From Peptide to Non-Peptide. 3. Atropisomeric GPIIbIIIa Antagonists Containing the 3,4-Dihydro-1*H*-1,4-benzodiazepine-2,5-dione Nucleus

Brent K. Blackburn,* Arthur Lee,* Mark Baier, Benjamin Kohl, Alan G. Olivero, Regina Matamoros, Kirk D. Robarge, and Robert S. McDowell

Department of Bioorganic Chemistry, Genentech, Inc., 460 Pt. San Bruno Boulevard, South San Francisco, California 94080

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The benzodiazepinedione class of non-peptidal GPIIbIIIa antagonists has been modified to allow the isolation of noninterconverting rotational isomers, or atropisomers, with the aim of examining their structure−activity relationships as compared to active RGD-containing peptides and other non-peptidal antagonists. Resolution of these antagonists was accomplished by the introduction of a *tert*-butyl group at N1 and a chlorine at C9 on the 3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione nucleus and enantiospecific substitution on the β-alanine side chain attached to N4. The relative configuration was determined by single-crystal X-ray analysis. Further, conformational analyses using *ab initio* calculations were performed to assess the conformational preferences about the β-alanine side chain. The data support a good topographical correlation between the benzodiazepinedione class of antagonists and the "cupped" presentation of the RGD tripeptide sequence found in the cyclic peptide G4120. The relationship between these compounds with other peptidal and non-peptidal antagonists is discussed.

Introduction

Proteins and peptides containing the tripeptide sequence Arg-Gly-Asp (RGD) have been shown to inhibit the adhesive and aggregatory functions of platelets by binding to platelet receptor GPIIbIIIa, whose natural ligands are fibrinogen and von Willebrand factor.[1,2] Fibrinogen binding to GPIIbIIIa represents the final common event that leads to platelet aggregation regardless of platelet activation and, in certain circumstances, is the primary cause of a variety of human cerebral and cardiovascular diseases.[3,4]

We have reported on the design, synthesis,[5] and structural characterization[6] of the RGD-containing cyclic peptide G4120 (*cyclo*-[-S(O)-Ac-Tyr-Arg-Gly-Asp-Cys-OH]), a potent GPIIbIIIa antagonist. Based on a model derived from the ^{1}H NMR structure determination of G4120 and ensemble molecular dynamics simulation of a series of GPIIbIIIa antagonists that included G4120,[7] a series of non-peptidal antagonists were designed.[8] These compounds utilize the benzodiazepinedione nucleus (e.g., **1**, Figure 1) to reproduce the "cupped" shape of the RGD sequence observed in the solution structure of G4120 (Figure 2).[6] The neutralizing antibody OPG2 binds specifically to GPIIbIIIa and features an RYD sequence in a similar conformation.[9] Deviation from this topography by forcing an extended conformation in the peptide or non-peptidal equivalent resulted in a loss of activity.[7,8,10,11] In contrast, several investigators have reported that the RGD sequence in potent RGD-containing cyclic peptides adopts an extended conformation as determined by ^{1}H NMR and X-ray crystallographic techniques.[12−15] Indeed, compounds designed to mimic the extended C7 conformation of a potent RGD cyclic peptide led to the discovery of other novel GPIIbIIIa antagonists based on the benzodiazepine nucleus.[16]

Benzodiazepinediones are known to exist as a mixture of two slowly interconverting enantiomeric conformational states (Figure 3).[17] The ^{1}H NMR spectrum of **1** showed an AB quartet for the methylene protons at position 3 of the seven-membered ring indicating that interconversion of the two possible rotational isomers is slow on the ^{1}H NMR time scale.[8] It was determined by variable temperature ^{1}H NMR for compound **1** (D_2O) that the energy barrier between these two enantiomeric states is 17 kcal/mol (T_c = 343K).[18] Of the two possible ring conformations shown in Figure 3, A correlates well with the fold and steric constraints of the cyclic peptide G4120, whereas B does not.[8] In order to assess the differential GPIIbIIIa binding affinities of these two isomers and attempt to provide support for the structural hypothesis that led to the design of the benzodiazepinedione class of GPIIbIIIa antagonists, a pair of noninterconverting rotational isomers, or atropiso-

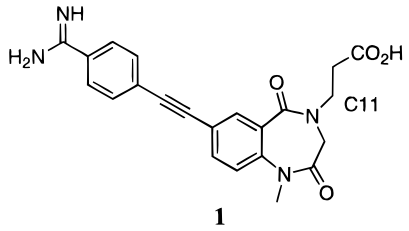

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Figure 1. Benzodiazepinedione GPIIbIIIa antagonist compound **1**.

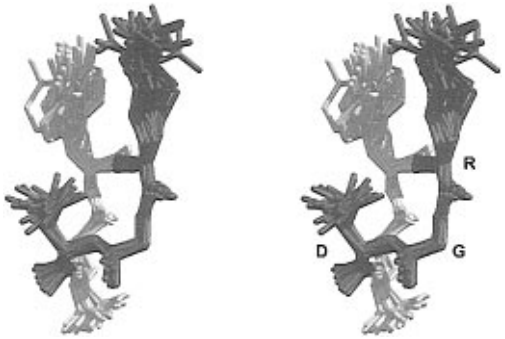

Figure 2. Stereoview of the ^{1}H NMR structures of *cyclo*-[-S(O)-Ac-Tyr-Arg-Gly-Asp-Cys-OH] (G4120). The RGD tripeptide sequence is highlighted in dark gray.

* Author to whom correspondence should be addressed.
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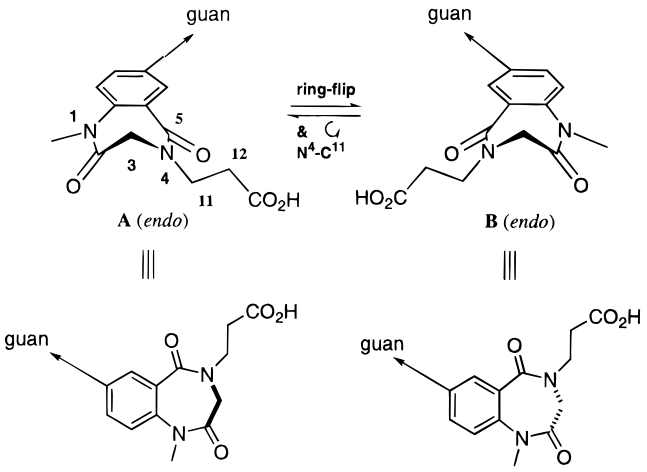


Figure 3. Atropisomeric conformers of the benzodiazepinedione GPIIbIIIa antagonists with β-alanine rotated *endo* to the aromatic ring. The guanidine surrogate has been abbreviated to "guan".

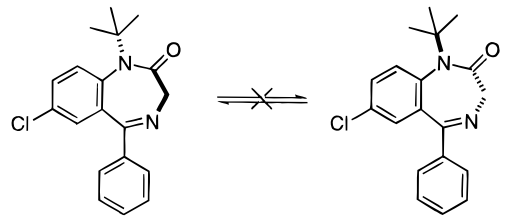


Figure 4. Benzodiazepinedione atropisomers.

mers,[19] were prepared and evaluated for their *in vitro* receptor antagonist and platelet antiaggregatory potencies.

Chemistry

Synthesis. The isolation of a pair of atropisomers has been reported for the structurally related 1,4-benzodiazepines by incorporation of the sterically demanding *tert*-butyl substituent at N1 (Figure 4).[20] Accordingly, our first attempt toward the preparation of noninterconverting rotational isomers included the incorporation of a *tert*-butyl group at the N1 position of the benzodiazepinediones.

To aid the separation of the two possible enantiomeric atropisomers, a stereogenic center on the β-alanine side chain of **1** (at C11) was introduced to yield distinguishable diastereoisomers. The effect of stereogenicity at C11 on the relative binding affinity was evaluated prior to the introduction of the N^1-*tert*-butyl group. Thus, compounds **2** and **3** (R^1, R^2 = Me, X = H) were prepared by methods shown in Scheme 1. The iodo-*N*-methylisatoic anhydride[8] was allowed to react with ethyl (*R*)- or (*S*)-3-aminobutanoate[21] followed by acylation with bromoacetyl bromide and ring closure with base to yield **6a**,**b**, respectively. Incorporation of the benzamidine moiety can be accomplished *via* palladium-mediated coupling with 4-ethynylbenzamidine (**15**) or 4-ethynylbenzonitrile (**16**) followed by stepwise elaboration of the nitrile into the amidine to furnish **2** and **3**, as previously described.[8] Hydrolysis of the resulting amidino ester yields the desired amidino acid adducts. Scheme 2 shows the methods used to prepare **15** and **16** from 4-bromobenzonitrile.[22,23] Inspection of the ^{1}H NMR of **2** and **3** indicated two interconverting conformers in a ratio of 3:1 (^{1}H NMR, D_2O).[24]

In an exploratory reaction to introduce the N^1-*tert*-butyl group, nucleophilic aromatic substitution methodology described by Meyers was examined.[25] Reaction of the 2-oxazolinoanisole **17** with the lithium *tert*-butylamide provided the *N*-*tert*-butylaniline **18** in moderate yield. Unfortunately, efforts to hydrolyze the oxazoline group resulted in the complete removal of the *tert*-butyl group (Figure 5).

Preparation of the anthranilic acid **4** was accomplished in a two-step synthesis from *p*-iodofluorobenzene (**19**) applying methodology previously employed by Bridges et al. (Figure 6).[26] Coupling of the enantiomerically pure ethyl (*S*)-3-aminobutanoate[21] to **4** followed by acylation with bromoacetyl bromide and ring closure afforded a diastereomeric pair of 7-iodobenzodiazepinediones **6c** (Scheme 1). These two isomers were separable by column chromatography but equilibrated to a 1:1 mixture at room temperature within 24 h as detected by ^{1}H NMR analysis. The mixture of iodoarenes **6c** were coupled with ethynylbenzamidine and hydrolyzed to yield **7** as a mixture of diastereoisomers. The diastereomeric pair was separated by RP-HPLC but again equilibrated at room temperature (^{1}H NMR).

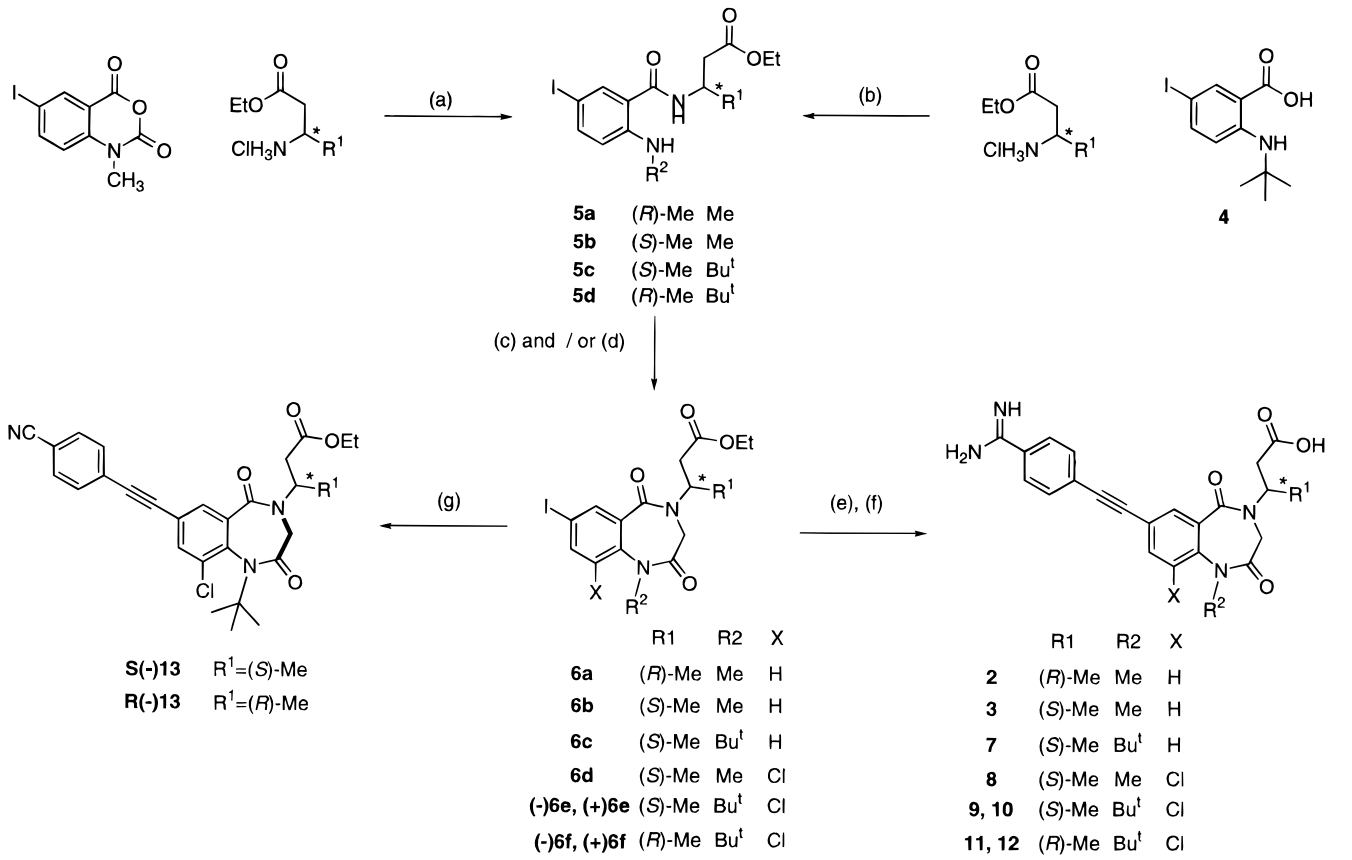
Syntheses of the 9-chlorobenzodiazepinedione analogs **8**−**12** were accomplished by allowing the anilines **5b**−**d** to react with chlorine in acetic acid followed by the standard sequence to form the seven-membered ring and attachment of ethynylbenzamidine (Scheme 1). Although the two possible diastereoisomers shown as compound **8** could be separated by column chromatography, a 1:1 mixture was detected by ^{1}H NMR within 24 h. In contrast, the diastereoisomers of the iodoarene intermediates **6e,f** could be separated by column chromatography to give (−)-**6e**, (+)-**6e**, (−)-**6f**, and (+)-**6f** and elaborated individually into the desired amidino acid derivatives **9**−**12**, respectively. No equilibration of the compounds **6e**,**f** or the products **9**−**12** could be detected within 1 week at room temperature by ^{1}H NMR analysis. Compounds (−)-**6e** and (−)-**6f** were converted into the ethynylbenzonitrile adducts (*S*)-(−)-**13** and (*R*)-(−)-**13** (Scheme 1), respectively, whose relative configurations were assigned by X-ray crystallography (*vida infra*).

Assays. Compounds were evaluated for their inhibitory potency first in an ELISA (enzyme-linked immunfluorencent solid-phase assay)-based system that measures the association of soluble GPIIbIIIa with fibrinogen coated on a microtiter plate.[5] Potent molecules were further evaluated for inhibition of platelet aggregation of human platelets in platelet rich plasma (PRP; 300 000 platelets/μL) stimulated with ADP (17.5 μM)[5] and, on selected compounds, with the thrombin receptor agonist peptide (TRAP; 20 μM).[27] The potency data for compounds **1**−**3**, **7**−**12** can be found in Table 1.

