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Synthesis of enantiomerically pure (*S*)- and (*R*)-fluoxetine (Prozac®) via a hetero Diels–Alder strategy

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Abstract—A new route to enantiomerically pure (*R*)- and (*S*)-fluoxetine is described using a hetero Diels-Alder strategy.

1. Introduction

Fluoxetine, marketed as racemate under the trade name Prozac®, is a potent and highly selective inhibitor of neutral serotonin-reuptake and is among the most important drugs for the treatment of psychiatric disorders and metabolic problems.[1] Due to its market value and the different pharmacological activities displayed by analogues of fluoxetine, several synthetic methods, including the enantioselective synthesis of both enantiomers, have been reported.[2–4] To the best of our knowledge, there has been no report in the literature about the synthesis of fluoxetine in racemic or enantiomerically pure form, using a hetero Diels–Alder strategy.[5–9] As part of our ongoing research program on hetero Diels–Alder reactions for the synthesis of useful intermediates in the preparation of biologically active molecules, using as a diene counterpart azadiene **1**, we anticipated that a hetero Diels–Alder (HDA) strategy would represent a powerful tool in the synthesis of a three carbon-chain segment[10] characterized by the presence at positions 1 and 3 of the amino and hydroxy functionalities. Moreover, this strategy may offer considerable opportunities for synthetic manipulations, including the building-up of a library of analogues of fluoxetine. Herein we report our preliminary results on the synthesis of enantiomerically pure (*S*)- and (*R*)-fluoxetine.

2. Results and discussion

Our strategic plane starts from the synthesis[11–13] of azadiene **1** prepared according to an already described procedure.[14–18] Reaction of diene **1** with benzaldehyde under BF_3-etherate mediated reaction conditions, gave rise to four isomeric products **2**, **3**, **4** and **5** in 82% combined yields (Scheme 1). Flash chromatography of the crude reaction mixture allowed the separation of the two couples of diastereomeric Diels–Alder adducts: the adducts **2** and **3** and the adducts **4** and **5** (Scheme 1). All attempts to isolate the epimeric couples of perhydroxazin-2-ones (**2** from **3** and **4** from **5**), although immaterial in our strategic plane (see below), failed so far. Careful analysis by ^{1}H NMR, NOE's experiments,[19] GC–mass spectra of the two diastereomeric couples allowed the attribution to each isomer of the structure depicted in Scheme 1.[20] The diastereoselectivity of the initial Diels–Alder cycloaddition looks very poor. This lack of diastereoselectivity could be explained assuming that the formation of the cycloadducts takes place via a competitive stepwise mechanism.[21] Final confirmation of the exact attribution was obtained by processing each couple (**2**, **3** and **4**, **5**) to the known aminols **14** and **15**. It is clear that each couple of epimers was characterized by the same absolute configuration at the C-6 stereocentre and a different configuration at the C-2 stereocentre (Scheme 1). This different configuration of the C-2 stereocentre is irrelevant to our strategic plan since the stereocentre in C-2 will be destroyed in the final step (Scheme 2). Elaboration of the two epimeric mixtures to (*S*) and (*R*)-fluoxetine was

