A Remarkable Two-Step Synthesis of Diverse 1,4-Benzodiazepine-2,5-diones Using the Ugi Four-Component Condensation

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A two-step, general synthesis of 1,4-benzodiazepine-2,5-diones (BZDs) is presented. This synthesis employs an Ugi four-component condensation using a convertible isocyanide (1-isocyanocyclohexene), followed by an acid-activated cyclization reaction. This synthesis represents a dramatically improved route to BZDs over those currently in the literature. In addition, since amino acids are not used as inputs, the potential for molecular diversity is much greater than that with existing syntheses. It was also found that BZDs substituted with methylenes at the C-3 and N-4 positions display conformational isomerism in the NMR spectra at room temperature. Variable-temperature NMR experiments support this observation and offer the interesting conclusion that the BZD core structure, in certain examples, might not be as rigid as previously supposed.

Introduction

1,4-Benzodiazepine-2,5-diones (BZDs) (**1**, Figure 1) constitute an important class of bioactive compounds, one that has received much attention lately. Members of this class have been identified as platelet aggregation inhibiting mimics of the arginine-glycine-aspartic acid (RGD) peptide sequence,[1] as anticonvulsant agents,[2−4] as precursors to the benzodiazepines,[5,6] as anxiolytic agents,[7] and as antitumor compounds.[8] Large numbers of both natural and synthetic BZDs are known.

Numerous syntheses of BZDs have appeared in the literature.[9−11] To this point, they have been based almost exclusively on the condensation of an anthranilic acid, an amino acid or derivative thereof, and various alkylating agents (Figure 2a). Variations on this basic theme have included use of isotoic anhydrides or 2-nitrobenzoyl chlorides as activated anthranilic acid precursors and N-substituted amino acids and esters in order to differentiate the amide nitrogens of the final BZD product. In addition, numerous methods for final closure of the seven-membered ring have been devised, including both acid- and base-mediated processes.

Most recently, the synthesis of BZDs has been adapted to solid support and a library format.[9,12,13] Like the benzodiazepines, the BZDs are well-suited for combinatorial synthesis: they possess a common core structure, well-defined loci of diversity, relatively available starting materials, and multiple potential points of attachment to the resin support. However, upon closer inspection, there are several drawbacks to the BZD syntheses currently in the literature. Foremost is the reliance upon commercially available amino acids and derivatives; there are perhaps no more than 100 of these, many of which are enantiomeric pairs. There is also the difficulty of alkylating an amide nitrogen and the corresponding limited number of viable alkylating agents. Use of *N*-alkylamino acids circumvents this but requires ad-

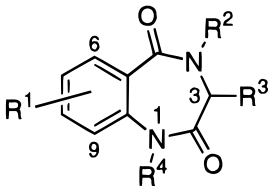

Figure 1.

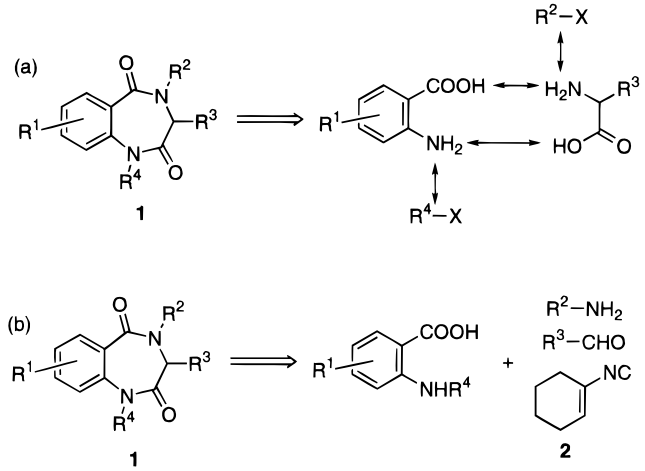

Figure 2.

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1996.

