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Asymmetric Synthesis of Substituted *anti*-β-Fluorophenylalanines

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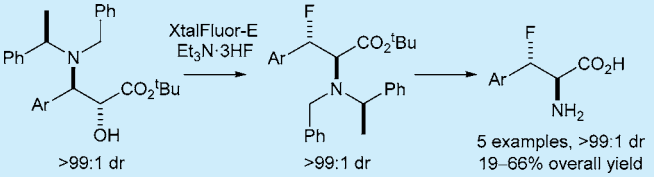
Supporting Information

ABSTRACT: A range of substituted *anti*-β-fluorophenylalanines was produced from the corresponding enantiopure α-hydroxy-β-amino esters using a stereospecific XtalFluor-E promoted rearrangement procedure as the key step. The requisite substrates are readily produced via aminohydroxylation of an α,β-unsaturated ester using our lithium amide conjugate addition methodology and, following rearrangement, deprotection of the resultant enantiopure β-fluoro-α-amino esters gives the corresponding enantiopure *anti*-β-fluorophenylalanines in good yield and high diastereoisomeric purity.



The incorporation of fluorine is known to dramatically alter the biological properties of organic molecules, and fluorination has become an established strategy for modifying lead compounds in medicinal chemistry.[1] Fluorinated α-amino acids have attracted significant attention in recent years, with several studies focusing on their incorporation into synthetic proteins and the resulting impact this may have on secondary structure and stability.[2] This research has justified synthetic efforts targeting fluorinated α-amino acids,[3,4] with approaches ranging from ring-opening of aziridines with fluoride[5] to metal-catalyzed cross-couplings[6] being employed.

As part of our research program concerning the asymmetric synthesis of functionalized amino acids,[7] we have recently reported an efficient protocol for the asymmetric synthesis of β-hydroxy-α-amino acids. Stereospecific rearrangement of enantiopure *anti*-α-hydroxy-β-amino esters **1** (which are readily derived from the corresponding α,β-unsaturated esters using our diastereoselective aminohydroxylation procedure[8]) upon treatment with either Ms_2O or Tf_2O promoted formation of the corresponding aziridinium ions **2**, which was followed by regioselective ring-opening with H_2O to give β-hydroxy-α-amino esters **3** in >99:1 dr. Subsequent *N*-deprotection and ester hydrolysis gave enantiopure *anti*-β-hydroxy-α-amino acids **4** in good yield and high diastereoisomeric purity (Figure 1).[9]

We envisaged that application of a similar protocol employing a deoxofluorinating agent to promote the rearrangement process (i.e., also proceeding via the intermediacy of an aziridinium ion) would allow the introduction of a β-fluoro substituent.[10] XtalFluor-E (in combination with $Et_3N{\cdot}3HF$) was originally reported as an efficient deoxofluorinating reagent[11] but has also found utility as a coupling reagent for amidation[12] and a cyclodehydration agent.[13] It has also been used as an OH-activator in combination with other nucleophiles for the ring expansion of prolinols and the halogenation of primary alcohols,[14] and has also been employed in the ring-opening fluorination of *N*-tosyl substituted aziridines.[15] Herein we describe a XtalFluor-E promoted rearrangement procedure as

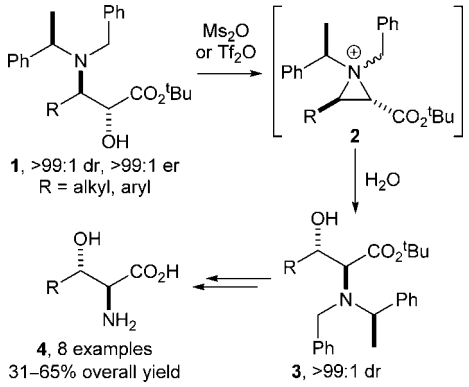


Figure 1. Asymmetric synthesis of β-hydroxy-α-amino acids **4**.

the key step in the synthesis of several enantiopure *anti*-β-fluorophenylalanines.

