JOC*Note*

Synthesis of a β-Amino Acid Pharmacophore via a β-Lactam Intermediate

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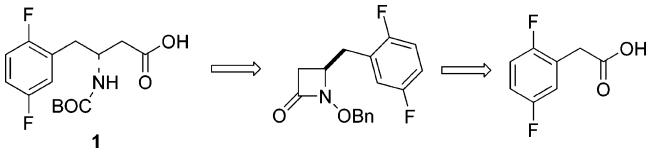

A stereoselective synthesis of (*R*)-β-amino acid **1** via a β-lactam intermediate is discussed.

As part of our ongoing research program for the discovery of new drug candidates, we recently required the stereoselective synthesis of the BOC-protected key intermediate (*R*)-β-amino acid **1** (Figure 1) on a kilogram scale. The selective synthesis of β-amino acids[1] has been the subject of tremendous effort principally due to their important biological activity[2] as enzyme inhibitors or as α-amino acid surrogates in the construction of peptides possessing unique conformational properties[3] (β-peptides). Furthermore, the β-amino acid pattern can be found in some interesting naturally occurring compounds.[4]

Arndt−Eistert homologation,[5] Curtius rearrangemen,[5] and asymmetric addition to imines[6] (i.e., Staudinger reaction) were abandoned due to potential issues for scale-up associated with the manipulation of hazardous material. So we turned our attention to the most promising procedures in terms of cost, efficiency, and scalability. Aspartic acid and its derivatives were first chosen as potential starting materials as they are inexpensive and have been successfully functionalized in the past into

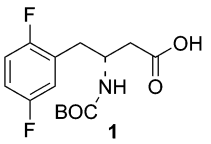

FIGURE 1. (*R*)-β-amino acid **1**.

elaborate β-amino acids.[7,8] The Friedel−Crafts acylation of 1,4-difluorobenzene **3** in the presence of $AlCl_3$ with commercially available (S)-*N*-trifluoroacetylaspartic anhydride **2** unfortunately led exclusively to the undesired α-acylated compound[9] **4** (Scheme 1). Contrary to what has been observed by Griesbeck[8] with toluene or *o*-xylene, none of the desired β-acylated **5** compound could be observed with **3**.

In an alternate approach, unsaturated esters are ideal substrates for Michael addition of chiral amines[10] and as shown by Miller,[11] for the asymmetric conjugate addition of azide ion. Unfortunately, due to the strong withdrawing electronic effect of the difluorophenyl ring, the synthesis of α,β-unsaturated ester **8** was found to be challenging. Precursor aldehyde **7** could only be made by oxidation of alcohol **6** with Dess−Martin periodinane or excess MnO_2. Swern oxidation of **6** led to complete decomposition. Furthermore, aldehyde **7** was very unstable and could not be purified, so it was used directly in the subsequent Wittig−Horner reaction. Treatment of **7** with methyl dimethoxyphosphono acetate and *t*-BuOK (DBU led to decomposition) in methanol gave some desired ester **8** alongside with a major compound **9** where the double bond has been isomerized α to the difluorophenyl ring in a 23:77 ratio (Scheme 2). Attempts to equilibrate this mixture with an excess of base led exclusively to the thermodynamically more stable styrene derivative **9**. [12]

Furthermore, the very elegant acyl halide−aldehyde cyclocondensation (AAC) developed by Nelson[13] could not be tried because it requires the use of unstable aldehyde **7**.

Thus, we turned our attention to the biomimetic synthesis of β-lactams discovered by Miller (Scheme 3).[14] Chiral β-lactams have been previously used as precursors to chiral β-amino acids;[15] however, little was known about the direct opening of *O*-benzyloxy-protected lactams to the corresponding β-amino acids.[16]

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(9) ^{1}H NMR ($CDCl_3$) for **4**: 3.62 (dt, *J* 19.4, 3.8, 1H), 3.86 (dt, *J* 3.8, 19.4, 1H), 5.01 (m, 1H), 7.17 (m, 1H), 7.29 (m, 1H), 7.47 (d, *J* 8.1, NH), 7.59 (m, 1H).

(10) (a) Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1411−1415. (b) Cohen, J. H.; Abdel-Magid, A. F.; Almond, H. R.; Maryanoff, C. A. *Tetrahedron Lett.* **2002**, *43*, 1977−1981.

