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The [2+2] Staudinger cycloadditive route to enantiopure azetidino[4,1-*d*][1,4]benzooxazepines

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Abstract—The [2+2] Staudinger cycloaddition between the C=N double bond of 2,3-dihydrobenzoxazepines **2** and **6** and a series of acetyl chlorides gave the azetidino[4,1-*d*][1,4]benzo oxazepines **3** and **7**, **8**, respectively. In the case of enantiopure **6**, the cycloaddition diastereoselectivity was markedly dependent from the substituent α to the imine.

1. Introduction

Due to their usefulness in the treatment of bacterial infections,[1] 2-azetidinone based antibiotics are of great relevance both in industrial and academic fields. Much effort has been devoted to the synthesis of new β-lactam antibiotics with enhanced antibacterial activity,[2] or featuring good resistance towards β-lactamases and dehydropeptidases.[3]

From this latter point of view, tricyclic β-lactams represent very promising candidates.[4] In line with our recent reports on the synthesis of tricyclic β-lactams,[5] here we describe a straightforward and convenient procedure for preparing racemic and enantiopure azetidino[4,1-*d*][1,4]benzoxazepine skeletons exploiting the [2+2] Staudinger cycloaddition between the C=N double bond of 2,3-dihydrobenzoxazepines and ketene derivatives, generated in situ from a series of acetyl chlorides.

2. Results and discussion

Preliminary experiments were carried out on the achiral 2,3-dihydrobenzoxazepine **2** aimed at optimising the experimental conditions. Compound **2** was readily synthesised in two steps starting from 2-fluoro-5-nitrobenzaldehyde diethylacetal by: (i) O-nucleophilic substitution of fluorine with ethanolamine, (ii) acidic hydrolysis of the diethylacetal function restoring the aldehyde group followed by spontaneous cyclisation (Scheme 1).

Subsequent treatment of **2** with acetoxy, phenoxy and phthalimidoacetyl chloride in the presence of triethylamine afforded the racemic *trans*-azetidino[4,1-*d*][1,4]-benzoxazepines **3a**–**c** in satisfactory yields. The structure of **3** has been assigned unambiguously by analytical and spectral data. The *trans* arrangement of the two hydrogens in the 3- and 4-positions of the azetidinone ring has been deduced by ^{1}H NMR from the vicinal scalar coupling constant of 2.1 Hz, which falls in the 2.1–2.8 Hz range typical for a *trans* reciprocal spatial arrangement in azetidinone derivatives.[6]

The enantiomerically pure **6a**–**c** were obtained starting from commercially available (*S*)-(+)-2-aminopropanol, (*S*)-(+)-phenylglycinol and (*S*)-(+)-2-amino-3-methyl-1-butanol, respectively, following the same procedure described for **2**. Compounds **6a**,**b** undergo [2+2] cycloaddition reaction with phenoxy and phthalimidoacetyl chloride, respectively, giving a diastereoisomeric mixture of **7a**,**b** and **8a**,**b** in about a 50:50 ratio (Scheme 2 and Table 1). The diastereoisomeric mixture could be separated by column chromatography over silica gel only in the case of cycloadducts **7b** and **8b** and their enantiomeric purity was checked by ^{1}H NMR using of Eu(hfc)$_3$ [tris(heptafluoropropyl hydroxymethylene-(+)camphorato)europium-(III)] as chiral shift reagent. In both cases, the enantiomeric excess (ee) was found to be over 98%.

