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A one-step synthesis of enantiopure 2-substituted 4,5-dihydro-1,4-benzodiazepine-3-ones via intramolecular azide cycloaddition

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Abstract—Starting from the appropriate azides bearing the (*S*)-1-phenylethylamine and the L-alanine benzylester as chiral pendants, a facile and effective synthetic route to the title compounds in their enantiopure form was developed with excellent product yields obtained. Basic hydrolysis of the ester group of the title compounds **3a**–**c** gave the corresponding, readily functionalisable carboxylic acids. Catalytic reduction of 2-benzyl derivatives **3c** and **3f** gave 4-functionalised 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones in enantiopure forms.

1. Introduction

Intramolecular 1,3-dipolar cycloadditions have been recognised as a powerful tool, leading to a large variety of both cyclic and open-chain molecules.[1] In recent years, the stereoselective version of these reactions have constituted as a key step in a number of syntheses of enantiopure molecules, which would be difficult to obtain by different routes.[2] Among the variety of available 1,3-dipolar species, stereoselective intramolecular azide cycloadditions play a key role in the construction of a number of valuable synthetic targets.[1c,2] Some examples of great interest are pyrrolizidine and indolizidine alkaloids,[3] clavicipitic acids[4] and biotin.[5] All of these synthetic approaches rely on the thermal degradation of the first-formed azide-alkene cycloadduct, namely the 4,5-dihydro-1,2,3-triazole ring, which usually shows low stability under the cycloaddition conditions.[6] This behaviour was herein investigated further with the aim of realizing an efficient, single-step synthesis of enantiopure 2-substituted 4,5-dihydro-1,4-benzodiazepine-3-ones starting from the appropriate homochiral azides. These heterocycles were further reacted to give readily functionalisable hydroxycarbonyl derivatives, as well as tetrahydro-1,4-benzodiazepine-3-ones. It should be noted that the latter compounds are of biological interest because they can act as fibrinogen receptor antagonists,[7] angiotensin analogues[8] and protein kinase C activators.[9]

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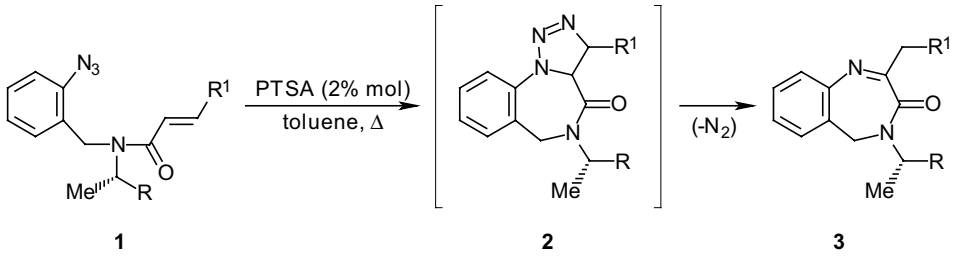
2. Results and discussion

Homochiral azides **1a**, **1c**, **1d** and **1f** (Scheme 1) were readily obtained through literature procedures[10] from the corresponding anilines by diazotisation of the latter, followed by treatment with sodium azide. The novel *N*-alkenoyl arylazides **1b** and **1e** were obtained in the same way with almost quantitative yields (see Section 4). Thermal treatment of **1a**–**f** in dry toluene and in the presence of a catalytic amount of PTSA (0.02 mol equiv) gave pure **3** with very good yields (92–98%) after crystallisation with diisopropyl ether. Structures **3** were deduced unambiguously from the analytical and spectral data. In particular, all the spectral data of the novel 2-substituted 4,5-dihydro-1,4-benzo diazepine-3-ones **3b**, **3c**, **3e** and **3f** agrees perfectly with those reported for the known **3a**, **3d**[10] and other closely related achiral compounds.[11]

