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Diastereoselective synthesis of enantiopure (α*R*)-2-methyl-4-(α-phenylethyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-ones

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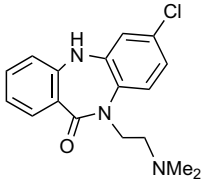
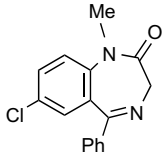
Abstract—(α*R*,2*R*)- and (α*R*,2*S*)-2-methyl-4-(α-phenylethyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-ones **7** and **8** were synthesised by an intramolecular azide cycloaddition followed by stereoselective reduction of a bicyclic ketimine.

1. Introduction

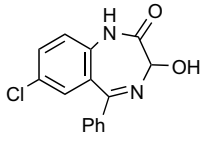
The 1,4-benzodiazepin-5-one skeleton is of interest because of its frequent presence in molecules with pharmacological activity.[1] Their use mainly concerns the pharmacotherapy of allergies (i.e., tarpane),[2] anxiety (i.e., diazepam and oxazepam),[3] epilepsy, convulsive states and emotional disorder (i.e., flumazenil).[4]



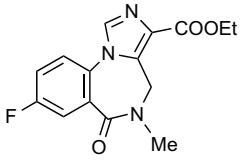
tarpane



diazepam



oxazepam



flumazenil

Several strategies of access to 1,4-benzodiazepin-5-ones are known,[5] but the structural variety within this class of drugs justifies continuing work on novel synthetic methodologies, particularly if they lead to enantiopure products.[6] In this context, we have previously reported a synthetic approach to 1,4-benzodiazepin-5-ones where the construction of the seven-membered ring relies upon an intramolecular cycloaddition of the azido group onto a multiple C–C bond.[7] We herein report a convenient extension of the same approach, which leads to 2-methyl-4-(α-phenylethyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-ones in enantiomerically pure form. To this end, we used as key intermediates *N*,*N*-disubstituted 2-azidobenzamides bearing both an ethylenic bond and the (*R*)-phenylethyl unity.

2. Results and discussion

The (*R*)-*N*-allyl-2-amino-*N*-(α-phenylethyl)-benzamides **3a**–**c** were synthesised by allylation of the amides **1a**–**c** and reduction of the nitroderivatives **2a**–**c** according to the procedure already reported for compound **3a**.[8] We previously found that diazotisation of **3a**, followed by treatment with sodium azide and subsequent reflux in toluene, gave the bicyclic ketimine **6a**.[9] We have now isolated the intermediate azido compound **4a** and proven the general feasibility of the sequence with the substrates **3b** and **c**. Curiously, as revealed by NMR spectroscopy, compounds **4a**–**c** exist at room

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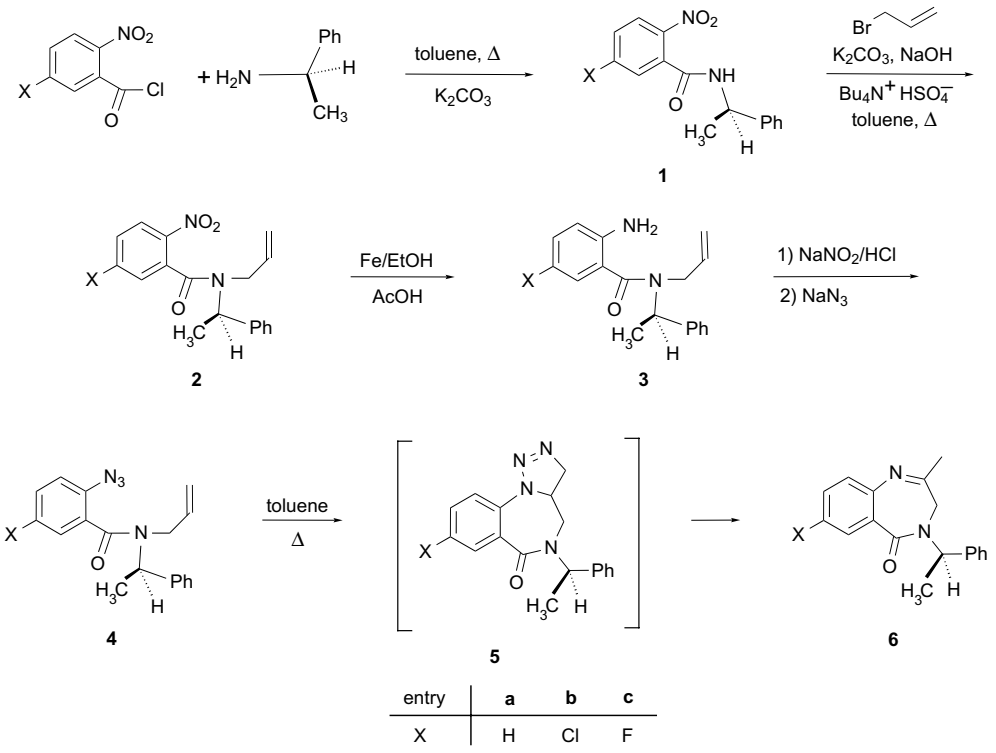
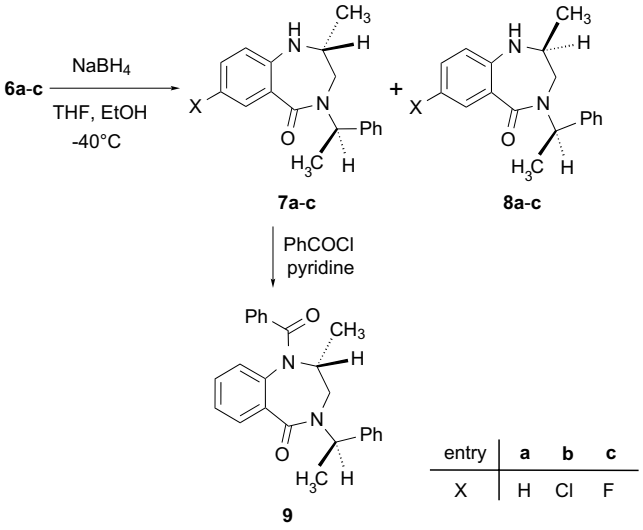


