An Enantio- and Diastereoselective Synthesis of Fluorinated β-Aminoalkyl-oxepine Derivatives through Mannich and Ring-Closing Metathesis Reactions

Santos Fustero,*[a,b] Elisabet Esteban,[a] Juan F. Sanz-Cervera,[a,b] Diego Jiménez,[a] Fatemeh Mojarrad[a]

[a] Departamento de Química Orgánica, Universidad de Valencia, Burjassot 46100, Spain

[b] Centro de Investigación Príncipe Felipe, Valencia 46013, Spain
Fax +34(96)3544939; E-mail: santos.fustero@uv.es

Received 28 July 2006

Dedicated to the memory of Professor Marcial Moreno Mañas

Abstract: The combination of a proline-catalyzed Mannich-type reaction between protected fluorinated aldimines and 4-pentenal followed by reduction and regioselective O-allylation gives γ-amino ethers that can then be used as substrates for ring-closing metathesis (RCM) reactions to afford fluorinated β-aminoalkyl-oxepines in a highly stereo- and enantioselective fashion.

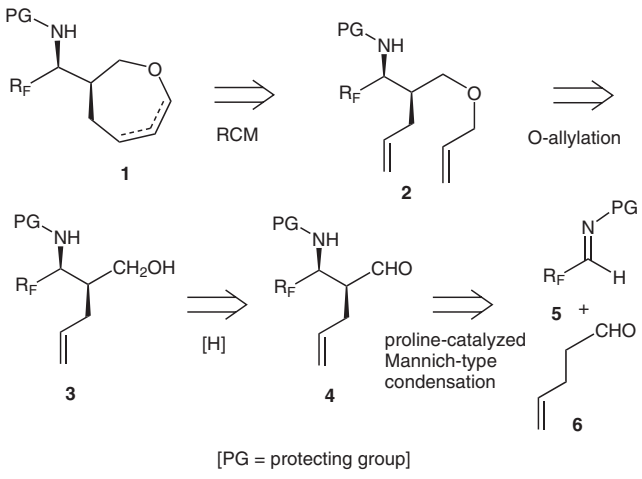
Key words: amino alcohols, fluorine, organocatalysis, Mannich reaction, metathesis, oxepines

Enantiopure β-amino acids and derivatives, such as γ-amino alcohols, have become appealing synthetic targets due to the fact that they are either present in or can be used as building blocks for a number of compounds with potential therapeutic properties.[1] In fact, several of these compounds have already been shown to display antifungal, antibiotic, and cytotoxic activity.[2] Moreover, because the presence of fluorine atoms in a potentially bioactive molecule can dramatically change not only its physical, but also its chemical properties, the preparation of fluorinated β-amino acids and their derivatives is also an important objective.[3]

However, few studies have focused on the preparation of cyclic, fluorinated β-amino acids. Our group has previously reported on the preparation of racemic *cis* seven-membered γ,γ-difluorinated β-amino acid derivatives in a sequence that starts with imidoyl halides.
These are condensed with suitable ester enolates to give intermediates that can subsequently be cyclized by means of a ring-closing olefin metathesis reaction. The product is then stereoselectively reduced to yield the desired compounds in good overall yields.[4]

At the same time, oxygen- and nitrogen-containing heterocyclic compounds have attracted considerable attention as a result of their biological activity and their presence in a variety of natural and unnatural products.[5] Thus, the asymmetric synthesis of oxygen heterocycles represents an important task because of the widespread occurrence of such structural motifs and their use as building blocks. Among oxygen heterocycles, seven-membered oxacycles are the central nuclei of numerous natural products. Numerous studies toward their synthesis have been reported because of their frequent natural occurrence and unusual biological properties.[6]

