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Enantioselective Synthesis of α-Fluoro-β^3-amino Esters: Synthesis of Enantiopure, Orthogonally Protected α-Fluoro-β^3-lysine

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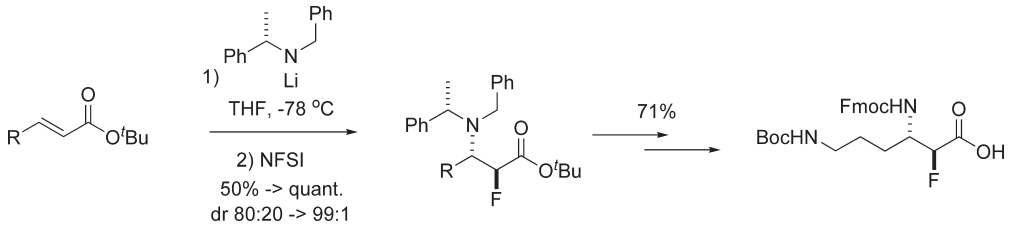
Received August 20, 2010



The scope of a tandem conjugate addition−fluorination sequence performed on α,β-unsaturated esters using the enantiopure lithium amide derived from (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine, and the electrophilic fluorinating agent *N*-fluorobenzenesulfonimide has been investigated. Using this method, α-fluoro-β^3-amino esters can be obtained in up to quantitative yield and 80:20 to >99:1 dr. This simple methodology does not rely on the use of α-amino acids from the chiral pool and thus provides the potential for the preparation of enantiopure α-fluoro-β^3-amino acids with a wide variety of side chains. Its utility was demonstrated through the synthesis of orthogonally protected (2*S*,3*S*)-α-fluoro-β^3-lysine.

Introduction

Fluorine has a van der Waals radius of 1.47 Å, which makes it only 3% smaller than oxygen and 23% larger than hydrogen.[1] It is considered the best isosteric replacement for both of these atoms. In addition, fluorine forms strong bonds with carbon, it can significantly affect the lipophilicity of a compound,[2] and its high electronegativity can have a considerable influence on the pK_a of proximal functional groups. There are numerous examples where fluorine has been successfully incorporated into bioactive compounds in place of hydrogen and oxygen. Such replacements can change the biological properties of the substrate significantly. In fact, fluorinated compounds constitute 5−15% of all small-molecule drugs launched over the last 50 years, and this proportion has increased markedly in the last 5 years.[3] Fluorinated substrates have also been widely used as enzyme mechanism probes and as enzyme inhibitors.[4] The involvement of fluorine in orthogonal multipolar interactions between protein-bound small molecules and protein residues has recently been highlighted.[5] The incorporation of fluorine into organic compounds can also have surprising conformational effects.[2,6] For these reasons, there is considerable interest in the preparation of fluorine-containing synthetic building blocks and intermediates.

β-Amino acids are also a class of compound that have received much attention because they are important components of bioactive natural products and peptidomimetics, they can enhance resistance to proteolysis, and peptides derived from β-amino acids possess fascinating and well-defined secondary structure.[7] Our interest in protease inhibition[8] led us to seek stereoselective routes to α-fluoro-β^3-amino acids, a group of compounds that are under-represented in the

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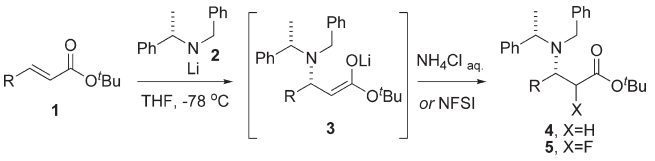
DOI: 10.1021/jo101600c Published on Web 10/08/2010

SCHEME 1. Synthesis of Protected (2*S*)-β^3-Amino Esters 4 and One-Pot Synthesis of Protected (2*S*)-α-Fluoro-β^3-Amino Esters 5 from α,β-Unsaturated Esters

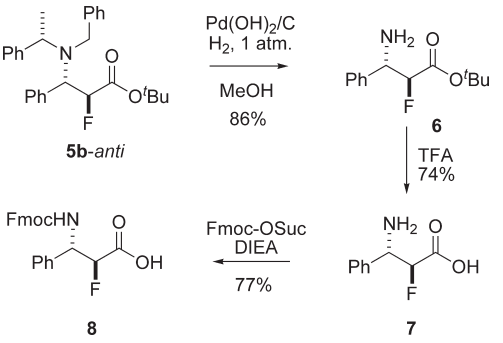


literature.[9] A number of the existing approaches to these compounds involve homologation of natural α-amino acids. Takei's group prepared an α-fluoro-β^3-homophenylalanine derivative by (diethylamino)sulfur trifluoride (DAST) treatment of the corresponding α-alcohol, which had been prepared in five steps from L-phenylalanine.[9e] Seebach's group has prepared protected α-fluoro-β^3-homoalanine by the treatment of protected L-threonine with DAST, a process that involves an aziridine intermediate.[9d] Abell and co-workers have used an approach involving the electrophilic fluorination of enolates derived from protected β-phenylalanine to produce α-fluoro-β^3-amino acid derivatives[9a] or acylated oxazolidinones to produce α-fluoro-β^2-amino acid derivatives.[9a,c] Jiang, Tan, and co-workers have developed an asymmetric Mannich reaction involving base-promoted addition of fluorinated β-keto acetyloxazolidinone and an *N*-acyloxyimine followed by decarboxylation.[9b]

We have chosen an approach involving an adaptation of Davies' diastereoselective conjugate addition of chiral lithium amides to α,β-unsaturated esters[10] followed by treatment of the intermediate enolate with the electrophilic fluorinating agent $(PhSO_2)_2NF$ (NFSI) in a tandem, one-pot reaction (Scheme 1). This simple methodology benefits from the use of readily prepared α,β-unsaturated esters and the high diastereoselectivity of the initial conjugate addition, which typically occurs in >98:2 dr at C3.[10] It also does not rely on the homologation of α-amino acids from the chiral pool, thus providing the potential for the preparation of α-fluoro-β^3-amino acids with a vast array of side chains. In a preliminary study,[11] we established that α-fluoro-β^3-amino esters **5** possessing hydrocarbon side chains could be prepared in this way with a dr of 83:17. In the case of the α-fluoro-β^3-phenylalanine derivative **5b**-*anti*, efficient deprotection gave the free amino acid **7**, which was Fmoc-protected, making it suitable for use in solid phase peptide synthesis (Scheme 2).[12] The amino acid **7** was also incorporated into an α-chymotrypsin inhibitor.[9a]

The success of the α-fluoro-β^3-amino ester motif in the inhibition of chymotrypsin[9a] prompted us to apply this functionality to the inhibition of trypsin-type proteases. This requires access to α-fluoro-β^3-amino acid derivatives with basic side chains, as trypsin-type proteases cleave proteins

SCHEME 2. Synthesis of (2*S*,3*S*)-*N*-Fmoc-α-fluoro-β^3-phenylalanine from (2*S*,3*S*,α*S*)-5b[10,12]



adjacent to these residues. Here, we report the results of an investigation into the scope of the conjugate addition−fluorination reaction (Scheme 1) and demonstrate its utility by applying it to the synthesis of a protected form of (*2S,3S*)-α-fluorinated β^3-lysine.

Results and Discussion

We first needed to establish that a range of precursors to ammonium side chains were compatible with the conditions used for the conjugate addition, as well as the combined conjugate addition−fluorination procedure. Thus, a series of α,β-unsaturated *tert*-butyl esters **1a**−**f** (Table 1) were prepared and subjected to conjugate addition−protonation to produce **4** and the one-pot conjugate addition−fluorination methodology that yields **5**. The results of this investigation, including yields and diastereoselectivities, are shown in Table 1.[13] Entry 2 is reproduced from a preliminary report.[11] In addition to the reactions of **1a**−**f**, similar experiments were also performed on the corresponding 6-chlorohexenoate; however, this compound did not appear to be compatible with our methodology (see the Supporting Information).

