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## SYNTHESIS OF TETRAHYDROFURFURYLAMINES RELATED TO MUSCARINE

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**Abstract** – A methodology that involves mesylation of readily available tetrahydrofuryl diols and subsequent displacement with selected amines to afford novel muscarine analogs has been outlined. Displacement of the primary mesylate takes place smoothly, while displacement of the secondary mesylate occurs in low yield. The use of triflates as an alternative has been sketched.

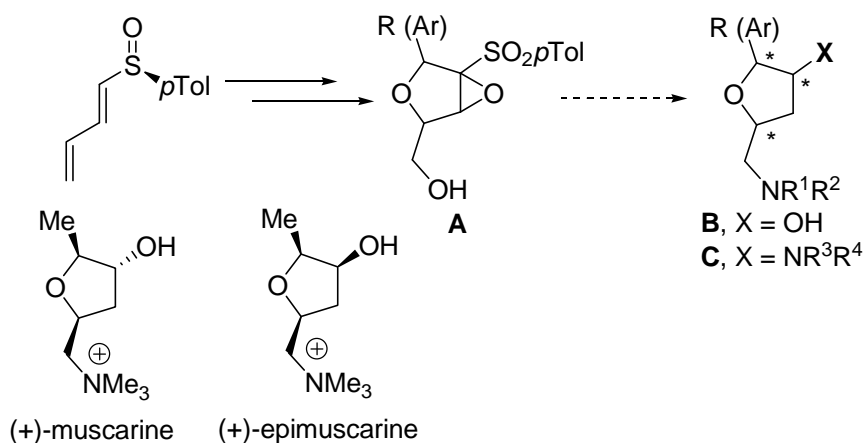
### INTRODUCTION

Tetrahydrofurans bearing nitrogen substituents are important fragments of a variety of biologically active compounds.<sup>1</sup> The muscarines are important examples of biologically active non-nucleosidic tetrahydrofurfurylamines,<sup>2</sup> and the preparation of muscarines and analogs is still an active field of research.<sup>3</sup> During the past few years we have been engaged in the development of effective routes to access tetrahydrofuranyl methanol derivatives **A** (Scheme 1) in just 4 synthetic operations from sulfinates through dienyl sulfoxides.<sup>4</sup> Within this context, we chose to address the preparation of muscarine analogs **B**,<sup>5</sup> or **C** from **A** with the purpose of exploring applications of our methodology and providing products suitable for preliminary biological testing. Considering the preliminary nature of this project it was decided to employ racemic materials but it should be mentioned that enantiopure substrates are also readily available from commercial (+)- and (-)-menthyl sulfinates.

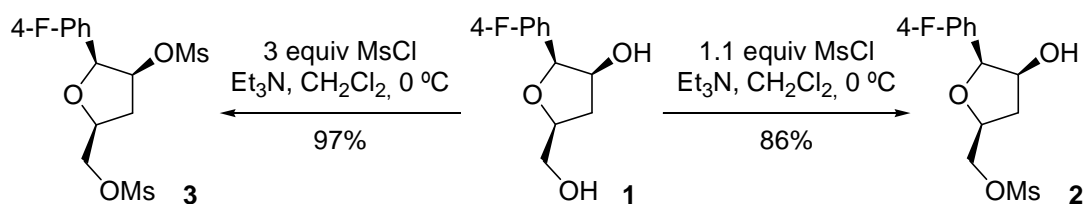
### RESULTS AND DISCUSSION

At the early stage of this project, we envisioned an early introduction of  $-NR^1R^2$ , either by reductive amination of an aldehyde precursor or by displacement of an activated primary alcohol derivative, followed by oxirane cleavage affording targets **B** and subsequent introduction of the  $-NR^3R^4$  moiety to produce

diamino derivatives **C**.<sup>6</sup> Unfortunately, all attempts to oxidize **A** (Ar = 4-F-Ph) to the aldehyde were unsuccessful and, interestingly, activation as a tosylate (TsCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub> or THF) was unexpectedly slow and took place in low yield. Furthermore, displacement of the tosylate with piperidine gave the expected product in good yield but this tetrahydrofurfurylamine turned out to be quite unstable.<sup>7</sup> At this point it was decided to focus our efforts on the selective functionalization of tetrahydrofuryl diols, readily obtained by reductive cleavage of oxiranes **A**.<sup>8</sup> In particular, diol (**1**) (Scheme 2) was selected as a model scaffold to examine this chemistry and formation of the mono- and dimesylated derivatives was easily accomplished as shown in Scheme 2 to produce mesylates (**2**) and (**3**) in excellent yields and as stable compounds that could be stored for months in a refrigerator.

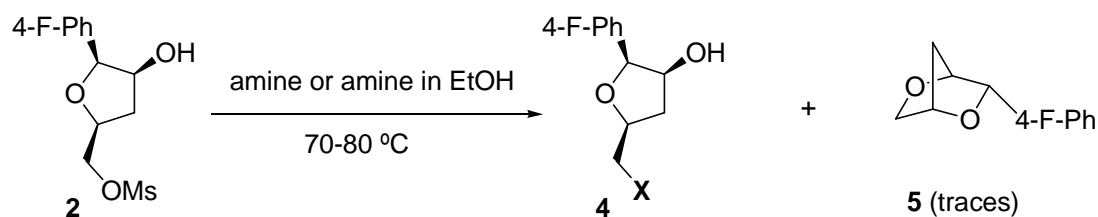


Scheme 1



Scheme 2

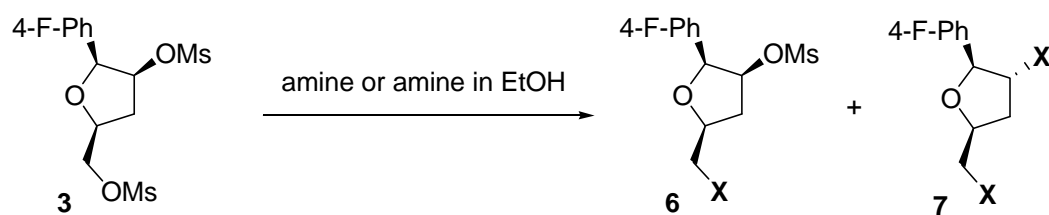
Table 1 gathers the results obtained for the displacement of primary mesylate (**2**) with representative amines. These processes afford good isolated yields of amino alcohols (**4**), structurally related with epimuscarine, along with trace amounts of bicyclic product (**5**), derived from intramolecular displacement of the free hydroxyl in (**4**) to the primary mesylate. It should be mentioned that optimal conditions for this transformation involved the use of an excess of amine, either neat or in EtOH at 80-90 °C. Other solvents (1-butanol, DMF, CH<sub>3</sub>CN) could also be employed but offered no particular advantage in these cases.

**Table 1.** Displacements of primary mesylate in **2** with amines

| Entry | Conditions                             | Product   | X                          | Yield <sup>a</sup> |
|-------|--|-----------|----------------------------|--------------------|
| 1     | benzylamine, 70 °C, 14 h               | <b>4a</b> | benzylamino                | 76%                |
| 2     | 4-phenylpiperidine, 70 °C, 10 h        | <b>4b</b> | 4-phenylpiperidino         | 71%                |
| 3     | <i>N</i> -methylpiperazine, 80 °C, 6 h | <b>4c</b> | <i>N</i> -methylpiperazino | 66%                |

<sup>a</sup> Combined yields of pure products isolated after chromatography.

The selective displacement of dimesylate (**3**) was then addressed and the results obtained are shown in Table 2. Thus, amino mesylates (**6**) were obtained smoothly with different primary and secondary amines using the conditions described above (Table 2, Entries 1-4). The use of the less nucleophilic aniline gave different results affording either a mixture of **6e** and starting material (Table 2, Entry 5) or, under more forcing conditions (Table 2, Entry 6) a mixture of **6e** and aminofurfurylamine (**7e**), derived from concurrent displacements of both mesylates.