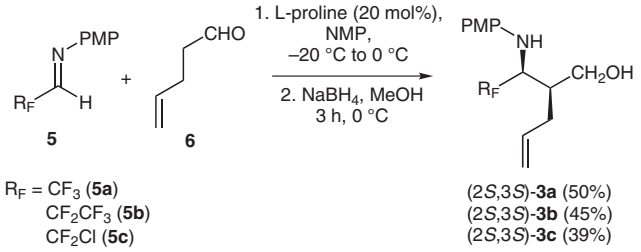
We have recently reported a highly diastereo- and enantioselective approach to fluorinated *syn* α-alkyl γ-amino alcohols by means of an indirect, proline-catalyzed Mannich-type reaction of fluorinated aldimines and aliphatic aldehydes.[7] These encouraging results led us to believe that this same strategy might be used in conjunction with an RCM reaction for the preparation of fluorinated seven-membered β-aminoalkyl oxacycles of the type **1** (Scheme 1). Organocatalysis has become one of the key research areas in synthetic organic chemistry. Its utility in asymmetric synthesis has been amply demonstrated; moreover, it has been successfully applied to Mannich reactions,[8,9] as well as many others.[10] The RCM has also been one of the most successful methods for the preparation of medium- or large-sized rings from acyclic diene precursors.[11] Thus, we now report on a highly diastereo- and enantioselective approach to fluorinated β-aminoalkyloxepines **1** by means of a synthetic strategy that uses an indirect, proline-catalyzed Mannich-type reaction of fluorinated aldimines and aliphatic aldehydes, followed by an O-allylation reaction, and finally an RCM reaction (retrosynthetic analysis, Scheme 1).



Scheme 1

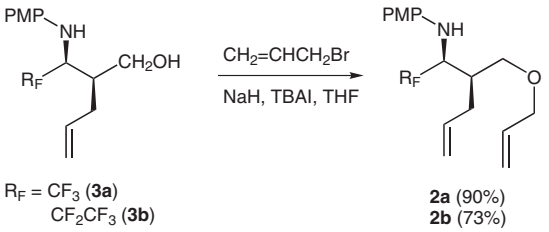
SYNTHESIS 2006, No. 23, pp 4087–4091
Advanced online publication: 02.11.2006
DOI: 10.1055/s-2006-950345; Art ID: C04906SS

The proline-catalyzed condensation between fluorinated imines **5a–c** and 4-pentenal (**6**) affords the corresponding fluorinated β-amino aldehydes **4a–c** in moderate yield.[7] Since fluorinated β-amino aldehydes **4a–c** are prone to epimerization, we immediately reduced them to the corresponding γ-amino alcohols **3a–c** with sodium borohydride in methanol at 0 °C. Thus, fluorinated γ-amino alcohols **3a–c** were obtained in moderate yields (39–50%), but with excellent diastereo- and enantioselectivities (*syn*:*anti* 96:4 and >99% ee in all three cases) (Scheme 2).



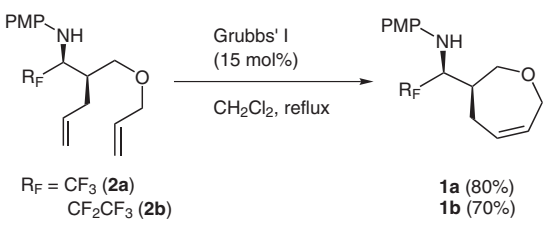
Scheme 2

For the O-allylation reaction, we decided to use sodium hydride and allyl bromide in tetrahydrofuran in the presence of 0.5 molar equivalents of tetrabutylammonium iodide (TBAI).[12] Thus, when γ-amino alcohols **3a**,**b** were treated with sodium hydride and allyl bromide in the presence of TBAI, the desired *O*-allyl γ-amino ethers **2a**,**b** were obtained in excellent yields (Scheme 3) and without any detectable N-alkylation.[13]



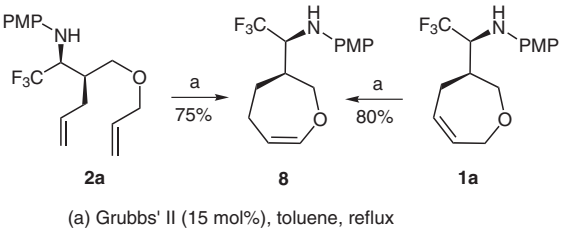
Scheme 3

Finally, when *O*-allyl γ-amino ethers **2a**,**b** were treated with Grubbs' first-generation catalyst [$(PCy_3)_2Cl_2Ru$=CHPh], an RCM reaction took place cleanly to afford the corresponding fluorinated β-aminoalkyl oxepines **1a**,**b** in high yield. (Scheme 4).