Variable Temperature (VT) ^{1}H NMR. Variable temperature ^{1}H NMR experiments were conducted on compounds **1**, **7**, **8**, and (*S*)-(−)-**13** using a Varian 300 MHz instrument in either DMSO-d_6 or tetramethylene-d_8 sulfone. Variable temperature ^{1}H NMR experiments on compounds **9**−**12** resulted in decomposition. Therefore, to assess the barrier to ring inversion for compounds substituted R^1 = Me, R^2 = Bu^t, X = Cl, the variable temperature experiments were conducted on the nitrile ester (*S*)-(−)-**13**. The temperature of coalescence was estimated by examination of the ^{1}H NMR spectra taken at temperatures ranging from 25 to 200 °C.

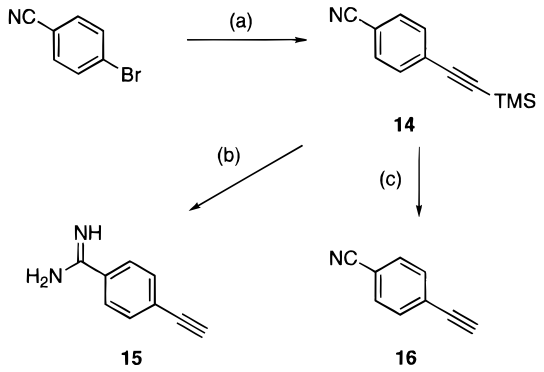
X-ray Crystallography. Large, clear, colorless, columnar crystals of compound (*S*)-(−)-**13** were obtained by slow crystallization from methylene chloride and

Scheme 1. Synthesis of Benzodiazepinediones[a]



[a] (a) DMF or CH_2Cl_2, Et_3N, DMAP; (b) EDC, HOBT, Et_3N; (c) Cl_2, AcOH; (d) i. $BrCH_2COBr$, ii. Cs_2CO_3, DMF or DBU, CH_2Cl_2 or $C_6H_5CH_3$; (e) Pd(II), Cu(I), Et_3N, **15**, DMF; (f) LiOH; (g) Pd(II), Cu(II), Et_3N, **16**, EtOAc.

Scheme 2. Synthesis of 4-Ethynylbenzamidine and 4-Ethynylbenzonitrile[a]



[a] (a) Pd(II), Cu(I), Et_3N, trimethylsilylacetylene, EtOAc; (b) i. H_2S, pyridine, ii. MeI, iii. NH_4OAc, EtOH; (c) K_2CO_3, MeOH.

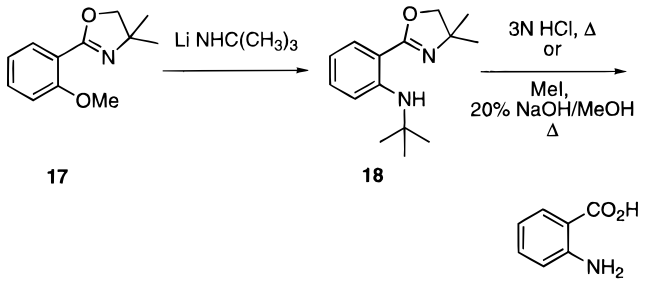


Figure 5. Attempt to prepare *N-tert*-butylanthranilic acid.

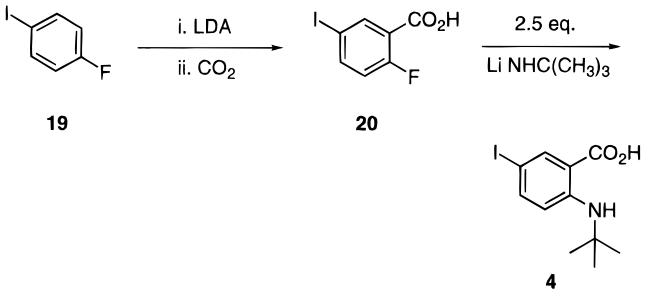


Figure 6. Synthesis of *N-tert*-butyl-5-iodoanthranilic acid.

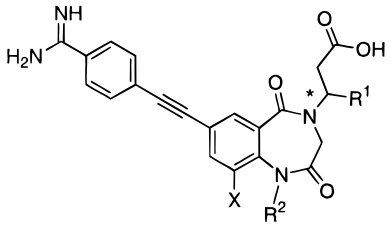
hexanes. Colorless, platelike crystals of compound (*R*)-(−)-**13** were obtained by slow crystallization from hexanes. The structures (*S*)-(−)-**13** (3495 unique reflections) and (*R*)-(−)-**13** (10 636 unique reflections) were solved by direct methods. Hydrogen atoms were assigned idealized locations and were included in structure factor calculations but were not refined.

Conformational Analysis. Relative energies of rotamers about the N4−C11 and C11−C12 bonds were calculated to ascertain whether steric interactions due to methyl substitution at C11 would be expected to influence the conformational profile of the β-alanine side chain. Models of (*S*)-(−)-**9**, (*R*)-(−)-**12**, and the desmethyl analog (R^1 = H, R^2 = Bu^t, X = Cl) were constructed in which the ethynylbenzamidine side chain was replaced by a hydrogen. Approximate local minima were obtained by systematically searching about the C3−N4−C11−C12 and N4−C11−C12−C(carboxylate) bonds at 10° intervals using SYBYL (Tripos Associates, St. Louis, MO), followed by energy minimization using MM2.[28] Each of the resulting structures was further refined by optimization at the 6-31G* [29] level using Gaussian-94.[30]

Results and Discussion

To assess the effect of chiral substitution at C11 on potency, compounds **2** and **3** were prepared and tested

Table 1. Activity of Benzodiazepinedione Analogs



entry	compd	R^1	R^2	X	$[\alpha]_D$ (deg)	IC_{50} (μM)[a] ELISA	ADP	TRAP
1	**1**[b]	H	Me	H	NA	0.011	0.12	0.213
2	**2**	(*R*)-Me	Me	H	+32.6	0.060	0.82	
3	**3**	(*S*)-Me	Me	H	−37.0	0.005	0.078	0.138
4	**7**	(*S*)-Me	Bu^t	H	+14.2[c]	0.003[d], 0.012[e]	0.092[c]	
5	**8**	(*S*)-Me	Me	Cl	−24.5[c]	0.007[c]	0.159[c]	0.313
6	**9**	(*S*)-Me	Bu^t	Cl	−85.5	0.002	0.034	0.060
7	**10**	(*S*)-Me	Bu^t	Cl	+71.3	0.14	1.5	
8	**11**	(*R*)-Me	Bu^t	Cl	−71.1	0.018	1.3	
9	**12**	(*R*)-Me	Bu^t	Cl	+90.7	0.065	1.3	

[a] Data are presented as an average of at least $n = 3$ unless otherwise noted. The standard deviation (SD) was always ±25% of the mean for the ELISA assay and ±20% for the PRP and TRAP platelet aggregation assays. [b] Data for compound **1** was taken from ref 8. [c] A 1:1 mixture of diastereoisomers. [d] A 3:1 mixture enriched in the faster eluting diastereoisomer ($n = 1$). [e] A 1:3 mixture enriched in the slower eluting diastereoisomer ($n = 1$).

in the protein−protein assay (ELISA) and physiologically relevant (PRP) platelet aggregation assay. The more potent mixture of interconverting diastereoisomers results from the (*S*)-β-methyl derivative **3**, which is 10-fold more potent than its enantiomer **2** (Table 1, entries 2 and 3). The absolute configuration of the more potent C11-substituted enantiomer is in contrast to the stereochemical preference observed for peptidal[31] and other non-peptidal GPIIbIIIa antagonists (Figure 7).[32−35] For example, substitution of the L-aspartic acid residue in RGD-containing peptides with the D-enantiomer results in reduced binding potency.[31]

One interpretation of this apparent anomalous result for **3**, based on aqueous-phase conformational preferences observed by the ^{1}H NMR which indicated a 3:1 ratio of the two interconverting isomers, is that asymmetric substitution at C11 influences the ratio of rotational isomers of the seven-membered ring such that the (*S*)-methyl derivative benefits the isomer that is productive for binding to GPIIbIIIa whereas the (*R*)-methyl derivative stabilizes the isomer that is unproductive for protein binding. Alternatively, these results may be accounted for by subtle variation in the rotational preferences in the β-alanine side chain upon substitution at C11 (*vida infra*).

To increase the barrier to interconversion of the two interconverting diastereoisomers, the N^1-*tert*-butyl derivative **7** was prepared and assayed. Although the barrier to interconversion was increased compared to **3** (VT ^{1}H NMR, **7** $T_c > 498$ K, $\Delta G^{\ddagger} > 23$ kcal/mol; **3** $T_c = 343$ K, $\Delta G^{\ddagger} = 17$ kcal/mol), the two diastereoisomers, which could be separated by reverse-phase chromatography, equilibrated within 24 h. Samples enriched 3:1 in the faster eluting isomer at the time of assay (ELISA) were shown to be more potent than samples enriched in the slower eluting diastereoisomer (Table 1, entry 4). These data are indicative of a stereochemical atropisomeric preference for GPIIbIIIa binding and that the diminished conformational freedom imposed by the N1 substituent does not limit its capacity to bind to GPIIbIIIa.

In our pursuit for noninterconverting rotational isomers, or atropisomers, it was postulated that the presence of an atom *ortho* to the N1 group would further increase the barrier to ring inversion. As a control, the N^1-methyl-C9-chloro analog **8** was produced to assess the effect on potency of a chlorine atom at position 9. As expected, the incorporation of a chlorine atom at C9 significantly increases the barrier to interconversion as compared to the deschloro analogs (VT ^{1}H NMR, **8** $T_c = 473$ K, $\Delta G^{\ddagger} = 23$ kcal/mol, **2** and **3** $T_c = 343$ K, $\Delta G^{\ddagger} = 17$ kcal/mol). However, the diastereoisomers of **8** also equilibrated to a 1:1 mixture in 24 h at room temperature after isolation by reverse-phase chromatography, consistent with the calculated half-life of interconversion ($t_{1/2}^{298K} = 2.6$ h).[36,37] The potency data for **8** indicate that the effect of C9 substitution with a chlorine atom is marginal (Table 1, entry 5). In contrast to **6c**, **7**, and **8**, the N^1-*tert*-butyl-9-chloro-substituted molecules **9**, **10**, (−)-**6e**, and (+)-**6e** showed no signs of equilibration over 1 week at room temperature (^{1}H NMR, RP-HPLC). The *R*-substituted atropisomers **11** and **12** were similarly prepared and also remained configurationally stable.

Upon assay, marked differences in the potencies of the atropisomers **9**−**12** were observed (Table 1, entries 6−9). The relative stereochemistry of the more potent analog (entry 6) and its diastereomer (entry 8) was assigned by X-ray crystallography of the benzonitrile ethyl ester analogs (*S*)-(−)-**13** and (*R*)-(−)-**13**, respectively. Attempts to obtain X-ray quality crystals of **9** or **11**, or their ethyl ester, were unsuccessful.

The asymmetric unit of (*S*)-(−)-**13** consists of a single molecule (Figure 8A). The β-alanine side chain is orientated *exo* to the benzodiazepinedione core with a C3−N4−C11−C12 dihedral angle of 57.3°. By contrast, the asymmetric unit of (*R*)-(−)-**13** contains two nonidentical molecules packed in layers with interlocking ethynylbenzonitrile side chains (Figure 8B); the layers are separated by a molecule of hexane. The two (*R*)-(−)-**13** molecules differ primarily in the β-alanine side chain conformations, having C3−C4−C11−C12 dihedral angles of −74.3° and −66.3°, respectively. No abnormal bond lengths or angles were observed for either compound. Both (*S*)-(−)-**13** and (*R*)-(−)-**13** feature the same atropisomer: the rms deviation of the benzodiazepine cores of (*S*)-(−)-**13** and the two molecules of (*R*)-(−)-**13** are 0.049 and 0.072 Å, respectively. Atomic coordinates are available as Supporting Information.

The results of the *ab initio* optimizations are summarized in Table 2. The optimized benzodiazepinedione cores adopt the extreme "boat" configuration and were virtually superimposible with the X-ray structures of (*S*)-(−)-**13** and (*R*)-(−)-**13**. The β-alanine side chain of the desmethyl analog displays little conformational preference: all six local minima (*exo* and *endo* conformations of the N4−C11 bond, each with three staggered rotamers about the C11−C12 bond) are within ~1 kcal/mol of each other. Both (*R*)- and (*S*)-methyl substitution at C11 imparts a slight preference for the *endo* orientation about the N4−C11 bond by 1.6 kcal/mol and 1.3 kcal/mol, respectively. The energetics of the C11−C12 rotamers are significantly impacted by methyl substitution at C11, as expected for substitution of a central atom of an sp^3-sp^3 bond. Interestingly, the global minimum of the *R*-substituted molecule was 1.1 kcal higher in energy than the global minimum of the *S*-substituted molecule. Since the *R*-substituted mol-

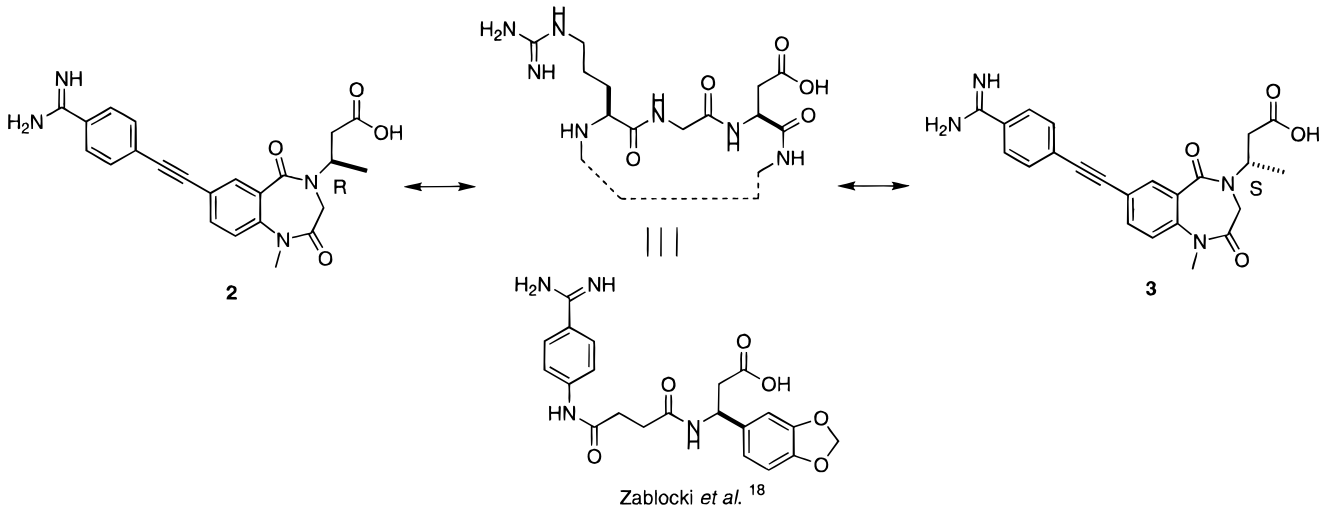


Figure 7. Stereochemical relationship of compounds **2** and **3** with RGD-containing peptides and an example of a non-peptidal antagonist.

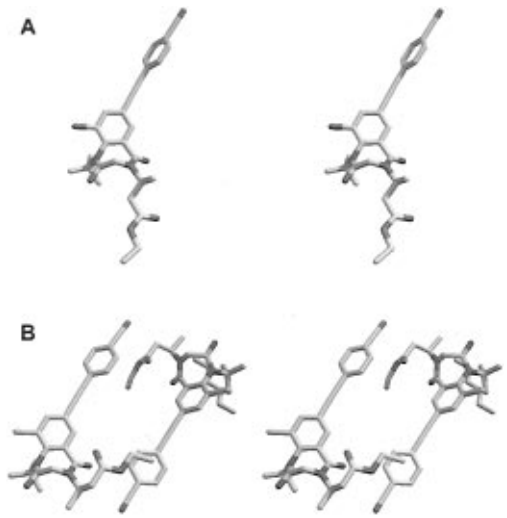


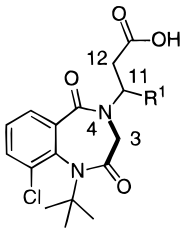
Figure 8. Stereoview of the X-ray crystal structure of (A) compound (*S*)-(−)-**13** and (B) compound (*R*)-(−)-**13** (conformers A and B and hexane).

ecule is the enantiomer of the ring-inverted *S*-substituted analog, these data suggest that the steric effect induced by (*S*)-methyl substitution at C11 should stabilize the atropisomer observed in the X-ray structures.

