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Synthesis of a Tetrahydropyran NK_1 Receptor Antagonist via Asymmetric Conjugate Addition

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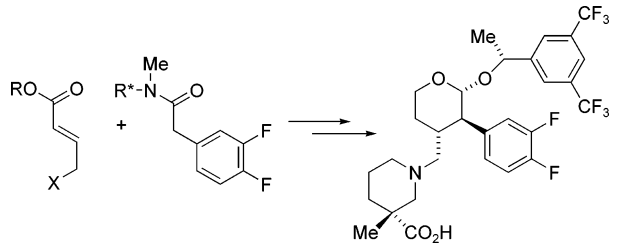

Two asymmetric syntheses of the NK_1 receptor antagonist 1-[2-(*R*)-{1-(*R*)-[3,5-bis(trifluoromethyl)-phenyl]ethoxy}-3-(*R*)-(3,4-difluorophenyl)-4-(*R*)-tetrahydro-2*H*-pyran-4-ylmethyl]-3-(*R*)-methylpiperidine-3-carboxylic acid (**1**) were developed. In both routes, the core tetrahydropyran stereochemistry was established by asymmetric conjugate addition to an α,β-unsaturated ester (**6**), using an amide of the chiral auxiliary pseudoephedrine. Selective ester reduction then allowed formation of lactone **2** with the thermodynamically preferred trans geometry. The chiral ether side chain (**3**) was attached by stereoselective acetal substitution. In the first route, the chiral piperidine ester fragment was installed at the end by N-alkylation. In the shorter second synthesis, this piece was appended to the Michael acceptor at the beginning.

Introduction

The neurokinin-1 (NK_1) receptor preferentially binds the tachykinin substance P, and this pathway plays an important role in the response to stressful and inflammatory stimuli.[1] An NK_1 receptor antagonist, as part of combination therapy, has been shown to prevent acute and delayed chemotherapy-induced nausea and vomiting.[2] The development of new NK_1 antagonists remains an active area of pharmaceutical research.[3]

The tetrahydropyran **1** was identified as a potent and selective antagonist of NK_1.[4] To further study this compound, an efficient and practical synthesis was required that would allow the preparation of kilogram quantities. Conceptually, **1** can be broken into three fragments, a trans-disubstituted lactone **2**, the chiral benzylic alcohol **3**, and the chiral piperidine fragment **4** (Scheme 1). An acetal formation related to glycosidation chemistry should join **2** and **3**, and N-alkylation would attach **4**.

Short syntheses of enantiopure fragments **3** and **4** were already established,[5,6] so the focus was on identifying an efficient method to prepare the core lactone **2**. In a previous synthesis of an analogue to **1**, the analogous lactone was assembled via an S_N2 reaction between the

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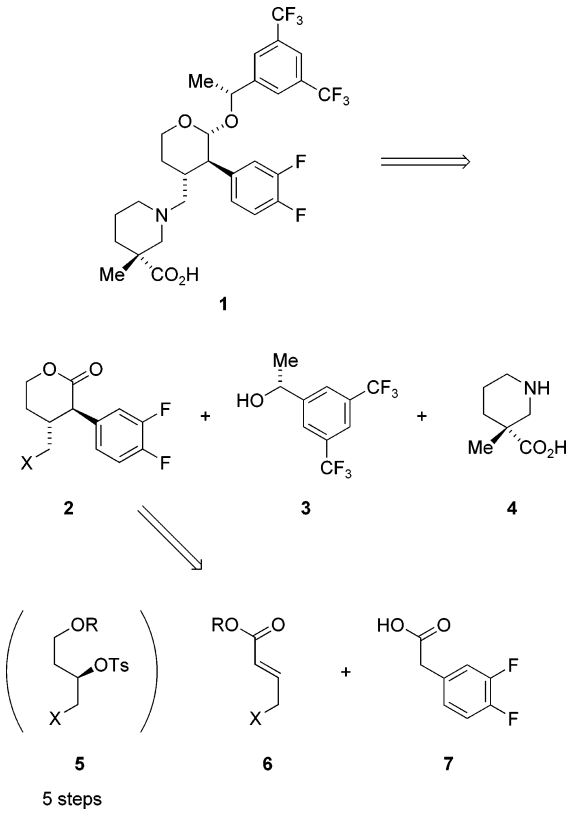
SCHEME 1



