Solid-Phase Synthesis of 1,4-Benzodiazepine-2,5-diones. Library Preparation and Demonstration of Synthesis Generality

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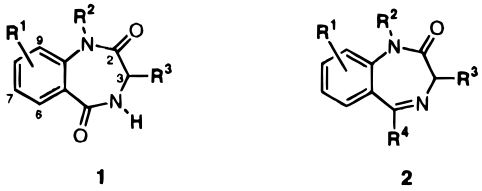
A general and expedient method has been developed for the solid-phase synthesis of 1,4-benzodiazepine-2,5-diones **1** from three commercially available components; anthranilic acids, α-amino esters, and alkylating agents. Reaction conditions have been developed to prepare either racemic compounds for lead identification efforts or optically pure compounds for lead optimization efforts. The incorporation of diverse functionality into the benzodiazepine products has also been demonstrated. On the basis of the scope and generality of the synthesis sequence, a library of 1,4-benzodiazepine-2,5-diones has been prepared from 11 alkylating agents, 12 anthranilic acids, and 19 α-amino esters (nine sets of enantiomeric pairs and glycine methyl ester hydrochloride). The library was prepared in a spatially separate format using a microtiter-based apparatus that is inexpensive and straightforward to construct from ordinary items found in an organic or bioorganic laboratory. The high quality of the 1,4-benzodiazepine-2,5-dione library has been demonstrated by evaluating representative compounds by HPLC analysis and ^{1}H NMR.

Introduction

The preparation and evaluation of small-molecule libraries has become an important part of the drug discovery process.[1−5] In these efforts, particular emphasis has been placed upon the preparation and evaluation of libraries based upon priviledged templates. The display of different functionality upon these templates has previously provided a number of potent and specific drugs or candidates toward different therapeutic targets.[6]

The 1,4-benzodiazepines are an important class of priviledged templates, and numerous derivatives have been identified that have selective activities against a diverse array of biological targets.[7] A subset of the 1,4-benzodiazepines, the 1,4-benzodiazepine-2,5-diones **1** (Figure 1), is the focus of this work. Derivatives have shown promise as antithrombotics.[8−11] They serve as precursors to the anthramycin family of antitumor antibiotics[12−19] as well as to the benzodiazepine receptor antagonist, flumazenil.[20] Structures related to flumazenil have experimental applications as ethanol-intoxication antagonists.[21−24] The 1,4-benzodiazepine-2,5-diones have also shown promise as herbicides.[25] In addition, the 1,4-benzodiazepine-2,5-dione core appears in a number of natural products.[26−29]



1 **2**

Figure 1. Benzodiazepine templates for library synthesis.

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We[30−32] and others[33] have previously reported the preparation of libraries of 1,4-benzodiazepines that belong to the 1,4-benzodiazepin-2-one class **2** (Figure 1). Recently, we have also reported a high-yielding and general method for the solid-phase synthesis of 1,4-benzodiazepine-2,5-diones **1**.[34] The strategy complements our synthesis of structures **2** because it allows much greater diversity to be introduced at the R_1 site. Two alternative solid-phase approaches to 1,4-benzodiazepine-2,5-diones have now also been reported by other researchers.[35,36] Here, we describe further exploration of the generality of our chemistry and application of the chemistry to the preparation of a 2508-member library of benzodiazepines **1**.

Results and Discussion

We sought to achieve three goals in designing an approach to prepare libraries of 1,4-benzodiazepine-2,5-diones: (1) Several different building block sets should be incorporated to provide rapid access to a large number of diverse compounds. (2) The building blocks used in the synthesis of the library should be readily accessible and ideally commercially available to facilitate rapid library synthesis. (3) The chemistry should be compatible with the display of as much functionality as possible including reactive functionality that is commonly found in drugs.

In order to acheive these goals, literature regarding the classical synthesis of 1,4-benzodiazepine-2,5-diones indicated that closure of the seven-membered ring would be the cornerstone of any approach. Ring closure via lactamization was the most often used method and clearly provided the highest yields and the most generality.[37−46] We rejected alkylative cyclizations,[10,47,48] since such closures are only precedented in the case where the amino acid portion of the benzodiazepine **1** (Figure 1) is derived from glycine (R^3 = H). We did not consider palladium-catalyzed carbonylative insertion due to the need for high temperatures and high pressures of CO and poor yields.[12,13,49−52] Finally, we chose not to employ the aza-Wittig cyclization[53] because this approach would require the use of 2-azidobenzoic acids as one of the components, few of which are commercially available.

Upon selecting lactamization as the cyclization method, we then designed a sequence that relied on the incorporation of three different components, anthranilic acids (R^1), alkylating agents (R^2), and α-amino esters (R^3). Over 30 anthranilic acids, 50 α-amino esters with the appropriate side-chain protection, and 100 alkylating agents are commercially available.[54] To expedite library generation, we required that incorporation of the anthranilic acid derivatives be accomplished without prior protection of either the aniline or carboxylic acid functionality.

The optimized synthesis approach is shown in Scheme 1 and begins with the attachment of the α-amino ester to the solid support, followed by acylation with an anthranilic acid, base-catalyzed lactamization, alkylation, and cleavage. A critical feature of the strategy is the attachment to the support as an *N*-alkyl substituent **5**, which provides a tertiary amide lactamization precursor **6** (Scheme 1). Literature pertaining to the cyclizations of small peptides indicates that the presence of backbone amide *N*-alkyl groups[55−60] enhances the equilibrium *cis*/*trans* ratio about these tertiary amides and, in a small peptide cyclization precursor, greatly enhances the rate of formation of cyclic peptide over dimer or oligomer.[60−63]

1,4-Benzodiazepine-2,5-dione Synthesis Sequence. According to this strategy, (chloromethyl)polystyrene (Merrifield resin) is derivatized by alkylation with the sodium salt of 4-hydroxy-2,6-dimethoxybenzaldehyde (**3**) to provide resin-bound aldehyde **4** (Scheme 1).[64,65] An α-amino ester is then loaded onto the support by reductive amination employing $NaBH(OAc)_3$ in 1% acetic acid

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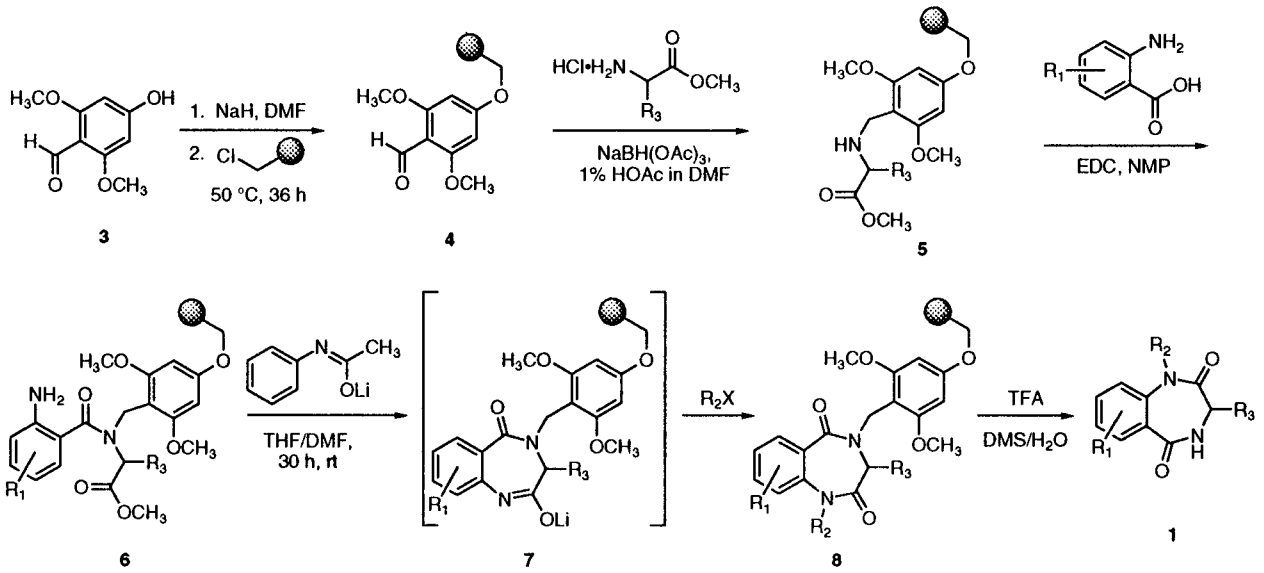
Scheme 1



in DMF. In order to minimize racemization, it is essential in this step that preequilibration of the resin-bound aldehyde and the α-amino ester be minimized (vide infra) before addition of the reducing agent to the reaction mixture. We commonly employ two different protocols for racemization free reductive amination. The $NaBH(OAc)_3$ can be premixed with resin-bound aldehyde **4** in 1% acetic acid in DMF followed by addition of an α-amino ester. Alternatively, the α-amino ester and reductant can be premixed in 1% acetic acid in DMF followed by addition of resin-bound aldehyde **4**.

Acylation of the resulting secondary amine **5** with commercially available unprotected anthranilic acids then provides the support-bound tertiary amide **6**. Optimization of this acylation step required considerable experimentation. For example, even the highly activated azabenzotriazole-based reagents recently developed by Carpino, such as HATU,[66] gave poor reaction conversion. Carbodiimides were the only coupling agents found to efficiently effect this transformation. Furthermore, good yields of acylated material were obtained only when the carbodiimides were employed in conjunction with the hydrochloride salt of a tertiary amine. EDC (1-ethyl-3-[3-(dimethylamino)propyl] carbodiimide·hydrochloride) proved to be the most efficient reagent since it contains an internal tertiary amine hydrochloride salt. To ensure that complete acylation occurs, the resin is subjected twice to this coupling procedure.

Solution studies indicated that base-catalyzed lactamization would be the most general way of producing the support-bound cyclic product **8** (R^2 = H). Ideally, cyclization would be accomplished under conditions sufficiently basic to provide the anilide anion **7** for subsequent alkylation to introduce the R^2 components of compounds **8** in the same reaction step. The lithium salt of acetanilide proved to be an optimal base for effecting these transformations. Because acetanilide has a pK_a of 21.5 in DMSO,[67] deprotonation and alkylation of amides, esters, or carbamates does not occur since these functionalities are all considerably more basic, with pK_a's greater than 24 in DMSO. Treatment of **6** with this base in DMF/THF (1:1) for 30 h followed by addition of an appropriate alkylating agent provides a fully derivatized, support-bound benzodiazepine **8**. Complete cyclization and alkylation (>95%) are observed according to this reaction sequence as determined after cleavage of benzodiazepines **8** from support. Cleavage is accomplished in good yields and high purity by final treatment with $TFA/Me_2S/H_2O$ (90:5:5).

According to the above-described synthesis sequence, the benzodiazepine products **1** are obtained without any loss of optical purity at the stereocenter introduced by the α-amino ester. Racemization in the reductive amination, anthranilic acid acylation, and cyclization steps could readily be detected by chiral HPLC analysis. Less than 1% racemization was observed for either benzodiazepine **1b** or benzodiazepine **1c** (Figure 2).

It was also necessary to show that no racemization occurs in the alkylation step. Unfortunately, since enantiomers of alkylated benzodiazepines separate poorly on Pirkle chiral HPLC columns,[68] it was necessary instead to hydrolyze the benzodiazepine and analyze the chiral integrity of the liberated amino acid. A sample of benzodiazepine **1o** (Figure 2) was heated at reflux in 6 N aqueous hydrochloric acid in order to liberate leucine. The methyl ester was formed using thionyl chloride in methanol, and separate aliquots of the amino ester were then acylated with (+)-MTPA chloride and with (−)-MTPA chloride. Gas chromatographic analysis indicated a 97/3 ratio of amino acid enantiomers. The 3% minor enantiomer most likely arose during the benzodiazepine hydrolysis step[69] and not in the course of benzodiazepine synthesis.

Chirality is derived from the commercially available α-amino ester starting materials. In some cases, the D-enantiomer of the starting material is much more expensive than the naturally occurring enantiomer or may not be available from commercial sources. For lead identification efforts it would be important to access both enantiomers of the 1,4-benzodiazepine-2,5-dione products in order to maximize the diverse display of functionality.

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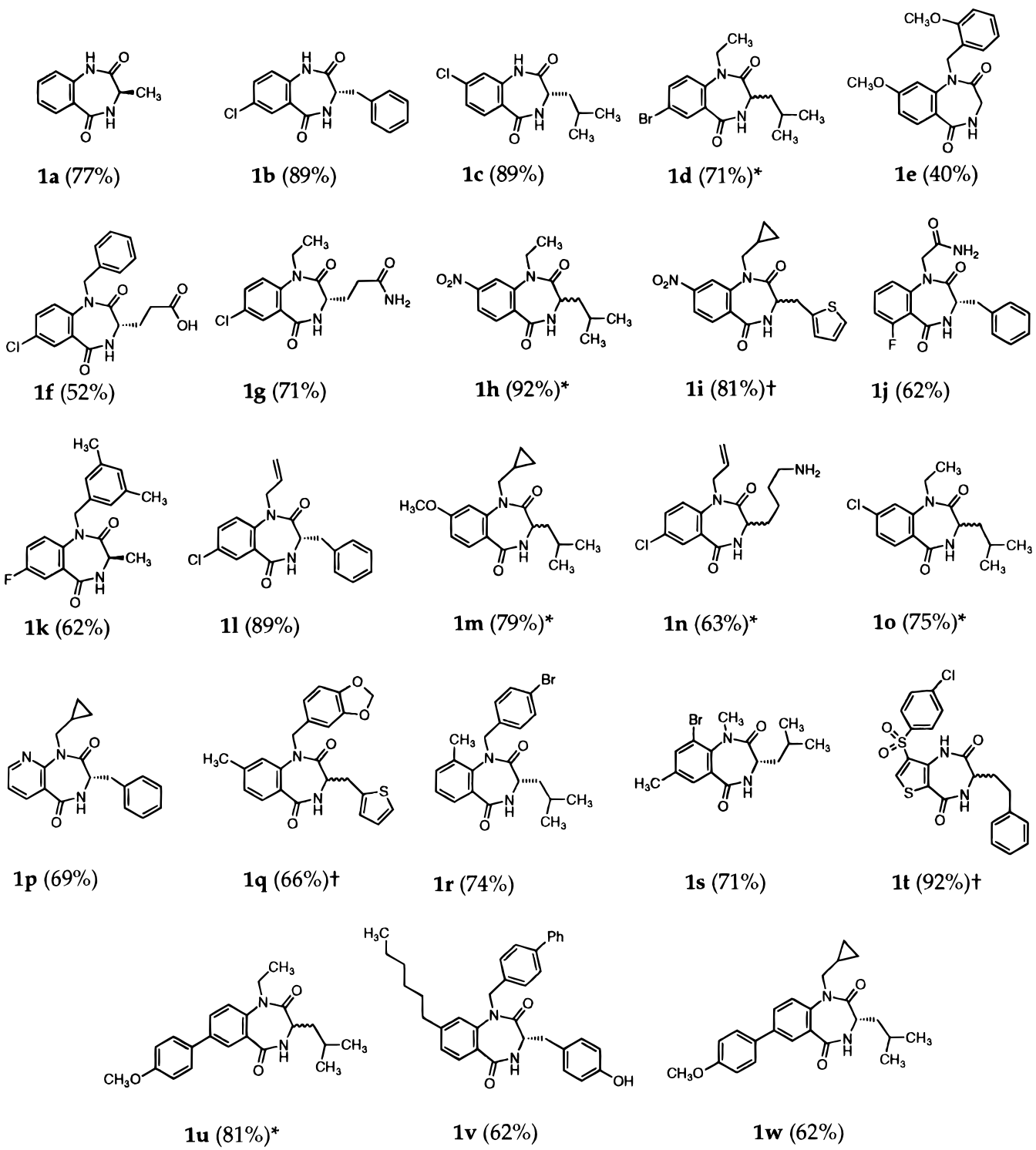

Figure 2. Benzodiazepine products. Yields are of purified material and are based upon the amino ester loading levels of the resin as determined according to the procedure described in the Experimental Section: (*) products formed under racemizing conditions described in text from enantiopure starting materials; (†) racemic products from commercially available racemic material.