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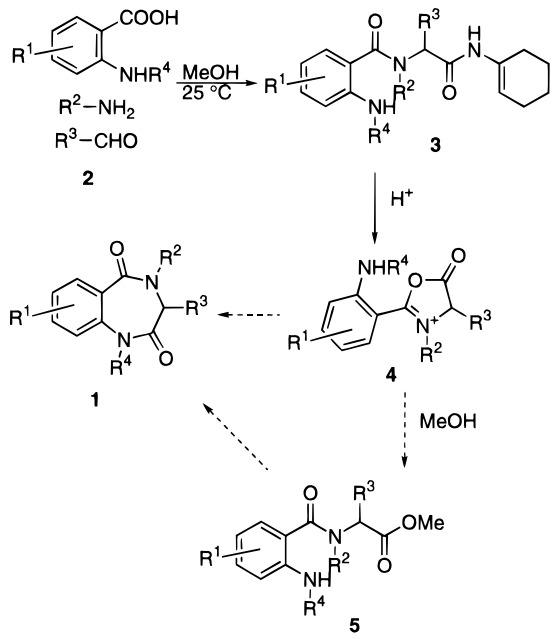
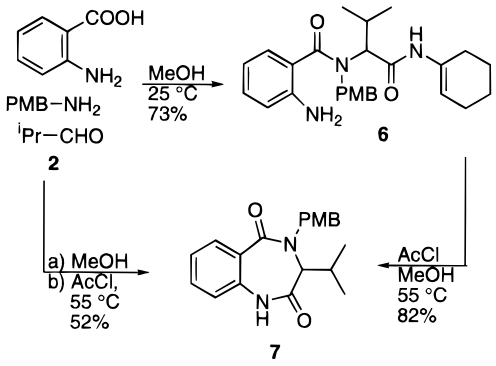
Scheme 1



Scheme 2[a]



[a] PMB, *p*-methoxybenzyl.

ditional synthetic effort to produce this input. Finally, use of a tether to solid support reduces the number of variable sites on the product molecule by one, although Ellman has addressed this through his "traceless" silicon linker.[14]

Our interests involve using the Ugi four-component condensation[15] (4CC) with a convertible isocyanide to rapidly synthesize diverse classes of compounds,[16] including BZDs (Figure 2b). The Ugi reaction is the one-pot condensation of a carboxylic acid, an amine, an aldehyde or ketone, and an isocyanide to yield an α-acylaminoamide. As a synthetic tool for creating diverse compound libraries, the Ugi reaction offers a large number of potential inputs, with the exception of the isocyanide input. To reduce the impact of the dearth of commercially available isocyanides, we have introduced the concept of a convertible isocyanide, one that can be exchanged, postcondensation, for another functionality. 1-Isocyanocyclohexene (**2**)[17] operates admirably in this regard, and we have accomplished the one-step synthesis of α-acylamino acids, ester, thioesters, pyrroles, and sugar derivatives from the 4CC product.[18,19] We had also previously shown a synthesis of 1,4-benzodiazepine-2,5-diones using this methodology.[19] In this article, we more fully describe this synthesis and the diverse BZDs that can be easily constructed.

Results and Discussion

Our goal was the synthesis of diverse 1,4-benzodiazepine-2,5-diones **1** using the Ugi reaction to generate the precursor α-acylaminoamide **3**, as shown in Scheme 1. We have shown[18] that the cyclohexenamide moiety in **3** is activated by acid, causing cyclization and ejection of cyclohexanimine to form the reactive azomethine ylide (münchnone)[20,21] intermediate **4**, which can be attacked by a variety of nucleophiles. We intended that the anthranilic nitrogen would act as the nucleophile once **4** was formed, thus closing the seven-membered ring to give **1**. Should such a transition state prove too strained to form, we anticipated that use of a nucleophilic solvent (e.g., methanol) would yield an ester **5** that should be displaced by the aryl amine under the same acidic conditions. This cycloamidation of an alkyl ester is precedented.[22] In either case, the end product is the same.

Issues that concerned us included the potential necessity of a protecting group for the anthranilic nitrogen; it was hoped that the aryl amine would not participate in the Ugi reaction, so that anthranilic acids could be employed "off-the-shelf" without manipulation. Second, there was the issue of acid-mediated cyclization: would the aryl nitrogen be a strong enough nucleophile to form the seven-membered ring, particularly with deactivating substituents on the aryl ring? Next, in order to reduce the number of synthetic steps and avoid alkylating the secondary amide after ring formation, we intended to test some N-substituted anthranilic acids for their performance in this synthesis. Finally, it was desired that this procedure demonstrably yield BZDs difficult to synthesize by other methods.