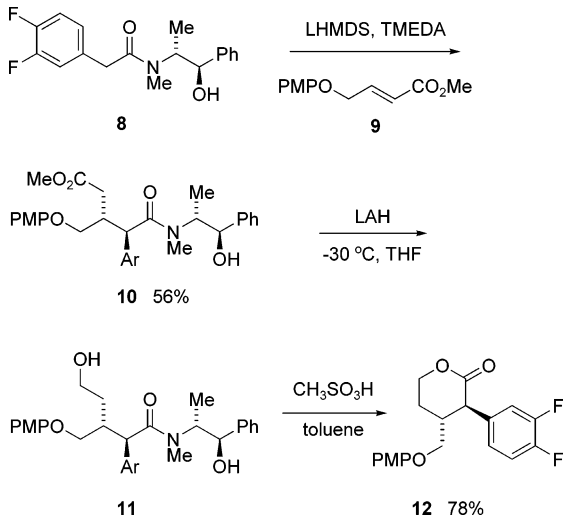
dianion of phenylacetic acid and an enantiopure secondary tosylate **5**, followed by oxygen deprotection and lactonization.[6] While practical, this route was lengthy since the synthesis of **5** required five steps including a kinetic resolution. In striving for a shorter overall route, we decided to try to access **2** through an asymmetric conjugate addition reaction to a Michael acceptor **6**.

Results and Discussion

Asymmetric Michael Addition. Conjugate addition of an amide derivative of 3,4-difluorophenylacetic acid to an α,β-unsaturated ester **6** was expected to give an amido ester. Selective reduction of the ester group to a primary alcohol should allow formation of the six-membered-ring lactone **2** with expulsion of the amine from the amide moiety. We knew that a cis/trans mixture of lactones could be epimerized to primarily the desired *trans*-**6** so the kinetic stereochemistry at the aryl-bearing enolate α-carbon was not critical. Several amine chiral auxiliaries were evaluated for their ability to control facial selectivity on the Michael acceptor, as determined by ee measurement after conversion to the crude trans lactone.[7] From these experiments, (*R*,*R*)-pseudoephedrine amide **8** was chosen.

Deprotonation of **8** with 2 equiv of LHMDS in the presence of TMEDA followed by the addition of acceptor **9** at −70 °C gave a mixture of amido esters in which the *anti*-(*R*,*R*) isomer **10** was the major product (Scheme 2).[7] The *p*-methoxyphenyl (PMP) protecting group on **9** was

SCHEME 2



chosen because of our previous experience that it provided crystalline intermediates in a related series of compounds.[6] Selective reduction of **10** to primary alcohol **11** was best accomplished with LAH below −30 °C. The stereoisomeric mixture of alcohols could then be cyclized to cis and trans lactones with a strong acid such as hydrochloric, *p*-toluenesulfonic, or methanesulfonic acid. Treatment of the lactones with catalytic DBU gave an equilibrium 94:6 trans/cis ratio, in which the trans lactone (**12**) ee was 87%.

Lactone Synthesis. Although (*R*,*R*)-lactone **12** was crystalline, isolation in pure form from the crude mixture proved to be difficult. A more successful approach was to achieve chemical and stereoisomeric purification by isolation of crystalline Michael adduct **10**, crystallized in 56% yield and 97.6% de from toluene/heptane.

From isolated **10**, reduction with LAH gave a single isomer of hydroxy amide **11**. Lactonization to **12** could be accomplished with anhydrous HCl, allowing for simple recovery of the crystallized pseudoephedrine HCl salt. However, HCl delivered **12** as a mixture with the cis lactone that required epimerization with DBU. The use of methanesulfonic acid for the cyclization minimized cis lactone formation and **12** could be crystallized from isopropyl acetate/heptane in 78% yield from **10** and 99.8% ee.

Acetal Formation. Having prepared the lactone, the next problem was stereoselective installation of the (*R*)-bis(trifluoromethyl)phenylethyl ether side chain. Reduction of **12** to lactol **13** could be done with DIBALH at −30 °C, or more conveniently with lithium tri-*tert*-butoxyaluminohydride at 0 °C (Scheme 3). The interconverting mixture of anomers crystallized as *all-trans*-**13** from toluene/hexanes. The glycosidation-like substitution reaction to give acetal **16** requires activation of the lactol. Several ester and imidate activations were tried. The best method was formation of the *p*-nitrobenzoates **14**, as an un-isolated trans/cis mixture, followed by BF_3-catalyzed substitution at −30 °C, to give **16** in 94:6 2,3-trans/2,3-cis selectivity. The high kinetic stereoselectivity is believed to be a steric result in which the bulky secondary alcohol adds trans to the aryl substituent in the di-pseudoaxial oxocarbenium intermediate **15**. If the reac-

