An Efficient Asymmetric Synthesis of 2-Substituted 1,4-Benzodiazepin-3-one as a Potential Molecular Scaffold

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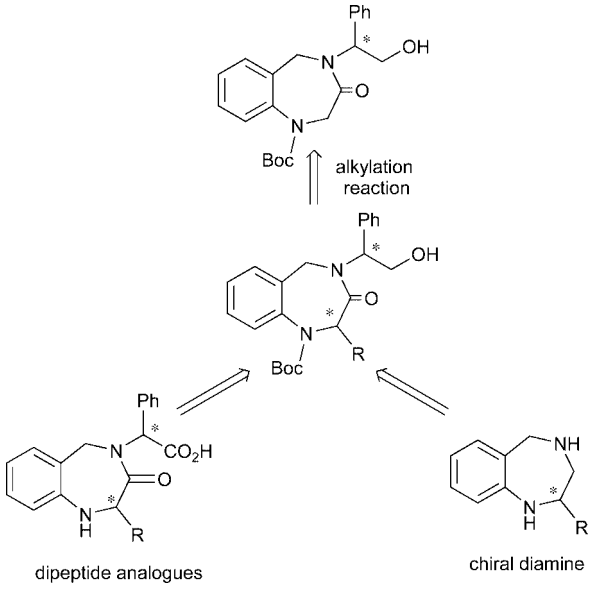
2-Substituted 1,4-benzodiazepine-2-one compounds (**9**–**12**) were obtained by a highly diastereoselective alkylation of a seven-membered ring benzolactam (**8**) in the presence of (*R*)-phenylglycinol as a chiral inductor. The corresponding acid derivative (**16**) afforded a conformationally constrained structure suitable for preparing peptidomimetic analogues useful as a novel molecular scaffold. After cleavage of the chiral appendage this approach might also lead efficiently to enantiomerically pure 2-substituted benzodiazepines (**15**).

Introduction

1,4-Benzodiazepine (1,4-BDZ) compounds have been extensively investigated owing to their important biological properties, and in recent times their structure has been widely used as a "molecular scaffold". Indeed, several of these nitrogen-containing heterocycles have been identified as antitumour antibiotics (DC-81),[1] anti-HIV[2] and antithrombotic[3] (Lotrafiban, SB-214857) agents, in addition to their well-known anxiolytic,[4] sedative[5] and anticonvulsant[6] activities. Moreover, because of both their structural motifs and physicochemical properties, this structure has been considered among novel non-peptide peptidomimetics. Indeed, 1,4-BDZ can act as a mimic of peptide secondary structures such as γ- and β-turns.[3,7]

As a consequence, numerous stereocontrolled synthetic approaches to 1,4-benzodiazepine compounds have been developed. Reductive cyclisation of amino aldehydes,[8] amino thioacetals,[9] cyclisation via isatoic anhydride by condensation with an amino acid derivative,[10] coupling of NCAs (*N*-carboxy α-amino acid anhydrides) with anthranilic acid derivatives,[11] condensation between 2-aminobenzophenone and α-substituted glycine derivatives[7a,12] or use of a chiral auxiliary attached to the 1,4-benzodiazepine structure,[10b,13,14] figure among the most important strategies. In some cases, an enzymatic resolution of the diastereomeric racemates of the final benzodiazepine has been successfully employed by using an immobilized form of *Candida antarctica* B lipase.[15] However, relatively little work has been done on the asymmetric synthesis of 2-substituted-1,4-benzodiazepines (Scheme 1).[16]



Scheme 1. Access to 2-substituted 1,4-benzodiazepine.

By targeting the synthesis of nitrogen-containing compounds of biological interest we are developing new synthetic methods based upon the diastereoselective alkylation of lactams using a chiral auxiliary from the chiral pool: phenylglycinol[17–19] or 2,3,4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid (DIGA).[20] In connection with our work on diastereoselective alkylations, we wish to report here a novel route towards the asymmetric synthesis of 1,4-benzodiazepine core derivatives. A chiral benzolactam derived from commercially available (*R*)-phenylglycinol was easily alkylated at the C-2 position by 1,4-stereoinduction of the enolate derivative of lactam (*R*)-**9**. This strategy led us to prepare several 2-substituted 1,4-BDZ in good to high diastereoselectivities and chemical yields. Further transforma-

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tions could lead to chiral diamine or dipeptide analogues (Scheme 1).

Results and Discussion

Prior to the diastereoselective alkylation step, we had to prepare the enantiopure 1,4-benzodiazepine-3-one **8** from (*R*)-phenylglycinol (Scheme 2).

This approach began with a reductive amination of aldehyde **1**, using standard methods, to introduce the chiral inductor. The nitro group was then readily reduced under hydrogenation conditions without cleavage of the chiral auxiliary. This absence of reactivity of such secondary benzyl derivatives of amino alcohols has already been observed previously.[18] Selective protection of both the primary alcohol with tBuPh$_2$SiCl and the aromatic amine with Boc$_2$O in the presence of NaH furnished the secondary benzylamine **6**. The resulting amine was then treated with bromoacetyl bromide[21] to give the *N*-acylated derivative **7**. Intramolecular cyclisation followed by silyl group deprotection was performed in a one-pot procedure, using NaH (3 equiv.) in DMF, to afford the seven-membered ring lactam **8** in 57% yield and 16% overall yield from **1**.

Our first experiments were conducted with two equivalents of lithiated base (*n*BuLi, *s*BuLi, *t*BuLi). The formation of the corresponding enolate was observed at –78 °C with *t*BuLi, but a higher temperature (–40 °C) was necessary to obtain complete deprotonation when *n*BuLi or *s*BuLi was used. Contrary to what has been observed in some other series,[17–20] the addition of lithium salts (LiBr, LiCl) did not improve the chemical yields. Furthermore, addition of HMPA led to a complex mixture of compounds. One of these side products was the dialkylated product arising from methylation at both the 2-position and the alcohol function. This could be detected when a combination of the following reaction conditions was present: a temperature higher than –78 °C and the presence of additives.