The stereochemical disposition of the more potent atropisomer **9** correlates with conformer A in Figure 3 and is consistent with the "cupped" shape of the RGD sequence observed in the NMR structure of G4120. To ideally map to the peptide conformation, the β-alanine side chain would be oriented *endo* to the fused ring system, yet the crystal structure of (*S*)-(−)-**13** shows an *exo* orientation. In both (*S*)-(−)-**13** and (*R*)-(−)-**13**, the β-alanine ethyl ester is tightly stacked against the benzonitrile aromatic rings of two neighboring molecules (Figure 9). Given that neither (*R*)- nor (*S*)-methyl substitution at C11 appears to induce a significant steric preference for *endo* vs *exo* orientation, it is likely that the orientation of the β-alanine side chain observed in the crystal structures results primarily from packing interactions.

Of the reasons proposed for the C11 (*S*)-methyl analog **3** displaying greater potency than its enantiomer **2**, the results of the *ab inito* calculations are consistent with the (*S*)-methyl derivative benefiting the conformer that is productive for binding to GPIIbIIIa. However, the potency data for **11**, which is locked into the same conformation as **9**, indicates that rotational preferences about the C11−C12 bond also play a role in reducing the potency for the C11 *R*-substituted benzodiazepinedione analogs.

Table 2. Relative Energies of Rotomers about the N4−C11 and C11−C12 Bonds for a Model of Compounds **9** and **12** and Their Corresponding C11 Desmethyl Analog



conformer		dihedral angle (deg) C3−N4−C11−C12	dihedral angle (deg) N4−C11−C12−C(O)	relative energy (kcal/mol) 6-31G*
(*S*)-(−)-**13** X-ray		57.3	177.0	
(*R*)-(−)-**13A** X-ray		−74.3	−52.0	
(*R*)-(−)-**13B** X-ray		−66.3	−50.5	
R^1 = H	*endo*	−102.6	61.3	0.31
	endo	−79.8	−69.1	1.46
	endo	−91.5	174.8	0.92
	exo	90.8	73.1	0.77
	exo	80.0	−82.1	0.00
	exo	83.2	−178.9	1.00
R^1 = (*S*)-CH_3	*endo*	−115.7	63.5	0.00[a]
	endo	−91.9	−70.3	5.06
	endo	−122.9	157.0	1.53
	exo	83.9	74.0	2.76
	exo	48.4	−112.1	6.05
	exo	63.3	165.9	1.30
R^1 = (*R*)-CH_3	*endo*	−103.2	64.1	0.00[a]
	endo	−59.5	−54.7	1.15
	endo	−71.9	−176.3	1.23
	exo	105.0	66.6	3.52
	exo	129.3	−69.2	1.61
	exo	122.7	−169.1	2.30

[a] The gobal minima for the (*S*)-Me and (*R*)-Me compound had energies of −1064.9695714 hartrees and −1064.9679437 hartrees, respectively, suggesting the (*S*)-substitution favors the (−) atropisomer by approximately 1 kcal/mol.

Conclusion

Synthesis, isolation, and characterization of the two possible atropisomers of the benzodiazepinedione class of GPIIbIIIa antagonists has been accomplished, in

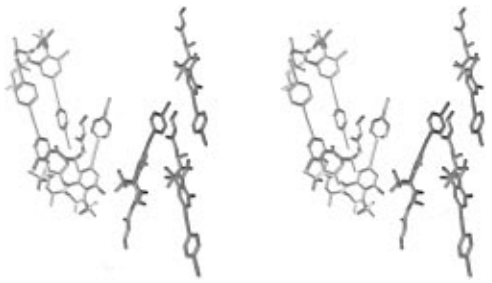


Figure 9. Stereoview of the expanded unit cell for compounds (*S*)-(−)-**13** (light gray) and (*R*)-(−)-**13** (dark gray) showing the packing near the β-alanine ethyl ester moiety.

which compound **9** represents a conformationally rigid and potent GPIIbIIIa antagonist. The data reported herein supports our original structural hypothesis that led to the design and synthesis of the benzodiazepinedione class of GPIIbIIIa antagonists, derived in part from the solution-phase structure of the cyclic peptide G4120.[8]

A structural comparison between the ^{1}H NMR structure of G4120, which exhibits a bend at the Gly methylene, and the solution-phase structures determined for other potent RGD-containing cyclic peptides, which are extended about the Gly residue, has been reported and indicates a striking dissimilarity between these classes of cyclic peptide antagonists.[13] Although each of these classes of cyclic peptides were independently used in the *de novo* design of potent non-peptidal antagonists, these results highlight the difficulty in attempting to define a single molecular pharmacophore for GPIIbIIIa binding,[38] especially considering the dynamic characteristics of either the purified or platelet-bound receptor[39−44] or the potential of multiple binding sites.[45−46] Furthermore, the possibility of different yet overlapping modes of receptor binding by the diverse set of known antagonists can not be ruled out. Further characterization of these antagonists for their inhibitory potential on activated or nonactivated platelets or on the receptor is therefore warranted.[47] The pharmacological response that may result from these different classes of GPIIbIIIa antagonists also remains to be determined.[48]

Experimental Section

General Methods. Melting points were determined on a Laboratory Devices Mel-Temp II melting point apparatus and are uncorrected. Proton spectra were recorded on a Varian VXR-300S spectrometer or Varian Unity Inova 400 NMR spectrometer at 293 K unless noted. Carbon NMR were recorded on a Varian VXR-300S spectrometer at 293 K unless noted. Samples were prepared in either $CDCl_3$, CD_3OD, DMSO-d_6, or deuterium oxide (99.9% ^{2}H atoms) purchased from Cambridge Isotope. Chemical shifts were measured relative to tetramethylsilane, at 0.0 ppm, HOD, at 4.85 ppm (^{1}H NMR), or $CDCl_3$ and CD_3OD (^{13}C NMR). The ^{1}H NMR assignments are described with the abbreviations s (singlet), d (doublet), t (triplet), q (quartet), p (pentuplet), m (multiplet), and b (broad), and all coupling constants are reported in hertz. ^{13}C NMR data are given with $CDCl_3$ or CD_3OD as the internal lock. Optical rotations were performed on a Perkin-Elmer 241 polarimeter at room temperature at the indicated wavelength; the concentrations are reported g/100 mL. High-resolution mass spectra were obtained on a JEOL JMS-HX110HF/HX110HF tandem MS/MS instrument using the positive-ion fast-atom bombardment (FAB) technique. C, H, and N analyses were conducted by Oneida Research Services, Whitesboro, NY. Elemental analyses observed outside ±0.4% of the calculated values are listed with the characterization data. Elemental analyses observed within ±0.4% of the calculated can be found in the Supporting Information and are noted here as C,H,N. X-ray crystallography instrumentation at the University of California, Berkeley, College of Chemistry X-Ray Crystallographic Facility (CHEXRAY) consists of two Enraf-Nonius CAD-4 diffractometers, each equipped with a nitrogen-flow low-temperature apparatus and controlled by a microVAX II computer. Both use Enraf-Nonius software as described in the CAD-4 Operation Manual, Enraf-Nonius, Delft, Nov. 1977, and updated thereafter. Calculations were performed on DEC MicroVax computers using locally modified versions of the Enraf-Nonius MolEN structure solution and refinement package and other programs. Heavy atom positional parameters for compounds (*S*)-(−)-**13** and (*R*)-(−)-**13**, and selected bond and torsion angles, can be found in Supporting Information. All concentrations were performed on a Büchi rotary evaporator.

Analytical thin-layer chromatography (TLC) was conducted on Whatman silica gel 60A M_{254} MK6F glass-coated plates and visualized by UV and/or charring with 0.2% ninhydrin in ethanol. Silica gel (SiO_2) 60 (230−400 mesh, E. Merck) was used for all preparative (flash) column chromatography purifications. High-pressure liquid chromatography (HPLC, UV detection at 214 or 254 nM) solvent gradient methods are listed below using the syntax (method: column, solvent gradient range, flow rate, time (%CH_3CN)). Gradient protocol A: Microsorb−Short One C_{18}, 4.6 × 100 mm, 0−100% CH_3CN/H_2O (0.1% TFA), 1.5 mL/min, 0:00 (0%), 9:00 (100%), 9:10 (100%), 11:00 (0%). B: Dynamax 83−303-C5, 4.6 × 250 mm, 0−100% CH_3CN/H_2O (0.1% TFA), 1.5 mL/min, 0:00 (0%), 9:00 (100%), 11:10 (100%), 12:00 (0%). C: Dynamax-60A 83-221-C C_{18}, 21.4 (i.d.) × 25 mm, 0−50% CH_3CN/H_2O (0.1% TFA), 10 mL/min, 0:00 (0%), 46:00 (50%), 67:00 (50%), 72:00 (0%). D: Vydac C_{18} 300 Å, 5 × 26 cm, 0−81% CH_3CN/H_2O (0.5% HOAc), 12 mL/min, 0:00−6:00 load, 6:00 (0%), 10:00 (18.5%), 13:00 (31.5%), 26:00 (31.5%), 50:00 (42%), 66:00 (50%), 79:00 (50%), 82:00 (81%), 84:00 (81%), 90:00 (0%). E: Vydac C_{18} 300 Å, 5 × 26 cm, isocratic : 20% CH_3CN/H_2O (0.5% AcOH), 10 mL/min. F: Vydac C_{18} 300 Å, 5 × 26 cm, 0−50% CH_3CN/H_2O (0.5% AcOH), 12 mL/min, 0:00−6:00 load, 6:00 (0%), 12:40 (10%), 26:00 (20%), 67:00 (50%), 78:00 (50%), 82:00 (81%), 84:00 (81%), 90:00 (0%). G: Microsorb−Short One C_{18}, 4.6 × 100 mm, 0−100% CH_3CN/H_2O (0.1% TFA), 1.5 mL/min, same method as B. H: Dynamax-60A 83-221-C C_{18}, 21.4 (i.d.) × 25 mm, 0−60% CH_3CN/H_2O (0.1% TFA), 10 mL/min, 0:00 (0%), 7:00 (20%), 80:00 (60%), 90:00 (80%), 97:00 (80%), 100:00 (0%). I: Dynamax-60A 83-221-C C_{18}, 21.4 (i.d.) × 25 mm, 0−50% CH_3CN/H_2O (0.1% TFA), 10 mL/min, 0:00 (0%), 5:00 (20%), 80:00 (50%), 90:00 (80%), 97:00 (80%), 100:00 (0%). Solvents and reagents were purchased from commercial sources and used as received.

***N-tert*-Butyl-5-iodoanthranilic Acid (4). (a)** To a solution of diisopropylamine (27 g, 39 mL, 0.275 mol, 1.2 equiv) in anhydrous THF (300 mL) at −78 °C was added *n*-BuLi (1.8 M in hexanes, 135 mL, 0.25 mol, 1.1 equiv). After stirring for 15 min, the LDA solution was added *via* cannula to a solution of 4-fluoro-1-iodobenzene (**19**) (50 g, 0.225 mol, 1 equiv) in THF (200 mL) at −78 °C. After stirring for 30 min the mixture was rapidly transferred to a vigorously stirred slurry of dry ice in Et_2O (1.5 L). The mixture was allowed to warm to 0 °C and then transferred to a separatory funnel. The solution was washed twice with H_2O (1 L). The aqueous layer was acidified with concentrated HCl until pH < 1 and extracted with Et_2O. The organic layer was washed with brine (1 L), dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The resulting residue was filtered, through a silica plug with 50% EtOAc/hexanes to yield 52.21 g (87%) of 2-fluoro-5-iodobenzoic acid (**20**) as a white solid: mp 147−150 °C; TLC R_f = 0.30 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) 8.32 (1H, dd, $^4J_{HF}$ = 6.8, $^4J_{HH}$ = 2.2, ArH C6-H), 7.86 (1H, m, ArH C4-H), 6.95 (1H, t, $^3J_{HH}$ = 8.8, $^3J_{HF}$ = 10.5, ArH C3-H); ^{13}C NMR ($CDCl_3$) 165.5, 163.9, 160.4, 143.4, 141.0, 120.5, 119.3, 199.0, 86.4; C,H,N.

(b) To a solution of *tert*-butylamine (36 g, 46 mL, 0.438 mol, 2.3 equiv) in THF (400 mL) at 0 °C was added *via* dropping funnel *n*-BuLi (1.84 M in hexanes, 227 mL, 0.42 mol, 2.2 equiv). The burgundy solution was stirred for 1h at 0 °C and then transferred *via* cannula to a solution of **20** in THF (400 mL) at −78 °C. The solution was stirred at −78 °C for 20 min, and then the reaction was quenched with 1 N HCl (500 mL).

After warming to room temperature, the yellow mixture was transferred to a separatory funnel, then extracted with EtOAc (400 mL), washed with brine (1 L), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by eluting through a silica plug with 10% acetone/CH_2Cl_2 yielding 19.9 g (33%) of **4** as a pale yellow solid, mp 163−167 °C dec; R_f = 0.30 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) 8.29 (1H, d, $^4J_{HH}$ = 2.2, ArH C6-H), 7.56 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.2, ArH C4-H), 6.78 (1H, d, $^3J_{HH}$ = 9.0, ArH C3-H) 1.43 (s, 9H, Bu^t); ^{13}C NMR ($CDCl_3$) 172.7, 149.5, 142.7, 141.1, 116.8, 112.5, 74.6, 51.5, 29.4; LRMS (FAB, M + H) 320.2; HRMS (FAB) *m*/*z* calcd for $C_{11}H_{14}N_1O_2$ 320.0148, found 320.0154; C,H,N.

***N*-[5-Iodo-2-(methylamino)benzoyl]-3(*R*)-aminobutanoic Acid, Ethyl Ester (5a).** Compound **5a** was prepared using a modified version of the procedure previously reported,[8] substituting CH_2Cl_2 for DMF and diisopropylethylamine (DIPEA) for triethylamine (Et_3N), in 47% yield, $[\alpha]^{24}_{589}$ +25.0° (*c* = 0.505, $CHCl_3$). Analytical data (^{1}H and ^{13}C NMR, mp, TLC, RP-HPLC, and HRMS) were identical with those obtained for its enantiomer **5b**.