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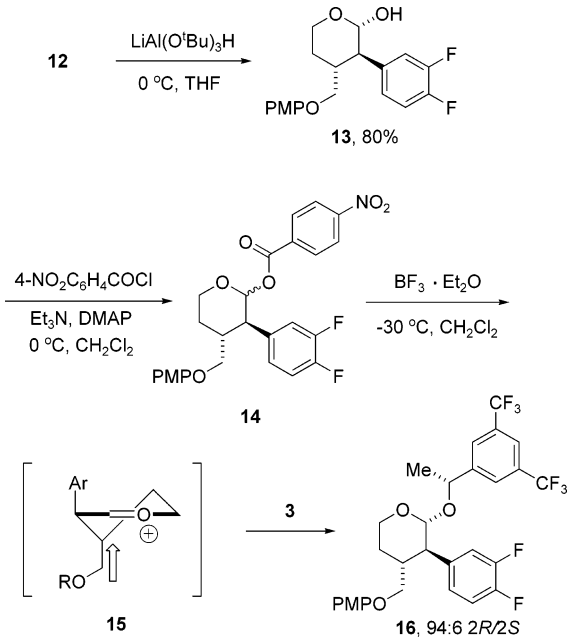
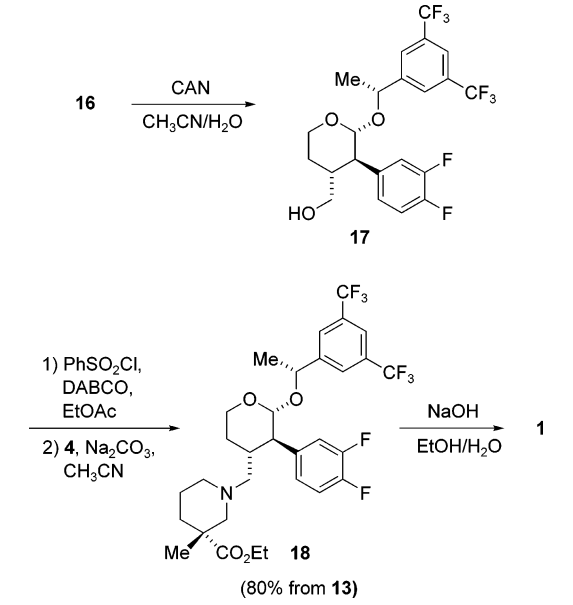
SCHEME 3



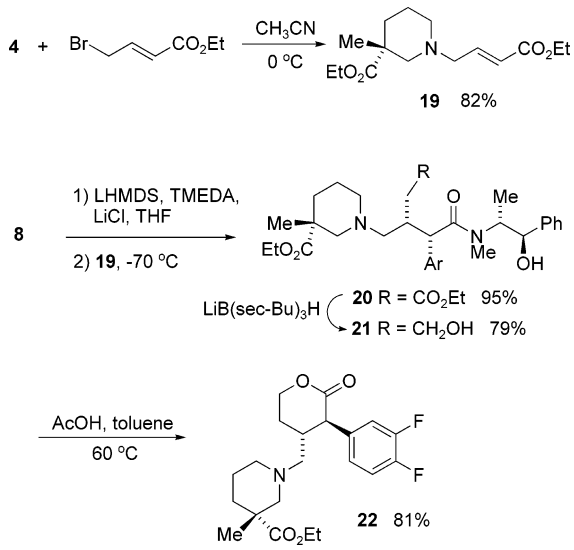
SCHEME 4



tion mixture is warmed before quenching, the product epimerizes to a lower thermodynamic ratio of 75:25.

Completion of the Synthesis. While *trans*,*trans*-**16** is a solid, it could not be isolated in high yield without chromatography. Instead, the crude reaction mixture was taken forward. Reaction with CAN cleaved the PMP protecting group to give **17**, which was also not isolated (Scheme 4). The primary alcohol was activated with benzenesulfonyl chloride and DABCO,[8] and the chiral piperidine fragment was then installed via N-alkylation. Addition of water to the acetonitrile reaction mixture directly crystallized **18** in high diastereomeric and chemical purity. The yield was 80% from the last isolated intermediate, lactol **13**. The synthesis was completed by

SCHEME 5



hydrolysis of the ethyl ester followed by crystallization of the salt with methanesulfonic acid. The overall yield was 25% from 3,4-difluorophenylacetic acid.

Second Generation Route. In considering possible shorter syntheses, we noted that installing the chiral piperidine fragment **4** at the beginning might eliminate three steps involved in the protecting group chemistry. It was expected, however, that carrying the aminoester through the entire synthesis would present challenges. The ethyl ester group would need to survive reductions of both the Michael adduct and the lactone as well as the lactone formation step. The tertiary amine might complicate lactonization and Lewis acid-catalyzed acetal formation.