Our initial investigations within this area focused on using the established reagent combination of XtalFluor-E and $Et_3N{\cdot}3HF$[11] for the rearrangement and deoxofluorination of racemic *anti*-α-hydroxy-β-amino ester **5**.[9] Treatment of **5** with XtalFluor-E and $Et_3N{\cdot}3HF$ gave *anti*-β-fluoro-α-amino ester **6** as a single diastereoisomer (>99:1 dr), which was isolated in 94% yield (Scheme 1). The relative *anti*-configuration within **6** was established unambiguously via single crystal X-ray diffraction analysis (Figure 2).[16] The formation of **6** in this reaction is entirely consistent with our proposed mechanism, whereby XtalFluor-E promotes formation of the corresponding aziridinium ion which is then regioselectively ring-opened by fluoride at the C(3)-position; this stereochemical outcome is in complete accordance with that observed upon formation of the corresponding *anti*-β-hydroxy-α-amino esters **3**.[9] Reaction of enantiopure α-hydroxy-β-amino ester **7**[7c,17] under the same conditions produced β-fluoro-α-amino ester **8** in 81% yield and

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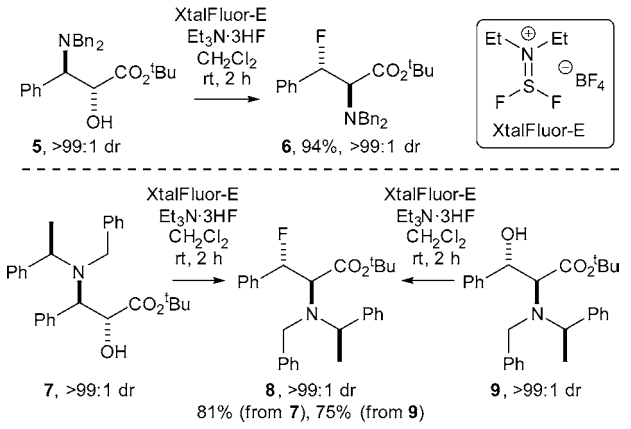
Scheme 1



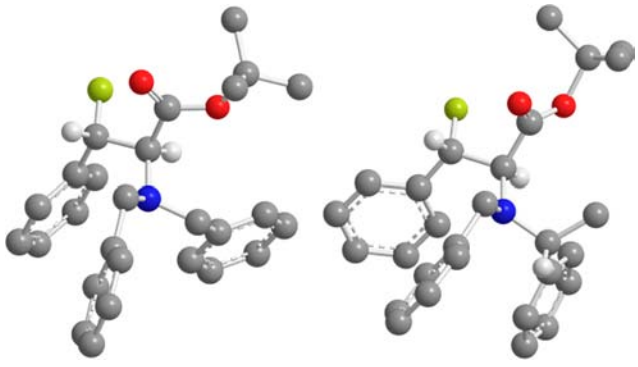
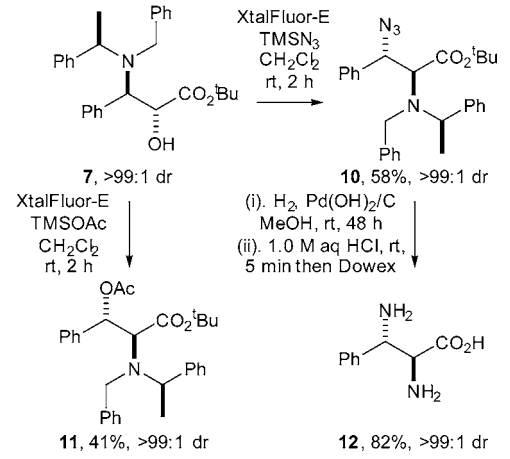


Figure 2. X-ray crystal structures of (*RS*,*SR*)-**6** [left] and (2*R*,3*S*,*αR*)-**8** [right] (selected H atoms are omitted for clarity).

