Enantioselective Synthesis of α-Amino Acids from Chiral 1,4-Benzodiazepine-2,5-diones Containing the α-Phenethyl Group

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Because of their fundamental importance in physiological events and because of their increasing use in pharmaceutical, agricultural, and food products, α- and *β*-amino acids are receiving extraordinary attention in biology, chemistry, and medicine.[1] In particular, an unprecedented degree of activity has been recorded in the field of enantioselective synthesis of chiral amino acids.[2,3]

Among the various methods available for the preparation of enantioenriched α-amino acids, those employing chiral glycine derivatives[4] have been particularly successful. On the other hand, (*R*)- and (*S*)-α-phenylethylamines are simple, yet efficient, chiral auxiliaries in asymmetric synthesis.[5] In the present work, a novel chiral glycine derivative was developed by incorporation of (*S*)-α-phenylethylamine [(*S*)-α-PEA] into 1,4-benzodiazepine-2,5-dione, (*S*)-**1**. 1,3-Stereoinduction in alkylation reactions of enolate (*S*)-**1**-Li was, as anticipated, significantly higher than the 1,4-stereoinduction achieved several years ago by Decorte et al.[6] in the related substrate (*S*)-**2**-Li (Scheme 1).

Results and Discussion

A. Synthesis of Enantiopure Benzodiazepinedione, (*S*)-1. As outlined in Scheme 2, *N*-methylisatoic anhydride was treated with (*S*)-α-PEA to give benzamide (*S*)-**3** in excellent yields (92% isolated). *N*-(Chloroacetyl)-*N*-methyl derivative (*S*)-**4** was obtained (88% yield) from the reaction of (*S*)-**3** with chloroacetyl chloride in triethylamine, and exposure to methanolic sodium methoxide provided (*S*)-**1** in 73% yield, after recrystallization. Thus, (*S*)-**1** was obtained in 57% overall yield (Scheme 2).

B. Conformational Features of (*S*)-1. Recrystallization of benzodiazepinedione (*S*)-**1** from diethyl ether afforded suitable crystals of the heterocycle, whose crystallographic structure is presented in Figure 1.[7] Salient features in the crystallographic structure are the anticipated[8] boat conformation of the ring and the orientation of the phenethyl group. As pointed out in the

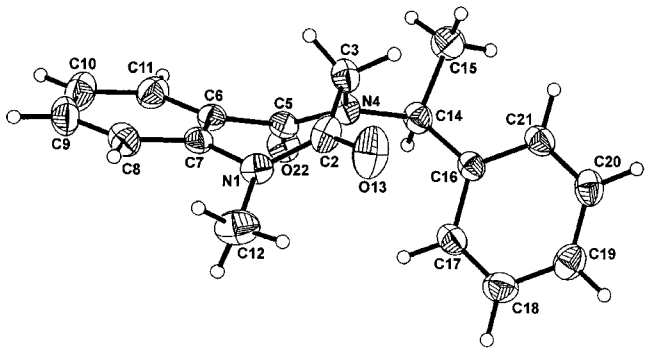
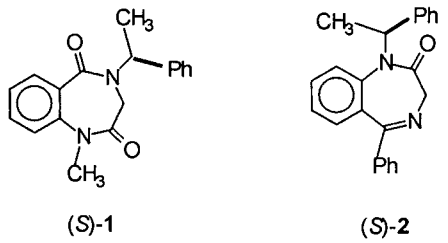


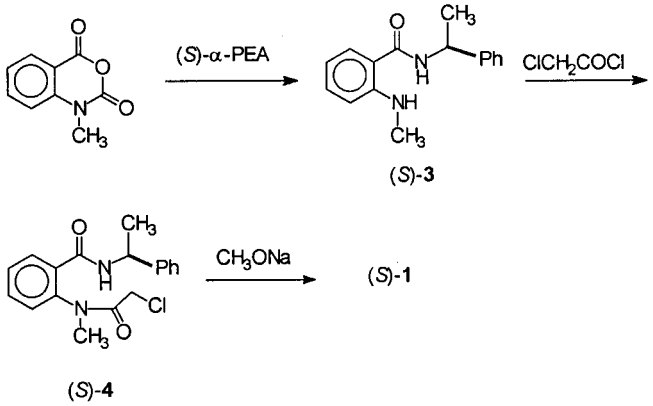
Figure 1. X-ray crystallographic structure and conformation of 1-methyl-4-*N*-[(*S*)-α-phenylethyl]-1,4-benzodiazepine-2,5-dione, (*S*)-**1**.[7]

Scheme 1



(*S*)-**1** (*S*)-**2**

Scheme 2



(1) In addition to a substantial number of monographs, a periodical journal, *Amino Acids*, Springer-Verlag, has been dedicated to the subject since 1994.

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(7) 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 Centre, 12 Union Road, Cambridge CB2 IEZ, U.K.