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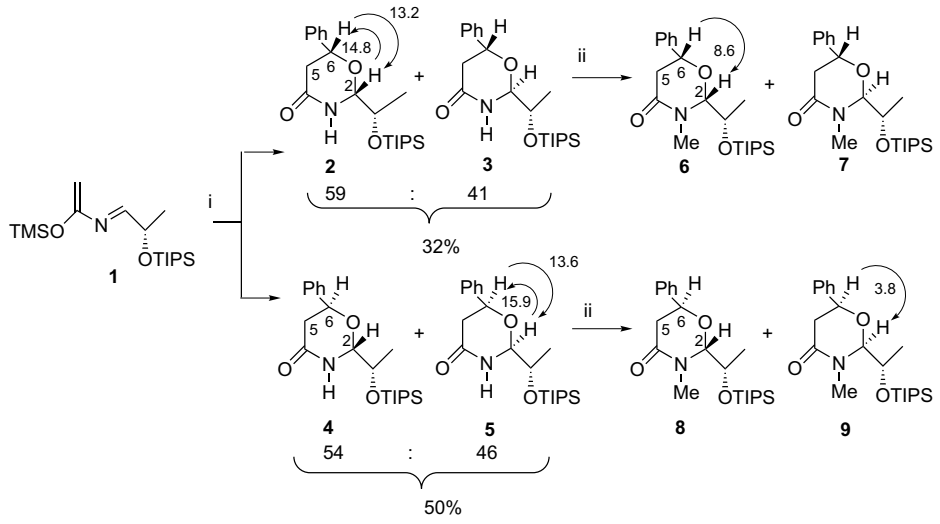
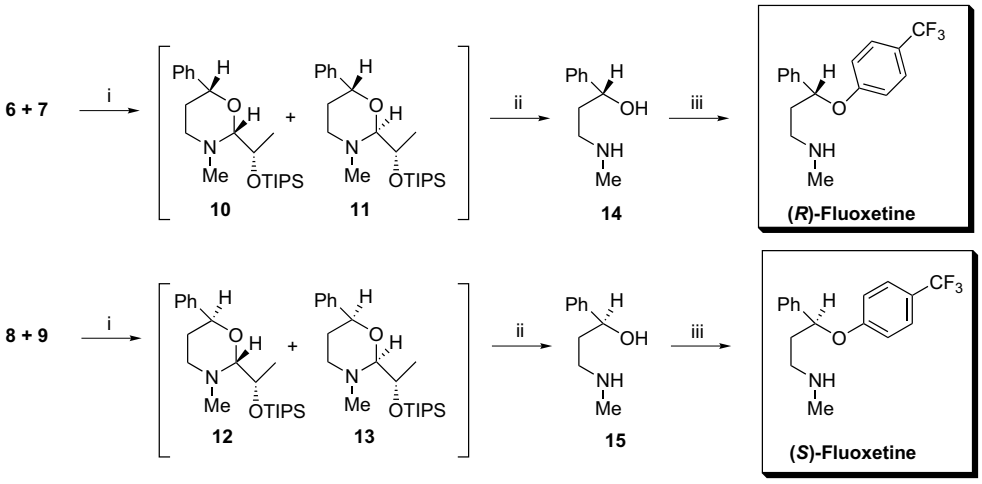


Scheme 1. Reagents and conditions: (i) BF_3, PhCHO, CH_2Cl_2, −78 °C to rt; (ii) LiHDSA, MeI, THF, 0 °C.



Scheme 2. Reagents and conditions: (i) Ph_2SiH_2, $RhH(CO)(PPh_3)_3$; (ii) HCl_{aq}; (iii) 4-Cl-Benzotrifluoride, NaH, DMSO, Ref. 23.

our next task. Accordingly, epimeric mixtures of compounds **2** and **3**, and **4** and **5** were treated with LiHMDSA and methyl iodide in order to get the corresponding *N*-methyl derivatives **6**, **7** and **8**, **9** in quantitative yields. Reduction of carboxy functionality occurred with diphenyl silane in the presence of catalytic amount of tris(triphenylphosphine)rhodium(I) carbonyl hydride[22] to give the perhydrooxazines, respectively, in yields up to 98%. Due to their relative instability, the crude reaction mixtures of **10**, **11** and **12**, **13** were used as such in the next step of our process. Accordingly, final mild ring opening of these compounds by means of diluted HCl furnished the enantiomerically pure (1*R*)-amino alcohol **14** presenting super imposable spectroscopic properties, including $[\alpha]_D$, with the literature data, in 60% (for amino alcohol **14**) and 67% (for amino alcohol **15**) overall yields based on the epimeric mixtures **2** and **3**, and **4** and **5**, respectively. Final conversion of intermediates **14** and **15** to the title compounds was achieved according to literature procedures.[23]

3. Conclusion

In conclusion we have developed a straightforward convergent synthesis of both enantiomers of fluoxetine by a hetero Diels–Alder approach. As anticipated, we feel that this approach is highly adaptable to a parallel synthesis of 3-amino-1-propanol derivatives and allows the introduction of high molecular diversity at position 1 of the carbonic skeleton and in the choice of the *N*- and *O*-substituents in the final compounds. Work in this field, as well as developing high stereocontrol in the first step of our strategic plan is currently underway.