Finally, the best results were obtained using *n*BuLi as base, performing the deprotonation at –40 °C, adding an excess of electrophile at –78 °C, then allowing the alkylation to proceed at –40 °C for 6 h. Under these conditions, methylated lactam **9** was obtained in 83% yield as a 98:2 ratio of two isomers. After chromatography, the major isomer was isolated as a pure compound. The absolute configuration of the newly created stereogenic centre of the major isomer [(2*R*,12*R*)-**9**] was unambiguously determined by single-crystal X-ray diffraction analysis (Figure 1). The stereochemistry of the newly created centre can be explained by the approach of the electrophile to the opposite side of the N–Li bond[17] (Figure 2).

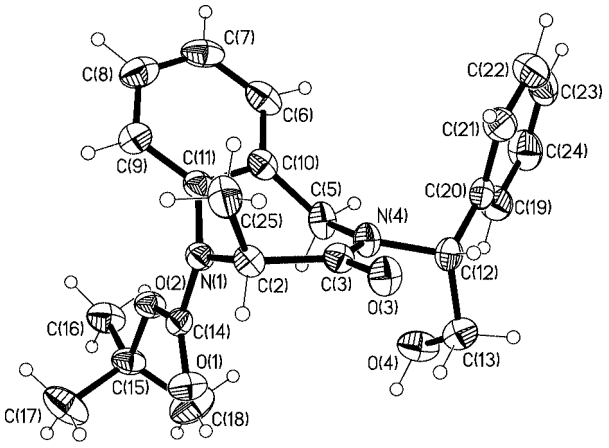
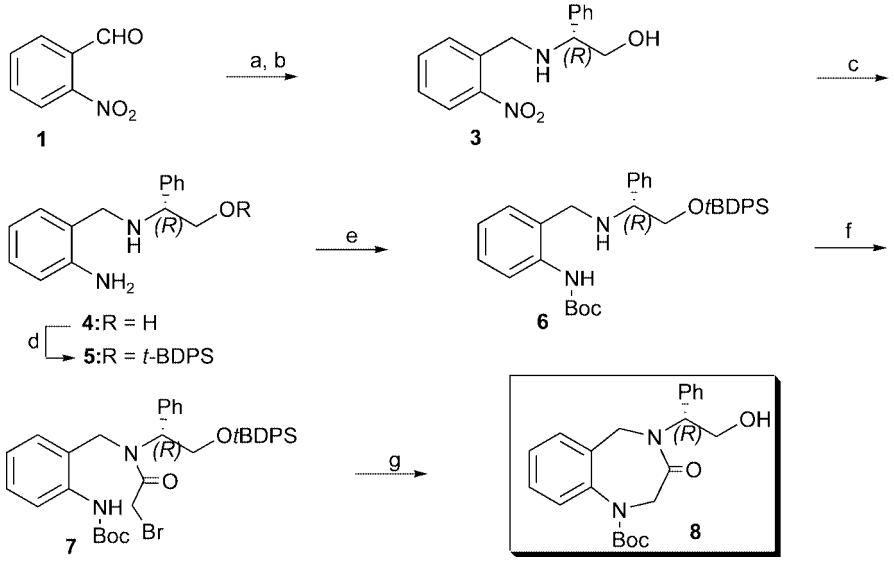


Figure 1. X-ray crystallographic structure and conformation of 2-methyl-3-oxo-2,3,4,5-benzodiazepine derivative **9**.



Scheme 2. Reagents and conditions: (a) (*R*)-phenylglycinol (**2**), MeOH, reflux, 3 h; (b) NaBH$_4$, room temp., overnight (quant.); (c) H$_2$ (1 atm)/10% Pd-C, EtOH, room temp. 18 h (83%); (d) tBuPh$_2$SiCl, imidazole, and DMF, room temp., 18 h (72%); (e) *i*. 95% NaH, anh. THF, 0 °C, 15 min; *ii*. Boc$_2$O, 0 °C to room temp., overnight (66%); (f) ClCOCH$_2$Br, NEt$_3$, CH$_2$Cl$_2$, –20 °C to room temp., overnight (71%); (g) 95% NaH 3 equiv., dry DMF, 0 °C to room temp. 3h30 min (57%).

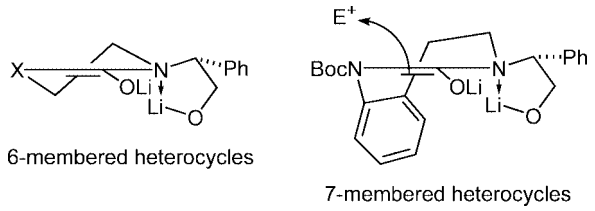
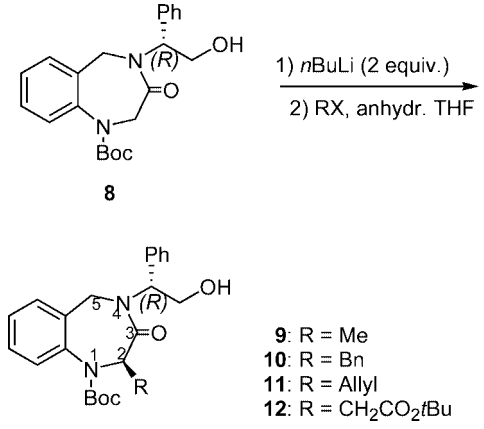


Figure 2. Rigid chelated enolate intermediate.

Under the above-mentioned conditions, different electrophiles (alkyl or allyl) were introduced into the C-2 position of the chiral benzodiazepine lactam **8**. The results for the preparation of compounds **10**–**12** are summarised in Table 1. Diastereomeric excesses (*de*) were determined by HPLC using an ODS column eluting with a CH_3CN/H_2O (40:60) system containing 0.1% TFA.

Table 1. Diastereoselective alkylations.

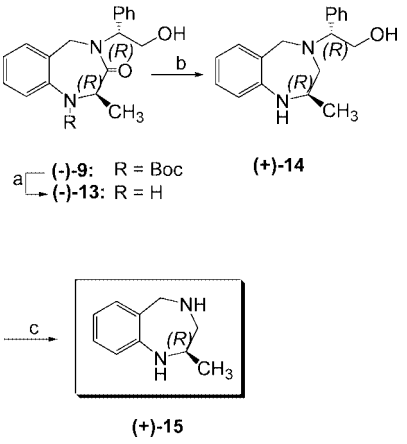


Entry	RX	Product	Yield [%]	*de* [%][a]
1	MeI	**9**	85	95
2	BnBr	**10**	63	93
3	$CH_2{=}CHCH_2I$	**11**	63	86
4	$BrCH_2CO_2tBu$	**12**	40	96

[a] Determined by HPLC analysis.