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(12) ^{1}H NMR ($CDCl_3$) for **9**: 3.29 (dd, J 1.4, 7.1, 2H), 3.74 (s, 3H), 6.38 (dt, J 7.1, 16, 1H), 6.59 (m, 1H), 6−86−7.04 (m, 2H), 7.15 (m, 1H).

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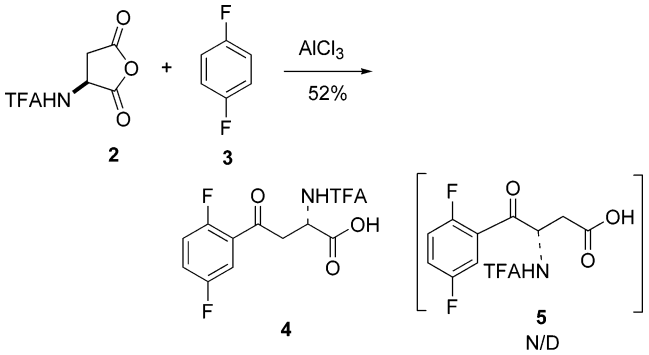
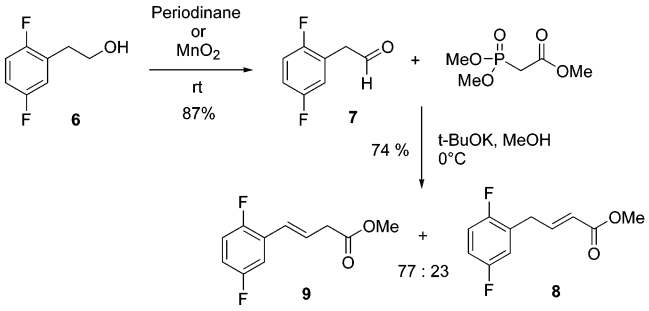
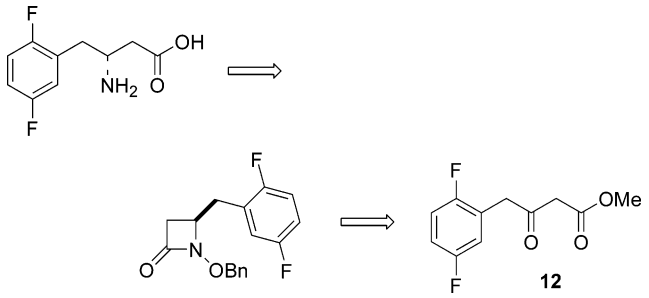
SCHEME 1. Friedel–Crafts Acylation



SCHEME 2. Wittig–Horner Reaction



SCHEME 3. Retrosynthetic Scheme



Precursor β-ketoester **12** was easily made using the following sequence (Scheme 4): acylation[17] of Meldrum's acid in the presence of 2,4,6-collidine[18] with 2,5-difluorophenylacetyl chloride, which was generated in situ from the corresponding acid **10** and oxalyl chloride. Meldrum intermediate **11** was simply isolated by crystallization after acidification of the crude basic aqueous extracts (NaOH) in 83% yield. Methanolysis of **11** gave the crude β-ketoester **12** after decarboxylation, and this solution was directly submitted to Noyori hydrogenation conditions[14c,f,g,19] using 0.4 mol % of [(*S*)-BINAP]$RuCl_2$. It is worth noting that the rate of the reaction is considerably increased by the addition of a catalytic amount of strong acid (HCl) as shown previously by King.[20] Under these conditions, (*S*)-β-hydroxy methyl ester **13** was obtained in quantitative yield with 91% ee.

Alternatively, (*S*)-β-hydroxy acid **14** could be obtained by enantioselective reduction[21] of β-ketoacid precursor **17** using (+)-DIP-Cl (diisopinocampheyl chloroborane) in 95% yield and 94% ee, in the presence of triethylamine (Scheme 4). However, due to the use of a stoichiometric amount of chiral reducer, this alternative route was not a viable process.

After solvent exchange from methanol to THF, the crude solution of **13** from hydrogenation was saponified with LiOH at room temperature and the resulting lithium carboxylate salt of **14** was extracted into water. Following partial reacidification to pH = 5, **14** was allowed to react with *O*-benzyl hydroxylamine using EDC as a coupling agent. Chiral *O*-benzyloxy amide **15** directly crystallized out from the aqueous solution after stirring at room temperature for a couple of hours in an excellent overall yield of 93% for the last four steps, starting from Meldrum derivative **11**. *This sequence was run on a 4 kg scale without any isolation of intermediates* (Scheme 4).