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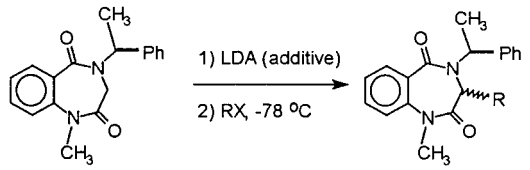
Table 1. Diastereoselectivity of Enolate (*S*)-1-Li Alkylations



(*S*)-1 5-10

entry	RX	additive	products	diastereomer ratio (*l*:*u*)	yield[a] (%)
1	CH_3I		**5**	19:81	63
2	CH_3I	1 equiv of LiCl	**5**	33:67	74
3	CH_3I	6 equiv of LiCl	**5**	43:57	89
4	CH_3I	6 equiv of HMPA	**5**	10:90	82
5	$PhCH_2Br$		**6**	85:15	74
6	$PhCH_2Br$	1 equiv of LiCl	**6**	75:25	79
7	$PhCH_2Br$	6 equiv of LiCl	**6**	62:38	82
8	$PhCH_2Br$	6 equiv of HMPA	**6**	91:9	91
9	EtI		**7**	26:74	78
10	EtI	10 equiv of LiCl	**7**	31:69	75
11	EtI	6 equiv of HMPA	**7**	17:83	77
12	*n*-BuI		**8**	27:73	55
13	*n*-BuI	10 equiv of LiCl	**8**	33:67	64
14	*n*-BuI	6 equiv of HMPA	**8**	19:81	73
15	*n*-PrI	6 equiv of HMPA	**9**	21:79	71
16	CH_2=CH-CH_2Br	6 equiv of HMPA	**10**	23:77	84

[a] Combined yield after purification.

literature,[9] $A^{1,3}$ strain[10] favors the conformation in which the C−H bond eclipses the adjacent carbonyl group.

C. Diastereoselectivity of Alkylation of Chiral Enolate (*S*)-1-Li. The results of alkyl halide addition (at −78 °C) to enolate (*S*)-**1**-Li, generated by metalation of the corresponding benzodiazepinedione with LDA, are summarized in Table 1. Moderate diastereoselectivities (diastereomeric excess = % of major diastereomer − % of minor diastereomer[11]) in the 46−70% range (entries 1, 5, 9, and 12) were found in the absence of additives as indicated by integration of the ^1H and ^{13}C NMR spectra of the crude products. Chemical yields were also moderate under these conditions (55−78%).

Recently,[12] addition of "inert" salts to reaction media has been found to affect the stereoselectivity of alkylation reactions. Thus, Table 1 includes data obtained in the presence of 1 or more equiv of lithium chloride. Disappointingly, diastereoselectivities (de) fell to the 14−38% range in the presence of 6−10 equiv of LiCl. Nevertheless, it was found that the chemical yields did improve substantially under these conditions (compare entries 3, 7, 10, and 13 with entries 1, 5, 9, and 12, Table 1). It is to be expected that seemingly contrasting observations as those reported here will be understood as knowledge of salt effects on structure and aggregation state of Li enolates is more advanced.[13]

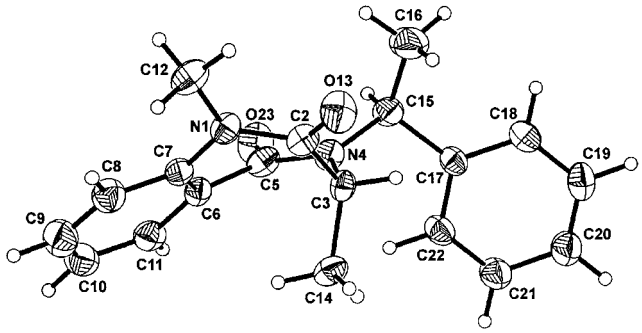


Figure 2. X-ray crystallographic structure and conformation of (1,3*R*)-dimethyl-4-*N*-[(*S*)-α-phenylethyl]-1,4-benzodiazepine-2,5-dione, (3*R*,1′*S*)-**5**.[7]

In contrast, use of hexamethylphosphoric triamide (HMPA)[14] is known to activate the reactions of lithium carbanions with electrophiles[15] and often to dramatically alter regio- and/or stereoselectivity.[16] In the present study, both the yields and diastereoselectivities of the alkylation reactions (entries 4, 8, 11, and 14, Table 1) improved significantly in the presence of 6 equivalents of HMPA.[17] Therefore, yields rose to 73−91%, with diastereoselectivities (de) as high as 82%.

D. Assignment of Configuration of the Diastereoisomeric Products 5−10. In the case of the methylated and benzylated main products, crystals suitable for X-ray crystallographic analysis were obtained. The resulting structures (Figures 2 and 3,[7] respectively) show an *unlike* relative configuration in the major product **5** but a *like* relative configuration in the predominant diastereomer of product **6**.[18] Thus, the configurations for the newly created stereogenic center at C(3) are *R* and *S*, respectively.

The absolute configuration of C(3) in the major diastereomeric products *u*-**5**, *l*-**6**, *u*-**7**, *u*-**8**, and *u*-**9** was also ascertained by acid hydrolysis to the known α-amino acids **11**−**15** (Table 2).[19] Although hydrolysis of **5**−**9** was not successful upon treatment with 6 N HCl,[4b,f] excellent results were achieved with 57% HI.[4e] Under these conditions, both amide groups were cleaved, and the phenethyl group was removed to give the desired amino acids in excellent yields (94−100% yield of the free amino acid after ion exchange purification). Finally, the configuration of product **10** was assigned by hydrogenation of the olefinic side chain to give the *n*-propyl analogue *u*-**9**.

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(18) For a discussion on the *like*/*unlike* stereochemical descriptors, see: (a) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654−660. (b) See also: Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, 1991; pp 52−54.

(19) The major isomer was separated prior to hydrolysis, so that enantiopure amino acids may be obtained.

