Diastereoselective alkylation of a chiral 1,4-benzodiazepine-2,5-dione containing the α-phenethyl group. Attempted asymmetric synthesis of α,β-diaminopropionic acid

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Dedicated to Dr. Joseph Muchowski, in appreciation of his contributions to chemistry in Mexico

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Abstract

Alkylation of chiral benzodiazepinedione (*S*)-**1** with LDA or LHMDS with *N*-(bromomethyl)-phthalimide (a protected derivative of bromomethylamine), via the lithium enolate of (*S*)-**1** in the presence of HMPA as cosolvent was accomplished in moderate yield and good diastereo-selectivity. Hydrolysis of the resultant major diastereomeric product (*S,R*)-**4** with 57% HI afforded the desired α,β-diaminopropionic acid **5** in good yield albeit in racemic form, probably due to β-elimination-addition of ammonia under these conditions.

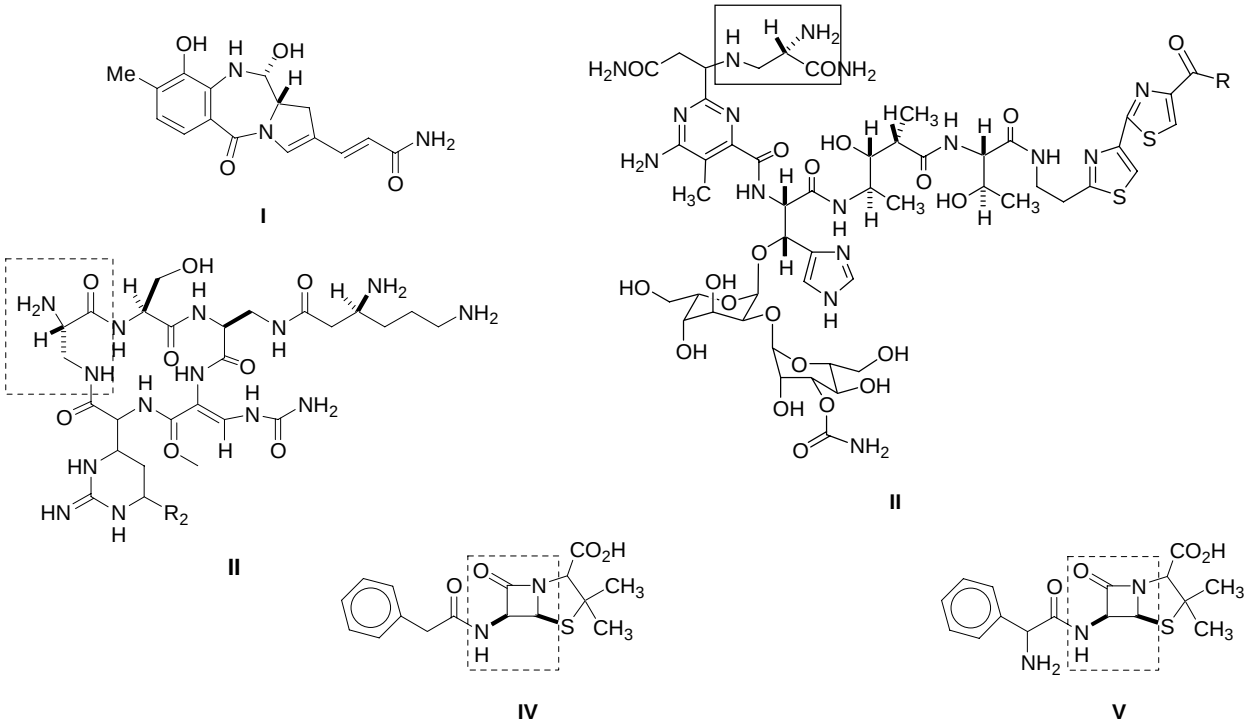
Keywords: Amino acids, benzodiazepinones, diastereoselective reactions, lithium enolates, chiral auxiliaries