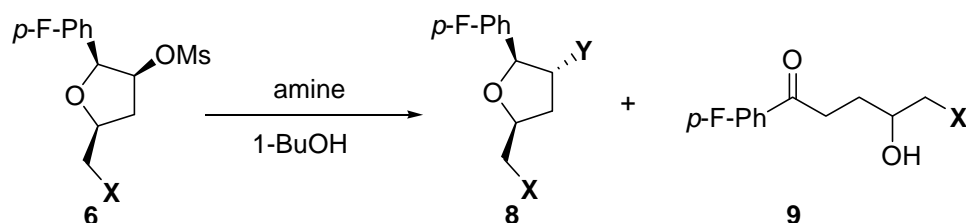
**Table 2.** Displacements of primary mesylate in **3** with amines

| Entry | Conditions                              | X                          | <b>6</b>        | <b>7</b>        | Yield <sup>a</sup> |
|-------|---|----------------------------|-----------------|-----------------|--------------------|
| 1     | benzylamine, 70 °C, 23 h                | benzylamino                | <b>6a</b>       | ---             | 93%                |
| 2     | 4-phenylpiperidine, 70 °C, 20 h         | 4-phenylpiperidino         | <b>6b</b>       | ---             | 72%                |
| 3     | <i>N</i> -methylpiperazine, 70 °C, 23 h | <i>N</i> -methylpiperazino | <b>6c</b>       | ---             | 68%                |
| 4     | piperidine, 70 °C, 8 h                  | piperidino                 | <b>6d</b>       | ---             | 82%                |
| 5     | aniline, EtOH 90 °C, 45 h               | anilino                    | <b>6e</b>       | ---             | 46% <sup>b</sup>   |
| 6     | aniline, 1-BuOH, 115 °C, 23 h           | anilino                    | <b>6e</b> (21%) | <b>7e</b> (30%) | 51%                |

<sup>a</sup> Combined yields of pure products isolated after chromatography. <sup>b</sup> Starting material (27%) was recovered.

Table 3 shows the results obtained for the displacement of the secondary mesylates of tetrahydrofurfurylamines (**6**). These reactions were carried out in 1-BuOH and required long reaction times (> 14 h) and high reaction temperatures (110-120 °C). Thus, the treatment of **6b** with piperidine gave, after 3 consecutive chromatographies on silica gel, a low yield of diamine (**8b**) along with acyclic ketone (**9b**), derived from ring cleavage of **6b** (Table 3, Entry 1). Entry 2 gathers the results obtained for the displacement of **6d** with benzylamine that are similar to those shown in Entry 1.<sup>9</sup> Finally, Entries 3 and 4 show that mesylates (**6a**) and (**6c**) could also be transformed similarly into aminotetrahydrofurfurylamines (**8a**) and (**8c**), although in these cases we were unable to obtain pure products from the crude mixtures by conventional chromatographic techniques.

**Table 3.** Displacements of secondary mesylate in **6** with amines

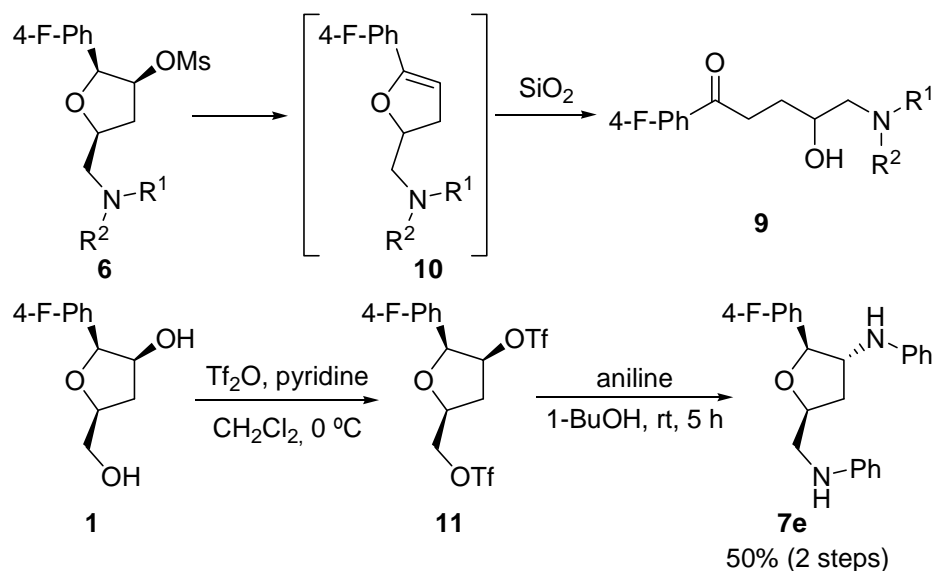


| Entry | Substrate                                  | Conditions                        | Y                  | <b>8</b> <sup>a</sup>        | <b>9</b> <sup>a</sup> |
|-------|--|-----------------------------------|--------------------|------------------------------|-----------------------|
| 1     | <b>6b</b> (X = 4-phenylpiperidino)         | piperidine, 110-120 °C, 27 h      | piperidino         | <b>8b</b> (29%)              | <b>9b</b> (26%)       |
| 2     | <b>6d</b> (X = piperidino)                 | benzylamine, 110-120 °C, 18 h     | benzylamino        | <b>8d</b> (21%)              | <b>9d</b> (47%)       |
| 3     | <b>6a</b> (X = benzylamino)                | 4-phenylpiperidine, 115 °C, 21 h  | 4-phenylpiperidino | <b>8a</b> (---) <sup>b</sup> | --- <sup>b</sup>      |
| 4     | <b>6c</b> (X = <i>N</i> -methylpiperazino) | aniline, 115-125 °C, 2 days, 13 h | anilino            | <b>8c</b> (---) <sup>b</sup> | --- <sup>b</sup>      |

<sup>a</sup> Yields of pure products isolated after chromatography. <sup>b</sup> The yield could not be determined.

Careful study of the <sup>1</sup>H NMR spectra of the crude reaction mixtures revealed that ketones (**9**) were not present in the crude mixtures; this suggested that perhaps the secondary mesylates were undergoing a competitive base-promoted elimination to produce dihydrofurans (**10**) (Scheme 3), that would evolve to ketones (**9**) upon chromatography on silica gel. In an effort to achieve milder reaction conditions, bistriflate (**11**) was prepared and the crude product was treated with aniline to produce a good yield of **7e**. Unfortunately, while the use of more basic amines (4-phenylpiperidine, benzylamine, *N*-methylpiperazine) afforded displacement products at lower temperatures (−40 to 0 °C), we were unable to cleanly separate the desired products from the excess amine used. The low yields found for the

displacements of the secondary mesylates and the difficulties associated with purification of the amino tetrahydrofurfurylamines obtained by this route prompted us to seek alternative strategies to access related regioisomeric amino tetrahydrofurfurylamines that will be disclosed in a forthcoming report.



Scheme 3

In summary, we have demonstrated the viability of a new strategy to access novel analogs of muscarine, as well as related amino tetrahydrofurfurylamines, a class of compounds that is scarcely documented in the literature. The biological activity of these products is currently being tested.

## EXPERIMENTAL

Reagents and solvents were handled by using standard syringe techniques. All reactions were carried out under an argon atmosphere. Hexane, toluene and  $\text{CH}_2\text{Cl}_2$  were distilled from  $\text{CaH}_2$ , and THF and  $\text{Et}_2\text{O}$  from sodium.  $(\text{MeO})_2\text{P}(\text{O})\text{Me}$ ,  $\text{Et}_3\text{N}$ , and  $i\text{-Pr}_2\text{NH}$  were distilled from  $\text{CaH}_2$ .  $\text{MsCl}$  was distilled from  $\text{P}_2\text{O}_5$ . Crude products were purified by flash chromatography on 230-400 mesh silica gel with distilled solvents. Analytical TLC was carried out on silica gel plates with detection by UV light, iodine, acidic vanillin solution, 10% phosphomolybdic acid solution in ethanol. All reagents were commercial products.  $\text{NaH}$  and  $\text{KH}$  (60% in mineral oil) were washed repeatedly with dry hexane and dried prior to use. Through this section, the volume of solvents is reported in mL/mmol of starting material.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 200, 300 or 400 MHz ( $^1\text{H}$ ) using  $\text{CDCl}_3$  as solvent and with the residual solvent signal as internal reference ( $\text{CDCl}_3$ , 7.24 and 77.0 ppm). The following abbreviations are used to describe peak patterns when appropriate: app (apparent), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Melting points are uncorrected. Low resolution mass spectra were recorded using the electronic impact technique with an ionization energy of 70 eV or using the atmospheric pressure

chemical ionization (APCI) or electrospray (ES) chemical ionization techniques in its positive or negative modes.