Scheme 4

Alternatively, when the *O*-allyl γ-amino ether **2a** was treated with Grubbs' second-generation catalyst [$(IHMes)(PCy_3)Cl_2Ru$=CHPh] in refluxing toluene and under a set of reaction conditions that our group has recently shown to favor double bond isomerization after the RCM reaction,[14] isomer **8** was obtained instead of **1a**. Interestingly, this compound can also be prepared from its isomer **1a** when it is subjected to the same reaction conditions (Scheme 5).



Scheme 5

In summary, the combination of a proline-catalyzed Mannich-type reaction between protected fluorinated aldimines and 4-pentenal, followed by reduction and O-allylation affords γ-amino ethers **2**. These compounds can then be used as substrates for RCM reactions that ultimately afford seven-membered fluorinated β-aminoalkyl oxacycles **1** in a highly stereo- and enantioselective fashion. To the best of our knowledge, this is the first time that compounds with this type of structure have been described in the literature.

All solvents were distilled prior to use. ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra were measured at 300 MHz, 282.4 MHz, and 75.5 MHz respectively, on a Bruker 300 spectrometer. IR spectra were recorded with a Thermo Nicolet 380 FT–IR infrared spectrometer. High resolution mass spectra were obtained on a VG Autospec (micromass) mass spectrometer. Column chromatography was performed on 100–200 mesh silica gel (Merck) using Hexane–EtOAc as eluent.

Preparation of Fluorinated γ-Amino Alcohols 3a–c; General Procedure

To a solution of the starting fluorinated imine[7] **5** (1 mmol) in *N*-methylpyrrolidone (1 mL), L-proline (0.20 mmol) was added and the resulting solution was stirred at r.t. for 45 min. The temperature was then lowered to –20 °C and 4-pentenal (2 mmol) was added via syringe over 1 min. The reaction was kept at –20 °C for 24 h, then at –10 °C for an additional 24 h, and finally at 0 °C for a further 24 h. The reaction mixture was then hydrolyzed by the addition of sat. aq NH_4Cl solution (5 mL), followed by quick extraction with EtOAc (3 × 10 mL). The organic phases were pooled together, washed once with sat. aq NaCl (10 mL) solution, and dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the crude residue was dissolved in dry MeOH (5 mL per mmol of starting fluorinated imine). The solution was cooled to 0 °C and treated with 5 mol equiv of $NaBH_4$, after which the reaction was allowed to reach r.t. and stirred for 5 h. Then, the reaction was quenched with sat. aq NH_4Cl solution and extracted into EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The corresponding fluorinated γ-amino alcohols **3** were isolated after silica gel column purification with hexane–EtOAc (4:1) as eluent.

(*S*)-2-[(*S*)-2,2,2-Trifluoro-1-(4-methoxyphenylamino)ethyl]pent-4-en-1-ol (3a)

Obtained in 50% yield in accordance with the general procedure described above. For complete physical and spectroscopic data of this compound, see ref. 7.

(*S*)-2-[(*S*)-2,2,2,3,3-Pentafluoro-1-(4-methoxyphenylamino)ethyl]pent-4-en-1-ol (3b)

Obtained in 45% yield in accordance with the general procedure described above. White solid; mp 78–79 °C; $[\alpha]_D^{25}$ +17.5 (c 0.77, $CHCl_3$).