***N*-[5-Iodo-2-(methylamino)benzoyl]-3(*S*)-Aminobutanoic Acid, Ethyl Ester (5b).** To a solution of 3(*S*)-aminobutanoic acid, ethyl ester hydrochloride (7.58 g, 45.28 mmol, 1.0 equiv) and anhydrous CH_2Cl_2 (175 mL) in an oven-dried 24/40 500 mL round bottom flask equipped with a stir bar at room temperature under an atmosphere of argon were added with 5-iodo-*N*-methylisatoic anhydride[8] (13.9 g, 45.87 mmol, 1.01 equiv) in 3 × 4.63 g portions, Et_3N (11.53 mL, 82.6 mmol, 1.8 equiv), and (dimethylamino)pyridine (0.84 g, 0.15 equiv). The turbid solution was stirred for 13 h to give a homogeneous purple solution. The reaction was quenched by pouring the mixture into a Erlenmeyer flask containing ice/10% citric acid. The layers were separated, and the aqueous layer was extracted additionally with dichloromethane. The dichloromethane layers were combined, washed once with water and once with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (stepped gradient elution 10% then 30% EtOAc/hexane) of the crude dark syrup followed by drying under high vacuum (1.0 mmHg, 16 h) afforded **5b** as a tan solid (66%): mp 63−64.5 °C; $[\alpha]^{24}_{589}$ −23.6° (*c* = 4.6, $CHCl_3$); TLC R_f = 0.55 (30% EtOAc/hexane); RP-HPLC (method A) t_R = 6.63 min; ^{1}H NMR ($CDCl_3$) 7.52 (1H, d, $^4J_{HH}$ = 2.0, ArH C6-H), 7.49 (1H, dd, $^3J_{HH}$ = 8.7, $^4J_{HH}$ = 2.0, ArH C4-H), 7.46 (1H, m, N*H*CH$_3$), 6.59 (1H, bd, $^3J_{HH}$ = 7.3, CON*H*CH(CH$_3$)), 6.40 (1H, d, $^3J_{HH}$ = 8.5, ArH C3-H), 4.45 (1H, m, NC*H*(CH$_3$)-CH$_2$), 4.19 (2H, q, $^3J_{HH}$ = 7.0, OCH$_2$), 2.83 (1.5H, s, NCH$_3$), 2.81 (1.5H, s, NCH$_3$), 2.60 (2H, dd, $^2J_{HH}$ = 5.4, $^3J_{HH}$ = 1.2, C*H*$_2$-CO$_2$), 1.29 (3H, d, $^3J_{HH}$ = 6.8, NCH(C*H*$_3$)CH$_2$), 1.27 (3H, t, $^3J_{HH}$ = 7.1, CO$_2$CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) 171.54, 167.54, 149.81, 140.87, 135.34, 117.55, 113.30, 74.03, 60.69, 42.19, 40.06, 29.49, 20.00, 14.18; LRMS (FAB) *m*/*z* 390 (M^+), 390 (100), 259.9; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{20}N_2IO_3$ 391.0519, found 391.0500; C,H,N.

***N*-[5-Iodo-2-(*tert*-butylamino)benzoyl]-3(*S*)-aminobutanoic Acid, Ethyl Ester (5c).** To a solution of **4** (2.38 g, 7.5 mmol, 1 equiv) in CH_2Cl_2 at 25 °C were added diisopropylethylamine (2.25 mL, 1.75 equiv) and then BOP reagent (3.63 g, 8.2 mmol, 1.1 equiv). To this solution was added a mixture (2.25 g, 13.4 mmol, 1.8 equiv) of 3(*S*)-aminobutanoic acid, ethyl ester hydrochloride and diisopropylamine (3.5 mL, 3 equiv) in CH_2Cl_2 (15 mL). The reaction mixture was stirred for 15 min then transferred to a separatory funnel, diluted with CH_2Cl_2, and washed with 1 N HCl (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting oil was further purified by passing through a silica plug with 10% EtOAc/hexanes as the eluting solvent to yield 2.60 g (81%) of **5c** as a slightly brown solid: mp 103−104 °; TLC R_f = 0.50 (20% EtOAc/hexanes); $[\alpha]^{24}_{589}$ −26.8° (*c* = 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 7.65 (1H, bs, NH), 7.54 (1H, d, $^4J_{HH}$ = 2.2, ArH C6-H), 7.43 (1H, dd, $^4J_{HH}$ = 2.2, $^3J_{HH}$ = 9.3, ArH), 6.69 (1H, d, $^3J_{HH}$ = 9.2, ArH C3-H), 4.46 (1H, m, NC*H*(CH$_3$)-CH$_2$), 4.17 (2H, q, $^3J_{HH}$ = 7.1, OCH$_2$), 2.58 (2H, d, $^3J_{HH}$ = 5.4, CH$_2$CO$_2$), 1.37 (9H, s, Bu^t), 1.29 (3H, d, $^3J_{HH}$ = 6.8, NCH(C*H*$_3$)-CH$_2$), 1.28 (3H, t, $^3J_{HH}$ = 7.08 OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) 171.6, 167.8, 148.0, 140.1, 136.0, 118.8, 116.8, 78.0, 60.7, 50.6, 42.2, 40.0, 29.5, 20.0, 14.2; LRMS (FAB, M + H) 434.2; HRMS (FAB) *m*/*z* calcd for $C_{17}H_{26}N_2O_3I$ 433.0989 found 433.0966; C,H,N.

***N*-[5-Iodo-2-(*tert*-butylamino)benzoyl]-3(*R*)-aminobutanoic Acid, Ethyl Ester (5d).** Compound **5d** was prepared using the method shown for **5c** substituting 3(*R*)-aminobutanoic acid, ethyl ester hydrochloride, prepared by transesterification of the benzyl ester[21] in ethanol, for the (*S*)-antipode. Purification through a plug of silica gel eluting with 10% ethyl acetate in hexanes afforded **5d** in 47% yield as a slightly tan solid: $[\alpha]^{24}_{589}$ +26.6°(*c* = 3.95, $CHCl_3$); HRMS (FAB) *m*/*z* calcd for $C_{17}H_{26}N_2O_3I$ 433.0989, found 433.1004.

1-Methyl-4-(3(*R*)-butanoic acid)-7-iodo-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, Ethyl Ester (6a). To a biphasic mixture of **5a** (0.269 g, 0.69 mmol, 1 equiv) in CH_2Cl_2 (15 mL) and a solution of $NaHCO_3$ (5 equiv) in water (100 mL) at 25 °C was added bromoacetyl bromide (30 equiv). The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (50 mL). The combined organics were washed with saturated $NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The mixture of bromoacetanilides was dissolved in dry CH_2Cl_2 to which DBU (0.105 mL**,** 0.69 mmol, 1.0 equiv) was added dropwise at 25 °C. After 10 min the reaction mixture was washed with 0.1 M HCl (50 mL), water (50 mL), and brine (50 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography and recrystallized from EtOAc/hexanes to yield **6a** in 60% yield (0.18 g), $[\alpha]^{24}_{589}$ +2.5°(*c* = 0.48, $CHCl_3$). Analytical data (^{1}H and ^{13}C NMR, mp, TLC, RP-HPLC, and HRMS) were identical with those obtained for its enantiomer **6b**.

1-Methyl-4-(3(*S*)-butanoic acid)-7-iodo-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, Ethyl Ester (6b). Compound **6b** was prepared using the procedure previously reported.[8] The reaction was quenched by the addition of 10% citric acid and the mixture concentrated to a residue. The residue was dissolved in ethyl acetate/water and transferred to a separatory funnel. The layers were separated, and the aqueous layer extracted additionally with ethyl acetate. The combined ethyl acetate extracts were washed once with water and once with brine, dried ($MgSO_4$), filtered, and concentrated to yield crude **6b**. Flash chromatography (stepped elution gradient 50% EtOAc/hexane then EtOAc) afforded pure **6b** and mixed fractions, of which **6b** was the major component. The mixed fractions were again chromatographed (same eluting conditions) to afford additional pure **6b** as a yellow solid, a 1:1 mixture of diastereomeric rotational isomers ($CDCl_3$): 80% yield; mp 136−137 °C; $[\alpha]^{24}_{589}$ −2.36° (*c* = 3.8, $CHCl_3$); TLC R_f = 0.09 (50% EtOAc/hexane); RP-HPLC (method A), t_R = 5.74 min; ^{1}H NMR ($CDCl_3$) 8.16 (0.5H, d, $^4J_{HH}$ = 2.2, ArH C6-H), 8.11 (0.5H, d, $^4J_{HH}$ = 2.2, ArH C6-H), 7.76 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.2, ArH C8-H), 6.90 (1H, d, $^3J_{HH}$ = 9.0, ArH C9-H), 5.19 (0.5H, m, NC*H*(CH$_3$)CH$_2$), 5.09 (0.5H, m, NC*H*(CH$_3$)-CH$_2$), 4.10, 4.06 (2H, 2 overlapping q's, $^3J_{HH}$ = 7.0, OCH$_2$), 3.79 (2H, AB$_q$, $^2J_{HH}$ = 15.5, $\delta\nu_{AB}$ = 8.55, C3-H), 3.32 (3H, s, NCH$_3$), 2.79 (0.5H, dd, $^2J_{HH}$ = 16.0, $^3J_{HH}$ = 9.0, CH$_2$CO$_2$), 2.50 (1.5H, m, CH$_2$CO$_2$), 1.33 (1.5H, d, $^3J_{HH}$ = 6.8, NCH(C*H*$_3$)CH$_2$), 1.27 (1.5H, d, $^3J_{HH}$ = 6.8, NCH(C*H*$_3$)CH$_2$), 1.23 (1.5H, t, $^3J_{HH}$ = 7.0, OCH$_2$C*H*$_3$), 1.19 (1.5H, t, $^3J_{HH}$ = 7.0, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$) 170.36, 170.26, 169.00, 168.85, 165.42, 165.24, 140.66, 140.62, 140.51, 140.33, 139.57, 139.48, 130.63, 130.47, 122.51, 122.37, 89.21, 89.17, 60.73, 60.50, 48.31, 47.93, 46.59, 45.89, 38.92, 38.48, 34.64, 34.59, 18.31, 18.09, 14.05; LRMS (FAB) *m*/*z* 431.0 (M + H)$^+$ 431.0 (100); HRMS (FAB) *m*/*z* calcd for $C_{16}H_{20}N_2O_4I$ 431.0468, found 434.0452; C,H,N.

1-(*tert*-Butyl)-4-(3(*S*)-butanoic acid)-7-iodo-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, Ethyl Ester (6c). Compound **6c** was prepared using a modified version of the procedure shown for compound **6a**, substituting 1 M potassium phosphate buffer (pH = 7) for the water and cooling to 0 °C for the bromoacylation step. After treatment with DBU the dichloromethane solution was poured into a separatory funnel, and washed twice with water, dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed *in vacuo*. The crude reaction mixture was submitted to flash chromatography (20% ethyl acetate in hexanes, loaded with methylene chloride) to yield **6c** (92%): mp 124 °C; $[\alpha]^{24}_{589}$ +36.6°(*c* = 1.5, MeOH);

RP-HPLC (method A) t_R = 6.38 min; ^{1}H NMR ($CDCl_3$) 8.06 (0.5H, d, $^4J_{HH}$ = 2.2, ArH), 8.03 (0.5H, d, $^4J_{HH}$ = 2.2, ArH), 7.72 (1H, dd, $^4J_{HH}$ = 2.2, $^3J_{HH}$ = 8.4, ArH), 6.94 (1H, bd, $^3J_{HH}$ = 8.5, ArH), 5.31 (0.5H, m, NC*H*(CH_3)CH_2), 4.99 (0.5H, m, NC*H*(CH_3)CH_2), 4.11 (2H, dq, $^3J_{HH}$ = 7.0, 7.0, OCH_2), 3.66 (2H, m, C3-H), 2.82 (1H, dd, $^3J_{HH}$ = 6.5, $^2J_{HH}$ = 15.87, CH_2CO_2), 2.52 (1H, m, CH_2CO_2), 1.44 (9H, s, Bu^t), 1.25 (3H, dt, $^3J_{HH}$ = 7.1, 7.1, OCH_2CH_3), 1.27 (3H, d, NCH(CH_3)CH_2); ^{13}C NMR ($CDCl_3$) 171.33, 170.96, 170.81, 170.58, 170.34, 170.22, 165.42, 165.18, 138.80, 138.75, 138.657, 138.04, 137.94, 134.22, 134.02, 127.97, 91.29, 91.25, 60.74, 60.55, 59.66, 59.58, 51.08, 49.15, 49.01, 48.95, 47.06, 39.06, 38.95, 29.43, 18.62, 17.87, 14.07; HRMS (FAB) *m*/*z* calcd for $C_{19}H_{26}IN_2O_4$ 473.0973, found: 473.0935; C,H,N.

1-Methyl-4-(3(*S*)-butanoic acid)-9-chloro-7-iodo-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, Ethyl Ester (6d). **(a)** To a solution of **5b** (1.06 g, 2.7 mmol) in acetic acid (5 mL) was added dropwise a solution of chlorine in acetic acid (3 mmol, prepared by bubbling Cl_2(g) into AcOH). The reaction mixture was stirred at room temperature for 2 h. A new product (TLC R_f = 0.5, 30% ethyl acetate in hexanes) was determined to be present with a small amount of unreacted starting material. An additional 0.3 mmol of chlorine in acetic acid was added and the reaction mixture stirred an additional 30 min. The reaction mixture was partitioned between ethyl acetate and water and the organic layer washed once with water. The organic layer was dried over anhydrous sodium sulfate and filtered, and the solvent was removed *in vacuo*. The product was purified by flash chromatography (30% ethyl acetate in hexanes) to obtain 1.07 g (93%) of *N*-[3-chloro-5-iodo-2-(methylamino)benzoyl]-3(*S*)-aminobutanoic acid, ethyl ester: mp 92 °C; RP-HPLC (method A) t_R = 6.34 min; $[\alpha]^{24}_{589}$ −4.84°(MeOH, *c* = 0.8); ^{1}H NMR ($CDCl_3$) 7.89 (1H, d, $^4J_{HH}$ = 2.2, ArH C6-H), 7.68 (1H, d, $^4J_{HH}$ = 2.2, ArH C4-H), 4.58 (1H, m, NC*H*(CH_3)CH_2), 4.16 (2H, q, $^3J_{HH}$ = 7.3, OCH_2), 2.83 (3H, s, NCH_3), 2.60 (2H, d, $^3J_{HH}$ = 5.1, CH_2CO_2), 1.33 (3H, d, $^3J_{HH}$ = 6.8, NCH(C*H*$_3$)CH_2), 1.27 (3H, t, $^3J_{HH}$ = 7.3, OCH_2CH_3); ^{13}C NMR (CD_3OD) 172.84, 169.44, 145.35, 139.53, 137.72, 126.45, 121.69, 76.84, 61.73, 49.85, 48.14, 44.50, 44.39, 41.44, 20.26, 14.60; LRMS (FAB) 427 (M + 3, 30), 426 (M + 2, 30), 425 (M + 1, 100), 424 (M^+, 70); HRMS (FAB) *m*/*z* calcd for $C_{14}H_{18}ClIN_2O_3$ 424.0051, found 424.0069. Anal. Calcd for $C_{14}H_{18}ClINO_3$: C, 39.60; H, 4.27; N, 6.60. Found : C, 40.06; H, 4.46; N, 6.51.

(b) Compound **6d** was prepared from *N*-[3-chloro-5-iodo-2-(methylamino)benzoyl-3(*S*)-aminobutanoic acid, ethyl ester (530 mg, 1.25 mmol) using the method described above for compound **6c**. The crude reaction mixture was submitted to flash chromatography (10% acetone in dichloromethane) to yield **6d** in 81% yield as a 3:2 ratio of rotational isomers (^{1}H NMR): RP-HPLC (method A) t_R = 6.31 min; $[\alpha]^{24}_{589}$ −17.9° (*c* = 2.6, MeOH); ^{1}H NMR ($CDCl_3$) 8.08 (0.6H, d, $^4J_{HH}$ = 2, ArH C6-H), 8.03 (0.4H, d, $^4J_{HH}$ = 2, ArH C6-H), 7.90 (1H, d, $^4J_{HH}$ = 2, ArH C8-H), 5.22 (0.4 H, m, NC*H*(CH_3)CH_2), 5.10 (0.6H, m, NC*H*(CH_3)CH_2), 4.11 (2H, dq, $^3J_{HH}$ = 7, 7, OCH_2), 3.78 (2H, m, C3-H), 3.28 (3H, s, NCH_3), 2.83 (0.6H, dd, $^3J_{HH}$ = 9, $^2J_{HH}$ = 16, CH_2CO_2), 2.54 (1.4H, m, CH_2CO_2), 1.36 (1.2H, d, $^3J_{HH}$ = 6.8, NCH(C*H*$_3$)CH_2), 1.28 (1.8H, d, $^3J_{HH}$ = 6.8, NCH(C*H*$_3$)CH_2), 1.24 (3H, t, $^3J_{HH}$ = 7.3, OCH_2CH_3); ^{13}C NMR (CD_3OD) 172.10, 171.01, 166.22, 166.18, 142.92, 139.52, 139.26, 138.98, 138.76, 135.22, 135.20, 131.36, 131.29, 91.79, 91.73, 61.78, 61.54, 49.74, 49.17, 46.73, 46.68, 39.40, 38.58, 37.61, 37.45, 18.59, 18.30, 14.54, 14.51; LRMS (FAB) 467 (M + 3, 33), 466(M + 2, 20) 465 (M + 1, 100), 419 (20); HRMS (FAB) *m*/*z* calcd for $C_{16}H_{19}O_4NClI$ 465.0078, found 465.0097; C,H,N.