**General Procedure for Mesylation.** To a cold (0 °C) solution of the alcohol in CH<sub>2</sub>Cl<sub>2</sub> (10 mL/mmol) was added Et<sub>3</sub>N (1.5 equiv for mesylation of one hydroxyl and 3.0 equiv for mesylation of two hydroxyls) followed by freshly distilled methanesulfonyl chloride (MsCl, 1.1 equiv for mesylation of one hydroxyl and 3.0 equiv for mesylation of two hydroxyls). The reaction mixture was stirred and allowed to warm up slowly to rt and monitored by TLC. When the reaction completed, it was quenched with saturated NaHCO<sub>3</sub> (4 mL/mmol) and H<sub>2</sub>O (4 mL/mmol), extracted with EtOAc (3 x 5 mL/mmol). The layers were separated, the organic layer was washed with a saturated solution of NaCl (5 mL/mmol), dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give a crude product that was purified by chromatography on silica gel using the appropriate mixture of solvents.

**Synthesis of (2S\*,3S\*,5S\*)-2-(4-fluorophenyl)-5-(methanesulfonyloxymethyl)tetrahydrofuran-3-ol (2).** From diol (**1**) (177 mg, 0.83 mmol, 1.0 equiv), MsCl (71 μL, 0.92 mmol, 1.1 equiv) and Et<sub>3</sub>N (0.17 mL, 1.25 mmol, 1.5 equiv), according to the general procedure (30 min), mesylate (**2**) was obtained. Purification by chromatography (30-100% EtOAc-CH<sub>2</sub>Cl<sub>2</sub>) afforded 198 mg (82%) of **2** as a colorless oil along with a small amount of dimesylated product (**3**) (16 mg, 5%) and traces of starting material (8 mg, 4%). Data for **2**: *R<sub>f</sub>* = 0.31 (50% EtOAc-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz) δ 1.47 (br s, 1 H, OH), 1.97 (app d, 1 H, *J* = 14.1 Hz, H-4β), 2.45 (ddd, 1 H, *J* = 13.9, 8.4, 5.5 Hz, H-4α), 3.05 (s, 3 H, CH<sub>3</sub> Ms), 4.30-4.50 (m, 4 H, CH<sub>2</sub>-OMs + H-3 + H-5), 4.89 (app s, 1 H, H-2), 7.05 (app t, 2 H, *J* = 8.8 Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 7.34 (dd, 2 H, *J* = 8.4, 5.6 Hz, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>). <sup>13</sup>C NMR (50 MHz)-DEPT δ 36.6 (CH<sub>2</sub>-4), 37.7 (CH<sub>3</sub> Ms), 71.8 (CH<sub>2</sub>-OMs), 72.9 (CH), 75.5 (CH), 85.5 (CH), 115.4 (2 CH-3', 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 21.4 Hz), 128.6 (2 CH-2', 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 8.0 Hz), 131.7 (C-1' 4-F-C<sub>6</sub>H<sub>4</sub>), 162.3 (C-4', 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 246.4 Hz). IR (film): 3400, 2920, 1604, 1509, 1276, 1224, 1092, 769 cm<sup>-1</sup>. MS (ES): 313 [M+Na]<sup>+</sup> (100%). Anal. Calcd for C<sub>12</sub>H<sub>15</sub>O<sub>5</sub>FS: C, 49.65; H, 5.21; S, 11.05. Found: C, 49.92; H, 5.02; S, 11.34.

**Synthesis of the dimesylated derivative of (2S\*,3S\*,5S\*)-2-(4-fluorophenyl)-5-hydroxymethyl-tetrahydrofuran-3-ol (3).** From diol (**1**) (403 mg, 1.90 mmol, 1.0 equiv), MsCl (0.44 mL, 5.70 mmol, 3.0 equiv) and Et<sub>3</sub>N (1.06 mL, 7.60 mmol, 4 equiv), according to the general procedure (20 min), mesylate (**3**) was obtained. Purification by chromatography (20-40% EtOAc-CH<sub>2</sub>Cl<sub>2</sub>) afforded 678 mg (97%) of **3** as white solid that was recrystallized from EtOAc-hexane. Data for **3**: mp 83-84 °C. *R<sub>f</sub>* = 0.48 (50% EtOAc-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (200 MHz) δ 2.32 (dd, 1 H, *J* = 14.3, 3.3 Hz, H-4), 2.40 (s, 3 H, CH<sub>3</sub> Ms), 2.68 (ddd, 1 H, *J* = 14.4, 8.5, 5.5 Hz, H-4), 3.08 (s, 3 H, CH<sub>3</sub> Ms), 4.32-4.54 (m, 3 H, CH<sub>2</sub>-OMs

+ H-5), 4.99 (d, 1 H,  $J = 3.1$  Hz, H-2), 5.23 (m, 1 H, H-3), 7.06 (app t, 2 H,  $J = 8.8$  Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 7.37 (dd, 2 H,  $J = 9.0, 5.3$  Hz, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>). <sup>13</sup>C NMR (50 MHz)  $\delta$  36.1 (CH<sub>2</sub>-4), 37.8 (CH<sub>3</sub> Ms), 37.9 (CH<sub>3</sub> Ms), 70.2 (CH<sub>2</sub>-OMs), 75.3 (CH), 81.2 (CH), 83.8 (CH), 115.3 (2 CH-3', 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 21.7$  Hz), 128.8 (2 CH-2', 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 8.0$  Hz), 130.6 (C-1', 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 3.1$  Hz), 162.6 (C-4', 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 247.2$  Hz). IR (KBr): 3029, 2934, 1607, 1512, 1351, 1173, 958, 905, 838 cm<sup>-1</sup>. MS (ES): 391 [M+Na]<sup>+</sup>, 386 [M+H<sub>2</sub>O]<sup>+</sup> (100%). Anal. Calcd for C<sub>13</sub>H<sub>17</sub>O<sub>7</sub>FS<sub>2</sub>: C, 42.38; H, 4.65; S, 17.41. Found: C, 42.01; H, 4.33; S, 17.73.

**General Procedure for Displacement of Mesylates with Amines.** To a solution of mesylate in EtOH, 1-butanol or DMF (2-10 mL/mmol) or in the amine (2-5 mL/mmol) was added the amine (5-10 equiv) and the mixture was heated to 70-90 °C for displacement of primary mesylates or to 110-140 °C for displacement of secondary mesylates. The reaction was monitored by TLC until disappearance of starting material, the solvent and excess amine were removed under reduced pressure and the crude reaction mixture was purified by column chromatography using the appropriate mixture of eluents.