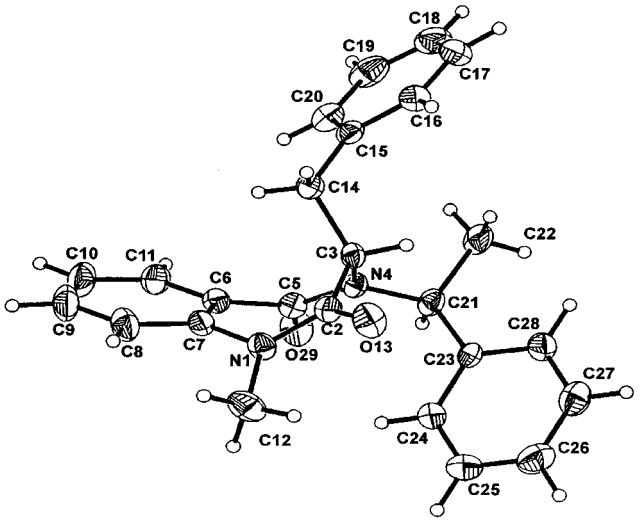
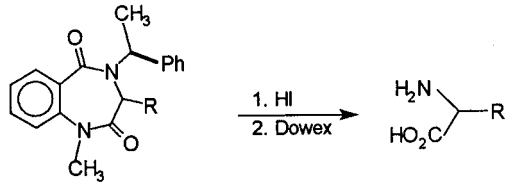


Figure 3. X-ray crystallographic structure and conformation of 1-methyl-(3*S*)-benzyl-4-*N*-[(*S*)-α-phenylethyl]-1,4-benzodiazepine-2,5-dione, (3*S*,1′*S*)-**6**.[7]

Table 2. Hydrolysis of Products 5−9 to the α-Substituted α-Amino Acids 11−15 with 57% HI at ca. 100 °C



5-9 **11-15**

starting material	R	product	yield (%)	$[\alpha]_{exptl}$	$[\alpha]^{20}_{lit}$
u-**5**	CH_3	(*R*)-**11**	96	−14.0	−14.2
l-**6**	$PhCH_2$	(*S*)-**12**	100	−31.9	−32.7
u-**7**	CH_3CH_2	(*R*)-**13**	94	−7.9	−7.9
u-**8**	*n*-Bu	(*R*)-**14**	97	−21.0	−21.2
u-**9**	*n*-Pr	(*R*)-**15**	93	−23.1	−24.0

E. Interpretation of the Stereochemical Pathways for Alkylation of (S)-1-Li. Complete geometry optimization (without symmetry constrains) was performed on the complete structure of enolate (*S*)-**1**-Li (Figure 4) at the ab initio level and within the frame of density functional theory (DFT) at the Becke3LYP/6-31G(*d,p*) level with the Gaussian 94 program (G94).[20] Perhaps the most interesting finding is that the global energy minimum for (*S*)-**1**-Li shows that lithium is bridged both to the enolate $^{\delta-}$C==C==O$^{\delta-}$ segment and to the phenyl ring in a bridged structure that resembles allyllithium[21] and that overcomes the conformation of the phenylethyl group that is usually favored by allylic $A^{1,3}$ strain (see section B).

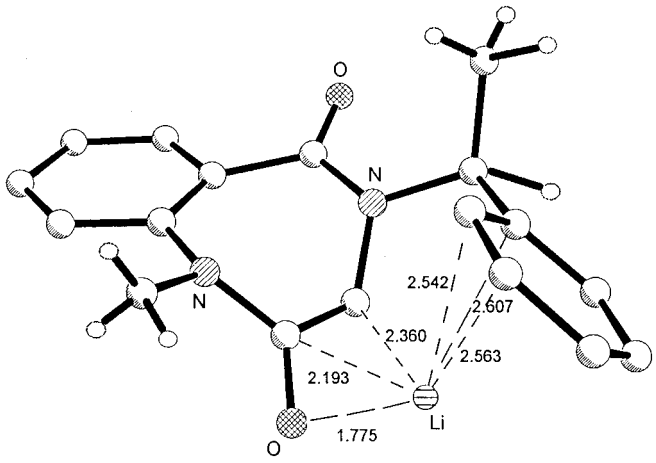


Figure 4. Global energy minimum geometry of enolate (*S*)-**1**-Li at the Becke3LYP/6-31G (d,p) level. HF energy: −956.730 405 8 hartrees (annotated distances in angstroms).

It can be appreciated in Figure 4 that because of Li^+ bridging to the phenyl ring it is the *Re* face of the reactive enolate that should be better exposed to addition to the electrophile, as is observed with alkyl halides (Table 1). In contrast, benzyl bromide may compete for lithium bridging, so that approach of this electrophile would be directed to the *Si* face of the enolate segment. Nevertheless, as pointed out by one reviewer, against this explanation stands the observation that best diastereoselectivities were obtained upon addition of 6 equiv of HMPA, an additive that is likely to compete for chelation of Li^+.[17] Thus, Figure 4 may not correspond to a proper representation of the enolate in solution.

In summary, chiral benzodiazepinedione (*S*)-**1** was prepared in good yield from *N*-methylisatoic anhydride and (*S*)-α-phenylethylamine. Enolate (*S*)-**1**-Li was alkylated in high yield and with good diastereoselectivity with various electrophiles and in the presence of HMPA as cosolvent. Hydrolysis of the main products *u*-**5**, *l*-**6**, *u*-**7**, *u*-**8**, and *u*-**9** with 57% HI proceeded in excellent yield to afford enantiopure α-substituted α-amino acids (*R*)-**11**, (*S*)-**12**, (*R*)-**14**, and (*R*)-**15**.