(+) and (−)-1-*tert*-Butyl-4-(3(*S*)-butanoic acid)-9-chloro-7-iodo-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, Ethyl Ester [(+)-6e and (−)-6e]. **(a)** To a solution of **5c** (1.50 g, 3.5 mmol, 1 equiv) in acetic acid (30 mL) at 25 °C was added Et_3N (0.70 g, 0.97 mL, 7.0 mmol, 2 equiv). To this mixture was added a solution of Cl_2 dissolved in acetic acid (3.44 mmol, prepared by bubbling Cl_2(g) into acetic acid). After stirring for 1 h at room temperature, the mixture was concentrated *in vacuo*, dissolved in EtOAc (50 mL), washed with 10% sodium bisulfate (50 mL), water (50 mL), and brine (50 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (15% EtOAc/hexanes) to yield 1.42 g (88%) *N*-[3-chloro-5-iodo-2-(*tert*-butylamino)benzoyl]-3(*S*)-aminobutanoic acid, ethyl ester as a colorless syrup: TLC R_f = 0.45 (20% EtOAc/hexanes); $[\alpha]^{24}_{589}$ +4.2° (*c* = 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 9.05 (1H, d, $^3J_{HH}$ = 8.0, CONH), 8.22 (1H, d, $^4J_{HH}$ = 2.0, ArH C6-H), 7.78 (1H, d, $^4J_{HH}$ = 2.0, ArH C4-H), 4.47 (1H, m, NC*H*(CH_3)CH_2), 4.13 (2H, q, $^3J_{HH}$ = 7.1, OCH_2), 3.63 (1H, bs, NH), 2.66 (1H, dd, $^2J_{HH}$ = 15.4, $^3J_{HH}$ = 5.1, C*H*HCO_2), 2.47 (1H, dd, $^2J_{HH}$ = 15.6, $^3J_{HH}$ = 6.6, CH*H*CO_2), 1.30 (3H, d, $^3J_{HH}$ = 6.8, NCH(C*H*$_3$)CH_2), 1.23 (3H, t, $^3J_{HH}$ = 7.1, OCH_2CH_3), 1.17 (9H, s, Bu^t); ^{13}C NMR ($CDCl_3$) 171.2, 164.8, 139.8, 139.4, 138.4, 134.8, 133.0, 87.6, 60.5, 57.7, 42.4, 40.3, 29.5, 19.6, 14.1; LRMS (FAB, M + H) 468.2; HRMS (FAB) *m*/*z* calcd for $C_{17}H_{24}N_2O_3ICl$ 467.0599, found 467.0587.

(b) To a biphasic mixture of *N*-[3-chloro-5-iodo-2-(*tert*-butylamino)benzoyl]-3(*S*)-aminobutanoic acid, ethyl ester (1.35 g, 2.9 mmol, 1 equiv) in CH_2Cl_2 (15 mL) and saturated $NaHCO_3$ (100 mL) at 25 °C was added *via* syringe pump over 1 h bromoacetyl bromide (17.51 g, 87 mmol, 30 equiv). The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (50 mL). The combined organics were washed with saturated $NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (25% EtOAc/hexanes) to yield a mixture of bromoacetanilides. This mixture (1.58 g, 2.7 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 to which DBU (0.49 g, 0.48 mL, 3.2 mmol, 1.2 equiv) was added dropwise at 25 °C. After 10 min the reaction mixture was washed with 0.1 M HCl (50 mL), water (50 mL), and brine (50 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography to yield a 3:2 mixture of diastereoisomers. The faster eluting isomer (−)-**6e** (0.73 g) was isolated as a white solid: mp 160−165 °C; TLC R_f = 0.32 (20% EtOAc/hexanes); $[\alpha]^{24}_{589}$ −78.3° (*c* = 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.97 (1H, d, $^4J_{HH}$ = 2.0, ArH C6-H), 7.88 (1H, d, $^4J_{HH}$ = 2.0, ArH C8-H), 4.89 (q, $^3J_{HH}$ = 7.2, NC*H*(CH_3)CH_2), 4.13 (2H, q, $^3J_{HH}$ = 7.0, OCH_2), 3.69 (1H, d, $^2J_{HH}$ = 14.7, C3-H), 3.56 (1H, d, $^2J_{HH}$ = 14.9, C3-H), 2.88 (1H, dd, $^2J_{HH}$ = 15.5, $^3J_{HH}$ = 6.5, C*H*HCO_2), 2.60 (1H, dd, $^2J_{HH}$ = 15.9, $^3J_{HH}$ = 9.0, CH*H*CO_2), 1.42 (9H, s, Bu^t), 1.31 (3H, d, $^3J_{HH}$ = 6.8, NCH(C*H*$_3$)CH_2), 1.26 (3H, t, $^3J_{HH}$ = 7.2, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) 170.7, 170.3, 164.2, 140.4, 137.3, 137.1, 136.8, 133.8, 92.1, 62.5, 60.6, 51.8, 50.2, 38.7, 28.1, 17.8, 14.1; LRMS (FAB, M + H) 507.2; HRMS (FAB) *m*/*z* calcd for $C_{19}H_{25}N_2O_4ICl$ 507.0548, found 507.0568; C,H,N. The slower eluting diastereoisomer (+)-**6e** (0.45g) was isolated as a colorless syrup: TLC R_f = 0.30 (20% EtOAc/hexanes); $[\alpha]^{24}_{589}$ +53.2° (*c* = 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.87 (1H, d, $^4J_{HH}$ = 2.0, ArH C6-H), 7.83 (1H, d, $^4J_{HH}$ = 2.1, ArH C8-H), 5.23 (1H, m, NC*H*(CH_3)CH_2), 4.03 (2H, q, $^3J_{HH}$ = 7.1, OCH_2), 3.58 (1H, d, $^2J_{HH}$ = 15.0, C3-H), 3.50 (1H, d, $^2J_{HH}$ = 15.0, C3-H), 2.44 (1H, dd, $^2J_{HH}$ = 14.9, $^3J_{HH}$ = 6.3, C*H*HCO_2), 2.39 (1H, dd, $^2J_{HH}$ = 14.9, $^3J_{HH}$ = 8.8, CH*H*CO_2), 1.35 (9H, s, Bu^t), 1.28 (3H, d, $^3J_{HH}$ = 7.0, NH(C*H*$_3$)CH_2), 1.17 (3H, t, $^3J_{HH}$ = 6.8, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) 170.5, 170.1, 164.4, 140.3, 137.1, 137.0, 136.6, 133.9, 92.1, 62.4, 60.7, 49.0, 47.3, 39.1, 28.1, 18.3, 14.0; LRMS 507.0 (M + H); HRMS (FAB) *m*/*z* calcd for $C_{19}H_{25}N_2O_4$-ICl 507.0548, found 507.0528 (81% overall yield). The absolute stereochemistry of the faster eluting isomer (−)-**6e** was assigned based on the X-ray crystal structure of compound (*S*)-(−)-**13**, *vida infra*.

(+)- and (−)-1-*tert*-Butyl-4-(3(*R*)-butanoic acid)-9-chloro-7-iodo-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, Ethyl Ester [(+)-6f and (−)-6f]. Compounds (+)-**6f** and (−)-**6f** were prepared using the method shown for (+)-**6e** and (−)-**6e** substituting **5d** for **5c.** Compound **(+)6f** is the enantiomer of compound (−)-**6e** and has identical spectral data (^{1}H and ^{13}C NMR). The same relationship holds for (−)-**6f** and (+)-**6e**.

(a) The crude *N*-[3-chloro-5-iodo-2-(*tert*-butylamino)benzoyl]-3(*R*)-aminobutanoic acid, ethyl ester prepared in part a of the experimental was purified by flash chromatography (15% EtOAc/hexanes) in 76% yield as a colorless syrup: $[\alpha]^{24}_{589}$ −4.4° (*c* = 2.8, $CHCl_3$); HRMS (FAB) *m*/*z* calcd for $C_{17}H_{25}N_2O_3$-ICl 467.0599, found 467.0605.

(b) The crude mixture of diastereoisomers prepared in part b from 0.9 g of *N*-[3-chloro-5-iodo-2-(*tert*-butylamino)benzoyl]-3(*R*)-aminobutanoic acid, ethyl ester was purified by flash

chromatography to yield 0.44 g of the faster eluting compound (+)-**6f** as a white solid: mp 158−162 °C; $[\alpha]^{24}_{589}$ +77.5° (*c* = 1.08, $CHCl_3$); HRMS (FAB) *m/z* calcd for $C_{19}H_{25}N_2O_4ICl$ 507.0548, found 507.0526; C,H,N. The slower eluting compound (−)-**6f** was a colorless syrup: 0.29g; $[\alpha]^{24}_{589}$ −51.0° (*c* = 1.3, $CHCl_3$); HRMS (FAB) *m/z* calcd for $C_{19}H_{25}N_2O_4ICl$ 507.0548, found 507.0535 (75% overall yield). The relative stereochemistry of the slower eluting isomer (−)-**6f** was assigned based on the X-ray crystal structure of compound (*R*)-(−)-**13**, *vida infra*.

4-[(Trimethylsilyl)ethynyl]benzonitrile (14). A 3-neck, 1 L round bottom flask equipped with a thermocouple probe, condensor, and stir bar was charged with 4-bromobenzonitrile (62 g, 0.34 mol, 1.0 equiv), Et_3N (200 mL, 1.48 mol, 4.3 equiv), and EtOAc (150 mL) immersed into a bath of water (25 °C). The white suspension was degassed by bubbling nitrogen through the solution for 10 min. Trimethylsilylacetylene (50 g, 0.51 mol, 1.5 equiv) was added and degassed for 4 min. Bis-(triphenylphosphine)palladium dichloride ($(Ph_3P)_3PdCl_2$; 1.2 g, 0.0017 mol, 0.005 equiv) and cuprous iodide (CuI; 0.65 g, 0.0034 mol, 0.01 equiv) were added as solids in one portion. The golden slurry turned dark within 5 min. The reaction was monitored to maintain an internal temperature of 50 °C, which began to drop after 2.5 h. TLC indicated the consumption of 4-bromobenzonitrile. The reaction mixture was diluted with ethyl acetate (400 mL) and the slurry filtered through a pad of Celite in a sintered glass funnel (medium frit). The tan solids were washed additionally with ethyl acetate until the filtrate was nearly colorless. The combined filtrates were concentrated *in vacuo* to yield a black, flaky solid (72 g). The crude product was loaded as a solid onto the top of a plug of dry silica gel (150 g) and eluted with 5% ethyl acetate/hexane to yield **14** in two crops (one which was yellow in color and the other which was light brown in color) which were indistinguishable by TLC and melting point. The combined yield of **14** was 96%: mp 96−98 °C; TLC R_f = 0.45 (10% EtOAc/hexane); RP-HPLC (method G) t_R = 8.10 min; ^{1}H NMR ($CDCl_3$) 7.57 (2H, d, $^3J_{HH}$ = 8.55, ArH), 7.51 (2H, d, $^3J_{HH}$ = 8.55, ArH), 0.24 (9H, s, Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) 132.36, 131.85, 127.91, 118.34, 111.68, 102.90, 99.48, −0.33; LRMS (FAB) *m/z* 200 $(M + H)^+$, 200 (100), 184; HRMS (FAB) *m/z* calcd for $C_{12}H_{14}NSi$ 200.0895, found 200.0885; C,H,N.

4-Ethynylbenzamidine (15). (a) A 1 L round bottom flask equipped with stir bar was charged with **14** (30.5 g, 0.15 mol), pyridine (120 mL), and Et_3N (60 mL). With efficient stirring, hydrogen sulfide gas (stench, perform in an efficient fume hood!!) was bubbled into the dark, homogeneous solution for a period of approximately 5 min. The 1 L flask was stoppered tightly with a glass 24/40 stopper and gently warmed in a water bath (temperature of the water bath did not exceed 50 °C). The flask was charged with additional hydrogen sulfide every 15 min for a period of 1 h. The reaction was monitored by TLC (25% ethyl acetate/hexanes). After the last addition of hydrogen sulfide, the reaction mixture was stirred at 50 °C for an additional 1.5 h, monitoring by TLC (25% ethyl acetate/hexanes), and the reaction was determined to be complete at this time. The reaction mixture was cooled to room temperature and a stream of nitrogen blown over the reaction mixture for 45 min to remove any excess hydrogen sulfide (perform in efficient fume hood with sash down). The dark solution was concentrated to give a residue which was azeotroped with toluene (2 × 20 mL) to remove the remaining pyridine. The residue was suspended in ethyl acetate (100 mL), adsorbed onto 70 g of silica gel, and concentrated *in vacuo* to a dry powder. The powder was loaded onto 500 g of silica gel and eluted with 25% ethyl acetate/hexane. Removal of the ethyl acetate/hexane and drying under vacuum gave 26 g (73%) of 4-[2-(trimethylsilyl)ethynyl]benz(thio)amide as a yellow powder: TLC R_f = 0.25 (25% EtOAc/hexane); RP-HPLC assay (method G) t_R = 7.59 min; ^{1}H NMR (DMSO-d_6) 9.92 (1H, bs, HN=CSH), 9.51 (1H, bs, HN=CSH), 7.86 (2H, d, $^3J_{HH}$ = 8.0, ArH), 7.46 (2H, d, $^3J_{HH}$= 8.0, ArH), 0.21 (9H, s, Si(CH_3)$_3$); LRMS (FAB) *m/z* 234 $(M + H)^+$, 234 (100), 217, 200, 184.