Scheme 1. Preparation and intramolecular cycloaddition of azides **4a**–**c**.

temperature as a 4:3 mixture of two conformers, probably due to restricted rotation around the amide bond. The conversion of **4a**–**c** to **6a**–**c**, carried out in refluxing toluene, proceeded in 54–72% yields. Since it is well known that the 4,5-dihydro-1,2,3-triazoles can thermally lose nitrogen,[10] the intermediacy of the intramolecular cycloadducts **5a**–**c** is reasonable (Scheme 1).

At this point, having in hand optically active substrates, we saw an opportunity of manipulating them to create a new stereocentre hopefully in a selective manner. The reaction of **6a** with $NaBH_4$ actually gave two products, which were isolated in their pure state by column chromatography in 53% and 9% yield. According to the ^1H NMR, their ratio in the crude mixture was 75:25. Spectroscopic and analytical investigations were consistent with two diastereoisomeric structures (Scheme 2), but did not allow the assignment of the configuration of the new stereocentre. Since both compounds **7a** and **8a** were oily materials, we converted the secondary amine group of the major diastereoisomer **7a** into the benzamide **9** with the aim of carrying out X-ray crystal structure analysis. The latter revealed an (*R*)-configuration at the stereocentre at position 2 (Fig. 1) thus allowing the absolute configurations (α*R*,2*R*) and (α*R*,2*S*) to be assigned to **7a** and **8a**, respectively. The same reaction occurred with the ketimines **6b** and **c** to give 7-chloro- and 7-fluoro-substituted 2-methyl-4-(α-phenylethyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-ones **7b** and **c** and **8b** and **c**, whose absolute configurations were inferred from their NMR spectra when compared to the **7a** and **8a**. It is noteworthy that the treatment of the ketimine **6a** with DIBALH as the reducing agent gave the same diastereoselectivity as the one observed with $NaBH_4$.



Scheme 2. Reduction of the ketimines **6a**–**c**.

3. Conclusion

A set of new enantiopure 1,4-benzodiazepin-5-ones has been made available utilising an intramolecular azide cycloaddition as a key step in building a bicyclic system. The synthetic interest is enhanced by their close structural analogy with those of widely used drugs.

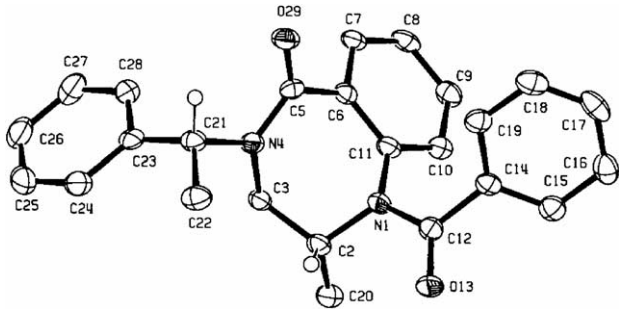


Figure 1. ORTEP plot of **9** (molecule A); for clarity, only hydrogen atoms bonded to chiral carbon atoms are reported. Thermal ellipsoids at 50% probability level; hydrogen atoms not to scale.

4. Experimental section

4.1. General

Melting points were measured on a Büchi B-540 heating unit and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on an Avance 400 Bruker. Mass spectra were determined on a WG-70EQ instrument. IR spectra were taken on a FT-IR Perkin–Elmer 1725X spectrophotometer. Optical rotations were measured on a Perkin–Elmer 343 plus polarimeter at the sodium D line.