Experimental Section[22]

2-(Methylamino)-*N*-[(*S*)-α-phenylethyl]benzamide, (*S*)-3. In a 25-mL round-bottom flask provided with a magnetic stirrer was placed 0.50 g (2.82 mmol) of *N*-methylisatoic anhydride in 5.0 mL of ethyl acetate, before the dropwise addition of 0.40 mL (3.20 mmol) of (*S*)-α-phenylethylamine. The reaction mixture was heated to 35 °C with stirring, until complete dissolution of the suspension. (TLC analysis, eluent hexane−AcOEt 70:30, indicated that the reaction was complete at this point.) Concentration in a rotatory evaporator gave the crude product, which was recrystallized from ether−hexane−ethyl acetate (30:55:15) to afford 0.66 g (92% yield) of benzamide (*S*)-**3**: mp 110−111 °C. $[\alpha]^{28}_D = -144.0$ ($c = 10$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.57 (d, $J = 6.6$ Hz, 3H), 2.83 (s, 3H), 5.24 (dq, $J_1 = 6.6$ Hz, $J_2 = 5.2$ Hz, 1H), 6.26 (b, 1H), 6.56 (t, $J = 7.9$ Hz, 1H), 6.66 (d, $J = 8.6$ Hz, 1H), 7.2−7.4 (m, 7H), 7.50 (b, 1H);

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(22) (a) For general experimental procedures, see: Juaristi, E.; López-Ruiz, H.; Madrigal, D.; Ramírez-Quirós, Y.; Escalante, J. *J. Org. Chem.* **1998**, *63*, 4706. (b) For a detailed description of the computational method, see: Cuevas, G.; Juaristi, E. *J. Am. Chem. Soc.* **1997**, *119*, 7545.

^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 22.0, 29.6, 48.9, 111.2, 114.4, 114.9, 126.1, 127.1, 127.3, 128.7, 132.9, 143.4, 150.6, 169.0.

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.59; H, 7.09. Found: C, 75.94; H, 7.14.

2-[*N*-(Chloroacetyl)methylamino]-*N*-[(*S*)-α-phenylethyl]-benzamide, (*S*)-4. In a 500 mL round-bottom flask was placed 3.60 g (14.16 mmol) of (*S*)-**3** and 180 mL of triethylamine before the addition of 30 mL of CH_2Cl_2. The resulting solution was cooled to 0 °C, and then 1.50 mL (18.4 mmol) of chloroacetyl chloride was added dropwise. The reaction mixture was stirred at 0 °C for 1.5 h and at ambient temperature for an additional hour. Solvent removal at reduced pressure afforded the crude product, which was washed with three 20-mL portions of 15% K_2CO_3 solution. Extraction with CH_2Cl_2 (3 × 20 mL) and concentration gave 4.2 g (90% yield) of crude product, which was purified by flash chromatography (hexane−AcOEt 90:10) to give 4.1 g (88% yield) of pure (*S*)-**4**: mp 91−93 °C. $[\alpha]^{28}_D = -34.0$ (c = 10, $CHCl_3$); ^{1}H NMR (400 MHz; 100 °C; DMSO-d_6) δ 1.46 (d, J = 6.9 Hz, 3H), 3.11 (b, 3H), 3.94 (b, 2H), 5.09 (dq, J^1 = 6.9 Hz, J^2 = 5.3 Hz, 1H), 7.2−7.58 (m, 9H), 8.54 (b, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 37.8, 41.6, 49.5, 126.3, 126.2, 127.7, 127.8, 128.8, 128.9, 129.0, 129.1, 129.2, 131.9, 168.8, 182.2.

Anal. Calcd for $C_{18}H_{19}ClN_2O_2$: C, 65.35; H, 5.79. Found: C, 65.89; H, 5.74.

1-Methyl-4-*N*-[(*S*)-α-phenylethyl]-1,4-benzodiazepine-2,5-dione, (*S*)-1. In a three-necked, round-bottom flask provided with a magnetic stirrer was placed 3.6 g (10.90 mmol) of (*S*)-**4**, which was dissolved with 40 mL of dry methanol under nitrogen before the addition of 150 mL of 0.1 M CH_3ONa (15.0 mmol). The reaction mixture was heated to reflux for 3 h, allowed to cool to ambient temperature, washed with brine solution, extracted with four 25-mL portions of CH_2Cl_2, and concentrated to give the crude product, which was recrystallized from diethyl ether to afford 2.60 g (73%, yield) of crystalline (*S*)-**1**: mp = 150−151 °C; $[\alpha]^{28}_D = +22.0$ (c = 6, CH_3OH); ^{1}H NMR (DMSO-d_6; 70 °C; 270 MHz) δ 1.56 (d, J = 7.2 Hz, 3H), 3.31 (b, 3H), 3.45 (d, J = 16.6 Hz, 1H), 3.71 (d, J = 16.6 Hz, 1H), 5.96 (q, J = 7.2 Hz, 1H), 7.17−7.95 (m, 9H); ^{13}C NMR ($CDCl_3$, 27 °C; 67.8 MHz) δ 16.0, 16.4, 34.6, 34.7, 46.2, 46.3, 52.3, 52.4, 120.7, 125.4, 125.6, 127.2, 128.5, 128.8, 130.8, 132.0, 139.7, 140.9, 167.0, 169.2, 169.8.