Table 1 reveals that the desired monofluorides **5** can be obtained in moderate (entries 5 and 6) to high yield (entry 3). In most cases, the fluorination stage of the one-pot procedure does not appear to be yield-limiting, as the yield of the fluoride **5** was only slightly lower than that of the unfluorinated product **4**. The fluorination step does, however, appear to be yield-limiting in the case of the silapiperazine **5f** (entry 6). In this case, the low yield of **5f** reflects a susceptibility of the silapiperazine to decomposition on exposure to NFSI.

With respect to the diastereoselectivity of the conjugate addition−fluorination sequence, there are two diastereoselective reactions that need to be considered. The first is the addition of (*S*)-lithium amide **2** to the α,β-unsaturated esters **1**. This reaction is well-known to give the 3*S* isomer in >98:2 dr,[10] and this was also found to be the case here; no measurable amounts of the 3*R* isomer were obtained. The second diastereoselective reaction is the fluorination with NFSI. Trapping of the intermediate enolates such as **3** with electrophiles typically

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(10) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833.

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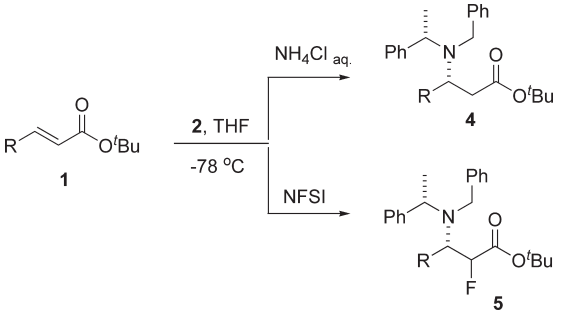
(12) The yields shown for the second and third steps in Scheme 2 result from optimization performed after the publication of ref 11. Bromfield, K. M. Ph.D. Dissertation, Monash University, Clayton, Victoria, Australia, 2005.

(13) A preliminary report[11] describes a reaction similar to the one that produced **5a** from the crotonate **1a**, but in the previous study, the experiment was performed with the corresponding ethyl ester. While the dr's obtained with the ethyl and *tert*-butyl esters were very similar, the yield was much lower for the ethyl ester (39%), presumably as a result of competing 1,2-addition of the lithium amide **2**. The use of the bulkier *tert*-butyl ester is known to limit this undesired side reaction.[10]

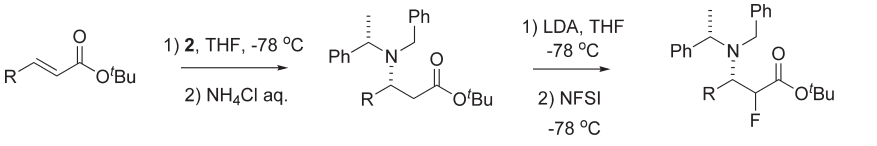
TABLE 1. Results of Conjugate Addition−protonation and Conjugate Addition−Fluorination Experiments Performed on α,β-Unsaturated Esters 1a−f



Entry	R	α,β-unsaturated ester	β³-amino ester	yield[b]	α-fluoro-β³-amino ester[a]	yield[c]	anti : syn[d]
1	Me	**1a**	**4a**	96%[e]	**5a**	62%	92:8
2	Ph	**1b**	**4b**	quant.[f]	**5b**	quant.	82:18[g]
3	TBSO	**1c**	**4c**	94%	**5c**	90%	80:20
4	TBSO	**1d**	**4d**	81%	**5d**	77%	94:6
5	Boc_2N	**1e**	**4e**	44%	**5e**	48%	88:12
6	Ph-Si-N	**1f**	**4f**	87%	**5f**	51%	>99:1

[a]NFSI added at −78 °C for **5a**,**b**,**d**, −60 °C for **5e**, −50 °C for **5c**, and −45 °C for **5f**. [b] >99:1 dr. [c]After chromatography. [d]Determined from the crude reaction mixture by integration of ^{1}H NMR resonances due to α-protons. [e]McWhorter reported an equivalent yield for this reaction.[14] [f]Davies reported an equivalent yield for this reaction.[15] [g]From ref 11.

SCHEME 3. Stepwise Conjugate Addition−fluorination Involving Deprotonation of Isolated (2*S*)-β³-Amino Esters 4b and 4c Followed by Fluorination with NFSI



1b (R=Ph)
1c (R=TBSO(CH$_2$)$_2$)

4b
4c

5b quant., *anti*:*syn* = 61:39
5c 93%, *anti*:*syn* = 72:28

gives the *anti*-compound as the major product; the 2*S*,3*S*,α*S* diastereomer in the case of **5.** This was previously confirmed to be the case for the reaction of the enolate **3b** with NFSI by X-ray crystallography performed on **5b**.[11] It was also confirmed for the reaction that produced the ethyl ester analogue of **5a**. NMR-based similarities between these previously published compounds and **5a**,**c**−**f** suggest that the *anti*-product or the 2*S*,3*S*,α*S* diastereomer is also the major product produced here. X-ray crystallography performed on a single crystal of **5c** (see the Supporting Information) supports this conclusion.

The dr's for the fluorination step were optimized by variation of the temperature of the NFSI addition and range from moderate (Table 1, entry 3) to very high (Table 1, entry 6). Using standard chromatographic and recrystallization techniques the 2*S* diastereomers of **5a**,**c**,**d**,**f** could be obtained in >99:1 dr while the 2*S* diastereomer of **5e** was purified to a dr of 98:2.

An alternative to the one-pot sequence shown in Scheme 1 is a stepwise procedure (Scheme 3). In order to compare these sequences, two β-amino esters **4b** and **4c** were deprotonated with LDA and quenched with NFSI at −78 °C. While yields of the fluorides **5b** and **5c** were equivalent to those obtained with the tandem method (quantitative and 93% respectively), the dr's were inferior. The reaction with **4c** was also repeated with the NFSI quench performed at −55 °C, but the result was equivalent to that obtained at −78 °C. These findings are in accord with the stereoselectivities recently reported for the stepwise fluorination of amide and Boc-protected forms of **4b** performed under very similar reaction conditions.[9a]

Three attempts to prepare an epimeric or (2*R*,3*S*,α*S*)-α-fluoro-β³-amino ester, **5**-*syn* were made. In the first, the 2-fluorocinnamate **9**[16] was treated with the lithium amide **2** then

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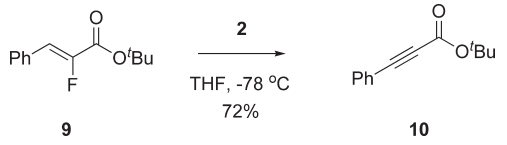
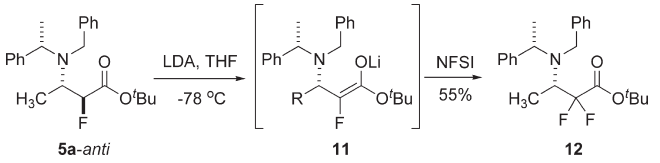
(15) Bull, S. D.; Davies, S. G.; Roberts, P. M.; Savory, E. D.; Smith, A. D. *Tetrahedron* **2002**, *58*, 4629.

(16) Elkik, E.; Imbeaux-Oudotte, M. *Bull. Soc. Chim. Fr.* **1987**, 861.