4.2. General procedure for the preparation of the (*R*)-2-nitro-*N*-(α-phenylethyl)-benzamides 1b,c

This compound was prepared as described in the literature for compound **1a**.[8]

Compound **1b**: 74% yield; mp 167–168 °C (from diisopropyl ether); $[\alpha]_D^{20} = +61.0$ (*c* 0.20, $CHCl_3$); IR (nujol): *v* 3320, 1646 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.63$ (3H, d, $J = 7.4$ Hz), 5.30 (1H, dq, $J = 7.0$, 7.4 Hz; after deuteriation: q, $J = 7.4$ Hz), 6.10 (1H, br d, $J = 7.0$ Hz, missing after deuteriation), 7.29–8.11 (8H, m); ^{13}C NMR ($CDCl_3$): $\delta = 21.3$ (q), 50.2 (d), 126.3 (d), 126.5 (d), 126.8 (d), 128.3 (d), 129.3 (d), 130.4 (d), 130.8 (d), 133.0 (d), 134.9 (s), 138.4 (s), 140.9 (s), 142.3 (s), 164.5 (s); MS: *m*/*z* 304 (M^+). Anal. Calcd for $C_{15}H_{13}ClN_2O_3$: C, 59.12; H, 4.30; N, 9.19. Found: C, 58.96; H, 4.41; N, 9.25.

Compound **1c**: 70% yield; mp 136–137 °C (from diisopropyl ether); $[\alpha]_D^{20} = +14.6$ (*c* 0.28, $CHCl_3$); IR (nujol): *v* 3325, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.59$ (3H, d, $J = 6.9$ Hz), 5.25 (1H, dq, $J = 6.6$, 6.9 Hz; after deuteriation: q, $J = 6.9$ Hz), 6.45 (1H, br d, $J = 6.6$ Hz, missing after deuteriation), 7.08 (1H, dd, $J = 2.4$, 7.6 Hz), 7.19 (1H, ddd, $J = 2.4$, 7.6, 9.0 Hz), 7.25–7.39 (5H, m), 8.08 (1H, dd, $J = 4.6$, 9.0 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 21.4$ (q), 50.1 (d), 116.6 (dd, $J_{C-F} = 23.6$ Hz), 117.5 (dd, $J_{C-F} = 22.1$ Hz), 126.8 (d), 127.8 (dd, $J_{C-F} = 7.7$ Hz), 128.1 (d), 129.2 (d), 136.2 (d, $J_{C-F} = 135.7$ Hz), 142.5 (s), 164.0 (s), 164.7 (s), 166.6 (s); MS: *m*/*z* 288 (M^+). Anal. Calcd for $C_{15}H_{13}FN_2O_3$: C, 62.50; H, 4.55; N, 9.72. Found: C, 62.49; H, 4.71; N, 9.52.

4.3. General procedure for the preparation of (*R*)-*N*-allyl-2-nitro-*N*-(α-phenylethyl)-benzamides 2b,c

The compounds were prepared as described in the literature for compound **2a**.[8]

Compound **2b**: 95% yield; oil; $[\alpha]_D^{20} = +144.1$ (*c* 0.34, $CHCl_3$); IR (neat): *v* 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.60$ (3H, d, $J = 6.9$ Hz), 4.65 (2H, d, $J = 5.0$ Hz), 5.37 (1H, d, $J = 10.6$ Hz), 5.44 (1H, d, $J = 17.3$ Hz), 6.03 (1H, tdd, $J = 5.0$, 10.6, 17.3 Hz), 6.12 (1H, q, $J = 6.9$ Hz), 6.97 (1H, d, $J = 9.2$ Hz), 7.30–7.42 (6H, m), 8.19 (1H, d, $J = 9.2$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 19.6$ (q), 46.0 (t), 58.1 (d), 113.5 (d), 114.2 (d), 114.7 (d), 115.3 (d), 115.4 (d), 116.2 (d), 116.4 (d), 119.3 (t), 128.2 (d), 128.9 (d), 136.2 (s), 138.5 (s), 141.3 (s), 163.4 (s), 168.5 (s); MS: *m*/*z* 344 (M^+). Anal. Calcd for $C_{18}H_{17}ClN_2O_3$: C, 62.70; H, 4.97; N, 8.12. Found: C, 62.73; H, 5.18; N, 7.97.

Compound **2c**: 71% yield; oil; $[\alpha]_D^{20} = +82.4$ (*c* 0.65, $CHCl_3$); IR (neat): *v* 1648 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.72$ (3H, d, $J = 7.1$ Hz), 4.35–4.80 (2H, m), 5.32 (1H, d, $J = 10.5$ Hz), 5.48 (1H, d, $J = 17.1$ Hz), 6.03 (1H, tdd, $J = 5.0$, 10.5, 17.1 Hz), 6.11 (1H, q, $J = 7.1$ Hz), 6.98 (1H, dd, $J = 2.7$, 9.2 Hz), 7.19 (1H, dd, $J = 2.7$, 7.7 Hz), 7.35–7.53 (5H, m), 8.25 (1H, dd, $J = 4.7$, 9.2 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 19.5$ (q), 48.5 (t), 52.4 (d), 115.0 (dd, $J_{C-F} = 24.1$ Hz), 116.7 (dd, $J_{C-F} = 23.6$ Hz), 117.6 (t), 126.8 (d), 128.0 (d), 128.2 (d), 128.4 (dd, $J_{C-F} = 6.9$ Hz), 129.0 (d), 136.4 (d, $J_{C-F} = 133.4$ Hz), 139.9 (s), 163.4 (s), 164.4 (s), 167.1 (s); MS: *m*/*z* 328 (M^+). Anal. Calcd for $C_{18}H_{17}FN_2O_3$: C, 65.85; H, 5.22; N, 8.53. Found: C, 65.99; H, 5.28; N, 8.71.

