A Novel Solid-Phase Synthetic Method for 1,4-Benzodiazepine-2,5-dione Derivatives

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Abstract: Utilizing polymer-bound anthranilic acid derivatives **1**, we were able to obtain the 1,4-benzodiazepine-2,5-dione derivatives **3** (R^3 = H, R^4 = H, MeO, Cl) through an unprecedented reaction sequence, reductive alkylation–N-protected amino acid coupling–deprotective cyclization, in 28–71% five-step overall isolated yields and 95–99% purities from Wang resin **4**. Applying the novel protocol to the resin **2**, the 7-benzamido-1,4-benzodiazepine-2,5-dione derivatives **3** (R^1 = Bn, R^4 = 7-BzNH) could be obtained in 19–42% seven- or eight-step overall isolated yields and 92–98% purities from AMEBA resin **7**.

Key words: combinatorial chemistry, solid-phase synthesis, anthranilic acid, benzodiazepine, cyclative cleavage

Solid-phase synthesis of combinatorial libraries has emerged as a powerful tool for efficient drug discovery process.[1] We have recently been exploring the potential of resin-bound anthranilic acid derivatives **1** and **2** as versatile intermediates for combinatorial generation of drug-like heterocyclic compound libraries[2] (Figure 1). Herein we would like to present a novel solid-phase synthetic method for 1,4-benzodiazepine-2,5-dione derivatives **3** from resin-bound anthranilic acid derivatives **1** and **2**.

Recently 1,4-benzodiazepine-2,5-dione derivatives, a subclass of general 1,4-benzodiazepines,[3] have attracted much attention for their interesting biological properties including the potential as a scaffold for RGD peptidomimetics,[4a] GPIIbIIIa-fibrinogen interaction antagonistic activity for antithrombotic agents,[4a–d] p53-HDM2 interaction antagonistic activity,[4e–h] cytotoxic[4i–k] and antiproliferative[4l] activities, cell adhesion inhibitory activity,[4m] and HDAC inhibitory activity[4n] for anticancer agents, IgE synthesis inhibitory activity in human B-cells for treatment of allergic diseases,[4o] GHS receptor antagonistic activity for treatment of obesity and related disorders,[4p] and endothelin receptor antagonistic activity.[4q]

The 1,4-benzodiazepine-2,5-dione skeleton was constructed in solution phase according to the following methods: (i) cyclization of 2-nitrobenzamides,[4i,5a–c] 2-azidobenzamides,[5d–f] or N-protected 2-aminobenzamides[5g–i] prepared from α-amino esters or *N*-carboxy amino acid anhydrides, (ii) postmodification of Ugi four-component condensation products from anthranilic acids or 2-nitrobenzoic acids,[6] (iii) condensation of isatoic anhydrides with α-amino acids or esters,[4a,7] (iv) ring closure of *N*-(α-haloacetyl) derivatives of 2-aminobenzamides,[4a,8] (v) treatment of *N*-(α-haloacetyl) derivatives of anthranilates with ammonia,[9] (vi) palladium-catalyzed carbonylative cyclization of *N*-(α-aminoacetyl) derivatives of 2-haloanilines.[10] Some other methods were also reported involving the reaction of α-amino ester coupled 2-carboxyphenyl triflate and ammonia[11a] and the condensation of 2-aminobenzamide and 2-phenyl-4-arylideneoxazolinones.[11b]