Introduction

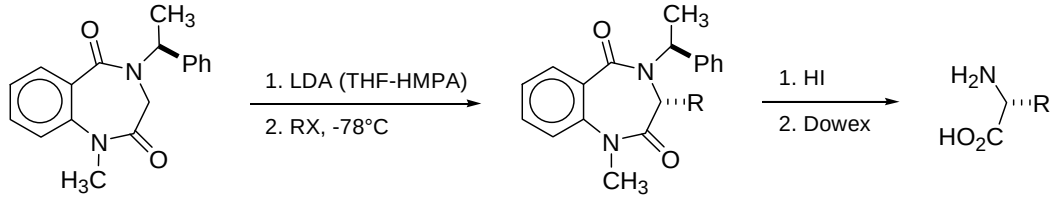
Several unusual α,β-diamino acids have been identified as constituents of biologically active natural products such as anthramycin (**I**),[1a] bleomycin (**II**),[1b] and capreomycin (**III**).[1c] Furthermore, α,β-diamino acids are essential precursors for the preparation of β-lactam antibiotics such as penicillin (**IV**) and ampicillin (**V**).[2]

Presently, there exists a limited number of methodologies for the enantioselective synthesis of α,β-diamino acids.[3] By contrast, a variety of methods is available for the preparation of enantio-enriched α-amino acids,[4] and among them, those employing chiral glycine derivatives have been particularly successful.[5] On the other hand, (*R*)- and (*S*)-α-phenylethylamines [(*R*)- and (*S*)-α-PEA] are simple, yet efficient chiral auxiliaries in asymmetric synthesis.[6] Indeed, a

novel chiral glycine derivative was recently developed by incorporation of (*S*)-α-phenylethylamine into 1,4-benzodiazepine-2,5-dione, (*S*)-**1**. The lithium enolate of (*S*)-**1** was alkylated with various electrophiles with high yield and with good diastereoselectivity, and hydrolysis of the main products afforded enantiopure α-amino acids (Scheme1).[7]



In the present work, the potential of (*S*)-**1** for the enantioselective synthesis of α,β-diamino propionic acid **5** was investigated.

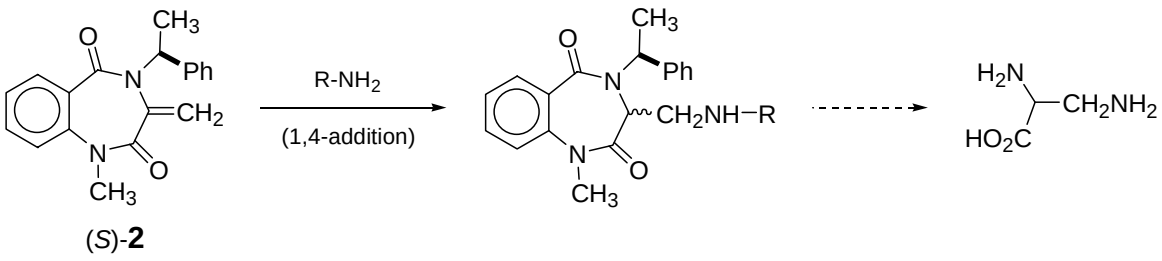


Scheme 1

Results and Discussion

A. Reaction of the lithium enolate of (*S*)-1 with formaldehyde

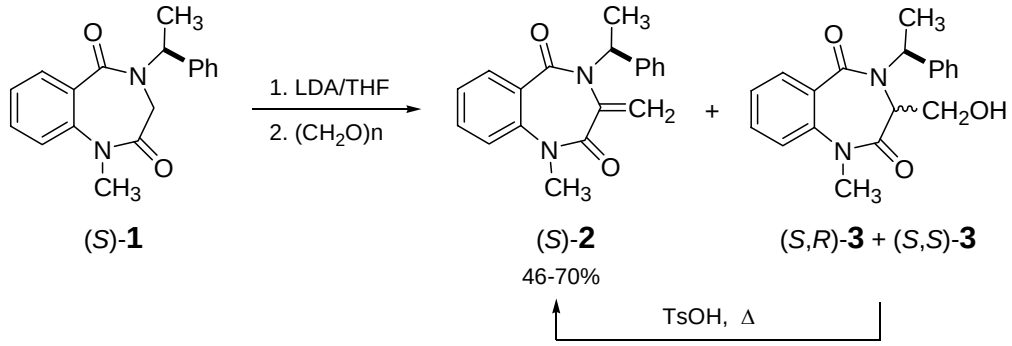
We first explored the possibility, if the 1,4-addition of N-nucleophiles to methylidene derivative (*S*)-**2**[8] followed by diastereoselective protonation of the resulting enolate would afford suitable precursors of the desired α,β-aminopropionic acid (Scheme 2).