4.4. General procedure for the preparation of (*R*)-*N*-allyl-2-amino-*N*-(α-phenylethyl)-benzamides 3b,c

The compounds were prepared as described in the literature for the compound **3a**.[8]

Compound **3b**: 78% yield; oil; $[\alpha]_D^{20} = +59.7$ (*c* 0.16, $CHCl_3$); IR (neat): *v* 3342, 1622 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.62$ (3H, d, $J = 7.0$ Hz), 3.12 (2H, d, $J = 4.8$ Hz), 4.44–4.66 (2H, m), 4.77 (2H, br s, missing after deuteriation), 5.90–6.00 (1H, m), 6.13 (1H, q, $J = 7.0$ Hz), 7.22–7.54 (7H, m), 8.19 (1H, d, $J = 8.8$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 18.5$ (q), 58.0 (d), 66.2 (t), 113.5 (d), 115.2 (t), 116.7 (d), 118.3 (d), 118.7 (d), 126.2 (d), 127.8 (d), 128.5 (d), 138.2 (s), 140.4 (s), 151.3 (s), 161.7 (s), 169.9 (s); MS: *m*/*z* 314 (M^+). Anal. Calcd for $C_{18}H_{19}ClN_2O$: C, 68.67; H, 6.08; N, 8.90. Found: C, 68.81; H, 5.88; N, 8.95.

Compound **3c**: 91% yield; oil; $[\alpha]_D^{20} = +129.7$ (*c* 0.50, $CHCl_3$); IR (neat): *v* 3328, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.64$ (3H, d, $J = 7.0$ Hz), 3.48–3.58 (1H, m), 3.89–4.36 (3H, m, after deuteriation 1H, m), 4.94–5.06 (2H, m), 5.30–5.61 (1H, m), 5.64–5.83 (1H, m), 6.64–6.95 (5H, m), 7.24–7.42 (3H, m); ^{13}C NMR ($CDCl_3$): $\delta = 19.1$ (q), 58.8 (d), 70.1 (t), 113.6 (d), 117.0 (t), 117.5 (dd, $J_{C-F} = 24.8$ Hz), 118.2 (d), 118.4 (dd,

$J_{C-F} = 21.8$ Hz), 127.7 (d), 128.0 (dd, $J_{C-F} = 7.0$ Hz), 128.9 (d), 140.6 (d, $J_{C-F} = 138.9$ Hz), 141.4 (s), 154.4 (s), 156.8 (s), 170.5 (s); MS: m/z 298 (M^+). Anal. Calcd for $C_{18}H_{19}FN_2O$: C, 72.46; H, 6.42; N, 9.39. Found: C, 72.48; H, 6.59; N, 9.28.

4.5. General procedure for the preparation of (*R*)-*N*-allyl-2-azido-*N*-(α-phenylethyl)-benzamides 4a–c

HCl (12 M, 2.2 mL, 27 mmol) was added to a solution of **3a–c** (0.27 mmol) in Et_2O (4 mL). After cooling at 0 °C, $NaNO_2$ (37 mg, 0.54 mmol) was added and the mixture was stirred for 30 min. NaN_3 (88 mg, 1.35 mmol) was then added and the solution stirred at room temperature for 40 min. After separation, the organic layer was washed with aqueous $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed under reduced pressure to give **4a–c** as a 4:3 mixture of two conformers.

Compound **4a**: 75% yield; oil; $[\alpha]_D^{20} = +71.4$ (c 0.23, $CHCl_3$); IR (neat): ν 2120, 1660 cm^{-1}; ^1H NMR ($CDCl_3$): *major conformer*: $\delta = 1.56$ (3H, br s), 3.30–3.61 (2H, m), 4.72 (1H, br s), 4.91–5.08 (1H, m), 5.35 (1H, br s), 5.81 (1H, br s), 7.00–7.45 (9H, m); *minor conformer*: $\delta = 1.56$ (3H, br s), 3.30–3.61 (2H, m), 4.51 (1H, br s), 4.74 (1H, br s), 4.91–5.08 (1H, m), 6.07 (1H, br s), 7.00–7.45 (9H, m); ^{13}C NMR ($CDCl_3$): *major conformer*: $\delta = 18.5$ (q), 44.9 (t), 51.7 (d), 116.7 (t), 118.5 (d), 124.8 (d), 125.3 (d), 126.6 (d), 127.6 (d), 127.9 (d), 128.5 (d), 130.3 (d), 131.3 (s), 138.3 (s), 140.3 (s), 168.6 (s); *minor conformer*: $\delta = 18.3$ (q), 47.8 (t), 57.1 (d), 116.3 (t), 119.0 (d), 125.0 (d), 126.5 (d), 127.1 (d), 127.3 (d), 128.1 (d), 128.3 (d), 130.2 (d), 131.3 (s), 138.3 (s), 140.3 (s), 169.4 (s); MS: m/z 306 (M^+). Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.72; H, 6.04; N, 18.18.