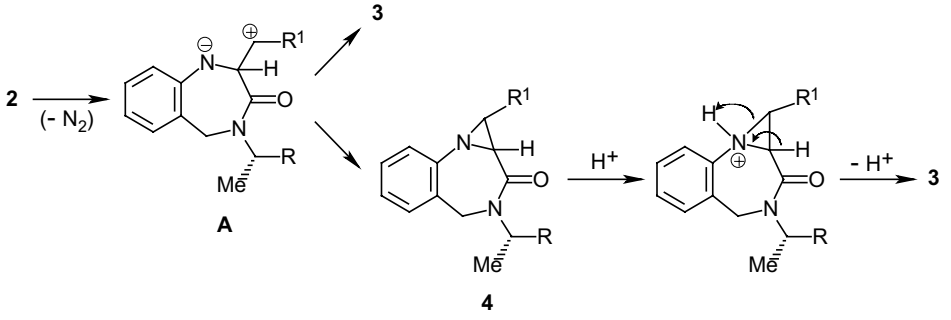
These results deserves some comments in order to account for the exclusive formation of compounds **3**. It should be noted that the intramolecular cycloaddition of the azido group onto the ethylenic bond form a tricyclic structure containing a 4,5-dihydro-1,2,3-triazole ring.[1,2] Furthermore, it has been well documented that, due to their thermal lability, 4,5-dihydro-1,2,3-triazoles undergo facile loss of nitrogen.[6a,b] On the basis of a number of previous studies dealing with the mechanistic aspects of nitrogen extrusion from 4,5-dihydro-1,2,3-triazoles, it is reasonable to assume the occurrence of the 1,3-dipolar intermediate **A** as a transient species (Scheme 2).[6] To this point, the fate of intermediate **A** follows two different pathways: (i)



1 2 3

Entry	a	b	c	d	e	f
R	COOBn	COOBn	COOBn	Ph	Ph	Ph
R^1	H	Me	Ph	H	Me	Ph

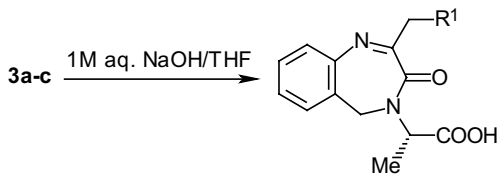
Scheme 1.



Scheme 2.

prototropic migration to give the final product **3**, and (ii) ring closure to the aziridino[2,1-*c*][1,4]benzo diazepinones **4**. As a matter of fact, thermal decomposition of primary cycloadducts **2a** and **2d** carried out in a previous work,[10] gave mixtures of the corresponding products **3** and **4**. To address the above azide-alkene cycloaddition protocol to a more preparative target, it was argued that the presence of a catalytic amount of PTSA could be effective in order to promote the transformation **4**→**3** through the mechanistic pathway outlined in Scheme 2.

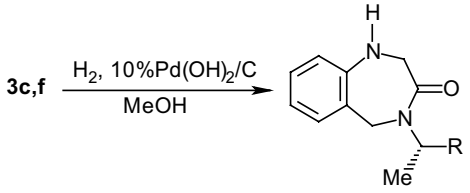
To provide the 4,5-dihydro-1,4-benzodiazepine-3-one scaffold with a readily functionalisable functional group, compounds **3a**–**c** were submitted to a basic hydrolysis of the benzylester group under mild conditions (1:1 aqueous sodium hydroxide–tetrahydrofuran at room temperature) to give the corresponding carboxylic acids **5a**–**c** (Scheme 3).



a: R = H, **b:** R = Me, **c:** R = Ph **5a-c**

Scheme 3.

As a further step of this work, 2-benzyl derivatives **3c** and **3f** were submitted to catalytic hydrogenation giving 4-functionalised 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones **6** and **7** in the enantiopure forms. It should be noted that upon hydrogenation in methanol in the presence of 10% Pd/C at room temperature and 15 psi of pressure, cleavage of the benzylester group was paralleled by the unexpected loss of the benzyl substituent at the 2-position of the 1,4-benzo diazepine-3-one ring (Scheme 4).



6: R = COOH
7: R = Ph

Scheme 4.

3. Conclusion

The intramolecular cycloadditions of homochiral *N*-alkenoyl-aryl azides **1** gave enantiopure 2-substituted

4,5-dihydro-1,4-benzodiazepin-3-ones **3** by in situ thermal decomposition of 3,3a,5,6-tetrahydro[1,2,3]triazolo[1,5-*a*]-[1,4]benzodiazepin-4-ones **2** as the primary cycloadducts. Further transformations of target products **3** provided a clean synthetic entry to enantiopure compounds **5**–**7** of potential pharmacological interest.

4. Experimental

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were taken with a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as parts per million from tetramethylsilane and *J* values are given in Hertz. Optical rotations, $[\alpha]_D^{25}$, were recorded on a Perkin–Elmer 241 polarimeter at the sodium D-line.