(*S*)-**2**

Scheme 2

To this end, benzodiazepinedione (*S*)-**1** was treated with lithium diisopropylamide (LDA) in THF, followed by the addition of paraformaldehyde. This synthetic procedure afforded the desired *exo* methylene derivative (*S*)-**2** in 46% yield and a mixture of diastereomeric carbinols (*S*,*R*)-**3** and (*S*,*S*)-**3** (ratio 88:12) in 52% yield (Scheme 3).



(*S*)-**1** (*S*)-**2** (*S*,*R*)-**3** + (*S*,*S*)-**3**

Scheme 3

The relative configuration of the major diastereomeric carbinol **3** was determined to be *unlike*,[9] i.e. (*S*,*R*)-**3**, by means of X-ray diffraction crystallography (Figure 1).[10]

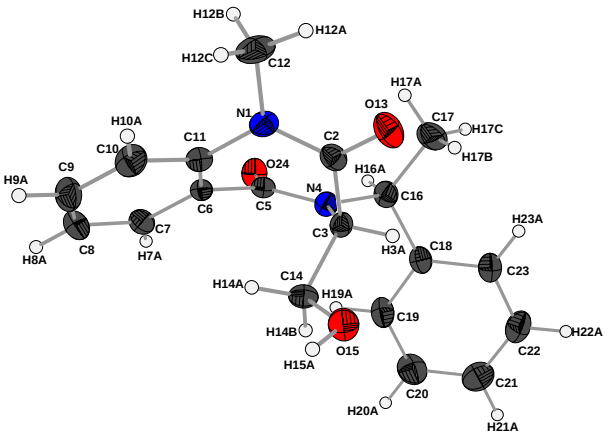


Figure 1. X-Ray crystallographic structure and solid-state conformation of (*S*,*R*)-**3**.[10]

Salient features in the crystallographic structure are the anticipated boat conformation of the heterocyclic ring[7,11] and the orientation of the phenethyl group. As pointed out in the literature,[12] 1,3-strain[13] favors the conformation in which the C-H bond eclipses the adjacent carbonyl group.

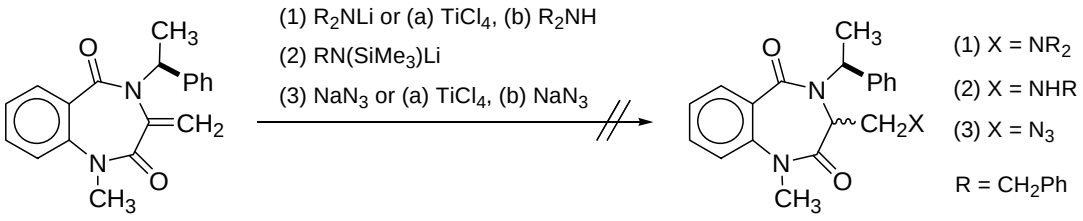
Interestingly, (*S*)-**2** exhibits two sets of ^{1}H and ^{13}C NMR signals at ambient temperature, in a 84:16 ratio. This observation is ascribed to a dynamic equilibrium between boat conformers *M* and *P* (Scheme 4).[14] From the inspection of Dreiding models, it is estimated that in conformer *P* the phenyl ring is in close proximity to one of the vinylic hydrogen atoms, whereas in the *M* conformer the phenyl ring is far away from the methylidene moiety. Since the predominant conformer in the ^{1}H NMR spectrum exhibits a signal at significantly high field (δ = 4.48) for one of the vinylic protons, whereas the minor conformer exhibits this proton at a normal δ = 5.40, it is concluded that the equilibrium *M* - *P* is displaced to the right; $\Delta G°_{298\ K}$ = –1.0 kcal/mol (Scheme 4).

Scheme 4

In order to increase the yield of the desired exocyclic enone (*S*)-**2**, the diastereomeric mixture of carbinols **3** was dehydrated by action of *p*-toluensulfonic acid. This reaction proceeded with 45% yield affording a total of 70% conversion of (*S*)-**1** into (*S*)-**2** (Scheme 3).