**Synthesis of (2*S*\*,3*S*\*,5*S*\*)-5-benzylaminomethyl-2-(4-fluorophenyl)tetrahydrofuran-3-ol (4a).**

From mesylate (**2**) (44 mg, 0.15 mmol, 1.0 equiv) in benzylamine (2 mL/mmol), according to the general procedure (70 °C, 14 h), amino alcohol (**4a**) was obtained. Purification by chromatography (0-5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 34 mg (76%) of **4a** as a pale yellow solid that was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>-hexane and 2 mg (7%) of (**5**) as a colorless oil. Data for **4a**: mp 101-102 °C.  $R_f = 0.15$  (5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz)  $\delta$  1.86 (dd, 1 H,  $J = 13.8, 2.6$  Hz, H-4), 2.47 (dd, 1 H,  $J = 13.3, 3.2$  Hz, CH<sub>2</sub>-NHBn), 2.53 (ddd, 1 H,  $J = 13.8, 10.1, 5.1$  Hz, H-4), 3.15 (dd, 1 H,  $J = 13.3, 3.2$  Hz, CH<sub>2</sub>-NHBn), 3.35 (br s, 2 H, OH + NH), 3.79 (d, 1 H,  $J = 13.2$  Hz, CH<sub>2</sub> Bn), 3.93 (d, 1 H,  $J = 13.1$  Hz, CH<sub>2</sub> Bn), 4.19 (dd, 1 H,  $J = 5.0, 2.6$  Hz, H-3), 4.39 (ddd, 1 H,  $J = 10.1, 4.4, 2.9$  Hz, H-5), 4.75 (d, 1 H,  $J = 2.2$  Hz, H-2), 7.01 (app t, 2 H,  $J = 8.8$  Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 7.24-7.34 (m, 7 H, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub> + Ph). <sup>13</sup>C NMR (75 MHz)  $\delta$  39.6 (CH<sub>2</sub>-4), 51.0 (CH<sub>2</sub>), 54.2 (CH<sub>2</sub>), 72.5 (CH), 76.7 (CH), 85.6 (CH), 114.9 (2 CH-3', 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 21.2$  Hz), 127.4 (CH Ph), 128.2 (2 CH-2', 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 8.1$  Hz), 128.4 (2 CH Ph), 128.6 (2 CH Ph), 133.5 (C-1', 4-F-C<sub>6</sub>H<sub>4</sub>), 138.9 (C Ph), 162.3 (C-4', 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 244.9$  Hz). IR (KBr): 3435, 3021, 2925, 2855, 1605, 1508, 1452, 1217, 1047, 880, 797, 701 cm<sup>-1</sup>. MS (ES): 302 [M+1]<sup>+</sup> (100%). Anal. Calcd for C<sub>18</sub>H<sub>20</sub>NO<sub>2</sub>F: C, 71.74; H, 6.69; N, 4.65. Found: C, 71.53; H, 6.62; N, 4.58. Partial data for (1*S*\*,3*S*\*,4*S*\*)-3-(4-fluorophenyl)-2,5-dioxabicyclo[2.2.1]heptane (**5**):  $R_f = 0.55$  (50% EtOAc-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (200 MHz)  $\delta$  2.05 (dd, 1 H,  $J = 10.0, 2.5$  Hz, H-7), 2.23 (dd, 1 H,  $J = 10.0, 2.6$  Hz, H-7), 3.74 (d, 1 H,  $J = 8.1$  Hz, H-6), 3.93 (d, 1 H,  $J = 8.1$  Hz, H-6), 4.52 (br s, 1 H, H-4), 4.72 (d, 1 H,  $J = 2.6$  Hz, H-1), 5.01 (s, 1 H, H-3), 7.03 (app t, 2 H,  $J = 8.7$  Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 7.32 (dd, 2 H,  $J = 9.0, 5.5$  Hz, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>). MS (ES): 195 [M+1]<sup>+</sup> (100%).

**Synthesis of (2*S*\*,3*S*\*,5*S*\*)-2-(4-fluorophenyl)-5-(4-phenylpiperidino)methyltetrahydrofuran-3-ol (4b).** From mesylate (**2**) (44 mg, 0.15 mmol, 1.0 equiv) in EtOH (5 mL/mmol) with 10 equiv of 4-phenylpiperidine (242 mg, 1.5 mmol), according to the general procedure (70 °C, 14 h), amino alcohol (**4b**) was obtained. Purification by chromatography (0-5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 38 mg (71%) of **4b** as a pale yellow solid that was recrystallized from 20% EtOAc-hexane. Data for **4b**: mp 132-133 °C. *R<sub>f</sub>* = 0.19 (5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz) δ 1.71 (dd, 1 H, *J* = 3.7, 1.6 Hz, Pip), 1.74-1.88 (m, 4 H, Pip), 1.98 (dd, 1 H, *J* = 13.7, 2.4 Hz, H-4), 2.41-2.60 (m, 4 H, 2 H Pip + H-4 + CH<sub>2</sub>-Pip), 2.87 (dd, 1 H, *J* = 14.7, 2.8 Hz, CH<sub>2</sub>-Pip), 2.99 (m, 1 H, Pip), 3.44 (m, 1 H, Pip), 4.15 (dd, 1 H, *J* = 4.6, 2.3 Hz, H-3), 4.40 (ddd, 1 H, *J* = 10.1, 4.3, 2.3 Hz, H-5), 4.74 (d, 1 H, *J* = 2.1 Hz, H-2), 6.85 (br s, 1 H, OH), 6.99 (app t, 2 H, *J* = 8.8 Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 7.15-7.24 (m, 5 H, Ph), 7.34 (app dd, 2 H, *J* = 8.3, 5.5 Hz, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>). <sup>13</sup>C NMR (50 MHz) δ 33.2, 39.3 (CH<sub>2</sub>-4), 41.8, 57.4, 57.6, 61.2, 72.6 (CH), 77.4 (CH), 85.7 (CH), 114.8 (2 CH-3', 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 21.4 Hz), 126.3 (CH Ph), 126.9 (2 CH Ph), 128.3 (2 CH-2', 4-F-C<sub>6</sub>H<sub>4</sub>), 128.4 (2 CH Ph), 133.6 (C-1', 4-F-C<sub>6</sub>H<sub>4</sub>), 145.6 (C Ph), 162.1 (C-4', 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 244.5 Hz). IR (KBr): 3058, 2943, 2826, 1603, 1512, 1215, 1065, 775, 759, 701 cm<sup>-1</sup>. MS (ES): 356 [M+1]<sup>+</sup> (100%). Anal. Calcd for C<sub>22</sub>H<sub>26</sub>NO<sub>2</sub>F: C, 74.34; H, 7.37; N, 3.94. Found: C, 74.01; H, 7.18; N, 3.73.

**Synthesis of (2*S*\*,3*S*\*,5*S*\*)-2-(4-fluorophenyl)-5-(*N*-methylpiperazino)methyltetrahydrofuran-3-ol (4c).** From mesylate (**2**) (33 mg, 0.11 mmol, 1.0 equiv) in *N*-methylpiperazine (2 mL/mmol), according to the general procedure (80 °C, 6 h), amino alcohol (**4c**) was obtained. Purification by chromatography (CH<sub>2</sub>Cl<sub>2</sub>-1:9:90 NH<sub>4</sub>OH-EtOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 22 mg (66%) of **4c** as a pale yellow oil. Data for **4c**: *R<sub>f</sub>* = 0.06 (9:1:90 EtOH-NH<sub>4</sub>OH-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz) δ 1.91 (dd, 1 H, *J* = 13.7, 2.4 Hz, H-4), 2.25 (s, 3 H, CH<sub>3</sub> piperazino), 2.41-2.68 (m, 5 H, 4 CH<sub>2</sub> piperazino + CH<sub>2</sub>-Pip), 2.84 (dd, 1 H, *J* = 14.7, 2.8 Hz, CH<sub>2</sub>-piperazino), 2.94 (br s, 1 H, OH), 4.15 (dd, 1 H, *J* = 4.5, 2.2 Hz, H-3), 4.37 (ddm, 1 H, *J* = 10.1, 2.0 Hz, H-5), 4.72 (s, 1 H, H-2), 7.00 (app t, 2 H, *J* = 8.8 Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 7.26-7.33 (m, 2 H, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>). <sup>13</sup>C NMR (50 MHz)-DEPT δ 39.3 (CH<sub>2</sub>-4), 45.7 (CH<sub>3</sub> piperazino), 54.6 (2 CH<sub>2</sub> piperazino), 56.0 (2 CH<sub>2</sub> piperazino), 61.0 (CH<sub>2</sub>-piperazino), 72.5 (CH), 77.2 (CH), 85.5 (CH-2), 114.2 (2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 21.4 Hz), 128.2 (2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 8.0 Hz), 133.6 (C-1' 4-F-C<sub>6</sub>H<sub>4</sub>), 162.0 (C-4' 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 244.9 Hz). IR (film): 3391, 2936, 2804, 1606, 1511, 1457, 1220, 1063, 777 cm<sup>-1</sup>. MS (ES): 295 [M+1]<sup>+</sup> (100%). Anal. Calcd for C<sub>16</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>F: C, 65.28; H, 7.88; N, 9.52. Found: C, 65.43; H, 7.64; N, 9.75.