Results are shown in Scheme 2 and Chart 1. Ugi 4CC reactions employing a variety of anthranilic acids (examples included electron-rich, electron-poor, and halogenated systems), amines, aldehydes and ketones, and 1-isocyanocyclohexene (**2**) proceeded in methanol at room temperature to yield the respective α-acylaminoamides, in yields that varied from poor to excellent. A variety of aldehydes were also accepted, with the exception that highly electron-rich or reactive aldehydes such as trimethoxybenzaldehyde or 2-furfural would not undergo the 4CC.

After these Ugi products were purified, two different methods of cyclization were employed. Milder procedures dissolved the 4CC product in methanol and then used acetyl chloride as a means of generating HCl. This reaction was then heated to 55 °C for several hours. In some cases, however, the cyclization failed to proceed or

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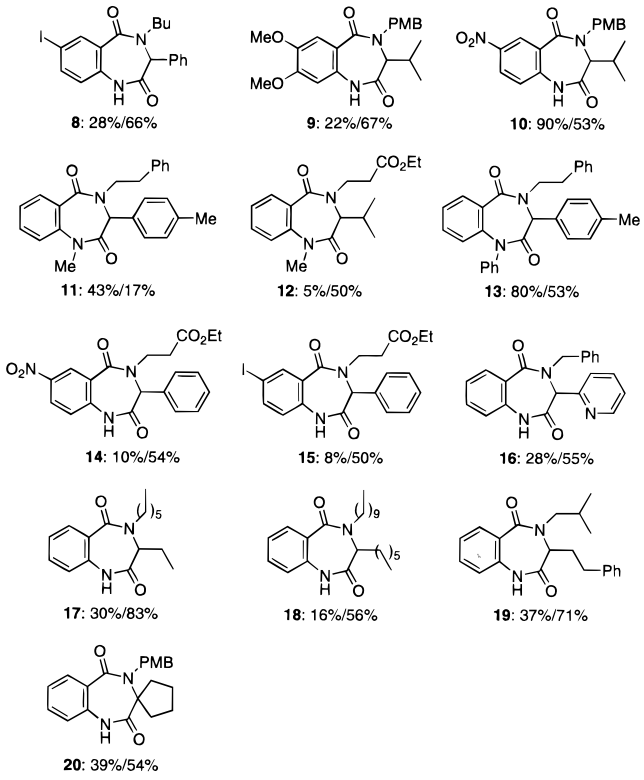
Chart 1. Product 1,4-Benzodiazepine-2,5-diones and Yields[a]



[a] The percentages following each compound number indicate the isolated, purified yields for the Ugi 4CC reaction and the acid-mediated cyclization reaction, respectively, as shown in Scheme 2.

produced only low yields at this temperature, necessitating more strenuous conditions. Then, the 4CC product was dissolved in toluene with a catalytic amount of methanol, an anhydrous HCl solution was added, and the reaction was heated to 100 °C. Purification yielded the 1,4-benzodiazepine-2,5-diones shown in Chart 1, in fairly reliably moderate to good yields. All compounds (except **20**) are racemic mixtures, because the Ugi 4CC yields a new stereocenter at the C-3 position. It also should be noted that **2** has contributed only a single carbon atom (C−2) to the final structure, thus erasing the isocyanide input almost completely.

As can be seen in Chart 1, a wide range of anthranilic acids is tolerated in the reaction procedure, including the 5-nitro, which would be expected to reduce dramatically the nucleophilicity of the aryl nitrogen. N-Substituted substrates also give reasonable yields. *N*-Phenyl product **13** is remarkable in that it is unavailable by other BZD syntheses that rely upon alkylation for N-substitution. While available N-substituted anthranilic acids are not numerous, reductive amination with a variety of aldehydes can provide this input with the expense of an additional step.

