.5 Hz), 1.82−2.15 (m, 4H), 2.80 (q, 1H, J = 8.9 Hz), 3.43 (dd, 1H, J = 10.1 and 7.3 Hz), 3.61 (s, 3H), 3.80 (q, 1H, J = 6.9 Hz), 4.36 (q, 1H, J = 4.6 Hz), 7.01 (m, 2H), 7.18 (m, 2H), 7.54 (s, 2H), 7.75 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 27.1, 32.0, 50.5, 51.8, 55.2, 75.6, 85.2, 115.6 (d, J = 20 Hz), 121.4, 123.9 (q, J = 190 Hz), 126.3, 128.9 (d, J = 10 Hz), 131.7 (q, J = 30 Hz), 137.8, 146.9, 162.5 (d, J = 240 Hz), 174.9; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −63.5, −116.5. Anal. Calcd for $C_{23}H_{21}F_7O_3$: C, 57.74; H, 4.42. Found: C, 57.67; H, 4.39.

Preparation of (1*S*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl-2,2,2-trichloroethanimidoate (30). To a solution of 8.00 kg (31.0 mol) of **5** in 37 L of a 4:1 mixture of cyclohexane/CH_2Cl_2 was added dropwise 4.92 kg (34.1 mol) of trichloroacetoritrile followed by 92 mL of DBU. The resulting mixture was stirred at room temperature for 5.5 h. The resulting reaction mixture was then washed with 27 L of water, 27 L of brine, and then concentrated under reduced pressure to a final volume of 15 L and a KF < 200 and was used without further purification. HPLC assay of the crude solution was 12.00 kg (96%) of **30**. An analytical sample was obtained by silica gel chromatography to give **30** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 (d, 3H, J = 6.4 Hz), 6.11 (q, 1H, J = 6.4 Hz), 7.85 (s, 1H), 7.91 (s, 2H), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.0, 75.5, 91.2, 121.9, 123.3 (q, J = 272 Hz), 126.1, 132.0 (q, J = 33 Hz), 144.1, 161.2; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −63.4. Anal. Calcd for $C_{12}H_8Cl_3F_6NO$: C, 35.80; H, 2.00; N, 3.48. Found: C, 36.19; H, 1.97; N, 3.44.

Preparation of Racemic 1-Deuterio-1-[3,5-bis(trifluoromethyl)phenyl]ethyl-2,2,2-trichloroethanimidoate (35). To a solution of 1.00 g (3.90 mmol) of 3′,5′-bis(trifluoromethyl)acetophenone in 30 mL of THF was added 3.90 mL of a 1 M solution of $LiAlD_4$ in THF. The resulting mixture was stirred at room temperature for 30 min and carefully quenched with 2 N HCl and extracted with MTBE. The MTBE extract was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to give 1.00 g (99%) of 1-deuterio-1-[3,5-bis(trifluoromethyl)phenyl]-ethanol as a white solid: mp 51−52 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53 (s, 3H), 2.95 (br s, 1H), 7.79 (s, 1H), 7.84 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3, 68.9 (t, J = 21 Hz), 121.3, 123.1 (q, J = 271 Hz), 125.7, 131.8 (q, J = 32 Hz), 148.2; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −63.5.

To a solution of 1.00 g (3.89 mol) of the above deuterio alcohol in 37 mL of a 4:1 mixture of cyclohexane/CH_2Cl_2 was added dropwise 4.92 g (34.1 mmol) of trichloroacetoritrile followed by 0.92 mL of DBU. The resulting mixture was stirred at room temperature for 5.5 h. The resulting reaction mixture was then washed with 27 mL of water, 27 mL of brine, and then concentrated under reduced pressure to give 1.20 g (96%) of **35** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 (s, 3H), 7.84 (s, 1H), 7.92 (s, 2H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.1, 75.5 (t, J = 21 Hz), 91.2, 121.9, 123.3 (q, J = 271 Hz), 126.1, 132.0 (q, J = 33 Hz), 144.1, 161.1; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −63.5.