**Synthesis of the mesylate of (2*S*\*,3*S*\*,5*S*\*)-5-benzylaminomethyl-2-(4-fluorophenyl)tetrahydrofuran-3-ol (6a).** From bismesylate (**3**) (92 mg, 0.25 mmol, 1.0 equiv) in EtOH (2 mL/mmol) with benzylamine (0.27 mL, 2.5 mmol, 10.0 equiv), according to the general procedure (70 °C, 23 h), aminomesylate (**6a**) was obtained. Purification by chromatography (0-5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 88 mg



(93%) of aminomesylate **6a** as a pale yellow oil. Data for **6a**:  $R_f = 0.22$  (5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz)  $\delta$  1.73 (br s, 1 H, NH), 2.20 (dd, 1 H,  $J = 14.6, 6.0$  Hz, H-4), 2.34 (s, 3 H, CH<sub>3</sub> Ms), 2.60 (ddd, 1 H,  $J = 14.6, 8.4, 6.3$  Hz, H-4), 2.87 (dd, 1 H,  $J = 12.3, 4.1$  Hz, CH<sub>2</sub>-NHBn), 2.96 (dd, 1 H,  $J = 12.3, 7.4$  Hz, CH<sub>2</sub>-NHBn), 3.84 (d, 1 H,  $J = 13.3$  Hz, CH<sub>2</sub> Bn), 3.90 (d, 1 H,  $J = 13.3$  Hz, CH<sub>2</sub>-Bn), 4.26 (m, 1 H, H-5), 4.88 (d, 1 H,  $J = 3.7$  Hz, H-2), 5.22 (ddd, 1 H,  $J = 6.2, 3.8, 1.6$  Hz, H-3), 7.03 (app t, 2 H,  $J = 8.7$  Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 7.32-7.37 (m, 7 H, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>+ Ph). <sup>13</sup>C NMR (50 MHz)  $\delta$  37.6, 37.8, 53.3 (CH<sub>2</sub>), 53.8 (CH<sub>2</sub>-Ph), 77.5 (CH-5), 82.1 (CH), 83.2 (CH), 115.1 (2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 21.4$  Hz), 127.0 (CH Ph), 128.1 (2 CH Ph), 128.4 (2 CH Ph), 128.9 (2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 8.0$  Hz), 131.3 (C-1' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 3.4$  Hz), 140.1 (C Ph), 162.5 (C-4' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 246.8$  Hz). IR (film): 3021, 2935, 1607, 1512, 1356, 1223, 1173, 1071, 916, 838 cm<sup>-1</sup>. MS (ES): 380 [M+1]<sup>+</sup> (100%). Anal. Calcd for C<sub>19</sub>H<sub>22</sub>NO<sub>4</sub>FS: C, 60.14; H, 5.84; N, 3.69. Found: C, 59.85; H, 6.06; N, 3.38.

**Synthesis of the mesylate of (2S\*,3S\*,5S\*)-2-(4-fluorophenyl)-5-(4-phenylpiperidino)methyltetrahydrofuran-3-ol (6b).** From bismesylate (**3**) (92 mg, 0.25 mmol, 1.0 equiv) in DMF (2 mL/mmol) with 4-phenylpiperidine (202 mg, 1.25 mmol, 5.0 equiv), according to the general procedure (70 °C, 20 h), aminomesylate (**6b**) was obtained. Purification by chromatography (0-5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 78 mg (72%) of aminomesylate (**6b**) as a pale yellow oil and 10 mg (9%) of starting material. Data for **6b**:  $R_f = 0.27$  (5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz)  $\delta$  1.82 (m, 5 H, Pip), 2.18 (dd, 1 H,  $J = 6.2, 1.9$  Hz, CH<sub>2</sub>-4), 2.22 (m, 2 H, Pip), 2.35 (s, 3 H, CH<sub>3</sub> Ms), 2.63-2.73 (m, 2 H, CH<sub>2</sub>-4 + CH<sub>2</sub>-Pip), 2.80 (dd, 1 H,  $J = 13.3, 6.8$  Hz, CH<sub>2</sub>-Pip), 3.07 (m, 1 H, Pip), 3.21 (m, 1 H, Pip), 4.31 (m, 1 H, H-5), 4.89 (d, 1 H,  $J = 3.9$  Hz, H-2), 5.23 (ddd, 1 H,  $J = 6.3, 3.9, 1.8$  Hz, H-3), 7.05 (app t, 2 H,  $J = 8.7$  Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 7.15-7.31 (m, 5 H, Ph), 7.38 (app dd, 2 H,  $J = 8.3, 5.4$  Hz, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>). <sup>13</sup>C NMR (75 MHz)-DEPT  $\delta$  33.3 (CH<sub>2</sub>), 33.4 (CH<sub>2</sub>), 37.8 (CH<sub>3</sub> Ms), 38.9 (CH<sub>2</sub>-4), 42.4 (CH Pip), 54.7 (CH<sub>2</sub>), 55.5 (CH<sub>2</sub>), 63.5 (CH<sub>2</sub>-Pip), 76.6 (CH), 82.1 (CH), 83.4 (CH), 115.1 (2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 21.7$  Hz), 126.1 (CH Ph), 126.8 (2 CH Ph), 128.4 (2 CH Ph), 129.0 (2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 8.1$  Hz), 131.5 (C-1' 4-F-C<sub>6</sub>H<sub>4</sub>), 146.3 (C Ph), 162.9 (C-4' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 246.8$  Hz). IR (film): 2927, 1663, 1602, 1512, 1355, 1223, 1174, 1067, 916, 757 cm<sup>-1</sup>. MS (ES): 434 [M+1]<sup>+</sup> (100%). Anal. Calcd for C<sub>23</sub>H<sub>28</sub>NO<sub>4</sub>FS: C, 63.72; H, 6.51; N, 3.23. Found: C, 63.49; H, 6.27; N, 3.02.

**Synthesis of the mesylate of (2S\*,3S\*,5S\*)-2-(4-fluorophenyl)-5-(N-methylpiperazino)methyltetrahydrofuran-3-ol (6c).** From bismesylate (**3**) (92 mg, 0.25 mmol, 1.0 equiv) in EtOH (2 mL/mmol) with N-methylpiperazine (0.28 mL, 2.5 mmol, 10.0 equiv), according to the general procedure (70 °C, 23 h), aminomesylate (**6c**) was obtained. Purification by chromatography (0-15% EtOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 63 mg (68%) of aminomesylate **6c** as a pale yellow oil. Data for **6c**:  $R_f = 0.08$  (9:1:90 EtOH-NH<sub>4</sub>OH-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz)  $\delta$  2.20 (ddd, 1 H,  $J = 14.5, 6.1, 1.7$  Hz, H-4), 2.30 (s, 3 H, CH<sub>3</sub>

piperazino), 2.36 (s, 3 H, CH<sub>3</sub> Ms), 2.49 (m, 2 H, 2 H piperazino), 2.59-2.83 (m, 9 H, 6 H piperazino + CH<sub>2</sub>-piperazino + H-4), 4.29 (m, 1 H, H-5), 4.89 (d, 1 H, *J* = 3.7 Hz, H-2), 5.23 (ddd, 1 H, *J* = 6.0, 3.8, 1.8, H-3), 7.06 (app t, 2 H, *J* = 8.7 Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 7.38 (app dd, 2 H, *J* = 8.4, 5.3 Hz, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>). <sup>13</sup>C NMR (50 MHz) δ 18.4 (CH<sub>3</sub> Ms), 38.6 (CH<sub>2</sub>), 45.9 (CH<sub>3</sub> piperazino), 53.7 (2 CH<sub>2</sub> piperazino), 55.0 (2 CH<sub>2</sub> piperazino), 62.9 (CH<sub>2</sub>-piperazino), 76.6 (CH), 82.0 (CH), 83.3 (CH), 115.0 (2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 21.4 Hz), 128.8 (2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 8.0 Hz), 131.4 (C-1' 4-F-C<sub>6</sub>H<sub>4</sub>), 162.5 (C-4' 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 246.8 Hz). IR (film): 2938, 2804, 1682, 1600, 1512, 1458, 1354, 1173, 1063, 1013, 969, 917, 838 cm<sup>-1</sup>. Anal. Calcd for C<sub>17</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub>FS: C, 54.82; H, 6.77; N, 7.52. Found: C, 55.14; H, 6.41; N, 7.76.