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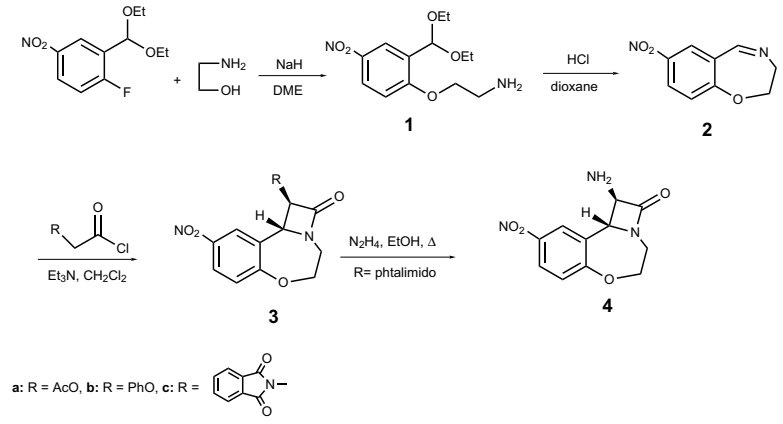
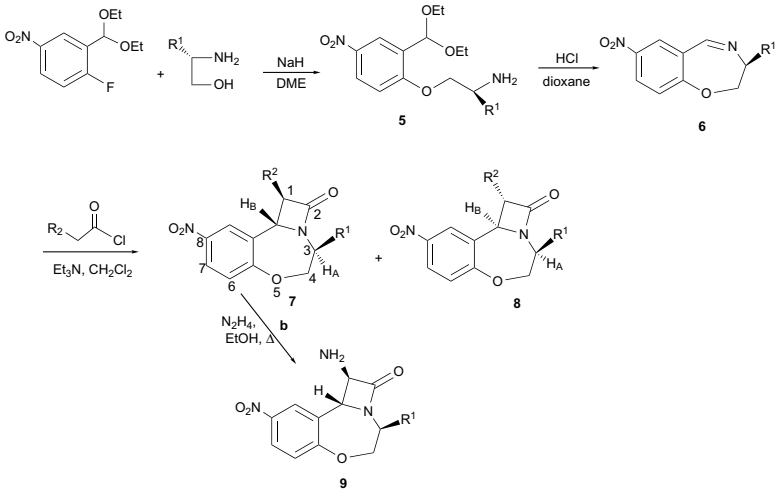


Scheme 1.



Entry	a	b	c
R_1	Me	Ph	iPr
R_2	PhO	Phthalimido	Phthalimido

Scheme 2.

Table 1. [2+2] Cycloadditions onto enantiopure **7** in dry dichloromethane

Entry	R^1	R^2	Product yield (%)[a] **7**+**8**	Product ratio[b] **7**:**8**
a	Me	PhO	47	55:45
b	Ph	Phthalimido	64	50:50
c	*i*-Pr	Phthalimido	59	100:0

[a] Cumulative yields.
[b] Deduced from ^{1}H NMR spectroscopy.

The absolute configurations of the newly formed stereocentres on the cycloadducts **7b** and **8b** were assigned unambiguously on the basis of NOESY experiments. These showed NOE enhancements of the signals of the hydrogens H_A and H_B, and this is possible only for a reciprocal spatial arrangement depicted by the formulae **8**. The stereochemistry of these cycloadducts has also been supported by computational calculation of their energy minima conformations optimised at the AM1[7] level. The computed distances between H_A and H_B[8] (**8a**: 2.89 Å; **8b**: 2.80 Å) are in good agreement with NOESY experiments. Conversely, the computed H_A–H_B

distance for the diastereoisomers **7a** and **7b** were 4.05 and 4.02 Å, respectively. These are too long for observing any NOE enhancements as confirmed by the absence of cross-peaks between these hydrogens in NOESY experiments.

The [2+2] cycloaddition between enantiopure **6c** and phthalimidoacetyl chloride afforded **7c** as the sole diastereoisomer in 59% yield. On the basis of NOESY experiments, we were able to assign the (1*R*,1*aR*) configuration to the newly formed stereocentres on the azetidinone ring.

To this point, the above results deserve some comments. The formation of cycloadducts **3**, **7** and **8**, which show the *trans* arrangement of the azetidinone ring can be accounted for by the accepted stereochemical model of the Staudinger reaction between *cis*-imines and ketenes.[9] Furthermore, as can be inferred from Table 1, the diastereoselectivity outcome of [2+2] cycloadditions onto enantiopure **6** was markedly dependent from the substituent α to the C=N double bond. This behaviour could be accounted by considering the steric encumbrance of the isopropyl substituent (R^1) towards the incoming phthalimido ketene with respect to methyl or phenyl substituents.

3. Conclusion

In conclusion, in order to functionalise further the prepared cycloadducts, the phthalimido protecting group in **3c** and **7b** has been removed giving the amino derivatives **4** and enantiopure **9** in good overall yields.

4. Experimental

4.1. General

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 AC 300 or a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. The NOESY experiments were acquired with 1024 data points for 512 increments, without zero-filling. A relaxation delay (*d*1) of 2 s and a mixing time (*d*8) of 700 ms (compound **7b**,**c**) or 800 ms (compound **8b**) was used. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter at the sodium D-line at 25 °C.