SCHEME 4. Treatment of 2-Fluorocinnamate 9 with Lithium Amide 2



SCHEME 5. Synthesis of Protected (3*S*,α*S*)-α,α-Difluoro-β^3-homoalanine 12

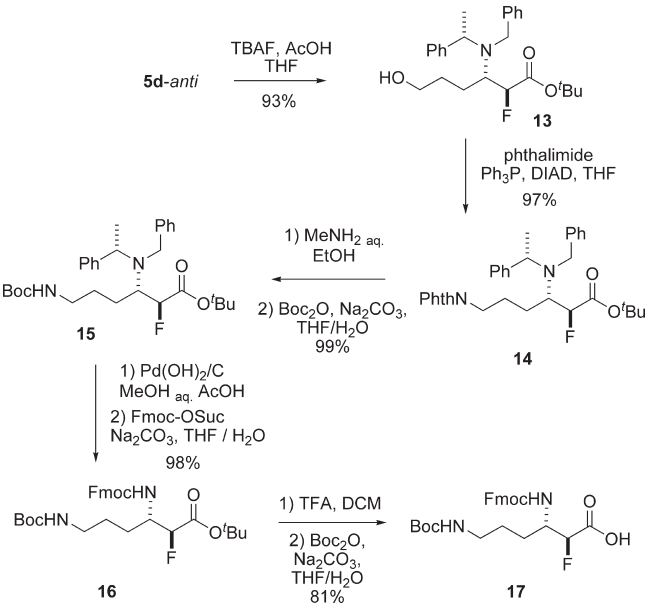


quenched with satd NH_4Cl. As protonation of the proposed enolate intermediate is predicted to occur *anti* to the large amine substituent, **5b**-*syn* was expected to be the major product. Instead, the lithium amide deprotonated the fluoroalkene, leading to elimination of fluoride and the formation of the alkyne **10** (Scheme 4). In the second approach, **5a** was deprotonated with LDA and quenched with the bulky proton source, 2,6-di-*tert*-butylphenol. This was expected to be an effective epimerization method as reprotonation was again expected to occur *anti* to the amine group, as seen previously with 2-alkyl-β-amino esters.[10] Unfortunately, the reprotonation proved to be unselective with an *anti*/*syn* dr of 48:52 being the result. As an alternative to this kinetically controlled enolate protonation, an epimerization under thermodynamic control was performed. In this case, pure **5a**-*anti* was treated with *t*-BuOH/*t*-BuOLi in THF over 6 days, but this only gave a dr of 80:20 in favor of the **5a**-*anti*.

α,α-Difluorinated-β^3-amino esters are also of considerable interest[9d,e,17] and an example of such a compound (**12**) was produced when the enolate **11** was quenched with NFSI (Scheme 5). The sequence of tandem conjugate addition-fluorination-deprotonation-fluorination thus provides access to enantiopure α,α-difluoro-β^3-amino esters. Alternative routes to this class of compounds involving the stereoselective addition of organozinc reagents to imines and sulfinimines have been described.[18]

Having established the effectiveness of the tandem conjugate addition-fluorination method, our attention turned to the synthesis of a fluorinated enantiopure β^3-lysine derivative. Of the potential terminal amine precursor functionalities described here, namely the *N*,*N*-diBoc-protected, silapiperazine, chloro, and siloxane, the α-fluoro-β^3-amino ester bearing the siloxane side chain **5d** was chosen for use in the synthesis of the target compound. This is because, as mentioned above, the 6-chlorohexenoate precursor is incompatible with the conjugate addition reaction, and the diBoc-protected hexanoate **5e**[19] and the silapiperazine **5f** were produced in low yield.

SCHEME 6. Synthesis of N^β-Fmoc-N^ε-Boc-2*S*-α-fluoro-β^3-lysine 17



Enantiopure **5d**-*anti* was thus converted to a protected form of α-fluoro-β^3-lysine **17** suitable for use in solid-phase peptide synthesis via a series of routine and high yielding steps (Scheme 6). This involved silyl ether cleavage to give the terminal alcohol **13**, conversion to the phthalimide **14** using Mitsunobu conditions, cleavage of the phthalimide to give the primary amine, and then Boc protection to furnish **15**. Removal of the benzyl groups by hydrogenolysis in the presence of Pearlman's catalyst followed by Fmoc protection gave **16**, and finally, cleavage of the *tert*-butyl ester and reprotection of the amine gave **17**.

Conclusion

A tandem procedure involving chiral lithium amide conjugate addition and fluorination with NFSI provides *anti*-α-fluoro-β^3-amino esters **5** from α,β-unsaturated esters **1** in 80:20 to >99:1 dr. In contrast, a stepwise approach involving deprotonation of enantiopure β^3-amino esters **4b**,**c** followed by fluorination yielded **5b**,**c** with lower dr's. Attempts to prepare selectively a *syn*-α-fluoro-β^3-amino ester by either epimerization of *anti*-**5a** or conjugate addition to a 2-fluoro-α,β-unsaturated ester **9** were unsuccessful. Deprotonation of a monofluoro-β^3-amino ester **5a** followed by fluorination with NFSI gave the corresponding α,α-difluorinated-β^3-amino ester **12**. Using the tandem methodology as a key step, an α,β-unsaturated ester bearing a siloxyl side chain **1d** was converted into enantiopure, orthogonally protected (2*S*,3*S*)-α-fluoro-β^3-lysine **17**. The methodology described here is not limited by the range of α-amino acids available from the chiral pool, and thus promises to provide access to a wide range of enantiopure *anti*-α-fluoro-β^3-amino acid derivatives.

Experimental Section

General Experimental Procedures. DCM was distilled from CaH, and THF was distilled from sodium benzophenone ketyl

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(18) (a) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Tetrahedron* **2008**, *64*, 4332. (b) Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yasuda, N.; Uekusa, H.; Ono, T.; Berbasov, D. O.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7448. (c) March, T. L.; Johnston, M. R.; Duggan P. J. *Book of Abstracts*, 19th International Symposium on Fluorine Chemistry, Jackson Hole, WY, 2009; Abstract 160, p 87.

(19) In this case, the yield of the conjugate addition reaction is compromised by isomerization of the double bond: Davies, S. G.; Garrido, N. M.; Kruchinin, D.; Ichihara, O.; Kotchie, L. J.; Price, P. D.; Price Mortimer, A. J.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1793.

immediately before use. All other reagents were purified according to Perrin,[20] with dried solvents stored over molecular sieves. TBAF (1 M in THF) was stored over molecular sieves after opening. The temperatures of the conjugate addition and fluorination experiments were controlled using an acetone/dry ice cryobath, with the periodic addition of dry ice used to maintain the temperature between ±3 °C of that stated. Thin-layer chromatography (TLC) was performed on precoated sheets of Merck silica gel 60 and visualized under UV light (254 nm), with ninhydrin or with $KMnO_4$. Column chromatography was carried out at atmospheric pressure using Davisil silica gel (LC60 Å, 40−63 μm).

Melting points were obtained with a hot-stage microscope and are uncorrected. Optical rotations are referenced to the sodium D line (589 nm) at the temperature specified. All NMR spectra were recorded at 293 K unless otherwise stated. Peaks were assigned with the aid of homonuclear (^{1}H−^{1}H) correlation spectroscopy (COSY) and heteronuclear (^{1}H−^{13}C) correlation spectroscopy (HMQC and HMBC) when required. ^{19}F NMR spectra are referenced to internal $CFCl_3$. HRMS data were obtained using positive-ion electrospray ionization (ESI-MS).