IR (neat): 3385, 1636, 1259, 1189, 1022, 797 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.52–1.60 (m, 1 H), 1.97–2.10 (m, 1 H), 2.19–2.30 (m, 1 H), 2.34–2.45 (m, 1 H), 3.49–3.64 (m, 2 H), 3.75 (s, 3 H), 3.76–3.82 (m, 1 H), 4.43–4.57 (m, 1 H), 5.07–5.13 (m, 2 H), 5.73–5.87 (m, 1 H), 6.68 (d, *J* = 8.9 Hz, 2 H), 6.78 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 30.5 (t), 40.5 (d), 53.4 (dd, $^2J_{C-F}$ = 24.2 Hz, 20.3 Hz), 55.7 (q), 61.9 (t), 114.7 (d), 115.0 (d), 117, 3 (t), 135.6 (d), 140.6 (s), 152.9 (s). The δ values for the carbon atoms in the C_2F_5 group were too weak to be measured because of their multiplicity, caused by coupling with the fluorine atoms.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –82.65 (s, 3 F), –119.03 (dd, J_{F-F} = 73.1 Hz, J_{F-H} = 7.2 Hz, 1 F), –123.51 (dd, J_{F-F} = 273.1 Hz, J_{F-H} = 19.9 Hz, 1 F).

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{18}F_5NO_2$: 340.13360; found: 340.13257.

(*S*)-2-[(*S*)-2-Chloro-2,2-difluoro-1-(4-methoxyphenylamino)ethyl]pent-4-en-1-ol (3c)

Obtained in 39% yield in accordance with the general procedure described above. White crystals; mp 112–114 °C; $[\alpha]_D^{25}$ –17.1 (c 0.54, $CHCl_3$).

IR (neat): 3424, 2924, 1255, 1520, 1198, 1104, 1058, 1026, 957, 917, 897, 818 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.51 (br s, 1 H), 2.00–2.12 (m, 1 H), 2.25–2.35 (m, 1 H), 2.39–2.49 (m, 1 H), 3.56–3.65 (m, 2 H), 3.75 (s, 3 H), 3.80 (dd, J_1 = 10.6 Hz, J_2 = 3.9 Hz, 1 H), 4.38 (t, *J* = 9.6 Hz, 1 H), 5.05–5.15 (m, 2 H), 5.73–5.88 (m, 1 H), 6.71 (d, *J* = 8.6 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 30.3 (t), 41.1 (d), 55.7 (q), 62.0 (t, $^2J_{C-F}$ = 23.1 Hz), 62.3 (t), 115.0 (d), 115.3 (d), 117.4 (d), 131.1 (t, $^1J_{C-F}$ = 299.4 Hz), 135.7 (d), 140.9 (s), 153.0 (s).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –57.01 (dd, J_{F-F} = 162.0 Hz, J_{F-H} = 10.2 Hz, 1 F), –57,72 (dd, J_{F-F} = 162.0 Hz, J_{F-H} = 10.2 Hz, 1 F).

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{19}ClF_2NO_2$: 306.10724; found: 306.10502.

Preparation of Fluorinated *O*-Allyl Amino Ethers 2a,b; General Procedure

The starting fluorinated amino alcohol **3** (0.08 mmol) was dissolved in anhydrous THF (1 mL), to which TBAI (0.5 mol equiv) was added. The resulting solution was cooled to 0 °C and NaH (1.2 mol equiv) was added, the reaction mixture was stirred for 25 min and then allyl bromide (3 mol equiv) was added. After the addition, the mixture was stirred at r.t. for 12 h. The reaction mixture was then hydrolyzed by addition of sat. aq NH_4Cl solution (10 mL), followed by extraction with EtOAc (3 × 10 mL). The organic phases were pooled together, washed once with sat. aq NaCl solution (10 mL), and dried over anhydrous Na_2SO_4. The volatile components were then removed under vacuum and the crude reaction mixture was purified by means of flash column chromatography on silica gel using hexane–EtOAc (20:1) to afford the desired *O*-allyl amino ether **2**.