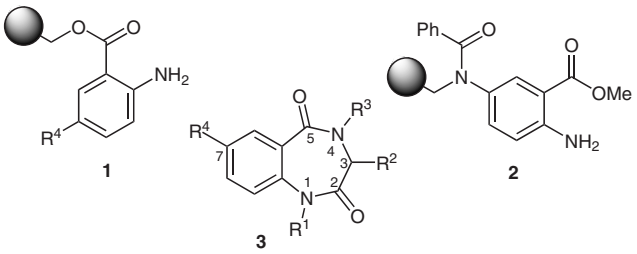

Figure 1

On the other hand, there were several reports regarding the solid-phase synthetic methods for 1,4-benzodiazepine-2,5-dione-based libraries. The first protocol in solution phase was actively adapted to the solid-phase synthesis of 1,4-benzodiazepine-2,5-dione derivatives varying the resin, attachment site, and substituents.[4o,12] Utilization of Ugi four-component condensation products was also reported to afford 1,4-benzodiazepine-2,5-dione derivatives through postcleavage cyclization starting from the resin-bound isonitriles,[13a–c] the resin-bound α-amino acids,[13d] or the resin-bound anthranilic acids.[13e] In addition, the solid-phase synthesis of 1,4-benzodiazepine-2,5-dione derivatives was performed utilizing the condensation of resin-bound isatoic anhydrides and α-amino acids.[14] As an example of so-called solid/solution-phase annulation (SPAn) reagents, the *N*-(α-bromoacetyl) derivative of a resin-bound anthranilic acid was utilized for the preparation of 1,4-benzodiazepine-2,5-dione derivatives from primary amines.[15]

Nearly all these reported solid-phase synthetic methods except the corresponding example of SPAn reagents are characterized by the common reaction sequence that forms the 1,4-benzodiazepine-2,5-dione skeleton through the prior formation of the amide bond between N-4 and C-5 and subsequent linkage between N-1 and C-2. On the other hand, it may be understood that it is needed to ex-

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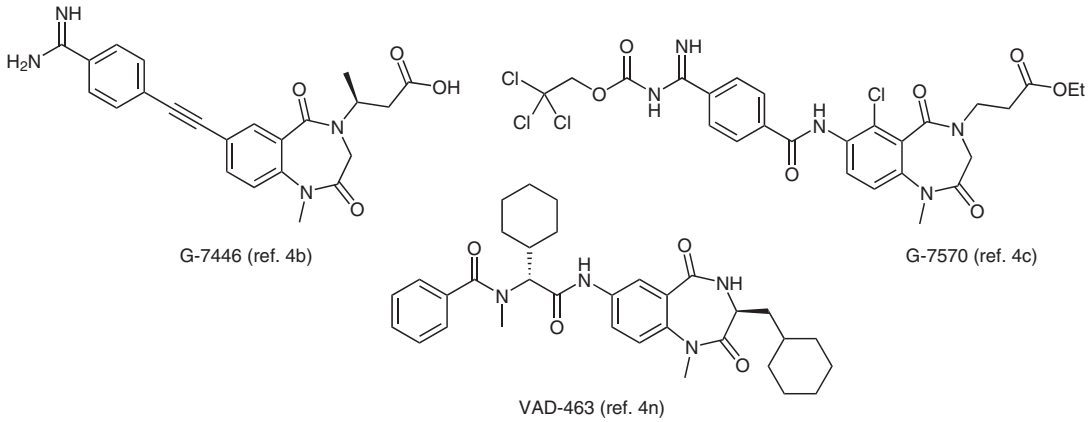
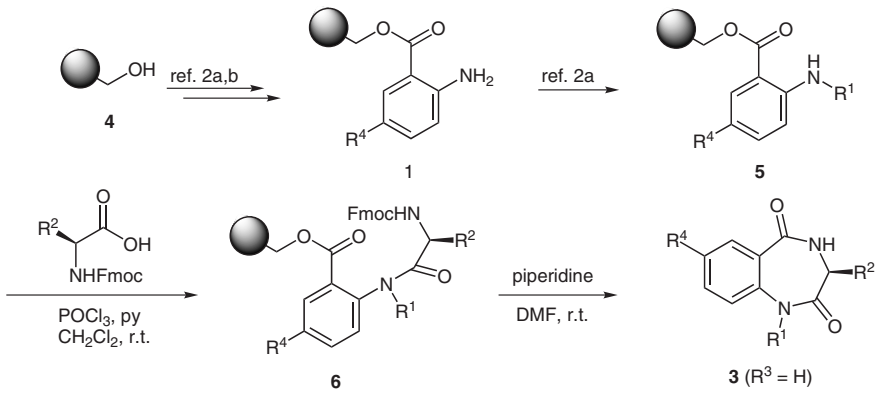