Representative Procedure A: Conjugate Addition−Protonation. Preparation of (3*S*,α*S*)-*tert*-Butyl-6-(*tert*-butyldimethylsilyloxy)-3-(*N*-benzyl-α-methylbenzylamino)hexanoate, 4d. To a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.11 mL, 0.55 mmol) in THF (2 mL) at −78 °C, under N_2, was added ^{n}BuLi (1.6 M in hexanes, 0.34 mL, 0.55 mmol). After 30 min, (*E*)-*tert*-butyl 6-(*tert*-butyldimethylsilyloxy)hex-2-enoate (**1d**) (110 mg, 0.37 mmol) in THF (1.5 mL) was added dropwise and the mixture stirred at −78 °C for 1.5 h before being quenched with saturated aq NH_4Cl (5 mL). The mixture was allowed to warm to 0 °C and then diluted with diethyl ether (20 mL) and H_2O (20 mL), the layers were separated, and the aqueous layer was further extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography on silica gel (1:19 diethyl ether/hexane) gave the product **4d** as a colorless oil (152 mg, 81%, dr ≥ 98:2): $[\alpha]^{20}_D = -5$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.2 Hz, 2H), 7.29−7.22 (m, 6H), 7.21−7.15 (m, 2H), 3.76 (q, J = 7.2 Hz, 1H), 3.73 (d, J = 14.8 Hz, 1H), 3.52 (t, J = 6.4 Hz, 2H), 3.43 (d, J = 14.8 Hz, 1H), 3.25 (nonet, J = 4.4 Hz, 1H), 1.90−1.79 (m, 3H), 1.51−1.38 (m, 3H), 1.34 (s, 9H), 1.28 (d, J = 6.8 Hz, 3H), 0.83 (s, 9H), −0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 143.0, 141.8, 128.24, 128.21, 128.1, 128.0, 126.9, 126.5, 79.9, 63.3, 58.1, 54.0, 50.1, 38.0, 30.7, 29.8, 28.0, 26.0, 20.3, −5.2; HRMS calcd for $C_{31}H_{50}NO_3Si$ 512.3554, found 512.3562 $[M + H]^+$.

(3*S*,α*S*)-*tert*-Butyl 5-(*tert*-Butyldimethylsilyloxy)-3-(*N*-benzyl-α-methylbenzylamino)pentanoate, 4c. The silyloxyaminopentanoate **4c** was prepared from (*E*)-*tert*-butyl 5-(*tert*-butyldimethylsilyloxy)pent-2-enoate (**1c**) (354 mg, 1.24 mmol) according to representative procedure A, with the following variation: after stirring at −78 °C for 2.5 h, the reaction was allowed to warm to −40 °C over 1 h before quenching. The product **4c** was obtained as a colorless oil that crystallized on standing (518 mg, 94%). A sample was recrystallized from 95% aq EtOH to give white needles, dr > 99:1: mp 77 °C; $[\alpha]^{20}_D = -6$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 2H), 7.35−7.22 (m, 8H), 3.85−3.71 (m, 4H), 3.56−3.49 (m, 2H), 1.96−1.88 (m, 2H), 1.77−1.68 (m, 1H), 1.58−1.50 (m, 1H), 1.41 (s, 9H), 1.36 (d J = 7.2 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 142.7, 141.5, 128.2, 128.1, 128.0, 126.9, 126.6, 79.9, 61.1, 58.0, 50.8, 50.1, 38.2, 36.4, 28.1, 26.0, 19.9, 18.3, −5.2, −5.3. HRMS calcd for $C_{30}H_{48}NO_3Si$ 498.3398, found 498.3395 $[M+H]^+$.

(3*S*,α*S*)-*tert*-Butyl 6-(*N*,*N*-Di-*tert*-butylcarbonyloxy)amino-(*N*-benzyl-α-methylbenzylamino)hexanoate, 4e. The di-Boc-protected aminohexanoate **4e** was prepared from (*E*)-*tert*-butyl 6-(*N*,*N*-di-*tert*-butylcarbonyloxy)aminohex-2-enoate **1e**[21] (156 mg, 0.40 mmol) according to representative procedure A. The product **4e** was obtained after column chromatography (1:4 diethyl ether/hexane) as a colorless oil (106 mg, 44%, dr ≥ 98:2): $[\alpha]^{20}_D = -7$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.2 Hz, 2H), 7.34−7.29 (m, 6H), 7.25−7.20 (m, 2H), 3.80 (q, J = 6.8 Hz, 1H), 3.76 (d, J = 14.8 Hz, 1H), 3.60−3.52 (m, 2H), 3.47 (d, J = 15.2 Hz, 1H), 3.35−3.28 (m, 1H), 2.01−1.90 (m, 1H), 1.89−1.82 (m, 2H), 1.60−1.44 (m, 20H), 1.39 (s, 9H), 1.37−1.23 (m, 2H), 1.34 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 152.7, 142.7, 141.5, 128.3, 128.1, 127.9, 126.9, 126.6, 81.9, 79.9, 57.8, 53.9, 50.1, 46.6, 37.9, 30.9, 28.1, 28.0, 27.2, 20.1; HRMS calcd for $C_{35}H_{53}N_2O_6$ 597.3898, found 597.3909 $[M + H]^+$.

(3*S*,α*S*)-*tert*-Butyl 6-(4,4-Diphenyl-1-aza-4-silacyclohex-1-yl)-3-(*N*-benzyl-α-methylbenzylamino)hexanoate, 4f. The silylpiperazine aminohexanoate **4f** was prepared from **1f** (138 mg, 0.33 mmol) according to representative procedure A, with the following variation: after being stirred at −78 °C for 2.5 h, the reaction was allowed to warm to −60 °C over 30 min before quenching. After a standard workup, the crude residue was redissolved in THF (3 mL), and phenyl isocyanate (0.016 mL, 0.144 mmol) was added in order to remove excess (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine. After being stirred under N_2 for 4 h, the solution was concentrated in vacuo and subjected to column chromatography (5:44:1 diethyl ether/hexane/Et_3N) to give the product **4f** as a colorless gum (180 mg, 87%, dr > 99:1): $[\alpha]^{20}_D = +2$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.54 (m, 4H), 7.43−7.20 (m, 16 H), 3.83 (q, J = 6.8 Hz, 1H), 3.80 (d, J = 15.2 Hz, 1H), 3.50 (d, J = 15.2 Hz, 1H), 3.33−3.27 (m, 1H), 2.82 (t, J = 6.2 Hz, 4H), 2.43−2.31 (m, 2H), 1.98 (dd, J = 14.8, 3.6 Hz, 1H), 1.88 (dd, J = 14.6, 9.4 Hz, 1H), 1.84−1.76 (m, 1H), 1.57−1.42 (m, 2H), 1.39 (s, 9H), 1.38−1.34 (m, 7H), 1.31−1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 143.2, 142.0, 134.8, 129.5, 128.3, 128.20, 128.18, 128.1, 128.0, 127.0, 126.6, 80.1, 58.6, 57.9, 54.1, 52.2, 50.1, 37.7, 31.6, 28.1, 24.1, 20.7, 10.8; HRMS calcd for $C_{41}H_{53}N_2O_2Si$ 633.3871, found 633.3871 $[M+H]^+$.