(b) A 24/40 500 mL round bottom flask equipped with a stirring bar was charged with 4-[2-(trimethylsilyl)ethynyl]-benz(thio)amide (18.4 g, 0.079 mol, 1.0 equiv), acetonitrile (100 mL), and methyl iodide (22.7 g, 9.9 mL, 0.16 mol, 2.0 equiv). The flask was equipped with a condensor, flushed with nitrogen, and heated to 50 °C (oil bath). After heating at 50 °C for 90 min, the reaction mixture was no longer homogeneous and TLC (25% ethyl acetate/hexane) indicated complete consumption of the thioamide. The solvent was removed *in vacuo* to give a light brown solid which was used without further purification. The (*S*)-methyl thioimidate was suspended in absolute ethanol (200 mL), and in an efficient fume hood the open flask was treated with ammonium acetate (25 g, 0.325 mol, 4.1 equiv). Within minutes the solution became dark red and homogeneous. The reaction mixture was heated to 50 °C (oil bath) for 2.5 h, and TLC (90% CH_2Cl_2:8% MeOH: 2% HOAc) indicated complete comsumption of the (*S*)-methyl thioimidate. A stream of nitrogen was blown over the flask for 30 min and the remaining ethanol removed under vacuum to a give a solid residue. The residue was triturated with diethyl ether (4 × 75 mL), water (5 × 50 mL), and a 1:1 mixture of diethyl ether:hexane (4 × 50 mL). The solids were transferred from the 500 mL round bottom flask to a crystallizing dish and dried overnight in a vacuum dessicator (1 mmHg) to afford 18.5 g of 4-[2-(trimethylsilyl)ethynyl]benzamidine as a tan powder (85%): mp 220−222 °C; RP-HPLC (method G) t_R = 6.35 min; ^{1}H NMR (DMSO-d_6 + F_3CCO_2D (10 μL)) 9.37, 9.30 (3H, 2 bs, H_2NC=N*H*), 7.80 (2H, d, $^3J_{HH}$ = 7.0, ArH), 7.68 (2H, d, $^3J_{HH}$ = 7.0, ArH), 0.24 (9H, s, Si(CH_3)$_3$; ^{13}C NMR (DMSO-d_6 + F_3CCO_2D (30 μL)) 165.20, 131.99, 128.51, 128.33, 127.38, 103.62, 98.20, −0.28; LRMS (FAB) *m/z* 217.1 $(M + H)^+$, 217 (100); HRMS (FAB) *m/z* calcd for $C_{12}H_{17}N_2Si$ 217.1161, found 217.1169; C,H,N.

(c) 4-[(Trimethylsilyl)ethynyl]benzamidine (21.5 g, 0.078 mol, 1.0 equiv) was suspended in methanol (150 mL) and then treated with potassium carbonate (7.5 g, 0.054 mol, 0.7 equiv). The slurry was stirred for 2 h at room temperature. The solution was concentrated *in vacuo*, suspended in water (100 mL), and filtered through a sintered glass funnel (medium frit). The solids were washed a second time with water (50 mL) and dried under vacuum (1 mmHg) in a vacuum dessicator to a constant weight to afford 13.0 g of **15** as a tan powder (90%). Typically the **15** reagent was used as the free base without additional purification. However, **15** could be further purified by preparative RP-HPLC (method C), t_R = 27−32 min, to give the trifluoroacetate salt as a white powder after lyophilization from acetonitrile/water (0.1% TFA): mp (free base) 145−148 °C, mp (TFA salt) >370 °C; RP-HPLC (method G) t_R = 3.87 min; ^{1}H NMR (DMSO-d_6 + F_3CCO_2D (10 μL)) 9.36 (3H, bs, H_2NC=NH), 7.81 (2H, d, $^3J_{HH}$ = 8.0, ArH), 7.70 (2H, d, $^3J_{HH}$ = 8.0, ArH), 4.51 (1H, s, CCH); ^{13}C NMR (DMSO-d_6 + F_3CCO_2D (30 μL)) 164.91, 132.07, 129.95, 128.23, 126.30, 83.99, 82.49; LRMS (FAB) *m/z* 145 $(M + H)^+$, 145 (100); HRMS (FAB) *m/z* calcd for $C_9H_9N_2$, 145.0765, found 145.0768; C,H,N.

4-Ethynylbenzonitrile (16). Compound **14** was desilylated with potassium carbonate in methanol.[23] The reaction mixture was stirred at room temperature for 16 h, and TLC (10% EtOAc/hexane) revealed that **14** had been completely consumed. The methanolic solution was concentrated to a residue, dissolved in water and ethyl acetate, and transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted additionally with ethyl acetate; the ethyl acetate layers were combined, washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated to a residue. Flash chromatography (10% EtOAc/hexane) afforded **16** as a white solid (80%): mp 154−156 °C; TLC R_f = 0.34 (10% EtOAc/hexane); RP-HPLC (method B) t_R = 6.05 min; ^{1}H NMR ($CDCl_3$) 7.63 (2H, d, $^3J_{HH}$ = 8.3, Ar-H), 7.58 (2H, d, $^3J_{HH}$ = 8.3, Ar-H), 3.31 (1H, s, CCH); ^{13}C NMR ($CDCl_3$) 132.61, 131.97, 126.93, 118.20, 112.27, 94.44, 91.70; LRMS (FAB) *m/z* 127.0 $(M + H)^+$; C,H,N.

1-*tert*-Butyl-4-(3(*S*)-butanoic acid)-7-[(4-cyanophenyl)-ethynyl]-9-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, Ethyl Ester [(*S*)-(−)-13]. A solution of (−)-**6e** (0.30 g, 0.6 mmol, 1 equiv) and **16** (0.15 g, 1.2 mmol, 2 equiv) in EtOAc (15 mL) was degassed and the reaction vessel purged with Ar at 25 °C. A catalytic amount of $(PPh_3)_2PdCl_2$ (4.2 mg) and CuI (2.3 mg) followed by Et_3N (300 mg, 410 μL, 5 equiv) were added sequentially, degassing with Ar after the addition of each reagent. The mixture was stirred for 2 h, and the

solvent was removed *in vacuo*. The crude product was purified by flash chromatography over two silica gel columns sequentially (30% EtOAc/hexanes), to yield (*S*)-(−)-**13** (0.28 g, 92%) as a slightly tan solid: mp 150−152 °C; TLC R_f = 0.73 (50% EtOAc/hexanes); $[\alpha]^{24}_{589}$ −133.6° (*c* = 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.85 (1H, d, $^4J_{HH}$ = 2.0, ArH C6-H), 7.71 (1H, d, $^4J_{HH}$ = 2.5, ArH C8-H), 7.67 (2H, d, $^3J_{HH}$ = 8.2, ArH), 7.60 (2H, d, $^3J_{HH}$ = 8.9, ArH), 4.92 (1H, m, NC*H*(CH_3)CH_2), 4.14 (2H, q, $^3J_{HH}$ = 7.1, OCH_2), 3.72 (1H, d, $^2J_{HH}$ = 14.5, C3-H), 3.59 (1H, d, $^2J_{HH}$ = 15.3, C3-H), 2.91 (1H, dd, $^2J_{HH}$ = 16.1, $^3J_{HH}$ = 6.1, C*H*CO_2), 2.62 (1H, dd, $^2J_{HH}$ = 15.8, $^3J_{HH}$ = 8.7, CH*H*CO_2), 1.44 (9H, s, Bu^t), 1.33 (3H, d, $^3J_{HH}$ = 7.0, NCH(C*H*$_3$)CH_2), 1.26 (3H, t, $^3J_{HH}$ = 7.0, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) 170.8, 170.4, 164.9, 137.8, 136.3, 134.7, 133.3, 132.2, 131.3, 126.9, 123.0, 118.2, 113.6, 112.4, 90.5, 90.2, 62.8, 60.6, 52.0, 50.3, 38.8, 28.1, 17.8, 14.2; LRMS (FAB, M + H) 506.2; HRMS (FAB) *m*/*z* calcd for $C_{28}H_{29}N_3O_4Cl$ 506.1847, found 506.1871; C,H,N. X-ray quality crystals of (*S*)-(−)-**13** were obtained by slow evaporation from 10% CH_2Cl_2/hexanes.

1-*tert*-Butyl-4-(3(*R*)-butanoic acid)-7-[(4-cyanophenyl)-ethynyl-9-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, Ethyl Ester [(*R*)-(−)-13]. Compound (*R*)-(−)-**13** was prepared using the method described for (*S*)-(−)-**13** substituting (−)-**6f** for (−)-**6e**: 89% yield, slightly tan solid; mp 150−152 °C; R_f = 0.71 (50% EtOAc/hexanes); [α]$^{24}_{589}$ −96.3° (*c* = 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.79 (1H, d, $^4J_{HH}$ = 1.9, ArH C6-H), 7.70 (1H, d, $^4J_{HH}$ = 2.1, ArH C8-H), 7.67 (2H, d, $^3J_{HH}$ = 8.5, ArH), 7.60 (2H, d, $^3J_{HH}$ = 8.5, ArH), 5.31 (1H, m, 1H, NC*H*(CH_3)CH_2), 4.09 (2H, q, $^3J_{HH}$ = 7.6, OCH_2), 3.65 (1H, d, $^2J_{HH}$ = 14.2, C3-H), 3.57 (1H, d, $^2J_{HH}$ = 15.2, C3-H), 2.54 (1H, dd, $^2J_{HH}$ = 14.2, $^3J_{HH}$ = 5.6, C*H*CO_2), 2.42 (1H, dd, $^2J_{HH}$ = 15.2, $^3J_{HH}$ = 8.4, CH*H*CO_2), 1.43 (9H, s, Bu^t), 1.34 (3H, d, $^3J_{HH}$ = 6.9, NCH(C*H*$_3$)CH_2), 1.22 (3H, t, $^3J_{HH}$ = 7.5, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) 170.6, 170.2, 165.2, 137.6, 136.1, 134.6, 133.3, 132.2, 132.1, 131.1, 126.9, 123.0, 118.2, 112.3, 90.4, 90.2, 62.7, 60.7, 49.0, 47.4, 39.1, 28.1, 18.3, 14.1; LRMS (FAB, M + H) 506.4; HRMS (FAB) *m*/*z* calcd for $C_{28}H_{29}N_3O_4Cl$ 506.1847 found 506.1859. Anal. Calcd for $C_{34}H_{43}N_3O_4Cl$ (0.5 hexanes): C, 68.04; H, 6.52; N, 7.56. Found: C, 63.88; H, 6.26; N, 6.99. X-ray quality crystals of (*R*)-(−)-**13** were obtained by dissolution, filtration, and slow evaporation from hexanes.

General Procedure for the Preparation of Amidino Acids 2, 3, and 7−12. (a) The iodoarene (1.0 equiv), **15** (1.8 equiv), dimethylformamide, and 5 equiv of Et_3N (or diisopropylethylamine for compounds **7**, **8**) were combined and deoxygenated. CuI (0.1 equiv) and $(Ph_3P)_2PdCl_2$ (0.05 equiv) were added and placed under nitrogen. The reaction was allowed to stir at 50−60 °C (or at room temperature for compounds **7**, **8**) monitoring by RP-HPLC. After cooling to room temperature, the solution was concentrated *in vacuo*. The crude amidino esters of compounds **7** and **8** were purified by preparative RP-HPLC, and the amidino esters of compounds **2**, **3**, and **9**−**12** were purified first by flash chromatography using 10% CH_3OH/0.1% AcOH/CH_2Cl_2 as the eluting solvent (compounds **2**, **9**−**12**) or 8% CH_3OH/2% AcOH/CH_2Cl_2, for compound **3**, and then by preparative RP-HPLC.

(b) The amidino ethyl esters were hydrolyzed with 1 *N* LiOH (3 equiv for compounds **2**, **3**, **7**, **8**; 5 equiv for compounds **9**−**12**) in a 3:2:1 solution of THF/H_2O/MeOH at 0 °C during the addition of LiOH (compounds **2**, **3**, **7**, **8**) or a 1:1 solution of THF/H_2O at room temperature (compounds **9**−**12**) monitoring by RP-HPLC. The reaction may be quenched with 4 N HCl in dioxane (compounds **2**, **3**) prior to concentration *in vacuo* and purification by RP-HPLC.

1-Methyl-4-(3(*R*)-butanoic acid)-7-[(4-amidinophenyl)-ethynyl]-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (2). (a) 1-Methyl-4-(3(*R*)-butanoic acid)-7-[(4-amidinophenyl)ethynyl]-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, ethyl ester: RP-HPLC (method F) followed by recrystallization from EtOH gave the amidino ester in 65% yield, $[\alpha]^{24}_{589}$ +53.3° (*c* = 0.57, CH_3OH). Analytical data (^{13}C and ^{1}H NMR) were identical with its enantiomer 1-methyl-4-(3(*S*)-butanoic acid)-7-[(4-amidinophenyl)ethynyl]-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, ethyl ester.

(b) RP-HPLC (method F) purification followed by recrystallization from EtOH gave **2** in 41% yield, $[\alpha]^{24}_{589}$ +32.6° (*c* = 0.95, CH_3OH). Analytical data (^{13}C and ^{1}H NMR) were identical with its enantiomer **3**.

1-Methyl-4-(3(*S*)-butanoic acid)-7-[(4-amidinophenyl)-ethynyl]-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (3). (a) 1-Methyl-4-(3(*S*)-butanoic acid)-7-[(4-amidinophenyl)ethynyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, ethyl ester: RP-HPLC (method D), lyophilization from H_2O/CH_3CN with 0.5% HOAc yielded the ethyl ester as a light yellow powder (ca. a 3:2 mixture of rotational isomers of the seven-membered ring, CD_3OD) in 61% yield; mp 228−230 °C; $[\alpha]^{24}_{589}$ −52.6° (*c* = 0.56, CH_3OH); TLC R_f = 0.96 (90% CH_2Cl_2, 8% CH_3OH, 2% AcOH); RP-HPLC (method D) t_R = 50−59 min, (method A) t_R = 5.62 min; ^{1}H NMR (CD_3OD) 7.97 (0.5H, d, $^4J_{HH}$ = 2.0, ArH C6-H), 7.90 (0.5H, d, $^4J_{HH}$ = 2.0, ArH C6-H), 7.82 (2H, d, $^3J_{HH}$ = 8.54, ArH), 7.76 (3H, m, $^3J_{HH}$ = 7.6, ArH C8-H, C_6H_4CC), 7.45 (0.5H, d, $^3J_{HH}$ = 8.5, ArH C9-H), 7.44 (0.5H, d, $^3J_{HH}$ = 8.5, ArH C9-H), 5.15 (1H, m, NC*H*(CH_3)CH_2), 4.10, 4.05 (2H, 2 overlapping q's, $^3J_{HH}$ = 7.0, OCH_2), 3.91 (2H, 2 overlapping AB_q's, $^2J_{HH}$ = 18.3, $\delta\nu_{AB}$ = 10.3, $^2J_{HH}$ = 12.2, $\delta\nu_{AB}$ = 16.5, C3-H), 3.39 (1.2H, s, NCH_3), 3.37 (1.8 H, s, NCH_3), 2.80 (0.5H, dd, $^2J_{HH}$ = 16.4, $^3J_{HH}$ = 9.8, CH_2CO_2), 2.61 (1.5H, m, CH_2CO_2), 1.33 (1.2 H, d, $^3J_{HH}$ = 7.0, NCH(C*H*$_3$)CH_2), 1.27 (1.8 H, d, $^3J_{HH}$ = 7.0, NCH(C*H*$_3$)CH_2), 1.23 (1.2H, t, $^3J_{HH}$ = 7.0, OCH_2CH_3), 1.19 (1.8H, t, $^3J_{HH}$ = 7.0, OCH_2CH_3); ^{13}C NMR (CD_3OD) 172.34, 172.25, 171.21, 171.05, 168.21, 167.87, 142.81, 136.29, 135.11, 134.87, 133.31, 130.22, 130.14, 129.85, 129.42, 129.26, 124.49, 123.18, 123.06, 120.79, 92.23, 92.15, 89.61, 61.89, 61.69, 46.86, 38.94, 35.19, 18.65, 18.20, 14.47; LRMS (FAB) *m*/*z* 447.2 (M + H)$^+$, 447.2 (100); HRMS (FAB) *m*/*z* calcd for $C_{25}H_{27}N_4O_4$ 447.2032, found 447.2011. Anal. Calcd for $C_{29}H_{35}F_3N_4O_7$ (1.0 TFA): C, 57.86; H, 4.86; N, 10.0. Found: C, 57.65; H, 5.58; N, 10.03.