Lactone Synthesis. Preparation of the chiral Michael acceptor **19** was done by reaction of piperidine **4** (as the di-*p*-toluoyl-D-tartaric acid salt from the resolution) with ethyl bromocrotonate (Scheme 5). The product was purified by crystallization of the tosylate salt, then converted to the free base before use.

Reaction of pseudoephedrine amide **8** with **19** under the previously used conditions gave results that were disappointing with respect to both yield and stereoselectivity. Fortunately, addition of lithium chloride (5 equiv) to the reaction mixture gave dramatically improved results, with **20** being formed in 95% yield and 92% de.[9] Although addition to acceptor **19** occurred from the *re* face as before, with LiCl the *syn* product was now formed.

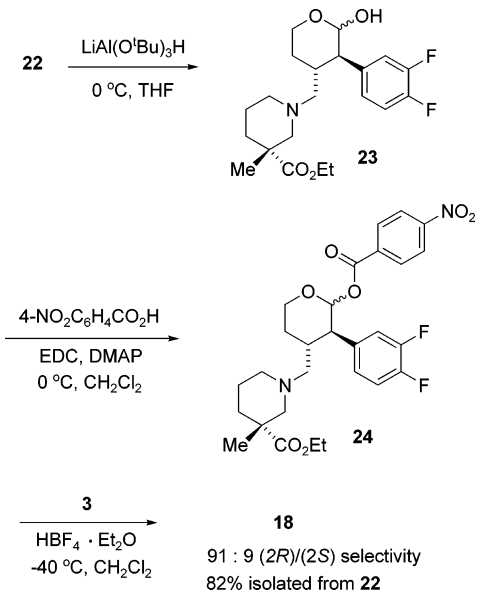
Attempted use of LAH for the reduction of **20** was not selective, with both ethyl esters apparently undergoing some reduction. Lithium tri-*sec*-butylborohydride, on the other hand, was selective. It seems that the adjacent quaternary center protects the nipecotate ester from reaction with this bulky reducing agent. The hydroxy-amide **21** was isolated in 79% yield by crystallization.

Acid-mediated cyclization of *syn*-hydroxy-amide **21** was slow, requiring 5 days at 60 °C, while the minor *anti* component in crude samples lactonized quickly. The lactone was formed in a trans/cis ratio of 85:15. After removal of pseudoephedrine by chromatography, the

(8) Hartung, J.; Hünig, S.; Kneuer, R.; Schwarz, M.; Wenner, H. *Synthesis* **1997**, 1433−1438.

(9) Smitrovich, J. H.; DiMichele, L.; Qu, C.; Boice, G. N.; Nelson, T. D.; Huffman, M. A.; Murry, J. *J. Org. Chem.* **2004**, *69*, 1903−1908.

SCHEME 6



trans isomer **22** was crystallized in 81% yield in the presence of DBU to epimerize the cis isomer.

Completion of the Synthesis. Attempted reduction of **22** with lithium tri-*sec*-butylborohydride suffered from apparent overreduction of the lactone. On the other hand, reaction with lithium tri-*tert*-butoxyaluminohydride was clean, with no overreduction and no reduction of the ethyl ester group observed (Scheme 6). The lactol was obtained as an oil that contained a mixture of anomers. Attempted acylations with *p*-nitrobenzoyl chloride gave several unidentified byproducts, but clean activation was achieved with *p*-nitrobenzoic acid, EDC, and catalytic DMAP.

BF_3 was not an effective catalyst for substitution of **24**. Catalytic BF_3 was inactivated by the amine, and over-stoichiometric quantities gave decomposition. On the other hand HBF_4 (1.2 equiv, −40 °C) induced clean substitution to a 91:9 ratio of 2,3-trans/2,3-cis isomers. As before, *trans*,*trans*-acetal **18** could be isolated in high purity by crystallization from acetonitrile/water. The yield from lactone **22**, the last isolated intermediate, was 82%, and at this point the original synthesis was intercepted. The overall yield of **1** in this formal total synthesis was 45% from 3,4-difluorophenylacetic acid.

Conclusion

Two efficient syntheses of NK_1 antagonist **1** were developed. Both approaches rely on asymmetric Michael addition of a pseudoephedrine amide enolate combined with diastereoselective acetal formation to establish the tetrahydropyran core stereochemistry. The second approach avoids protecting group manipulations by incorporating the piperidine ester fragment into the Michael acceptor and carrying it through the entire synthesis.

Experimental Section

Reaction solvents were purchased in anhydrous form or dried over 3A molecular sieves. Reactions were carried out under an atmosphere of dry nitrogen. Column chromatography was carried out on silica gel (230−400 mesh). IR spectra were recorded from thin films of neat samples on microporous polyethylene sheets. In the NMR spectra of amide compounds, the separated signals of minor rotamers are indicated with an asterisk.