Additionally, a spiro system was synthesized using cyclopentanone (**20**), but interestingly, the corresponding cyclohexanone 4CC product failed to cyclize under acidic conditions, due perhaps to unfavorable steric compression, and yielded instead the uncyclized methyl ester. Many of the compounds in Chart 1 are difficult to synthesize from standard methods using amino acid sources, as the products **11**, **13**, **16**, and **18**−**20** demonstrate, corresponding to tolylglycine, pyridylglycine, pentylglycine, homophenylalanine, and 1-aminocyclopentanecarboxylic acid, respectively.

Conformational Isomerism in the BZDs. Interestingly, the ^{1}H NMR spectra of **17**-**19**, featuring alkyl chains at N-4 and C-3, display slow interconversion of conformers on the NMR time scale in $CDCl_3$ and in DMSO-d_6 at room temperature. Ratios of the two conformers, measured at H-3, are 1.8:1, 1.8:1, and 2:1, respectively. This finding is remarkable because the benzodiazepinedione framework is touted as a rigid, "cupped" structure appropriate for the defined 3-D presentation of various functional groups.[1] It appears from these examples that certain members of this compound class may not be as rigid as expected.

Variable-temperature (VT) NMR experiments on these three compounds in DMSO-d_6 support this conformational isomerism. The isomeric resonances in began to broaden at 37 °C, merged at 60 °C, and coalesced into single resonances between 80 and 100 °C. Very similar results were observed in VT experiments on **18** and **19**, although the isomeric proton resonances in **19** did not merge until 100 °C was reached. It appears from these few examples that BZDs in which the C-3 and N-4 positions are substituted with immediately adjacent methylenes exhibit this type of conformational isomerism.

One-Pot BZD Synthesis. We have also attempted a one-pot, single-step synthesis of the BZDs, particularly **7** (Scheme 2). Thus, the four Ugi reaction components were combined in methanol and stirred for several hours. When TLC analysis indicated the reaction had stopped, the reaction mixture was diluted with THF, HCl was added, and the mixture was heated. As shown in Scheme 2, a 52% yield of **7** was obtained after purification. As can be seen, the yield is nearly the same as the overall yield of the two-step procedure. This procedure has not worked in all cases, however, and perhaps the equivalent of water that is produced in the Ugi reaction in the one-pot procedure prevents the cyclization from occurring. We most often observe a large number of product spots by TLC in these cases, with the only recognizable product being the uncyclized carboxylic acid derivative of the Ugi 4CC product.

Conclusions

We have presented here a novel two-step procedure for the synthesis of diverse 1,4-benzodiazepine-2,5-diones. This synthesis takes advantage of the maximal input diversity offered by the Ugi four-component condensation and avoids the limitations imposed by traditional syntheses that rely upon annulating amino acid derivatives onto anthranilic acids. We have also uncovered some interesting evidence concerning conformational isomerism in the BZD skeleton. It appears that alkyl substitution at the N-4 and C-3 positions induces a slow conformer interconversion that can be witnessed by NMR.

Experimental Section

General Procedures. All reactions unless otherwise indicated were performed in oven- or flame-dried glassware under an inert atmosphere. Solvents were distilled immediately prior to use: THF from sodium/benzophenone ketyl, methanol from magnesium turnings, CH_2Cl_2 from P_2O_5, and toluene from calcium hydride. Anhydrous HCl (1 M in ether) was purchased from Aldrich and used directly.

General Procedure for Ugi Four-Component Condensation. The amine (1.25 equiv), and aldehyde (1.0 equiv) are dissolved in methanol to an approximate concentration of 1 M in each. This solution is allowed to stand for 1 h, and then the carboxylic acid (1.0 equiv) is added, followed by the isocyanide (1.0 equiv) as a 1 M solution in hexanes. The resulting solution is allowed to stir at room temperature for 12−36 h. When reaction is complete by TLC (3:1−1:1 hexanes/ethyl acetate), it is quenched by addition of a saturated sodium bicarbonate solution and extracted twice with ethyl acetate. After drying over Na_2SO_4, the organic layer is removed in vacuo, and the residue is purified by flash column chromatography on silica gel, eluting with hexanes to 1:1 hexanes/ethyl acetate gradient.