(b) Crude **3**, a yellow powder, was dissolved in a mixture of 2.5 H_2O/1.0 CH_3CN/0.05 TFA, filtered through a pipet containing a cotton plug, and purified by preparative RP-HPLC (method F), t_R = 63−67 min, to afford **3** (acetate salt) as a light yellow powder (ca. 3:2 mixture of rotational isomers, CD_3OD) after lyophilization from H_2O/CH_3CN with 0.5% HOAc in 86% yield: RP-HPLC (method A) t_R = 4.85 min; ^{1}H NMR (CD_3OD) 7.97 (0.33H, d, $^4J_{HH}$ = 2.0, ArH C6-H), 7.89 (0.67H, d, $^4J_{HH}$ = 2.0, ArH C6-H), 7.82 (1H, d, $^3J_{HH}$ = 5.4, ArH), 7.79 (1H, d, $^3J_{HH}$ = 5.4, ArH), 7.76 (1H, d, $^3J_{HH}$ = 8.3, ArH), 7.72 (1H, dd, $^4J_{HH}$ = 2.0, $^3J_{HH}$ = 8.3, ArH C8-H), 7.59 (1H, d, $^3J_{HH}$ = 8.3, ArH), 7.43 (1H, d, $^3J_{HH}$ = 8.3, ArH C9-H), 5.32 (0.6H, m, NC*H*(CH_3)CH_2), 5.07 (0.4H, m, NC*H*(CH_3)CH_2), 3.92 (2H, AB_q, $^2J_{HH}$ = 15.0, $\delta\nu_{AB}$ = 18.7, C3-H), 3.39 (1.80H, s, NCH_3), 3.37 (1.20H, s, NCH_3), 2.77 (0.20H, dd, $^2J_{HH}$ = 16.5, $^3J_{HH}$ = 9.2, CH_2CO_2), 2.50 (1.8H, m, CH_2CO_2), 1.32 (1.2H, d, $^3J_{HH}$ = 7.0, NCH(C*H*$_3$)CH_2), 1.29 (1.8H, d, $^3J_{HH}$ = 7.0, NCH(C*H*$_3$)CH_2); ^{13}C NMR (CD_3OD) 174.16, 174.05, 171.22 ,171.16, 168.18, 167.82, 142.81, 142.51, 136.24, 136.17, 135.04, 134.92, 133.26, 130.22, 130.19, 129.88, 129.23, 123.13, 122.93, 120.78, 120.74, 92.21, 89.56, 39.23, 38.85, 35.19, 35.02, 18.55, 18.11; LRMS (FAB) *m*/*z* 419.17 (M + H)$^+$ 419.1(100); HRMS (FAB) *m*/*z* calcd for $C_{23}H_{23}N_4O_4$ 419.1719, found 419.1719.

An analytical sample was prepared by dissolving a portion of the acetate salt (100 mg) in 10 mL of 20% CH_3CN/H_2O containing 1.0 mL of TFA and lyophilized. To remove any excess trifluoroacetic acid, the lyophilized powder was dissolved in 10 mL of 20% CH_3CN/H_2O and lyophilized a second time to yield the more soluble trifluoroacetate salt of **3** as a 55/45 mixture of diastereomeric rotational isomers (^{1}H NMR, CD_3OD): $[\alpha]^{24}_{589}$ −34.1° (*c* = 0.57, CH_3OH); ^{1}H NMR (CD_3OD) 7.99 (0.55H, d, $^4J_{HH}$ = 2.0, ArH C6-H), 7.95 (0.45H, d, $^4J_{HH}$ = 2.0, ArH C6-H),7.83 (2H, d, $^3J_{HH}$ = 8.60, ArH), 7.77 (3H, dd overlapping with a d, $^4J_{HH}$ = 2.0, $^3J_{HH}$ = 8.1, ArH C8-H, $^3J_{HH}$ = 8.1, ArH), 7.46 (0.45H, d, $^3J_{HH}$ = 8.61, ArH C9-H), 7.45 (0.55H, d, $^3J_{HH}$ = 8.61, ArH C9-H), 5.14 (1H, m, NC*H*(CH_3)-CH_2), 3.94 (2H, 2 overlapping AB_q's, $^2J_{HH}$ = 15.4, $\delta\nu_{AB}$ = 18.9, $^2J_{HH}$ = 15.4, $\delta\nu_{AB}$ = 16.7, C3-H), 3.41 (1.35H, s, NCH_3), 3.38 (1.65H, s, NCH_3), 2.81 (0.6H, dd, $^2J_{HH}$ = 16.5, $^3J_{HH}$ = 9.0, CH_2-CO_2), 2.60 (1.4H, m, CH_2CO_2), 1.35 (1.35H, d, $^3J_{HH}$ = 7.0, NCH-(C*H*$_3$)CH_2), 1.30 (1.65H, d, $^3J_{HH}$ = 7.0, NCH(C*H*$_3$)CH_2); C,H,N.

1-*tert*-Butyl-4-(3(*S*)-butanoic acid)-7-[(4-amidinophenyl)ethynyl]-3,4,dihydro-1*H*-1,4-benzodiazepine-2,5-dione (7). (a) 1-*tert*-Butyl-4-(3(*S*)-butanoic acid)-7-[(4-amidinophenyl)ethynyl]-3,4,dihydro-1*H*-1,4-benzodiazepine-2,5-dione, ethyl ester was obtained in 33% yield after purification by RP-HPLC (method H) as a white solid: mp = 216−220 °C;

$[\alpha]^{24}_{589}$ +27.6° (c = 1.5, CH_3OH); RP-HPLC (method A) t_R = 5.73 min; ^1H NMR (CD_3OD) 7.82 (2H, d, $^3J_{HH}$ = 8.8, ArH), 7.76 (3H, m, ArH C6-H, C_6H_4CC), 7.70 (1H, dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.0, ArH C8-H), 7.43 (1H, d, $^3J_{HH}$ = 8.3, ArH C9-H), 5.24 (1H, m, NC*H*(CH_3)CH_2), 4.10 (2H, q, $^3J_{HH}$ = 7.2, OCH_2), 3.72 (2H, m, C3-H), 2.5−2.85 (2H, m, CH_2CO_2), 1.46 (9H, s, Bu^t), 1.31 (3H, d, $^3J_{HH}$ = 7.1, NCH(C*H*$_3$)CH_2), 1.21(3H, t, $^3J_{HH}$ = 7.2, OCH_2CH_3); ^{13}C NMR (CD_3OD) 173.27, 172.90, 172.26, 168.44, 168.22, 167.87, 140.79, 140.66, 134.51, 133.94, 133.85, 133.35, 132.95, 129.71, 129.58, 129.22, 128.74, 122.60, 122.55, 91.96, 91.90, 90.17, 61.88, 61.75, 61.14, 61.02, 51.47, 50.19, 39.52, 29.76, 18.89, 18.12, 14.47; LRMS (FAB) 489 (M + 1, 100), 433 (80); HRMS (FAB) m/z calcd for $C_{28}H_{33}N_4O_4$ 489.2502, found 489.2481; C,H,N.

(b) RP-HPLC purification (method I) yielded **7** (57%) as a white solid: mp 240 °C dec; $[\alpha]^{24}_{589}$ −14.2° (c = 0.4, CH_3OH); RP-HPLC (method A) t_R = 5.23, 5.35 min; ^1H NMR (CD_3OD) 7.84 (1H, d, $^3J_{HH}$ = 8 ArH), 7.83 (1H, d, $^3J_{HH}$ = 5 ArH), 7.78 (1H, d, $^3J_{HH}$ = 5 ArH), 7.74 (1H, d, $^3J_{HH}$ = 8 ArH), 7.68 (0.5H, dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.0, ArH C8-H), 7.65 (0.5H, dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.0, ArH C8-H), 7.60 (0.5H, bs, ArH C6-H), 7.57 (0.5H, bs, ArH C6-H), 7.43 (0.5H, d, $^3J_{HH}$ = 8.3, ArH C9-H), 7.42 (0.5H, d, $^3J_{HH}$ = 8.3, ArH C9-H), 5.40 (1H, m, NC*H*-(CH_3)CH_2), 3.76 (2H, m, C3-H), 2.48 (2H, m, CH_2CO_2), 1.96 (3H, s, CH_3CO_2H), 1.47 (9H, s, Bu^t), 1.30 (3H, d, $^3J_{HH}$ = 6.6, NCH(C*H*$_3$)CH_2); ^{13}C NMR (CD_3OD) 173.36, 173.07, 168.48, 168.24, 167.80, 140.84, 140.58, 134.36, 134.08, 133.91, 133.35, 133.00, 129.76, 129.67, 129.51, 129.46, 129.26, 129.22, 128.64, 122.54, 122.50, 92.02, 90.03, 61.15, 61.00, 51.67, 50.80, 29.75, 18.97, 18.08; LRMS (FAB) 460 (M + 1, 90), 405 (100), 319 (15); HRMS (FAB) m/z calcd for $C_{26}H_{29}N_4O_4$ 461.2189, found 461.2190; C,H,N.

1-Methyl-4-(3(*S*)-butanoic acid)-7-[(4-amidinophenyl)-ethynyl]-9-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (8). (a) RP-HPLC purification (method H) yielded 1-methyl-4-(3(*S*)-butanoic acid)-7-[(4-amidinophenyl)ethynyl]-9-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, ethyl ester (58%) as a white solid: mp = 216 °C; RP-HPLC (method A) t_R = 5.73 min; $[\alpha]^{24}_{589}$ +11.8° (c = 0.7, CH_3OH); ^1H NMR (CD_3OD) 7.91 (1H, d, $^4J_{HH}$ = 2, ArH), 7.90 (1H, d, $^4J_{HH}$ = 2, ArH), 7.84 (2H, d, $^3J_{HH}$ = 8.8, ArH), 7.81 (2H, d, $^3J_{HH}$ = 8.8, ArH), 5.16 (1H, m, NC*H*(CH_3)CH_2), 4.09 (2H, m, OCH_2), 3.97 (0.5H, d, $^2J_{HH}$ = 15.4, C3-H), 3.91 (1H, s, C3-H), 3.85 (0.5H, d, $^2J_{HH}$ = 15.4, C3-H), 3.31 (3H, s, NCH_3), 2.84 (0.5H, dd, $^3J_{HH}$ = 10, $^2J_{HH}$ = 16.6, CH_2CO_2), 2.64 (0.5H, s, CH_2CO_2), 2.61 (0.5H, s, CH_2CO_2), 2.59 (0.5H, dd, $^3J_{HH}$ = 4.6, $^2J_{HH}$ = 16.6, CH_2CO_2), 1.34 (1.5 H, d, $^3J_{HH}$ = 6.8, NCH(C*H*$_3$)CH_2), 1.27 (1.5H, d, $^3J_{HH}$ = 6.8, NCH(C*H*$_3$)CH_2), 1.24 (1.5H, t, $^3J_{HH}$ = 7, OCH_2CH_3), 1.22 (1.5H, $^3J_{HH}$ = 7, OCH_2CH_3); ^{13}C NMR (CD_3OD) 172.45, 171.28, 167.73, 167.19, 139.99, 139.71, 137.40, 134.29, 133.49, 133.27, 132.98, 130.99, 130.93, 129.67, 129.30, 123.61, 123.54, 91.31, 91.11, 90.63, 90.53, 61.99, 61.77, 46.71, 39.41, 38..59, 37.78, 37.58, 18.60, 18.29, 14.50; LRMS (FAB) 483 (M + 3, 33), 482 (M + 2, 30), 481 (M + 1, 100); HRMS (FAB) m/z calcd for $C_{25}H_{26}O_4N_4Cl$ 481.1642, found 481.1654; C,H,N.

(b) RP-HPLC purification (method I) yielded **8** (72%) as a white solid: mp 206 °C; RP-HPLC (method A) t_R = 5.08, 5.17 min; $[\alpha]^{24}_{589}$ −24.5° (c = 0.6, CH_3OH); ^1H NMR (CD_3OD) 7.90 (1H, s, ArH), 7.81 (5H, m, ArH), 5.16 (1H, m, NC*H*(CH_3)CH_2), 3.97 (0.5H, d, $^2J_{HH}$ = 15.2, C3-H), 3.91 (1H, s, C3-H), 3.85 (0.5H, d, $^2J_{HH}$ = 15.2, C3-H), 3.32 (3H, s, NCH_3), 2.84 (0.5H, dd, $^3J_{HH}$ = 11.3, $^2J_{HH}$ = 16.9, CH_2CO_2), 2.56 (1H, s, CH_2CO_2), 2.59 (0.5H, dd, $^3J_{HH}$ = 4.6, $^2J_{HH}$ = 16.9, CH_2CO_2), 1.34 (1.5 H, d, J = 6.8, NCH(C*H*$_3$)CH_2), 1.27 (1.5H, d, $^3J_{HH}$ = 6.8, NCH-(C*H*$_3$)CH_2); ^{13}C NMR (CD_3OD) 174.09, 171.35, 171.24, 167.84, 167.18, 140.14, 139.76, 137.35, 137.28, 134.59, 134.45, 133.48, 133.33, 133.14, 131.02, 130.85, 129.79, 129.32, 123.60, 123.52, 91.03, 91.01, 90.69, 90.65, 47.09, 46.84, 39.25, 38.58, 37.74, 37.50, 18.51, 18.23; LRMS (FAB) 455 (M + 3, 33), (M + 2, 20), 453 (M + 1, 100); HRMS (FAB) m/z calcd for $C_{23}H_{22}ClN_4O_4$ 453.1329, found 453.1344. Anal. Calcd for $C_{25}H_{26}ClF_3N_4O_8$ (1.0 TFA, 2.0 H_2O): C, 49.80; H, 4.35; N, 9.29. Found: C, 49.97; H, 5.30; N, 10.52.

1-*tert*-Butyl-4-(3(*S*)-butanoate)-7-[(4-amidinophenyl)-ethynyl]-9-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (9). (a) RP-HPLC purification (method F) yielded (−)-1-*tert*-butyl-4-(3(*S*)-butanoic acid)-7-[(4-amidinophenyl)-ethynyl]-9-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, ethyl ester (79%) as a white solid after lyophilization from 20% CH_3CN/H_2O: $[\alpha]^{24}_{589}$ −87.4° (c = 0.42, CH_3OH); RP-HPLC (method A) t_R = 6.24 min; ^1H NMR (CD_3OD) 7.89 (1H, d, $^4J_{HH}$ = 1.9, ArH C6-H), 7.85 (2H, d, $^3J_{HH}$ = 8.6, ArH), 7.80 (2H, d, $^3J_{HH}$ = 8.7, ArH), 7.79 (1H, d, ^4J = $_{HH}$1.9, ArH C8-H), 4.94 (1H, q, $^3J_{HH}$ = 6.7, NC*H*(CH_3)CH_2), 4.11 (2H, q, $^3J_{HH}$ = 7.6, OCH_2), 3.82 (1H, d, $^2J_{HH}$ = 15.1, C3-H), 3.66 (1H, d, $^2J_{HH}$ = 13.8, C3-H), 2.86 (1H, dd, $^2J_{HH}$ = 15.1, $^3J_{HH}$ = 6.3, C*H*HCO_2), 2.64 (1H, dd, $^2J_{HH}$ = 15.1, $^3J_{HH}$ = 8.8, CH*H*CO_2), 1.43 (9H, s, Bu^t), 1.29 (3H, d, $^3J_{HH}$ = 7.2, NCH(C*H*$_3$)CH_2), 1.25 (3H, t, $^3J_{HH}$ = 7.2, OCH_2CH_3); ^{13}C NMR (CD_3OD) 172.4, 172.3, 167.8, 167.2, 139.1, 137.6, 136.2, 134.9, 133.5, 132.0, 129.9, 129.3, 129.2, 124.6, 91.5, 90.5, 63.7, 61.8, 52.4, 51.4, 39.5, 28.6, 18.0, 14.5; LRMS (FAB, M + H) 523.2; HRMS (FAB) m/z calcd for $C_{28}H_{32}N_4O_4Cl$ 523.2112, found 523.2094. Anal. Calcd for $C_{30}H_{34}ClF_3N_4O_7$ (1.0 TFA, 1.0 H_2O): C, 55.01; H, 5.23; N, 8.55. Found C, 55.37; H, 5.83; N, 8.58.