We therefore chose to develop conditions whereby racemic benzodiazepine products could be obtained under mild conditions from the enantiomerically pure α-amino ester starting materials. Complete racemization could be accomplished, presumably by imine tautomerization, by preequilibrating the α-amino ester·HCl salt, 0.3 equiv of *i*-Pr_2EtN, and the resin-bound aldehyde **4** for 6 h before addition of the $NaBH(OAc)_3$. Chiral HPLC analysis of benzodiazepine product **1c** prepared using these initial reductive amination conditions confirmed that complete racemization had in fact occurred.

Products and Yields. We have synthesized a diverse array of 1,4-benzodiazepine-2,5-diones to demonstrate the versatility of the described synthesis sequence and to determine which derivatives should be incorporated into a library. We have been able to incorporate an array of sterically and electronically diverse anthranilic acids, both unfunctionalized and functionalized α-amino esters, and a variety of alkylating agents.

Simple amino acids work well in this protocol, as well as those with functionalized side chains: Benzodiazepines **1f**, **1i**, **1v**, and **1n** are derived from glutamic acid,

thienylalanine, tyrosine, and lysine, respectively. Compound **1g** is derived from glutamine. Glutamine methyl ester, when incorporated without side-chain protection, provided a succinimide side product resulting from side-chain cyclization with the methyl ester. When the dimethoxybenzhydrol group[70] was used as a side-chain protecting group, glutamine provided products in comparable yield to other amino acids.

Attempts to incorporate serine met with failure, as the large majority of material isolated after attempting to synthesize a serine-containing benzodiazepine was derived from elimination of the β-hydroxyl group.[71] The incorporation of valine proceeds with low conversion due to incomplete acylation in the anthranilic acid acylation step as determined by recovery of significant amounts of unacylated valine methyl ester after cleavage from support.

We have been able to incorporate anthranilic acids containing electron-rich (e.g., **1m**) and electron-poor functionality (e.g. **1i**), a host of halogenated structures (e.g., **1c**,**d**,**n**,**j**), as well as heterocyclic analogs (**1p**,**t**). Unfortunately, attempts to alkylate **1t** led to product that was only 60% alkylated, presumably because the pK_a of the anilide proton of the thienodiazepine **1t** is slightly higher than that of the other benzodiazepines synthesized.

According to our synthesis strategy, the anthranilic acids are employed without aniline protection. For the compounds shown in Figure 2, no aniline acylation was observed as determined by ^{1}H NMR or TLC analysis of the unpurified benzodiazepine products from support. The presence of electron-donating functionality on the anthranilic acid *para* with respect to the aniline does result in significant acylation of the unprotected aniline. In the case of 5-iodoanthranilic acid, the desired product was contaminated with approximately 15−20% of higher order oligomers, and 5-acetamidoanthranilic acid provided only oligomeric products.

In order to further increase the diversity of the benzodiazepine products, we have demonstrated the functionalization of aryl bromide-containing benzodiazepines with the Suzuki coupling reaction.[72] This reaction is an ideal carbon−carbon bond-forming method for the synthesis of compounds by combinatorial methods due to its compatibility with a wide range of functionality and high reaction yields. In addition, there are many commercially available arylboronic acids, and alkylboranes can readily be accessed through in situ hydroboration methods. There are now also a number of reports in the literature of solid-phase applications of these reactions.[2,73,74]

Benzodiazepines synthesized from 4- and 5-bromoanthranilic acids have been successfully subjected to Suzuki cross-coupling reaction conditions. Before benzodiazepine **1d** was cleaved from support, an aliquot of resin was subjected to cross-coupling with *p*-methoxybenzeneboronic acid employing Pd(PPh$_3$)$_4$ as the catalyst in THF at reflux to furnish **1u** after cleavage from support. Benzodiazepine **1v** is an example of coupling reaction with an alkylborane derived from *B*-hexyl-9-BBN (prepared in situ by hydroboration) with a benzodiazepine derived from 4-bromoanthranilic acid. We have also explored Suzuki reactions employing conditions reported by Johnson in the synthesis of prostaglandin analogs[75] because the conditions reportedly allow reactions to be performed at significantly lower temperatures. Product **1w** was synthesized in 78% overall yield employing a DMF/THF/H$_2$O solvent system and bis(diphenylphosphino)ferrocenepalladium(II) chloride [PdCl$_2$(dppf)] as catalyst. Heating the reaction mixture to 50 °C was required in order to ensure reaction completion.

Library Synthesis. The library was prepared predominantly to demonstrate that our synthetic method proceeds with high fidelity, even when executed in a parallel format. To this end, rigorous characterization of representative members of the library was required, and thus, a spatially separate parallel synthesis was employed. The development of detailed structure−activity relationships upon biological evaluation of the spatially separate library should also be straightforward.

The key to producing a high-quality library in a parallel format requires the identification of the appropriate solid support on which to synthesize the library, and to a similar extent, the apparatus used to hold and filter the support so that the synthesis can be performed efficiently. There are a number of paradigms reported in the literature for the spatially separate manipulation of solid supports in the context of parallel synthesis.[76−78] Our most important selection criteria was that we employ apparatus configured in a standard 96-well microtiter format. A great deal of instrumentation has been developed for the manipulation of materials in a microtiter format, e.g., multichannel pipet devices, filtration units, and microtiter-based concentrators.

Library Synthesis Employing Chiron Mimotopes Pin Apparatus. We intially employed the Chiron Mimotopes pin apparatus, originally developed by Geysen for peptide epitope mapping.[79−81] In this apparatus, 96 polyethylene pins are placed into a supporting block so that each pin fits into a separate well of a 96-well microtiter plate, thus allowing use of microtiter-based instrumentation. In addition, we had previously prepared a number of 1,4-benzodiazepin-2-one libraries[30,31] and a β-turn mimetic library[82] employing this apparatus. Unfortunately, we encountered two significant problems with the Mimitopes apparatus in the synthesis of libraries of 1,4-benzodiazepine-2,5-diones. First, the pins were

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(71) In preliminary studies, good yields of 1,4-benzodazepine-2,5-diones incorporating serine were obtained by performing the cyclization with pyridinium hydrochloride in DMF at 90 °C for 48 h. However, the trifluoroacetic acid-mediated cleavage step resulted in significant trifluoroacetylation of the primary hydroxyl. We have not previously observed trifluoroacetylation of secondary alcohols or phenols during the cleavage step. Benzodiazepines incorporating phenylalanine and glycine were also prepared in good yield using these modified cyclization conditions.

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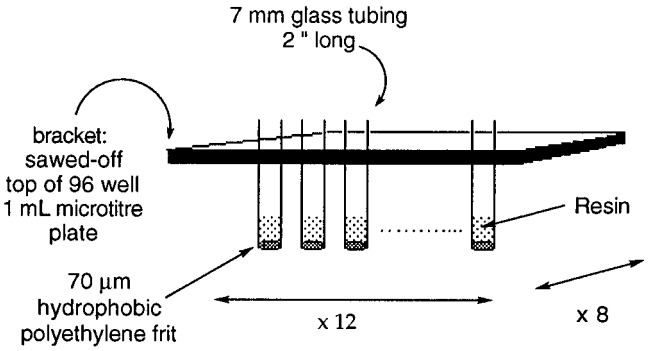

Figure 3. Multitube parallel synthesis apparatus.

only available derivatized with amine functional groups. This required that we reengineer our linker for attachment through amine functionality. Of more serious concern, we observed variable yields in 1,4-benzodiazepine-2,5-dione synthesis on pins, indicating that significant chemistry reoptimization would be necessary. We therefore decided to explore alternative library synthesis apparatus that would allow us to use commercially available resin.

Library Synthesis on Beads. The Diversomer apparatus of DeWitt and co-workers allows the use of polystyrene beads;[33] however, it is not compatible with a microtiter format. We therefore decided to design a high-throughput parallel synthesis apparatus that could be made quickly with relatively little expense and that would be compatible with a microtiter format; it is shown in schematic form in Figure 3. It consists of three parts, a 96-hole (8 × 12) bracket, a series of 96 7-mm (outer diameter) glass tubes, and hydrophobic polyethylene frits, which have been sealed into one end of each of the tubes by heating. Reagents are delivered into the tubes by submerging them in a 96 2-mL well microtiter block. A detailed account of the construction and use of this apparatus is documented in the Experimental Section. For the sake of simplicity, this will be referred to as the multitube apparatus.

Several features of this apparatus make it attractive for use in the context of parallel synthesis. Construction is easy. It is made from ordinary items found in an organic or bioorganic chemistry lab. In several days, 17 blocks (~1500 discrete reaction tubes) can be constructed for a total cost of under $500. Part or all of the apparatus may be reused, depending on the conditions to which it is subjected. Commercially available Beckman 2 mL deep-well microtiter plates serve as reaction vessels. Finally, the apparatus seems to be amenable to many conditions that would be encountered over the course of organic synthesis, e.g., acidic and basic conditions, as well as compatibility with a range of protic and aprotic solvents. Elevated temperatures may be a problem since the polyethylene frits begin to deform around 60 °C.

Synthesis of a Library of 1,4-Benzodiazepine-2,5-diones. Each amino acid and each anthranilic acid that were incorporated into our library were rigorously demonstrated to provide 1,4-benzodiazepine-2,5-diones in good to high yield (see, e.g., Figure 2). Every alkylating agent was similarly evaluated, with the exception of the 2-(bromomethyl)naphthalene, which we considered equivalent in reactivity to the other benzylic halides. Many components were successfully tested in more than one combination. Ultimately, we selected 12 anthranilic acids, 11 alkylating agents, and 10 α-amino esters (19 if both enantiomers are counted). These are shown in Figure 4.

The synthesis of the library was then carried out in a split−split format. Equal portions of resin were first derivatized with the 10 α-amino esters. The α-amino esters derived from alanine, naphthylalanine, and thienylalanine were loaded under the nonracemizing conditions, since they were available in racemic form. Glycine was also loaded under these conditions. The remaining α-amino esters were loaded employing the racemizing conditions. In every case, infrared spectroscopy indicated complete disappearance of the aldehyde, which was replaced by a strong ester carbonyl stretch. The flasks were weighed, and equal portions of the product resin mass was removed from each flask and placed into each of 12 12-mL filter cartridges fitted with 70-μm hydrophobic polyethylene frits (available from Applied Separations). At the end of this splitting operation, 120 filter cartridges had been charged with resin.

After the EDC-mediated acylations were performed and the resins rinsed clean, the beads were suspended as an isopycnic slurry[83] in 3:2 dichloroethane/DMF. Under isopycnic conditions, the solvated beads and the solvent have the same density, and therefore, the beads do not settle after agitation and remain evenly distributed for resin transfer. All of the resins in all 120 filter cartridges were taken up in the same volume of this mixture, and aliquots of equal volume were removed from the cartridges and placed in the appropriately addressed tubes in the multitube reaction apparatus. In this way, approximately 15 mg dry weight of resin was transfered to each tube. Given that the mixture was isopycnic and equal volumes were added to all tubes, we expected the number of moles of benzodiazepine precursor delivered to each tube to be the same. A small portion of resin was saved from each of the 120 filter cartridges in case a particular benzodiazepine needed to be remade.

Two columns in every multitube plate were left empty, providing an apparatus that was effectively 80 (10 × 8) tubes per plate. Thus, after cleavage into a 96-well microtiter plate, two columns would be left blank for biological controls during assays. Sixteen multitube plates, plus one that was only half full, were required. These plates were transferred to small polypropylene bins in a nitrogen bag (former pipet rack covers), and a 0.25 M solution of lithium acetanilide in 1:1 THF/DMF was added to induce cyclization. After 48 h, each plate was transferred to another bin that had been charged with a DMF solution of 0.4 M alkylating agent. After 6 h, the contents of the tubes were rinsed repeatedly and the product benzodiazepines were cleaved into microtiter wells.

Library Evaluation. The integrity of the library was evaluated in two ways. First, exact yields were obtained by HPLC analysis for multiple benzodiazepines. For these benzodiazepines the relative extinction coefficient of the benzodiazepine to the internal standard nitrotoluene was used to determine the quantity of material. Second, ^{1}H NMR spectra were obtained from compounds in 36 randomly chosen wells.

The first set of benzodiazepines evaluated were from wells corresponding to structures whose UV absorbance relative to the internal standard *p*-nitrotoluene had been

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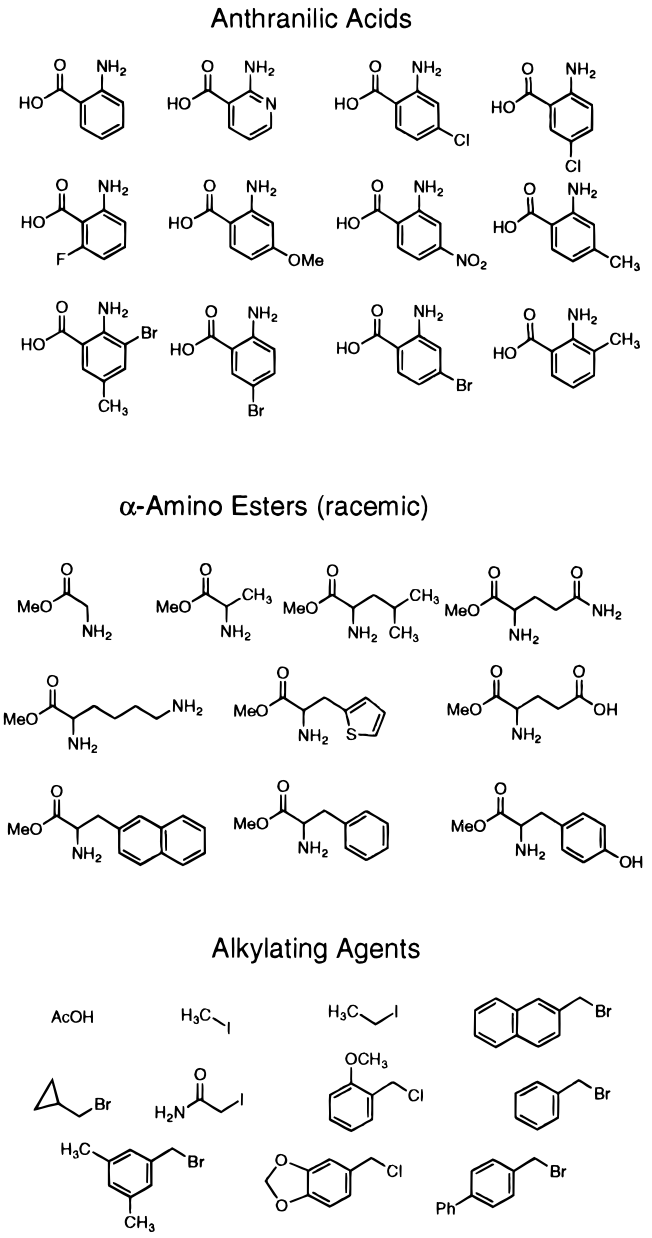

Figure 4. Components used in the synthesis of the 1,4-benzodiazepine-2,5-dione library.

determined for purified derivatives prepared on a large scale (see the Experimental Section). Yields were calculated by delivery of a stock solution of the nitrotoluene internal standard to the contents of a particular well, followed by HPLC analysis. Results are presented in Table 1. Entry 7 corresponds to a well that contained insoluble product; the yield for this benzodiazepine is omitted. However, an alkylated version of this benzodiazepine was obtained in 2.8 μmol yield (Table 1, entry 5).