Compound **4b**: 64% yield; oil; $[\alpha]_D^{20} = +122.9$ (c 0.18, $CHCl_3$); IR (neat): ν 2112, 1633 cm^{-1}; ^1H NMR ($CDCl_3$): *major conformer*: $\delta = 1.67$ (3H, d, $J = 6.6$ Hz), 3.42–3.68 (2H, m), 4.12–4.36 (1H, m), 4.76–4.99 (1H, m), 5.06–5.20 (1H, m), 5.98 (1H, br s), 7.08–7.70 (8H, m); *minor conformer*: $\delta = 1.57$ (3H, d, $J = 6.6$ Hz), 3.42–3.68 (2H, m), 4.53–4.71 (1H, m), 4.76–4.99 (1H, m), 5.29–5.51 (1H, m), 6.14 (1H, br s), 7.08–7.70 (8H, m); ^{13}C NMR ($CDCl_3$): *major conformer*: $\delta = 18.9$ (q), 45.4 (t), 52.2 (d), 112.4 (d), 117.4 (t), 121.2 (d), 125.6 (d), 128.2 (d), 128.5 (d), 128.9 (d), 130.5 (d), 130.8 (s), 137.4 (s), 140.4 (s), 162.5 (s), 167.4 (s); *minor conformer*: $\delta = 18.8$ (q), 48.2 (t), 57.6 (d), 109.0 (d), 116.9 (t), 122.9 (d), 126.9 (d), 128.2 (d), 128.5 (d), 128.8 (d), 130.6 (d), 131.0 (s), 137.4 (s), 140.5 (s), 162.5 (s), 168.8 (s); MS: m/z 340 (M^+). Anal. Calcd for $C_{18}H_{17}ClN_4O$: C, 63.44; H, 5.03; N, 16.44. Found: C, 63.29; H, 4.88; N, 16.59.

Compound **4c**: 68% yield; oil; $[\alpha]_D^{20} = +136.6$ (c 0.60, $CHCl_3$); IR (neat): ν 2121, 1646 cm^{-1}; ^1H NMR ($CDCl_3$): *major conformer*: $\delta = 1.66$ (3H, br s), 3.38–3.58 (2H, m), 4.80 (1H, br s), 5.04–5.11 (1H, m), 5.79–5.92 (1H, br s), 6.13 (1H, q, $J = 7.0$ Hz), 7.07–7.48 (8H, m); *minor conformer*: $\delta = 1.66$ (3H, br s), 3.38–3.58 (2H, m), 4.53 (1H, br s), 4.84 (1H, br s), 5.94–6.10 (1H, m), 6.23 (1H, q, $J = 7.0$ Hz), 7.07–7.48 (8H, m); ^{13}C NMR ($CDCl_3$): *major conformer*: $\delta = 18.9$ (q), 45.0 (t), 52.2 (d), 115.9 (dd, $J_{C-F} = 22.9$ Hz), 117.2 (t), 119.7 (dd, $J_{C-F} = 21.6$ Hz), 121.0 (dd, $J_{C-F} = 8.4$ Hz), 126.9 (d), 127.8 (d), 128.4 (d), 129.0 (d), 133.1 (s), 134.5 (d, $J_{C-F} = 139.2$ Hz), 158.5 (s), 161.0 (s), 167.3 (s); *minor conformer*: $\delta = 18.7$ (q), 48.1 (t), 57.6 (d), 114.0 (dd), 114.8 (dd), 116.7 (t), 122.4 (dd), 127.0 (d), 127.8 (d), 128.4 (d), 128.9 (d), 131.3 (s), 134.7 (d), 158.8 (s), 161.3 (s), 168.1 (s); MS: m/z 324 (M^+). Anal. Calcd for $C_{18}H_{17}FN_4O$: C, 66.65; H, 5.28; N, 17.27. Found: C, 66.72; H, 5.16; N, 17.39.

4.6. General procedure for the preparation of (*R*)-2-methyl-4-(α-phenylethyl)-3,4-dihydro-benzo[*e*][1,4]diazepin-5-ones 6a–c

A solution of **4a–c** (0.21 mmol) in toluene (4 mL) was refluxed for 3 h. The evaporation of the solvent under reduced pressure left a residue, which was chromatographed on a silica gel column using hexane/AcOEt 1:2 as eluent to give **6a–c** as a white solid.

Compound **6a**: see literature.[9]

Compound **6b**: 72% yield; mp 109–111 °C (from diisopropyl ether); $[\alpha]_D^{20} = +307.1$ (c 0.40, $CHCl_3$); IR (CH_2Cl_2): ν 1622 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.54$–1.63 (6H, m), 3.36, 3.43 (2H, AB system, $J = 14.0$ Hz), 6.23 (1H, q, $J = 7.1$ Hz), 7.20–7.48 (7H, m), 8.08 (1H, dd, $J = 1.5$, 7.4 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 15.6$ (q), 21.1 (q), 43.6 (t), 50.5 (d), 126.8 (d), 128.1 (d), 128.3 (d), 128.7 (d), 128.9 (d), 129.9 (d), 132.9 (s), 133.8 (s), 137.2 (s), 139.3 (s), 164.6 (s), 173.9 (s); MS: m/z 312 (M^+). Anal. Calcd for $C_{18}H_{17}ClN_2O$: C, 69.12; H, 5.48; N, 8.96. Found: C, 69.29; H, 5.39; N, 9.09.