Figure 2

ploit the R^4 substituent as well as the R^1, R^2, and R^3 substituents in order to fully realize the potential of the 1,4-benzodiazepine-2,5-dione scaffold for construction of combinatorial libraries from the inspection of some examples of 1,4-benzodiazepine-2,5-dione derivatives (Figure 2, structure **3**). As a novel approach to solid-phase synthesis of 1,4-benzodiazepine-2,5-dione derivatives, we envisioned that the resin-bound anthranilic acid derivatives **1** and **2** could be adapted to an unprecedented reaction sequence, even in solution phase, that constructs the ring skeleton through the prior formation of the amide bond between N-1 and C-2 and subsequent linkage between N-4 and C-5 using N-protected amino acids as connecting building blocks,[16] and that in particular the intermediate resin **2** could provide 1,4-benzodiazepine-2,5-dione derivatives encompassing diverse amino-related functional groups for R^4 substituent (Schemes 1 and 2).

In order to confirm the possibilities, we first started the investigation from the resin-bound anthranilic acid derivatives **1** prepared by our previously reported procedure[2a,b] from Wang resin **4** (Scheme 1). The *N*-benzylation of the resin **1a** (R^4 = H) under the reported conditions[2a] gave the *N*-benzylated anthranilate resin **5a** (R^4 = H, R^1 = Bn). Reaction of the intermediate **5a** with *N*-Fmoc-protected phenylalanine (R^2 = Bn, 3 equiv) in the presence of $POCl_3$ (3 equiv) and pyridine (6 equiv) in CH_2Cl_2 at room temperature afforded the amino acid coupled anthranilate resin **6a** (R^4 = H, R^1 = Bn, R^2 = Bn).[17] Deprotection of the resin **6a** in 20% piperidine–DMF at room temperature directly furnished the 1,4-benzodiazepine-2,5-dione derivative **3a** (Table 1) through the subsequent spontaneous cyclative cleavage[18] in one pot. Although the racemization-prone phenylalanine was used,[19] significant racemization was not observed for the reaction sequence (<1%) as determined by chiral HPLC analysis of the derivative **3a** compared with that of the corresponding racemic reference. The reaction sequence was successfully applied to the resin-bound anthranilic acid derivatives **1** under the above established conditions to afford some 1,4-benzodiazepine-2,5-dione derivatives **3** (R^3 = H) in 28–71% five-step overall isolated yields and 95–99% purities from Wang resin **4** as summarized in Table 1. The solid-phase reactions to the final products **3** were checked by on-bead ATR-FTIR spectroscopy and the compounds **3** in Table 1 are unknown except **3a**[4n] and **3e**,[20] and all final products **3a–o** were characterized on the basis of ^{1}H NMR, ^{13}C NMR, and LC–UV–MS spectral data.

Utilizing the novel protocol established for the resin-bound anthranilic acid derivatives **1** (Scheme 1), we proceeded to the preparation of the 1,4-benzodiazepine-2,5-dione derivatives **3** with amino-related benzamido functionality at the 7-position from the resin intermediate **2** (Scheme 2). The resin intermediate **2**, prepared on the basis of our previously reported procedure,[2b] was subjected