>99:1 dr, and reaction of *β*-hydroxy-*α*-amino ester **9**[9] under identical conditions also produced **8** in 75% yield and >99:1 dr (Scheme 1). The relative configuration within **8** was established unambiguously via single crystal X-ray diffraction analysis (Figure 2),[16] and the absolute (2*R*,3*S*,*αR*)-configuration of **8** was assigned by reference to the known (*R*)-configuration of the *α*-methylbenzyl fragment. Furthermore, the determination of a Flack *x* parameter[18] of −0.11(11) for the structure of **8** confirmed this assignment. These data therefore confirm the intermediacy of the corresponding aziridinium ion upon reaction of both regioisomeric substrates **7** and **9**.

Substituting $Et_3N{\cdot}3HF$ for either $TMSN_3$ or TMSOAc produced the corresponding azide **10** or acetate **11**[19] as single diastereoisomers (>99:1 dr) in 58% and 41% isolated yield, respectively (Scheme 2). The relative configurations within **10** and **11** were established unambiguously via single crystal X-ray diffraction analyses (Figure 3),[16] and the absolute (2*S*,3*S*,*αR*)-configurations of **10** and **11** were assigned in each case by reference to the known (*R*)-configuration of the *α*-methylbenzyl fragment. Furthermore, the determination of Flack *x* parameters[18] of −0.1(2) and −0.12(15) for the structures of **10** and **11**, respectively, confirmed these assignments. Subsequent tandem reduction/hydrogenolysis of **10** followed by hydrolysis of the *tert*-butyl ester moiety gave *anti*-*α*,*β*-diamino acid **12**, which was isolated in 82% yield (from **10**) and >99:1 dr after purification on Dowex 50WX8-200 ion-exchange resin (Scheme 2).[20] The specific rotation of this sample of **12** {$[\alpha]_D^{20}$ −7.2 (*c* 0.4 in 6 N HCl)} was found to be equal to the literature value reported by Lin et al. claimed for *ent*-**12** {lit.[21] $[\alpha]_D^{20}$ −8.0 (*c* 0.65 in 6 N HCl)}, which was reported without evidence for their stereochemical assignment in an enantioselective synthesis.[21] As our stereochemical assignment for **12** is completely secure, these specific rotation data therefore suggest that the stereochemical assignment of Lin et al. is in error.

Scheme 2



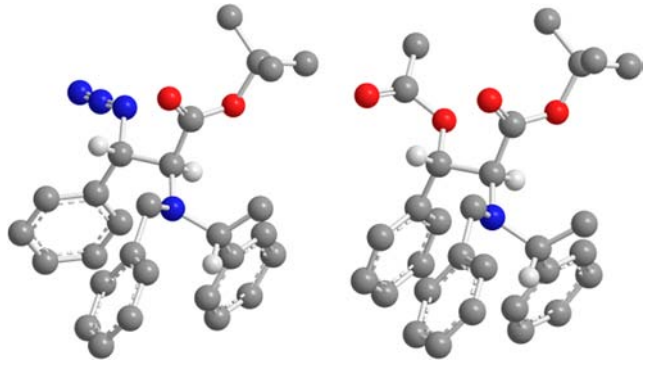


Figure 3. X-ray crystal structures of (2*S*,3*S*,*αR*)-**10** [left] and (2*S*,3*S*,*αR*)-**11** [right] (selected H atoms are omitted for clarity).

Attempted *N*-deprotection of *β*-fluoro-*α*-amino ester **8** via several hydrogenolytic protocols resulted in substantial competitive defluorination. In the hope that alternative deprotection strategies would be more efficacious, the corresponding *N*-allyl substituted compound **14** was prepared in 96% yield and >99:1 dr from the known *α*-hydroxy-*β*-amino ester **13**.[22] Removal of the *N*-*α*-methylbenzyl group within **14** was achieved via *N*-oxidation with *m*-CPBA followed by in situ Cope elimination of the resultant *N*-oxide **15**, which gave hydroxylamine **16** in only 13% isolated yield. The yields of this reaction were found to be somewhat variable, and neither attempted *N*-deallylation of **16** nor attempted reduction of the N−O bond within **16** was successful. *N*-Deallylation of **14**, however, upon treatment with $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid (DMBA) gave **17** in 39% yield and >99:1 dr. Sequential treatment of **17** with $NaBrO_3$[23] followed by HCl effected removal of the *N*-*α*-methylbenzyl group and hydrolysis of the ester moiety to give (2*R*,3*S*)-*β*-fluorophenylalanine **18**, which was isolated as the corresponding hydrochloride salt **18**·HCl in 47% yield and >99:1 dr. Similar treatment of the *N*-benzyl substituted analogue **8** gave **18** directly in 53% isolated yield after treatment of **18**·HCl with propylene oxide[24] (Scheme 3).