Compound **6c**: 54% yield; mp 126–127 °C (from diisopropyl ether); $[\alpha]_D^{20} = +339.0$ (c 0.30, $CHCl_3$); IR (CH_2Cl_2): ν 1634 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.58$–1.65 (6H, m), 3.32, 3.42 (2H, AB system, $J = 14.3$ Hz), 6.22 (1H, q, $J = 7.2$ Hz), 7.11–7.58 (7H, m), 7.77 (1H, dd, $J = 1.7$, 8.8 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 16.5$ (q), 25.7 (q), 43.0 (t), 51.9 (d), 117.2 (dd, $J_{C-F} = 25.0$ Hz), 119.4 (dd, $J_{C-F} = 24.7$ Hz), 128.2 (d), 128.5 (dd, $J_{C-F} = 8.1$ Hz), 128.8 (d), 129.2 (d), 140.8 (d, $J_{C-F} = 131.6$ Hz), 142.8 (s), 159.3 (s), 161.7 (s), 166.4 (s), 169.7 (s); MS: m/z 296 (M^+). Anal. Calcd for $C_{18}H_{17}FN_2O$: C, 72.96; H, 5.78; N, 9.45. Found: C, 73.01; H, 5.89; N, 9.66.

4.7. General procedure for the reaction of 6a–c with $NaBH_4$

A solution of $NaBH_4$ (7.6 mg, 0.20 mmol) in water (0.4 mL) was added dropwise at −20 °C to a solution of **4a–c** (0.14 mmol) in THF (0.3 mL) and EtOH (0.3 mL). After cooling for 1 h at −40 °C and for 15 h at −20 °C, the mixture was poured in water (20 mL), adjusted to

pH 11 with 40% aqueous NaOH and extracted with Et_2O (30 mL × 3). The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was chromatographed on a silica gel column to give **7a–c** and **8a–c**.

Entry a: elution with AcOEt/hexane 2:1 gave **8a** (9%) and **7a** (53%).

4.7.1. (αR,2R)-2-Methyl-4-(α-phenylethyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one 7a. Oil; $[\alpha]_D^{20} = -24.1$ (*c* 0.34, $CHCl_3$); IR (CH_2Cl_2): *v* 3058, 1629 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.06$ (3H, d, $J = 6.3$ Hz), 1.62 (3H, d, $J = 7.0$ Hz), 2.97 (1H, dd, $J = 4.0$, 15.2 Hz), 3.04 (1H, dd, $J = 9.2$, 15.2 Hz), 3.57 (1H, br s, missing after deuteriation), 3.76 (1H, ddq, $J = 4.0$, 6.3, 9.2 Hz), 6.26 (1H, q, $J = 7.0$ Hz), 6.58 (1H, dd, $J = 1.1$, 8.1 Hz), 6.87 (1H, ddd, $J = 1.1$, 7.7, 8.1 Hz), 7.18–7.36 (6H, m), 7.88 (1H, dd, $J = 1.8$, 7.7 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 16.8$ (q), 20.3 (q), 47.7 (t), 51.3 (d), 56.7 (d), 119.4 (d), 119.7 (d), 122.8 (s), 127.1 (d), 128.4 (d), 128.7 (d), 132.4 (d), 132.5 (d), 141.0 (s), 143.9 (s), 170.0 (s); MS: *m/z* 280 (M^+). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.92; H, 7.21; N, 9.86.

4.7.2. (αR,2S)-2-Methyl-4-(α-phenylethyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one 8a. Oil; $[\alpha]_D^{20} = +155.0$ (*c* 0.36, $CHCl_3$); IR (CH_2Cl_2): *v* 3054, 1622 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.77$ (3H, d, $J = 6.3$ Hz), 1.49 (3H, d, $J = 7.0$ Hz), 2.79 (1H, tq, $J = 6.3$, 6.4 Hz), 2.99 (2H, d, $J = 6.4$ Hz), 3.49 (1H, br s, missing after deuteriation), 6.24 (1H, q, $J = 7.0$ Hz), 6.54 (1H, d, $J = 8.0$ Hz), 6.86 (1H, dd, $J = 7.4$, 7.6 Hz), 7.15–7.46 (6H, m), 7.88 (1H, dd, $J = 1.3$, 7.6 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 15.9$ (q), 21.0 (q), 46.8 (t), 51.5 (d), 55.5 (d), 119.1 (d), 119.5 (d), 122.6 (s), 127.5 (d), 128.2 (d), 128.7 (d), 131.8 (d), 132.2 (d), 139.9 (s), 143.8 (s), 169.6 (s); MS: *m/z* 280 (M^+). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.17; H, 7.03; N, 9.82.

Entry b: elution with AcOEt/hexane 3:1 gave **8b** (11%) and **7b** (48%).