B. Lack of reactivity of enone (*S*)-2 towards the conjugate addition of N-nucleophiles

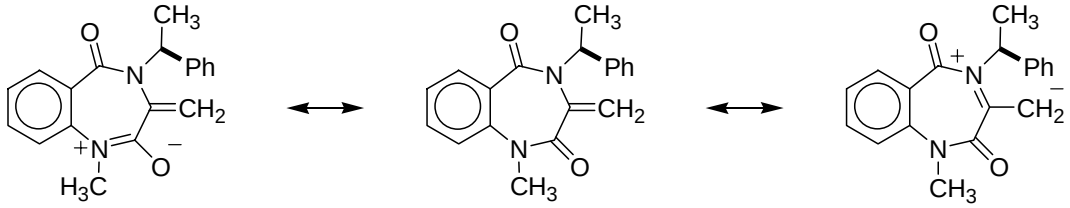
Scheme 5 summarizes the different conditions under which enone (*S*)-**2** was treated with various N-nucleophiles, in an attempt to achieve a 1,4-addition.



(*S*)-**2**

Scheme 5

The failure to accomplish this addition reaction may be explained in terms of structural and electronic limitations present in (*S*)-**2**. In particular, the boat conformation of (*S*)-**2** prevents coplanarity between the double bond and the carbonyl group, drastically reducing both conjugation and electrophilic reactivity in this π system. Furthermore, electron donation from either nitrogen will deactivate the enone segment towards nucleophilic addition (Scheme 6).

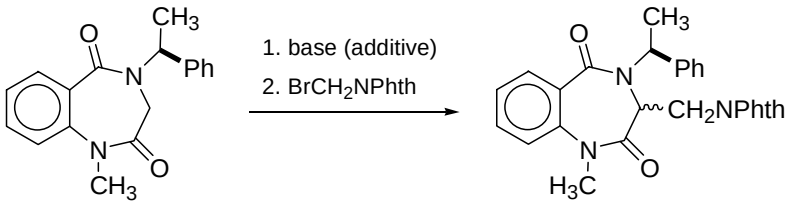


(*S*)-**2**

Scheme 6

C. Diastereoselective alkylation of the Li enolate of (*S*)-1 with *N*-(bromomethyl)phthalimide

The results of the electrophilic addition of *N*-(bromomethyl)phthalimide[16] (at –78°C) to the lithium enolate of (*S*)-**1**, generated by metallation of the corresponding benzodiazepinedione with LDA or lithium hexamethyldisylazide (LHMDS), are summarized in Scheme 7. Poor diastereoselectivities in the 12–40% range (entries 1 and 3) were found in the absence of additives, as revealed by integration of ^1H and ^{13}C NMR spectra of the crude product mixtures. Chemicals yields were also poor under these conditions (10–38%).



(*S*)-**1** (*S*,*R*)-**4** and (*S*,*S*)-**4**

Entry	Base	Additive (equiv.)	(*S*,*R*)-**4**: (*S*,*S*)-**4**	Yield [%]
1	LDA	-	70:30	10
2	LDA	HMPA (2)	82:18	42
3	LHMDS	-	56:44	38
4	LHMDS	HMPA (2)	73:27	48
5	LHMDS	HMPA (6)	85:15	52
6	LHMDS	LiCl (3)	39:61	61
7	LHMDS	LiCl (6)	42:58	60

Scheme 7

Recently,[7,17] addition of "inert" salts to the reaction media has been found to affect the stereoselectivity of alkylation reactions. Thus, Scheme 7 includes data obtained in the presence of 3 or 6 equivalents of lithium chloride (entries 6 and 7). Disappointingly, diastereoselectivities remained low in the 16–42% range. Nevertheless, it was found that the chemical yields did improve substantially under these conditions (compare entry 3 with entries 6 and 7, Scheme 7). Unexpectedly, the major diastereomeric product in the absence of LiCl corresponds to the *unlike* configuration, whereas the *like* diastereomer becomes predominant in the presence of the salt. It is to be expected that seemingly contrasting observations as those reported here will be understood when the knowledge about salt effects on structure and aggregation state of lithium enolates is more advanced.[18]

In contrast, use of hexamethylphosphoric triamide (HMPA)[19] is known to activate the reactions of organolithium compounds with electrophiles,[20] and to alter regio- and/or stereo-selectivity.[7,21] In the present study, both yields and diastereoselectivities of the alkylation reaction (cf. entries 1 and 2, and entries 3, 4 and 5, Scheme 7) improved significantly in the presence of HMPA.