Scheme 1

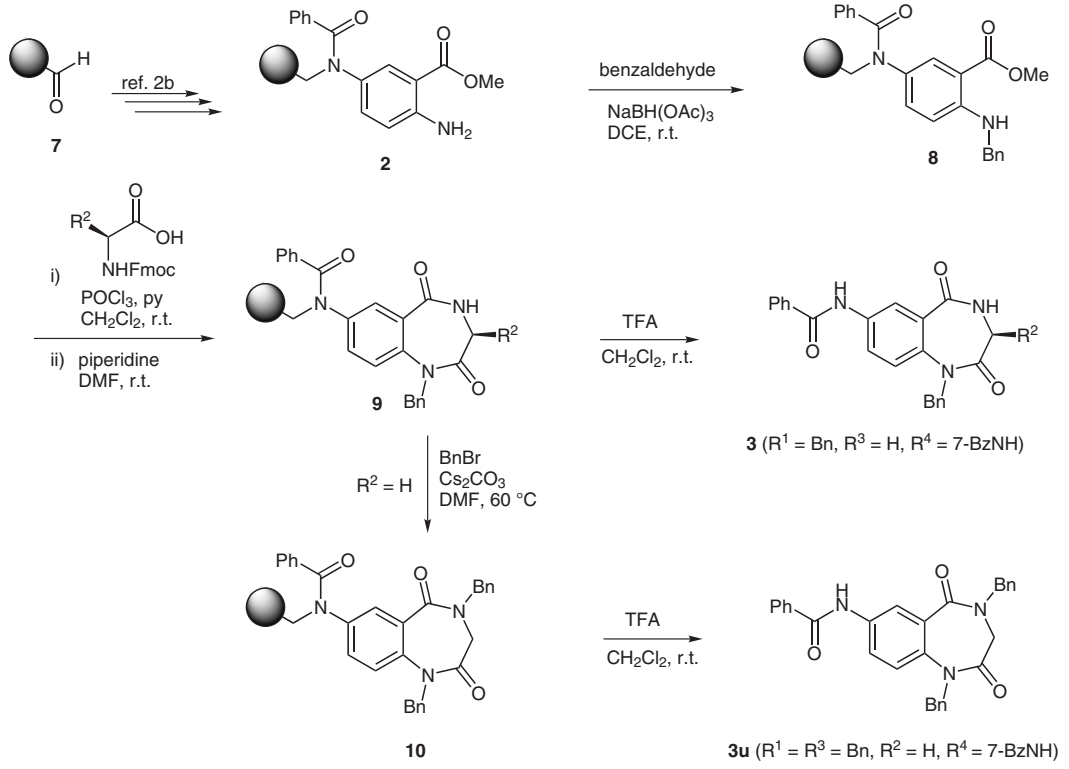
Table 1 Yields and Purities of Compounds **3a–o** (R^3 = H)

Compd.	R^4	R^1	R^2	Yield (%)[a]	Purity (%)[b]
3a	H	Bn	Bn	52	99
3b	H	Bn	*s*-Bu	49	98
3c	H	Bn	*i*-Bu	65	99
3d	H	Bn	Me	46	99
3e	H	Bn	H	38	99
3f	H	4-MeOBn	Bn	66	99
3g	H	4-FBn	Bn	68	95
3h	H	4-O_2NBn	Bn	70	99
3i	MeO	Bn	Bn	37	99
3j	MeO	2-MeBn	Bn	41	99
3k	MeO	3-FBn	Bn	39	98
3l	MeO	*i*-Bu	Bn	29	99
3m	Cl	Bn	Bn	71	99
3n	Cl	4-NCBn	Bn	65	99
3o	Cl	pyridyl-3-methyl	Bn	28	99

[a] Five-step overall isolated yields from Wang resin **4** (loading capacity = 0.92 mmol/g) after silica gel column chromatography.
[b] Determined on the basis of LC–UV(200–400 nm)–MS spectrum of the isolated products after silica gel column chromatography.

to the reaction sequence (reductive alkylation using benzaldehyde, Fmoc-protected amino acid coupling, and deprotective cyclization) to afford the resin-bound 1,4-benzodiazepine-2,5-dione derivatives **9**. The cleavage of the resins **9** was accomplished in 50% TFA–CH_2Cl_2 at room temperature successfully to give the final products, 7-benzamido-1,4-benzodiazepine-2,5-dione derivatives **3** (R^1 = Bn, R^3 = H, R^4 = 7-BzNH) in 35–42% seven-step overall isolated yields and 92–98% purities from AMEBA resin **7**. The results are summarized in Table 2. To exploit the possibility for the preparation of 1,4-benzodiazepine-2,5-diones with substituents at the 4-position, the resin **9** (R^2 = H) was treated with benzyl bromide (3 equiv) in the presence of Cs_2CO_3 (3 equiv) in DMF at 60 °C, and the subsequent cleavage in 50% TFA–CH_2Cl_2 at room temperature gave the expected N-benzylated product **3u** (R^1 = R^3 = Bn, R^2 = H, R^4 = 7-BzNH) in 19% eight-step overall isolated yield and 96% purity from AMEBA resin **7**. Similarly in the case of the resin **1**, the solid-phase reactions in Scheme 2 were also checked by on-bead ATR-FTIR spectroscopy. Significant racemization was not observed for the reaction sequence (<1%) as determined by chiral HPLC analysis of the derivative **3p**. The compounds **3** (R^4 = 7-BzNH) in Table 2 are all unknown and were characterized on the basis of ^{1}H NMR, ^{13}C NMR, and LC–UV–MS spectral data.