(b) RP-HPLC purification (method F) yielded **9** (75%) after lyophylization from 20% CH_3CN/H_2O; $[\alpha]^{24}_{589}$ −88.5° (c = 0.3, CH_3OH); RP-HPLC (method A) t_R = 5.65 min; ^1H NMR (CD_3-OD) 7.89 (d, 1H, $^4J_{HH}$ = 2.2, 1H, ArH C6-H), 7.84 (2H, d, $^3J_{HH}$ = 8.5, ArH), 7.79 (2H, d, $^3J_{HH}$ = 8.1, ArH), 7.79 (1H, d, $^4J_{HH}$ = 2.0, ArH C8-H), 4.92 (1H, m, NC*H*(CH_3)CH_2), 3.82 (1H, d, $^2J_{HH}$ = 15.2, C3-H), 3.66 (1H, d, $^2J_{HH}$ = 15.1, C3-H), 2.85 (1H, dd, $_2J_{HH}$ = 16.4, $^3J_{HH}$ = 6.6, C*H*HCO_2), 2.62 (1H, dd, $^2J_{HH}$ = 16.1, $^3J_{HH}$ = 8.1, CH*H*CO_2), 1.43 (9H, s, Bu^t), 1.30 (3H, d, $^3J_{HH}$ = 7.2, NCH(C*H*$_3$)CH_2); ^{13}C NMR (CD_3OD) 174.2, 172.5, 167.9, 167.2, 139.1, 137.6, 136.2, 134.8, 133.5, 131.9, 129.8, 129.3, 129.2, 124.6, 91.5, 90.5, 63.8, 52.0, 51.7, 39.5, 28.6, 18.0; LRMS (FAB, M + H) 495.2; HRMS (FAB) m/z calcd for $C_{26}H_{28}N_4O_4$-Cl 495.1799, found 495.1794. Anal. Calcd for $C_{28}H_{32}ClF_3N_4O_8$ (1.0 TFA, 2.0 H_2O): C, 52.14; H, 5.00; N, 8.69. Found C, 52.33; H, 5.44; N, 8.71.

1-*tert*-Butyl-4-(3(*S*)-butanoate)-7-[(4-amidinophenyl)-ethynyl]-9-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (10). (a) RP-HPLC purification (method F) yielded (+)-1-*tert*-butyl-4-(3(*S*)-butanoic acid)-7-[(4-amidinophenyl)-ethynyl]-9-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, ethyl ester (74%) as a white solid after lyophilization from 20% CH_3CN/H_2O: $[\alpha]^{24}_{589}$ +62.5° (c = 0.24, CH_3OH); RP-HPLC (method A) t_R = 6.19 min; ^1H NMR (CD_3OD) 7.89 (1H, d, $^4J_{HH}$ = 1.9, ArH C6-H), 7.85 (2H, d, $^3J_{HH}$ = 8.6, ArH), 7.79 (2H, d, $^3J_{HH}$ = 8.8, ArH), 7.73 (1H, d, $^4J_{HH}$ = 2.0, ArH C8-H), 5.23 (1H, m, NC*H*(CH_3)CH_2), 4.07 (2H, q, $^3J_{HH}$ = 7.5, OCH_2), 3.70 (2H, s, C3-H), 2.56 (2H, m, CH_2CO_2), 1.43 (9H, s, Bu^t), 1.32 (3H, d, $^3J_{HH}$ = 7.0, NCH(C*H*$_3$)CH_2), 1.20 (3H, t, $^3J_{HH}$ = 7.4, OCH_2CH_3); ^{13}C NMR (CD_3OD) 172.6, 172.2, 167.8, 167.6, 139.0, 137.6, 136.2, 135.0, 133.5, 131.7, 129.9, 129.3, 129.2, 124.7, 91.5, 90.5, 63.7, 61.9, 39.6, 28.6, 18.6, 14.5 (2 peaks under CD_3OD); LRMS (FAB, M + H) 523.2; HRMS (FAB) m/z calcd for $C_{28}H_{32}N_4O_4Cl$ 523.2112, found 523.2101; C,H,N.

(b) RP-HPLC purification (method F) yielded **10** in 70% yield after lyophilization from 20% CH_3CN/H_2O: $[\alpha]^{24}_{589}$ +71.3° (c = 0.23, CH_3OH); RP-HPLC (method A) t_R = 5.75 min; ^1H NMR (CD_3OD) 7.89 (1H, d, $^4J_{HH}$ = 1.9, ArH C6-H), 7.85 (2H, d, $^3J_{HH}$ = 8.6, ArH), 7.79 (2H, d, $^3J_{HH}$ = 8.6, ArH), 7.76 (1H, d, $^4J_{HH}$ = 1.9, ArH C8-H), 5.24 (1H, m, $^3J_{HH}$ = 7.6, NC*H*(CH_3)CH_2), 3.70 (2H, s, C3-H), 2.55 (2H, m, CH_2CO_2), 1.45 (9H, s, Bu^t), 1.33 (3H, d, $^3J_{HH}$ = 7.2, NCH(C*H*$_3$)CH_2); ^{13}C NMR (CD_3OD) 174.1, 172.7, 167.9, 167.6, 138.9, 137.7, 136.1, 134.9, 133.5, 131.8, 129.9, 129.3, 129.2, 124.7, 91.4, 90.6, 63.7, 39.4, 28.6, 18.5 (2 peaks under CD_3OD); LRMS (FAB, M + H) 495.2; HRMS (FAB) m/z calcd for $C_{26}H_{28}N_4O_4Cl$ 495.1799, found 495.1801; C,H,N.

1-*tert*-Butyl-4-(3(*R*)-butanoate)-7-[(4-amidinophenyl)-ethynyl]-9-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (11). (a) RP-HPLC purification (method F) yielded (−)-1-*tert*-butyl-4-(3(*R*)-butanoate)-7-[(4-amidinophenyl)ethynyl]-9-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, ethyl ester (64%) as a white solid after lyophilization from 20% CH_3CN/H_2O: $[\alpha\ ]^{24}_{589}$ −58.2° (c = 0.17, CH_3OH); RP-HPLC (method A) t_R = 6.21 min; ^1H NMR (CD_3OD) 7.90 (1H, d, $^4J_{HH}$ = 1.9, ArH C6-H), 7.86 (2H, d, $^3J_{HH}$ = 8.6, ArH), 7.80 (2H, d, $^3J_{HH}$ = 8.3, ArH), 7.74 (1H, d, $^4J_{HH}$ = 1.8, ArH C8-H), 5.24 (1H, m, NC*H*(CH_3)CH_2), 4.08 (2H q, $^3J_{HH}$ = 7.4, OCH_2), 3.72 (2H, s, C3-H), 2.57 (2H, m, CH_2CO_2), 1.44 (9H, s, Bu^t), 1.32

(3H, d, $^3J_{HH}$ = 7.0, NCH(C*H*$_3$)CH$_2$), 1.20 (3H, t, $^3J_{HH}$ = 6.9, OCH$_2$C*H*$_3$); ^{13}C NMR (CD_3OD) 172.6, 172.2, 167.8, 167.5, 138.9, 137.6, 136.2, 135.0, 133.5, 131.7, 129.9, 129.3, 129.2, 124.7, 91.5, 90.5, 63.7, 61.8, 39.5, 28.6, 18.6, 14.5 (2 peaks under CD_3OD); LRMS (FAB, M + H) 523.4; HRMS (FAB) *m/z* calcd for $C_{28}H_{32}N_4O_4Cl$ 523.2112, found 523.2126; C,H,N.

(b) RP-HPLC purification (method F) yielded **11** (71%) after lyophilization from 20% CH_3CN/H_2O: $[\alpha]^{24}_{589}$ −71.1° (*c* = 0.46, CH_3OH); RP-HPLC (method A) t_R = 5.73 min; ^{1}H NMR (CD_3OD) 7.89 (1H, d, $^4J_{HH}$ = 1.9, ArH C6-H), 7.86 (2H, d, $^3J_{HH}$ = 8.1, ArH), 7.79 (2H, d, $^3J_{HH}$ = 8.7, ArH), 7.76 (1H, d, $^4J_{HH}$ = 2.0, ArH C8-H), 5.25 (1H, m, NC*H*(CH$_3$)CH$_2$), 3.84 (1H, d, $^2J_{HH}$ = 15.7, C3-H), 3.67 (1H, d, $^2J_{HH}$ = 15.2Hz, C3-H), 2.85 (1H, dd, $^2J_{HH}$ = 15.1, $^3J_{HH}$ = 6.3, C*H*HCO$_2$), 2.51 (1H, dd, $^2J_{HH}$ = 15.5, $^3J_{HH}$ = 8.2, CH*H*CO$_2$), 1.41 (9H, s, Bu^t), 1.32 (3H, d, $^3J_{HH}$ = 6.9, NCH(C*H*$_3$)CH$_2$); ^{13}C NMR (CD_3OD) 174.0, 172.7, 167.8, 167.6, 138.9, 137.7, 136.1, 134.9, 133.5, 131.8, 129.9, 129.3, 129.2, 124.7, 91.4, 90.5, 63.7, 39.4, 28.6, 18.5 (2 peaks under CD_3OD); LRMS 495.2 (M + H); HRMS (FAB) *m/z* calcd for $C_{26}H_{28}N_4O_4Cl$ 495.1799, found 495.1779. Anal. Calcd for $C_{28}H_{33}ClF_3N_4O_{8.5}$ (1.0 TFA, 1.5 H_2O): C, 52.88; H, 4.91; N, 8.81. Found C, 52.84; H, 4.41; N, 8.63.

1-*tert*-Butyl-4-(3(*R*)-butanoic acid)-7-[(4-amidinophenyl)ethynyl]-9-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (12). (a) RP-HPLC purification (method C) yielded (+)-1-*tert*-butyl-4-(3(*R*)-butanoic acid)-7-[(4-amidinophenyl)-ethynyl]-9-chloro-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione, ethyl ester (79%) as a white solid after lyophilization from 20% CH_3CN/H_2O: $[\alpha]^{24}_{589}$ +95.2° (*c* = 0.25, CH_3OH); RP-HPLC (method A) t_R = 6.25 min; ^{1}H NMR (CD_3OD) 7.90 (1H, d, $^4J_{HH}$ = 1.9, ArH C6-H), 7.86 (2H, d, $^3J_{HH}$ = 7.4, ArH), 7.80 (2H, d, $^3J_{HH}$ = 8.7, ArH), 7.80 (1H, d, $^4J_{HH}$ = 1.9, ArH C8-H), 4.95 (1H, m, $^3J_{HH}$ = 7.0, NC*H*(CH$_3$)CH$_2$), 4.13 (2H, q, $^3J_{HH}$ = 7.2, OCH$_2$), 3.83 (1H, d, $^2J_{HH}$ = 14.1 C3-H), 3.66 (1H, d, $^2J_{HH}$ = 14.1, C3-H), 2.87 (1H, dd, $^2J_{HH}$ = 16.0, $^3J_{HH}$ = 6.9, C*H*HCO$_2$), 2.64 (1H, dd, $^2J_{HH}$ = 16.1, $^3J_{HH}$ = 8.0, CH*H*CO$_2$), 1.44 (9H, s, Bu^t), 1.32 (3H, d, $^3J_{HH}$ = 7.0, NCH(C*H*$_3$)CH$_2$), 1.20 (3H, t, $^3J_{HH}$ = 7.0, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (CD_3OD) 172.4, 172.3, 167.8, 167.2, 139.1, 137.6, 136.2, 134.9, 133.5, 132.0, 129.9, 129.3, 129.3, 124.7, 91.5, 90.5, 63.7, 61.8, 52.4, 51.4, 39.5, 28.6, 18.1, 14.5; LRMS (FAB, M + H) 523.4; HRMS (FAB) *m/z* calcd for $C_{28}H_{32}N_4O_4Cl$ 523.2112, found 523.2093; C,H,N.

(b) RP-HPLC purification (method F) yielded **12** (87%) after lyophilization from 20% CH_3CN/H_2O + 0.1% TFA: $[\alpha]^{24}_{589}$ +90.7° (*c* = 0.37, CH_3OH); RP-HPLC (method A) t_R = 5.64 min; ^{1}H NMR (CD_3OD) 7.89 (1H, d, $^4J_{HH}$ = 2.0, ArH C6-H), 7.86 (2H, d, $^3J_{HH}$ = 8.6, ArH), 7.80 (2H, d, $^3J_{HH}$ = 8.8, ArH), 7.80 (1H, d, $^4J_{HH}$ = 2.0, ArH C8-H), 4.93 (1H, m, NC*H*(CH$_3$)CH$_2$), 3.84 (1H, d, $^2J_{HH}$ = 15.5, C3-H), 3.67 (1H,d, $^2J_{HH}$ = 15.5, C3-H), 2.85 (1H, dd, $^2J_{HH}$ = 16.1, $^3J_{HH}$ = 6.7, C*H*HCO$_2$), 2.62 (1H, dd, $^2J_{HH}$ = 16.1, $^3J_{HH}$ = 7.9, CH*H*CO$_2$), 1.44 (9H, s, Bu^t), 1.31 (3H, d, $^3J_{HH}$ = 7.0, NCH(C*H*$_3$)CH$_2$); ^{13}C NMR (CD_3OD) 174.1, 172.4, 167.8, 167.2, 139.1, 137.6, 136.2, 134.8, 133.5, 132.0, 129.9, 129.3, 129.2, 124.6, 91.4, 90.5, 63.7, 52.5, 51.6, 39.4, 28.6, 18.0; LRMS (FAB, M + H) 495.2; HRMS (FAB) *m/z* calcd for $C_{26}H_{28}N_4O_4Cl$ 495.1799, found 495.1812. Anal. Calcd for $C_{28}H_{32}ClF_3N_4O_8$ (1.0 TFA, 2.0 H_2O): C, 52.14; H, 5.00; N, 8.69. Found C, 51.93; H, 5.63; N, 8.43.

Crystallographic Data and Data Collection Parameters for (*S*)-(−)-13. Large, columnar crystals of (*S*)-(−)-**13** were obtained by slow crystallization from CH_2Cl_2/hexanes.

Crystal parameters: $C_{28}H_{28}N_3O_4Cl$, *M* = 506.0; *a* = 9.2135(16) Å, *b* = 10.5830(20) Å, *c* = 13.7750(23) Å; α = 90.0°, *β* = 94.122(14)°, *γ* = 90.0°; *V* = 1339.7(7) Å^3, *Z* = 2, D_{calc} = 1.25 g cm^{-3}, space group $P2_1$, crystal dimensions 0.26 × 0.40 × 0.45 mm; number of reflections collected 3760, unique reflections 3495.

Crystallographic Data and Data Collection Parameters for (*R*)-(−)-13. A colorless platelike crystal of (*R*)-(−)-**13** was prepared by slow recrystallization hexanes.

Crystal parameters: $ClO_4N_3C_{31}H_{35}$, *M* = 549.09; *a* = 10.2189(1) Å, *b* = 13.2252(2) Å, *c* = 43.4972(5) Å; *V* = 5878.5-(1) Å^3, *Z* = 8, D_{calc} = 1.241 g cm^{-3}, space group $P2_12_12_1$ (No. 19), crystal dimensions = 0.08 × 0.31 × 0.45 mm; number of reflections used for unit cell determination (2*θ* range) = 999 (3.0−45.0°), number of reflections collected 28 614, unique reflections 10 636.

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Supporting Information Available: Listing of elemental analyses on selected comounds and atomic coordinates and selected bond angles for the X-ray crystal structures (*R*)-(−)-**13** and (*S*)-(−)-**13** (11 pages). See any current masthead page for ordering information.

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