Ring closure of **15** to β-lactam **16** via Mitsunobu reaction was found to be more problematic. On a small scale and using typical conditions (THF, PPh_3/DIAD 1 equiv), the reaction proceeded very smoothly and gave the expected β-lactam in 93% isolated yield with complete inversion of configuration. Unfortunately, we were unable to drive the reaction to completion on a larger scale (>100 g). Increasing of the amount of PPh_3/DIAD or using a more electron-rich phosphine, P(*t*-Bu)$_3$, led to the formation of a large amount of elimination byproduct (styrene derivative). Fortunately, by conducting the reaction in toluene instead of THF, we were able to reach complete conversion and minimize the elimination side reaction to less than 3% yield. Furthermore, H_2-DIAD and triphenylphosphine oxide produced during the reaction can be easily removed by simple filtration of the toluene solution, facilitating the β-lactam isolation. Then, solvent exchange to MeOH and cooling to −20 °C led to the crystallization of the chiral β-lactam **16** in 78% yield and with >99.5% ee[22] (Scheme 4).

Finally, we were delighted to see that when treated with MeONa[23] in methanol, opening of β-lactam **16** and subsequent catalytic hydrogenation[24] (Pd/C) gave the corresponding β-aminoester **18**; saponification with LiOH with in situ BOC trapping then revealed the desired optically pure (*R*)-β-amino acid **1** in 85% overall yield (Scheme 5).

(14) (a) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7026–7032. (b) Miller, M. J.; Bajwa, J. S.; Mattingly, P. G.; Peterson, K. *J. Org. Chem.* **1982**, *47*, 4928–4933. (c) Guzzo, P. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4862–4867. (d) Durham, T. B.; Miller, M. J. *Org. Lett.* **2002**, *4*, 135–138. (e) Bulychev. A.; Bellettini, J. R., O'Brien, M.; Crocker, P. J.; Samama, J.-P.; Miller, M. J.; Mobashery, S. *Tetrahedron* **2000**, *56*, 5719–5728. (f) Durham, T. B.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 27–34. (g) Durham, T. B.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 35–42. See also: Yang, H. W.; Romo, D. *J. Org. Chem.* **1999**, *64*, 7657–7660.

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(16) Known examples required two- to four-step deprotection/protection for opening. See ref 14g.

(17) Capozzi, G.; Roelens, S.; Talami, S. *J. Org. Chem.* **1993**, *58*, 7932–7936.

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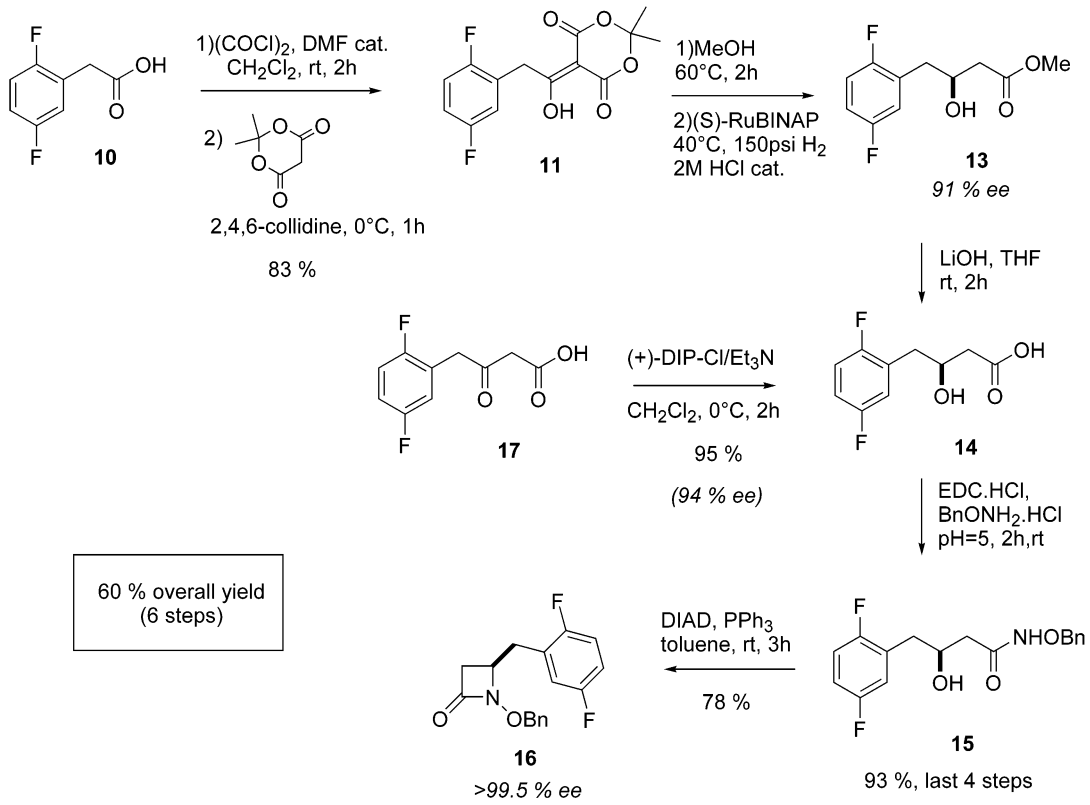
(22) The ee is increased from 92 to >99.5% during crystallization in MeOH.