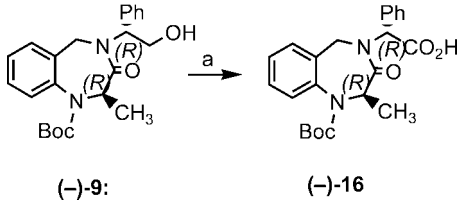
The expected alkylation reactions α to the amide took place in good to excellent yield. Nevertheless, a lower yield was obtained with *tert*-butylbromoacetate as an electrophile (entry 4). The absolute configuration of the 2-alkyl or 2-allyl compounds was assigned by analogy to the (2*R*,12*R*)-**9** derivative.

The preparation of the chiral diamine from the chiral benzodiazepine lactam could be achieved by a three-step procedure: *N*-Boc-deprotection in acidic medium (TFA/CH_2Cl_2), followed by reduction of the carbonyl group with $LiAlH_4$ and finally cleavage of the chiral appendage by catalytic hydrogenation in the presence of 5% HCl ethanolic solution. Following that procedure, the (2*R*,12*R*)-**9** benzolactam was transformed into the seven-membered ring diamine **15** without detectable racemisation (chiral GC analysis; Scheme 3).



Scheme 3. Synthesis of chiral diamine **15**. Reagents and conditions: (a) TFA/CH_2Cl_2 (1:1), 0 °C to room temp., 2 h (90%); (b) $LiAlH_4$, room temp. to reflux, overnight (91%); (c) H_2 (1 atm)/10% Pd-C, 5% HCl/EtOH, room temp., 8 h (65%).

A dipeptide mimic could also be obtained by simple oxidation of the primary alcohol of compound **9** using Jones' reagent to afford the corresponding acid **16** in 68.5% yield (Scheme 4).[17] In the course of the synthesis of compound **16**, no epimerisation was detected by ^1H NMR spectroscopy or HPLC analysis. The 2-substituted 1,4-benzodiazepine-3-one acids are constrained dipeptide analogues that could promote particular secondary structures of peptides, such as β- or γ-turns. It should be noted that other amino acid derived β-amino alcohols can act as chiral auxiliaries leading to a large variety of dipeptide analogues.



Scheme 4. Synthesis of dipeptide analogue **16**. Reagents and conditions: (a) Jones' reagent, acetone, 0 °C, 30 min (68.5%).

In summary, chiral benzolactam **8** has been prepared in good yield by standard reactions from 2-nitrobenzaldehyde and with (*R*)-phenylglycinol as the source of chirality. We have proposed an easy methodology to provide 2-substituted 1,4-benzodiazepines with good stereoselectivities and chemical yields by alkylation with various electrophiles. Cleavage of the chiral appendage provides a conformationally restricted enantiopure diamine [(+)-**15**] whose use as a possible chiral ligand in future reactions might be possible. The corresponding acid derivative of 1,4-benzodiazepin-3-one [(+)-**16**] could be used as a molecular scaffold and its incorporation into a peptide sequence would give us more information about the effect of this peptidomimetic on the peptide conformation. These studies are currently in progress.

Experimental Section

General: Solvents were purified by conventional methods prior to use. TLC was performed on Merck 60F-250 silica gel plates and column chromatography with silica gel SI 60 (230–240 mesh). Melting points were measured on a Kofler apparatus and are uncorrected. Elemental analyses were carried out on a Carlo–Erba EA 1100 analyser. NMR spectra were recorded on a Bruker DPX 300 spectrometer operating at 300 MHz for ^{1}H and 75.4 MHz for ^{13}C NMR. This probe is equipped with pulsed-field (*z*) gradients. Chemical shifts (δ) are expressed in ppm relative to TMS for ^{1}H and ^{13}C nuclei; coupling constants (*J*) are given in Hertz (Hz). Optical rotations were measured using a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_\lambda = \alpha_{obs}/c$ (*c* in g/100 mL, l-dm cell). IR spectra were recorded using KBr pellets or NaCl plates, and only partial data are reported. Mass spectra were obtained on an HP5890 spectrometer (electronic impact 70 eV).

Diastereomeric excesses (*de*) were determined by HPLC using an ODS (4.6×250 mm; 5 μm) column eluting with a CH_3CN/H_2O (40:60) system containing 0.1% TFA.

(*R*)-2-(2-Nitrobenzylamino)-2-phenylethanol (3): A solution of 2-nitrobenzaldehyde (**1**; 4.85 g, 32.12 mmol, 1.1 equiv.) and (*R*)-phenylglycinol (**2**, 4.0 g, 29.20 mmol) in methanol (70 mL) was heated at reflux for 3 h. The mixture was cooled to 0 °C and $NaBH_4$ (2.2 g, 58.4 mmol) was added portionwise over 30 min. The reaction mixture was allowed to warm to room temperature and stirred overnight. Then, 10% aq. $NaHCO_3$ solution (20 mL) was slowly added at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (3×75 mL), and the organic layers were combined, washed with brine (3×50 mL) and H_2O (3×50 mL), dried with $MgSO_4$ and then concentrated under reduced pressure to give 2-(2-nitrobenzylamino)-2-phenylethanol (**3**, 8.2 g, quant.) as a pale-yellow powder which was used without further purification. $[\alpha]_D^{20} = -47$ (*c* = 0.85, EtOH). IR (neat): $\tilde{\nu}_{max} = 3319\ cm^{-1}$, 3062, 2918, 2854, 1608, 1578, 1524, 1494, 1453, 1429, 1342, 1108, 1060, 922, 860, 790, 765, 748, 702. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.90 (d, *J* = 7.92 Hz, 1 H, H-6), 7.60–7.20 (m, 8 H, Ar), 4.02 (d, *J* = 14.2 Hz, 1 H, CH_{2a}NH), 3.85 (d, *J* = 14.2 Hz, 1 H, CH_{2b}NH), 3.80 (m, 1 H, CH_{2a}OH), 3.68 (dd, *J* = 10.87, 4.08 Hz, 1 H, CH_{2b}OH), 3.55 (m, 1 H, C*H*–Ph), 2.55 (br., 2 H, N*H*, O*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) 149.28, 140.10 and 135.32 (C), 133.17, 131.71, 128.80, 128.22, 127.85, 127.38 and 124.82 (CH, Ar), 69.66 (CH_2OH), 67.05 (CH–Ph), 48.69 (CH_2NH) ppm.