Preparation of (1*R*,2*R*,3*S*)-3-[(*R*)-1-(3,5-Bistrifluoromethylphenyl)-ethoxy]-2-(4-fluorophenyl)-cyclopentane Carboxylic Acid Triethylamine Solvate (44). To a solution of 1.30 kg (5.46 mol) of **12** in 4.0 L of 1,2-dichloroethane was added 4.38 kg (10.92 mol) of imidate **30** in 8 L of heptane. The reaction mixture was purged with N_2 for 15 min and cooled to −16 °C. To the resulting mixture was added in one portion 75.2 mL (0.55 mol) of HBF_4 in Et_2O. The reaction mixture was stirred below −15 °C for 18 h, warmed to 15 °C, and filtered to remove insoluble trichloroacetamide. The filtrate was concentrated under reduced pressure, and the residue was redissolved in 13 L of MeOH and 1.2 L of water. The solution was cooled to 5 °C, and 1.90 kg (33.9 mol) of solid KOH was added in portions while maintaining the internal reaction temperature below 25 °C. The reaction mixture was warmed to 35 °C for 3.5 h, cooled to room temperature, and diluted with 15 L of water. The aqueous layer was washed with toluene (2 × 33 L), cooled to 10 °C, and acidified with 4 L of concentrated HCl. To the milky suspension was added 18 L of MTBE, and the layers were well mixed for 30 min and allowed to settle. The layers were separated, and the aqueous layer was back-extracted with 18 L of MTBE. The combined organic extracts were washed with 24 L of saturated $NaHCO_3$, 24 L of water, and then concentrated under reduced pressure to a final volume of 3 L and a KF of <300. HPLC assay of the organic layer indicated 1.68 kg (66%) of the corresponding carboxylic acid. The crude reaction mixture was then diluted with 10 L of heptane, and 218 g (2.15 mol) of NEt_3 was added in one portion. The resulting slurry of **44** was heated to 70 °C, stirred at this temperature for 30 min, and slowly cooled to room temperature. The slurry was filtered, and the product was dried under vacuum/N_2 sweep for 8 h. The diastereomeric ratio was 42:1. The crude solid was redissolved at 65 °C in a mixture consisting 2.0 L of MTBE and 7 L of heptane. The reaction temperature was then allowed to cool to 18 °C over a 4 h period and filtered. The wet cake was washed with 2 L of 4:1 heptane/MTBE and then dried under vacuum/N_2 sweep for 12 h to afford 1.52 kg (54%) of **44** (diastereomeric ratio >110:1) as a white solid: mp 128−129 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (t, 4.5 H, J = 7.3 Hz), 1.35 (d, 3H, J = 6.5 Hz), 1.85 (m, 1H), 2.05 (m, 3H), 2.67 (q, 1H, J = 8.7 Hz), 2.85 (q, 3H, J = 7.3 Hz), 3.31 (dd, 1H, J = 10.1 and 8.7 Hz), 3.66 (q, 1H, J = 7.1 Hz), 4.47 (q, 1H, J = 6.5 Hz), 6.83 (m, 2H), 7.04 (m, 2H), 7.43 (s, 2H), 7.66 (s, 1H), 11.40 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.2, 24.7, 27.1, 30.5, 44.8, 50.8, 55.2, 75.4, 84.9, 115.1 (d, J = 20 Hz), 121.1, 121.9 (q, J = 190 Hz), 126.1, 129.0, 131.5 (q, J = 30 Hz), 137.3, 147.0, 161.6 (d, J = 240 Hz), 179.9; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −63.4, −117.8. Anal. Calcd for $C_{22}H_{19}F_7O_3 \cdot {}^1/_2NEt_3$: C, 58.31; H, 5.19; N, 1.36. Found: C, 58.01; H, 5.20; N, 1.33.

Preparation of *tert*-Butyl Nipecotate (48). Method A. To a stirred solution of 62.05 g (0.236 mmol) of (*R*)-piperidine-1,3-dicarboxylic acid-1-benzyl ester **45**[26] in 500 mL of CH_2Cl_2 was added 2.1 mL of concentrated H_2SO_4. Isobutylene gas was then bubbled through the reaction mixture for 4 h, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with 100 mL of $NaHCO_3$, and the layers were separated. The organic layer was dried over $MgSO_4$ and concentrated to give 69.0 g (92%) of (*R*)-piperadine-1,3-dicarboxylic acid-1-benzyl ester-3-*tert*-butyl ester as a colorless oil which was used in the next reaction without further purification.