In conclusion, we were able to establish a novel efficient protocol for the construction of 1,4-benzodiazepine-2,5-dione skeleton utilizing the resin-bound anthranilic acid derivatives **1** and **2**.[21] The reaction sequence, reductive alkylation–N-protected amino acid coupling–deprotective



Scheme 2

cyclization, was unprecedented even in solution phase and in particular the intermediate resin **2** enabled us to exploit the diverse amino-related functionalities at the 7-position of the scaffold. The examination of the scope and limitation of the protocol for diversification of the substituents of 1,4-benzodiazepine-2,5-dione skeleton is currently in progress focusing on the amino-related functionalities other than amido group.

Table 2 Yields and Purities of the Compounds **3p–u** (R^4 = 7-BzNH)

Compound	R^1	R^2	R^3	Yield (%)[a]	Purity (%)[b]
3p	Bn	Bn	H	40	98
3q	Bn	*i*-Bu	H	35	95
3r	Bn	*i*-Pr	H	39	93
3s	Bn	Me	H	42	95
3t	Bn	H	H	38	92
3u	Bn	H	Bn	19	96

[a] Seven- or eight-step overall isolated yields from AMEBA resin **7** (loading capacity = 1.6 mmol/g) after silica gel column chromatography.
[b] Determined on the basis of LC–UV (200–400 nm)–MS spectrum of the isolated products after silica gel column chromatography.

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(17) Although several other conditions for the resin **5a** and *N*-Fmoc-protected phenylalanine (R^2 = Bn, 3 equiv) were examined varying coupling agent [DCC, DIC, EDC, *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU), BOP, PyBOP, 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate (CIP), 1,1′-carbonyldiimidazole (CDI), *N*,*N*′-disuccinimidyl carbonate (DSC), or diphenylphosphoryl azide (DPPA)], additive [none, *N*-hydroxybenzotriazole (HOBt), 1-hydroxy-7-aza-benzotriazole (HOAt), or *N*-hydroxysuccinimide (HOSu)], base [none, pyridine, Et_3N, diisopropylethylamine (DIEA), or NMM], solvent [CH_2Cl_2, THF, DMF, or *N*,*N*-dimethyl-acetamide (DMA)] at r.t. or elevated temperatures, they did not bring any significant change on the resin **5a** when judged on the basis of on-bead ATR-FTIR spectroscopy.

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(19) Kovacs, J. *Racemization and Coupling Rates of N-α-Protected Amino Acid and Peptide Active Esters: Predictive Potential, In The Peptides*, Vol. 2; Gross, E.; Meienhofer, J., Eds.; Academic: New York, **1980**, 485–539.

(20) Mohiuddin, G.; Reddy, P. S. N.; Ahmed, K.; Ratnam, C. V. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1985**, *24*, 905.