4.7.3. (αR,2R)-7-Chloro-2-methyl-4-(α-phenylethyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one 7b. Oil; $[\alpha]_D^{20} = -18.7$ (*c* 0.24, $CHCl_3$); IR (CH_2Cl_2): *v* 3054, 1622 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.09$ (3H, d, $J = 6.3$ Hz), 1.64 (3H, d, $J = 7.0$ Hz), 3.03 (1H, dd, $J = 4.0$, 15.2 Hz), 3.57 (1H, br s, missing after deuteriation), 3.75 (1H, dd, $J = 9.2$, 15.2 Hz), 4.24 (1H, ddq, $J = 4.0$, 6.3, 9.2 Hz), 6.27 (1H, q, $J = 7.0$ Hz), 6.54 (1H, dd, $J = 1.1$, 8.1 Hz), 7.25 (1H, dd, $J = 1.1$, 7.7 Hz), 7.18–7.40 (5H, m), 7.89 (1H, d, $J = 2.5$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 19.8$ (q), 20.6 (q), 50.7 (d), 52.2 (t), 53.9 (d), 113.7 (d), 119.5 (s), 122.3 (s), 126.7 (d), 128.6 (d), 128.7 (d), 129.0 (d), 130.5 (d), 138.3 (s), 140.2 (s), 166.5 (s); MS: *m/z* 314 (M^+). Anal. Calcd for $C_{18}H_{19}ClN_2O$: C, 68.67; H, 6.08; N, 8.90. Found: C, 68.70; H, 5.88; N, 8.79.

4.7.4. (αR,2S)-7-Chloro-2-methyl-4-(α-phenylethyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one 8b. Oil; $[\alpha]_D^{20} = +108.1$ (*c* 0.38, $CHCl_3$); IR (CH_2Cl_2): *v* 3061, 1620 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.85$ (3H, d, $J = 6.3$ Hz), 1.56 (3H, q, $J = 7.0$ Hz), 3.02 (1H, tq, $J = 6.3$, 6.4 Hz), 3.19 (2H, d, $J = 6.4$ Hz), 3.58 (1H, br s, missing after deuteriation), 6.24 (1H, q, $J = 7.0$ Hz), 6.50 (1H, d, $J = 8.0$ Hz), 7.15 (1H, dd, $J = 7.4$, 7.6 Hz), 7.28–7.36 (5H, m), 7.88 (1H, d, $J = 1.3$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 19.0$ (q), 21.4 (q), 50.9 (d), 52.8 (d), 52.9 (t), 113.5 (d), 119.7 (s), 122.0 (s), 126.8 (d), 128.1 (d), 128.2 (d), 128.3 (d), 130.7 (d), 137.2 (s), 140.1 (s), 166.1 (s); MS: *m/z* 314 (M^+). Anal. Calcd for $C_{18}H_{19}ClN_2O$: C, 68.67; H, 6.08; N, 8.90. Found: C, 68.51; H, 5.93; N, 9.06.

Entry c: elution with AcOEt/hexane 3:1 gave **8c** (12%) and **7c** (45%).

4.7.5. (αR,2R)-7-Fluoro-2-methyl-4-(α-phenylethyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one 7c. Oil; $[\alpha]_D^{20} = -23.1$ (*c* 0.01, $CHCl_3$); IR (CH_2Cl_2): *v* 3045, 1634 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.05$ (3H, d, $J = 6.3$ Hz), 1.66 (3H, d, $J = 7.0$ Hz), 2.96–3.04 (2H, m), 3.42 (1H, br s, missing after deuteriation), 3.77 (1H, ddq, $J = 4.1$, 6.3, 8.9 Hz), 6.24 (1H, q, $J = 7.0$ Hz), 6.60 (1H, dd, $J = 4.5$, 8.7 Hz), 6.98 (1H, ddd, $J = 3.0$, 8.7, 9.4 Hz), 7.28–7.42 (5H, m), 7.58 (1H, dd, $J = 3.0$, 9.4 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 17.1$ (q), 20.9 (q), 47.7 (t), 51.8 (d), 57.4 (d), 118.0 (dd, $J_{C-F} = 23.5$ Hz), 119.5 (dd, $J_{C-F} = 22.8$ Hz), 121.8 (dd, $J_{C-F} = 7.0$ Hz), 127.6 (d), 127.8 (d), 129.0 (d), 139.9 (d, $J_{C-F} = 134.9$ Hz), 141.2 (s), 156.4 (s), 158.8 (s), 169.2 (s); MS: *m/z* 298 (M^+). Anal. Calcd for $C_{18}H_{19}FN_2O$: C, 72.46; H, 6.42; N, 9.39. Found: C, 72.51; H, 6.63; N, 9.51.