The spectroscopic data for **18** were in excellent agreement with literature values.[4f,25] However, the specific rotation for **18** was found to be highly solvent dependent, with a complete

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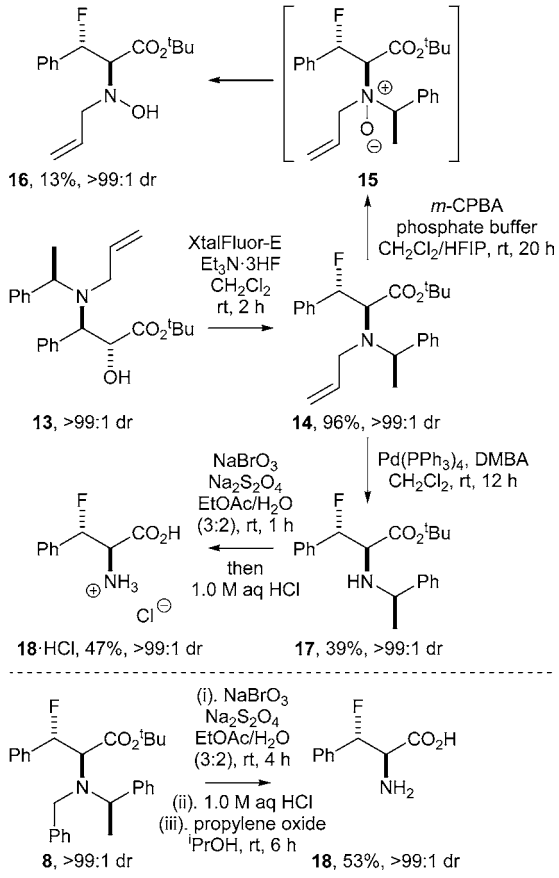
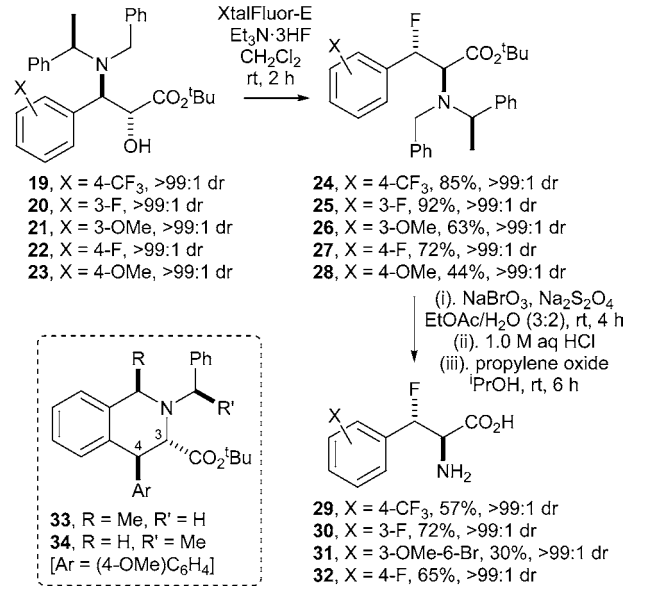
Scheme 3



Scheme 4



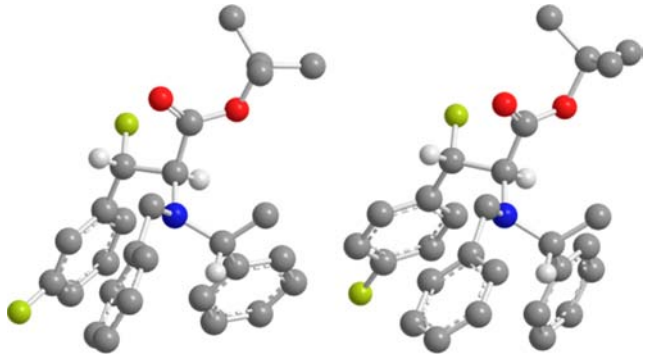


Figure 4. X-ray crystal structures of (2*R*,3*S*,α*R*)-**25** [left] and (2*R*,3*S*,α*R*)-**27** [right] (selected H atoms are omitted for clarity).