To 66.00 g (0.21 mol) of the above compound in 300 mL of EtOH and 100 mL of EtOAc was added 1.00 g of 10% Pd/C. The mixture was stirred under an atmosphere of 20 psi hydrogen for 8 h, and the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue distilled to give 32 g (90%) of *tert*-butylnipecotate **48** as a colorless oil: bp 110−112 °C/15 mmHg; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (m, 1H), 1.44 (s, 9H), 1.49 (br s, 1H), 1.63 (m, 2H), 1.97 (m, 1H), 2.33 (m, 1H), 2.63 (dt, 1H, J = 10.1 and 3.0 Hz), 2.77 (dd, 1H, J = 12.5 and 9.3 Hz), 2.93 (dt, 1H, J = 12.5 and 3.9 Hz), 3.13 (dd, 1H, J = 12.5 and 3.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.9, 27.7, 28.3, 43.7, 46.7, 48.9, 80.3, 174.1. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.77; H, 10.55; N, 7.55.

Method B. To a solution of 850 g (5.13 mol) of (*R*)-nipecotic acid hydrochloride **47** in 13.9 L of *tert*-butyl acetate was added dropwise 3.90 L (4.37 kg, 30.8 mol) of $BF_3 \cdot OEt_2$. The resulting mixture was stirred for 45 min at which point the internal temperature was ∼9 °C. To the clear yellow solution was added 17.8 L of water, and the layers were well mixed for 15 min and the bottom aqueous layer was separated. To the aqueous layer was added 25 L of toluene, and the biphasic mixture was cooled to 0 °C, and 16. 3 L of 5 N NaOH was added at such a rate that the internal temperature was maintained below 25 °C. The layers were separated, and the aqueous layer was back-extracted with 25 L of toluene. The combined toluene extracts were combined and concentrated under reduced pressure to afford 727 g (77%) of **48** as a clear oil, which was identical to that prepared by method A and was used without further purification.

Preparation of [(1*R*,2*R*,3*S*)-3-{(*R*)-1-(3,5-Bistrifluoromethylphenyl)-ethoxy}-2-(4-fluorophenyl)-cyclopentyl]-methanol (24). To a solution of 2.30 kg (2.23 mol) of **44** in 12 L of toluene was added 4.46 L (4.46 mol) of a 1 M solution of $BH_3 \cdot THF$. The resulting solution was heated to 65 °C for 3 h, cooled to room temperature, and inversely quenched into 7 L of 1 M HCl solution. The layers were well mixed for 20 min, allowed to settle for 30 min, and the bottom aqueous layer was removed. The organic layer was washed with 5 L of water and was azeotropically dried to a final volume of 3 L and a KF of <200 and was used in the next reaction without further purification. HPLC assay gave 966 g (96%).

Preparation of (*R*)-1-[(1*R*,2*R*,3*S*)-3-{(*R*)-1-(3,5-Bistrifluoromethyl-phenyl)-ethoxy}-2-(4-fluorophenyl)-cyclopentylmethyl]-piperidine-3-carboxylic Acid *tert*-Butyl Ester (49). To a stirred solution of 268 g (0.595 mol) of crude **24** in 1.1 L of toluene was added 100.0 g (0.775 mol) of *i*-Pr_2NEt. The mixture was cooled to 9 °C, and 124.4 g (0.714 mol) of methanesulfonic anhydride was added portionwise over 10 min while maintaining the internal reaction temperature <40 °C. The reaction mixture was stirred at 38 °C for 1.25 h and cooled to room temperature. To the resulting mixture was added an additional 131.0 g (1.01 mol) of *i*-Pr_2NEt followed by 207.12 g (1.12 mol) of **48**. The reaction mixture was heated to reflux for 16 h, cooled to room temperature, and quenched with 1.6 L of saturated NH_4Cl. The layers were separated, and the toluene layer was washed with 1.6 L of saturated NH_4Cl and 800 mL of water. The solvent was removed under reduced pressure,