(21) **Representative Procedures for Preparation of Compounds 3**

Preparation of (*S*)-2-{Benzyl[2-(Fmoc-amino)-3-phenylpropionyl]amino}benzoate Resin (6a; R^4 = H, R^1 = Bn, R^2 = Bn): To a mixture of the resin **5a**[2a,b] (R^4 = H, R^1 = Bn, 100 mg, theoretically 0.077 mmol) and Fmoc-phenylalanine (93 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) at r.t. were added pyridine (37 mg, 0.46 mmol) and phosphorous oxychloride (37 mg, 0.23 mmol). The mixture was stirred at r.t. for 10 h and the resin was filtered, washed several times with CH_2Cl_2, DMF, MeOH, H_2O, and MeOH, and dried in a vacuum oven to give **6a** (124 mg). On-bead ATR-FTIR: 3418 (NH), 3028, 2921, 1722 (OC=O, NH-Fmoc, overlapped), 1664 (NC=O), 1601, 1512, 1492, 1451, 1241, 1076, 1028, 824, 757, 738, 697 cm^{-1}.

Preparation of (*S*)-1,3-Dibenzyl-1,4-benzodiazepine-2,5-dione (3a; R^4 = H, R^1 = Bn, R^2 = Bn): To the resin **6a** (R^4 = H, R^1 = Bn, R^2 = Bn, 124 mg, theoretically 0.074 mmol) was added 20% piperidine–DMF (2 mL) and the mixture was stirred at r.t. for 7.5 h. The mixture was filtered and washed with CH_2Cl_2. The filtrate was evaporated in vacuo and the residue was purified by a silica gel column chromatography (*n*-hexane–EtOAc, 1:1) to afford **3a** (14 mg, 52%; 99% purity on the basis of LC–UV–MS spectrum). Chiral HPLC analysis of the derivative **3a** was performed using CHIRALCEL OD-H (0.46 × 25 cm, DAICEL) column, 10% EtOH in hexane eluent at 0.6 mL/min flow rate, and UV detector at λ = 254 nm and showed a major peak at the t_R = 22.40 min and a trace (<1%) at t_R = 20.20 min. In the case of the corresponding racemic reference prepared from racemic phenylalanine by the same method, the HPLC spectrum showed two peaks at t_R = 21.87 and 23.17 min under the same conditions. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.08 (dd, *J* = 7.9, 14.5 Hz, 1 H), 3.48 (dd, *J* = 6.7, 14.5 Hz, 1 H), 4.14 (m, 1 H), 5.10 (d, *J* = 15.7 Hz, 1 H), 5.14 (d, *J* = 15.7 Hz, 1 H), 6.74 (br d, *J* = 5.4 Hz, 1 H), 7.10 (d, *J* = 7.2 Hz, 2 H), 7.20–7.30 (m, 10 H), 7.44 (dt, *J* = 1.5, 8.4 Hz, 1 H), 7.80 (dd, *J* = 1.5, 7.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.8, 52.2, 53.8, 122.3, 126.2, 126.8, 127.1, 127.5, 128.8, 129.4, 130.4, 132.6, 136.3, 136.6, 140.1, 168.4, 169.7 (shortage of two aromatic carbon peaks maybe due to peak overlapping). ESI–MS: *m*/*z* = 357 $[M + H]^+$.

Preparation of Methyl 5-Benzamido-2-benzylamino-benzoate Resin (8): To a mixture of the resin **2**[2b] (460 mg, theoretically 0.53 mmol), prepared from AMEBA resin (1.6 mmol/g), and benzaldehyde (169 mg, 1.59 mmol) in DCE (5 mL) at r.t. was added $NaBH(OAc)_3$ (338 mg, 1.59 mmol). The mixture was stirred at r.t. for 5 h and the resin was filtered, washed several times with CH_2Cl_2, DMF, MeOH, H_2O and MeOH, and dried in a vacuum oven to give **8** (482 mg). On-bead ATR–FTIR: 3365 (NH), 3026, 2922, 1681 (OC=O), 1643 (NC=O), 1610, 1587, 1505, 1494, 1451, 1382, 1214, 1196, 1156, 1113, 1029, 819, 756, 697 cm^{-1}.