Compounds **1a**, **1c**, **1d** and **1f**[10] and **3a** and **3d**[10] are already known in the literature.

4.1. Synthesis of *N*-alkenoyl aryl azides 1b and 1e

A solution of 2-[*N*-(1-(*S*)-phenylethyl)-*N*-(1-oxo-2-(*E*)-butenyl)]aminomethyl aniline[12] or 2-{*N*-[1-(*S*)-(1-benzyloxycarbonyl)ethyl]-*N*-(1-oxo-2-(*E*)-butenyl)}aminomethyl aniline[12] (10.0 mmol) in aqueous hydrochloric acid (6 M, 8.0 mL) and acetic acid (4.0 mL) was treated with sodium nitrite (1.04 g, 15.0 mmol) under stirring and cooling at 0–5 °C. After 30 min, the mixture was treated with cold diethyl ether (25 mL) and sodium azide (3.22 g, 0.05 mol) was added portionwise under vigorous stirring and ice-cooling. After 1 h, the organic layer was separated, washed with 5% aqueous sodium hydrogen carbonate (30 mL), then with water (50 mL) and dried over sodium sulfate. Evaporation of the solvent gave crude products **1b** and **1e**. The residue was chromatographed on a silica gel column with hexane–AcOEt (2:1) to give pure **1b** and **1e**.

4.1.1. 2-{*N*-[1-(*S*)-(1-Benzyloxycarbonyl)ethyl]-*N*-(1-oxo-2-(*E*)-butenyl)}methylamino phenylazide 1b. 3.40 g, 90%. Yellow oil. $[\alpha]_D^{25} = -15.2$ (*c* 0.21, $CHCl_3$); IR (neat) 2130, 1740 cm^{-1}; ^{1}H NMR δ: 1.41 (3H, d, *J* 7.1, C*H*$_3$–CH<), 1.82 (3H, d, *J* 7.2, C*H*$_3$–CH=), 4.40 (1H, d, *J* 17.5, –C*H*$_2$–), 4.58 (1H, d, *J* 17.5, –C*H*$_2$–), 5.11 (1H, q, *J* 7.1, CH$_3$–C*H*<), 5.18 (2H, s, –OC*H*$_2$Ph), 6.17 (1H, dd, *J* 15.4, 7.1, –C*H*=), 6.8–7.4 (9H, m, aromatics), 7.70 (1H, d, *J* 15.4, –CO–C*H*=). MS *m*/*z*: 378 (M^+). Anal. Calcd for $C_{21}H_{22}N_4O_3$: C, 66.65; H, 5.86; N, 14.81. Found: C, 66.69; H, 5.90; N, 14.88.

4.1.2. 2-[*N*-(1-(*S*)-Phenylethyl)-*N*-(1-oxo-2-(*E*)-butenyl)]-methylamino phenylazide 1e. 2.88 g, 92%. Orange oil. $[\alpha]_D^{25} = -66.0$ (*c* 0.24, $CHCl_3$); IR (neat) 2130, 1660 cm^{-1}; ^{1}H NMR δ: 1.38 (3H, d, *J* 7.7, C*H*$_3$–CH<), 1.80 (3H, d, *J* 7.0, C*H*$_3$–CH=), 4.20 (1H, d, *J* 17.9, –C*H*$_2$–), 4.32 (1H, d, *J* 17.9, –C*H*$_2$–), 5.84 (1H, q, *J* 7.7, CH$_3$–C*H*<), 6.50 (1H, dd, *J* 15.3, 7.0, –C*H*=), 6.8–7.4 (9H, m, aromatics), 7.75 (1H, d, *J* 15.3, –CO–C*H*=). MS *m*/*z*: 320 (M^+). Anal. Calcd for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.27; H, 6.33; N, 17.53.

4.2. Thermal behaviour of *N*-alkenoyl aryl azides 1a–e in the presence of catalytic amounts of PTSA

A solution of *N*-alkenoyl aryl azides **1a**–**e** (5.0 mmol) and PTSA (17 mg, 0.1 mmol) in dry toluene (250 mL) was refluxed under a nitrogen atmosphere for 4 h. Evaporation of the solvent gave a residue that was crystallised with diisopropylether to give pure **3a**–**e**.