(*E*)-1-(3-Ethoxycarbonylallyl)-3-(*R*)-methylpiperidine-3-carboxylic Acid Ethyl Ester (19). To a suspension of (*R*)-ethyl-3-methylpiperidine-3-carboxylate di-*p*-toluoyl-D-tartaric acid salt[6] (1.82 g, 5.0 mmol) and diisopropylethylamine (2.18 mL, 12.5 mmol) in acetonitrile (18 mL) at 0 °C was added ethyl-4-bromocrotonate (0.688 mL, 5.0 mmol) over 5 min. After 3 h at 0 °C, the solution was partitioned between aq Na_2CO_3 and toluene, and the organic layer was washed with aq 10% NH_4Cl followed by water. *p*-Toluenesulfonic acid monohydrate (0.904 g, 4.75 mmol) was added and the solution was evaporated to dryness. The tosylate salt was crystallized from isopropyl acetate, giving 1.86 g (4.1 mmol, 82%). White solid; mp 92.8−93.5; ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 1H), 6.91 (ddd, J = 15.7, 7.6, 6.0 Hz, 1H), 6.32 (d, J = 15.7 Hz, 1H), 4.30−4.26 (m, 4H), 4.04−3.90 (m, 2H), 3.73 (br d, J = 12.5 Hz, 1H), 3.45 (br d, J = 12.1 Hz, 1H), 3.01 (td, J = 12.5, 2.7 Hz, 1H), 2.86 (d, J = 12.6 Hz, 1H), 2.38 (s, 3H), 2.22 (br d, J = 13.4 Hz, 1H), 1.91 (m, 1H), 1.67 (m, 1H), 1.54 (td, J = 13.5, 3.6 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.2, 166.3, 143.8, 141.8, 135.6, 131.0, 130.0, 127.1, 63.3, 62.2, 58.7, 58.6, 54.5, 44.0, 32.6, 24.2, 22.2, 21.5, 14.6, 14.4; IR 3456, 1725, 1664 cm^{-1}. Anal. Calcd for $C_{22}H_{33}NO_7S$: C, 58.00; H, 7.30; N, 3.07. Found: C, 57.94; H, 7.30; N, 3.03.

1-[3-(*S*)-(3,4-Difluorophenyl)-2-(*R*)-ethoxycarbonylmethyl-3-{N-[(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylcarbamoyl}propyl]-3-(*R*)-methylpiperidine-3-carboxylic Acid Ethyl Ester (20). A suspension of amide **8** (1.00 g, 3.13 mmol) and LiCl (0.66 g, 15.65 mmol) in THF (2 mL) was sparged with nitrogen, then cooled to 0 °C. LHMDS (1.0 M in THF, 6.26 mL, 6.26 mmol) was added dropwise. After 30 min at 0 °C the solution was cooled to −20 °C and **19** (free base, 0.938 g, 3.31 mmol) was added. After 30 min at −20 °C, the reaction was quenched with aq 30% NH_4Cl and EtOAc was added. The organic layer was separated and washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (10:90 to 40:60 EtOAc/hexanes) gave **20** in 92% de (1.79 g, 2.97 mmol, 95%). Colorless oil; ^{1}H NMR (400 MHz, CD_3CN 3:2 rotamer ratio) δ 7.42−7.07 (m, 8H), 7.03−6.93* (m, 2H), 4.64* (m, 1H), 4.62 (d, J = 6.0 Hz, 1H), 4.58 (br s, 1H), 4.28* (br s, 1H), 4.47* (dd, J = 9.2, 3.2 Hz, 1H), 4.13 (dd, J = 6.4, 2.8 Hz, 1H), 4.10 (d, J = 7.6 Hz, 1H), 4.05 (q, J = 7.2 Hz, 2H), 3.90* (d, J = 8.4 Hz, 1H), 3.86 (q, J = 7.2 Hz, 2H), 2.82* (s, 3H), 2.79 (m, 2H), 2.76 (s, 3H), 2.64 (m, 1H), 2.32−2.22 (m, 2H), 2.11−2.04 (m, 2H), 2.02 (d, J = 5.6 Hz, 2H), 1.96 (s, 1H), 1.90 (m, 1H), 1.53 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H), 1.17* (t, J = 7.2 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H), 1.08 (s, 3H), 1.07* (s, 3H), 0.97* (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 176.5*, 174.2, 173.2*, 172.9, 171.0*, 150.3 (dd, J_{CF} = 248.2, 12.8 Hz), 149.6 (dd, J_{CF} = 248.2, 12.8 Hz), 142.0, 141.4*, 134.1-(dd, J_{CF} = 4.8, 4.0 Hz), 128.5*, 128.2, 127.6, 126.8*, 126.5, 125.1 (m), 118.5* (d, J_{CF} = 17.7 Hz), 117.9 (d, J_{CF} = 17.7 Hz), 117.2 (d, J_{CF} = 17.7 Hz), 116.8* (d, J_{CF} = 17.7 Hz), 75.9, 75.1*, 62.4, 60.3*, 60.2, 60.1*, 60.0, 59.2, 58.3, 54.3, 53.7*, 48.1, 47.6*, 43.6, 43.4*, 37.3*, 36.4, 34.2, 33.8*, 33.4, 33.3*, 27.2*, 24.4, 23.6, 23.1*, 20.9*, 15.5*, 14.21, 14.18, 14.14 (2C); IR 3411, 1725, 1624, 1514 cm^{-1}. Anal. Calcd for $C_{33}H_{44}F_2NO_6$: C, 65.76; H, 7.36; N, 4.65. Found: C, 65.70; H, 7.45; N, 4.31.