(*R*)-2-(2-Aminobenzylamino)-2-phenylethanol (4): A suspension of 2-(2-nitrobenzylamino)-2-phenylethanol (**3**; 8.2 g, 30.15 mmol) and 10% Pd/C (150 mg) in absolute ethanol (150 mL) was hydrogenated for 18 h at room temperature and 1 atm pressure until TLC indicated that reduction was complete. Then, the reaction mixture was filtered through Celite to remove the catalyst and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (cyclohexane/AcOEt, 50:50) to afford 6.0 g of compound **4** as a yellow oil (25.0 mmol, 83%). $[\alpha]_D^{20} = -126$ (*c* = 1, EtOH). IR (neat): $\tilde{\nu}_{max} = 3334\ cm^{-1}$, 3027, 2841, 1621, 1583, 1495, 1455, 1314, 1282, 1200, 1101, 1048, 752, 703. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40–7.25 (m, 5 H, Ar), 7.10 (t, *J* = 7.42 Hz, 1 H, H-5), 6.95 (d, *J* = 7.17 Hz, 1 H, H-3), 6.68 (m, 2 H, H-4 and H-6), 3.90–3.50 (m, 5 H, CH_2NH, C*H*-Ph and CH_2OH), 3.45 (br., 4 H, N*H*, NH_2, O*H*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 146.0 and 140.3 (C), 129.95, 128.56, 128.33, 127.56 and 127.28 (CH, Ar), 123.88 (C), 117.99 and 115.81 (CH, Ar), 66.63 (CH_2OH), 64.08 (CH-Ph), 49.83 (CH_2NH) ppm.

2-{[(*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-phenylethylamino]methyl}-phenylamine (5): *tert*-Butylchlorodiphenylsilane (2.16 mL, 8.26 mmol) was added dropwise to a solution of **4** (2.0 g, 8.26 mmol) and imidazole (0.55 g, 8.26 mmol) in dry DMF (25 mL). The mixture was then stirred at room temperature for 18 h under argon atmosphere, and H_2O (15 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3×20 mL) and the organic layer was washed with 10% aq. $NaHCO_3$ (2×15 mL) solution, brine (2×15 mL) and H_2O (2×15 mL), dried with $MgSO_4$ and the solvent was evaporated to give a residue. The residue was purified by flash column chromatography (cyclohexane/AcOEt, 92:8) to provide 2.86 g of compound **5** as a yellow oil (5.95 mmol, 72%). $\alpha]_D^{20} = -48$ (*c* = 1, EtOH). IR (neat): $\tilde{\nu}_{max} = 3435\ cm^{-1}$, 3320 (NH), 3069, 2930, 2857, 1618, 1495, 1460, 1427, 1112, 823, 743, 701. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.63–7.53 (m, 4 H, Ar), 7.45–7.23 (m, 11 H, Ar), 7.08 (t, *J* = 7.5 Hz, 1 H, H-5), 6.98 (d, *J* = 7.17 Hz, 1 H, H-3), 6.71–6.63 (m, 2 H, H-4 and H-6), 4.50 (br., 3 H, N*H*, NH_2), 3.80–3.70 (m, 4 H, CH_2OH, CH_{2a}NH and C*H*-Ph), 3.56 (d, *J* = 12.51 Hz, 1 H, CH_{2b}NH), 1.02 (s, 9 H, 3×CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 146.7 and 140.9 (C), 135.74 and 135.69 (CH, Ar), 133.56 and 133.41 (C), 129.96, 129.87, 129.79, 128.53, 128.39, 127.83, 127.79, 127.76 and 127.59 (CH, Ar), 124.50 (C), 117.96 and 115.80 (CH, Ar), 68.60 (CH_2O), 64.87 (CH-Ph), 50.83 (CH_2NH), 26.99 (3×CH_3), 19.34 (C) ppm.

***tert*-Butyl 2-{[(*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-phenylethylamino]methyl}phenylcarbamate (6):** A solution of **5** (5, 3.3 g, 6.87 mmol) in THF (10 mL) was cooled to 0 °C under argon and then a suspension of 95% NaH (0.177 g, 7 mmol) in THF (5 mL) was added dropwise. After stirring at the same temperature for 15 min, a solution of Boc_2O (1.5 g, 6.87 mmol) in THF (5 mL) was added to the reaction mixture. The resulting suspension was stirred at room temperature for 18 h, cooled to 0 °C and quenched by careful addition of H_2O (5 mL). The mixture was warmed to room temperature and poured into CH_2Cl_2. The organic layer was separated, washed successively with aq. $NaHCO_3$ saturated solution (3×20 mL), H_2O (2×20 mL) and brine (2×20 mL), dried with $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (cyclohexane/ AcOEt, 97:3) to obtain 2.63 g of compound **6** as a yellow oil (66%). $[\alpha]_D^{20} = -25$ (*c* = 1, EtOH). IR (neat): $\tilde{\nu}_{max} = 3293\ cm^{-1}$ (NH), 2976, 2934, 2852, 1724 (N–CO), 1589, 1516, 1452, 1366, 1233, 1156, 1127, 1111, 1045, 1023, 830, 773, 704. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.62 (br., 1 H, N*H*Boc), 8.02 (d, *J* = 8.19 Hz, 1 H, H-6), 7.65–7.55 (m, 4 H, Ar), 7.49–7.23 (m, 12 H, Ar), 7.05 (d, *J* = 7.42 Hz, 1 H, H-3), 6.92 (t, *J* = 7.42 Hz, 1 H, H-4), 3.77–3.68 (m, 4 H, CH_2OH, CH_{2a}NH and C*H*–Ph), 3.50 (d, *J* = 12.8 Hz, 1 H, CH_{2b}NH), 2.40 (br., 1 H, N*H*), 1.56 (s, 9 H, Boc), 1.02 (s, 9 H, 3×CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 153.34 (CO, Boc), 139.90 and 139.22 (C), 135.70 and 135.65 (CH, Ar), 133.46 and 133.25 (C), 129.96, 129.90, 129.47, 128.67, 128.40, 127.90, 127.89 and 127.82 (CH, Ar), 127.03 (C), 122.22 and 119.62 (CH, Ar), 79.66 (C), 68.61 (CH_2O), 65.71 (CH–Ph), 51.68 (CH_2NH), 28.65 (3×CH_3, Boc), 27.02 (3×CH_3), 19.33 (C).