***N*-[(2*S*,3*S*)-3-(Allyloxymethyl)-1,1,1-trifluorohex-5-en-2-yl]-4-methoxyaniline (2a)**

Obtained in 90% yield as a yellowish oil in accordance with the general procedure described above. $[\alpha]_D^{25}$ +8.44 (c 0.93, $CHCl_3$).

IR (neat): 3649, 2932, 1647, 1513, 1234, 1133, 1107, 1039, 994, 920, 819, 765, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.90–2.00 (m, 1 H), 2.17–2.34 (m, 2 H), 3.37 (dd, J_1 = 9.3 Hz, J_2 = 9.3 Hz, 1 H), 3.49 (dd, J_1 = 9.3 Hz, J_2 = 3.7 Hz, 1 H), 3.72–3.75 (m, 1 H), 3.75 (s, 3 H), 3.77–3.91 (m, 2 H), 4.13–4.27 (m, 1 H), 4.99–5.21 (m, 4 H), 5.64–5.86 (m, 2 H), 6.67 (d, *J* = 8.6 Hz, 2 H), 6.78 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 30.8 (t), 38.6 (d), 55.7 (q), 56.5 (q, $^2J_{C-F}$ = 26.8 Hz), 69.2 (t), 72.0 (t), 114.8 (d), 115.1 (d), 117.1 (t), 117.4 (t), 126.7 (q, $^1J_{C-F}$ = 283.2 Hz), 134.5 (d), 135.6 (d), 141.1 (s), 152.9 (s).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.05 (d, J_{F-H} = 8.0 Hz, 3 F).

HRMS (EI): *m*/*z* calcd $C_{17}H_{22}NO_2F_3$: 329.16026; found: 329.16061.

***N*-[(3*S*,4*S*)-4-(Allyloxymethyl)-1,1,1,2,2-pentafluorohept-6-en-3-yl]-4-methoxyaniline (2b)**

Obtained in 73% yield as a yellowish oil in accordance with the general procedure described above. $[\alpha]_D^{25}$ +11.8 (c 0.88, $CHCl_3$).

IR (neat): 3392, 2932, 1642, 1514, 1186, 1120, 1039, 1019, 918, 817, 730 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.92–2.08 (m, 1 H), 2.29–2.44 (m, 2 H), 3.28 (dd, J_1 = 9.5 Hz, J_2 = 9.5 Hz, 1 H), 3.48 (dd, J_1 = 9.5 Hz, J_2 = 3.8 Hz, 1 H), 3.61 (d, *J* = 11.2 Hz, 1 H), 3.75 (s, 3 H), 3.78–3.94 (m, 2 H), 4.39–4.57 (m, 1 H), 5.03–5.29 (m, 4 H), 5.70–5.93 (m, 2 H), 6.63 (d, *J* = 9.0 Hz, 2 H), 6.76 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 30.8 (t), 38.4 (d), 53.3 (dd, $^2J_{C-F}$ = 24.1 Hz, $^2J_{C-F}$ = 19.5 Hz), 55.7 (q), 69.1 (t), 71.8 (t), 114.6 (d), 114.8 (d), 116.9 (t), 117.2 (t), 134.5 (d), 135.6 (d), 140.8 (s), 152.7 (s). The δ values for the carbon atoms in the C_2F_5 group, which appeared in the δ = 100–150 range, were too weak to be measured because of their multiplicity, caused by coupling with the fluorine atoms.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –82.75 (s, 3 F), –119.04 (dd, J_{F-F} = 272.5 Hz, J_{F-H} = 6.8 Hz, 1 F), –123.79 (dd, J_{F-F} = 272.5 Hz, J_{F-H} = 22.8 Hz, 1 F).

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{23}NO_2F_5$: 380.16490; found: 380.16070.