reversal in the specific rotation of **18** being observed upon changing the solvent from H_2O to MeOH {$[\alpha]_D^{20}$ +14.4 (*c* 0.5 in H_2O); $[\alpha]_D^{20}$ −13.3 (*c* 0.3 in MeOH)}. While this phenomenon is interesting in its own right and has previously been observed in related systems,[26] the specific rotation recorded in MeOH was found to be equal to the value for *ent*-**18** reported by Davis et al. {lit.[4f] $[\alpha]_D^{23}$ −14.5 (*c* 0.4 in MeOH)}. As our stereochemical assignment for **18** is completely secure, this literature value appears to be incorrect; however, this discrepancy can easily be accounted for, as the literature value was most likely recorded in H_2O, and not MeOH as originally reported,[26,27] and the stereochemical assignments of Davis et al.[4f] therefore remain secure.

The substrate scope of this protocol was evaluated next upon subjection of a range of known *anti*-α-hydroxy-β-amino esters **19**−**22**[9] to XtalFluor-E and $Et_3N{\cdot}3HF$, which gave *anti*-β-fluoro-α-amino esters **24**−**27** in 63−92% yield and >99:1 dr. In the case of **23** (X = 4-OMe),[9] however, an 80:20 mixture of **28** and the corresponding 1,2,3,4-tetrahydroisoquinolines [**33** + **34**] was observed in the crude reaction mixture, from which **28** was isolated in 44% yield and >99:1 dr, and a 68:32 mixture of **33** (>99:1 dr) and **34** (>99:1 dr), respectively, was isolated in 8% combined yield (Scheme 4). The relative 3,4-*anti*-configurations within **33** and **34** were assigned from the diagnostic values of the ^{1}H NMR ^3J coupling constants observed between the C(3)*H* and C(4)*H* protons (for **33** $^3J_{3,4}$ = 3.7 Hz; for **34** $^3J_{3,4}$ = 2.4 Hz).[28] Presumably, **33** and **34** are formed as a result of ring-opening of the aziridinium intermediate to give the corresponding benzylic carbonium ion (which is assisted by the presence of the electron donating *p*-methoxy group), followed by competitive Friedel−Crafts alkylation-type cyclization of either the *N*-α-methylbenzyl or *N*-benzyl groups, respectively. For both **25** (X = 3-F) and **27** (X = 4-F), their relative configurations were established unambiguously via single crystal X-ray diffraction analyses (Figure 4).[16] The absolute (2*R*,3*S*,α*R*)-configurations of **25** and **27** were assigned in each case by reference to the known (*R*)-configuration of the α-methylbenzyl fragment. Furthermore, the determination of Flack *x* parameters[18] of 0.02(12) and −0.01(10) for the structures of **25** and **27**, respectively, confirmed these assignments. The relative and absolute configurations of **24**, **26**, and **28** were assigned by analogy to those of **8**, **25**, and **27**. Sequential treatment of **24**, **25**, and **27** with $NaBrO_3$ and HCl gave the corresponding β-fluoro-α-amino acids **29**, **30**, and **32** in good yield (57−72%) as single diastereoisomers (>99:1 dr) in each case. For deprotection of **26** (X = 3-OMe), however, bromination at the C(6′)-position was also observed upon treatment with $NaBrO_3$ during the *N*-debenzylation step, giving **31** in 30% yield and >99:1 dr (Scheme 4). Attempted deprotection of **28** (X = 4-OMe) led to substantial decomposition, presumably due to the increased lability of the β-fluoro moiety in this case.