***tert*-Butyl 2-[{2-Bromo-*N*-[(*R*)-2-(*tert*-butyldiphenylsilyloxy)-1-phenylethyl]acetamido}methyl]phenylcarbamate (7):** A solution of amine **6** (1 g, 1.72 mmol) and triethylamine (0.6 mL, 4.3 mmol) in anhydrous CH_2Cl_2 (8 mL) was cooled to –20 °C under argon. Bromoacetyl bromide (0.225 mL, 2.59 mmol) was dissolved in CH_2Cl_2 (5 mL) and was added dropwise over 15 min with stirring. The reaction mixture was warmed to room temperature and stirred overnight. Then, the mixture was washed with 5% aq. $NaHCO_3$ solution (3×20 mL), and brine (3×20 mL), dried with $MgSO_4$, filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (cyclohexane/AcOEt, 96:4) to afford 856 mg of compound **7** as a yellow oil (1.22 mmol, 71%).

$[\alpha]_D^{20}$ = –64 (*c* = 1, EtOH). IR (neat): $\tilde{\nu}_{max}$ = 3298 cm^{-1}, 3071, 2932, 2858, 1726, 1639, 1591, 1523, 1450, 1366, 1300, 1240, 1159, 1113, 1051, 823, 741, 702. ^1H NMR ($CDCl_3$, 300 MHz): δ = 10.10 (br., 1 H, N*H*Boc), 7.90 (d, *J* = 8.19 Hz, 1 H, H-6), 7.65–7.55 (m, 4 H, Ar), 7.49–7.23 (m, 12 H, Ar), 7.05 (d, *J* = 7.42 Hz, 1 H, H-3), 6.92 (t, *J* = 7.42 Hz, 1 H, H-4), 4.30–3.70 (m, 7 H, CH_2OH, CH_2NH, CH_2Br and C*H*-Ph), 3.50 (d, *J* = 12.8 Hz, 1 H, CH_{2b}NH), 1.56 (s, 9 H, Boc), 1.02 (s, 9 H, 3×CH_3) ppm. LSIMS: *m*/*z* = 701 $[M]^+$

***tert*-Butyl 2,3,4,5-Tetrahydro-4-[(*R*)-2-hydroxy-1-phenylethyl]-3-oxobenzo[*e*][1,4]diazepine-1-carboxylate (8):** Compound **7** (0.5 g, 0.713 mmol) was dissolved in dry DMF (12 mL) and cooled to 0 °C with an ice bath. Then, a suspension of 95% NaH (0.56 g, 2,2 mmol) dissolved in dry DMF (5 mL) was added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 3.5 h under argon. The mixture was cooled again to 0 °C and quenched by careful addition of H_2O (2 mL). The resulting solution was then diluted with AcOEt (200 mL) and washed successively with 10% aq. $NaHCO_3$ solution (3×100 mL), H_2O (3×100 mL) and brine (3×100 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated under vacuum to give a crude which was purified by flash column chromatography (cyclohexane/AcOEt, 88:12) to afford deprotected benzodiazepine **8** (155 mg, 0.406 mmol, 57%) as a white solid. M.p. 159 °C. $[\alpha]_D^{20}$ = –127 (*c* = 1, EtOH). IR (neat): $\tilde{\nu}_{max}$ = 3393 cm^{-1}, 2924, 2853, 1702, 1618, 1497, 1459, 1368, 1248, 1158, 1047, 1027, 963, 865, 758, 701. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.4–7.2 (m, 7 H), 7.09 (t, *J* = 7.4 Hz, 1 H, H-8), 6.56 (d, *J* = 7.4 Hz, 1 H, H-9), 6.05 (dd, *J* = 5.4, 7.9 Hz, 1 H, C*H*–Ph), 4.80 (d, *J* = 18.2 Hz, 1 H, H-2), 4.43 (d, *J* = 18.2 Hz, 1 H, H-2′), 4.26 (d, *J* = 14.3 Hz, 1 H, H-5), 4.3–4.1 (m, 2 H, CH_2OH), 4.01 (d, *J* = 14.3 Hz, 1 H, H-5′), 1.41 (s, 9 H, Boc) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.6 (3-CO), 154.0 (CO, Boc), 141.7, 136.6 and 134.8 (C), 129.0, 128.8, 127.4 and 127.3 (CH-Ar), 81.6 (C), 61.7 (*C*H_2OH), 59.0 (*C*H-Ph), 52.5 (2-CH_2), 44.7 (5-CH_2), 28.3 (3×CH_3, Boc) ppm. MS (FAB): *m*/*z* = 383 $[MH]^+$. $C_{22}H_{26}N_2O_4$ (382.45): calcd. C 69.09, H 6.85, N 7.32; found C 69.13, H 6.93, N 7.34.

General Procedure for Diastereoselective Alkylation at the 2-Position to Provide a 2-Substituted 1,4-Benzodiazepine (9–12): Benzodiazepine **8** (1 equiv.) was dissolved in anhydrous THF (2 mL) under argon, cooled in a dry ice/acetone bath to –78 °C, and treated slowly with *n*BuLi in THF solution (2 equiv.). Then, the resulting orange solution was warmed to –40 °C for 15 min and cooled again to –78 °C to introduce the appropriate alkyl or allyl halide (1.5 equiv.). The reaction mixture was stirred for between 6 h and overnight at –40 °C depending on the electrophile. The reaction was quenched by addition of aq. NH_4Cl saturated solution (2 mL), H_2O was added (3 mL) and extracted with CH_2Cl_2 (3×5 mL). The organic layer was washed with brine (2×5 mL) and H_2O (2×5 mL), filtered, dried with $MgSO_4$ and the solvents evaporated in vacuo. The crude products were purified by column chromatography on silica gel (cyclohexane/AcOEt, 70:30). The absolute configuration of **9** was established by single-crystal X-ray analysis.