Relatively small quantities of the benzodiazepines with a 6-fluoro substituent (Table 1, entries 6 and 13) were produced. This is not unexpected given that the yield of benzodiazepines made on a large scale with this anthranilic acid were also low. The benzodiazepine derived from alanine, Table 1, entry 17, was recovered in almost four times the average quantity. Other alanine-containing benzodiazepines appeared in equally high yield relative to the nonalanine benzodiazepines. The benzodiazepine represented by entry 1 (Table 1) was also produced in greater than expected quantities. The observed variations are most likely due to variations in the equimolar distribution techniques for partitioning resin as described previously rather than synthesis fidelity. Excluding alanine, the average quantity produced is 2.7 μmol with a standard deviation (σ_n) of 0.9 μmol.

Table 1. Yields of Selected Benzodiazepines[a]

entry	R^1	R^2	R^3	yield (μmol)
1	7-Cl	benzyl	$(CH_2)_2CO_2H$	4.8
2	9-pyridyl	*c*-$(C_3H_5)CH_2$	$CH_2C_6H_5$	3.6
3	8-Me	piperonyl	2-thienylmethyl	3.3
4	7-Cl	piperonyl	$CH_2C_6H_5$	2.4
5	9-Br, 7-Me	methyl	$CH_2CH(CH_3)_2$	2.8
6	6-F	NH_2COCH_2	$CH_2C_6H_5$	1.8
7	9-Br, 7-Me	H	$CH_2CH(CH_3)_2$	not soluble
8	8-Me	4-phenylBn	$CH_2C_6H_4OH$	2.4[b]
9	8-O_2N	*c*-$(C_3H_5)CH_2$	2-thienylmethyl	2.0
10	7-Cl	ethyl	$(CH_2)_2CONH_2$	2.4
11	7-Cl	NH_2COCH_2	$CH_2C_6H_4OH$	2.3
12		ethyl	$CH_2C_6H_5$	2.4[c]
13	6-F	3,5-diMeBn	2-thienylmethyl	1.1
14	7-Cl	methyl	CH_2-2-$(C_{10}H_7)$	2.6
15	8-O_2N	ethyl	$CH_2CH(CH_3)_2$	2.4
16	8-OMe	2-MeOBn	H	4.0
17	8-OMe	benzyl	CH_3	9.7

[a] UV absorbances of the listed derivatives were determined relative to the internal standard (*p*-nitrotoluene) were predetermined (see Table 8). [b] This yield is based on the corresponding R^1 = 8-hexyl derivative, entry 13, Table 8 (Experimental Section). [c] The benzodiazepine in entry 12 coeluted with *p*-nitrotoluene. Thus, 9-fluoreneone was used as an internal standard.

Table 2. Evaluation of Benzodiazepines

entry	R^1	R^2	R^3	UV ratio of Bz/Std[a]	yield (μmol)
1	7-Br	*c*-$(C_3H_5)CH_2$	H	3.59	2.7
2	7-Br	*c*-$(C_3H_5)CH_2$	$(CH_2)_4NH_2$	4.12	3.1
3	7-Br	*c*-$(C_3H_5)CH_2$	$(CH_2)_2CO_2H$	3.35	2.5
4	7-Br	*c*-$(C_3H_5)CH_2$	$CH_2C_6H_4OH$	2.87	2.2
5	7-Br	*c*-$(C_3H_5)CH_2$	$CH_2CH(CH_3)_2$	3.03	2.3
6	7-Br	*c*-$(C_3H_5)CH_2$	CH_2-(2-$C_{10}H_7$)	3.65	2.7
7	7-Br	*c*-$(C_3H_5)CH_2$	$CH_2C_6H_5$	3.47	2.6
8	7-Br	*c*-$(C_3H_5)CH_2$	2-thienylmethyl	5.31	4.0
9	7-Br	*c*-$(C_3H_5)CH_2$	$(CH_2)_2CONH_2$	1.13	0.8
10	7-Br	*c*-$(C_3H_5)CH_2$	CH_3	12.5	9.4

[a] UV ratio of benzodiazepine to the standard 4-nitrotoluene was based upon the relative chromophore of a related benzodiazepine prepared from 5-bromoanthranilic acid (entry 14, Table 8).

We then evaluated a series of benzodiazepines from a randomly chosen plate. All benzodiazepines in this plate had been alkylated with (bromomethyl)cyclopropane. In order to directly compare benzodiazepines incorporating each of the different amino acids, we examined all the benzodiazepines in this plate substituted at position 7 with a bromide (see Table 2). The chromophore of these benzodiazepine-2,5-diones are dominated by the anthranilic acid portion of the molecules; we therefore assumed that the extinction coefficient of each derivative would be approximately equal. The quantity of each benzodiazepine produced, with the exception of the benzodiazepine derived from glutamine (Table 2, entry 9) and alanine (Table 2, entry 10), fall within a factor of 2. The average quantity produced is 2.5 μmol with a standard deviation of 0.8 μmol.

For each of the compounds evaluated (with the exception of the glutamine-derived compounds), HPLC with detection at 252 nm indicated that the desired product was in all cases the major UV active peak and in most cases (~80%) the only observed UV active peak aside from the internal standard. The dimethoxybenzhydrol protecting group used to protect glutamine during ben-

zodiazepine synthesis to some extent complicated the evaluation of these benzodiazepines by HPLC.

^{1}H NMR spectra of compounds from 36 randomly chosen wells were obtained in order to evaluate the purity of the components of the library and to characterize them as well.[84] On the basis of the ^{1}H NMR spectra, the correct benzodiazepine could be unequivocally assigned for 35 of the 36 wells. For 31 of the 35 wells the desired benzodiazepine product was not contaminated with any related material. For two of the wells the desired benzodiazepine was contaminated with ~25−35% of a related compound, and for the final two wells the desired benzodiazepine was contaminated with an equal amount of a related impurity.

While in almost every case the only product related to our benzodiazepine synthesis was the desired compound, we found varying amounts of the plasticizer dioctylphthalate in some wells and varying amounts of another unrelated aliphatic impurity in some wells. Efforts to isolate and characterize this second impurity by extractive and chromatographic methods were unsuccessful.

Conclusion

A general and expedient method for the solid-phase synthesis of 1,4-benzodiazepine-2,5-diones has been developed. Three commerically available components, anthranilic acids, α-amino esters, and alkylating agents, are employed to introduce functionality. Reaction conditions were developed to prepare either racemic compounds for lead identification efforts or optically pure compounds for lead optimization efforts. The incorporation of diverse functionality into the benzodiazepine products was demonstrated, including the incorporation of amines, amides, carboxylic acids, phenols, ethers, thiophenes, pyridines, halogens, sulfones, and nitro groups. Limitations to the chemistry were also identified.

On the basis of the scope and generality of the synthesis sequence, a library of 1,4-benzodiazepine-2,5-diones was prepared from 11 alkylating agents, 12 anthranilic acids, and 19 α-amino esters (nine sets of enantiomeric pairs and glycine methyl ester hydrochloride) to give 2508 total compounds, or 1320 spatially separate compounds. In order to prepare the library, a microtiter-based apparatus was developed that is inexpensive and straightforward to prepare from ordinary items found in an organic or bioorganic laboratory. The high quality of the benzodiazepine-2,5-dione library prepared with this apparatus was demonstrated by evaluating representative compounds by HPLC analysis and ^{1}H NMR.

The reported solid-phase synthesis sequence, demonstration of scope and generality of the chemistry, and methods for library synthesis should significantly expedite lead identification or optimization efforts based upon the 1,4-benzodiazepine-2,5-dione structure. In addition, the described multitube apparatus should have broad applicability to parallel synthesis efforts towards a range of different applications.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. The α-amino esters were purchased from Bachem, Novabiochem, or Advanced Chemtech. The anthranilic acids were purchased from Aldrich, Lancaster, TCI America, or Maybridge, through their American distributor, Ryan Scientific. The synthesis of two anthranilic acids that are not commercially available is described directly below this paragraph. Anhydrous *N*,*N*-dimethylformamide (DMF) and anhydrous 1-methyl-2-pyrrolidinone (NMP) were purchased from Aldrich. Tetrahydrofuran was distilled under N_2 from sodium/benzophenone immediately prior to use unless sieve-dried THF was used (indicated when used). It was not necessary to use distilled solvents for rinsing of resin. Flash column chromatography was carried out using Merck 60 230−400-mesh silica gel. Thin layer chromatography (TLC) analyses were performed with Uniplate 250 μm silica gel plates from Analtech, Newark, DE (catalog no. 21521). ^{1}H NMR spectra were obtained with a UCB Bruker AM-400 or AM-500 FT spectrometer. Proton-decoupled ^{13}C spectra were obtained at 101 or 126 MHz with the same instruments with a line broadening of 1.5 Hz. Chemical shifts are reported in ppm. Coupling constants are reported in Hz. Unless otherwise noted, spectra were obtained in $CDCl_3$ with residual $CHCl_3$ as an internal standard at 7.25 ppm; spectra obtained in DMSO-d_6 were referenced to the residual DMSO-d_5, 2.49 ppm; spectra obtained in acetonitrile-d_3 were referenced to residual acetonitrile-d_2 at 1.94 ppm. NMR samples from the library were obtained by dissolving the entire contents of the well in 0.75 mL of acetonitrile-d_3 or methanol-d_4. Elemental analyses were performed by M-H-W Labs, Phoenix, AZ, or by the University of California, Department of Chemistry Microanalytical Laboratory. Chloromethylpolystyrene (1% cross-linked) resin was obtained from Novabiochem, catalog no. 01-64-0007, 200−400 mesh size. (Aminomethyl)polystyrene was obtained from Novabiochem or Bachem. A filtration cannula (Pharmacia, Uppsala, Sweden) is useful for filtration of resins in round-bottom flasks.

4-Methoxyanthranilic Acid. This compound was prepared according to a modified literature procedure from 4-methyl-3-nitroanisole (available from Aldrich) through the intermediate 4-methoxy-2-nitrobenzoic acid.[85] In 150 mL of HOAc was suspended 9.74 g of 4-methoxy-2-nitrobenzoic acid (49.4 mmol) in a round-bottom flask. To this was added 75 mL of EtOAc in order to help dissolve the starting material. The solution was subsequently degassed by purging the contents of the flask with N_2 for 30 min. A catalytic amount of 10% Pd/C was added, and with vigorous stirring, the flask was fitted with an H_2 balloon and purged rapidly with this gas. The contents of the flask were stirred at rt for 12 h under 1 atm of H_2. The product and starting material had identical R_f values when TLC plates were eluted with 1:1 hexanes/EtOAc. Completion was determined by the drastically different appearance of the two compounds when TLC plates were held under mixed short-wave UV light. The aniline was extremely fluorescent, glowing blue on the TLC plate, while the starting material was not. The heterogeneous mixture was filtered through a plug of Celite, and the clear fluorescent liquid was concentrated in vacuo. As the volume reduced, 5.85 g (35.0 mmol, 71%) of off-white needles precipitated, mp 165−167 °C (color change/decomposition begins, lit.[18] mp 166 °C). A second crop of product could be isolated by further reducing the volume of the supernatant. These combined crops of product were used directly in the benzodiazepine synthesis described below.

4-Bromoanthranilic Acid. This compound was prepared from 4-amino-2-nitrobenzoic acid (available from Research Plus) through the intermediate 4-bromo-2-nitrobenzoic acid. To a solution of 4-amino-2-nitrobenzoic acid (1.00 g, 5.49 mmol) in 48% aqueous HBr, which was cooled in an ice bath to 0 °C, was added 16.4 mL of H_2O. A solution of $NaNO_2$ (0.38 g, 5.5 mmol) in 13.7 mL of H_2O was prepared. The solution of $NaNO_2$ was added dropwise to the solution of 4-amino-2-nitrobenzoic acid (still at 0 °C). The reaction mixture was initially cloudy but after 5 min turned clear orange. In a separate 500-mL, round-bottom flask was dissolved CuBr (1.04 g, 7.25 mmol) in 18 mL of 48% aqueous HBr. The flask was

(84) Glutamine-containing benzodiazepines were not evaluated since they were contaminated with the dimethoxybenzhyrol cleavage side product.

(85) Ullman, F.; Dootson, P. *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 9−24.

fitted with a magnetic stir bar and was cooled to 0 °C. The diazonium salt of 4-amino-2-nitrobenzoic acid was transferred to an addition funnel and was added dropwise with vigorous stirring to the solution of CuBr, generating a deep purple solution. *Caution must be used when working up diazonium-forming reactions. HNO_2 is not stable in aqueous solution and may decompose, producing NO_2. NO_2 is an insidious poison and exposure to it may be deadly. Appropriate precautions should be taken.* The contents of the reaction flask were concentrated in vacuo (not quite to dryness) and slurried in 200 mL of EtOAc and 1 N aqueous HCl. The phases were separated, and the aqueous layer was extracted again with EtOAc (2 × 100 mL). The combined organic layers were dried and concentrated in vacuo to a green solid (the color presumably due to residual copper salts). The green solid was dissolved in 50 mL of EtOAc and decolorized on a Florisil plug (eluting with excess EtOAc). Concentration in vacuo yielded 4-bromo-2-nitrobenzoic acid as a yellow solid (0.80 g, 60% yield). This diazotization was scaled up, and the product bromide was carried on without further purification to generate 4-bromoanthranilic acid according to literature procedure.[86] In a large, round-bottom flask charged with 130 mL of concentrated NH_4OH was dissolved 4-bromo-2-nitrobenzoic acid (6.52 g, 26.5 mmol). In a separate conical flask was dissolved 65 g (160 mmol) of ammonium iron(II) sulfate in 130 mL of H_2O. This light green solution was added to the solution of 4-bromo-2-nitrobenzoic acid with magnetic stirring. On contact, the light green solution became dark green and then rust colored. The mixture was heated at reflux for 2 min and cooled. The rust-colored suspension was filtered though a pad of Celite, which was then rinsed with water and aqueous NH_4OH. The dark brown filtrate was acidified with concentrated aqueous HCl, and the resulting pink turbid suspension was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with H_2O, dried, and concentrated in vacuo. The resulting residue was decolorized on a silica plug, eluting with 1% HOAc in 2:1 hexanes/EtOAc. Concentration in vacuo of the eluant provided 3.3 g (62% yield) of a slightly brown solid, mp 222−223 °C (lit.[86] mp 222 °C). Anal. Calcd for $C_7H_6NO_2Br$: C, 38.92; H, 2.80; N, 6.48. Found: C, 39.17; H, 2.80; N, 6.59.

Aldehyde-Derived Polystyrene 4. To a flame-dried, 2-L, three-neck, round-bottom flask fitted with a mechanical stirrer and an Ar inlet were added 15.3 g (84.2 mmol) of 4-hydroxy-2,6-dimethoxybenzaldehyde[87] and DMF (800 mL). The solution was degassed by bubbling Ar through it for 30 min. Under a gentle positive Ar flow, 1.92 g (79.9 mmol) of 95% NaH was added slowly in ∼0.5 g aliquots. The addition of NaH was complete in 15 min. An off-white/yellow solid slowly precipitated as the solution turned dark red. As H_2 evolved, the solution was continually purged with a stream of Ar. After 30 min, H_2 evolution ceased, and Merrifield resin (chloromethylpolystyrene, 1% divinylbenzene, 31.7 g, loading level 0.76 mmol g^{-1}, 24.1 mmol) added, and the Ar purge continued for 15 min. The contents were stirred mechanically for 36 h while being heated at 50 °C. The DMF suspension was diluted with CH_3OH (200 mL) and filtered with a filtration cannula. The resin was then rinsed with DMF/CH_3OH 1:1 (2 × 500 mL), DMF (5 × 500 mL), CH_2Cl_2 (7 × 500 mL), and CH_3OH (4 × 400 mL). The salmon-colored resin was dried in vacuo to a constant weight of 33.4 g. A strong aldehyde carbonyl stretch was observed in the IR (KBr) spectrum of this resin: 1690 cm^{-1}.