4.2.1. 2-Methyl-4-[1-(*S*)-(1-benzyloxycarbonyl)ethyl]-4,5-dihydro-1,4-benzodiazepine-3-one 3a. 1.51 g, 95%.[10]

4.2.2. 2-Ethyl-4-[1-(*S*)-(1-benzyloxycarbonyl)ethyl]-4,5-dihydro-1,4-benzodiazepine-3-one 3b. 1.68 g, 96%. White powder, mp 76–78 °C (from diisopropyl ether). $[\alpha]_D^{25} = +241.0$ (*c* 0.22, $CHCl_3$); IR (Nujol) 1740, 1650 cm^{-1}; ^{1}H NMR δ: 1.21 (3H, t, *J* 8.1, C*H*$_3$CH$_2$–), 1.44 (3H, d, *J* 7.7, C*H*$_3$–CH<), 2.90 (2H, t, *J* 8.1, CH$_3$C*H*$_2$–), 4.10 (2H, s, –C*H*$_2$–), 5.15 (2H, s, –OC*H*$_2$Ph), 5.36 (1H, q, *J* 7.7, CH$_3$–C*H*<), 6.8–7.4 (9H, m, aromatics); ^{13}C NMR δ: 19.80 (q), 20.48 (q), 22.55 (t), 49.80 (q), 51.28 (t), 52.20 (d), 126.0–130.0, 136.50 (s), 137.88 (s), 140.21 (s), 148.18 (s), 169.70 (s), 173.44 (s). MS *m*/*z*: 350 (M^+). Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.03; H, 6.34; N, 8.06.

4.2.3. 2-Benzyl-4-[1-(*S*)-(1-benzyloxycarbonyl)ethyl]-4,5-dihydro-1,4-benzodiazepine-3-one 3c. 1.90 g, 92%. White powder, mp 64–65 °C (from diisopropyl ether). $[\alpha]_D^{25} = +135.1$ (*c* 0.20, $CHCl_3$); IR (Nujol) 1735, 1660 cm^{-1}; ^{1}H NMR δ: 1.40 (3H, d, *J* 7.8, C*H*$_3$–CH<), 2.87 (2H, s, –C*H*$_2$–Ph), 4.25 (2H, s, –C*H*$_2$–), 5.10 (2H, s, –OC*H*$_2$Ph), 5.44 (1H, q, *J* 7.8, CH$_3$–C*H*<), 6.1–7.4 (14H, m, aromatics); ^{13}C NMR δ: 21.16 (q), 27.98 (t), 51.11 (q), 54.55 (t), 57.12 (d), 125.0–132.0, 135.66 (s), 137.00 (s), 142.23 (s), 147.62 (s), 170.80 (s), 176.23 (s). MS *m*/*z*: 412 (M^+). Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86; N, 6.79. Found: C, 77.76; H, 5.90; N, 7.84.

4.2.4. 2-Methyl-4-(1-(*S*)-phenylethyl)-4,5-dihydro-1,4-benzodiazepine-3-one 3d. 1.32 g, 95%.[10]

4.2.5. 2-Ethyl-4-(1-(*S*)-phenylethyl)-4,5-dihydro-1,4-benzodiazepine-3-one 3e. 1.43 g, 98%. White powder, mp 91–93 °C (from diisopropyl ether). $[\alpha]_D^{25} = +54.6$ (*c* 0.24, $CHCl_3$); IR (neat) 1630 cm^{-1}; ^{1}H NMR δ: 1.22 (3H, d, *J* 8.0, C*H*$_3$CH$_2$–), 1.72 (3H, d, *J* 7.7, C*H*$_3$–CH<), 2.76 (2H, t, *J* 8.0, CH$_3$C*H*$_2$–), 4.24 (1H, d, *J* 16.8, –C*H*$_2$–), 4.38 (1H, d, *J* 16.8, –C*H*$_2$–), 5.66 (1H, q, *J* 7.7, CH$_3$–C*H*<), 7.0-7.5 (9H, m, aromatics); ^{13}C NMR δ: 18.87 (q), 20.56 (q), 23.37 (t), 50.85 (t), 52.45 (d), 123.0–130.0, 136.60 (s), 137.90 (s), 140.10 (s), 148.23 (s), 168.85 (s). MS *m*/*z*: 292 (M^+). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.09; H, 6.92; N, 9.64.