(*R*)-*tert*-Butyl 2,3,4,5-Tetrahydro-4-[(*R*)-2-hydroxy-1-phenylethyl]-2-methyl-3-oxobenzo[*e*][1,4]diazepine-1-carboxylate (9): The synthesis was performed following the general procedure. After work up and purification, we obtained 68.7 mg of 2-methylbenzodiazepine **9** (0.173 mmol, 83%). $[\alpha]_D^{20}$ = –186.3 (*c* = 1, EtOH). IR (neat): $\tilde{\nu}_{max}$ = 3383 cm^{-1}, 2978, 2935, 1697 (CO), 1601, 1499, 1475, 1458, 1432, 1391, 1368, 1326, 1258, 1164, 1126, 1095, 1057, 847, 761, 701. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.4–7.1 (m, 7 H), 7.01 (m, 1 H, H-8), 6.18 (d, *J* = 7.2 Hz, 1 H, H-9), 6.08 (dd, *J* = 5.4, 8.2 Hz, 1 H, C*H*–Ph), 5.47 (br., 1 H, H-2), 4.49 (d, *J* = 13.9 Hz, 1 H, H-5), 4.29–4.25 (m, 1 H, CH_2OH), 4.2–4.1 (m, 1 H, CH_2OH′), 3.75 (d, *J* = 13.9 Hz, 1 H, H-5′), 3.10 (br., 1 H, OH), 1.40 (m, 9 H, Boc), 1.30 (d, *J* = 7.17 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.2 (3-CO), 153.9 (CO, Boc), 139.4, 135.3 and 134.8 (C), 129.3, 128.8, 128.5, 128.2, 128.1 and 127.4 (CH-Ar), 62.07 (*C*H_2OH), 59.0 (*C*H-Ph), 44.6 (5-CH_2), 28.4 (3×CH_3), 20.1 (CH_3) ppm. LSIMS: *m*/*z* 419 $[M + 23]^+$, 397 $[MH]^+$, 341, 221. $C_{23}H_{28}N_2O_4$ (396.48): calcd. C 69.67, H 7.12, N 7.07; found C 69.44, H 7.36, N 7.14.

(*R*)-*tert*-Butyl 2-Benzyl-2,3,4,5-tetrahydro-4-[(*R*)-2-hydroxy-1-phenylethyl)-3-oxobenzo[*e*][1,4]diazepine-1-carboxylate (10): The synthesis was performed following the general procedure. After work up and purification, we obtained 62 mg of 2-benzylbenzodiazepine **10** (0.132 mmol, 63%) as a pale-yellow oil. $[\alpha]_D^{20}$ = –64 (*c* = 1, EtOH). IR (neat): $\tilde{\nu}_{max}$ = 3420 cm^{-1}, 3008, 2979, 2931, 1702 (N–CO), 1614, 1497, 1455, 1431, 1387, 1368, 1326, 1255, 1216, 1158, 1117, 1048, 1025, 943, 852, 756, 700. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.4–7.1 (m, 12 H, Ar), 7.02 (t, *J* = 7.2 Hz, 1 H, H-8), 6.21–6.12 (m, 2 H, H-9 and C*H*-Ph), 5.89 (br., 1 H, H-2), 4.49 (d, *J* = 14.1 Hz, 1 H, H-5), 4.40–4.30 (m, 1 H, CH_2OH), 4.29–4.15 (m, 1 H, CH_2OH′), 3.78 (d, *J* = 14.1 Hz, 1 H, H-5′), 3.58 (d, *J* = 15.4 Hz, 1 H, CH_2Ph), 3.10 (br., 1 H, OH), 2.52 (q, 1 H, H-2), 2.40 (m, 1 H, CH_2Ph′) 1.40–1.10 (m, 9 H, Boc) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.3 (3-CO), 154.1 (CO, Boc), 139.0, 129.6 and 128.9 (C), 128.6, 126.6, 126.3 and 128.2 (CH-Ar), 62.2 (*C*H_2OH), 59.3 (*C*H-Ph), 44.7 (5-CH_2), 39.07 (CH_2Ph), 28.1 (3×CH_3, Boc) ppm. LSIMS: *m*/*z* = 416 $[MH - t\text{Bu}]^+$. $C_{29}H_{32}N_2O_4$ (472.57): calcd. C 73.70, H 6.83, N 5.93; found C 68.98, H 7.09, N 6.28.

(*R*)-*tert*-Butyl 2-Allyl-2,3,4,5-tetrahydro-4-[(*R*)-2-hydroxy-1-phenylethyl]-3-oxobenzo[*e*][1,4]diazepine-1-carboxylate (11): The title compound was obtained according to the general procedure. After work up, the crude was purified by column chromatography on silica gel (cyclohexane/AcOEt, 70:30) to give 56 mg of 2-allylbenzodiazepine (**11**, 0.133 mmol, 63.5%) as a pale-yellow oil. $[\alpha]_D^{20}$ = –166 (*c* = 1, EtOH). IR (neat): $\tilde{\nu}_{max}$ = 3422 cm^{-1}, 2978, 2931, 1702 (CO), 1615, 1497, 1458, 1386, 1368, 1325, 1254, 1162, 1047, 1024, 921, 854, 757, 700. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.4–7.2 (m, 7 H, Ar), 7.02–6.96 (m, 1 H, H-8), 6.15 (d, *J* = 7.41 Hz, 1 H, H-9), 6.10 (dd, *J* = 8.0, 5.5 Hz, 1 H, C*H*-Ph), 5.91–5.78 (m, 1 H, CH_2-C*H*=CH_2), 5.57 (q, 1 H, H-2), 5.17–5.06 (m, 2 H, CH_2–CH=CH_2), 4.50 (d, *J* = 13.9 Hz, 1 H, H-5), 4.33–4.10 (m, 2 H, CH_2OH), 3.76 (d, *J* = 13.9 Hz, 1 H, H-5′), 2.89 (d, *J* = 14.1 Hz, 1 H, CH_2–CH=CH_2), 2.55 (br., 1 H, OH), 2.10–1.96 (m, 1 H, CH_2–CH=CH_2′) 1.37 (m, 9 H, Boc) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.98 (3-CO), 154.39 (CO, Boc), 139.18, 136.58 and 135.29 (C), 134.99 (CH_2-*C*H=CH_2), 129.63, 128.86, 128.56, 128.27 and 128.07 (CH-Ar), 118.0 (CH_2-CH=*C*H_2), 62.11 (*C*H_2OH), 59.12 (*C*H-Ph), 44.57 (CH_2-5), 37.62 (*C*H_2-CH=CH_2), 28.32 (3×CH_3, Boc) ppm. LSIMS: *m*/*z* = 445 $[M + 23]^+$, 366 $[MH - t\text{Bu}]^+$, 246. $C_{25}H_{30}N_2O_4$ (422.52): calcd. C 71.07, H 7.16, N 6.63; found C 70.91, H 7.39, N 6.61.