Preparation of Fluorinated β-Aminoalkyloxepines 1a–b; General Procedure

A solution of Grubbs first generation ruthenium catalyst $(PCy_3)_2Cl_2Ru{=}CHPh$ (15 mol%) in dry CH_2Cl_2 was added via cannula to a solution of amino ethers **2a–c** (0.08 mmol) in CH_2Cl_2 (4 mL, 0.02 M). The resulting dark brown solution was kept at r.t. until TLC indicated that the starting material was no longer present (usually 1 h). The solvents were removed under reduced pressure and the residue was purified by means of flash column chromatography on silica gel using hexane–EtOAc (9:1).

4-Methoxy-*N*-{(*S*)-2,2,2-trifluoro-1-[(*S*)-2,3,4,7-tetrahydrooxepin-3-yl]ethyl}aniline (1a)

Obtained in 80% yield as a yellowish oil in accordance with the general procedure described above. $[\alpha]_D^{25}$ –30.5 (c 0.93, $CHCl_3$).

IR (neat): 3607, 2925, 2854, 1736, 1716, 1513, 1365, 1231, 1128, 1036, 820, 695 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$,): δ = 2.40–2.51 (m, 3 H), 3.51 (d, *J* = 9.8 Hz, 1 H), 3.75 (s, 3 H), 3.76–3.95 (m, 3 H), 4.13–4.30 (m, 2 H), 5.65–5.78 (m, 2 H), 6.63 (d, *J* = 8.7 Hz, 2 H), 6.80 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 26.7 (t), 40.1 (d), 55.7 (q), 57.7 (q, ^2J = 27.0 Hz), 70.3 (t), 73.2 (t), 114.9 (d), 115.1 (d), 128.6 (d), 130.1 (q, ^1J = 284.8 Hz), 130.5 (d), 140.8 (s), 153.0 (s).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.86 (d, *J* = 7.2 Hz, 3 F).

HRMS (EI): *m/z* calcd for $C_{15}H_{18}F_3NO_2$: 301.12896; found: 301.12900.

4-Methoxy-*N*-{(*S*)-2,2,3,3,3-pentafluoro-1-[(*S*)-2,3,4,7-tetrahydrooxepin-3-yl]propyl}aniline (1b)

Obtained in 70% yield in accordance with the general procedure described above. Yellowish oil; $[\alpha]_D^{25}$ +2.54 (c 0.74, $CHCl_3$).

IR (neat): 3456, 3016, 2970, 2943, 1739, 1511, 1366, 1229, 1205, 1181, 1120, 1024, 820, 729 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41–2.49 (m, 2 H), 2.54–2.67 (m, 1 H), 3.48 (d, *J* = 9.9 Hz, 1 H), 3.75 (s, 3 H), 3.75–3.79 (m, 1 H), 3.90 (dd, J_1 = 12.4 Hz, J_2 = 3.3 Hz, 1 H), 3.92–4.03 (m, 1 H), 4.14–4.22 (m, 2 H), 5.59–5.77 (m, 2 H), 6.58 (d, *J* = 8.9 Hz, 2 H), 6.77 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 26.6 (t), 40.4 (d), 55.3 (dd, $^2J_{C-F}$ = 24.7 Hz, $^2J_{C-F}$ = 20.6 Hz), 55.7 (q), 70.2 (t), 73.5 (t), 114.6 (d), 115.0 (d), 128.4 (d), 130.3 (d), 140.3 (s), 152,9 (s). The δ values for the carbon atoms in the C_2F_5 group, which appeared in the δ = 100–150 range, were too weak to be measured because of their multiplicity, caused by coupling with the fluorine atoms.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –82.19 (s, 3 F), –117.57 (dd, J_{F-F} = 274.0 Hz, J_{F-H} = 6.7 Hz, 1 F), –124.5 (dd,1F, J_{F-F} = 273.8 Hz, J_{F-H} = 20.1 Hz).

HRMS (EI): *m/z* calcd for $C_{16}H_{18}F_5NO_2$: 351.12577; found: 351.12498.