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.46; H, 6.12. Found: C, 73.24; H, 6.27.

General Procedure for the Reaction of Benzodiazepinedione Enolate. [(*S*)-1-Li] with Electrophiles. A solution of (*i*-Pr)$_2$NH (0.25 mL, 1.83 mmol) in 15 mL of dry THF was cooled to 0 °C before the slow addition of 1.0 equiv of *n*-BuLi (ca. 1.9 M in hexane). The resulting solution was stirred at 0 °C for 40 min and then cooled to −78 °C before the dropwise addition of 0.50 g (1.70 mmol) of (*S*)-**1** in 10 mL of dry THF. Stirring was continued for 1 h at −78 °C in order to secure the complete formation of the enolate. The alkylating agent (2.50 mmol, 1.5 equiv) was added dropwise, and then 1.0 mL of dry THF was added via syringe. The reaction mixture was stirred at −78 °C until the reaction was complete (TLC monitoring). At this point, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with four portions of CH_2Cl_2. The combined extracts were dried over anhyd Na_2SO_4, filtered, and concentrated. Final purification was accomplished by flash chromatography.

(1,3*R*)-Dimethyl-4-[(*S*)-α-phenylethyl]-1,4-benzodiazepine-2,5-dione, (3*R*,1′*S*)-5, *u*-5. The general procedure was followed with 0.30 g (1.02 mmol) of (*S*)-**1** in 7.0 mL of THF, 1.1 mL of HMPA (6.19 mmol), 0.09 mL (1.10 mmol) of (*i*-Pr)$_2$NH, 0.62 mL (1.1 mmol) of 1.9 M *n*-BuLi, and 0.10 mL (0.23 g, 1.60 mmol) of methyl iodide. The isolated product (0.26 g, 82% yield) consisted of a 90:10 mixture of (3*R*,1′*S*)-**5** and (3*S*,1′*S*)-**5** diastereomeric products, which were separated by flash column chromatography (hexanes−ethyl acetate, 95:5 → 90:10) to give 0.15 g (48% yield) of the major product, *u*-**5**: mp 101−102 °C. $[\alpha]^{28}_D = -91.0$ (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.52 (d, J = 7.2 Hz, 3H), 1.62 (d, J = 7.2 Hz, 3H), 3.37 (s, 3H), 4.11 (q, J = 7.2 Hz, 1H), 6.32 (q, J = 7.2 Hz, 1H), 7.10−7.94 (m, 9H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 15.4, 15.8, 35.9, 53.0, 54.8, 120.7, 125.4, 127.9, 127.9, 128.5, 130.0, 130.9, 132.0, 139.4, 139.8, 166.0, 171.8.

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.05; H, 6.53. Found: C, 74.39; H, 6.68.

1-Methyl-(3*S*)-benzyl-4-[(*S*)-α-phenylethyl]-1,4-benzodiazepine-2,5-dione, (3*S*,1′*S*)-6, *l*-6. The general procedure was followed with 0.50 g (1.70 mmol) of (*S*)-**1** in 10 mL of THF, 1.8 mL (6.08 mmol) of HMPA, 0.26 mL (0.18 g, 1.83 mmol) of (*i*-Pr)$_2$NH, 0.90 mL (1.70 mmol) of 1.9 M *n*-BuLi, and 0.30 mL (0.43 g, 2.53 mmol) of benzyl bromide. The isolated product (0.59 g, 91% yield) consisted of a 91:9 mixture of (3*S*,1′*S*)-**6** and (3*R*,1′*S*)-**6** diastereomeric products, which were separated by flash column chromatography (hexane−AcOEt 90:10) to give 0.40 g (61% yield) of the major product, *l*-**6**: mp 160−161 °C; $[\alpha]^{28}_D = -117.2$ (c = 5.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (d, J = 7.2 Hz, 3H), 2.43 (dd, J^1 = 9.9 Hz, J^2 = 13.2 Hz, 1H), 2.60 (dd, J^1 = 7.3 Hz, J^2 = 13.2 Hz, 1H), 3.20 (s, 3H), 4.12 (dd, J^1 = 9.9 Hz, J^2 = 7.3 Hz, 1H), 6.16 (q, J = 7.2 Hz, 1H), 6.91−8.06 (m, 14 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.0, 35.7, 53.3, 61.8, 120.9, 125.6, 127.3, 127.4, 127.9, 128.0, 128.4, 128.6, 128.7, 129.2, 129.8, 130.9, 132.3, 136.4, 139.6, 140.0, 166.7, 170.3.

Anal. Calcd for $C_{25}H_{24}N_2O_2$: C, 78.12; H, 6.25. Found: 78.50; H, 6.22.

1-Methyl-(3*R*)-ethyl-4-[(*S*)-α-phenylethyl]-1,4-benzodiazepine-2,5-dione, (3*R*,1′*S*)-7, *u*-7. The general procedure was followed with 0.25 g (0.85 mmol) of (*S*)-**1** in 5.0 mL of THF and 0.9 mL of HMPA, 0.13 mL (0.09 g, 0.93 mmol) of diisopropylamine, 0.49 mL (0.93 mmol) of 1.9 M *n*-BuLi, and 0.10 mL (0.195 g, 1.25 mmol) of ethyl iodide. The isolated product (0.21 g, 77% yield) consisted of a 83:17 mixture of (3*R*,1′*S*)-**7** and (3*S*,1′*S*)-**7** diastereomeric products, which were separated by flash chromatography (hexanes−ethyl acetate 95:5) to give 0.13 g (47% yield) of the major product, *u*-**7**, and 36 mg (13% yield) of the minor product, *l*-**7**.