Racemization-Free Loading of an α-Amino Ester To Obtain Solid Support 5. This procedure may be used for racemization-free loading of an α-amino ester hydrochloride to support-bound aldehyde **4**. A 50-mL round-bottom flask was charged with 1% HOAc in DMF (20 mL) and a magnetic stir bar. To the flask was added 0.500 g of aldehyde-derived resin **4** and $NaBH(OAc)_3$ (0.636 g, 3.00 mmol), generating a white, turbid suspension. It may be necessary to pulverize the chunks in commercially available $NaBH(OAc)_3$ before addition. The suspension was stirred gently, and an α-amino ester (3.00 mmol) was dissolved, also with gentle stirring. Alternatively, the reductant and the α-amino ester may be premixed in the same volume of 1% HOAc in DMF and the same mass of dry resin **4**. An aliquot of this resin was removed after 20 min and rinsed with DMF (7 × 20 mL), CH_2Cl_2 (7 × 20 mL), and finally, CH_3OH (3 × 10 mL). The aldehyde stretch was no longer observed. This procedure was repeated at 60 min to ensure that there were no additional changes in the IR spectrum. The bulk of the resin was then rinsed with CH_3OH (1 × 10 mL), DMF (7 × 20 mL), CH_2Cl_2 (7 × 20 mL), and finally, CH_3OH (3 × 10 mL). The resin was dried in vacuo to a constant weight IR (KBr) 1736 cm^{-1} (s).

Racemizing Procedure for the Loading of α-Amino Esters 5. A general procedure is described for loading of any α-amino ester hydrochloride to support-bound aldehyde **4** when racemic product is desired from scalemic α-amino ester. In a three-neck, 250-mL, round-bottom flask was placed a small magnetic stir bar and 1% HOAc in DMF (50 mL). In this solvent mixture was suspended 6.00 g of aldehyde-derivatized resin **4**. To this was added the α-amino ester hydrochloride of choice (22.2 mmol) and distilled *i*-Pr_2EtN (0.859 g, 6.66 mmol). The system was stirred gently for 6 h, after which time $NaBH(OAc)_3$ (4.70 g, 22.2 mmol) was added. It may be necessary to pulverize the chunks that form in this reagent before addition. The suspension was stirred gently for 36 h, at which point CH_3OH was added to the resin to quench the excess reductant and dissolve the borate salts that were present. The solution was then removed from the resin via filtration cannula and the resin rinsed with DMF (7 × 50 mL), CH_2Cl_2 (7 × 50 mL), and finally, CH_3OH (3 × 20 mL). The resin was dried to a constant weight in vacuo, and IR (KBr) indicated that the aldehyde carbonyl stretch had been replaced by an ester carboxyl stretch (∼1740 cm^{-1}).

Determination of Resin Substitution Level. The loading of resin-bound α-amino esters is quantitated by acetylation of the free amine of **5** followed by cleavage with subsequent determination of the mass balance of the silica gel purified product. A typical experiment follows: A 50-mL flame-dried round-bottom flask was charged with a magnetic stir bar and 20 mL of a mixture of pyr/Ac_2O (2:1) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP). To this flask, with gentle stirring, was added ∼0.500 g of α-amino ester resin. The flask was fitted with a rubber septum, equipped with an Ar inlet, and gently heated to no more than 50 °C. After 12 h, the solution was removed from the resin by filtration cannula and the resin was washed with DMF (7 × 20 mL), CH_2Cl_2 (7 × 20 mL), and finally, CH_3OH (3 × 10 mL), which desolvates the resin. The resin was then dried in vacuo to a constant weight, and a known mass was presolvated in 10 mL of CH_2Cl_2 and stirred with a magnetic stir bar for 5 min. A filtration cannula was then used to remove the CH_2Cl_2, and care was taken not to accidentally remove any resin from the flask as the cannula was removed. The resin was then treated with 20 mL of a solution of TFA/Me_2S/H_2O (90:5:5) and stirred for a minimum of 12 h. After 12 h, the contents of the flask were filtered into a round-bottom flask, and the resin and filter paper were repeatedly washed with CH_2Cl_2 and then CH_3OH. The filtrate was concentrated in vacuo, and the product *N*-acetyl α-amino ester was purified by flash column chromatography and the mass balance obtained. The above acetylation procedure was performed on phenylalanine methyl ester resin (0.500 g), and 0.420 g of the acetylated resin was cleaved as described above. Silica gel purification eluting with 2:1−1:1 hexanes/EtOAc yielded 34.5 mg (0.156 mmol) of clear oil (that later solidified). The loading is therefore determined to be 0.156 mmol/0.420 g resin or *0.37 mmol g^{-1}* resin. An identical experiment performed on leucine-derived resin from the same lot of **4** showed the resin to be substituted at *0.36 mmol g^{-1}* resin. Such loadings are typical when starting with commercially available Merrifield resin that is functionalized at a loading of ∼0.7 mmol g^{-1}. Such a loading experiment was performed every time a new lot of aldehyde-derived resin was synthesized, and all yields are based on loading levels obtained in this manner.

General Procedure for Synthesis of 1,4-Benzodiazepine-2,5-diones 1. A typical procedure for the generation

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of 1,4-benzodiazepine-2,5-diones follows. In an oven-dried, 50-mL, round-bottom flask with a dry magnetic stir bar was placed 0.500 g (0.185 mmol) of α-amino ester resin **5**. The flask was fitted with a rubber septum, and 5 mL of *N*-methylpyrrolidinone (NMP) was added. Once the resin was solvated (3 min), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide·HCl (EDC, 0.425 g, 2.22 mmol) was added. It may be necessary to pulverize the chunks that form in this reagent before addition. After the solution became saturated in EDC (most of the EDC will dissolve over the course of 5 min), the anthranilic acid of choice was slowly added (1.85 mmol). *It is imperative that the EDC and resin be allowed to mix thoroughly before addition of anthranilic acid and that the anthranilic acid be added slowly*. This minimizes side reactions that can occur with the unprotected aniline functionality. The reaction mixture was stirred gently for 8−12 h. For some anthranilic acids (4-Cl, 4-NO_2), a precipitate formed as the reaction proceeded. The precipitate was so fine that it was easily removed during the rinses with the filtration cannula. The resin was rinsed with DMF (7 × 20 mL), CH_2Cl_2 (7 × 20 mL), and finally CH_3OH (3 × 10 mL). The acylation and rinsing were repeated (2 h is adequate) to ensure reaction completion, and the resin was dried to a constant weight in vacuo. Nitro-containing anthranilic acids may require a third subjection. Cyclization and alkylation were then accomplished in one pot: The acylated resin **6** was placed in a 50-mL, round-bottom flask fitted with a small, magnetic stir bar and purged gently with Ar for 5 min. In a separate flame-dried, 50-mL, round-bottom flask was placed a magnetic stir bar and acetanilide (4.44 mmol), followed by 7.5 mL of THF. This flask was purged with Ar for 5 min. The flask was then cooled in a dry ice/acetone bath to −78 °C. A fraction of the compound may precipitate on cooling (this does not affect the reaction). A hexanes solution of *n*-BuLi (1.48 mL, 2.5 M, 3.7 mmol) was added dropwise over 10 min with rapid stirring. The suspension became slightly yellow and sometimes turned into a gelatin over the course of 30 min. DMF (7.5 mL) was then added to homogenize the solution. After all solids dissolved, the mixture was stirred at −78 °C for another 15 min, warmed to rt, and then transferred via metal cannula into the flask containing the resin (which was under Ar at rt). The suspension was stirred gently at rt for 30 h under an Ar atmosphere. Alkylating agent (7.40 mmol) was added via syringe, and stirring was continued until the suspension no longer turned pH paper dark green or blue. This typically took 3−6 h. The alkylating solution was removed via filtration cannula and the resin was rinsed with DMF (7 × 20 mL), CH_2Cl_2 (7 × 20 mL), and finally CH_3OH (3 × 10 mL) and dried in vacuo to a constant weight. The benzodiazepines were then cleaved from support. A known mass of resin was swelled with CH_2Cl_2. The CH_2Cl_2 was removed with a filtration cannula, taking care not to lose any resin on the cannula as it was removed from the flask. The benzodiazepines made by this method are cleaved and characterized below.

Benzodiazepine 1a. The support-bound benzodiazepine was prepared according to the above procedure from anthranilic acid and (*R*)-alanine methyl ester hydrochloride, and acetic acid was substituted for an alkylating agent. The scalemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.314 g (0.107 mmol) of this resin in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 2:1 EtOAc/hexanes provided 15.7 mg (0.083 mmol, 77% yield) of a fine, white, amorphous powder. IR (KBr): 3272, 3173, 3060, 2919, 1705, 1675, 1478, 1408, 755 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.21 (d, 3, J = 6.8), 3.76−3.82 (m, 1), 7.08 (d, 1, 8.0), 7.20 (t, 1, J = 7.1), 7.47−7.51 (m, 1), 7.71 (dd, 1, J = 1.5, 7.9), 8.39 (d, 1, J = 5.1), 10.3 (s, 1). ^{13}C NMR (101 MHz, DMSO-d_6): δ 13.8, 47.3, 120.9, 123.8, 126.2, 130.4, 132.2, 136.7, 167.7, 172.2. HRMS (FAB$^+$) m/e: 191.0822 (MH^+ $C_{10}H_{11}N_2O_2$ requires 191.0821).

Benzodiazepine 1b. The support-bound benzodiazepine was prepared according to the above procedure from 5-chloroanthranilic acid, (*S*)-phenylalanine methyl ester hydrochloride, and acetic acid. The scalemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.170 g (0.0595 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 3:1 hexanes/EtOAc provided 15.9 mg (0.053 mmol, 89% yield) of an amorphous glass. IR (KBr): 3425, 3232, 3067, 2932, 1685, 1652, 1479, 1432, 1353, 1221, 1128, 828, 700 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.85 (dd, 1, J = 9.2, 14.3), 3.11 (dd, 1, J = 5.1, 14.3), 3.92−3.98 (m, 1), 7.11 (d, 1, J = 8.9), 7.18 (t, 1, J = 7.2), 7.24 (t, 2, J = 7.2), 7.30 (d, 2, J = 7.4), 7.57 (dd, 1, J = 2.3, 8.7), 7.61 (d, 1, J = 2.5), 8.65 (d, 1, J = 6.1), 10.51 (s, 1). ^{13}C NMR (101 MHz, $CDCl_3$, one drop CD_3OD): δ 34.0, 53.7, 122.5, 126.7, 127.0, 128.6, 129.1, 130.5, 133.0, 134.5, 136.1, 167.7, 171.1. HRMS (FAB$^+$) m/e: 301.0741 (MH^+ $C_{16}H_{14}N_2O_2$-Cl requires 301.0744). Anal. Calcd for $C_{16}H_{13}O_2N_2Cl$: C, 63.91; H, 4.36; N, 9.32. Found: C, 63.71; H, 4.45; N, 9.15.

Benzodiazepine 1c. The support-bound benzodiazepine was prepared according to the above procedure from 4-chloroanthranilic acid, (*S*)-leucine methyl ester hydrochloride, and acetic acid. The scalemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.350 g (0.123 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 2:1 hexanes/EtOAc provided 29 mg (0.109 mmol, 89% yield) of a white powder, mp 244−248 °C (decomposition begins). IR (KBr): 3427, 3164, 2967, 1664, 1604, 1473, 1427, 1216 (w), 1098 (w), 828 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 0.76 (d, 3, J = 6.5), 0.85 (d, 3, J = 6.5), 1.54 (t, 2, J = 7.0), 1.65−1.70 (m, 1), 3.62−3.67 (m, 1), 7.13 (s, 1), 7.26 (m, 1), 7.74 (d, 1, 8.5), 8.49 (d, 1, J = 5.6), 10.45 (s, 1). ^{13}C NMR (101 MHz, DMSO-d_6): δ 21.5, 22.8, 23.8, 36.1, 50.1, 120.2, 123.8, 125.0, 132.3, 136.3, 138.1, 166.8, 171.5. Anal. Calcd for $C_{13}H_{15}O_2N_2Cl$: C, 58.55; H, 5.67; N, 10.50. Found: C, 58.67; H, 5.81; N, 10.46.

Benzodiazepine 1d. The benzodiazepine was prepared according to the above procedure from 5-bromoanthranilic acid, (*S*)-leucine methyl ester hydrochloride, and EtI. The scalemic α-amino ester was loaded according to the racemizing conditions. Cleavage of 0.500 g (0.170 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography, eluting with 4:1−3:1 hexanes/EtOAc yielded, 41.0 mg (0.121 mmol) of an amorphous white solid (71% yield). IR (KBr): 3441 (b), 2967, 1670, 1598 (w), 1440, 1396 (w), 1256 (w), 1124 (w) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 0.73 (d, 3, J = 6.3), 0.82 (d, 3, J = 6.3), 0.99 (t, 3, J = 6.6), 1.57−1.74 (m, 3), 3.59−3.71 (m, 2), 4.03−4.10 (m, 1), 7.44 (d, 1, J = 9.2), 7.74−7.80 (m, 2), 8.67 (d, 1, J = 5.8). ^{13}C NMR (101 MHz, DMSO-d_6): δ 13.1, 21.7, 22.8, 23.8, 36.3, 42.2, 50.1, 117.7, 125.0, 131.6, 131.7, 134.8, 138.6, 166.2, 169.3. Anal. Calcd for $C_{15}H_{19}O_2N_2Br$: C, 53.11; H, 5.65; N, 8.26. Found: C, 52.89; H, 5.61; N, 8.12.

Benzodiazepine 1e. The support-bound benzodiazepine was prepared according to the above procedure from 4-methoxyanthranilic acid (vide supra), glycine methyl ester hydrochloride, and 2-methoxybenzyl chloride. The α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.392 g (0.128 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 5:1 EtOAc/hexanes followed by neat ethyl acetate after product began to elute provided 16.9 mg (0.052 mmol, 40% yield) of a white fluffy powder, mp 99−100 °C. IR (KBr): 3435, 2935, 1642, 1608, 1660, 1248, 1118, 1096 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.52 (b s, 1), 3.67 (s, 3), 3.73 (s, 3), 3.80 (b s, 1), 4.85 (d, 1, J = 15.6), 5.20 (d, 1, J = 16.6), 6.77−6.83 (m, 2), 6.87−6.89 (m, 2), 7.02 (d, 1, J = 7.4), 7.16 (d, 1, J = 7.6), 7.56 (d, 1, J = 8.5), 8.56 (t, 1, J = 5.1). ^{13}C NMR (101 MHz, DMSO-

d_6): δ 45.0, 45.7,55.1, 55.5, 107.6, 110.6, 111.4, 119.9, 121.7, 124.3, 128.1, 128.4, 131.4, 141.3, 156.7, 161.5, 167.7, 169.1. Anal. Calcd for $C_{18}H_{18}O_4N_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.20; H, 5.61; N, 8.32.