4.2. 2-Fluoro-5-nitrobenzaldehyde diethylacetal

To a stirred solution of 2-fluoro-5-nitrobenzaldehyde (0.5 g, 3.0 mmol) in absolute ethanol (20 mL) triethylorthoformate (0.53 mL, 3.2 mmol) and two drops of 97% sulfuric acid were added. The reaction was monitored by TLC (eluent: diethylether/light petroleum 2:3). After 3 h the reaction is completed and, in order to neutralise the sulfuric acid, quenched with triethylamine, then taken up with water (20 mL) and extracted with diethylether (5×10 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure giving 2-fluoro-5-nitrobenzaldehyde diethylacetal (0.69 g, 95%) as yellow oil. IR (film) 1530, 1350 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (dt, 6H, *J* 1.7, 7.0 Hz), 3.5–3.7 (m, 4H), 5.70 (s, 1H), 7.1–8.5 (m, 3H); ^{19}F NMR ($CDCl_3$) δ −108.5; MS *m*/*z* 243 (M^+).

4.3. (2-Bis-ethoxyethyl-4-nitro)phenyl-2-aminoethylethers 1 and 5. General procedure

To a suspension of 60% (dispersion in mineral oil) sodium hydride (0.24 g, 5.9 mmol) in dry ethylene glycol dimethylether (15 mL) the appropriate ethanolamine (5.9 mmol) was slowly added, then 2-fluoro-5-nitrobenzaldehyde diethylacetal (1.43 g, 5.9 mmol) was added and the solution colour turned to orange/red. The reaction was monitored by TLC (eluent: diethyl ether–light petroleum 5:2). After 1–5 h at room temperature, the reaction was quenched with water (20 mL) and extracted with dichloromethane (3×10 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure giving crude (2-bis-ethoxyethyl-4-nitro)phenyl-2-aminoethylethers **1** and **5a**–**c**, which were used without further purification.

4.3.1. Compound 1. (1.56 g, 98%). Yellow oil; IR (Nujol) 3390, 1520, 1340, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, *J* 7.0, 6H), 1.50 (br s, 2H), 3.05 (t, *J* 5.1, 2H), 3.4–3.6 (m, 4H), 4.05 (t, *J* 5.1, 2H), 5.65 (s, 1H), 6.8–8.4 (m, 3H); MS *m*/*z* 270 (M^+). Anal. Calcd for $C_{13}H_{20}N_2O_5$: C, 54.92; H, 7.09; N, 9.85. Found: C, 54.90; H, 7.1; N, 9.77.

4.3.2. Compound 5a (from (*S*)-(+)-2-amino-1-propanol). (1.64 g, 98%). Yellow oil; $[\alpha]_D^{25} = +7.1$ (*c* 1.28, $CHCl_3$); IR (Nujol) 3350, 1510, 1340, 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1–1.3 (m, 9H), 1.70 (br s, 2H), 3.7–3.4 (m, 5H), 3.7–3.8 (m, 1H), 4.05 (dd, *J* 4.1, 8.9, 2H), 5.75 (s, 1H), 6.9–8.5 (d, *J* 2.9, 1H); MS *m*/*z* 284 (M^+). Anal. Calcd for $C_{14}H_{22}N_2O_5$: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.34; H, 7.44; N, 9.37.

4.3.3. Compound 5b (from (*S*)-(+)-phenylglycinol). (2.08 g, 98%). Yellow oil; $[\alpha]_D^{25} = +25.6$ (*c* 0.87, $CHCl_3$); IR (Nujol) 3380, 1520, 1340, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2–1.3 (m, 6H), 1.90 (br s, 1H), 3.4–3.6 (m, 4H), 4.10 (dd, *J* 8.6, 8.7, 1H), 4.20 (dd, *J* 8.7, 3.9, 1H), 4.5 (dd, *J* 8.6, 3.9, 1H), 6.9–8.5 (m, 8H); MS *m*/*z* 346 (M^+). Anal. Calcd for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.34; H, 6.7; N, 7.75.