(3*R*,1′*S*)-7: mp = 90−91 °C; $[\alpha]^{28}_D = +100.0$ (c = 0.35, EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.25 (t, J = 7.7 Hz, 3H), 0.61−1.05 (m, 2H), 1.61 (d, J = 7.1 Hz, 3H), 3.38 (s, 3H), 3.88 (dd, J^1 = 9.9 Hz, J^2 = 6.7 Hz, 1H), 6.31 (q, 7.1 Hz, 1H), 7.09−7.91 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.7, 15.9, 23.2, 35.9, 53.2, 60.9, 120.6, 125.5, 128.0, 128.3, 128.6, 129.4, 130.1, 130.9, 132.1, 139.6, 139.7, 166.1, 171.4.

Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88. Found: C, 74.55; H, 6.98.

(3*S*,1′*S*)-7: mp = 128−130 °C; $[\alpha]^{28}_D = +27.0$ (c = 1, AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.75 (t, J = 7.7 Hz, 3H), 1.27 (m, 2H), 1.60 (d, J = 6.95 Hz, 3H), 3.20 (s, 3H), 3.87 (t, J = 8.4 Hz, 1H), 6.34 (q, J = 7.0 Hz, 1H), 7.06−7.91 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.0, 16.2, 23.7, 35.7, 53.0, 61.2, 120.3, 125.3, 127.4, 128.0, 128.5, 129.4, 130.8, 132.1, 139.6, 139.7, 166.5, 170.7.

Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88. Found: C, 74.99; H, 6.95.

1-Methyl-(3*R*)-*n*-butyl-4-[(*S*)-α-phenylethyl]-1,4-benzodiazepine-2,5-dione, (3*R*,1′*S*)-8, *u*-8. The general procedure was followed with 0.70 g (2.38 mmol) of (*S*)-**1** in 13 mL of THF and 2.54 mL of HMPA, 0.35 mL (0.26 mg, 2.56 mmol) of diisopropylamine, 1.23 mL (2.28 mmol) of 1.9 M *n*-BuLi, and 0.30 mL (0.48 mg, 2.63 mmol) of *n*-butyl iodide. The isolated product (0.61 g, 73% yield) consisted of a 81:19 mixture of (3*R*,1′*S*)-**8** and (3*S*,1′*S*)-**8** diastereomeric products, which were separated by flash chromatography (hexanes−ethyl acetate 100:0 → 90:10) to give 0.31 g (52% yield) of the major product, *u*-**8**, and 0.09 g (11% yield) of the minor product, *l*-**8**.

(3*R*,1′*S*)-8: mp 108−109 °C; $[\alpha]^{28}_D = +85.1$ (c = 0.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.26 (t, J = 7.2 Hz, 3H), 0.55−1.21 (m, 6H), 1.63 (d, J = 7.3 Hz, 3H), 3.36 (s, 3H), 3.90 (dd, J^1 = 9.9 Hz, J^2 = 6.5 Hz, 1H), 6.34 (q, J = 7.2 Hz, 1H), 7.10−7.92 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.6, 15.8, 23.2, 29.7, 35.7, 35.8, 53.2, 60.8, 120.5, 125.4, 128.0, 128.2, 128.5, 130.0, 130.8, 132.0, 139.5, 139.7, 166.1, 171.3.

Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.43; H, 7.43. Found: C, 75.48; H, 7.46.

(3*S*,1′*S*)-8: mp 130−131 °C; $[\alpha]^{28}_D = +36.2$ (c = 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.69 (t, J = 6.9 Hz, 3H), 0.98−1.30 (m, 6H), 1.60 (d, J = 6.9 Hz, 3H), 3.19 (s, 3H), 3.94 (dd, $J^1 \cong J^2$ = 7.3 Hz, 1H), 6.31 (q, J = 6.9 Hz, 1H), 7.06−7.91 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 16.2, 22.1, 28.6, 30.2, 35.7, 53.1, 59.9, 120.6, 125.3, 127.4, 127.9, 128.5, 129.5, 130.8, 132.1, 139.6, 139.7, 166.6, 170.7.

Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.43; H, 7.43. Found: C, 75.24; H, 7.36.

1-Methyl-(3*R*)-*n*-propyl-4-[(*S*)-α-phenylethyl]-1,4-benzodiazepine-2,5-dione, (3*R*,1′*S*)-9, *u*-9. The general procedure was followed with 1.4 g (4.76 mmol) of (*S*)-**1** in 28 mL of THF and 5.08 mL of HMPA, 0.72 mL (0.56 g, 5.5 mmol) of diisopropylamine, 2.9 mL (5.5 mmol) of 1.9 M *n*-BuLi, and 0.55 mL (0.97 g, 5.71 mmol) of *n*-propyl iodide. The isolated product (0.61 g, 73% yield) consisted of a 79:21 mixture of (3*R*,1′*S*)-**9** and (3*S*,1′*S*)-**9** diastereomeric products, which were separated by flash chromatography (hexanes−ethyl acetate, 97.5:2.5 → 90:10) to give 0.153 g (13% yield) of the minor product, *l*-**9**, and 0.576 g (69% yield) of the major product, *u*-**9**.