4.2.6. 2-Benzyl-4-(1-(*S*)-phenylethyl)-4,5-dihydro-1,4-benzodiazepine-3-one 3f. 1.72 g, 97%. White powder, mp 73–75 °C (from diisopropyl ether). $[\alpha]_D^{25} = +107.1$ (*c* 0.14, $CHCl_3$); IR (neat) 1650 cm^{-1}; ^{1}H NMR δ: 1.83 (3H, d,

J 7.6, C*H*$_3$–CH<, 2.85 (2H, s, –C*H*$_2$–Ph), 4.20 (1H, d, *J* 17.9, –C*H*$_2$–), 4.35 (1H, d, *J* 17.9, –C*H*$_2$–), 5.42 (1H, q, *J* 7.6, CH$_3$–C*H*<), 6.7–7.6 (14H, m, aromatics); ^{13}C NMR δ: 21.67 (q), 27.17 (t), 51.36 (t), 52.80 (d), 122.0–129.0, 136.34 (s), 137.88 (s), 138.12 (s), 139.20 (s), 148.76 (s), 169.85 (s). MS *m*/*z*: 354 (M$^+$). Anal. Calcd for $C_{24}H_{22}N_2O$: C, 81.33; H, 6.26; N, 7.90. Found: C, 81.37; H, 6.29; N, 7.98.

4.3. Basic hydrolysis of 2-substituted-4,5-dihydro-1,4-benzodiazepine-3-ones 3a–c

A solution of **3a**–**c** (1.2 mmol) in tetrahydrofuran (25 mL) and 1 M aqueous sodium hydroxide (25 mL) was stirred at room temperature for 5 h. Aqueous hydrochloric acid (1 M) was added to pH 3 and the mixture was extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water (50 mL), dried over sodium sulfate and evaporated. Crystallisation from isopropanol gave pure **5a**–**c**.

4.3.1. 2-Methyl-4-[1-(*S*)-(1-hydroxycarbonyl)ethyl]-4,5-dihydro-1,4-benzodiazepine-3-one 5a. 0.22 g, 75%. White powder, mp 112–114 °C (from diisopropanol). $[\alpha]_D^{25} = +76.0$ (*c* 0.17, $CHCl_3$); IR (Nujol) 3340, 1700, 1660 cm^{-1}; ^{1}H NMR δ: 1.36 (3H, d, *J* = 7.9, C*H*$_3$–CH<), 2.59 (3H, s, C*H*$_3$–), 4.16 (2H, s, –C*H*$_2$–), 5.33 (1H, q, *J* 7.9, CH$_3$–C*H*<), 7.1–7.4 (4H, m, aromatics), 10.80 (1H, br s, –COO*H*); ^{13}C NMR δ: 20.31 (q), 23.12 (q), 48.87 (t), 51.82 (d), 127.0–131.0, 136.22 (s), 140.88 (s), 148.36 (s), 168.37 (s), 180.20 (s). MS *m*/*z*: 246 (M$^+$). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.44; H, 5.76; N, 11.43.

4.3.2. 2-Ethyl-4-[1-(*S*)-(1-hydroxycarbonyl)ethyl]-4,5-dihydro-1,4-benzodiazepine-3-one 5b. 0.27 g, 87%. White powder, mp 93–94 °C (from diisopropanol). $[\alpha]_D^{25} = +129.6$ (*c* 0.23, $CHCl_3$); IR (Nujol) 3350, 1710, 1660 cm^{-1}; ^{1}H NMR δ: 1.16 (3H, t, *J* 8.0, C*H*$_3$–CH<), 1.48 (3H, d, *J* 7.8, C*H*$_3$CH$_2$–), 2.46 (2H, q, *J* 8.0, CH$_3$–C*H*$_2$–), 4.33 (2H, s, –C*H*$_2$–), 5.21 (1H, q, *J* 7.8, CH$_3$–C*H*<), 7.0–7.4 (4H, m, aromatics), 10.50 (1H, br s, –COO*H*); ^{13}C NMR δ: 21.33 (q), 20.67 (q), 22.40 (t), 51.16 (t), 53.24 (d), 125.0–131.0, 136.43 (s), 140.70 (s), 148.94 (s), 168.89 (s), 182.34 (s). MS *m*/*z*: 260 (M$^+$). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.64; H, 6.23; N, 10.83.