In conclusion, a range of five enantiopure *anti*-β-fluorophenylalanines have been prepared in three steps from the corresponding α,β-unsaturated esters. Diastereoselective amino-

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hydroxylation of the α,β-unsaturated esters was followed by the stereospecific XtalFluor-E promoted rearrangement of the resultant *anti*-α-hydroxy-β-amino esters to give the corresponding *anti*-β-fluoro-α-amino esters in >99:1 dr. Subsequent *N*-deprotection and ester hydrolysis of these fluorinated substrates was achieved via sequential treatment with $NaBrO_3$ and HCl to give the *anti*-β-fluorophenylalanines in good yield and high diastereoisomeric purity. This is the most concise strategy to access enantiopure *anti*-β-fluorophenylalanines reported to date.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of ^1H and ^{13}C NMR spectra, and crystallographic data (for structures CCDC 1054001−1054006). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) (a) Salwiczek, M.; Nyakatura, E. K.; Gerling, U. I. M.; Ye, S.; Koksch, B. *Chem. Soc. Rev.* **2012**, *41*, 2135. (b) Buer, B. C.; Marsh, E. N. G. *Protein Sci.* **2012**, *21*, 453. (c) Marsh, E. N. G. *Acc. Chem. Res.* **2014**, *47*, 2878. (d) Gerling, U. I. M.; Salwiczek, M.; Cadicamo, C. D.; Erdbrink, H.; Czekelius, C.; Grage, S. L.; Wadhwani, P.; Ulrich, A. S.; Behrends, M.; Haufe, G.; Koksch, B. *Chem. Sci.* **2014**, *5*, 819.

(3) Qui, X.-L.; Qing, F.-L. *Eur. J. Org. Chem.* **2011**, 3261.

(4) For representative examples of the syntheses of β-fluoro-α-amino acids, see: (a) Loy, R. S.; Hudliky, M. *J. Fluorine Chem.* **1976**, *7*, 421. (b) Tsushima, T.; Sato, T.; Tsuji, T. *Tetrahedron Lett.* **1980**, *21*, 3591. (c) Ayi, A.; Guedj, R. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2045. (d) Pansare, S. V.; Vederas, J. C. *J. Org. Chem.* **1987**, *52*, 4804. (e) Kaneko, C.; Chiba, J.; Toyota, A.; Sato, M. *Chem. Pharm. Bull.* **1995**, *43*, 760. (f) Davis, F. A.; Srirajan, V.; Titus, D. D. *J. Org. Chem.* **1999**, *64*, 6931. (g) Lu, D.-F.; Liu, G.-S.; Zhu, C.-L.; Yuan, B.; Xu, H. *Org. Lett.* **2014**, *16*, 2912.

(5) (a) Ayi, A. I.; Remli, M.; Guedj, R. *J. Fluorine Chem.* **1981**, *18*, 93. (b) Tsushima, T.; Kawada, K.; Nishikawa, J.; Sato, T.; Tori, K.; Tsuji, T. *J. Org. Chem.* **1984**, *49*, 1163.

(6) Shi, G.; Cao, Z.; Zhang, X. *J. Org. Chem.* **1985**, *60*, 6608.

(7) (a) Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2013**, *78*, 2500. (b) Davies, S. G.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 8680. (c) Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 8885. (d) Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Ford, J. G.; Klauber, D. J.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2014**, *79*, 10932. (e) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Shah, R. S.; Thompson, A. L.; Thomson, J. E. *Org. Lett.* **2014**, *16*, 1354.

(8) (a) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833. (b) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 1111.

(9) Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, *70*, 5849.