Representative Procedure B: Tandem Conjugate Addition−Fluorination. Synthesis of (2*S*,3*S*,α*S*)-*tert*-Butyl 6-(*tert*-Butyldimethylsilyloxy)-3-(*N*-benzyl-α-methylbenzylamino)-2-fluorohexanoate, 5d. To a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.135 mL, 0.65 mmol) in THF (2 mL) at −78 °C, under N_2, was added ^{n}BuLi (1.6 M in hexanes, 0.41 mL, 0.65 mmol). After 30 min, (*E*)-*tert*-butyl 6-(*tert*-butyldimethylsilyloxy)hex-2-enoate (**1d**) (*E*/*Z* 97:3, 130 mg, 0.43 mmol) in THF (1.5 mL) was added dropwise, and the mixture was stirred at −78 °C for 2.5 h and then allowed to warm to −30 °C over 30 min. The solution was recooled to −78 °C, and NFSI (205 mg, 0.65 mmol) in THF (1 mL, dissolution aided by sonication for < 1 min) was added dropwise. After being stirred at −78 °C for 1 h, the solution was allowed to warm to 0 °C over 30 min then quenched with saturated aq NH_4Cl (4 mL). The mixture was diluted with H_2O (20 mL) and poured into hexane (20 mL). The layers were separated, and the organic layer was washed with H_2O (2 × 10 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Analysis of the crude product showed dr = 94:6. Column chromatography (1:19 diethyl ether/hexane) gave the *2S*-fluoride **5d-*anti*** as a colorless oil (177 mg, 77%, dr = 98:2): $[\alpha]^{20}_D = +7$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 7.6 Hz, 2H), 7.37−7.25 (m, 8H), 4.45 (d, J = 50.0 Hz, 1H), 4.16 (d, J = 15.2 Hz, 1H), 3.94 (q, J = 6.8 Hz, 1H), 3.67 (d, J = 15.2 Hz, 1H), 3.56 (t, J = 6.4 Hz), 3.39 (ddd, J = 31.2, 9.6, 3.6 Hz), 1.96−83 (m, 1H), 1.73−1.60 (m, 1H), 1.54−1.50 (m, 1H), 1.45 (s, 9H), 1.39−1.27 (m, 1H), 1.34 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.048 (s, 6H); ^{13}C NMR (100 MHz,

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(21) Carretero, J. C.; Arrayás, R. G. *J. Org. Chem.* **1998**, *63*, 2993.

$CDCl_3$) δ 168.4 (d, J = 24.4 Hz), 142.1, 141.7, 128.2, 128.1, 128.0, 127.9, 127.0, 126.5, 90.0 (d, J = 188.8 Hz), 82.2, 63.0, 58.1, 57.9, 50.7 (d, J = 4.5 Hz), 30.6, 27.9, 25.9, 23.4 (d, J = 5.2 Hz), 20.0, 18.2, −5.36, −5.38. ^{19}F NMR (282 MHz, $CDCl_3$) δ −200.0 (dd, J = 50.7, 31.2 Hz); HRMS calcd for $C_{31}H_{49}FNO_3Si$ 530.3460, found 530.3465 $[M + H]^+$.

(2*S*,3*S*,α*S*)-*tert*-Butyl 3-(*N*-Benzyl-α-methylbenzylamino)-2-fluorobutanoate, 5a. The fluoroaminobutanoate **5a** was prepared from (*E*)-*tert*-butyl crotonate **1a** (134 mg, 0.94 mmol) according to representative procedure B, with the following variation: after NFSI addition, stirring was continued at −78 °C for 1 h, and then the reaction mixture was allowed to warm to −30 °C over 1.5 h before being quenched. Analysis of the crude product by ^{1}H NMR showed dr = 92:8. Column chromatography (3:7 diethyl ether/hexane) gave a mixture of the C2 epimers as a colorless oil (217 mg, 62%). Recrystallization from hexane gave the *2S*-fluoride **5a**-*anti* (195 mg, 56%) as white needles: mp 82.5−84 °C; $[\alpha]^{20}_D$ = +22 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.6 Hz, 2H), 7.36−7.20 (m, 8 H), 4.65 (dd, J = 50.4, 2.0 Hz, 1H), 3.99 (q, J = 6.8 Hz, 1H), 3.98 (d, J = 14.8 Hz, 1H), 3.84 (d, J = 14.8 Hz, 1H), 3.47−3.33(m, 1H), 1.38 (s, 9H), 1.34 (d, J = 6.8 Hz, 3H), 1.15 (dd, J = 7.2, 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4 (d, J = 24.8 Hz), 143.6, 141.9, 128.23, 128.18, 128.1, 127.7, 126.8, 126.6, 92.3 (d, J = 188.0 Hz), 82.1, 58.1, 53.4 (d, J = 18.8 Hz), 50.6 (d, J = 4.0 Hz), 27.9, 17.2, 12.2 (d, J = 5.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −202.5 (dd, J = 49.7, 30.2 Hz); HRMS calcd for $C_{23}H_{31}FNO_2$ 372.2333, found 372.2336 $[M + H]^+$.

(2*S*,3*S*,α*S*)-*tert*-Butyl 5-(*tert*-Butyldimethylsilyloxy)-3-(*N*-benzyl-α-methylbenzylamino)-2-fluoropentanoate, 5c. The fluoroamino pentanoate **5c** was prepared from (*E*)-*tert*-butyl 5-(*tert*-butyldimethylsilyloxy)pent-2-enoate **1c** (105 mg, 0.37 mmol) according to representative procedure B, with the following variation: NFSI was added at −50 °C, and stirring was continued for 1 h, after which time the solution was quenched and allowed to warm to 0 °C. The product was obtained as a colorless oil which crystallized on standing (171 mg, 90%, dr 80:20). Recrystallization from acetone (slow evaporation) gave the major isomer *2S*-fluoride **5c**-*anti* as white needles (118 mg, 62%): mp 109−110 °C; $[\alpha]^{20}_D$ = +4 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.24 (m, 10H), 4.26 (dd, J = 50.4, 0.8 Hz, 1H), 4.12 (d, J = 14.4 Hz, 1H), 3.94−3.86 (m, 2H), 3.83−3.71 (m, 2H), 3.65 (dd, J = 15.2, 1.6 Hz, 1H), 1.86−1.78 (m, 1H), 1.55−1.48 (m, 1H), 1.49 (s, 9H), 1.38 (d, J = 7.2 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4 (d, J = 24.7 Hz), 141.3, 141.2, 128.4, 128.3, 128.2, 128.1, 127.2, 126.7, 90.7 (d, J = 187.3 Hz), 82.3, 59.7, 57.0, 53.6 (d, J = 18.7 Hz), 50.7, 30.3 (d, J = 4.9 Hz), 28.0, 26.1, 19.4, 18.4, −5.2, −5.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −199.1 (dd, J = 51.8, 32.3 Hz); HRMS calcd for $C_{30}H_{47}FNO_3Si$ 516.3304, found 516.3306 $[M + H]^+$.

(2*S*,3*S*,α*S*)-*tert*-Butyl 6-(*N*,*N*-Di-*tert*-butylcarbonyloxy)amino-(*N*-benzyl-α-methylbenzylamino)-2-fluorohexanoate, 5e. The fluoroamino hexanoate **5e** was prepared from (*E*)-*tert*-butyl 6-(*N*,*N*-di-*tert*-butylcarbonyloxy)aminohex-2-enoate **1e** (130 mg, 0.34 mmol) according to representative procedure B, with the following variation: NFSI was added at −60 °C, and after 1.5 h the reaction was allowed to warm to −35 °C over 30 min before quenching. Analysis of the crude mixture by ^{1}H NMR showed a dr of 88:12. Column chromatography (1:9 to 1:3 diethyl ether/hexane) gave a colorless oil as a mixture of isomers (277 mg, 48%, dr 93:7). A portion of this was further purified by chromatography (1:9 diethyl ether/hexane) to give a sample with a dr of 98:2: $[\alpha]^{20}_D$ = +5 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43(d, J = 7.6 Hz, 2H), 7.36−7.23 (m, 8H), 4.36 (d, J = 50.0 Hz, 1H), 4.12 (d, J = 14.4 Hz, 1H), 3.91 (q, J = 6.8 Hz, 1H), 3.64 (d, J = 16.4 Hz, 1H), 3.62−3.53 (m, 2H), 3.40 (ddd, J = 31.5, 9.6, 3.2 Hz, 1H), 2.03−1.92 (m, 1H), 1.70−1.58 (m, 1H), 1.57−1.40 (m, 2H), 1.50 (s, 18H), 1.44 (s, 9H), 1.33 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0 (d, J = 25.0 Hz), 152.60, 152.55, 141.9, 128.3, 128.2, 128.13, 128.06, 127.2, 126.6, 90.1 (d, J = 190.0 Hz), 82.4, 82.0, 58.1 (d, J = 4.6 Hz), 57.6, 50.8, 46.5, 28.04, 27.97, 27.2, 24.6, 19.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ −199.1 (dd, J = 51.8, 32.3 Hz); HRMS calcd for $C_{35}H_{51}FN_2NaO_6$ 637.3623, found 637.3645 $[M + Na]^+$.