**Synthesis of the mesylate of (2*S*\*,3*S*\*,5*S*\*)-2-(4-fluorophenyl)-5-(piperidinomethyl)tetrahydrofuran-3-ol (6d).** From bismesylate (**3**) (33 mg, 0.11 mmol, 1.0 equiv) in piperidine (2 mL/mmol), according to the general procedure (70 °C, 8 h), aminomesylate (**6d**) was obtained. Purification by chromatography (0-5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 44 mg (82%) of aminomesylate **6d** as a pale yellow oil. Data for **6d**: *R*<sub>f</sub> = 0.09 (5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz) δ 1.41 (m 2 H, Pip), 1.56 (m, 4 H, Pip), 2.15 (ddd, 1 H, *J* = 14.6, 6.3, 1.9 Hz, CH<sub>2</sub>-4), 2.34 (s, 3 H, CH<sub>3</sub> Ms), 2.38-2.66 (m, 6 H, 4 H Pip+CH<sub>2</sub>-4+CH<sub>2</sub>-Pip), 2.71 (dd, 1 H, *J* = 13.3, 6.8 Hz, CH<sub>2</sub>-Pip), 4.25 (dddd, 1 H, *J* = 12.9, 8.2, 6.3, 4.6 Hz, H-5), 4.86 (d, 1 H, *J* = 3.9 Hz, H-2), 5.20 (ddd, 1 H, *J* = 6.1, 3.9, 1.8 Hz, H-3), 7.03 (app t, 2 H, *J* = 8.7 Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 7.35 (dd, 2 H, *J* = 8.9, 5.4 Hz, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>). <sup>13</sup>C NMR (50 MHz)-DEPT δ 24.1 (CH<sub>2</sub> Pip), 25.9 (2 CH<sub>2</sub> Pip), 37.8 (CH<sub>3</sub> Ms), 38.9 (CH<sub>2</sub>-4), 55.3 (2 CH<sub>2</sub> Pip), 63.9 (CH<sub>2</sub>-Pip), 76.6 (CH-5), 82.1 (CH), 83.3 (CH), 115.0 (2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 21.7 Hz), 128.9 (2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 8.0 Hz), 131.5 (C-1' 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 3.1 Hz), 162.5 (C-4' 4-F-C<sub>6</sub>H<sub>4</sub>, *J*<sub>C-F</sub> = 246.8 Hz). IR (film): 2936, 2855, 2782, 1608, 1512, 1354, 1174, 1071, 911, 836 cm<sup>-1</sup>. MS (ES): 358 [M+1]<sup>+</sup>. Anal. Calcd for C<sub>17</sub>H<sub>24</sub>NO<sub>4</sub>FS: C, 57.12; H, 6.77; N, 3.92. Found: C, 57.39; H, 6.93; N, 4.18.

**Synthesis of the mesylate of (2*S*\*,3*S*\*,5*S*\*)-5-anilinomethyl-2-(4-fluorophenyl)tetrahydrofuran-3-ol (6e).** From bismesylate (**3**) (22 mg, 0.06 mmol, 1.0 equiv) in EtOH (5 mL/mmol) with aniline (0.11 mL, 1.20 mmol, 20.0 equiv), according to the general procedure (90 °C, 45 h), aminomesylate (**6e**) was obtained. Purification by chromatography (0-5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 10 mg (46%) of aminomesylate **6e** as a pale yellow oil and 6 mg (27%) of starting material. Data for **6e**: *R*<sub>f</sub> = 0.36 (5% EtOAc-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (200 MHz) δ 2.29 (ddd 1 H, *J* = 14.8, 5.5, 1.5 Hz, CH<sub>2</sub>-4), 2.36 (s, 3 H, CH<sub>3</sub> Ms), 2.68 (ddd, 1 H, *J* = 14.8, 8.8, 6.0 Hz, CH<sub>2</sub>-4), 3.38 (dd, 1 H, *J* = 13.0, 6.8 Hz, CH<sub>2</sub>-NHPh), 3.48 (dd, 1 H, *J* = 13.0, 4.2 Hz, CH<sub>2</sub>-NHPh), 4.09 (br, 1 H, NH), 4.40 (m, 1 H, H-5), 4.93 (d, 1 H, *J* = 3.7 Hz, H-2), 5.26 (ddd, 1 H, *J* = 6.0, 3.5, 1.3 Hz, H-3), 6.64-6.76 (m, 3 H, Ph), 7.05 (app t, 2 H, *J* = 8.7 Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 7.11-7.23 (m, 2 H, Ph), 7.35 (app dd, 2 H, *J* = 8.4, 5.3 Hz, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>). <sup>13</sup>C NMR (50 MHz) δ

37.5, 38.0, 48.1 (CH<sub>2</sub>-NH), 76.7 (CH-5), 82.1 (CH), 83.4 (CH), 113.1 (2 CH-2' Ph), 115.2 (2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 21.5$  Hz), 117.8 (CH-4' Ph), 128.9 (2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 8.1$  Hz), 129.3 (2 CH-3' Ph), 131.1 (C-1' 4-F-C<sub>6</sub>H<sub>4</sub>), 148.0 (C-1' Ph), 162.7 (C-4' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 247.5$  Hz). IR (film): 3370, 3023, 2932, 1692, 1602, 1511, 1441, 1354, 1173, 908, 754 cm<sup>-1</sup>. Anal. Calcd for C<sub>18</sub>H<sub>20</sub>NO<sub>4</sub>FS: C, 59.16; H, 5.52; N, 3.83. Found: C, 59.41; H, 5.24; N, 3.60.

**Synthesis of (2S\*,3R\*,5S\*)-3-anilino-5-anilinomethyl-2-(4-fluorophenyl)tetrahydrofuran (7e).**

From bismesylate (**3**) (92 mg, 0.25 mmol, 1.0 equiv) in 1-butanol (2 mL/mmol) with aniline (0.23 mL, 2.5 mmol, 10.0 equiv), according to the general procedure (115 °C, 23 h), diamine (**7e**) was obtained. Purification by chromatography (0-0.5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 27 mg (30%) of diamine (**7e**) as a pale yellow oil and 18 mg (21%) of aminomesylate (**6e**). Data for **7e**:  $R_f = 0.55$  (5% EtOH-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz) δ 2.03 (ddd 1 H,  $J = 12.8, 6.5, 3.8$  Hz, H-4), 2.23 (dt, 1 H,  $J = 12.8, 8.2$  Hz, H-4), 3.32 (dd, 1 H,  $J = 12.9, 7.0$  Hz, CH<sub>2</sub>-NHPh), 3.47 (dd, 1 H,  $J = 12.9, 3.7$  Hz, CH<sub>2</sub>-NHPh), 3.93 (m, 1 H, H-3), 4.03 (br, 2 H, 2 NH), 4.46 (ddm, 1 H,  $J = 6.6, 3.7$  Hz, H-5), 4.67 (d, 1 H,  $J = 5.1$  Hz, H-2), 6.50 (m, 2 H, Ph), 6.64 (m, 2 H, Ph), 6.72 (m, 2 H, Ph), 7.02 (app t, 2 H,  $J = 8.7$  Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 7.10-7.22 (m, 4 H, Ph), 7.37 (dd, 2 H,  $J = 8.4, 5.4$  Hz, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>). <sup>13</sup>C NMR (50 MHz) δ 36.8 (CH<sub>2</sub>-4), 48.2 (CH-3), 61.5 (CH<sub>2</sub>-NHPh), 77.5 (CH-5), 86.6 (CH-2), 113.1 (2 CH Ph), 113.6 (2 CH Ph), 115.4 (2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 21.4$  Hz), 117.8 (CH Ph), 118.2 (CH Ph), 127.7 (2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 8.0$  Hz), 129.3 (4 CH Ph), 136.4 (C-1' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 3.1$  Hz), 146.6 (C Ph), 148.1 (C Ph), 162.5 (C-4' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 246.1$  Hz). IR (film): 3398, 3050, 2920, 1602, 1507, 1224, 1069, 833, 749, 692 cm<sup>-1</sup>. MS (ES): 363 [M+1]<sup>+</sup> (100%), 270. Anal. Calcd for C<sub>23</sub>H<sub>23</sub>N<sub>2</sub>OF: C, 76.22; H, 6.40; N, 7.73. Found: C, 76.53; H, 6.09; N, 7.98.