4.3.4. Compound 5c (from (*S*)-(+)-2-amino-3-methyl-1-butanol). (1.80 g, 98%). Yellow oil; $[\alpha]_D^{25} = +14.9$ (*c* 0.89, $CHCl_3$); IR (Nujol) 3390, 1519, 1340, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, *J* 6.8, 6H), 8.2–8.3 (m, 6H), 1.6 (br s, 2H), 1.7–1.8 (m, 1H), 3.0–3.1 (m, 1H), 3.5–3.6 (m, 4H), 3.9 (dd, *J* 8.9, 7.7, 1H), 4.2 (dd, *J* 8.9, 3.7, 1H), 5.8 (s, 1H), 6.9–8.5 (m, 3H); MS *m*/*z*

312 (M^+). Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.88; H, 8.58; N, 8.64. Found: C, 58.87; H, 8.65; N, 8.65.

4.4. 7-Nitro-2,3-dihydrobenzo[*f*][1,4]oxazepines 2 and 6a–c. General procedure

To a solution of the appropriate **1** or **5a**–**c** (4.6 mmol) in dioxane (30 mL), 37% aqueous hydrochloric acid was added to pH 4 until a white solid was formed. After 15–30 min at room temperature the reaction mixture was neutralised with 5% aqueous sodium hydrogencarbonate, the solution became clear and was stirred for further 30–60 min. Water (20 mL) was added and the mixture was extracted with dichloromethane (3×50 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure giving crude 7-nitro-2,3-dihydrobenzo[*f*][1,4]oxazepines **2** and **6a**–**c**.

In the case of compounds **2** and **6a** the residue was chromatographed on a silica gel column with diethylether.

4.4.1. Compound 2. (0.64 g, 73%). Yellow solid; mp 105–106 °C (from diisopropyl ether); IR (Nujol) 1640, 1510, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0–4.1 (m, 2H), 4.3–4.4 (m, 2H), 7.1–8.3 (m, 3H), 8.20 (s, 1H); MS *m*/*z* 192 (M^+). Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.28; H, 4.19; N, 14.59.

4.4.2. Compound (3*S*)-6a. (0.57 g, 60%). Yellow solid; mp 116–117 °C (from diisopropylether); $[\alpha]_D^{25} = -113.7$ (*c* 1.13, $CHCl_3$); IR (Nujol) 1635, 1515, 1335 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, *J* 6.8, 3H), 4.0–4.1 (m, 2H), 4.1–4.2 (m, 1H), 7.0–8.3 (m, 3H), 8.10 (s, 1H); MS *m*/*z* 206 (M^+). Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.58. Found: C, 56.28; H, 4.90; N, 13.59.

4.4.3. Compound (3*S*)-6b. (1.1 g, 90%). Yellow solid; mp 130–132 °C (from light petroleum); $[\alpha]_D^{25} = -25.0$ (*c* 1.13, $CHCl_3$); IR (Nujol) 1650, 1510, 1335 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.20 (dd, *J* 12.2, 6.1, 1H), 4.55 (d, *J* 12.2, 1H), 5.0 (br s, 1H), 7.0–8.3 (m, 8H), 8.40 (s, 1H); MS *m*/*z* 268 (M^+). Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.18; H, 4.49; N, 10.46.

4.4.4. Compound (3*S*)-6c. (1.03 g, 96%). Thick oil; $[\alpha]_D^{25} = -53.4$ (*c* 0.69, $CHCl_3$); IR (Nujol) 1645, 1520, 1340, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) 0.9–1.0 (m, 6H), 1.8–1.9 (m, 1H), 3.5–3.6 (m, 1H), 4.1 (dd, *J* 12.1, 5.1, 1H), 4.35 (d, *J* 12.1, 1H), 7.05–8.3 (m, 3H); 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, 61.58; H, 6.0; N, 11.94. Compound **6c** was used without further purification.

4.5. Azetidino[4,1-*d*][1,4]benzoxazepines 3 and 7, 8. General procedure

A solution of 7-nitro-2,3-dihydrobenzo[*f*][1,4]oxazepine **2** or **6a**–**c** (1.0 mmol) and triethylamine (20% molar excess with respect to acyl chloride) in dry dichloromethane (15 mL) was cooled under nitrogen at −5/−10 °C. The appropriate acyl chloride (acetoxyacetyl chloride: 3.5 mmol; phenoxyacetyl chloride 1.1 mmol; phthalimidoacetyl chloride 6.0 mmol) was slowly added. The mixture was stirred at −5 °C for 30 min, then it was allowed to stand at room temperature for 2–4 h. Dichloromethane (50 mL) was added and the mixture was washed first with brine (25 mL) and then with water (30 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure giving crude **3**, **7** and/or **8**. The residue was chromatographed on a silica gel column under vacuo with ethyl acetate (**3a**,**c**) or diethylether (**3b**) affording pure **3a**–**c**.