(3*S*,1′*S*)-9: mp 159−160 °C; $[\alpha]^{28}_D = -19.6$ ($c = 0.94$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.68 (t, $J = 5.9$ Hz, 3H), 1.11−1.25 (m, 4H), 1.58 (d, $J = 7.2$ Hz, 3H) 3.17 (s, 3H), 3.93 (dd, $J^1 \cong J^2 = 8.17$ Hz, 1H), 6.80 (q, $J = 7.2$, 1H), 7.05 (d, $J = 8.4$ Hz, 1H), 7.2−7.4 (m, 6H), 7.47 (td, $J^1 = 7.91$ Hz, $J^2 = 1.73$ Hz, 1H), 7.89 (dd, $J^1 = 7.91$ Hz, $J^2 = 1.73$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 13.7, 16.3, 20.0, 32.8, 35.7, 53.2, 59.8, 120.4, 125.3, 127.4, 128.0, 128.5, 130.9, 132.1, 139.7, 166.6, 170.8.

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 75.13; H, 7.14. Found: C, 74.93; H, 7.33.

(3*R*,1′*S*)-9: mp 129−131 °C; $[\alpha]^{28}_D = -43.4$ ($c = 1.1$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.38 (t, $J = 6.9$ Hz, 3H), 0.8−0.9 (m, 4H), 1.65 (d, $J = 7.2$ Hz, 3H), 3.35 (s, 3H), 3.35 (s, 3H), 3.98 (dd, $J^1 = 10.6$ Hz, $J^2 = 10.1$ Hz, 1H), 6.37 (q, 7.2 Hz, 1H), 7.14 (d, $J = 7.9$ Hz, 1H), 7.26−7.54 (m, 7H), 7.92 (t, $J = 7.8$ Hz, 1H); ^{13}C ($CDCl_3$, 67.5 MHz) δ 11.4, 16.8, 20.5, 32.2, 34.3, 52.9, 58.4, 120.9, 125.8, 127.1, 128.2, 128.4, 130.5, 132.4, 139.1, 165.8, 169.1.

1-Methyl-(3*R*)-(2-propenyl)-4-[(*S*)-α-phenylethyl]-1,4-benzodiazepine-2,5-dione, (3*R*,1′*S*)-10, *u*-10. The general procedure was followed with 0.25 g (0.85 mmol) of (*S*)-**1** in 5 mL of THF, 0.9 mL (3.04 mmol) of HMPA, 0.26 mL (0.18 g, 1.83 mmol) of $(i\text{-Pr})_2$NH, 0.45 mL (0.85 mmol) of 1.9 M *n*-BuLi, and 0.084 mL (0.118 g, 1.02 mmol) of allyl bromide. The isolated product (0.211 g, 74.3% yield) consisted of a 77:23 mixture of (3*R*,1′*S*)-**10** and (3*S*,1′*S*)-**10** diastereomeric products, which were separated by flash chromatography (hexanes−ethyl acetate 100:0 → 90:10) to give 44.3 mg (0.132 mmol, 22% yield) of the minor product, *l*-**10**, and 141.4 mg (0.423 mmol, 67% yield) of the major product, *u*-**10**.

(3*S*,1′*S*)-10: mp 102−104 °C; $[\alpha]^{28}_D = -123.33$ ($c = 0.3$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.54 (δ, $J = 6.6$ Hz, 1H), 1.91−1.98 (m, 2H), 3.14 (s, 3H), 3.98 (dd, $J^1 \cong J^2 = 9.2$ Hz, 1H), 4.67 (dd, $J^1 = 1.32$, $J^2 = 17.2$ Hz, 1H), 4.91 (dd, $J^1 = 1.32$ Hz, $J^2 = 9.9$ Hz, 1H), 5.9 (ddd, $J^1 = 7.2$ Hz, $J^2 = 9.9$ Hz, $J^3 = 17.2$ Hz, 1H), 7.04 (d, $J = 9.2$ Hz, 1H), 7.21−7.31 (m, 6H), 7.47 (t, $J = 7.3$ Hz, 1H), 7.89 (d, $J = 9.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 34.8, 35.6, 53.1, 59.3, 118.7, 120.5, 125.4, 127.4, 128.0, 128.5, 129.4, 130.9, 132.1, 132.4, 139.6, 166.5, 170.1.

Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.45; H, 6.57. Found: C, 75.55; H, 6.75.

(3*R*,1′*S*)-10: mp 139−141 °C; $[\alpha]^{28}_D = -29.7$ ($c = 0.3$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (ddd, $J^1 = 10.28$, $J^2 = 10.6$, $J^3 = 7.3$ Hz, 1H), 1.60 (d, $J = 7.3$ Hz, 3H), 1.61 (m, 1H), 3.34 (s, 3H), 4.01 (dd, $J^1 = 10.3$, 10.6 Hz, 1H), 4.35 (dd, $J^1 = 16.8$ Hz, $J^2 = 1.3$, 1H), 4.65 (dd, $J^1 = 9.88$ Hz, $J^2 = 1.3$ Hz, 1H), 4.91 (ddt, $J^1 = 16.8$ Hz, $J^2 = 9.88$, $J^3 = 6.9$ Hz, 1H), 6.30 (q, $J = 7.3$ Hz, 1H), 7.1 (d, $J = 8.08$ Hz, 1H), 7.24−7.42 (m, 6H), 7.48 (dd, $J^1 = 8.0$ Hz, $J^2 = 7.3$ Hz, 1H), 7.90 (dd, $J^1 = 7.7$ Hz, $J^2 = 1.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.4, 34.8, 35.6, 53.1, 59.3, 118.7, 120.5, 125.4, 127.4, 128.0, 128.5, 129.4, 130.9, 132.1, 132.4, 139.6, 166.5, 170.1.