(10) For selected examples concerning the ring-opening of aziridinium ions with a fluorinating agent, see: (a) Gani, D.; Hitchcock, P. B.; Young, D. W. *J. Chem. Soc., Chem. Commun.* **1983**, 898. (b) Floreancig, P. E.; Swalley, S. E.; Trauger, J. W.; Dervan, P. B. *J. Am. Chem. Soc.* **2000**, *122*, 6342. (c) Hook, D. F.; Gessier, F.; Noti, C.; Kast, P.; Seebach, D. *ChemBioChem* **2004**, *5*, 691. (d) Ye, C.; Shreeve, J. M. *J. Fluorine Chem.* **2004**, *125*, 1869. (e) Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Synlett* **2007**, 263. (f) Déchamps, I.; Gomez Pardo, D.; Cossy, J. *Eur. J. Org. Chem.* **2007**, 4224. (g) Duthion, B.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2010**, *12*, 4620. (h) Orliac, A.; Routier, J.; Charvillon, F. B.; Sauer, W. H. B.; Bombrun, A.; Kulkarni, S. S.; Gomez Pardo, D.; Cossy, J. *Chem.—Eur. J.* **2014**, *20*, 3813. (i) Chong, H.-S.; Sun, X.; Chen, Y.; Wang, M. *Tetrahedron Lett.* **2015**, *56*, 946.

(11) (a) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050. (b) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401.

(12) Orliac, A.; Gomez Pardo, D.; Bombrun, A.; Cossy, J. *Org. Lett.* **2013**, *15*, 902.

(13) Pouliot, M.-F.; Angers, L.; Hamel, J.-D.; Paquin, J.-F. *Org. Biomol. Chem.* **2012**, *10*, 988.

(14) (a) Cochi, A.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2011**, *13*, 4442. (b) Lam, Y.; Houk, K. N.; Cossy, J.; Gomez Pardo, D.; Cochi, A. *Helv. Chim. Acta* **2012**, *95*, 2265. (c) Pouliot, M.-F.; Mahé, O.; Hamel, J.-D.; Desroches, J.; Paquin, J.-F. *Org. Lett.* **2012**, *14*, 5428.

(15) Nonn, M.; Kiss, L.; Haukka, M.; Fustero, S.; Fülöp, F. *Org. Lett.* **2015**, *17*, 1074.

(16) Crystallographic data (excluding structure factors) for **6**, **8**, **10**, **11**, **25**, and **27** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1054001−1054006, respectively.

(17) Bunnage, M. E.; Chernega, A. N.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2373.

(18) (a) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876. (b) Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143.

(19) A 76:24 mixture of **11** and **8**, respectively, was observed in the ^1H NMR spectrum of the crude reaction mixture, from which only **11** was isolated in 41% yield and >99:1 dr.

(20) The β-acetoxy substituted analogue **11** was not deprotected to the corresponding β-hydroxy-α-amino acid, as the overall yield could not be superior to our previous synthesis of this target compound from **7**; see ref 9.

(21) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 855.

(22) (a) Davies, S. G.; Polywka, M. E. C.; Fenwick, D. R.; Reed, F. PCT Int. Appl. (1995), WO 9518134. (b) Davies, S. G.; Fenwick, D. R.; Ichihara, O. *Tetrahedron: Asymmetry* **1997**, *8*, 3387.

(23) Corr, M. J.; O'Hagan, D. *J. Fluorine Chem.* **2013**, *155*, 72.

(24) O'Donnell, M. J.; Barney, C. L.; McCarthy, J. R. *Tetrahedron Lett.* **1985**, *26*, 3067.

(25) Kaneko, C.; Chiba, J.; Toyota, A.; Sato, M. *Chem. Pharm. Bull.* **1995**, *43*, 760.

(26) Davis, F. A. 2015, personal communication.

(27) It was noted that the specific rotations for all the other β-fluoro-α-amino acids reported in ref 4f were recorded in H_2O and not MeOH.

(28) ^1H NMR coupling constants in the order of $^3J_{3,4}$ = 1.5−4.0 Hz are usually observed for 3,4-*anti*-1,2,3,4-tetrahydroisoquinolines, whereas values of $^3J_{3,4}$ = 5.5−6.0 Hz are typically observed for 3,4-*syn*-1,2,3,4-tetrahydroisoquinolines; see: (a) Brozda, D.; Koroniak, L.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3017. (b) Chen, W.; Cui, J.; Zhu, Y.; Hu, X.; Mo, W. *J. Org. Chem.* **2012**, *77*, 1585. (c) Hammad, S. F.; Smith, F. T. *J. Heterocycl. Chem.* **2013**, *50*, 114.

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