4.5.1. Compound 3a. (0.11 g, 36%). Mp 175–176 °C; IR (Nujol) 1750, 1515, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3H), 3.4–3.5 (m, 1H), 4.0–4.1 (m, 2H), 4.4–4.5 (m, 1H), 4.90 (d, *J* 0.9, 1H), 5.6 (d, *J* 0.9, 1H), 7.1–8.6 (m, 3H); MS *m*/*z* 292 (M^+). Anal. Calcd for $C_{13}H_{12}N_2O_6$: C, 53.43; H, 4.14; N, 9.58. Found: C, 53.46; H, 4.16; N, 9.60.

4.5.2. Compound 3b. (0.12 g, 37%). Mp 132–133 °C; IR (Nujol) 1770, 1520, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (ddd, *J* 2.9, 5.2, 13.7, 1H), 4.20 (ddd, *J* 3.5, 8.3, 13.7, 1H), 4.33 (ddd, *J* 3.5, 5.2, 12.8, 1H), 4.40 (ddd, *J* 2.9, 8.2, 12.8, 1H), 5.10 (d, *J* 1.6, 1H), 5.15 (d, *J* 1.6, 1H), 6.9–8.1 (m, 8H); MS *m*/*z* 314 (M^+). Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.58. Found: C, 62.58; H, 4.36; N, 8.56.

4.5.3. Compound 3c. (0.09 g, 24%). Mp 210 °C; IR (Nujol) 1770, 1720, 1520, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.5–3.6 (m, 1H), 4.1–4.2 (m, 2H), 4.4–4.5 (m, 1H), 5.20 (d, *J* 2.4, 1H), 5.30 (d, *J* 2.4, 1H), 7.1–8.1 (m, 7H); MS *m*/*z* 379 (M^+). Anal. Calcd for $C_{19}H_{13}N_3O_6$: C, 60.16; H, 3.45; N, 11.08. Found: C, 60.14; H, 3.46; N, 11.1.

4.5.4. Compounds 7a + 8a. As 55:45 diastereomeric mixture (47%); mp 50–60 °C; $[\alpha]_D^{25} = +21$ (*c* 1.01, $CDCl_3$); IR (Nujol) 1760, 1525, 1345 cm^{-1}. Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.54; H, 4.76; N, 8.21. Diastereoisomeric ratio was determined from methyl signals at ^1H NMR ($CDCl_3$) δ 1.65 (d, *J* 6.6, 3H), and 1.35 (d, *J* 6.6, 3H), whose integral was 55:45, respectively. Other signals: 3.9–4.5 (m, 3H), 5.1–5.2 (m, 2H), 7.0–7.4 (m, 6H), 7.9–8.1 (m, 2H).

4.5.5. Separation of pure diastereoisomers (1*R*,1a*R*,3*S*)-7b and (1*S*,1a*S*,3*S*)-8b from the diastereoisomeric mixture. The crude diastereoisomeric mixture was purified firstly from all by-products by column chromatography over silica gel using dichloromethane–ethyl acetate 9:1 as eluent, then the two diastereoisomers of **7b** and **8b** separated by another chromatography on a silica gel column eluent: diethylether–light petroleum 7:3.

4.5.6. Compound (1*R*,1a*R*,3*S*)-7b. (0.15 g, 32%). White solid; mp 220 °C; $[\alpha]_D^{25} = -108.0$ (*c* 0.70, $CHCl_3$); IR (Nujol) 1775, 1715, 1515, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.3–4.4 (m, 2H), 5.28 (d, *J* 2.3, 1H), 5.30 (dd, *J* 4.15, 9.7, 1H), 5.70 (d, *J* 2.3, 1H), 7.1–8.1 (m, 12H); MS *m*/*z* 455 (M^+). Anal. Calcd for $C_{25}H_{17}N_3O_6$:

C, 65.93; H, 3.76; N, 9.23. Found: C, 65.94; H, 3.76; N, 9.21. Ee >96%.