Preparation of (*S*)-Methyl 5-Benzamido-2-{benzyl[2-

(Fmoc-amino)-3-phenylpropionyl]amino}benzoate Resin (R^2 = Bn): To a mixture of the resin **8** (100 mg, theoretically 0.10 mmol) and Fmoc-phenylalanine (116 mg, 0.300 mmol) in CH_2Cl_2 (2 mL) at r.t. were added pyridine (47 mg, 0.60 mmol) and phosphorus oxychloride (46 mg, 0.30 mmol). The mixture was stirred at r.t. for 10 h and the resin was filtered, washed several times with CH_2Cl_2, DMF, MeOH, H_2O and MeOH, and dried in a vacuum oven to give the amino acid coupled intermediate resin (R^2 = Bn, 125 mg). On-bead ATR-FTIR: 3418 (NH), 3027, 2924, 1724 (OC=O, N-Fmoc, overlapped), 1650 (2 × NC=O, overlapped), 1611, 1504, 1493, 1450, 1264, 1197, 1159, 1030, 822, 757, 735, 698 cm^{-1}.

Preparation of (*S*)-7-Benzamido-1,3-dibenzyl-1,4-benzodiazepine-2,5-dione Resin (9; R^2 = Bn): To the amino acid coupled intermediate resin (R^2 = Bn, 139 mg, theoretically 0.11 mmol) at r.t. was added 20% piperidine–DMF (2 mL). The mixture was stirred at r.t. for 7.5 h and the resin was filtered, washed several times with CH_2Cl_2, DMF, and MeOH, and dried in a vacuum oven to give **9** (R^2 = Bn, 112 mg). On-bead ATR-FTIR: 3418 (NH), 3027, 2923, 1662 (3 × NC=O, overlapped), 1610, 1493, 1450, 1263, 1195, 1158, 1115, 1031, 824, 734, 698 cm^{-1}.

Preparation of (*S*)-7-Benzamido-1,3-dibenzyl-1,4-benzodiazepine-2,5-dione (3p; R^1 = R^2 = Bn, R^3 = H, R^4 = 7-BzNH): To the resin **9** (R^2 = Bn, 112 mg, theoretically 0.10 mmol) at r.t. was added 50% TFA–CH_2Cl_2 (2 mL). The mixture was stirred at r.t. for 12 h and the mixture was filtered and washed with CH_2Cl_2. The filtrate was evaporated in vacuo and the residue, dissolved in CH_2Cl_2, was passed through a SAX cartridge and washed with CH_2Cl_2. The filtrate was evaporated in vacuo and the residue was purified by a silica gel column chromatography (*n*-hexane–EtOAc, 1:1) to afford **3p** (19 mg, 40%; 98% purity on the basis of LC–UV–MS spectrum). Chiral HPLC analysis of the derivative **3p** was performed using the same protocol as that for the derivative **3a** and showed a major peak at t_R = 70.42 min and a trace (<1%) at t_R = 53.44 min. In the case of the corresponding racemic reference prepared from racemic *N*-Fmoc-phenylalanine by the same method, the HPLC spectrum showed two peaks at t_R = 52.28 and 71.32 min under the same conditions: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.00 (dd, *J* = 8.1, 14.4 Hz, 1 H), 3.43 (dd, *J* = 6.5, 14.4 Hz, 1 H), 4.14 (m, 1 H), 5.02 (d, *J* = 15.5 Hz, 1 H), 5.17 (d, *J* = 15.5 Hz, 1 H), 6.31 (br, 1 H), 7.08 (d, *J* = 6.5 Hz, 2 H), 7.16–7.28 (m, 9 H), 7.43 (t, *J* = 7.9 Hz, 2 H), 7.53 (t, *J* = 7.4 Hz, 1 H), 7.78 (d, *J* = 2.6 Hz, 1 H), 7.86 (d, *J* = 8.5 Hz, 2 H), 8.32 (dd, *J* = 2.6, 8.9 Hz, 1 H), 8.84 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.9, 52.1, 53.8, 121.3, 123.5, 124.8, 127.0, 127.2, 127.3, 127.6, 128.7, 128.8, 128.9, 129.3, 132.2, 134.5, 135.7, 135.9, 136.5, 136.7, 166.1, 168.1, 169.4 (shortage of one aromatic carbon peak maybe due to peak overlapping). ESI–MS: *m*/*z* = 476 $[M + H]^+$.