4. Experimental

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian 200 MHz or on Varian Gemini 300 MHz or on Varian Mercury 400 MHz spectrometers. Chemical shifts are reported in the δ scale and coupling

constants (J) reported in hertz. Infrared spectra were recorded on a Perkin–Elmer spectrum BX spectrophotometer. Mass spectra were recorded on Finnigan MAT GCQ spectrometer. Solvents were distilled according to standard procedure before use.

4.1. (2*R*,6*R*)-2-((*S*)-1-Triisopropylsilyloxyethyl)-6-phenyl-1,3-oxazinan-4-one 2, (2*S*,6*R*)-2-((*S*)-1-triisopropylsilyloxyethyl)-6-phenyl-1,3-oxazinan-4-one 3, (2*R*,6*S*)-2-((*S*)-1-triisopropylsilyloxyethyl)-6-phenyl-1,3-oxazinan-4-one 4 and (2*S*,6*S*)-2-((*S*)-1-triisopropylsilyloxyethyl)-6-phenyl-1,3-oxazinan-4-one 5

A solution of (2*S*)-2-(triisopropylsilyloxy)-*N*-(trimethylsilyl) propanimine was prepared by the dropwise addition of lithium bis(trimethylsilyl)amide (1 M in THF, 1.10 mmol, 1.10 mL) to a cooled (0 °C) hexane solution (5 mL) of (2*S*)-2-(triisopropylsilyloxy)propionaldehyde (0.23 g, 1.00 mmol). The reaction mixture was stirred for 40 min at the same temperature. Trimethylsilyl chloride (1.10 mmol, 0.15 mL) was added in one portion and this solution stirred for 15 min at 0 °C and then for 1 h at room temperature. The mixture was cooled at 0 °C and triethylamine (2.20 mmol, 0.30 mL) added in one portion. After stirring this mixture for 5 min at 0 °C, acetyl chloride (1.10 mmol, 78 μL) was slowly added by syringe. Stirring was maintained for 15 min at 0 °C and then 1.5 h at room temperature. The yellow solution was filtered through Celite and the solvent removed in vacuo to give 3-trimethylsilyloxy-2-azadiene **1** as a yellow oil. IR (neat, cm^{-1}): 2944, 2867, 1684, 1577, 1464. ^1H NMR (300 MHz, $CDCl_3$), δ: 7.83 (d, 1H, $J = 6.0$ Hz), 4.45 (m, 1H), 4.42 (s, 1H), 4.19 (s, 1H), 1.34 (d, 3H, $J = 6.6$ Hz), 1.02 (m, 21H), 0.21 (s, 9H).

To a cooled (−78 °C) solution of PhCHO (1.00 mmol, 0.102 mL) in CH_2Cl_2 (10 mL) was added BF_3–Et_2O (1.00 equiv, 0.160 mL). The mixture was stirred for 10 min and then 3-trimethylsilyloxy-2-azadiene **1** (2.0 equiv, 2.00 mmol in 5 mL of CH_2Cl_2) slowly added. The reaction mixture was stirred for 8 h while the temperature was allowed to reach room temperature. The reaction was quenched with a saturated solution of $NaHCO_3$ (aq), extracted with CH_2Cl_2, the organic phase dried over Na_2SO_4 and the solvent removed in vacuo. The crude reaction mixture was chromatographed on silica gel (eluents cyclohexane/ethyl acetate 6/4) and the oily products separated as the couple of diastereoisomers **2**, **3** and **4**, **5** in a 40:60 ratio and 82% overall yield. Within each couple the ratio between the two isomers was 59:41 for the **2**, **3** couple and 54:46 for the **4**, **5** couple.

A careful analysis of the ^1H and ^{13}C NMR (400 MHz), making large use of decoupling and NOE's technique allowed the attributions of each series of signals to the corresponding isomer.