Diastereomers (*S*,*R*)-**4** and (*S*,*S*)-**4** were separated by flash chromatography. The major product was recrystallized from methanol-dichloromethane (9:1) to afford suitable crystals for X-ray diffraction analysis.[10] Figure 2 presents the solid state conformation and that permits the assignment of the relative *unlike* configuration. In addition, Figure 2 reveals a boat conformation with *P* helicity,[14] a coplanar orientation of the C-H bond at the phenethyl group and the adjacent carbonyl (as dictated by 1,3 strain[13]), and a molecular arrangement that allows for π-π stacking between the aromatic rings.[22]

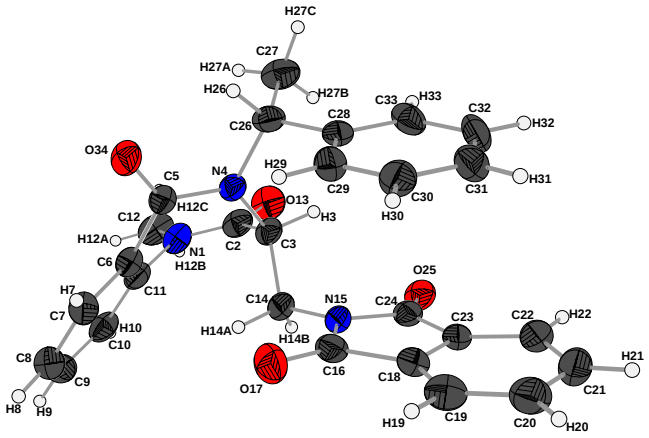
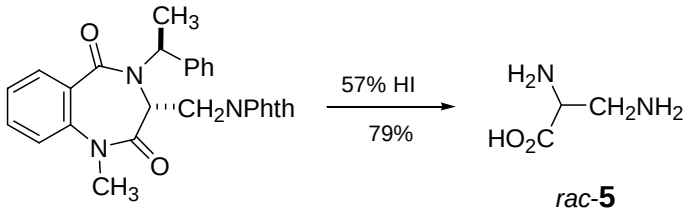


Figure 2. X-Ray crystallographic structure and solid-state conformation of (*S*,*R*)-**4**.[10]

D. Hydrolysis of (*S*,*R*)-4 to give α,β-diaminopropionic acid 5

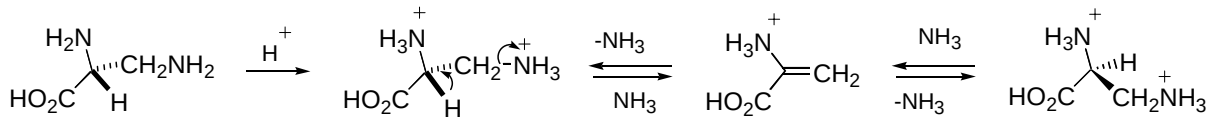
Acid hydrolysis of alkylated precursor (*S*,*R*)-**6** was best achieved with 57% HI.[5a,7,23] Under these conditions, both amide groups were cleaved, and both the phenethyl and phthalimido groups were removed to give the desired α,β-diaminopropionic acid **5** in good yield (79%) as free amino acid after chromatographic purification on a silica gel column with methanol/NH_4OH/2-propanol (1:1:2) as eluent.[24] (Scheme 8).



(*S*,*R*)-**4** *rac*-**5**

Scheme 8

Hydrolysis of (*S*,*R*)-**4** goes along with racemization and is presumed to occur via β-elimination of ammonia (Scheme 9), as suggested by Rapoport et al.[25] for cysteine derivatives.



(*R*)- **5** (*S*)-**5**·$(H^+)_2$

Scheme 9

Conclusions

In summary, chiral benzodiazepinedione (*S*)-**1** was prepared in good yield from *N*-methylisatoic anhydride and (*S*)-α-phenylethylamine. The lithium enolate of (*S*)-**1** was alkylated with *N*-(bromomethyl)phthalimide in the presence of HMPA as cosolvent with moderate yield (52%) and good diastereoselectivity (85% ds). Hydrolysis of the main product (*S*,*R*)-**4** with 57% HI afforded α,β-diaminopropionic acid **5** in good yield (79%), but unfortunately, under these conditions racemization occurred. Alternative reaction conditions for the conversion of (*S*,*R*)-**4** into (*R*)-**5** are presently being explored.