Benzodiazepine 1f. The support-bound benzodiazepine was prepared according to the above procedure from 5-chloroanthranilic acid, H-(*S*)-Glu(*t*-Bu)-OMe·HCl, and benzyl bromide. The scalemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.528 g (0.169 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 60:40:1 hexanes/EtOAc/HOAc provided 32.5 mg (0.087 mmol, 52% yield) of an amorphous white powder. IR (KBr): 3432, 3272, 2919, 2849, 1670, 1441, 1207, 730 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.85−1.92 (m, 1), 2.00−2.07 (m, 1), 2.28−2.34 (m, 2), 3.85−3.90 (m, 1), 4.93 (d, 1, J = 16.0), 5.33 (d, 1, J = 16.0), 7.06 (d, 2, J = 7.1), 7.18−7.25 (m, 3), 7.49 (d, 1, J = 8.4), 7.56−7.59 (m, 2), 8.80 (d, 1, J = 5.8). ^{13}C NMR (101 MHz, DMSO-d_6): δ 23.5, 29.8, 49.5, 51.0, 124.7, 126.7, 127.1, 128.5, 128.9, 129.7, 131.4, 131.8, 137.0, 138.0, 166.3, 170.0, 174.0. Anal. Calcd for $C_{19}H_{17}O_4N_2$-Cl: C, 61.22; H, 4.60; N, 7.52. Found: C, 61.22; H, 4.76; N, 7.35.

Benzodiazepine 1g. The support-bound benzodiazepine was prepared according to the above procedure from 5-chloroanthranilic acid, H-(*S*)-Gln(Dod)-OMe·HCl,[70] and ethyl iodide. The scalemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.464 g (0.142 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 2:1 hexanes/EtOAc provided 31.0 mg (0.100 mmol, 70% yield) of an amber powder. It was necessary to weight this powder out immediately; it was extraordinarily hygroscopic and visibly liquefied with atmospheric water within minutes after isolation. IR (KBr): 3427, 3208, 2933, 1669, 1602, 1444, 1207, 1133, 1028, 826, 801, 721 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.00 (t, 3, J = 7.0), 1.79−1.84 (m, 1), 1.93−1.97 (m, 1), 2.13 (t, 2, J = 7.2), 3.64−3.72 (m, 2), 4.06−4.12 (m, 1), 6.72 (b s, 1), 7.25 (b s, 1), 7.52 (d, 1, J = 9.3), 7.63−7.66 (m, 2), 8.72 (d, 1, J = 5.8). ^{13}C NMR (101 MHz, DMSO-d_6): δ 13.1, 23.6, 30.6, 42.1, 51.4, 124.8, 128.7, 129.7, 131.5, 131.9, 138.0, 166.2, 169.3, 173.6. HRMS (FAB^+) m/e: 310.0961 (MH^+ $C_{14}H_{17}N_3O_3Cl$ requires 310.0958).

Benzodiazepine 1h. The support-bound benzodiazepine was prepared from 4-nitroanthranilic acid, (*S*)-leucine methyl ester hydrochloride, and EtI according to the above procedure. The scalemic α-amino ester was loaded according to the racemizing conditions. This benzodiazepine required a third subjection in the EDC-mediated acylation step. Cleavage of 0.450 g (0.153 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography, eluting with 3.5:1 hexanes/EtOAc, yielded 43.0 mg (0.141 mmol, 92% yield) of a white solid: mp 179.5−180.5 °C. IR (KBr): 3427 (b), 3204, 3098, 2960, 2868, 1703, 1670, 1539, 1440, 1354, 1249, 1223, 1131, 802, 742 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 0.72 (d, 3, J = 6.1), 0.83 (d, 3, J = 6.1), 1.03 (t, 3, J = 7.0), 1.57−1.65 (m, 3), 3.65−3.68 (m, 1), 3.75−3.82 (m, 1), 4.15−4.20 (m, 1), 7.93 (d, 1, J = 8.5), 8.11 (d, 1, J = 8.5), 8.22 (s, 1), 8.85 (d, 1, J = 5.9). ^{13}C NMR (101 MHz, DMSO-d_6): δ 13.0, 21.5, 22.7, 23.7, 36.1, 42.1, 49.9, 117.9, 119.8, 131.1, 135.0, 140.0, 149.4, 165.1, 169.3. Anal. Calcd for $C_{15}H_{19}O_4N_3$: C, 59.00; H, 6.27; N, 13.76. Found: C, 58.97; H, 6.48; N, 13.69.

Benzodiazepine 1i. The support-bound benzodiazepine was prepared according to the above procedure from 4-nitroanthranilic acid, 3-(2-thienyl)-D,L-alanine methyl ester hydrochloride, and (bromomethyl)cyclopropane. Racemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.390 g (0.150 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 3:1 hexanes/EtOAc provided 43.6 mg (0.121 mmol, 81% yield) of an amorphous yellow powder. A small aliquot of this product was taken up in a drop of ethyl acetate and precipitated by addition of hexanes. The supernatant was decanted from the product yielding a fine yellow crystals, mp 173 °C (decomposition begins). IR (KBr): 3472, 3260, 3096, 2934, 1669, 1527, 1442, 1347, 1232 (w), 1155 (w), 697 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 0.08−0.15 (m, 2), 0.31−0.35 (m, 2), 0.80−0.88 (m, 1), 3.19 (dd, 1, J = 8.1, 15), 3.29−3.34 (m, 1), 3.73 (dd, 1, J = 6.5, 14.5), 3.97 (dd, 1, J = 6.2, 14.2), 4.06 (dd, 1, J = 7.5, 14.6), 6.87−6.90 (m, 1), 6.92−6.94 (m, 1), 7.28 (dd, 1, J = 1.2, 5.1), 7.90 (d, 1, J = 8.6), 8.10 (dd, 1, J = 2.1, 8.6), 8.33 (d, 1, J = 2.0), 9.08 (d, 1, J = 6.4). ^{13}C NMR (101 MHz, DMSO-d_6): δ 3.1, 3.9, 9.8, 28.1, 50.9, 53.7, 118.9, 120.1, 124.6, 126.7, 131.1, 135.2, 139.3, 140.4, 149.5, 166.1, 169.3. HRMS (FAB^+) m/e: 372.1027 (MH^+ $C_{18}H_{18}N_3O_4S$ requires 372.1018).

Benzodiazepine 1j. The support-bound benzodiazepine was prepared according to the above procedure from 6-fluoroanthranilic acid, (*S*)-phenylalanine methyl ester hydrochloride, and iodoacetamide. The scalemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.340 g (0.120 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography, eluting with 3:100 *i*-PrOH/EtOAc, yielded 25.0 mg (0.073 mmol) of an amorphous yellow solid (62% yield). IR (KBr): 3276, 3157, 1678, 1618, 1473, 1394, 1242, 1032, 1006, 755, 703, 624 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.91 (dd, 1, J = 9.4, 14.3), 3.07 (dd, 1, J = 4.9, 14.3), 4.02−4.07 (m, 1), 4.24 (d, 1, J = 16.7), 4.43 (d, 1, J = 16.8), 7.11−7.18 (m, 4), 7.24 (t, 2, J = 7.1), 7.29 (d, 2, J = 7.0), 7.52−7.57 (m, 2), 8.82 (d, 1, J = 7.3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 33.3, 51.0, 53.4, 113.1 (d, J_{FC} = 21.4), 117.8 (d, J_{FC} = 15.3), 118.1, 126.3, 128.1, 129.2, 132.3 (d, J_{FC} = 10.4), 137.7, 141.6, 159.5 (d, J_{FC} = 258), 163.3, 169.1, 170.1. HRMS (FAB^+) m/e: 342.1252 (MH^+ $C_{18}H_{17}N_3O_3F$ requires 342.1254).

Benzodiazepine 1k. The support-bound benzodiazepine was prepared according to the above procedure from 5-fluoroanthranilic acid, (*R*)-alanine methyl ester hydrochloride, and 3,5-dimethylbenzyl bromide. The scalemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.433 g (0.143 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 2:1 hexanes/EtOAc provided 29.1 mg (0.892 mmol, 62% yield) of an amorphous off-white powder. IR (KBr): 3434, 2925, 1665, 1492, 1451, 1197 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.26 (d, 3, J = 6.7), 2.14 (s, 6), 3.93−3.98 (m, 1), 4.80 (d, 1, J = 16.0), 5.30 (d, 1, J = 16.0), 6.65 (s, 2), 6.78 (s, 1), 7.35−7.41 (m, 2), 7.52 (dd, 1, J = 4.6, 8.9), 8.78 (d, 1, J = 5.7). ^{13}C NMR (101 MHz, DMSO-d_6): δ 14.0, 20.8, 47.4, 49.3, 115.2 (d, J_{FC} = 23.8), 119.0 (d, J_{FC} = 23.2), 124.4, 125.1 (d, J_{FC} = 7.6), 128.4, 132.0 (d, J_{FC} = 7.6), 135.7, 137.0, 137.4, 158.9 (d, J_{FC} = 243), 166.3, 170.8. HRMS (FAB^+) m/e: 327.1502 (MH^+ $C_{19}H_{20}N_2O_2F$ requires 327.1509).

Benzodiazepine 1l. The support-bound benzodiazepine was prepared according to the above procedure from 5-chloroanthranilic acid, (*S*)-phenylalanine methyl ester hydrochloride, and allyl bromide. The scalemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.319 g (0.111 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography, eluting with 4:1 hexanes/EtOAc, yielded 33.6 mg (0.098 mmol) of an amorphous white solid (89% yield). IR (KBr): 3447 (b), 3072, 3033, 2940, 1670, 1479, 1440, 1354 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.91 (dd, 1, J = 8.9. 14.2), 3.12 (dd, 1, J = 5.45, 14.2), 4.01−

4.06 (m, 1), 4.40 (dd, 1, J = 5.4, 16.5), 4.59 (dd, 1, J = 4.7, 16.5), 5.01−5.09 (m, 2), 5.68−5.77 (m, 1), 7.14−7.18 (m, 1), 7.23 (t, 2, J = 7.1), 7.29 (d, 2, J = 7.1), 7.47 (d, 1, J = 8.8), 7.57 (d, 1, J = 2.6), 7.62 (dd, 1, J = 2.6, 8.8), 8.86 (d, 1, J = 6.4). ^{13}C NMR (101 MHz, DMSO-d_6): δ 33.6, 49.1, 53.6, 116.7, 124.5, 126.3, 128.1, 128.7, 129.3, 129.6, 131.1, 131.8, 133.0, 137.6, 138.3, 166.3, 169.4. Anal. Calcd for $C_{19}H_{17}O_2N_2Cl$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.83; H, 5.20; N, 8.18.

Benzodiazepine 1m. The support-bound benzodiazepine was prepared according to the above procedure from 4-methoxyanthranilic acid (vide supra), (*S*)-leucine methyl ester hydrochloride, and (bromomethyl)cyclopropane. The scalemic α-amino ester was loaded according to the racemizing conditions. Cleavage of 0.428 g (0.145 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography, eluting with 4:1−2:1 hexanes/EtOAc, yielded 36.0 mg (0.114 mmol) of a white solid (79% yield), mp 133−135 °C. IR (KBr): 3434 (b), 3184, 3079, 2954, 1664, 1611, 1453, 1381, 1262, 1223, 1124, 1032, 841, 795 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.05−0.10 (m, 2), 0.27−0.31 (m, 2), 0.72 (d, 3, J = 6.3), 0.81 (d, 4, J = 6.3), 1.57−1.68 (m, 3), 33.57−3.67 (m, 2), 3.83 (s, 3), 3.99 (dd, 1, J = 7.4, 14.5), 6.91 (dd, 1, J = 2.1, 8.7), 7.01 (d, 1, J = 2.1), 7.62 (d, 1, J = 8.6), 8.41 (d, 1, J = 5.8). ^{13}C NMR (101 MHz, DMSO-d_6): δ 13.0, 13.7, 19.9, 31.7, 32.7, 33.8, 46.4, 60.2, 60.8, 65.5, 118.1, 121.9, 132.8, 140.9, 151.2, 171.8, 177.4, 179.9. HRMS (FAB$^+$) m/e: 317.1858 (MH$^+$ $C_{18}H_{25}N_2O_3$ requires 317.1865).

Benzodiazepine 1n. The support-bound benzodiazepine was prepared according to the above procedure from 5-chloroanthranilic acid, H-Lys(Boc)-OMe·HCl, and allyl bromide. The scalemic α-amino ester was loaded according to the racemizing conditions. Cleavage of 0.405 g (0.137 mmol) of this resin by stirring in 20 mL 90:5:5 of TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 90:10:1 CH_2Cl_2/CH_3OH/NH_4OH provided 28 mg (0.087 mmol, 63% yield) of a viscous glass. IR (thin film): 3177, 3079, 2940, 1670, 1598, 1572, 1486, 1446, 1367, 1210, 736 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ 1.37−1.40 (m, 1), 1.40−1.48 (m, 1), 1.48−1.52 (m, 2), 1.72−1.79 (m, 1), 1.90−1.97 (m, 1), 2.66 (t, 2, J = 7.0), 3.80 (t, 1, J = 6.5), 4.46 (dd, 1, J = 5.5, 16.3), 4.60 (dd, 1, J = 5.0, 16.3), 5.11−5.15 (m, 2). 5.78−5.84 (m, 1), 7.47 (d, 1, J = 8.8), 7.58 (dd, 1, J = 2.6, 8.8), 7.73 (d, 1, J = 2.5). ^{13}C NMR (101 MHz, DMSO-d_6): δ 24.0, 28.9, 31.9, 41.5, 51.5, 53.8, 117.7, 125.7, 130.3, 132.1, 132.5, 133.6, 134.0, 140.1, 169.4, 171.6. HRMS (FAB$^+$) m/e: 322.1319 (MH$^+$ $C_{16}H_{21}N_3O_2Cl$ requires 322.1322).

Benzodiazepine 1o. The support-bound benzodiazepine was prepared according to the above procedure from 4-chloroanthranilic acid, (*S*)-leucine methyl ester hydrochloride, and EtI. The scalemic α-amino ester was loaded according to the racemizing conditions. Cleavage of 0.440 g (0.150 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography, eluting with 3:1 hexanes/EtOAc, yielded 33.0 mg (0.112 mmol) of an amorphous off-white powder (75% yield). IR (KBr): 3441 (b), 2967, 1689, 1657, 1598, 1440 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.73 (d, 3, J = 6.3), 0.82 (d, 3, J = 6.3), 0.98 (t, 3, J = 7.0), 1.45−1.65 (m, 3), 3.61 (m, 1), 3.70 (m, 1), 4.13 (m, 1), 7.39 (d, 1, J = 8.3), 7.58 (s, 1), 7.68 (d, 1, 8.3), 8.62 (d, 1, 5.8). ^{13}C NMR (101 MHz, DMSO-d_6): δ 13.0, 21.6, 22.8, 23.8, 36.3, 42.0, 50.1, 122.5, 125.7, 128.8, 131.1, 136.5, 140.4, 166.8, 169.4. HRMS (FAB$^+$) m/e: 295.1212 (MH$^+$ $C_{15}H_{20}N_2O_2Cl$ requires 295.1213).

Pyridodiazepine 1p. The support-bound benzodiazepine was prepared according to the above procedure from 2-aminopyridine-3-carboxylic acid, (*S*)-phenylalanine methyl ester hydrochloride, and (bromomethyl)cyclopropane. The scalemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.398 g (0.130 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 2:1 hexanes/EtOAc provided 28.8 mg (0.090 mmol, 69% yield) of an amorphous white powder. IR (KBr): 3432, 3072, 2919, 1664, 1559, 1426, 1401, 1226, 1097, 786, 752, 700 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.00−0.02 (m, 1), 0.15−0.18 (m, 1), 0.28−0.31 (m, 2), 0.92−0.96 (m, 1), 2.94 (dd, 1, J = 9.0, 14.0), 3.16 (dd, 1, J = 4.9, 14.0), 3.98−4.05 (m, 3), 7.16−7.18 (m, 1), 7.23 (t, 2, J = 7.1), 7.30−7.36 (m, 3), 8.07 (d, 1, J = 6.7), 8.63 (d, 1, J = 2.9), 8.85 (d, 1, J = 6.1). ^{13}C NMR (101 MHz, DMSO-d_6): δ 2.9, 3.6, 10.1, 33.6, 48.4, 53.7, 120.9, 124.3, 126.3, 128.1, 129.4, 137.6, 139.5, 150.5, 151.2, 166.3, 169.7. Anal. Calcd for $C_{19}H_{19}O_2N_3$: C, 71.10; H, 5.96; N, 13.07. Found: C, 71.10; H, 6.18; N, 12.92.