Compound **2**: IR (neat, cm^{-1}): 3201, 2942, 2866, 1675, 1463; ^1H NMR (400 MHz, $CDCl_3$), δ: 7.30 (m, 5H), 6.37 (br s, 1H), 5.07 (d, 1H, $J = 3.6$ Hz), 4.86 (dd, 1H, $J_1 = 4.4$, $J_2 = 10.8$ Hz), 4.19 (dq, 1H, $J_1 = 3.6$, $J_2 = 6.0$ Hz), 2.68 (dd, 1H, $J_1 = 4.4$, $J_2 = 17.6$ Hz), 2.61 (dd, 1H, $J_1 = 10.8$, $J_2 = 17.6$ Hz), 1.24 (d, 3H, $J = 6.0$ Hz), 1.06 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 168.73, 139.61, 128.72, 128.39, 125.56, 84.88, 76.09, 68.64, 39.75, 17.95, 15.74, 12.08; MS (*m*/*z*): 378, 334, 316, 202, 188, 131.

Compound **3**: IR (neat, cm^{-1}): 3201, 2942, 2866, 1675, 1463; ^1H NMR (400 MHz, $CDCl_3$), δ: 7.37 (m, 5H), 6.39 (br s, 1H), 5.14 (pt, 1H, $J = 5.6$ Hz), 4.36 (dd, 1H, $J_1 = 1.2$, $J_2 = 6.4$ Hz), 3.97 (qt, 1H, $J = 6.4$ Hz), 2.85 (dd, 1H, $J_1 = 5.6$, $J_2 = 16.8$ Hz), 2.75 (dd, 1H, $J_1 = 6.4$, $J_2 = 16.8$ Hz), 1.23 (d, 3H, $J = 6.4$ Hz), 1.06 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 168.46, 138.66, 128.72, 128.39, 126.53, 83.32, 72.16, 70.54, 36.53, 19.69, 18.05, 12.51; MS (*m*/*z*): 334, 202, 187 131.

4.2. (2*R*,6*S*)-*tert*-Butyl 2-((*S*)-1-triisopropylsilyloxyethyl)-4-oxo-6-phenyl-1,3-oxazinane-3-carboxylate 16 and (2*S*,6*S*)-*tert*-butyl 2-((*S*)-1-triisopropylsilyloxyethyl)-4-oxo-6-phenyl-1,3-oxazinane-3-carboxylate 17

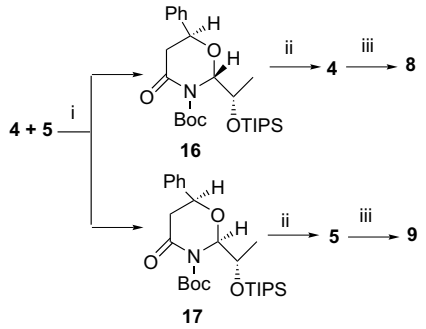
t-Boc derivatives were obtained, in quantitative yields, by the addition of *t*-Boc anhydride (2.0 equiv, 436 mg), TEA (2.0 equiv, 0.3 mL) and DMAP (cat.) to a CH_2Cl_2 (10 mL) solution of perhydrooxazin-2-one **4** and **5** (1.00 mmol, 377 mg) at room temperature. The solution obtained was stirred for 12 h. The reaction was quenched with a saturated solution of NH_4Cl and extracted with CH_2Cl_2. The collected organic phases were dried over Na_2SO_4 and the solvent removed in vacuo. The diastereoisomers **16** and **17** were separated by flash chromatography on silica gel (eluents cyclohexane/ethyl acetate 9:1).