Experimental Section[26]

Conversion of 1-methyl-4-[(1S)-1-phenylethylethyl]-3,4-dihydro-1*H*-[1,4]benzodiazepine-2,5-dione (S)-1 into (*S*)-2 and (*S*,*R*)-3 and (*S*,*S*)-3. A solution of (*i*-Pr)$_2$NH (0.18 g, 1.83 mmol) in dry THF (15 mL) was cooled to 0° C before BuLi (1.9 M in hexane, 0.9 mL) was slowly added. The resulting solution was stirred at 0° C for 40 min and then cooled to –78° C before a solution (*S*)-**1** (0.50 g, 1.7 mmol) in dry THF (10 mL) was added dropwise. Stirring was continued at –78° C for 40 min in order to secure the complete formation of the enolate. A suspension of paraformaldehyde (0.14 g, 5.0 mmol) in dry THF (10 mL) was added dropwise, and the reaction mixture was stirred at –78° C for 3 h and at 0° C for 8 h. At this point, the reaction was quenched by the addition of methanol (0.5 mL), and extracted with CH_2Cl_2 (four portions of 20 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. Final purification was accomplished by flash chromatography (hexane/ethyl acetate, 70:30) to give enone (*S*)-**2** (0.24 g, 46% yield) and the diastereomeric mixture of carbinols (*S*,*R*)-**3** and (*S*,*S*)-**3** (0.29 g, 52% yield). When this mixture was heated in methanol at reflux in the presence of *p*-toluensulfonic acid, an additional crop of enone (*S*)-**2** (0.13 g) was obtained, increasing the total yield of (*S*)-**2** to 70%.

1-Methyl-3-methylidene-4-[(*S*)-1-phenylethyl]-3,4-dihydro-1*H*-[1,4]benzodiazepine-2,5-dione (*S*) (2). Colorless crystals mp 87–88° C; $[\alpha]_D^{25}$ = +75.1 (c = 0.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.67 (d, *J* = 7.1 Hz, 3H), 3.4 (s, 3H), 4.48 (s, 1H), 5.38 (s, 1H), 6.30 (q, *J* = 7.1 Hz; 1H), 7.04–7.90 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.2, 35.0, 54.2, 119.7, 120.3, 125.4, 127.6, 127.7, 127.8, 128.3, 128.4, 130.8, 131.8, 138.3, 140.1, 141.3, 166.0, 169.4; EI-MS (15 eV): *m*/*z* 306 (M^+), 265, 248, 215, 188, 145, 134, 105, 79. Anal. calcd for $C_{19}H_{18}O_2N_2$ (306.36): C, 74.48; H, 5.92. Found: C, 74.46; H, 6.32.

(3*R*)-Hydroxymethyl-1-methyl-4-[(*S*)-phenylethyl]-3,4-dihydro-1*H*-[1,4]benzodiazepine-2,5-dione (*S*,*R*) (3). Colorless crystals mp = 195–196 °C, $[\alpha]_D^{25}$ = +111.2 (c = 9.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.61 (d, *J* = 7.1 Hz, 3H), 1.88 (s, 1H), 2.71 (dd, *J* = 6.8, 11.2 Hz, 1H), 2.98 (dd, *J* = 9.3, 11.1 Hz, 1H), 3.48 (s, 3H), 4.15 (dd, *J* = 6.9, 9.2 Hz, 1H), 6.27 (q, *J* = 7.1 Hz, 1H), 7.15–7.44 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.0, 36.3, 53.4, 60.8, 61.5, 121.4,

126.1, 128.4, 128.7, 129.2, 129.7, 131.4, 132.7, 139.7, 139.9, 166.4, 170.5. Anal. calcd for $C_{19}H_{20}O_3N_2$ (324.37): C, 70.35; H, 6.22. Found: C, 70.20; H, 6.35.