1-{2-(*R*)-[(*S*)-(3,4-Difluorophenyl){N-[(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylcarbamoyl}methyl]-4-hydroxybutyl}-3-(*R*)-methylpiperidine-3-carboxylic Acid Ethyl Ester (21). To a solution of **20** (1.07 g, 1.78 mmol) in toluene (5 mL) below −20 °C was added LiB(sec-Bu)$_3$H (6.0 mL of 1.0 M in THF, 6.0 mmol) over 15 min. The solution was stirred 2 h at −21 °C, then carefully quenched with 30% hydrogen peroxide (2.5 mL). **CAUTION:** Hydrogen gas evolution and large exotherm. The mixture was diluted with water

and warmed to ambient temperature. The aqueous layer was removed. The organic layer was washed with aq 10% Na_2SO_3 followed by water, then evaporated to a foam. Crystallization from heptane/EtOAc 4:1 gave 0.792 g (1.41 mmol, 79%). White solid; mp 117.8−118.4; ^{1}H NMR (400 MHz, CD_3OD, 3.3:1 rotamer ratio) δ 7.41−7.17 (m, 7H), 7.12 (m, 1H), 4.79 (br s, 1H), 4.65 (d, J = 7.7 Hz, 1H), 4.50* (d, J = 8.4 Hz, 1H), 4.27−4.05 (m, 2H), 3.97* (d, J = 9.2 Hz, 1H), 3.81 (d, J = 9.5 Hz, 1H), 3.49−3.33 (m, 2H), 2.95 (s, 3H), 2.92 (br s, 2H), 2.91* (s, 3H), 2.47 (m, 1H), 2.33* (dd, J = 12.3, 9.5 Hz, 1H), 2.23 (dd, J = 12.5, 9.4 Hz, 1H), 2.13−2.04 (m, 3H), 1.89 (br s, 1H), 1.63 (m, 2H), 1.53* (m, 1H), 1.41 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.29−1.13 (m, 2H), 1.24* (t, J = 7.2 Hz, 3H), 1.15 (s, 3H), 1.13* (s, 3H), 1.06* (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 177.1, 176.9*, 174.6, 173.9*, 151.0 (dd, J_{CF} = 245.8, 12.7 Hz), 150.8* (dd, J_{CF} = 245, 12 Hz), 150.2 (dd, J_{CF} = 244.9, 12.8 Hz), 144.1, 143.5*, 137.9* (m), 136.9 (dd, J_{CF} = 5.3, 4.1 Hz), 129.3*, 129.1, 128.8*, 128.4, 128.2*, 127.5, 127.1* (dd, J_{CF} = 6.4, 3.2 Hz), 126.6 (dd, J_{CF} = 6.2, 3.3 Hz), 119.1* (d, J_{CF} = 17.7 Hz), 118.6 (d, J_{CF} = 17.6 Hz), 118.0 (d, J_{CF} = 17.1 Hz), 117.6* (d, J_{CF} = 17.1 Hz), 76.2, 75.3*, 64.2 (br), 63.6*, 63.1, 61.3, 61.2*, 61.1, 59.2*, 54.2, 51.7, 50.9*, 44.1, 44.0*, 39.9*, 39.0, 36.3*, 36.1, 33.1, 27.8, 24.9*, 23.8, 23.6*, 16.2*, 14.6, 14.51, 14.48*; IR 3381, 1725, 1624 cm^{-1}. Anal. Calcd for $C_{31}H_{42}F_2N_2O_5$: C, 66.41; H, 7.55; N, 5.00. Found: C, 66.32; H, 7.47; N, 4.98.