Benzodiazepine 1q. The support-bound benzodiazepine was prepared according to the above procedure from 4-methylanthranilic acid, 3-(2-thienyl)-D,L-alanine methyl ester hydrochloride, and piperonyl chloride. The racemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.332 g (0.085 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 3:1−2:1 hexanes/EtOAc provided 23.5 mg (0.056 mmol, 66% yield) of an off-white amorphous powder. IR (KBr): 3448, 3283, 2927, 1665, 1649, 1612, 1500, 1438, 1248, 1041, 696 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 3), 3.17 (dd, 1, J = 8.2, 15.0), 3.33−3.37 (m, 1), 3.90−3.95 (m, 1), 4.83 (d, 1, J = 15.5), 5.25 (d, 1, J = 15.5), 5.94 (s, 2), 6.56 (b d, 1, J = 8.0), 6.60 (d, 1, J = 1.4), 6.74 (d, 1, J = 7.9), 6.89 (dd, 1, J = 3.5, 5.0), 6.93 (b s, 1), 7.09 (b d, 1, J = 7.9), 7.29 (dd, 1, J = 1.2, 5.1), 7.32 (b s, 1), 7.46 (d, 1, J = 7.98), 8.74, (d, 1, J = 6.2). ^{13}C NMR (101 MHz, DMSO-d_6): δ 20.9, 28.2, 49.2, 54.0, 100.9, 107.3, 108.1, 120.3, 123.0, 124.6, 126.6, 126.7, 127.1, 129.3, 131.0, 137.7, 138.9, 139.6, 142.3, 146.2, 147.3, 167.4, 169.7. HRMS (FAB$^+$) m/e: 420.1136 (M$^+$ $C_{23}H_{20}N_2O_4S$ requires 420.1144).

Benzodiazepine 1r. The support-bound benzodiazepine was prepared according to the above procedure from 3-methylanthranilic acid, (*S*)-leucine methyl ester hydrochloride, and 4-bromobenzyl bromide. The scalemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.355 g (0.112 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 4.5:1 hexanes/EtOAc provided 34.5 mg (0.083 mmol, 74% yield) of an amorphous white powder. IR (KBr): 2966, 1654, 1637, 1560, 1542, 1508, 1090, 832, 803 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.68 (d, 3, J = 6.4), 0.78 (d, 3, J = 6.4), 1.54 (t, 2, 6.9), 1.59−1.66 (m, 1), 2.40 (s, 3), 3.56 (q, 1, J = 6.5), 4.22 (d, 1, J = 14.7), 5.31 (d, 1, J = 14.6), 6.94 (d, 2, J = 8.2), 7.31 (t, 1, J = 7.5), 7.33 (d, 2, J = 8.2), 7.43 (d, 1, J = 7.9), 7.49 (d, 1, J = 7.6), 8.47 (d, 1, J = 6.0). Anal. Calcd for $C_{21}H_{23}N_2O_2$-Br: C, 60.73; H, 5.58; N, 6.74. Found: C, 60.90; H, 5.69; N, 6.65.

Benzodiazepine 1s. The support-bound benzodiazepine was prepared according to the above procedure from 3-bromo-5-methylanthranilic acid, leucine methyl ester hydrochloride, and iodomethane. The scalemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.248 g (0.073 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 3:1−2:1 hexanes/EtOAc provided 21.5 mg (0.064 mmol, 88% yield) of an amorphous white powder. Two compounds eluted separately from each other. On standing, the second to elute converted into the first. The two compounds are atropisomers, which results from substitution at the 3-position. Equilibration occurs to provide

the most stable atropisomer. Gilman[88,89] and Blackburn[9] have previously detailed atropisomerism in benzodiazepine derivatives. IR (KBr): 3271, 2955, 1667, 1447, 1108, 779 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.73 (d, 3, J = 5.5), 0.79 (d, 3, J = 5.5), 1.59 (m, 3), 2.35 (s, 3), 3.16 (s, 3), 3.61 (m, 1), 7.50 (s, 1), 7.77 (s, 1), 8.65 (d, 1, J = 5.5). ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.3, 22.2, 23.0, 24.4, 36.3, 37.6, 50.7, 119.1, 129.3, 132.9, 137.4, 137.6, 139.1, 167.2, 171.2. HRMS (FAB$^+$) m/e: 339.0705 (MH^+ $C_{15}H_{20}N_2O_2Br$ requires 339.0708).

Thienodiazepine 1t. The support-bound benzodiazepine was prepared according to the above procedure from 3-amino-4-(4-chlorobenzenesulfonyl)thiophene-2-carboxylic acid, D,L-homophenylalanine methyl ester hydrochloride, and HOAc. The racemic α-amino ester was loaded according to the nonracemizing conditions. Cleavage of 0.323 g (0.101 mmol) of this resin by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 2:1 hexanes/EtOAc provided 42.3 mg (0.092 mmol, 90% yield) of an amorphous white powder. IR (KBr): 2900, 1715, 1654, 1561, 1502, 1355, 1220, 1155, 1091, 750, 667, 615 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.76−1.85 (m, 1), 1.96−2.05 (m, 1), 2.51−2.64 (m, 2), 3.63−3.69 (m, 1), 7.10 (d, 2, J = 7.0), 7.15 (d, 1, J = 7.1), 7.23 (t, 2, J = 7.1), 7.73 (d, 2, J = 8.6), 7.99 (d, 2, J = 8.6), 8.68 (d, 1, J = 4.7), 8.86 (s, 1), 9.43 (s, 1). ^{13}C NMR (101 MHz, DMSO-d_6) δ 30.0, 31.2, 52.2, 125.9, 126.2, 128.2, 128.3, 129.1, 130.0, 130.5, 133.4, 139.1, 139.4, 139.5, 141.1, 162.3, 168.8. Anal. Calcd for $C_{21}H_{17}N_2O_4S_2Cl$: C, 54.72; H, 3.72; N, 6.08. Found: C, 54.88; H, 3.90; N, 5.87.

Benzodiazepine 1u. This is a Suzuki cross-coupling product. In a 100-mL round-bottom flask was suspended 0.500 g (0.180 mmol) of the resin from which **1d** was cleaved in 30 mL of THF. After the resin had completely solvated (5 min), 2 N aqueous K_2CO_3 (5 mL) was added to the flask generating a biphasic liquid. With magnetic stirring, 4-methoxybenzeneboronic acid (0.281 g, 1.85 mmol) was added, and the flask was fitted with a reflux condenser. A long needle was dropped through the reflux condenser, and the system was purged with Ar. After 30 min, $Pd(PPh_3)_4$ (0.100 g, 0.086 mmol) was added, and the suspension was purged with Ar for another 15 min. The purge needle was removed, and the system was heated at reflux for 18 h under 1 atm of Ar. The yellow/orange solution was removed from the resin by filtration cannula, and the resin was rinsed with DMF (7 × 20 mL), CH_2Cl_2 (7 × 20 mL), and finally CH_3OH (3 × 10 mL). The resin was dried in vacuo to a constant weight, and 0.320 g (0.106 mmol) was cleaved by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h. Gravity filtration and rinsing of the resin and filter paper with excess CH_2Cl_2 and CH_3OH yielded a crude yellow solid upon evaporation in vacuo. Silica gel chromatography 2:1 hexanes/EtOAc yielded 24.0 mg (0.066 mmol, 62% yield) of white solid, mp 202−204 °C (phase change and subsequent decomposition). IR (KBr): 3454 (b), 3177, 3046, 2960, 1690, 1664, 1611, 1493, 1453, 1256, 1183, 1117, 1032, 828 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 0.74 (d, 3, J = 6.1), 0.82 (d, 3, J = 6.0), 1.03 (t, 3, J = 6.8), 1.60−1.69 (m, 3), 3.62−3.68 (m, 1), 3.71−3.79 (m, 1), 3.80 (s, 3), 4.07−4.14 (m, 1), 7.04 (d, 2, J = 8.1), 7.52 (d, 1, J = 8.3), 7.67 (d, 2, J = 8.1), 7.84−7.87 (m, 2), 8.59 (d, 1, J = 5.8). ^{13}C NMR (101 MHz, DMSO-d_6): δ 13.1, 21.7, 22.7, 23.8, 36.4, 42.1, 50.2, 55.1, 114.5, 123.1, 126.4, 127.7, 129.6, 130.2, 130.6, 136.7, 137.8, 159.2, 167.5, 169.3. Anal. Calcd for $C_{22}H_{26}O_3N_2$: C, 72.11; H, 7.15; N, 7.64. Found: C, 71.99; H, 7.00; N, 7.43.

Benzodiazepine 1v. The support-bound benzodiazepine was prepared according to the above procedure from 4-bromoanthranilic acid, H-(*S*)-Tyr(*t*-Bu)-OMe·HCl, and 4-phenylbenzyl bromide. The scalemic α-amino ester was loaded according to the nonracemizing conditions. A Suzuki reaction was then performed with *B*-hexyl-9-BBN. In a 10-mL, flame-dried, round-bottom flask was dissolved 9-BBN dimer (0.506 g, 2.02 mmol) in 7 mL of THF. A dry stir bar was introduced into the flask, and the contents were cooled with stirring to 0 °C. Over the course of 7 min was added 1-hexene (0.65 mL, 5.2 mmol) via syringe. The reaction mixture was warmed to rt and stirred for 6 h. This solution was then transferred via cannula into a 50-mL, round-bottom flask containing the resin derivatized with the benzodiazepine (0.70 g, 0.24 mmol) that was presolvated in 7 mL of THF and 5 mL of 2 N aqueous K_2CO_3. The flask was fitted with a reflux condenser and a needle passed through the top of the condenser into the solution. The solution was then degassed by bubbling Ar through it for 20 min. A catalytic amount of $Pd(PPh_3)_4$ was then added and purging continued for 10 min. The reaction mixture was stirred with a magnetic stirrer for 20 h while being heated at reflux. The solution was removed from the resin by filtration cannula, and the resin was rinsed with DMF (7 x 20 mL), CH_2Cl_2 (7 × 20 mL), and finally CH_3OH (3 × 10 mL). The resin was dried in vacuo to a constant weight, and 0.418 g (0.137 mmol) was cleaved by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h. Gravity filtration and rinsing of the resin and filter paper with excess CH_2Cl_2 and CH_3OH yielded a crude yellow solid upon evaporation in vacuo. Silica gel chromatography 2:1 hexanes/EtOAc yielded 55.2 mg (0.106 mmol, 77% yield) of white solid, mp 176−178 °C. IR (KBr): 3430 (b), 3100, 3026, 2927, 1657, 1612, 1517, 1443, 1385, 1224, 1174, 1130, 1008, 834, 757, 698 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 0.79 (t, 3, J = 6.5), 1.17−1.22 (m, 6), 1.50 (t, 2, J = 6.5), 2.56 (t, 2, J = 7.5), 2.83 (dd, 1, J = 8.6, 14.2), 3.07 (dd, 1, J = 5.5, 14.3), 3.89 (q, 1, J = 6.0), 5.00 (d, 1, J = 15.9), 5.39 (d, 1, J = 15.9), 6.62 (d, 2, J = 8.4), 7.06 (d, 1, J = 8.0), 7.10 (d, 2, J = 8.4), 7.15 (d, 2, J = 8.1), 7.30−7.34 (m, 2), 7.42 (t, 2, J = 7.6), 7.46 (d, 1, J = 7.9), 7.51 (d, 2, J = 8.2), 7.59 (d, 2, J = 7.2), 8.66 (d, 1, J = 6.2), 9.2 (s, 1). ^{13}C NMR (101 MHz, DMSO-d_6): δ 13.8, 21.9, 28.1, 30.2, 31.0, 32.9, 34.8, 49.1, 54.2, 114.9, 122.1, 125.7, 126.4, 126.5, 127.3, 127.4, 127.5, 127.8, 128.8, 129.4, 130.3, 136.6, 138.8, 139.0, 139.5, 146.9, 155.8, 167.5, 170.2. Anal. Calcd for $C_{35}H_{36}O_3N_2$: C, 78.92; H, 6.81; N, 5.26. Found: C, 78.74; H, 6.84; N, 5.07.

Benzodiazepine 1w. This is a Suzuki cross-coupling product. The support-bound benzodiazepine, prepared according to the above procedure from 5-bromoanthranilic acid, leucine methyl ester hydrochloride (nonracemizing reductive amination conditions), and (bromomethyl)cyclopropane, was suspended (0.500 g, 0.180 mmol) in 4 mL of THF, 4 mL of DMF, and 1 mL of H_2O. After the resin had completely solvated (5 min), $CsCO_3$ (0.61 g, 1.87 mmol) was added to the flask. With magnetic stirring, 4-methoxybenzeneboronic acid (0.577 g, 3.80 mmol) was added, followed by addition of $[PdCl_2(dppf)]$[75] (0.100 g, 0.122 mmol). The solution was heated gently to 55 °C for 12 h under 1 atm of N_2. The black solution was removed from the resin by filtration cannula and was rinsed with a solution of saturated KCN in DMSO (in order to remove the Pd) followed by DMF (7 × 20 mL), CH_2Cl_2 (7 × 20 mL), and finally CH_3OH (3 × 10 mL). *Caution! Extreme care should be used during rinsing with KCN in DMSO. This mixture is toxic and may be deadly on skin contact. Appropriate precautions should be taken. Rinses should be disposed of accordingly.* The resin was dried in vacuo to a constant weight, and 0.450 g (0.144 mmol) was cleaved by stirring in 20 mL of 90:5:5 TFA/Me_2S/H_2O for 36 h yielded a crude yellow residue after gravity filtration, rinsing of the resin and filter paper with CH_2Cl_2 (4 × 15 mL) and CH_3OH (2 × 10 mL), and concentration. Silica gel chromatography eluting with 2:1 hexanes/EtOAc provided 44.0 mg (0.112 mmol, 78% yield) of a white powder, mp 85−86 °C. IR (KBr): 2953, 1654, 1555, 1486, 1444, 1364, 1246, 1180, 1025, 870, 828, 668, 553 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 0.10 (m, 2), 0.31 (m, 2), 0.74 (d, 3, J = 6.3), 0.82 (m, 4), 1.59−1.67 (m, 3), 3.61−3.80 (m, 2), 3.80 (s, 3), 4.04 (dd, 1, J = 14.4, 7.6), 7.03, (d, 2, J = 8.8), 7.57 (d, 1, J = 8.5), 7.68 (d, 2, J = 8.8), 7.86 (dd, 1, J = 8.5, 2.4), 7.88 (d, 1, J = 2.25), 8.61 (d, 1, J = 6.1). ^{13}C NMR (101 MHz, DMSO-d_6): δ 3.5, 4.3, 10.4, 22.2, 23.2, 24.3, 36.9, 50.6, 51.1, 55.7, 115.0, 124.2, 126.9, 128.2, 129.9, 130.9, 131.1, 137.2, 138.6, 159.7, 168.1, 170.3. Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.19; H, 6.96; N, 7.14.

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Racemization Study. Benzodiazepine **1c** was prepared according to the racemization-free procedure described previously. HPLC analysis[68] (chiral column, D-phenylglycine derivatized silica, 5% *i*-PrOH in isooctane eluant, 4 mL/min flow rate, UV detection at 262 nm) of benzodiazepine **1c**, prepared under racemization-free conditions, indicated a single enantiomer, t_R = 45.4 min. A fully racemized sample of **1c** was also prepared by allowing preequilibration in the reductive amination step for 6 h in the presence of *i*-Pr_2EtN. Analysis of the racemized sample under the same HPLC conditions indicated two well-separated peaks of approximate equal area, t_R = 41.8, 44.8 min, confirming that complete racemization had occurred.