4.3.3. 2-Benzyl-4-[1-(*S*)-(1-hydroxycarbonyl)ethyl]-4,5-dihydro-1,4-benzodiazepine-3-one 5c. 0.30 g, 78%. White powder having mp 163–165 °C (from diisopropanol). $[\alpha]_D^{25} = +289.6$ (*c* 0.38, $CHCl_3$); IR (Nujol) 3340, 1710, 1650 cm^{-1}; ^{1}H NMR δ: 1.76 (3H, d, *J* 7.9, C*H*$_3$–CH<), 2.75 (2H, s, –C*H*$_2$–Ph), 4.28 (2H, s, –C*H*$_2$–), 5.20 (1H, q, *J* 7.9, CH$_3$–C*H*<), 7.1–7.4 (9H, m, aromatics), 10.55 (1H, br s, –COO*H*); ^{13}C NMR δ: 20.85 (q), 25.95 (t), 50.55 (t), 53.67 (d), 125.0–131.0, 136.20 (s), 137.90 (s), 140.38 (s), 148.76 (s), 167.58 (s), 181.10 (s). MS *m*/*z*: 322 (M$^+$). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.83; H, 5.60; N, 8.75.

4.4. Catalytic hydrogenation of 2-substituted-4,5-dihydro-1,4-benzodiazepine-3-ones 3c and 3f

A solution of **3c** or **3f** (0.5 mmol) in MeOH (20 mL) was treated with 10% Pd(OH)$_2$/C (0.14 g) and stirred under a hydrogen atmosphere (15 psi) for 24 h. The mixture was filtered through a Celite pad, and the solvent was removed under reduced pressure and the residue chromatographed on silica gel column with hexane–AcOEt (2:1) to afford 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones **6** and **7**.

4.4.1. 4-[1-(*S*)-(1-Hydroxycarbonyl)ethyl]-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one 6. 50 mg, 43%. Pale yellow powder, mp 116–118 °C (from diisopropanol). $[\alpha]_D^{25} = -35.1$ (*c* 0.77, $CHCl_3$); IR (Nujol) 3240, 1710, 1645 cm^{-1}; ^{1}H NMR δ: 1.43 (3H, d, *J* 8.1, C*H*$_3$–CH<), 3.95 (1H, d, *J* 14.6, –HN–C*H*$_2$–), 4.12 (1H, br s, –N*H*), 4.27 (1H, d, *J* 16.6, –C*H*$_2$–), 4.38 (1H, d, *J* 14.6, –HN–C*H*$_2$–), 4.86 (1H, d, *J* 16.6, –C*H*$_2$–), 5.36 (1H, q, *J* 8.1, CH$_3$–C*H*<), 6.5–7.1 (4H, m, aromatics), 10.40 (1H, br s, –COO*H*); ^{13}C NMR δ: 21.93 (q), 27.19 (t), 38.16 (t), 56.37 (d), 125.0–131.0, 136.45 (s), 137.81 (s), 168.10 (s), 179.22 (s). MS *m*/*z*: 234 (M$^+$). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.57; H, 5.98; N, 12.02.

4.4.2. 4-[(1-(*S*)-(1-Phenylethyl)]-1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one 7. 52 mg, 39%. Pale yellow powder, mp 85–87 °C (from diisopropyl ether). $[\alpha]_D^{25} = -107.1$ (*c* 0.14, $CHCl_3$); IR (Nujol) 3230, 1715, 1655 cm^{-1}; ^{1}H NMR δ: 1.49 (3H, d, *J* 7.9, C*H*$_3$–CH<), 4.03 (1H, d, *J* 14.6, –HN–C*H*$_2$–), 4.10 (1H, br s, –N*H*), 4.22 (1H, d, *J* 16.7, –C*H*$_2$–), 4.35 (1H, d, *J* 14.6, –HN–C*H*$_2$–), 4.44 (1H, d, *J* 16.7, –C*H*$_2$–), 6.02 (1H, q, *J* 7.9, CH$_3$–C*H*<), 6.5–7.4 (9H, m, aromatics); ^{13}C NMR δ: 20.16 (q), 30.15 (t), 41.12 (t), 53.87 (d), 126.0–132.0, 135.22 (s), 138.11 (s), 171.36 (s), 180.98 (s). MS *m*/*z*: 266 (M$^+$). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.80; H, 6.78; N, 10.57.

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