4.7.6. (αR,2S)-7-Fluoro-2-methyl-4-(α-phenylethyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one 8c. Oil; $[\alpha]_D^{20} = +81.7$ (*c* 0.14, $CHCl_3$); IR (CH_2Cl_2): *v* 3092, 1625 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.85$ (3H, d, $J = 6.3$ Hz), 1.58 (3H, d, $J = 7.0$ Hz), 2.06 (1H, br s, missing after deuteriation), 2.81–3.04 (3H, m), 6.21 (1H, q, $J = 7.0$ Hz), 6.55 (1H, dd, $J = 4.5$, 8.7 Hz), 6.72 (1H, dd, $J = 4.4$, 8.4 Hz), 7.32–7.48 (6H, m); ^{13}C NMR ($CDCl_3$): $\delta = 16.2$ (q), 20.9 (q), 46.4 (t), 51.9 (d), 56.2 (d), 117.9 (dd, $J_{C-F} = 23.3$ Hz), 119.6 (dd, $J_{C-F} = 22.6$ Hz), 122.8 (dd, $J_{C-F} = 7.2$ Hz), 127.7 (d), 128.4 (d), 129.1 (d), 138.1 (d, $J_{C-F} = 136.1$ Hz), 140.1 (s), 140.8 (s), 159.1 (s) 169.3 (s); MS: *m/z* 298 (M^+). Anal. Calcd for $C_{18}H_{19}FN_2O$: C, 72.46; H, 6.42; N, 9.39. Found: C, 72.38; H, 6.53; N, 9.22.

4.8. (αR,2R)-1-Benzoyl-2-methyl-4-(α-phenylethyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one 9

Benzoyl chloride (5.0 mL, 4.31 mmol) was dropped into a solution, previously cooled to 0 °C, of **7a** (0.54 g, 1.93 mmol) in pyridine (10 mL). After stirring at rt for 2 days, the mixture was poured into 5% aqueous HCl and extracted with CH_2Cl_2 (20 mL × 3). The organic

layer was washed with aqueous $NaHCO_3$ (20 mL × 2) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude solid chromatographed on a silica gel column using light petroleum/AcOEt (1:1) as the eluent to give 630 mg of **9** (85%). Mp 156–157 °C (from diisopropyl ether); $[\alpha]_D^{20} = -362.9$ (*c* 0.28, $CHCl_3$); IR (nujol): *v* 1638, 1629 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.12$ (3H, d, $J = 6.3$ Hz), 1.72 (3H, d, $J = 7.2$ Hz), 2.84 (1H, dd, $J = 12.6$, 15.2 Hz), 3.11 (1H, dd, $J = 5.3$, 15.5 Hz), 5.11 (1H, ddq, $J = 5.3$, 6.3, 12.6 Hz), 6.24 (1H, q, $J = 7.2$ Hz), 6.62 (1H, d, $J = 7.8$ Hz), 7.15–7.41 (12H, m), 7.85 (1H, dd, $J = 1.3$, 7.7 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 15.8$ (q), 18.4 (q), 47.9 (t), 51.3 (d), 57.3 (d), 127.6 (d), 128.0 (d), 128.4 (d), 128.6 (d), 128.9 (d), 129.1 (d), 129.2 (d), 130.2 (d), 130.4 (d), 131.8 (d), 135.2 (s), 135.8 (s), 136.4 (s), 140.8 (s), 169.4 (s), 171.0 (s); MS: m/z 384 (M^+). Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29. Found: C, 78.22; H, 6.10; N, 7.36.

4.9. X-ray crystallographic analysis of 9

Single-crystal X-ray diffraction measurements were performed on a Bruker SMART-APEX diffractometer, equipped with a Bruker KRIOFLEX low temperature device; graphite monochromator, Mo-Kα radiation ($\lambda = 0.71073$ Å). $C_{25}H_{24}N_2O_2$, $M_r = 384.46$, monoclinic, space group $P2_1$, $a = 11.895(2)$, $b = 8.7488(11)$, $c = 29.595(4)$ Å, $\beta = 95.163(8)°$, $V = 3067.4(8)$ Å^3, $Z = 6$, $D_c = 1.249$ g cm^{-3}, μ(Mo-Kα) = 0.080 mm^{-1}. Data were collected at $T = 90$ K, because the crystals were very poorly diffracting at room temperature; 24233 collected data up to $2\theta = 55°$; 7401 unique [5633 with $I_0 > 2\sigma(I_0)$], $R_{ave} = 0.0526$. Structure solved by SIR-92[11] and refined by SHELX97[12]; final disagreement factors for all (observed) reflections: $R_w(F^2) = 0.0891(0.0839)$ and $R = 0.0612(0.0417)$, goodness-of-fit = 0.991. The asymmetric unit contains three independent molecules signed as A, B and C. Figure 1 shows a projection of molecule A; the numbering scheme of the three molecules is exactly the same. The cyclic nucleus of the three molecules is very similar, while large differences are found for the torsion angles around the bonds C12–C14 and C21–C23; for example, the torsion angles N4–C21–C23–C24 and O13–C12–C14–C19 are 127.2(7), 112.0(6), 165.1(2) and −128.1(3), −146.5(2), −131.9(3)° for molecules A, B and C, respectively. All crystallographic data (excluding structure factors) were deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 223466. Copies of the data can be obtained free of charge on application to CCDC, 2 Union Road, Cambridge CB2 1EZ, UK, e-mail: deposit@ccdc.cam.ac.uk.

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