Methoxy-*N*-{(*S*)-2,2,3,3,3-pentafluoro-1-[(*S*)-2,3,4,5-tetrahydrooxepin-3-yl]propyl}aniline (8)

This method is analogous to the one used in the preparation of compounds **1a**–**b**, except that Grubbs' second-generation catalyst (IHMes)(PCy_3)Cl_2Ru=CHPh is used and the solvent is toluene under reflux. Either **1a** or **2a** can be used as starting material. Under these conditions and with this catalyst (15 mol%), the reaction took 4 h to complete. After flash column chromatography purification on silica gel using hexane–EtOAc (15:1), the yield was 80% (from **1a**) or 75% (from **2a**), obtained as a yellowish oil. $[\alpha]_D^{25}$ +18.8 (c 0.67, $CHCl_3$).

IR (neat): 3392, 3015, 2970, 2925, 2854, 1738, 1651, 1511, 1365, 1231, 1131, 1037, 820, 758, 731, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.80–1.93 (m, 1 H), 1.94–2.08 (m, 1 H), 2.14–2.23 (m, 2 H), 2.32–2.43 (m, 1 H), 3.62 (d, *J* = 8.9 Hz, 1 H), 3.75 (s, 3 H), 3.81–3.94 (m, 1 H), 3.96 (dd, J_1 = 12.3 Hz, J_2 = 4.7 Hz, 1 H), 4.20 (dd, J_1 = 12.3 Hz, J_2 = 3.6 Hz, 1 H), 4.73–4.75 (m, 1 H), 6.29 (d, *J* = 6.6 Hz, 1 H), 6.66 (d, *J* = 9.0 Hz, 2 H), 6.79 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 23.7 (t), 27.2 (t), 40.5 (d), 55.7 (q), 59.4 (q, $^2J_{C-F}$ = 28.0 Hz), 74.0 (t), 108.4 (d), 114.9 (d), 115.1 (d), 126.1 (q, $^1J_{C-F}$ = 285.0 Hz), 140.9 (s), 148.9 (d), 153.0 (d).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –72.71 (d, J_{F-H} = 7.2 Hz, 3 F).

HRMS (EI): *m/z* calcd for $C_{15}H_{18}F_3NO_2$: 301.12896; found: 301.12859.

Acknowledgment

The authors thank the Ministerio de Educación y Ciencia (BQU2003-01610 and CTQ2006-01317/BQU) and the Generalitat Valenciana (GR03-193 and GV05/079) for financial support. E.E. and D.J. express their thanks for predoctoral fellowships from the aforementioned institutions.

References

(1) Reviews: (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117. (b) Hintermann, T.; Seebach, D. *Chimia* **1997**, *51*, 244. (c) Scarborough, R. M. *Curr. Med. Chem.* **1999**, *6*, 971. (d) Abdel-Magid, A. F.; Cohen, J. H.; Maryanoff, C. A. *Curr. Med. Chem.* **1999**, *6*, 955. (e) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E.; Soloshonok, V., Eds.; Wiley-Interscience: New York, **2005**.

(2) (a) Fernández, R.; Rodríguez, J.; Quiñoa, E.; Riguera, R.; Muñoz, L.; Fernández-Suarez, M.; Debitus, C. J. *J. Am. Chem. Soc.* **1996**, *118*, 11635. (b) Hu, T.; Panek, J. J. *J. Org. Chem.* **1999**, *64*, 3000.

(3) (a) *Organo-Fluorine Compounds,* In *Houben-Weyl Methods of Organic Chemistry*, Vol. E10a-c; Georg Thieme Verlag: Stuttgart, **2000**. (b) *Fluorine-containing Amino Acids: Synthesis and Properties*; Kukhar, V. P.; Soloshonok, V. A., Eds.; Wiley: Chichester, **1995**.

(4) Fustero, S.; Bartolome, A.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Soler, J. G.; Ramírez de Arellano, C.; Fuentes, A. S. *Org. Lett.* **2003**, *5*, 2523.