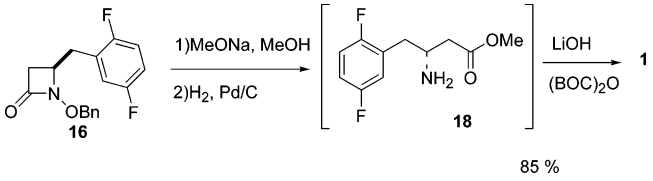
(23) Similarly, treatment of β-lactam **16** with LiOH in THF/water give the corresponding β-amino acid.

(24) When the hydrogenation is performed on the β-lactam **16**, the NO–Bn bond is cleaved instead of the N–OBn bond, giving the N-hydroxyl β-lactam.

SCHEME 4. Synthesis of β-Lactam Intermediate 16



SCHEME 5. Opening of β-Lactam



In conclusion, we have successfully developed a scaled process of chiral amino acid **1**. This process can be run economically on a kilogram scale. The sequence involves a four-step "through process" where isolation procedures are kept to a minimum.

Experimental Section

5-[1-Hydroxy-2-(2,5-difluorophenyl)ethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione 11. Oxalyl chloride (2.544 kg, 1.719 L, 20.049 mol) was slowly added to a slurry of 2,5-difluorophenylacetic acid **10** (3 kg, 17.429 mol, MW 172.13) and DMF (9 mL) in dichloromethane (11 L) at 25−30 °C over 1.5 h. CO, CO_2, and HCl gas evolved through the addition. The mixture was stirred for 2 h at rt until the end of gas evolution. CH_2Cl_2 and excess $(COCl)_2$ were distilled off (20−25 °C, 28 mmHg). CH_2Cl_2 (2 L) was added to the residue, and the resulting solution was then slowly added to a mixture of Meldrum's acid (2.637 kg, 18.30 mol) and collidine (4.224 kg, 4.6 L, 34.857 mol) in dichloromethane (18 L) at −5 °C over 2 h. The resulting pale yellow solution was stirred for 1 h at 0 °C, and then10.4 L of 6 M HCl was charged at 0 °C over 5 mn. The layers were separated, and the organic layer was extracted with 69 L of 1 M NaOH and then with 34 L of 1 M NaOH. The combined basic aqueous layers were acidified with 37% HCl (approximately 8.5 L) until pH = 1. The solid was filtered off and washed with water (30−50 L) to remove the yellow color and then dried over N_2 stream for 5 days to yield 4.3 kg (83%) of white solid **11**. Mp: 89−91 °C. ^{1}H NMR ($CDCl_3$): 1.77 (s, 6H), 4.49 (s, 2H), 6.95−7.07 (m, 3H). ^{13}C NMR: 26.9, 35.1, 91.9, 105.4, 115.8 dd, 116.4 dd, 118.0 dd, 122.6 dd, 156.8 d, 159.2 d, 160.3, 170.5, 193.0. IR: 1204, 1425, 1498, 1579, 1736, 2848, 2922. Anal. Calcd for $C_{14}H_{12}F_2O_5$: C, 56.38; H, 4.06; F, 12.74. Found: C, 56.13; H, 3.66; F, 13.04.