(*R*)-*tert*-Butyl 2-[(*tert*-Butoxycarbonyl)methyl]-2,3,4,5-tetrahydro-4-[(*R*)-2-hydroxy-1-phenylethyl)-3-oxobenzo[*e*][1,4]diazepine-1-carboxylate (12): The synthesis was performed following the general procedure. After work up and purification, we obtained 40 mg of benzodiazepine **12** (0.084 mmol, 40%) as a pale-yellow oil. $[\alpha]_D^{20}$ = –96 (*c* = 1, EtOH). IR (neat): $\tilde{\nu}_{max}$ = 3428 cm^{-1}, 2978, 2931, 1707 (CO), 1629, 1497, 1458, 1389, 1368, 1323, 1257, 1154, 1049, 1027, 946, 847, 758, 700. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.35–7.20 (m, 7 H, Ar), 7.03 (t, *J* = 7.0 Hz, 1 H, H-8), 6.30–6.15 (m, 1 H, H-9), 6.05–6.00 (m, 1 H, C*H*–Ph), 5.90–5.65 (m, 1 H, H-2), 4.47 (d, *J* = 14.07 Hz, 1 H, H-5), 4.40–4.10 (m, 2 H, CH_2OH), 3.78 (d, *J* = 14.07 Hz, 1 H, H-5′), 3.15–2.85 (m, 1 H, CH_2COO*t*Bu), 2.32 (br.,

1 H, OH), 2.30–2.15 (m, 1 H, CH_2COO*t*Bu), 1.48 (s, 9 H, 3 × CH_3), 1.34 (q, 9 H, Boc) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.15 (3-CO), 169.44 (CO_2*t*Bu), 153.75 (CO, Boc), 138.93, 136.44 and 135.17 (C), 129.44–127.80 (9 × CH-Ar), 80.90 (C), 61.84 (*C*H_2OH), 59.45 (*C*H-Ph), 58.10 (2-CH), 44.84 (CH_2-5), 39.51 (*C*H_2CO), 28.17 (3 × CH_3), 28.02 (3 × CH_3, Boc) ppm. LSIMS: *m*/*z* = 518 [M – 1 + 23] $^+$, 440 [MH – *t*Bu]$^+$, 383 [MH – 2*t*Bu]$^+$, 366 [M – *t*Bu – *Ot*Bu]$^+$. $C_{28}H_{36}N_2O_6$ (496.59): calcd. C 67.72, H 7.31, N 5.64; found C 68.02, H 7.86, N 5.79.

(*R*)-1,2,4,5-Tetrahydro-4-[(*R*)-2-hydroxy-1-phenylethyl]-2-methyl-benzo[*e*][1,4]diazepin-3-one (13): 2-Methylated benzodiazepine **9** (380 mg, 0.96 mmol) was dissolved in TFA/CH_2Cl_2 solution (20 mL, 1:1) at 0 °C under argon. The reaction mixture was stirred for 2 h at room temperature and then quenched with aqueous 10 N NaOH solution (10 mL). The mixture was extracted with AcOEt (3 × 20 mL), the organic layers were combined and washed successively with brine (3 × 25 mL), H_2O (3 × 25 mL), filtered, and concentrated under reduced pressure. The crude was purified by column chromatography (CH_2Cl_2/AcOEt, 40:60) to afford 254 mg of *N*-deprotected benzodiazepine **13** (0.86 mmol, 90%) as a yellow oil. $[\alpha]_D^{20}$ = –27.5 (*c* = 1, EtOH). IR (neat): $\tilde{\nu}_{max}$ = 3566 cm^{-1}, 3480, 3352, 2982, 2936, 1654 (3-CO), 1645, 1609, 1583, 1494, 1456, 1328, 1262, 1219, 1157, 1122, 1065, 1047, 850, 743, 696. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.14 (s, 5 H), 6.94–6.90 (m, 1 H, H-8), 6.43 (d, *J* = 7.9 Hz, 1 H, H-6), 6.34–6.26 (m, 1 H, H-7), 6.11 (d, *J* = 7.17 Hz, 1 H, H-9), 5.84 (dd, *J* = 8.13, 5.12 Hz, 1 H, C*H*–Ph), 5.20 (d, *J* = 16.5 Hz, 1 H, H-5), 4.82 (q, *J* = 6.39 Hz, 1 H, H-2), 4.20–4.10 (m, 4 H, CH_2OH, OH, NH), 3.77 (d, *J* = 16.5 Hz, 1 H, H-5′), 1.44 (d, *J* = 6.39 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.4 (3-CO), 145.1 and 136.8 (C), 129.2, 128.4, 128.2, 128.0 and 127.7 (CH-Ar), 119.6 (C), 117.7 and 116.2 (CH-Ar), 61.7 (*C*H_2OH), 58.9 (*C*H-Ph), 50.3 (2-CH), 47.5 (5-CH_2), 17.2 (CH_3) ppm. LSIMS: *m*/*z* = 278 [M – H_2O] $^+$, 131. $C_{18}H_{20}N_2O_2$ (296.36): calcd. C 72.95, H 6.80, N 9.45; found C 73.18, H 6.91, N 9.48.