Compound **16**: oil. $[\alpha]_D = +20.3$ ($c = 0.89$, $CHCl_3$); IR (neat, cm^{-1}): 2939, 2859, 1772, 1719, 1447, 1387, 1367; ^1H NMR (300 MHz, $CDCl_3$), δ: 7.40 (m, 5H), 5.90 (dd, 1H, $J_1 = 6.0$, $J_2 = 9.0$ Hz), 5.44 (d, 1H, $J = 2.7$ Hz), 4.55 (m, 1H), 2.73 (m, 2H), 1.56 (s, 9H), 1.40 (d, 3H, $J = 6.6$ Hz), 1.12 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 167.46, 151.36, 140.69, 128.68, 128.17, 125.56, 87.09, 83.18, 72.63, 71.15, 41.62, 27.98, 19.02, 18.08, 12.70. Anal. Calcd for $C_{26}H_{43}NO_5Si$: C, 65.37; H, 9.07. Found: C, 65.42; H, 9.09.

Compound **17**: oil. $[\alpha]_D = -103.9$ ($c = 0.79$, $CHCl_3$); IR (neat, cm^{-1}): 2943, 2866, 1775, 1718, 1457, 1391, 1369; ^1H NMR (300 MHz, $CDCl_3$), δ: 7.40 (m, 5H), 5.56 (d, 1H, $J = 2.4$ Hz), 4.90 (dd, 1H, $J_1 = 3.0$, $J_2 = 11.0$ Hz), 4.32 (m, 1H), 2.80 (m, 2H), 1.58 (s, 9H), 1.29 (d, 3H, $J = 6.3$ Hz), 1.10 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 168.09, 151.67, 139.29, 128.49, 127.98, 125.29, 89.22, 83.89, 73.22, 69.22, 42.09, 27.82, 17.96, 16.87, 12.44. Anal. Calcd for $C_{26}H_{43}NO_5Si$: C, 65.37; H, 9.07. Found: C, 65.40; H, 9.08.

4.3. Synthesis of oxazinones 4 and 5 form *t*-Boc derivatives 16 and 17 (Scheme 3)

To a solution of *t*-Boc derivative **16** (or **17**) (1 mmol) in CH_2Cl_2 (5 mL) was added a solution of CF_3COOH 20% in CH_2Cl_2 (5 mL). The solution was stirred for 5 min at room temperature and then quenched with $NaHCO_3$



Scheme 3. Reagents and conditions: (i) $(t\text{-Boc})_2O$, TEA, DMAP (98%); (ii) CF_3COOH (20% in DCM) 98%; (iii) see Scheme 1.

satd after which it was extracted with CH_2Cl_2. The organic phases were dried over Na_2SO_4 and concentrated in vacuo to give product **4** (or **5**) in quantitative yield (Scheme 3).

Compound **4**: oil. $[\alpha]_D = +49.5$ ($c = 0.80$, $CHCl_3$); IR (neat, cm^{-1}): 3201, 2942, 2866, 1675, 1463; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.35 (m, 5H), 6.22 (br s, 1H), 5.26 (dd, 1H, $J_1 = 3.6$, $J_2 = 6.0$ Hz), 4.57 (d, 1H, $J = 3.2$ Hz), 3.96 (dq, 1H, $J_1 = 3.2$, $J_2 = 6.0$ Hz), 2.91 (dd, 1H, $J_1 = 6.0$, $J_2 = 17.2$ Hz), 2.79 (dd, 1H, $J_1 = 3.6$, $J_2 = 17.2$ Hz), 1.19 (d, 3H, $J = 6.0$ Hz), 0.90 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 168.98 137.77, 128.68, 128.58, 127.08, 80.35, 72.75, 68.90, 35.38, 18.09, 17.09, 11.98. MS (*m*/*z*): 334, 202, 187, 131. Anal. Calcd for $C_{21}H_{35}NO_3Si$: C, 66.80; H, 9.34. Found: C, 66.88; H, 9.35.