Methyl 4-(2,5-Difluorophenyl)-3-oxobutanoate 12. A solution of Meldrum's derivative **11** (4.3 kg) was refluxed in anhydrous methanol (20 L) for 2.5 h. CO_2 gas evolved during the reflux period. A pure sample was obtained through MTBE/hexane crystallization. Mp: 38 °C. ^{1}H NMR ($CDCl_3$): 3.50 (s, 2H), 3.69 (s, 3H), 3.83 (s, 2H), 6.86−6.94 (m, 2H), 6.94−7.00 (m, 1H). Enol form: 3.48 (s), 3.67 (s), 12.04 (s). ^{13}C NMR: 42.7, 48.3, 52.3, 115.5 dd, 116.3 dd, 118.1 dd, 122.3 dd, 172.8, 198.3. IR: 1014, 1497, 1716, 2956. Anal. Calcd for $C_{11}H_{10}F_2O_3$: C, 57.90; H, 4.42; F, 16.65. Found: C, 57.69; H, 4.11; F, 16.56.

***N*-Benzyloxy-4-(2,5-difluorophenyl)-3(*S*)-hydroxybutanamide 15.** The preceding solution was divided into two batches (approximately 12 L each) and degassed for 15 min with bubbling N_2, and then 70 mL of 2 N HCl followed by (S)-BINAP-$RuCl_2$ (22.3 g, 0.4 mol %) were added to each batch, which was then submitted to hydrogenation (H_2, 150 psi) at 60 °C for 4−5 h. Both batches were combined for the next step. Chiral HPLC indicated 91% ee for β-hydroxy ethyl ester **13**. ^{1}H NMR ($CDCl_3$): 2.46 (dd, J 16.7, 9, 1H), 2.56 (dd, J 16., 3.2, 1H), 2.75 (br, OH), 3.71 (s, 3H), 4.29 (m, 1H), 6.90 (m, 1H), 6.96−7.02 (m, 2H).

The preceding methanol solution of β-hydroxyester was solvent switched to THF (17 L final volume) using 35 L of THF with a minimal residual volume of 5 L (20−25 °C, 28 mmHg). Then, a solution of $LiOH·H_2O$ (2370 g, 56.48 mol) in water (12 L) was added at 20−25 °C. The solution was stirred for 30 min, MTBE (8 L) was added, and the layers were separated. The aqueous layer was extracted with MTBE (2 × 8 L), and then the combined organic layers were back-extracted with water (8 L). The combined aqueous layers containing β-hydroxy acid **14** were used directly for the next step. ^{1}H NMR ($CDCl_3$): 2.51 (dd, J 16.7, 8.7, 1H), 2.59 (dd, J 16.7, 3.5, 1H) 2.85 (m, 2H), 4.31 (m, 1H), 6.88 (m, 1H), 6.90−7.02 (m, 2H).

To the preceding aqueous solution was added HCl (3.5 L, 42 mol, 37% aq) and then *O*-benzylhydroxyamine hydrochloride (2705 g, 16.94 mol) followed by slow addition of EDC·HCl (4060 g, 21.18 mol) over 15 min at 20−30 °C. The resulting mixture was stirred for 1 h at 20−22 °C while the hydroxamate precipitated. The light pink solid was filtered off and washed with water (3 × 12 L) and with heptane (3 × 12 L) and then dried over N_2 stream for 3 days (yield: 4.27 kg, 93% last four steps). Chiral HPLC indicated 92% ee. $[\alpha]_{589} = +12.96$ ($c = 1$ $CHCl_3$). Mp: 70−72 °C. ^{1}H NMR major rotamer (273 K, $CDCl_3$): 2.15 (dd, *J* 9.2, 15.1, 1H), 2.26 (dd, *J* 2.5, 15.1, 1H), 2.75 (m, 2H), 3.70 (br, OH), 4.21 (m, 1H), 4.87 (dd, *J* 11.6, 15.3, 2H), 6.87−7.01 (m, 3H), 7.35 (m, 5H), 8.9 (br, NH). IR: 1495, 1653, 2847, 3214. Anal. Calcd for $C_{17}H_{17}F_2NO_3$: C, 63.54; H, 5.33; F, 16.65; N, 4.36. Found: C, 63.59; H, 5.04; F, 12.01; N, 4.32.