An additional HPLC study was performed with **1b**, synthesized from the more racemization-prone phenylalanine.[90] Benzodiazepine **1b** was prepared according to the racemization-free procedure described previously. A racemized sample of **1b** was also prepared. This racemized sample served as an HPLC standard. HPLC analysis[5] (chiral column, D-phenylglycine derivatized silica, 4% *i*-PrOH in hexanes eluant, 9.99 mL/min flow rate, UV detection at 252 nm) of benzodiazepine **1b**, prepared under racemization-free conditions indicated a major enantiomer, t_R = 29.5 min and a trace of a second (< 1%), t_R = 35.7 min. Analysis of the racemized sample under the same conditions indicated two well-separated peaks, t_R = 30.5 min and t_R = 35.8 min.

Benzodiazepine **1o** was also prepared employing racemization-free conditions. To verify that during and after alkylation significant racemization was not able to occur, we heated benzodiazepine **1o** in 6 N aqueous HCl at reflux for 12 h in order to liberate the amino acid portion of this benzodiazepine. The liquid was evaporated in vacuo to a yellow residue that was subsequently dissolved in 10 mL of CH_3OH. To this mixture was added $SOCl_2$ (28 mL, 0.40 mmol). The mixture was heated at reflux for 3 h, and the volatile contents of the flask were removed in vacuo. The yellow residue was then dissolved in 10 mL of CH_2Cl_2 and partitioned in equal volumes into two round-bottom flasks. One portion was treated with 5 drops of (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride, (*R*)-MTPA chloride, and 5 drops of Et_3N, and the other portion was treated with 5 drops of (*S*)-MTPA chloride and 5 drops of Et_3N. After the reactions were allowed to proceed for 12 h, the reaction solutions were each washed with 1 N aqueous HCl (3 × 2 mL), 5% aqueous K_2CO_3 (2 × 2 mL), saturated aqueous $NaHCO_3$ (2 mL), and brine (2 mL). The organic layers were dried over $MgSO_4$, and the crude residues were purified on a silica plug, eluting with 1:1 hexanes/EtOAc. The diastereomeric ratio of the products formed was evaluated by capillary GC analysis (HP-1, 150−200 °C, 1 deg/min ramp, 20 psi). The sample prepared from the (*R*)-MTPA chloride indicated a major diastereomer (t_R = 26.0 min, 97%) of (*R*)-MTPA-(*S*)-Leu-OMe, and a minor diastereomer (t_R = 27.0 min, 3%). The sample prepared from (*S*)-MTPA chloride indicated a minor diastereomer of (*R*)-MTPA-(*S*)-Leu-OMe (t_R = 26.0 min, 3%) and a major diastereomer (t_R = 27.1 min, 97%). This experiment demonstrates that racemization occurred to a maximum extent of 3% in this leucine-derived benzodiazepine. It is most likely that the racemization occurs in the benzodiazepine hydrolysis step[69] and not during the benzodiazepine synthesis.

Construction of Multitube Apparatus. The apparatus consists of three parts: a bracket, a tube, and a filter frit. The bracket, which secured the individual reactor tubes in place, was made by sawing off the top ~1/6 in. of 96 1-mL well microtiter plates. The individual reaction tubes were made by cutting 1500 identical 2 in. pieces of 7 mm (outer diameter) glass tubing using a diamond-bladed glass saw with a 2-in. stop to ensure uniformity. The filter frits were introduced onto each of these by heating one end in a Bunsen burner until yellow-hot and melting it directly into a 70 μm hydrophobic polyethylene filter disk (purchased from Applied Separations, catalog no. 2427), taking the time to ensure that the entire bottom of the tube was sealed, with no obvious large pores or holes. Before the tubes cooled, a thermally resistant cloth was used to wipe away the excess polyethylene from around the outside of the tube. After these tubes cooled, they were introduced manually into the bracket creating a reactor of 12 × 8 (96) spatially separate reaction tubes per bracket, leaving most of the tube below the bracket. Only ~1/4 in. was left above the bracket. It was useful to let the brackets sit in a desiccator that had been charged with 50 mL of THF for 30 min prior to inserting the filter tubes. This helped to swell the plastic, allowing for easy insertion. On standing for 2 h on the bench top, the plastic shrinks and seals around the tubes. This apparatus is shown in schematic form in Figure 3.

Table 3. Amounts Used for the Loading α-Amino Esters under Racemization Conditions

label	amino ester	FW (g/mol)	concn (M)	total vol (mL)	mmol ester	mass (g)	*i*-Pr_2EtN (mL)	reductant (g)
L	Leu	181.7	0.15	50	7.50	1.36	0.393	1.59
F	Phe	215.7	0.15	50	7.50	1.62	0.393	1.59
Y	Tyr	287.8	0.15	50	7.50	2.16	0.393	1.59
E	Glu	253.8	0.15	50	7.50	1.90	0.393	1.59
Q	Gln	422.9	0.15	50	7.50	3.17	0.393	1.59
K	Lys	296.8	0.15	50	7.50	2.23	0.393	1.59

Library Synthesis. Coupling of Linker to Support. In an oven-dried, two-neck, 2000-mL round-bottom flask, fitted with an oven-dried mechanical stirring arm, was dissolved 18.56 g (182.2 g mol^{-1}, 102 mmol) of 4-hydroxy-2,6-dimethoxybenzaldehyde[87] in 400 mL of dry DMF. The solution was purged with Ar for 20 min. To this solution, with cooling to 0 °C, under constant positive Ar pressure, was added 2.45 g (24.00 g mol^{-1}, 97 mmol) of 95% NaH in four aliquots. The dark orange solution evolved H_2 (g) rapidly and turned a turbid blood red color and then finally became cloudy orange in appearance. After the evolution of H_2 ceased, the suspension was purged continuously with Ar under vigorous mechanical stirring and was simultaneously allowed to warm to rt. After 20 min, 50.0 g (34.5 mmol of chloride) of Merrifield resin (200−400 mesh chloromethylpolystyrene, 1% divinylbenzene crosslink, 0.69 mmol Cl^-/g resin) was added with constant gentle mechanical stirring under gentle positive pressure of Ar, taking care not to let the Ar flow blow the resin out of the flask as it was being added. The mixture was then heated to 100 °C for 30 min and cooled to 50 °C where it was allowed to stir under an atmosphere of Ar for 36 h. The resin was rinsed with 2:1 DMF/MeOH (3 × 500 mL), DMF (7 × 375 mL), CH_2Cl_2 (7 × 400 mL), and finally MeOH (4 × 300 mL). After being dried in vacuo, the resin had assumed the tan color of the linker aldehyde. A strong aldehyde carbonyl stretch was observed in the IR (KBr) spectrum of this resin: 1690 cm^{-1}.

Reductive Aminations, Racemizing Procedure. In each of six tared 100-mL round-bottom flasks was placed 3.5 g of aldehyde resin. To this was added 50 mL of 1% HOAc in DMF. After the resin had solvated (5 min), one α-amino ester (amounts are found in Table 3) was added to each flask, which was then labeled with the code for that particular α-amino ester. To each flask was then added a catalytic amount of *i*-Pr_2EtN (0.291 g, 2.25 mmol). The mixtures were secured on a shaker table and allowed to agitate for 9 h. The reductant, $NaBH(OAc)_3$ (1.59 g, 7.50 mmol), was then added. After 6 h, an IR spectrum of the resin containing H-Leu-OMe·HCl indicated that the reaction had proceeded to completion. The resins were washed with 1:1 DMF/MeOH (1 × 30 mL), DMF (7 × 30 mL), CH_2Cl_2 (7 × 30 mL), and MeOH (4 × 20 mL). A Kim Wipe was inserted into the mouth of each flask and the resins dried in a vacuum desiccator for 18 h. Infrared spectra (KBr) were obtained, and all resins showed a strong ester carbonyl absorbance at ~1740 cm^{-1}.

Reductive Aminations, Nonracemizing Loading of Racemic α-Amino Esters and Glycine. Into four tared 100-mL round-bottom flasks was aliquoted 3.5 g of the aldehyde resin. To each of them was added 50 mL of DMF and 0.5 mL of HOAc. Upon addition of the acetic acid, the resin turned from bright orange to yellow. $NaBH(OAc)_3$ (1.59 g, 7.50 mmol) was added and dissolved, followed immediately by the α-amino

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Table 4. Amounts Used for the Loading α-Amino Esters under Racemization-Free Conditions

label	amino ester	FW (g/mol)	concn (M)	total vol (mL)	mmol	mass (g)	reductant (g)
G	Gly	125.6	0.15	50	7.50	0.94	1.59
A	Ala	139.6	0.15	50	7.50	1.05	1.59
U	2-Nal	245.3	0.15	50	7.50	1.84	1.59
X	2-Thi	221.7	0.15	50	7.50	1.66	1.59

Table 5. Distribution of α-Amino Ester-Derivatized Resin by Mass

label	amino ester	FW (g/mol)	recovered mass (g)	0.9/12 of resin to each cartridge (g)
L	Leu	181.7	3.55	0.266
F	Phe	215.7	3.79	0.284
Y	Tyr	287.8	3.95	0.296
E	Glu	253.8	3.92	0.294
Q	Gln	422.9	4.21	0.316
K	Lys	296.8	3.88	0.291
G	Gly	125.6	3.59	0.268
A	Ala	139.6	3.64	0.273
U	2-Nal	245.3	3.93	0.295
X	2-Thi	221.7	3.84	0.288

Table 6. Amounts Used for the Anthranilic Acid Acylation Step

label	anthranilic acid (abbr Ant)	FW (g/mol)	concn (M)	vol (mL)	mmol	mass (mg)	EDC (mg, M)
A	anthranilic acid (Ant)	137.1	0.35	3.0	1.05	144	247, 0.43
B	4-Cl Ant	171.6	0.35	3.0	1.05	180	247, 0.43
C	5-Cl Ant	171.6	0.35	3.0	1.05	180	247, 0.43
D	6-F Ant	155.1	0.35	3.0	1.05	162	247, 0.43
E	3-Me Ant	151.7	0.35	3.0	1.05	159	247, 0.43
F	4-Br Ant	216.0	0.35	3.0	1.05	227	247, 0.43
G	5-Br Ant	216.0	0.35	3.0	1.05	227	247, 0.43
H	4-MeO Ant	167.2	0.35	3.0	1.05	175	247, 0.43
I	4-nitro Ant	182.1	0.35	3.0	1.05	191	247, 0.43
J	4-Me Ant	151.7	0.35	3.0	1.05	159	247, 0.43
K	3-Br, 5-Me Ant	230.1	0.35	3.0	1.05	242	247, 0.43
L	3-pyridine Ant	138.1	0.35	3.0	1.05	145	247, 0.43

esters (amounts are shown in Table 4). The flasks were secured on the shaker table. As the reduction proceeded, the color of the resin became even lighter. After 3 h, the resins were given the same rinse sequence described in the preceding experimental procedure and were dried in vacuo for 12 h, and IR (KBr) spectra were obtained. All resins showed a strong ester carbonyl stretch at ~1740 cm^{-1}.

Acylations were performed in 120 12-mL filter cartridges with 70 μm hydrophobic polyethylene frits, purchased from Applied Separations (catalog no. 2427). In order to deliver an equimolar amount of resin-bound α-amino ester into each of these reaction vessels, the total mass of each of the α-amino ester-derivatized resins was obtained based on the tare of the round-bottom flasks. This total mass was then divided by 12 (corresponding to acylation with 12 anthranilic acids). In order to have a small amount of resin left over, this quantity was then multiplied by 0.9. These masses are shown in the last column of Table 5. The resin corresponding to each α-amino ester was then distributed into 12 filter cartridges according to the mass in the right most column of Table 5. The total number of filter cartridges was 120; each was labeled in duplicate according to the α-amino ester resin contained within and the anthranilic acid to be acylated.

Acylation of Resin-Bound α-Amino Esters. The bottom of each of the 120 12-mL filter cartridges was sealed with an 8 mm rubber septum and to each of them was added 1-methyl-2-pyrrolidinone (NMP, 3 mL) and the coupling agent EDC (see Table 6 for amounts). Some EDC remained undissolved until the anthranilic acid was added. Before addition of the anthranilic acid, the mixture of EDC, NMP, and resin was agitated on a vortex mixer for 10 s. The anthranilic acid (Table 6) was then added and immediately vortexed to homogeneity. The cartridges were sealed with a 14/20 rubber septum at the top and placed upright in a box on a shaker table. After 12 h of agitation, the filter cartridges were rinsed, 12 at a time, using a Visiprep filter cartridge filtration apparatus obtained from Supelco (catalog no. 5-7030). The rinses consisted of soaking the resin in each cartridge with DMF (5 mL) as many times as was needed until the supernatant that was removed was colorless. Each resin sample was then soaked for 5 min in CH_2Cl_2 (5 × 5 mL). The acylation and rinsing was repeated in an identical manner, with the exception that an additional rinse with MeOH (3 × 5 mL) was performed at the end. All 120 filter cartridges were sealed at the top with a 14/20 rubber septum and dried in a vacuum desiccator overnight.

Resin Distribution, Cyclization, and Alkylation. The cartridges were removed from the vacuum desiccator, and a mixture of 3:2 1,2-dichloroethane/DMF was found to be isopycnic[83] with respect to the resins in a randomly chosen cartridge. Since each cartridge had a structurally unique resin-bound benzodiazepine precursor, there was concern that 3:2 dichloroethane/DMF might not be isopycnic with respect to the contents of all the cartridges. This was found not to be the case. In particular, for each cartridge after dilution, no visible settling of the resin was observed over 10 s. We felt that this was sufficient to ensure that removal of equal volume aliquots from 120 equal total volume slurries would allow for equimolar distribution.

The contents of every cartridge were suspended in excess 3:2 dichloroethane/DMF and agitated on a vortex mixer until completely solvated. The liquid was removed by suction, the cartridge bottom was stoppered with an 8 mm white rubber septum, and 2 mL of 3:2 dichloroethane/DMF was delivered by a Pipetman. Aliquots of 240 μL of the contents of each cartridge were transfered to 10 separate reaction tubes. The volume was delivered as 2 × 120 μL portions to help average out any variation. Aliquoting was performed with a Pipetman, fitted with tips whose ends had been cropped to provide a wider bore to accommodate free passage of polymer beads. Enough extra resin in each cartridge remained to remake at least one benzodiazepine if necessary.

A total of 16.5 multitube plates were filled, and each of these plates was blotted on a terry cloth towel, which helped to draw solvent out of the tubes. Several polypropylene covers from pipet tip racks (referred to as polypropylene bins) were then used as small solvent reservoirs and filled with DMF. Each multitube plate was submerged in DMF 1 in. high (2 × 1 min). The filter bottoms were blotted on terry cloth towels in between rinses. Several large polypropylene tubs were then filled 1 in. high with THF, and the tubes were submerged and soaked (3 × 30 min), allowing the tubes to drain in between soakings. The multitube plates were then submerged quickly in THF (3×) and blotted on terry cloth towels in between rinses. The plates were then soaked in 4-Å sieve-dried THF for 36 h in an N_2 glove bag over 4-Å sieves.