(5) (a) Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. *Tetrahedron* **2002**, *58*, 6795; and references cited therein. (b) Szawkalo, J.; Zawadzka, A.; Wojtasiewitcz, K.; Leniewski, A.; Drabowicz, J.; Czarnocki, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 3619.

(6) (a) Batchelor, R.; Hoberg, J. O. *Tetrahedron Lett.* **2003**, *44*, 9043; and references cited therein. (b) Wong, J. C. Y.; Lacombe, P.; Sturino, C. F. *Tetrahedron Lett.* **1999**, *40*, 8751. (c) Adams, J. A.; Heron, N. M.; Koss, A.-M.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 854. (d) Suginome, M.; Iwanami, T.; Ito, Y. *J. Am. Chem. Soc.* **2001**, *123*, 4356. (e) Lecourné, F.; Ollivier, J. *Org. Biomol. Chem.* **2003**, *1*, 3600. (f) Trost, B. M.; Brown, B. S.; McEachern, E. J.; Kuhn, O. *Chem. Eur. J.* **2003**, *9*, 4442.

(7) (a) Fustero, S.; Jiménez, D.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Esteban, E.; Simón-Fuentes, A. *Org. Lett.* **2005**, *7*, 3433. (b) Our group has previously described a less convenient enantioselective synthesis of this class of compounds that uses (–)-8-phenylmenthol as a chiral auxiliary, see: Fustero, S.; Pina, B.; Salavert, E.; Navarro, A.; Ramírez de Arellano, M. C.; Fuentes, A. S. *J. Org. Chem.* **2002**, *67*, 4667.

(8) Tanaka, F.; Barbas, C. F. III *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E.; Soloshonok, V., Eds.; Wiley-Interscience: New York, **2005**, Chap. 9, 195–214.

(9) For representative examples of organocatalyzed Mannich reactions, see: (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (c) Watanabe, S.; Córdova, A.; Tanaka, F.; Barbas, C. F. III *Org. Lett.* **2002**, *4*, 4519. (d) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F. III *J. Am. Chem. Soc.* **2002**, *124*, 1866. (e) Notz, W.; Tanaka, T.; Watanabe, S.; Chowdari, S. N.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F. III *J. Org. Chem.* **2003**, *68*, 9624. (f) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushihima, T.; Shoji, M.; Sakai, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 3677. (g) Notz, W.; Tanaka, T.; Barbas, C. F. III *Acc. Chem. Res.* **2004**, *37*, 580. (h) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (i) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243. (j) Córdova, A. *Chem. Eur. J.* **2004**, *10*, 1987. (k) Zhuang, W.; Saaby, S.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 4476. (l) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.

(10) (a) *Asymmetric Organocatalysis*; Berkessel, A.; Gröger, H., Eds.; Wiley-VCH: Weinheim, **2005**. For reviews, see: (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (c) Dalko, P. I.; Moisan, D. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

(11) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (d) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (e) Roy, R. *Chem. Commun.* **2000**, 519. (f) Percy, J. M.; Pintat, S. *Chem. Commun.* **2000**, 607. (g) Kariuki, B. M.; Owton, W. M.; Percy, J. M.; Pintat, S.; Smith, C. A.; Spencer, N. S.; Thomas, A. C.; Watson, M. *Chem. Commun.* **2002**, 228.

(12) (a) Reeves, W. P.; Hilbrich, R. G. *Tetrahedron* **1976**, *32*, 2235. (b) Hopfinger, A.; Sjoeberg, K. *J. Mol. Catal.* **1983**, *20*, 105. (c) Ishido, Y.; Tsutsumi, H.; Inaba, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 521.

(13) In the case of γ-amino alcohol **2c**, however, the yield in the O-allylation reaction was substantially lower because of competitive side reactions. As the O-allylation product turned out to be very difficult to purify, we decided not to continue with this substrate.

(14) Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706.