Conversion of (*S*)-1 into 1-methyl-4-[(1*S*)-1-phenylethyl]-3-[(3*R*)-phthalimidomethyl]-3,4-dihydro-1*H*-[1,4]benzodiazepine-2,5-dione (*S,R*) (4). In a 50 mL round-bottomed flask equipped with a magnetic stirrer and under nitrogen atmosphere was placed benzodiazepinedione (*S*)-**1** (0.26 g, 0.89 mmol) in dry THF (10 mL). The resulting solution was cooled to –78° C before lithium hexamethyldisylazide (1.0 M in THF, 0.29 mL, 1.08 mmol) was added dropwise. The solution was stirred at –78° C for 1h, treated with HMPA (0.93 mL, 5.39 mmol, 6.0 equiv.) and *N*-(bromomethyl)phthalimide (0.22 g, 0.90 mmol) in THF (10 mL). The reaction mixture was stirred at –78° C until completion (tlc monitoring), quenched with methanol (0.5 mL), and extracted with CH_2Cl_2 (four portions of 15 mL each). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. Final purification was accomplished by flash chromatography (hexane/ethyl acetate/methylene chloride, 4:2:1) to give the distereomeric mixture of (*S*,*R*)-**4** and (*S*,*S*)-**4** (0.21 g, 52%) ratio 85:15. Crystallization from methanol/ methylene chloride (9:1) afforded the pure major isomer (*S*,*R*)-**4** (orthorhombic crystals) and the minor isomer (*S*,*S*)-**4** (colorless needles).

(*S,R*) 4. mp 202–203 °C; $[\alpha]_D^{25}$ = +102.8 (c = 12, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.60 (d, *J* = 7.4 Hz, 3H), 3.05 (dd, *J* = 8.1, 13.8 Hz, 1H), 3.28 (dd, *J* = 7.6, 13.8 Hz, 1H), 3.41 (s, 3H), 4.41 (t, *J* = 7.9 Hz, 1H), 6.34 (q, *J* = 7.1 Hz, 1H), 6.90–8.09 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.1, 35.9, 36.2, 53.2, 57.7, 121.7, 123.6, 125.6, 127.6, 127.9, 128.5, 129.3, 131.6, 132.2, 133.8, 139.0, 139.5, 166.4, 167.1; EI-MS (15 eV): *m*/*z*: 453 (M^+), 334, 294, 263, 235, 175, 133, 105, 60. Anal. calcd for $C_{27}H_{23}N_3O_4$ (630.73): C, 71.52; H, 5.08. Found: C, 71.48; H, 5.22.

(*S,S*) 4. mp 238–239 °C; $[\alpha]_D^{25}$ = +12.5 (c = 11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.74 (d, *J* = 6.9 Hz, 3H), 3.19 (s, 3H), 3.19 (s, 3H), 3.48–3.57 (m, 2H), 4.17 (dd, *J* = 5.8, 10.2 Hz, 1H), 6.36 (q, *J* = 7.3 Hz, 1H), 6.88–8.06 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.8, 35.8, 37.3, 53.4, 57.7, 121.4, 123.5, 125.4, 127.5, 128.0, 128.6, 131.1, 131.6, 132.4, 132.4, 134.2, 138.7, 139.0, 166.4, 167.5, 168.3; EI-MS (15 eV): *m*/*z* 453 (M^+), 438, 348, 334, 292, 237, 189, 160, 105, 50.

Hydrolysis of (*S,R*)-4 to α,β-diaminopropionic acid (5). A suspension of (*S,R*)-**4** (0.5 g, 1.103 mmol) in HI (57%, 5 mL) was heated in an sealed ampoule to 90 °C for 42 h; the solution was then allowed to cool to ambient temperature and extracted four times with EtOAc. The aqueous phase was evaporated to afford the crude amino acid hydroiodide **5**·HI, which was purified by silica gel (one gram per 10 mg of amino acid) with 2-propanol/methanol/ammonium hydroxide (2:1:1) as eluent.[24] The desired amino acid **5** (91 mg, 79% yield) was obtained as a white powder, mp = 236–237 °C (lit.[27] mp 234–235 °C); ^{1}H NMR (D_2O, 400 MHz): δ 2.99 (dd, *J* = 6.6, 13.9 Hz, 1H), 3.11(dd, *J* = 5.8, 13.6 Hz, 1H), 3.50 (t, *J* = 6.2 Hz, 1H); ^{13}C NMR (D_2O, 100 MHz): δ 42.2, 54.2, 176.9.

Acknowledgments

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10. Atomic coordinates for all the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, UK. Deposition numbers: CCDC 197255, CCDC 203144.

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