3-(*R*)-Methyl-1-[2-oxo-3-(*R*)-(3,4-difluorophenyl)tetrahydropyran-4-(*R*)-ylmethyl]piperidine-3-carboxylic Acid Ethyl Ester (22). A solution of hydroxy-amide **21** (1.12 g, 2.00 mmol) and acetic acid (0.47 mL, 8.2 mmol) in toluene (11.5 mL) was stirred at 60 °C for 5 days. The reaction mixture was quenched into aq 5% Na_2CO_3 and EtOAc. The layers were separated and the organic layer was washed with 5% Na_2CO_3, then evaporated. Column chromatography (40% EtOAc/hexanes) gave a trans/cis mixture of lactones. The trans lactone was crystallized from 5% EtOAc/heptane. Addition of DBU (0.0015 mL, 0.01 mmol) to epimerize the cis isomer, and partial evaporation to remove EtOAc, gave **22** (0.642 g, 1.62 mmol, 81%). White solid; mp 79.3−80.1 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.25−7.17 (m, 2H), 7.06 (m, 1H), 4.48 (m, 1H), 4.40 (m, 1H), 4.18−4.03 (m, 2H), 3.62 (d, J = 10.4 Hz, 1H), 2.85 (br d, J = 10.0 Hz, 1H), 2.53 (br m, 1H), 2.36 (m, 1H), 2.19 (dd, J = 12.7, 9.2 Hz, 1H), 2.14 (m, 1H), 2.04 (dd, J = 12.7, 4.2 Hz, 1H), 2.03−1.94 (br m, 2H), 1.89−1.78 (m, 2H), 1.57 (m, 1H), 1.47 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.10 (m, 1H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 178.4, 175.2, 151.5 (dd, J_{CF} = 246.3, 12.8 Hz), 150.9 (dd, J_{CF} = 246.2, 12.8 Hz), 137.4 (dd, J_{CF} = 5.6, 4.0 Hz), 127.0 (dd, J_{CF} = 6.3, 3.8 Hz), 119.4 (d, J_{CF} = 17.9 Hz), 118.3 (dd, J_{CF} = 17.3 Hz), 69.4, 65.0, 62.9, 61.7, 54.7, 51.7, 44.9, 38.2, 34.3, 28.2, 24.7, 24.4, 14.7; IR 1728 cm^{-1}. Anal. Calcd for $C_{21}H_{27}F_2NO_4$: C, 63.78; H, 6.88; N, 3.54. Found: C, 63.60; H, 6.89; N, 3.55.

1-[3-(*R*)-(3,4-Difluorophenyl)-2-hydroxytetrahydro-2*H*-pyran-4-(*R*)-ylmethyl]-3-(*R*)-methylpiperidine-3-carboxylic Acid Ethyl Ester (23). To a −15 °C solution of lactone **22** (1.00 g, 2.52 mmol) in THF (10 mL) was added LiAl(O^{t}Bu)$_3$H (3.16 mL of 1.0 M in THF, 3.16 mmol) over 5 min. The reaction mixture was stirred at −5 °C for 90 min, then quenched with aqueous potassium sodium tartrate. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and evaporated to an oil. The residue was dissolved in ethyl acetate, filtered through a pad of silica gel, and evaporated to an oil. The crude product was used in the subsequent step without further purification. ^{1}H NMR (400 MHz, CD_3OD, both anomers, 1.3:1 ratio) δ 7.22 (ddd, J = 12.3, 8.0, 2.0 Hz, 1H), 7.18−6.98 (m, 5H), 4.94 (d, J = 2.9 Hz, 1H), 4.61 (d, J = 8.3 Hz, 1H), 4.14−4.06 (m, 5H), 3.99 (ddd, J = 11.7, 4.6, 1.5 Hz, 1H), 3.66 (td, J = 12.2, 2.0 Hz, 1H), 3.59 (ddd, J = 11.3, 5.0, 1.5 Hz, 1H), 2.74 (br s, 2H), 2.59 (dd, J = 11.8, 2.9 Hz, 1H), 2.52 (br s, 2H), 2.39 (m, 1H), 2.18 (m, 1H), 2.10−1.80 (m, 12H), 1.80−1.41 (m, 6H), 1.35−1.27 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.09 (m, 1H), 1.041 (s, 3H), 1.037 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD, both anomers) δ 178.47, 178.45, 151.53 (dd, J_{CF} = 245.7, 12.6 Hz), 151.25 (dd, J_{CF} = 245.1, 12.6 Hz), 150.48 (dd, J_{CF} = 245.0, 12.8 Hz), 150.41 (dd, J_{CF} = 244.9, 12.7 Hz), 139.65 (dd, J_{CF} = 5.6, 4.0 Hz), 139.41 (dd, J_{CF} = 5.6, 4.0 Hz), 127.15 (dd, J_{CF} = 6.0, 3.2 Hz), 126.15 (m), 119.35 (d, J_{CF} = 17.4 Hz), 118.41 (d, J_{CF} = 17.3 Hz), 117.98 (d, J_{CF} = 17.1 Hz), 117.49 (d, J = 16.9 Hz), 100.18, 94.63, 66.53, 65.04, 63.94, 63.53, 61.61, 60.15, 55.30, 54.80, 54.63, 53.18, 44.79, 39.84, 34.39, 34.36, 33.15, 32.68, 32.63, 32.16, 31.08, 30.26, 24.61, 24.32, 24.29, 23.85, 14.72, 14.58; IR 3419, 1727 cm^{-1}.