**Synthesis of the bistriflate of (2S\*,3S\*,5S\*)-2-(4-fluorophenyl)-5-hydroxymethyltetrahydrofuran-3-ol (11) and (2S\*,3R\*,5S\*)-3-anilino-5-anilinomethyl-2-(4-fluorophenyl)tetrahydrofuran (7e).**

To a cold (0 °C) solution of diol (**1**) (21 mg, 0.1 mmol, 1.0 equiv) in 1 mL of CH<sub>2</sub>Cl<sub>2</sub> was added pyridine (48 μL, 0.60 mmol, 6.0 equiv) and triflic anhydride (84 μL, 0.50 mmol, 5.0 equiv). After 10 min the mixture was quenched with NaHCO<sub>3</sub>, extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 4 mL), the layers were separated, the organic layer was washed with saturated NaCl (4 mL), dried over MgSO<sub>4</sub>, filtered and concentrated to give crude (**11**) that was monitored by <sup>1</sup>H NMR. This crude was dissolved in 0.2 mL of 1-butanol and aniline (0.1 mL, 1 mmol, 10.0 equiv) was added. The reaction mixture was stirred at rt for 5 h, the solvent was removed and the crude was purified by chromatography (50-100% CH<sub>2</sub>Cl<sub>2</sub>-hexane) to afford 18 mg (50% two steps) of diamine (**7e**) as a colorless oil. Data for **11**:  $R_f = 0.61$  (50% EtOAc-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (200 MHz) δ 2.34 (dd, 1 H,  $J = 15.6, 5.7$  Hz, H-4), 2.87 (ddd, 1 H,  $J = 15.6, 8.8, 5.7$  Hz, H-4), 4.54 (m, 1 H, H-5), 4.68 (m, 2 H, CH<sub>2</sub>-OTf), 5.08 (d, 1 H,  $J = 3.1$  Hz, H-2), 5.44 (m, 1 H, H-3), 7.10 (app t, 2 H,

$J = 8.7$  Hz, 4-F-C<sub>6</sub>H<sub>4</sub>), 7.38 (app dd, 2 H,  $J = 8.6, 5.3$  Hz, 4-F-C<sub>6</sub>H<sub>4</sub>).

**Synthesis of (2*S*\*,3*R*\*,5*S*\*)-2-(4-fluorophenyl)-5-(4-phenylpiperidino)methyl-3-piperidinotetrahydrofuran (8b) and 1-(4-fluorophenyl)-4-hydroxy-5-(4-phenylpiperidino)pentan-1-one (9b).**

From aminomesylate (**6b**) (78 mg, 0.18 mmol, 1.0 equiv) in 1-butanol (2 mL/mmol) with piperidine (0.36 mL, 3.6 mmol, 20.0 equiv), according to the general procedure (120 °C, 14 h), diamine (**8b**) was obtained. Purification by chromatography (0-15% EtOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 20 mg (31%) of ring-cleavage product (**9b**) as a colorless oil and 46 mg of impure diamine (**8b**) that had to be purified twice to produce pure (**8b**), 20 mg (26%) as pale yellow oil. Data for **8b**:  $R_f = 0.09$  (15% EtOH-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (200 MHz)  $\delta$  1.20-1.60 (m, 6 H), 1.81 (m, 4 H), 2.20 (m, 4 H), 2.43 (m, 5 H), 2.64 (m, 2 H), 2.96-3.24 (m, 3 H), 4.32 (m, 1 H, H-5), 4.79 (d, 1 H,  $J = 6.2$  Hz, H-2), 6.99 (app t, 2 H,  $J = 8.7$  Hz, 2 CH 4-F-C<sub>6</sub>H<sub>4</sub>), 7.13-7.39 (m, 7 H, 2 CH 4-F-C<sub>6</sub>H<sub>4</sub> + Ph). <sup>13</sup>C NMR (75 MHz)  $\delta$  24.4 (CH<sub>2</sub>), 26.1 (2 CH<sub>2</sub>), 33.3 (CH<sub>2</sub>), 33.4 (CH), 33.6 (CH<sub>2</sub>), 42.5 (CH<sub>2</sub>), 52.1 (2 CH<sub>2</sub>), 54.9 (CH<sub>2</sub>), 55.4 (CH<sub>2</sub>), 64.1 (CH<sub>2</sub>), 72.9 (CH), 82.3 (CH), 115.0 (2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 21.2$  Hz), 126.1 (CH Ph), 126.9 (2 CH Ph), 128.3 (2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 8.1$  Hz), 128.4 (2 CH Ph), 138.5 (C-1' 4-F-C<sub>6</sub>H<sub>4</sub>), 146.4 (C Ph), 162.1 (C-4' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 244.8$  Hz). IR (film): 3021, 2933, 2847, 2797, 1603, 1510, 1453, 1223, 1068, 831, 699 cm<sup>-1</sup>. MS (ES): 423 [M+1]<sup>+</sup> (100%). Anal. calcd for C<sub>27</sub>H<sub>35</sub>FN<sub>2</sub>O: C, 76.74; H, 8.35; N, 6.63. Found: C, 76.35; H, 8.67; N, 6.37. Data for **9b**:  $R_f = 0.20$  (1:2:7 CH<sub>2</sub>Cl<sub>2</sub>-EtOH-NH<sub>4</sub>OH). <sup>1</sup>H NMR (300 MHz)  $\delta$  1.56-1.99 (m, 6 H, CH<sub>2</sub>-3 + 4 H Pip), 2.07 (td, 1 H,  $J = 11.7, 2.6$  Hz, OH), 2.41 (m, 4 H, CH<sub>2</sub>-2 + 2 H Pip), 2.92 (m, 1 H, Pip), 3.10 (ddd, 1 H,  $J = 17.4, 8.3, 6.8$  Hz, H-5), 3.12 (m, 2 H, Pip), 3.21 (ddd, 1 H,  $J = 17.4, 8.3, 5.7$  Hz, H-5), 3.77 (m, 1 H, H-4), 7.11 (dd, 2 H,  $J = 8.9, 8.5$  Hz, 2 CH 4-F-C<sub>6</sub>H<sub>4</sub>), 7.15-7.31 (m, 5 H, Ph), 8.01 (dd, 2 H,  $J = 8.9, 5.4$  Hz).

**Synthesis of (2*S*\*,3*R*\*,5*S*\*)-3-benzylamino-2-(4-fluorophenyl)-5-piperidinomethyltetrahydrofuran (8d) and 1-(4-fluorophenyl)-4-hydroxy-5-piperidinopentan-1-one (9d).**

From amino mesylate (**6d**) (94 mg, 0.26 mmol, 1.0 equiv) in 1-butanol (2 mL/mmol) with benzylamine (0.57 mL, 5.26 mmol, 20.0 equiv), according to the general procedure (110 °C, 7 h; 120 °C 16 h), followed by removal of 1-butanol and addition of benzylamine (2 mL/mmol) and further heating (120 °C, 5 h), diamine (**8d**) was obtained. Purification by chromatography (twice, 0-20% EtOH-CH<sub>2</sub>Cl<sub>2</sub>) afforded 34 mg (47%) of ring-cleavage product (**9d**) as a colorless oil and 20 mg (< 21%) of impure diamine (**8d**) as a pale yellow oil. Partial data for **8d**:  $R_f = 0.08$  (15% EtOH-CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (300 MHz)  $\delta$  1.88 (dt, 1 H,  $J = 12.8, 8.2$  Hz, H-4), 2.04 (m, 1 H, H-4), 3.16 (m, 1 H, H-3), 3.70 (d, 1 H,  $J = 13.3$  Hz, CH<sub>2</sub> Bn), 3.75 (d, 1 H,  $J = 13.3$  Hz, CH<sub>2</sub> Bn), 4.54 (m, 1 H, H-5), 4.62 (d, 1 H,  $J = 5.5$  Hz, H-2). Data for **9d**:  $R_f = 0.22$  (7:2:1 CH<sub>2</sub>Cl<sub>2</sub>-EtOH-NH<sub>4</sub>OH). <sup>1</sup>H NMR (200 MHz)  $\delta$  1.43 (m 2 H, Pip), 1.56 (m, 4 H, Pip), 1.62 (m, 1 H, H-3), 1.89 (dddd, 1 H,  $J = 14.0, 8.5, 6.7, 3.2$  Hz, H-3), 2.24 (dd, 1 H,  $J = 12.3, 10.0$  Hz, H-5), 2.35 (dd, 1