General Procedure for the Hydrolysis of the Alkylated Benzodiazepinediones 11−15. A suspension of 1 mmol of adduct in 5 mL of 57% HI was heated in a sealed ampule to 95−100 °C until the starting material was consumed (TLC monitoring). 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 chloride, which was adsorbed to acidic ion-exchange resin Dowex 50W × 8. The resin was washed with distilled H_2O until the washings came out neutral, and then the free amino acid was recovered with 1 N aqueous NH_3. Evaporation afforded the crystalline amino acid, which was dried under vacuum at 40 °C.

(*R*)-Alanine, (*R*)-11. Derivative (3*R*,1′*S*)-**5** (0.20 g, 0.65 mmol) was hydrolyzed according to the general procedure to afford 55.2 mg (0.62 mmol, 96% yield) of pure free amino acid (*R*)-**5**: mp 291 °C dec (lit.[23a] mp 291 °C dec); $[\alpha]^{28}_D = -14.0$ ($c = 6$, 1 N HCl) [lit.[23a] $[\alpha]^{28}_D = -14.2$ ($c = 6$, 1 N HCl)]; ^{1}H NMR (D_2O, 400 MHz) δ 1.44 (d, $J = 7.3$ Hz, 3H), 3.74 (q, $J = 7.3$ Hz, 1H).

(*S*)-Phenylalanine, (*S*)-12. Derivative (3*S*,1′*S*)-**6** (0.25 g, 0.65 mmol) was hydrolyzed according to the general procedure to afford 106 mg (quantitative yield) of pure, free amino acid (*S*)-**12**: mp 270−274 °C (lit.[23d] mp 270−275 °C); $[\alpha]^{28}_D = -31.9$ ($c = 2$, H_2O) [lit.[23d] $[\alpha]^{28}_D = -32.7$ ($c = 2$, H_2O)]; ^{1}H NMR (D_2O, 400 MHz) δ 3.07 (dd, $J^1 = 14.3$ Hz, $J^2 = 8.1$ Hz, 1H), 3.24 (dd, $J^1 = 14.3$ Hz, $J^2 = 5.1$ Hz, 1H), 3.94 (dd, $J^1 = 14.3$ Hz, $J^2 = 5.1$ Hz, 1H), 7.27−7.38 (m, 5H).

(*R*)-2-Aminobutyric Acid, (*R*)-13. Derivative (3*R*,1′*S*)-**7** (230 mg, 0.71 mmol) was hydrolyzed according to the general procedure to afford 68.7 mg (94% yield) of pure, free amino acid (*R*)-**6**: mp > 298 °C (lit.[23b] mp > 300 °C); $[\alpha]^{28}_D = -7.8$ ($c = 4$, H_2O) [lit.[23b] $[\alpha]_D = -7.9$ ($c = 4$, H_2O)]; ^{1}H NMR (D_2O, DCl, 400 MHz) δ 0.93 (t, $J = 7.7$ Hz, 3H), 1.84 (m, 2H), 3.67 (t, $J = 5.8$ Hz, 1H).

(*R*)-Norleucine, (*R*)-14. Derivative (3*R*,1′*S*)-**8** (208 mg, 0.59 mmol) was hydrolyzed according to the general procedure to afford 75 mg (97% yield) of pure, free amino acid (*R*)-**14**: mp > 300 °C (lit.[23c] mp > 300 °C); $[\alpha]_D = -21.0$ ($c = 4.7$, 6 N HCl)] [lit.[23c] $[\alpha]^{28}_D = -21.2$ ($c = 4.7$, 6 N HCl)]; ^{1}H NMR (D_2O, DCl 400 MHz) δ 0.90 (t, $J = 7.4$ Hz, 3H), 1.27−1.50 (m, 6H), 1.78−2.00 (m, 2H), 3.82 (t, $J = 6.2$ Hz, 1H).

(*R*)-Norvaline, (*R*)-15. Derivative (3*R*,1′*S*)-**9** (300 mg, 0.59 mmol) was hydrolyzed according to the general procedure to afford 97.3 mg (93% yield) of pure, free amino acid (*R*)-**15**: mp >300 °C (lit.[23e] mp >300 °C); $[\alpha]_D = -23.1$ ($c = 10$, 5 N HCl)] [lit.[23e] $[\alpha]^{28}_D = -24.0$ ($c = 10$, 5 N HCl)]; ^{1}H NMR (D_2O, 300 MHz) δ 0.77 (t, $J = 7.3$ Hz, 3H), 1.17−1.34 (m, 2H), 1.56−1.75 (m, 2H), 3.57 (t, $J = 6.6$ Hz, 1H).

Determination of the Absolute Configuration of the Major Product in Compounds 10. Catalytic Hydrogenation of *u*-10 To Give *u*-9. To determine the absolute configuration of allylic products **10**, a chemical correlation was carried out. Thus, 400 mg (1.19 mmol) of the major diastereomeric product **10,** 4 mL of dry methanol, and 32 mg (10% w/w) of Pd/C 10% were suspended in a hydrogenation flask vessel and reduced in a hydrogen atmosphere (50 psi) during 30 min. The resulting mixture was filtered off on a Celite bed, and the filtrate was concentrated on a rotatory evaporator to give 390 mg (97% yield) of the reduced compound *u*-**9**.

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