(2*S*,3*S*,α*S*)-*tert*-Butyl 6-(4,4-Diphenyl-1-aza-4-silacyclohex-1-yl)-3-(*N*-benzyl-α-methylbenzylamino)-2-fluorohexanoate, 5f. The fluoroamino hexanoate **5f** was prepared from **1f** (136 mg, 0.32 mmol) according to representative procedure B, with the following variation: NFSI was added at −45 °C, and after 2 h the reaction mixture was allowed to warm to −10 °C over 45 min before being quenched. After a standard workup, the sulfonimide byproducts were removed by filtration through a plug of silica (1:2 diethyl ether/hexane), and the filtrate was concentrated in vacuo. The residue was redissolved in dry DCM (2 mL), and phenyl isocyanate (22 μL, 0.20 mmol) was added in order to remove excess (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine. After being stirred under N_2 for 3.5 h, the mixture was concentrated in vacuo and subjected to column chromatography (5:44:1 diethyl ether/hexane/Et_3N) to give **5f**-*anti* as a colorless gum (107 mg, 51%, dr > 99:1): $[\alpha]^{20}_D$ = +13 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.54 (m, 4H), 7.45−7.23 (m, 16H), 4.50 (d, J = 50.4 Hz, 1H), 4.16 (d, J = 15.8 Hz, 1H), 3.94 (q, J = 6.8 Hz, 1H), 3.66 (d, J = 15.8 Hz, 1H), 3.37 (ddd, J = 30.8, 10.0, 3.6 Hz, 1H), 2.81 (t, J = 6.0 Hz, 4H), 2.42−2.30 (m, 2H), 1.85−1.75 (m, 1H), 1.70−1.59 (m, 1H), 1.53−1.40 (m, 10H), 1.40−1.27 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4 (d, J = 25.0 Hz), 142.4, 141.8, 135.6, 134.6, 129.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.1, 126.5, 89.9 (d, J = 189.0 Hz), 82.2, 58.3, 58.1 (d, J = 19.0 Hz), 57.9, 52.0, 50.7 (d, J = 5.0 Hz), 27.9, 25.2 (d, J = 5.0 Hz), 24.4, 20.3, 11.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −200 (bs); HRMS calcd for $C_{41}H_{52}FN_2O_2Si$ 651.3777, found 651.3777 $[M + H]^+$.

Representative Procedure C-Stepwise Fluorination. Fluorination of 4c. *Fluorination at −55 °C:* To a solution of diisopropylamine (0.034 mL, 0.24 mmol) in dry THF (2 mL) at 0 °C was added ^{n}BuLi (1.6 M in hexanes, 0.16 mL, 0.24 mmol) and the solution stirred for 20 min, after which time it was cooled to −78 °C. The amino ester **4c** (96 mg, 0.19 mmol) in THF (1.5 mL) was added dropwise and the solution stirred for another 1 h before being warmed to −55 °C. A solution of NFSI (89 mg, 0.28 mmol) in THF (1.5 mL) was added and stirring continued at −55 °C for 3 h followed by warming to 0 °C over a further 1 h before quenching with saturated aq NH_4Cl (4 mL). Ether (25 mL) and H_2O (25 mL) were added and the layers separated. The ether layer was washed with H_2O (25 mL) and brine (25 mL) and then dried (Na_2SO_4) and concentrated in vacuo. Crude ^{1}H NMR showed a 69:31 mixture of *anti*/*syn* isomers. Passage through a plug of silica (1:9 ether/hexane) gave a white solid (93 mg, 93%), which was recrystallized from acetone to give **5c**-*anti* (59 mg, 59%) as white needles. *Fluorination at −78 °C:* To a solution of diisopropylamine (0.033 mL, 0.23 mmol) in dry THF (2 mL) at 0 °C was added ^{n}BuLi (1.5 M in hexanes, 0.15 mL, 0.23 mmol) and the solution stirred for 20 min, after which time it was cooled to −78 °C. The amino ester **4c** (94 mg, 0.19 mmol) in THF (1.5 mL) was added dropwise and the solution stirred for another 1 h. A solution of NFSI (86 mg, 0.27 mmol) in THF (1.5 mL) was added dropwise with stirring continued at −78 °C for 3 h, after which the solution was allowed to warm to −35 °C over 1.5 h and then quenched with saturated aq NH_4Cl (4 mL). Ether (25 mL) and H_2O (25 mL) were added and the layers separated. The ether layer was washed with H_2O (25 mL) and brine (25 mL) and then dried (Na_2SO_4) and concentrated in vacuo. A ^{1}H NMR spectrum of the crude reaction mixture showed **5c** as a 72:28 mixture of *anti*/*syn* isomers. The product was not further purified.

Treatment of (*Z*)-*tert*-Butyl-α-fluorocinnamate 9 with Lithium (*S*)-*N*-Benzyl-*N*-(α-methylbenzyl)amide, 2. To a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.11 mL, 0.54 mmol) in THF (2 mL) at −78 °C, under N_2, was added ^{n}BuLi (1.5 M in hexanes, 0.36 mL, 0.54 mmol). After 20 min, a solution of

(*Z*)-*tert*-butyl-α-fluorocinnamate[22] (85 mg, 0.38 mmol) in THF (1.5 mL) was added dropwise. The resulting dark yellow solution was stirred at −78 °C for 2 h and then quenched with saturated aq NH_4Cl (2 mL). After being warmed to rt, the mixture was diluted with DCM (10 mL), and H_2O (10 mL) was added. The layers were separated, the aqueous layer was further extracted with DCM (2 × 10 mL), and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Some decomposition of the crude reaction mixture appeared to occur, and subsequent column chromatography (1:2 DCM/hexane) yielded the known[23] phenylacetylene derivative **10** (55 mg, 72%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.55 (d, *J* = 6.9 Hz, 2H), 7.45−7.32 (m, 3H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 132.7, 130.1, 128.3, 119.9, 83.6, 83.3, 81.9, 27.9; HRMS calcd for $C_{13}H_{14}O_2Na$ 225.0891, found 225.0886 $[M + Na]^+$.

Attempted Epimerization of Fluoroamino Ester 5a. Kinetically Controlled Epimerization. To a solution of diisopropylamine (0.047 mL, 0.33 mmol) in dry THF (1.5 mL) at 0 °C was added ^{n}BuLi (1.5 M in hexanes, 0.22 mL, 0.33 mmol) and the solution stirred for 20 min. The amino ester **5a** (89 mg, 0.24 mmol) in THF (1.5 mL) was added dropwise and the solution stirred at 0 °C for 30 min before being cooled to −78 °C. A solution of 2,6-di-*tert*-butylphenol (68 mg, 0.33 mmol) in THF (1.5 mL) was added dropwise and stirring continued at −78 °C for 2 h, after which time the solution was quenched with saturated aq NH_4Cl (5 mL) and allowed to warm to rt. Ether (20 mL) and H_2O (20 mL) were added and the layers separated. The aqueous layer was extracted with ether (10 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. A ^{1}H NMR spectrum of the crude reaction mixture showed **5a** as a 48:52 mixture of *anti*/*syn* isomers, which were not isolated or resolved.