H,  $J = 12.3, 3.7$  Hz, H-5), 2.21-2.35 (m, 2 H, Pip), 2.55-2.65 (m, 2 H, Pip), 3.07 (ddd, 1 H,  $J = 17.4, 8.1, 6.7$  Hz, H-2), 3.20 (ddd, 1 H,  $J = 17.4, 8.6, 5.8$  Hz, H-2), 3.72 (m, 1 H, H-4), 7.10 (app t, 2 H,  $J = 8.6$  Hz, 2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>), 8.00 (dd, 2 H,  $J = 6.8, 5.4$  Hz, 2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>). Partial <sup>13</sup>C NMR (50 MHz) data  $\delta$  29.9 (CH<sub>2</sub>-3), 25.6 (2 CH<sub>2</sub> Pip), 28.9 (CH<sub>2</sub> Pip), 34.5 (CH<sub>2</sub>-2), 54.5 (2 CH<sub>2</sub> Pip), 64.5 (CH<sub>2</sub>-5), 65.2 (CH-4), 115.5 (2 CH-3' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 21.8$  Hz), 130.5 (2 CH-2' 4-F-C<sub>6</sub>H<sub>4</sub>,  $J_{C-F} = 9.2$  Hz). IR (film): 3358, 2953, 2855, 1683, 1598, 1507, 1453, 1224, 1156, 1039, 840, 698 cm<sup>-1</sup>. MS (ES): 280 [M+1]<sup>+</sup> (100%). Anal. Calcd for C<sub>16</sub>H<sub>22</sub>NO<sub>2</sub>F: C, 68.79; H, 7.94; N, 5.01. Found: C, 68.93; H, 7.61; N, 5.27.

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## REFERENCES AND NOTES

1. AZT: (a) H. Mitsuya, K. J. Weinhold, P. A. Furman, M. H. St. Clair, S. N. Lehrman, R. C. Gallo, D. Bolognesi, D. W. Barry, and S. Broder, *Proc. Natl. Acad. Sci. U.S.A.*, 1985, **82**, 7096. Puromycins: (b) M. S. Motawia, M. Meldal, M. Sofan, P. Stein, E. B. Pedersen, and C. Nielsen, *Synthesis*, 1995, 265 and references cited therein. Isonucleosides: (c) D. M. Huryn, B. C. Sluboski, S. Y. Tam, L. J. Todaro, and M. Weigle, *Tetrahedron Lett.*, 1989, **30**, 6259 (d) V. Nair and Z. M. Nuesca, *J. Am. Chem. Soc.*, 1992, **114**, 7951. (e) Y. Díaz, F. Bravo, and S. Castellón, *J. Org. Chem.*, 1999, **64**, 6508. C-nucleosides: (f) B. Doboszewski, C. K. Chu, and H. V. Halbeek, *J. Org. Chem.*, 1988, **53**, 2777. (g) E. Sochacka, B. Nawrot, K. W. Pankiewicz, and K. A. Watanabe, *J. Med. Chem.*, 1990, **33**, 1995. (h) V. Jeanneret, F. Gasparini, P. Péchy, and P. Vogel, *Tetrahedron*, 1992, **48**, 10637. (i) L. Kværnø, R. H. Wightman, and J. Wengel, *J. Org. Chem.*, 2001, **66**, 5106. Imifuramine: (j) S. Harusawa, T. Imazu, S. Takashima, L. Araki, H. Ohishi, T. Kurihara, Y. Sakamoto, Y. Yamamoto, and A. Yamatodani, *J. Org. Chem.*, 1999, **64**, 8608. Pachastrissamine: (k) N. Sudhakar, A. R. Kumar, A. Prabhakar, B. Jagadeesh, and B. V. Rao, *Tetrahedron Lett.*, 2005, **46**, 325. (l) P. Bhaket, K. Morris, C. S. Stauffer, and A. Datta, *Org. Lett.*, 2005, **7**, 875. (m) Y. Du, J. Liu, and R. J. Linhardt, *J. Org. Chem.*, 2006, **71**, 1251. (n) C. Ribes, E. Falomir, M. Carda, and J. A. Marco, *Tetrahedron*, 2006, **62**, 5421. For tetracyclic aminotetrahydrofurans with CNS activity, see: (o) J. M. Bartolomé, A. Alcudia, J. I. Andrés, J. M. Cid, M. García, A. Megens, M. A. Toledo, and A. A. Trabanco, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2898 and previous papers by this group.
2. Muscarine is an acetylcholine mimetic; there are many subtypes of muscarinic receptors and a connection between low levels of acetylcholine and Alzheimer's disease has been proposed. See: (a) P.-C. Wang and M. M. Joullié, *The Alkaloids*, ed. by A. Brossi, Academic Press, 1984, **23**, 327. (b)

- W. Z. Antkowiak and R. Antkowiak, *The Alkaloids*, ed. by A. Brossi, Academic Press, 1991, **23**, 189.
- (c) Z. Jin, *Nat. Prod. Rep.*, 2005, **22**, 196 and references cited therein. (d) R. Dahlbom, *Stereoselectivity of Cholinergic and Anticholinergic Agents, in Stereochemistry and Biological Activity of Drugs*, ed. by E. J. Ariëns, Blackwell Scientific, Oxford, 1983, pp. 127-142. (e) R. Baker and J. Saunders, *Ann. Rep. Med. Chem.*, 1989, **24**, 31. (f) A. Fisher, R. Brandeis, I. Karton, Z. Pittel, S. Dachir, M. Sapir, Y. Grunfeld, A. Levy, and E. Heldman, *Novel Approaches to the Treatment of Alzheimer's Disease, in Advances in Behavioral Biology*, ed. by E. M. Meyer, J. W. Simpkins, and J. Yamamoto, Plenum Press, New York, 1989, vol. 36, p. 11.
- For recent references, see: (a) D. W. Knight, D. E. Shaw, and E. R. Staples, *Eur. J. Org. Chem.*, 2004, 1973 and references cited therein. (b) J. Hartung, P. Kunz, S. Laug, and P. Schmidt, *Synlett*, 2003, 51 and references cited therein.
  - R. Fernández de la Pradilla, P. Manzano, C. Montero, J. Priego, M. Martínez-Ripoll, and L. A. Martínez-Cruz, *J. Org. Chem.*, 2003, **68**, 7755.
  - Several muscarine analogs, including isomuscarines, hydroxymuscarines, epoxymuscarines, 3-deoxy-3-fluoromuscarines, 5-benzylaminomuscarines, have been prepared before, see: (a) P.-C. Wang and M. M. Joullié, *J. Org. Chem.*, 1980, **45**, 5359. (b) J. Kuzsmann and P. Dvortsák, *Carbohydr. Res.*, 1983, **123**, 209. (c) S. J. Mantell, P. S. Ford, D. J. Watkin, G. W. J. Fleet, and D. Brown, *Tetrahedron*, 1993, **49**, 3343. (d) J. Kuzsmann, *Carbohydr. Res.*, 1985, **142**, 71. (e) G. Shapiro, D. Buechler, and S. Hennet, *Tetrahedron Lett.*, 1990, **31**, 5733. (f) P. Bravo, G. Resnati, P. Angeli, M. Frigerio, F. Viani, A. Arnone, G. Marucci, and F. Cantalamessa, *J. Med. Chem.*, 1992, **35**, 3102. (g) J. C. Norrild and C. Pedersen, *Synthesis*, 1997, 1128. (h) V. Popsavin, M. Popsavin, L. Radić, O. Berić, and V. Ćirin-Novta, *Tetrahedron Lett.*, 1999, **40**, 9305.
  - (a) R. Fernández de la Pradilla, C. Montero, J. Priego, and L. A. Martínez-Cruz, *J. Org. Chem.*, 1998, **63**, 9612. (b) R. Fernández de la Pradilla, C. Alhambra, A. Castellanos, J. Fernández, P. Manzano, C. Montero, M. Ureña, and A. Viso, *J. Org. Chem.*, 2005, **70**, 10693.
  - At this point the origin of the lack of stability of this tetrahydrofurfurylamine remains unclear and may be tentatively attributed to intramolecular oxirane cleavage with formation of an unstable ammonium species that evolves into a complex mixture of products.
  - Diol (**1**) was obtained in good yield as described in ref. 6(b) by treatment of the sulfonyloxirane precursor with (PhSe)<sub>2</sub> in the presence of an excess of NaBH<sub>4</sub> in EtOH (90%, 85:15 mixture at the secondary alcohol).
  - To rule out free radical processes occurring at these elevated temperatures, some experiments were carried out again in the presence of the free radical inhibitor BHT but this led to no significant changes in yields and ratios.