***N*-Benzyloxy-4(*R*)-[1-methyl-(2.5-difluorobenzyl)]-2-oxoazetidine 16.** Triphenylphosphine (3638 g, 13.87 mol) was slowly added to a solution of diisopropyl azadicarboxylate (2804 g, 2730 mL, 13.87 mol) in toluene (43 L) at such a rate that the temperature did not rise above 25 °C over 30 min. Then, β-hydroxamate **15** (4051 g, 12.61 mol) was added portionwise at 20−30 °C over 30 mn. During the addition of hydroxamate, a precipitate appeared (mixture of triphenylphosphine oxide and reduced DIAD) and the color turned black. After 2 h, the solids were filtered off and washed with 5 L of toluene, and the combined filtrates were solvent switched to methanol (final volume 20 L) using 35 L of methanol (20−25 °C, 28 mmHg). The solution was cooled to −30 °C for 30 min while the β-lactam crystallized out. The slurry was then filtered, and the white crystals were washed with cold methanol/water 9:1 (4 × 8 L, −20 C). Yield: 3 kg, 78%. Chiral HPLC indicated 99.7% ee. $[\alpha]_{589} = +9.24$ ($c = 1$, $CHCl_3$). Mp: 80 °C. ^{1}H NMR ($CDCl_3$): 2.38 (dd, *J* 13.8, 2.4, 1H), 2.64−2.72 (m, 2H), 2.92 (ddd, *J* 14.2, 5.1, 0.9, 1H), 3.68 (m, 1H), 4.92 (d, *J* 14.8, 1H), 4.94 (d, *J* 14.8, 1H), 6.81 (m, 1H), 6.88−7.01 (m, 2H), 7.38 (m, 5H). ^{13}C NMR: 31.8, 37.9, 57.2, 78.3, 115.1 dd, 116.5 dd, 117.6 dd, 125.2 dd, 128.7, 129.1, 129.3, 135.4, 156.7 d, 159.1 d, 163.9. IR: 728, 1043, 1496, 1774. Anal. Calcd for $C_{17}H_{15}F_2NO_2$: C, 67.32; H, 4.98; F, 12.53; N, 4.62. Found: C, 67.22; H, 4.80; F, 12.66; N, 4.68.

***N*-BOC-4-(2,5-difluorophenyl)-3(*R*)-aminobutanoic Acid 1.** To a solution of β-lactam **16** (0.52 g, 1.72 mmol) in MeOH (10 mL) was added MeONa (0.5 M in MeOH, 5.2 mL) at rt. After 10 min, 10% Pd/C (0.5 g) was added, and the mixture was submitted to hydrogenation (rt, H_2 40 psi) for 1 h. Catalyst was filtered off and the solvent evaporated to give crude free amine **18** which was used directly due to instability. ^{1}H NMR ($CDCl_3$): 1.45 (br, 2NH), 2.35 (dd, *J* 15.9, 8.8, 1H), 2.51 (dd, *J* 15.9, 4.1, 1H), 2.68 (dd, *J* 13.5, 7.6, 1H), 2.78 (dd, *J* 13.5, 5.5, 1H), 3.50 (m, 1H), 3.70 (s, 3H), 6.88−6.96 (m, 2H), 6.97−7.03 (m, 1H).

Crude amine **18** was dissolved in THF (5 mL), and triethylamine (0.36 mL, 2.6 mmol) was added followed by BOC_2O (0.45 g, 2.0 mmol). After 10 min at rt, $LiOH·H_2O$ (0.14 g, 3.5 mmol) was added and the resulting mixture was stirred overnight at rt. The solution was extracted twice with MTBE (2 × 20 mL), and after phase separation, the aqueous layer was reacidified with satd NaH_2PO_4 and back-extracted with MTBE (20 mL) to yield after crystallization (MTBE/hexane) 0.46 g (85% overall yield from **16**) of **1**. $[\alpha]_{589} = +27.0$ ($c = 0.38$ $CHCl_3$). Mp: 103−105 °C. ^{1}H NMR ($CDCl_3$) mixture of rotamers: 1.38 (s, 9H), 2.55−2.67 (m, 2H), 2.93 (m, 2H), 4.2 (m, 1H), 5.11 (br, NH), 6.88−7.02 (m, 3H), 10.2 (br, OH). ^{13}C NMR: 28.3, 33.6, 37.9, 17.7, 114.8, dd, 116.3 dd, 117.9 dd, 126.5 dd, 125.2, 156.7 d, 159.2 d, 176.3. IR: 813.5, 1053.6, 1165, 1496, 1522, 1686, 2912, 2939, 3359. HRMS: calcd for $C_{15}H_{19}F_2NO_4$ 315.1282, found 315.1281.

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