4.5.7. Compound (1*S*,1a*S*,3*S*)-8b. (0.15 g, 32%). White solid; mp 208–210 °C; $[\alpha]_D^{25} = +354.6$ (*c* 0.80, $CHCl_3$); IR (Nujol) 1775, 1725, 1510, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25 (dd, *J* 13.0, 3.0, 1H), 4.77 (dd, *J* 2.7, 13.0, 1H), 5.05 (t, *J* 2.4, 1H), 5.50 (d, *J* 2.6, 1H), 5.55 (d, *J* 2.6, 1H), 7.1–8.1 (m, 12H); MS *m*/*z* 455 (M^+). Anal. Calcd for $C_{25}H_{17}N_3O_6$: C, 65.93; H, 3.76; N, 9.23. Found: C, 65.96; H, 3.74; N, 9.24. Ee >96%.

4.5.8. Compound (1*R*,1a*R*,3*S*)-7c. (0.25 g, 59%). After column purification collected as white solid; mp 123–124 °C; $[\alpha]_D^{25} = -221.3$ (*c* 1.06, $CHCl_3$); IR (Nujol) 1765, 1720, 1520, 1390, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, *J* 6.8, 3H), 1.25 (d, *J* 6.7, 3H), 2.10–2.15 (m, 1H), 4.0–4.1 (m, 1H), 4.20 (d, *J* 6.1, 2H), 5.15 (d, *J* 2.1, 1H), 5.25 (d, *J* 2.1, 1H), 7.0–8.0 (m, 7H); MS *m*/*z* 421 (M^+). Anal. Calcd for $C_{22}H_{19}N_3O_6$: C, 62.70; H, 4.54; N, 9.97. Found: C, 62.69; H, 4.52; N, 9.94. Ee >96%.

4.6. 1-Amino-2-oxo-8-nitro-1,3,4,9b-tetrahydro-azetidino[4,1-*d*][1,4]benzoxazepine 4 and (+)-1(*R*)-amino-2-oxo-3(*S*)-phenyl-8-nitro-1,3,4,9b(*S*)-tetrahydro-azetidino[4,1-*d*][1,4] benzoxazepine 9

To a suspension of **3c** or **7b** (0.25 mmol) in absolute ethanol (4 mL) a solution of monohydrate hydrazine (0.27 mmol) in absolute ethanol (2 mL) was slowly added. The mixture was refluxed for 2.5 h (TLC ethyl acetate as eluent). Evaporation of the solvent gave solid, which was chromatographed on silica gel column under vacuo with dichloromethane–methanol 9:1 (in the case of **3c**) or ethyl acetate (in the case of **7b**) giving pure **4** or enantiomerically pure **9**.

4.6.1. Compound 4. (49 mg, 70%). Yellow solid; mp 194–195 °C; IR (Nujol) 3370, 1730, 1520, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (br s, 2H), 3.3–3.4 (m, 1H), 4.0–4.1 (m, 1H), 4.15 (d, *J* 2.4, 1H), 4.35–4.40 (m, 1H), 4.60 (d, *J* 2.4, 1H), 7.1–8.1 (m, 3H); MS *m*/*z* 281 (M^+). Anal. Calcd for $C_{11}H_{11}N_3O_6$: C, 53.01; H, 4.45; N, 16.86. Found: C, 63.05; H, 4.44; N, 16.84.

4.6.2. Compound (1*R*,1a*R*,3*S*)-9. (54 mg, 60%). Yellow solid; mp 189–190 °C; $[\alpha]_D^{25} = -90.0$ (*c* 0.57, $CHCl_3$); IR (Nujol) 3360, 1760, 1510, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (br s, 2H); 4.0 (s, 1H); 4.1–4.2 (m, 1H); 4.3–4.4 (m, 1H); 4.80 (s, 1H); 4.15 (d, *J* 4.3, 1H); 5.3 (d, *J* 4.3, 1H); 7.1–8.1 (m, 8H). Anal. Calcd for $C_{17}H_{15}N_3O_4$: C, 62.76; H, 4.65; N, 12.92. Found: C, 62.78; H, 4.64; N, 12.90.

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