and the residue was used in the next reaction without further purification. HPLC assay of **49** was 330 g (90%). An analytical sample was obtained by purification on silica gel to give **49** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (m, 2H), 1.33 (d, 3H, J = 6.4 Hz), 1.43 (s, 9H), 1.49 (m, 1H), 1.61 (m, 1H), 1.77 (m, 3H), 1.92 (m, 2H), 2.06 (m, 2H), 2.29 (m, 3H), 2.41 (m, 1H), 2.62 (dd, 1H, J = 10.1 and 8.1 Hz), 2.83 (m, 1H), 3.68 (q, 1H, J = 7.1 Hz), 4.47 (q, 1H, J = 6.4 Hz), 6.91 (m, 2H), 7.05 (m, 2H), 7.39 (s, 2H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9, 24.7, 25.1, 28.3, 29.7, 30.3, 38.5, 39.7, 53.2, 54.0, 56.9, 62.2, 75.5, 80.3, 84.2, 115.8 (d, J = 20 Hz), 124.4, 125.1 (d, J = 190 Hz), 126.3, 129.3 (d, J = 10 Hz), 131.4 (q, J = 30 Hz), 135.1, 146.5, 162.4 (d, J = 240 Hz), 174.7; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −63.2, −115.5. Anal. Calcd for $C_{32}H_{38}F_7NO_3$: C, 62.23; H, 6.20; N, 2.27. Found: C, 61.94; H, 5.99; N, 2.25.

Preparation of (*R*)-1-[(1*R*,2*R*,3*S*)-3-{(*R*)-1-(3,5-Bistrifluoromethyl-phenyl)-ethoxy}-2-(4-fluorophenyl)-cyclopentylmethyl]-piperidine-3-carboxylic Acid Hydrochloride (1). To a solution of 314 g (0.508 mol) of **49** in 725 mL of 1,2-dichloroethane was added 196 mL (2.54 mol) of TFA. The mixture was heated to 80 °C for 12 h, cooled to room temperature, and concentrated under reduced pressure. The crude residue was redissolved in 2 L of 1,2-dichloroethane and washed with saturated $NaHCO_3$ (2 × 600 mL) and 500 mL of water. The organic layer was concentrated under reduced pressure and redissolved in 2 L of MTBE. The organic layer was concentrated again under reduced pressure and dissolved in 1 L of MTBE. HPLC assay gave 271 g (95%) of **1**, and the KF was <250. To the resulting MTBE solution was added 284 mL of a 2 M solution of HCl in diethyl ether. The slurry of the HCl salt was stirred at room temperature for 3.5 h and was filtered to afford 258 g (85%) of crystalline HCl salt **1** as a colorless solid: $[\alpha]_D$ +58.0 (*c* 1.00, MeOH); mp 185−186 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (d, 3H, J = 6.4 Hz), 1.40 (m, 1H), 1.84 (m, 3H), 2.13−2.67 (m, 8H), 2.82 (m, 1H), 3.00 (m, 1H), 3.17 (m, 1H), 3.40 (br d, 1H, J = 10.6 Hz), 3.49 (br d, 1H, J = 10.6 Hz), 3.67 (q, 1H, J = 7.1 Hz), 4.46 (q, 1H, J = 6.4 Hz), 6.91 (m, 2H), 7.08 (m, 2H), 7.38 (s, 2H), 7.65 (s, 1H), 9.14 (br s, 1H), 10.92 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9, 24.7, 25.1, 29.7, 30.3, 38.5, 39.7, 53.2, 54.0, 56.9, 62.2, 75.5, 84.2, 115.8 (d, J = 20 Hz), 124.4, 125.1 (d, J = 190 Hz), 126.3, 129.3 (d, J = 10 Hz), 131.4 (q, J = 30 Hz), 135.1, 146.5, 162.4 (d, J = 240 Hz), 172.7; ^{19}F NMR ($CDCl_3$, 75 MHz) δ −63.4, −115.7. Anal. Calcd for $C_{28}H_{30}F_7NO_3$·HCl: C, 56.24; H, 5.23; N, 2.34. Found: C, 56.22; H, 5.19; N, 2.28.

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