Thermodynamically Controlled Epimerization. A solution of dry ^{t}BuOH (0.12 mL, 1.61 mmol) in THF (1.5 mL) was cooled to 0 °C, and LiHMDS (1 M in THF; 0.74 mL, 0.74 mmol) was added. After the solution was stirred for 15 min, a solution of **5a** (71 mg, 0.19 mmol) in THF (1 mL) was added dropwise and the mixture allowed to stir under N_2 at rt for 6 days. The solvent was then removed in vacuo, brine (25 mL) was added, and the mixture was poured into ether (25 mL). The ether layer was separated, dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (1:9 ether/hexane) afforded 51 mg (72%) of **5a** as an 80:20 mixture of *anti*/*syn* C2 epimers.

(3*S*,α*S*)-*tert*-Butyl 3-(*N*-Benzyl-α-methylbenzylamino)-2,2-difluorobutanoate, 12. ^{n}BuLi (1.6 M in hexanes, 0.13 mL, 0.21 mmol) was added to a solution of diisopropylamine (30 μL, 0.21 mmol) in THF (2 mL) and stirred for 20 min. The solution was then cooled to −78 °C, and the monofluoroamino ester **5a**-*anti* (52 mg, 0.14 mmol) in THF (1 mL) was added dropwise. After the reaction mixture was allowed to warm to 0 °C over 2 h, the solution was recooled to −60 °C, NFSI (53 mg, 0.17 mmol) in THF (1 mL) was added dropwise, and the mixture was allowed to warm to rt overnight. The resulting dark yellow solution was diluted with diethyl ether (20 mL) and H_2O (20 mL), the layers were separated, and the aqueous layer was further extracted with diethyl ether (20 mL). The organic layers were combined and washed with brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (1:1 DCM/hexane) performed on the residues gave the difluoro compound **12** (30 mg, 55%) as a colorless oil that could be crystallized from cold hexane: mp 61−63 °C; $[\alpha]^{20}_D$ = −8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.33−7.21 (m, 8H), 4.06 (q, *J* = 7.2 Hz, 1H), 3.97 (d, *J* = 14.4 Hz, 1H), 3.75 (d, *J* = 14.4 Hz, 1H), 3.64−3.56 (m, 1H), 1.46 (s, 9H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5 (t, *J* = 31.3 Hz), 142.8, 141.1, 128.7, 128.2, 128.04, 127.96, 126.9, 126.7, 116.8 (dd, *J* = 258.8, 252.9 Hz), 83.9, 59.3, 54.7 (dd, *J* = 25.8, 20.8 Hz), 50.3, 27.7, 16.3, 10.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.0 (dd, *J* = 254.5, 11.6 Hz), −117.0 (dd, *J* = 253.1, 18.1); HRMS calcd for $C_{23}H_{30}F_2NO_2$ 390.2239, found 390.2241 $[M + H]^+$.

(2*S*,3*S*,α*S*)-*tert*-Butyl 6-Hydroxy-3-(*N*-benzyl-α-methylbenzylamino)-2-fluorohexanoate, 13. To the *2S*-fluoride **5d**-*anti* (842 mg, 1.59 mmol) in dry THF (8 mL) were added TBAF (1 M in THF, 3.33 mL, 3.33 mmol) and glacial AcOH (0.29 mL, 4.99 mmol), and the resulting solution was stirred at 40 °C for 6 h. The reaction mixture was then concentrated in vacuo and the residue redissolved in diethyl ether (50 mL), washed with saturated aq $NaHCO_3$ (50 mL), H_2O (2 × 30 mL), and brine (50 mL), and then dried (Na_2SO_4) and again concentrated in vacuo. Column chromatography (1:4 EtOAc/hexane) performed on the residue yielded **13** (614 mg, 93%) as a colorless oil: $[\alpha]^{20}_D$ = +6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.38−7.22 (m, 8H), 4.51 (dd, *J* = 50.0, 0.8 Hz, 1H), 4.18 (d, *J* = 15.2, 1H), 3.96 (q, *J* = 6.8 Hz, 1H), 3.68 (d, *J* = 15.6 Hz, 1H), 3.55 (t, *J* = 6.4 Hz, 2H), 3.41 (ddd, *J* = 31.2, 9.6, 3.2 Hz, 1H), 1.93−1.83 (m, 1H), 1.75−1.56 (m, 2H), 1.47−1.37 (m, 1H), 1.46 (s, 9H), 1.35 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6 (d, *J* = 24.0 Hz), 142.4, 141.8, 128.4, 128.3, 128.1, 128.0, 127.3, 126.6, 89.9 (d, *J* = 188.8 Hz), 82.5, 62.7, 58.4, 58.0 (d, *J* = 18.8 Hz), 50.8 (d, *J* = 4.4 Hz), 30.0, 28.0, 23.3 (d, *J* = 5.6 Hz), 20.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −199.9 (dd, *J* = 50.7, 31.2 Hz); HRMS calcd for $C_{25}H_{35}FNO_3$ 416.2595, found 416.2601 $[M + H]^+$.

(2*S*,3*S*,α*S*)-*tert*-Butyl 6-(Isoindole-1,3-dione)-3-(*N*-benzyl-α-methylbenzylamino)-2-fluorohexanoate, 14. A solution of the alcohol **13** (240 mg, 0.58 mmol), PPh_3 (227 mg, 0.87 mmol), and phthalimide (128 mg, 0.87 mmol) in dry THF (6 mL) was cooled to 0 °C, and DIAD (0.18 mL, 0.87 mmol) was added dropwise. The resulting mixture was allowed to warm to rt overnight, concentrated in vacuo, and then subjected to column chromatography (1:4 EtOAc/hexane) to give the phthalimide (307 mg, 97%) as a colorless oil: $[\alpha]^{20}_D$ = +9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.83 (m, 2H), 7.73−7.70 (m, 2H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.36−7.21 (m, 8H), 4.35 (d, *J* = 50.0 Hz, 1H), 4.13 (d, *J* = 15.2 Hz, 1H), 3.93 (d, *J* = 6.8 Hz, 1H), 3.74−3.60 (m, 3H), 3.44 (ddd, *J* = 15.6, 9.2, 2.2 Hz, 1H), 2.14−2.04 (m, 1H), 1.78−1.65 (m, 2H), 1.42 (s, 9H), 1.37−1.27 (m, 1H), 1.35 (d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3 (d, *J* = 24.2 Hz), 168.2, 141.7, 141.3, 133.8, 132.2, 128.4, 128.3, 128.1, 128.0, 127.2, 126.6, 123.1, 90.0 (d, *J* = 189.4 Hz), 82.5, 57.8, 57.6 (d, *J* = 18.6 Hz), 50.8 (d, *J* = 4.7 Hz), 38.0, 27.9, 26.1, 24.5 (d, *J* = 5.3 Hz), 20.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −199.7 (dd, *J* = 49.7, 30.2 Hz); HRMS calcd for $C_{33}H_{38}FN_2O_4$ 545.2810, found 545.2815 $[M + H]^+$.