Cyclizations were performed using lithiated acetanilide in a THF/DMF solution: In a 2-L, oven-dried, round-bottom flask, fitted with a large magnetic stir bar, was placed 500 mL of 4-Å sieve-dried THF. To this was added 55.0 g (407 mmol, 135.2 g mol^{-1}) of acetanilide. The acetanilide had been dried in vacuo overnight. This solution was cooled to −78 °C, and the flask was purged with dry N_2. With rapid stirring, *n*-butyllithium (2.5 M in hexanes, 150 mL, 375 mmol) was added dropwise by syringe over the course of 1.5 h. As the addition proceeded, a white solid precipitated from the reaction mixture. After *n*-BuLi addition was complete, the contents of the flask were warmed to rt as solids continued to precipitate. Once at rt, 1 L of dry DMF was added over 30 min. All solids dissolved. The flask containing the 0.25 M cyclization cocktail was moved into an N_2 glovebag.

Into each of 17 of the 40 small polypropylene bins was poured between 75 and 100 mL of the cyclization cocktail. Each of the multitube plates was removed from the 4-Å sieve/THF bin, blotted on a terry cloth towel, which had dried over night in a N_2 glovebag, and transferred into the small polypropylene bins containing the 75−100 mL of cyclization cocktail. A multichannel pipet device was then used to remove cyclization cocktail from the bottom of the polypropylene reaction bins and drop it down from the tops of the reactor tubes in order

Table 7. Amounts Used for the Alkylation Step[a]

label	alkylating agent	FW (g/mol)	*d* (g/mL)	concn (M)	mol	mass, vol (g, mL)
A	none (AcOH)	60.05	1.049	0.40	0.030	1.80, 1.72
B	methyl iodide	141.94	2.280	0.40	0.030	4.26, 1.86
C	ethyl iodide	155.97	1.513	0.40	0.030	4.68, 3.09
D	4-Phbenzyl bromide	247.13		0.40	0.030	7.41 g
E	piperonyl chloride	170.60		0.40	0.030	5.18 g
F	3,5-dimethylBnBr	199.10		0.40	0.030	5.97 g
G	*o*-MeOBnCl	156.61		0.40	0.030	4.70 g
H	(bromomethyl)-cyclopropane	135.00	1.410	0.40	0.030	4.05, 2.87
I	2-(bromomethyl)-naphthalene	221.10		0.40	0.030	6.63 g
J	benzyl bromide	171.04	1.438	0.40	0.030	5.13, 3.57
K	iodoacetamide	187.96		0.40	0.030	5.64 g

[a] Amounts are calculated on the basis of a volume of stock solution of 75 mL.

to ensure that the resin was properly bathed in the cyclization cocktail. These cyclization conditions were maintained for 40 h, over which time the volume of the cyclization cocktail had reduced and some white solid had precipitated.

Solutions of the alkylating agents (0.4 M, 75 mL) were prepared in the remaining dry polypropylene bins employing the amounts shown in Table 7. With the exception of 3,4-(methylenedioxy)benzyl (piperonyl) chloride and 2-methoxybenzyl chloride, the liquid alkylating agents were eluted from a plug of basic alumina prior to use. The solid alkylating agents were used without any further purification or preparation, except 3,5-dimethylbenzyl bromide. This solid was dissolved in a minimal volume of hexanes and eluted from a plug of basic alumina prior to use. The 3,4-(methylenedioxy)-benzyl chloride (piperonyl chloride) and 2-methoxybenzyl chloride were obtained from Trans World Chemicals as 50%-by-weight solutions in CH_2Cl_2, stabilized with $CaCO_3$. These solutions were passed through a 0.2-μm nylon syringe tip filter and concentrated in vacuo *without heating* prior to use.

The resin blocks were removed from the cyclization cocktail, blotted on a terry cloth towel, and transferred to the bins containing the alkylating agents. A multichannel pipet device was used to bathe each of the wells in the solution. The multitube plates were configured such that only one alkylating agent was used for each of eight multitube plates. For the remaining eight plates only two alkylating agents were used. Alkylation reactions were therefore straightforward to perform since they were carried out in bins rather than requiring that the stock solutions be aliquoted into individual wells of microtiter plates. Alkylations were allowed to continue for 6−8 h. The multitube plates were blotted on towels until all the alkylation cocktails had drained and transferred to bins containing DMF to soak.

The multitube plates were then repeatedly submerged in at least 1 in. of DMF and allowed to soak for at least 5 min. This was repeated five times with blotting in between each rinse. The plates were then rinsed in the same manner with THF and then allowed to soak overnight in THF-filled polypropylene bins in an N_2 glovebag. After 12 h, they were blotted on terry cloth towels and given three quick rinses by submerging them in THF, 1 in. deep. Although probably not necessary, they were soaked overnight again in THF. After 12 h, they were all soaked in CH_2Cl_2 (7 × 20 min) to remove the THF.

Cleavages. Into every well (except in the first and last columns, which were left blank for controls during biological assay) of 17, 96 2-mL well microtiter plates was added ~1 mL of 90:5:5 TFA/$(CH_3)_2S$/H_2O by glass pipet. The tubes of the multitube plates were slowly submerged into the cleavage cocktail, taking care not to accidentally force TFA up over the edges of each well as the tubes filled. Cleavages were allowed to proceed for 36−40 h. The plates were removed slowly, allowing liquid to drain into the wells, and immediately submerged into a second plate, charged with a rinse cocktail of 1:1 dichloroethane/CH_3CN. The plate with the TFA mixture were concentrated in a Jouan microtiter plate concentrator. After all the TFA was removed, the rinse cocktails from the appropriate wells were combined using a multichannel pipet device and reconcentrated. When brought to dryness, the bottom of each well had a small orange or yellow pellet. The wells with glutamine-containing benzodiazepines had red pellets at the bottom, the color presumably derived from the dimethoxybenzhydrol protecting group.

Table 8. Relative Chromophores of Benzodiazepines to Nitrotoluene Standard[a]

entry	R^1	R^2	R^3	factor
1	7-Cl	ethyl	$(CH_2)_2CONH_2$	0.37
2	7-Cl	benzyl	$(CH_2)_2CO_2H$	0.38
3	9-pyridyl	*c*-$(C_3H_5)CH_2$	$CH_2C_6H_5$	0.55
4	8-MeO	2-MeOBn	H	0.39
5	8-NO_2	ethyl	$CH_2CH(CH_3)_2$	0.24
6	7-Cl	H	$CH_2C_6H_5$	0.35
7	8-Me	piperonyl	2-thienylmethyl	0.30
8	7-Cl	piperonyl	$CH_2C_6H_5$	0.25
9	8-O_2N	*c*-$(C_3H_5)CH_2$	2-thienylmethyl	0.26
10	9-Br, 7-Me	methyl	$CH_2CH(CH_3)_2$	0.40
11	6-F	NH_2COCH_2	$CH_2C_6H_5$	0.53
12	9-Br, 7-Me	H	$CH_2CH(CH_3)_2$	0.37
13	8-hexyl	4-phenylBn	$CH_2C_6H_4OH$	0.20
14	7-Br	ethyl	$CH_2CH(CH_3)_2$	0.25
15	7-Cl	NH_2COCH_2	$CH_2C_6H_4OH$	0.28
16	−	ethyl	$CH_2C_6H_5$	12.4[b]
17	8-MeO	benzyl	CH_3	0.42
18	6-F	3,5-diMeBn	2-thienylmethyl	0.46
19	7-Cl	methyl	CH_2-2-$(C_{10}H_7)$	0.24

[a] Correction factors by which HPLC ratios of benzodiazepine to internal standard (*p*-nitrotoluene) would need to be multiplied to obtain the actual ratio of benzodiazepine to standard. UV absorbance detection was monitored at 252 nm. A sample calculation appears in the Experimental Section. [b] The benzodiazepine in entry 16 coeluted with *p*-nitrotoluene. This factor was measured relative to 9-fluoreneone.

Determination of Yields by ^{1}H NMR Combined with HPLC with UV Detection. The correction factors found in Table 8 were all calculated according to the following protocol. *p*-Nitrotoluene (~2 mg) and the selected benzodiazepine (~4 mg) were dissolved in DMSO-d_6. The exact ratio of the benzodiazepine (Bz) to the internal standard (Std) was determined by ^{1}H NMR integration. A portion of the mixture was then injected onto an analytical RP-HPLC column (ramp 40−100% MeOH in H_2O over 40 min, UV detection at 252 nm) to obtain the ratio of UV responses of the benzodiazepine relative to the internal standard. With this information the correction factor (*C*) could be calculated:

$$C = (\text{Std/Bz})_{\text{HPLC}} \times (\text{Bz/Std})_{\text{NMR}}$$

In order to determine the exact quantity of a benzodiazepine in the library, the following protocol was used. The well from the library corresponding to the desired benzodiazepine was diluted with 1.00 mL of a solution of 1:2:0.5 MeOH/CH_3CN/1,2-dichloroethane. This solvent mixture was used instead of DMSO to allow for easy reconcentration. The contents of the well were repeatedly drawn up into a pipet to ensure that everything had dissolved. A Pipetman was used to transfer 10 μL from the well to a small vial. A solution of the internal standard *p*-nitrotoluene (0.1 mg mL^{-1}) was added so as to deliver 0.03 μmol (41.1 μL) of the internal standard. This sample was mixed thoroughly after addition of five drops of DMF. Injection onto RP-HPLC, with ramp and UV detection as above, provides the ratio of benzodiazepine to standard. The ratio of benzodiazepine to standard by UV absorbance and the correction factor (*C*) are then used to calculate the quantity of the benzodiazepine: $(\text{Bz/Std})_{\text{HPLC}}$ × C (correction factor) × 0.03 μmol (quantity of Std).

Full characterization has previously been provided for most of the benzodiazepines evaluated above. Complete characterization for an additional five benzodiazepines that had been synthesized on large scale during the development of this synthetic methodology and that were used in library yield calculation follows.

Benzodiazepine (Table 8, Entry 16). IR (KBr): 3272, 2943, 1654, 1602, 1460, 1400, 1240, 1129, 761, 703 cm^{-1}. ^{1}H

NMR (400 MHz, DMSO-d_6): δ 0.99 (t, 3, J = 7.0), 2.90 (dd, 1, J = 8.9, 14.2), 3.11 (dd, 1, J = 5.4), 14.1), 3.68−3.74 (m, 1), 3.79−3.85 (m, 1), 4.11−4.16 (m, 1), 7.14−7.16 (m, 1), 7.22 (dd, 2, J = 7.1, 7.5), 7.27−7.31 (m, 3), 7.47 (d, 1, J = 7.9), 7.56−7.60 (m, 2), 8.68 (d, 1, J = 6.2). ^{13}C NMR (101 MHz, DMSO-d_6): δ 13.0, 33.6, 42.1, 53.9, 122.7, 125.6, 126.3, 128.1, 129.3 (b), 129.9, 132.2, 137.9, 139.1, 167.5, 169.3. Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.40; H, 5.98; N, 9.39.

Benzodiazepine (Table 8, Entry 15). IR (KBr): 2965, 1677, 1519, 1440, 1368, 1210, 1137, 841 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.78 (dd, 1, J = 9.3, 14.3), 2.98 (dd, 1, J = 5.0, 14.4), 3.87−3.90 (m, 1), 4.22 (d, 1, J = 16.8), 4.41 (d, 1, J = 16.8), 6.61 (d, 2, J = 8.4), 7.06 (d, 2, J = 8.4), 7.17 (b s, 1), 7.35 (d, 1, J = 8.8), 7.56 (d, 1, J = 2.6), 7.59 (b s, 1), 7.62 (dd, 1, J = 2.6, 8.8), 8.72 (d, 1, J = 6.3), 9.22 (s, 1). ^{13}C NMR (101 MHz, DMSO-d_6): δ 32.7, 50.8, 53.7, 114.9, 124.5, 127.5, 128.7, 129.5, 130.2, 130.7, 131.8, 139.2, 155.9, 166.2, 169.3, 169.9. HRMS (FAB$^+$) m/e: 374.0910 (MH$^+$ $C_{18}H_{17}N_3O_4Cl$ requires 374.0908).

Benzodiazepine (Table 8, Entry 8). IR (KBr): 3256, 2883, 1669 (s), 1560, 1488, 1438, 1351, 1244, 1190, 1101, 1042, 932, 812 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.94 (dd, 1, J = 8.9, 14.0), 3.15 (dd, 1, J = 5.2, 14.0), 4.04−4.09 (m, 1), 4.81, (d, 1, J = 15.6), 5.27 (d, 1, J = 15.5), 5.94 (b s, 2), 6.54 (d, 1, J = 7.7), 6.59 (s, 1), 6.75, (d, 1, J = 7.8), 7.17 (t, 1, J = 7.1), 7.23 (t, 2, J = 7.1), 7.31 (d, 2, J = 7.1), 7.51−7.53 (m, 2), 7.58 (d, 1, J, 8.5), 8.90 (d, 1, J = 6.3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 33.6, 49.1, 53.6, 101.0, 107.3, 108.2, 120.4, 124.9, 126.4, 128.1, 128.8, 129.4, 129.8, 130.7, 131.5, 131.8, 137.7, 137.9, 146.3, 147.4, 166.2, 169.9. HRMS (FAB$^+$) m/e: 434.1038 (M$^+$ $C_{24}H_{19}N_2O_4Cl$ requires 434.1033).

Benzodiazepine (Table 8, Entry 19). IR (KBr): 3060, 2931, 1664, 1432, 1123, 826 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.05 (dd, 1, J = 8.74, 14.2), 3.28−3.31 (m, 4), 4.05−4.10 (m, 1), 7.44−7.46 (m, 4), 7.53−7.56 (m, 1), 7.63 (dd, 1, J = 3.3, 8.8), 7.76−7.83 (m, 4), 8.88 (d, 1, J = 6.3). ^{13}C NMR (126 MHz, DMSO-d_6): δ 33.9, 35.0, 53.6, 124.2, 125.5, 126.0, 127.3, 127.4, 127.6, 127.7, 127.8, 128.7, 129.3, 130.2, 131.7, 131.8, 132.8, 135.4, 139.6, 166.3, 170.1. HRMS (FAB$^+$) m/e: 365.1049 (MH$^+$ $C_{21}H_{18}N_2O_2Cl$ requires 365.1057).

Benzodiazepine (Table 8, Entry 18). IR (thin film): 2916, 1672, 1611, 1468, 1390, 1233 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.14 (s, 6) 3.20 (dd, 1, J = 8.0, 14.9), 3.33−3.39 (m, 1), 4.08−4.13 (m, 1), 4.89 (d, 1,J = 16.0), 5.27 (d, 1, J = 16.0), 6.69 (b s, 2), 6.80 (b s, 1), 6.90−6.92 (m, 1), 6.94−6.95 (m, 1), 7.11 (t, 1, J = 9.0), 7.28−7.31 (m, 2), 7.46−7.51 (m, 1), 9.07 (d, 1, J = 7.1). ^{13}C NMR (126 MHz, DMSO-d_6): δ 21.1, 28.4, 49.8, 54.2, 113.8 (d, J_{FC} = 21.5), 118.9, 119.1 (d, J_{FC} = 15.0), 124.7, 125.0, 127.1, 128.8, 132.7 (d, J_{FC} = 10.0), 137.1, 137.8, 139.8, 141.0 (b), 159.9 (d, J_{FC} = 252.9), 163.7, 170.3. HRMS (FAB$^+$) m/e: 409.1377 (MH$^+$ $C_{23}H_{22}FN_2O_2S$ requires 409.1386).

HPLC Conditions. The same conditions were used both when evaluating yields and when determining the correction factors (C). The samples were prepared as described immediately above. Samples were injected at 40% MeOH in H_2O on an analytical C-18 reversed-phase HPLC column, ramp 40−100% MeOH in H_2O over 40 min, UV detection at 252 nm. However, an isocratic solvent system of 70% MeOH in H_2O was used in order to minimize slight chromophore variation compared with entry 13, Tables 3 and 4. The correction factors of these benzodiazepines were used interchangeably in yield calculations since they only differ in the length of the C-8 alkyl group.

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Supporting Information Available: ^{1}H NMR spectra for library members (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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