Compound **5**: oil. $[\alpha]_D = -37.3$ ($c = 0.82$, $CHCl_3$); IR (neat, cm^{-1}): 3201, 2942, 2866, 1675, 1463; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.36 (m, 5H), 6.53 (br s, 1H), 4.83 (dd, 1H, $J_1 = 3.6$, $J_2 = 12.0$ Hz), 4.61 (d, 1H, $J = 6.8$ Hz), 3.90 (m, 1H), 2.71 (dd, 1H, $J_1 = 3.6$, $J_2 = 17.2$ Hz), 2.59 (dd, 1H, $J_1 = 12.0$, $J_2 = 17.2$ Hz), 1.33 (d, 3H, $J = 6.4$ Hz), 1.09 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 168.10, 139.86, 128.63, 128.17, 125.44, 87.51, 76.04, 71.45, 39.29, 19.72, 18.11, 12.65; MS (*m*/*z*): 334, 202, 187, 131. Anal. Calcd for $C_{21}H_{35}NO_3Si$: C, 66.80; H, 9.34. Found: C, 66.92 H, 9.38.

4.4. (2*R*,6*R*)-2-((*S*)-1-Triisopropylsilyloxyethyl)-3-methyl-6-phenyl-1,3-oxazinan-4-one 6 and (2*S*,6*R*)-2-((*S*)-1-triisopropylsilyloxyethyl)-3-methyl-6-phenyl-1,3-oxazinan-4-one 7

To a solution of **2** and **3** (1.00 mmol, 377 mg) in THF (10 mL) at 0 °C was added HMDSLA (1 M in THF, 1.0 equiv, 1.0 mL). The reaction was stirred for 20 min, MeI (8 equiv, 0.498 mL) added and the solution warmed to room temperature. Stirring was then maintained for 2 h at the same temperature. A saturated solution of NH_4Cl was added, the organic solvent removed in vacuo and the obtained aqueous solution extracted with AcOEt. The organic phases were collected, dried over Na_2SO_4 and concentrated in vacuo. The crude reaction mixture was controlled by ^{1}H NMR analysis and used without purification for the next step. Yield >98%.

4.5. (2*R*,6*S*)-2-((*S*)-1-Triisopropylsilyloxyethyl)-3-methyl-6-phenyl-1,3-oxazinan-4-one 8 and (2*S*,6*S*)-2-((*S*)-1-triisopropylsilyloxyethyl)-3-methyl-6-phenyl-1,3-oxazinan-4-one 9

Following the same procedure but using **4** and **5**, compounds **8** and **9** were prepared in quantitative yields.

Compound **8**: oil. $[\alpha]_D = -15.2$ ($c = 1.50$ MeOH); IR (neat, cm^{-1}): 3201, 2942, 2866, 1675, 1463; ^{1}H NMR (200 MHz, $CDCl_3$), δ: 7.30 (m, 5H), 5.61 (pt, 1H, $J = 6.2$ Hz), 4.91 (d, 1H, $J = 2.2$ Hz), 4.22 (m, 1H), 2.90 (s, 3H), 2.62 (m, 2H), 1.26 (d, 3H, $J = 6.6$ Hz), 1.01 (m, 21H); ^{13}C NMR (50 MHz, $CDCl_3$), δ: 167.42, 139.74, 128.69, 128.19, 126.02, 88.85, 72.40, 69.74, 37.88, 30.47, 18.86, 18.05, 12.48; MS (*m*/*z*): 338 (M^+-43), 216, 190, 131. Anal. Calcd for $C_{22}H_{37}NO_3Si$: C, 67.47; H, 9.52. Found: C, 67.54; H, 9.54.

Compound **9**: oil. $[\alpha]_D = -62.5$ ($c = 0.92$ $CHCl_3$); IR (neat, cm^{-1}): 3201, 2944 2871, 1675, 1463; ^{1}H NMR (200 MHz, $CDCl_3$), δ: 7.30 (m, 5H), 4.82 (d, 1H, $J = 2.5$ Hz), 4.78 (dd, 1H, $J_1 = 2.2$, $J_2 = 11.4$ Hz), 4.22 (m, 1H), 2.88 (s, 3H), 2.80–2.42 (m, 2H), 1.16 (d, 3H, $J = 6.2$ Hz), 1.00 (m, 21H); ^{13}C NMR (50 MHz, $CDCl_3$), δ: 168.51, 139.87, 128.60, 127.85, 125.43, 90.75, 73.59, 68.84, 40.17, 29.57, 18.21, 16.54, 12.60; MS (*m*/*z*): 338 (M^+-43), 216, 190, 131. Anal. Calcd for $C_{22}H_{37}NO_3Si$: C, 67.47; H, 9.52. Found: C, 67.35; H, 9.50.