1-[3-(*R*)-(3,4-Difluorophenyl)-2-(4-nitrobenzoyloxy)tetrahydro-2*H*-pyran-4-(*R*)-ylmethyl]-3-(*R*)-methylpiperidine-3-carboxylic Acid Ethyl Ester (24). To a solution of crude **23** (theoretical 2.52 mmol from previous reaction), *p*-nitrobenzoic acid (0.634 g, 3.80 mmol), and DMAP (31 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added EDC (0.606 g, 3.16 mmol) in three portions. After 90 min at 0 °C, the solution was quenched with water and partitioned between CH_2Cl_2 and aq 10% NH_4Cl. The organic layer was washed with 1 N NaOH and water, then evaporated to a yellow foam. The 2*R*/2*S* diastereomer ratio was 93:7. The mixture was used in the subsequent reaction without further purification. A small sample of the 2*R* isomer was purified by column chromatography (3.5:1 hexanes/EtOAc) and recrystallized from acetonitrile/water. White solid; mp 131.2−132.0 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 8.22 (m, 2H), 8.04 (m, 2H), 7.29 (m, 1H), 7.16 (m, 2H), 5.87 (d, J = 8.4 Hz, 1H), 4.14−4.05 (m, 3H), 3.81 (dd, J = 11.8, 2.5 Hz, 1H), 2.76 (dd, J = 10.6, 8.5 Hz, 1H), 2.74 (br s, 1H), 2.48 (br s, 1H), 2.21 (m, 1H), 2.11−1.95 (m, 4H), 1.90 (br m, 1H), 1.79 (br m, 1H), 1.55−1.34 (m, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.09 (m, 1H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 177.3, 164.0, 152.0, 151.1 (dd, J_{CF} = 245.6, 12.7 Hz), 150.1 (dd, J_{CF} = 244.8, 12.5 Hz), 137.9 (dd, J_{CF} = 5.6, 4.0 Hz), 135.8, 131.7, 126.2 (dd, J_{CF} = 6.0, 3.5 Hz), 124.7, 118.3 (d, J_{CF} = ∼18 Hz, partly under solvent), 118.2 (d, J_{CF} = 17.9 Hz), 98.9, 66.5, 64.4, 62.5, 61.0, 54.5, 51.2, 44.2, 38.7, 34.0, 30.4, 24.4, 23.9, 14.7; IR 1732 cm^{-1}. Anal. Calcd for $C_{28}H_{32}F_2N_2O_7$: C, 61.53; H, 5.90; N, 5.13. Found: C, 61.42; H, 5.75; N, 5.07.

1-[2-(*R*)-{1-(*R*)-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-3-(*R*)-(3,4-difluorophenyl)-4-(*R*)-tetrahydro-2*H*-pyran-4-ylmethyl]-3-(*R*)-methylpiperidine-3-carboxylic Acid Ethyl Ester (18). The crude nitrobenzoate mixture **24** (theoretical 2.52 mmol) and alcohol **3** (0.650 g, 2.52 mmol) were combined in CH_2Cl_2 (14 mL) and cooled to −50 °C. HBF_4 etherate (0.414 mL, 3.02 mmol) was added in one portion, and the mixture was stirred at −40 °C. After 2.5 h, the reaction was quenched with aq 5% Na_2CO_3 and warmed. The layers were separated and the organic layer was washed once with water, then evaporated to a pale yellow solid. The residue was recrystallized from acetonitrile/water 3:1 giving a white solid. Yield was 1.31 g, 2.05 mmol, 81.5% from lactone **22**.

Supporting Information Available: Experimental procedures and characterization data for compounds **1**, **8**−**14**, and **16**−**18**; ^{1}H NMR spectra for compounds **11** and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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