(2*S*,3*S*,α*S*)-*tert*-Butyl 6-(*N*-*tert*-Butylcarbonyloxy)amino-3-(*N*-benzyl-α-methylbenzylamino)-2-fluorohexanoate, 15. The phthalimide **14** (139 mg, 0.26 mg) was dissolved in EtOH (6 mL), and $MeNH_2$ in H_2O (41% w/w, 1.25 mL) was added. After being stirred for 2.5 h, the resulting mixture was concentrated in vacuo, and H_2O (20 mL) and diethyl ether (20 mL) were added. The aqueous layer was extracted with diethyl ether (2 × 10 mL), and the combined organic layers were washed with 2 M NaOH (40 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was redissolved in THF/H_2O (4:1, 2 mL), and then Na_2CO_3 (54 mg, 0.51 mmol) and Boc_2O (0.062 mL, 0.27 mmol) were added. After 3 h, saturated aq NH_4Cl (10 mL) and diethyl ether (20 mL) were added. The layers were then separated, and the ether layer was washed with H_2O (2 × 10 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (1:4 diethyl

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ether/hexane) performed on the residue gave the Boc-protected amine **15** as a colorless gum (130 mg, 99%): $[\alpha]^{20}_D = +10$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2H), 7.38−7.23 (m, 8H), 4.48 (d, J = 50.0 Hz, 1H), 4.49 (bs, 1H), 4.15 (d, J = 15.2 Hz, 1H), 3.94 (q, J = 6.8 Hz, 1H), 3.66 (d, J = 15.6 Hz, 1H), 3.38 (ddd, J = 31.0, 9.8, 3.2 Hz, 1H), 3.07−2.99 (m, 2H), 1.86−1.76 (m, 1H), 1.71−1.60 (m, 1H), 1.54−1.44 (m, 1H), 1.49 (s, 9H), 1.45 (s, 9H), 1.34 (d, J = 6.8 Hz, 3H), 1.35−1.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4 (d, J = 24.1 Hz), 155.8, 142.2, 141.6, 128.3, 128.2, 128.01, 127.98, 127.3, 126.6, 89.9 (d, J = 189.3 Hz), 82.5, 79.0, 58.2, 57.8 (d, J = 18.5 Hz), 50.8 (d, J = 4.5 Hz), 40.4, 28.4, 28.0, 27.2, 24.4 (d, J = 5.4 Hz), 20.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −200.7 (dd, J = 49.1, 31.0 Hz); HRMS calcd for $C_{30}H_{44}FN_2O_4$ 515.3280, found 515.3286 $[M + H]^+$.

(2*S*,3*S*)-*tert*-Butyl 6-(*N*-*tert*-Butylcarbonyloxy)amino-3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-2-fluorohexanoate, 16. The Boc-protected amine **15** (138 mg, 0.26 mmol) was dissolved in MeOH/H_2O/AcOH (45:4:1, 3 mL), and $Pd(OH)_2$/C (20 wt %, 53 mg) was added. After being stirred under an atmosphere of H_2 for 7 h, the mixture was filtered through Celite and concentrated in vacuo. The residue was diluted with EtOAc (20 mL), and saturated aq $NaHCO_3$ (20 mL) was added. The layers were separated, and the organic layer was washed with H_2O (20 mL). The aqueous layer was then extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in THF/H_2O (4:1, 2 mL), and Na_2CO_3 (54 mg, 0.51 mmol) was added. The mixture was cooled to 0 °C and Fmoc-OSuc (91 mg, 0.27 mmol) added portionwise, with stirring continued at 0 °C for 1 h and then at rt for 1.5 h. DCM (25 mL) and H_2O (25 mL) were then added, the layers were separated, and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (1:1 diethyl ether/hexane) performed on the residue gave the protected 2*S*-fluoro-β^3-lysine **16** as a colorless oil that solidified on standing (144 mg, 98%): mp = 89−91 °C; $[\alpha]^{20}_D = -6$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.6 Hz, 2H), 7.60 (d, J = 7.4 Hz, 2H), 7.46 (t, J = 7.4 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 5.21 (bs, 1H), 4.84 (dd, J = 49.2, 2.4 Hz, 1H), 4.58 (bs, 1H), 4.50−4.40 (m, 2H), 4.42−4.10 (m, 1H), 4.21 (t, J = 6.8 Hz, 1H), 3.16−3.06 (m, 2H), 1.60−1.45 (m, 4H), 1.50 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (d, J = 23.5 Hz), 155.96, 155.92, 143.7, 141.3, 127.7, 127.0, 125.01, 124.95, 119.97, 119.94, 90.1 (d, J = 186.8 Hz), 83.4, 79.2, 66.8, 52.2 (d, J = 19.3 Hz), 47.2, 40.0, 28.4, 28.0, 26.4, 25.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −203.6 (dd, J = 49.4, 26.0 Hz); HRMS calcd for $C_{30}H_{39}FN_2O_6Na$ 565.2690, found 565.2683 $[M + Na]^+$.

(2*S*,3*S*)-6-(*N*-*tert*-Butylcarbonyloxy)amino-3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-2-fluorohexanoic Acid, 17. The ester **16** (47 mg, 0.087 mmol) was dissolved in dry DCM (2 mL), and TFA (1 mL) was added. After being stirred for 3 h, the solution was concentrated in vacuo, and excess TFA was removed via coevaporation with $CHCl_3$ (2 × 5 mL). The residue was redissolved in THF/H_2O (1:1, 3 mL), and Na_2CO_3 (37 mg, 0.35 mmol) was added, followed by Boc_2O (0.024 mL, 0.10 mmol). The resulting mixture was allowed to stir overnight. The THF was then removed in vacuo, and the residue was diluted with saturated aq $NaHCO_3$ (10 mL) and then washed with diethyl ether (10 mL). The aqueous layer was acidified to pH 2 with 6 M HCl, at which time a white precipitate was formed. The whole mixture was then extracted with $CHCl_3$ (3 × 10 mL), and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give a white foam. This was passed over a plug of silica (1:1 EtOAc/hexane to 100% EtOAc) to give the Fmoc-protected 2*S*-fluoro-β^3-amino acid **17** as a white powder (34 mg, 81%): mp = 152−155 °C; $[\alpha]^{20}_D = -5$ (c = 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 7.6 Hz, 2H), 7.71 (d. J = 7.2 Hz, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.4 Hz, 2H), 6.78 (t, J = 5.0 Hz, 1H), 4.90 (dd, J = 49.0, 3.0 Hz, 1H), 4.34−4.21 (m, 3H), 3.91−3.82 (m, 1H), 3.35 (bs, 1H), 2.89 (q, J = 6.0 Hz, 2H), 1.55−1.42 (m, 2H), 1.41−1.27 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $(CD_3)_2O$) δ 169.5 (d, J = 23.0 Hz), 156.9, 156.7, 145.1, 144.0, 142.1, 128.5, 127.9, 126.2, 126.1, 120.8, 91.1 (d, J = 188.1 Hz), 79.2, 78.5, 68.0, 67.0, 53.6 (d, J = 20.4 Hz), 48.0, 40.6, 28.6, 27.5, 26.2 (d, J = 3.84 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −204.8 (dd, J = 49.1, 25.7 Hz); HRMS calcd for $C_{26}H_{31}FN_2O_6Na$ 509.2064, found 509.2059 $[M + Na]^+$.

Acknowledgment. We are grateful to Flinders University for providing a Graduate Scholarship for T.L.M. and CSIRO for providing a scholarship top-up for T.L.M. and research funding. We thank Jonathan White, University of Melbourne, for determining the X-ray crystal structure of **5c** and Franziska Conrad for her early work with compounds **4e** and **5e**. The Australian Research Council is acknowledged for LIEF funding (LE0668489) for NMR spectrometers.

Supporting Information Available: Detailed experimental procedures for the preparation of **1d** and **1f**, characteristic ^{1}H NMR data for *syn* and *anti* diastereomers of **5a**−**f**, ^{1}H and ^{13}C NMR spectra for all new compounds, and X-ray data for **5c**. This material is available free of charge via the Internet at http://pubs.acs.org.