4.6. (2*R*,6*R*)-2-((*S*)-1-Triisopropylsilyloxyethyl)-3-methyl-6-phenyl-1,3-oxazinane 10 and (2*S*,6*R*)-2-((*S*)-1-triisopropylsilyloxyethyl)-3-methyl-6-phenyl-1,3-oxazinane 11

Ph_2SiH_2 (2.5 equiv, 0.461 mL) and $RhH(CO)(PPh_3)_3$ (1%) were added to a solution of **6** and **7** (1.0 mmol, 391 mg) in THF (10 mL) at room temperature and the stirring maintained for 15 h. THF was removed in vacuo, HCl (1 M) added and the reaction extracted with Et_2O. The aqueous phase was neutralized with NaOH (5 M) (pH = 10–12) and then extracted with Et_2O. The organic phases were dried over Na_2SO_4 and the solvent evaporated. The crude reaction mixture obtained was used without purification for the last step of the synthesis.

Following the same protocol but using a solution of **8** and **9**, compounds **12** and **13** were prepared.

4.7. (*R*)-3-(Methylamino)-1-phenylpropan-1-ol 14

To a solution of **10** and **11** in MeOH (10 mL) was added HCl (1 M) (5 mL/mmol) and the mixture heated at 90 °C for 1.5 h. The solution was cooled at room temperature, after which MeOH was removed in vacuo and the aqueous solution extracted with Et_2O. The aqueous solution was neutralized with NaOH (5 M) and extracted with CH_2Cl_2. The organic phases were collected, dried over Na_2SO_4 and the solvent removed in vacuo to give prod-

uct **14** as a pure enantiomer. Yield: 60%, **14**: oil. $[\alpha]_D = +37.5$ ($c = 1.2$, $CHCl_3$). IR (neat, cm^{-1}): 3303, 3061, 2938, 2854, 1492. ^1H NMR (300 MHz, $CDCl_3$), δ: 7.30 (m, 5H), 4.95 (dd, 1H, $J_1 = 3.3$, $J_2 = 8.7$ Hz), 4.20 (br s, 2H), 2.88 (m, 2H), 2.46 (s, 3H), 1.85 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 145.02, 128.14, 126.86, 125.54, 75.27, 50.21, 36.75, 35.82.

4.8. (*S*)-3-(Methylamino)-1-phenylpropan-1-ol 15

This compound was prepared starting from the diastereomeric mixture **8** and **9**, following the protocol described for compound **14**. Yield: 67%.

Compound **15**: oil. $[\alpha]_D = -36.0$ ($c = 1.0$, $CHCl_3$); IR (neat, cm^{-1}): 3303, 3061, 2938, 2854, 1492; ^1H NMR (300 MHz, $CDCl_3$), δ: 7.30 (m, 5H), 4.95 (dd, 1H, $J_1 = 3.3$, $J_2 = 8.7$ Hz), 4.20 (br s, 2H), 2.88 (m, 2H), 2.46 (s, 3H), 1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 145.02, 128.14, 126.86, 125.54, 75.27, 50.21, 36.75, 35.82.

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19. No NOE's effects between the C2H and C6H were observed for products **3** and **4**. The NOE's effect, between the C2H and C6H, for product **2** was determined by identifying and irradiating the corresponding signals in the ^1H NMR spectra of the mixture of isomers **2** and **3**.
20. A confirmation of the correct structures' attributions depicted in Scheme 1 come from the sequence of reactions reported (Scheme 3). Unfortunately, due to difficulty in separating the two Boc derivatives of **2** and **3** by flash chromatography, this sequence could not be repeated for those last compounds.
21. For a detailed discussion on this aspect see: Panunzio, M.; Bongini, A.; Monari, M.; Tamanini, E.; Bandini, E. *Tetrahedron* **2004**, *60*, 8347–8356.
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