(*R*)-2-[(*R*)-2,3-Dihydro-2-methyl-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl]-2-phenylethanol (14): Lactam **13** (153 mg, 0. 517 mmol) was dissolved in anhydrous THF (15 mL), stirred at room temperature under argon and carefully treated with $LiAlH_4$ (88 mg, 2.32 mmol). The reaction mixture was heated to reflux overnight and then cooled to 0 °C, whereupon a solution of concentrated NH_4OH (1 mL) in THF (6 mL) was added dropwise. The suspension was stirred at room temperature for 1 h, diluted with H_2O (10 mL) and extracted with AcOEt (3 × 15 mL). The combined organic layers were washed with brine (2 × 15 mL), filtered, dried with $MgSO_4$ and the solvent evaporated off. The crude was purified by column chromatography (CH_2Cl_2/MeOH, 98:2) to afford 133 mg of the benzodiazepine **14** (0.47 mmol, 91%) as a colourless oil. $[\alpha]_D^{20}$ = +56 (*c* = 0.84, EtOH). IR (neat): $\tilde{\nu}_{max}$ = 3323 cm^{-1}, 2925, 2859, 1604, 1483, 1453, 1360, 1327, 1294, 1262, 1166, 1069, 1026, 966, 893, 866, 767, 707. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40–7.30 (m, 6 H, Ar), 7.15–7.09 (m, 1 H, H-8), 6.90–6.85 (m, 1 H, H-7), 6.76–6.73 (m, 1 H, H-9), 4.05–3.80 (m, 4 H, C*H*-Ph, CH_2OH and H-5), 3.50 (d, *J* = 14.07 Hz, 1 H, H-5), 3.24–3.18 (m, 1 H, H-2), 2.87 (d, *J* = 12.58 Hz, 1 H, H-3), 2.63 (dd, *J* = 12.58, 9.36 Hz, 1 H, H-3′), 1.12 (d, *J* = 6.66 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.62 and 137.43 (C), 130.50 (CH-Ar), 128.94 (C), 128.54, 128.44, 128.04, and 127.85 (CH-Ar), 120.88 (CH-7), 118.99 (CH-9), 67.89 (*C*H-Ph), 62.63 (CH_2-3), 61.61 (*C*H_2OH), 55.28 (CH_2-5), 51.42 (CH-2), 20.86 (CH_3) ppm. LSIMS: *m*/*z* = 282 [M]$^+$, 120 [MH – CHPh – CH_2OH]$^+$, 145. $C_{18}H_{22}N_2O$ (282.38): calcd. C 76.56, H 7.85, N 9.92; found C 76.84, H 8.26, N 10.23.

(*R*)-2,3,4,5-Tetrahydro-2-methyl-1*H*-benzo[*e*][1,4]diazepine (15): The amine **14** (150 mg, 0.532 mmol) was dissolved in 5% ethanolic HCl solution (25 mL) in the presence of 10% Pd/C (64 mg) and the mixture was hydrogenated at atmospheric pressure for 48 h. The catalyst was then filtered off, and the filtrate was partially evaporated, diluted with AcOEt and made basic with aqueous 10% NH_4OH solution. The mixture was extracted with AcOEt (3 × 20 mL), the combined organic layers were dried with $MgSO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 90:10) to obtain 56 mg of diamine **15** as a pale-brown oil (0.345 mmol, 65%). $[\alpha]_D^{20}$ = +52 (*c* = 1, EtOH). IR (neat): $\tilde{\nu}_{max}$ = 3400 cm^{-1}, 2977, 2900, 1646, 1453, 1410, 1087, 1047, 880, 668. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.12–7.09 (m, 2 H, H-6 and H-8), 6.86–6.75 (m, 2 H, H-9 and H-7), 4.58 (br., 2 H, NH), 4.02 (d, *J* = 14.46 Hz, 1 H, H-5), 3.80 (d, *J* = 14.46 Hz, 1 H, H-5′), 3.15–3.01 (m, 2 H, H-3 and H-2), 2.65 (dd, *J* = 13.18, 9.61 Hz, 1 H, H-3′), 1.18 (d, *J* = 6.39 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 148.6 (C), 130.2, 130.0 and 128.4 (CH-Ar), 121.2 (C), 119.6 (CH-Ar), 57.1 (3-CH_2), 54.1 (2-CH), 52.9 (5-CH_2), 20.6 (CH_3). MS: *m*/*z* = 162 [M]$^+$, 142, 118 (100). $C_{10}H_{14}N_2$ (162.23): calcd. C 74.03, H 8.70, N 17.27; found C 73.72, H 8.96, N 16.89.

(*R*)-2-[(*R*)-1-(*tert*-Butoxycarbonyl)-2,3-dihydro-2-methyl-3-oxo-1*H*-benzo[*e*][1,4]diazepin-4(5*H*)-yl]-2-phenylacetic Acid (16): The 2-methylbenzodiazepine **9** (45 mg, 0.114 mmol) was dissolved in acetone (1 mL) and cooled to 0 °C with an ice-water bath. The solution was treated with freshly prepared Jones' reagent (2.7 g of CrO_3 + 7 mL of water + 2.3 mL of concd. H_2SO_4; 44 µL, 1.1 equiv.), and stirred for 30 min at 0 °C. 2-Propanol (1 mL) was then added and the mixture was stirred for 30 min more. H_2O was added (10 mL) and the aqueous phase was extracted with AcOEt (2 × 10 mL). The organic layers were combined, washed with water, (2 × 10 mL), brine (2 × 10 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (cyclohexane/AcOEt/acetic acid, 70:30:0.5) to obtain 32 mg of the acid **16** as a colourless oil (0.078 mmol, 68.5%). $[\alpha]_D^{20}$ = –155 (*c* = 1, EtOH). IR (neat): $\tilde{\nu}_{max}$ = 3453 cm^{-1}, 2979, 2930, 1744 (CO_2 H), 1706 (1-NCO), 1638 (3-CON), 1498, 1459, 1389, 1324, 1255, 1208, 1165, 1124, 1092, 1048, 924, 856, 759, 738, 702. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.50–6.95 (m, 9 H, Ar), 6.68 (s, 1 H, C*H*–Ph), 6.14 (br., 1 H, CH-9), 5.55 (br., 1 H, H-2), 4.74 (d, *J* = 14.58 Hz, 1 H, H-5), 3.85 (d, *J* = 14.58 Hz, 1 H, H-5′), 1.38 (s, 9 H, Boc), 1.31 (d, *J* = 7.41 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.80 (CO_2 H), 172.50 (3-CO), 153.87 (CO, Boc), 138.90, 135.30 and 133.98 (C), 129.34, 129.13, 128.81, 128.67, 128.0, 127.58 and 127.20 (CH–Ar), 81.12 (C), 61.46 (*C*H–Ph), 56.14 (2-CH), 45.49 (5-CH_2), 28.12 (3 × CH_3), 19.52 (CH_3) ppm. MS-CI: *m*/*z* = 411 [MH]$^+$, 355 [MH – *t*Bu]$^+$. $C_{23}H_{26}N_2O_5$ (410.46): calcd. C 67.30, H 6.38, N 6.82; found C 67.82, H 6.89, N 6.66.

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