General Procedure for 1,4-Benzodiazepine-2,5-dione Cyclization (A). The Ugi 4CC reaction product is azeotropically dried with benzene or toluene and then dissolved in methanol to an approximate concentration of 0.1M. After adding distilled acetyl chloride (10 equiv), the flask is capped and then heated to 55 °C for 6 h. The reaction mixture is quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. After removal of dried solvent in vacuo, the residue is purified via flash column chromatography (silica, 2:1 hexanes/ethyl acetate to 1:2 gradient) or preparative TLC (2:1 hexanes/ethyl acetate).

General Procedure for 1,4-Benzodiazepine-2,5-dione Cyclization (B). The Ugi 4CC reaction product is azeotropically dried with benzene or toluene, then dissolved toluene with a catalytic amount of methanol to an approximate concentration of 0.1M. After adding a 1 M solution of HCl in ether (10 equiv), the flask is placed under a positive pressure of dry nitrogen, allowing for venting and then heated to 100 °C for 6 h. The reaction mixture is quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. After removal of dried solvent in vacuo, the residue is purified via flash column chromatography (silica, 2:1 hexanes/ethyl acetate to a 1:2 gradient) or preparative TLC (2:1 hexanes/ethyl acetate).

Full characterization data for **6**, **7**, **8**, and the Ugi product precursor to **8** have been published previously.[19] Characterization of the Ugi product precursors to 1,4-benzodiazepine-2,5-diones **9**−**20** was made difficult by extreme NMR peak broadening due to slow amide rotation, making NMR less than ideal for diagnostic purposes. Accordingly, all Ugi precursors to **9**−**20** were subjected to high resolution mass spectrometry after isolation and purification, and all exhibited satisfactory results.

1-Isocyanocyclohexene (2). Our procedure[19] and that of other groups[17,23,24] have been published previously.

(*R*,*S*)-7,8-Dimethoxy-3-isopropyl-4-(4-methoxybenzyl)-1,4-benzodiazepine-2,5-dione (9). See procedure A: yield 67%; IR (neat) 3220, 2965, 1684, 1611, 1514, 1252 cm^{-1}; ^1H NMR (400 MHz) δ 8.45 (s, 1), 7.45 (s, 1), 7.30 (d, 2, J = 8.6), 6.83 (d, 2, J = 8.7), 6.35 (s, 1), 5.09 (d, 1, J = 14.4), 4.46 (d, 1, J = 14.4), 3.93 (s, 3), 3.87 (s, 3), 3.75 (s, 3), 3.60 (dd, 1, J = 11.5, 1.3), 1.76 (dqq, 1, J = 6.6, 6.6, 6.6), 0.84 (d, 3, J = 6.6), 0.65 (d, 3, J = 6.6). ^{13}C NMR (101 MHz) δ 171.4, 165.8, 159.2, 152.4, 146.1, 130.2, 129.0, 128.7, 118.7, 113.9, 112.6, 102.6, 71.1, 56.2, 56.1, 55.2, 54.8, 27.2, 19.7, 19.4; HRMS (EI) m/z (M^+) calcd 398.1842, found 398.1837.

(*R*,*S*)-3-Isopropyl-4-(4-methoxybenzyl)-7-nitro-1,4-benzodiazepine-2,5-dione (10). See procedure A: yield 53%; IR (neat) 2965, 2928, 1696, 1618, 1512, 1339, 1248 cm^{-1}; ^1H NMR (400 MHz) δ 8.92 (d, 1, J = 2.7), 8.63 (s, 1), 8.28 (dd, 1, J = 8.8, 2.7), 7.30 (d, 2, J = 8.7), 6.99 (d, 1, J = 8.8), 6.85 (d, 2, J = 8.7), 5.15 (d, 1, J = 14.3), 4.46 (d, 1, J = 14.3), 3.78 (s, 3), 3.68 (dd, 1, J = 11.7, 1.2), 1.66 (m, 1), 0.84 (d, 3, J = 6.6), 0.70 (d, 3, J = 6.5). ^{13}C NMR (101 MHz) δ 171.4, 164.0, 159.5, 144.3, 139.5, 130.3, 128.0, 127.9, 127.4, 127.0, 120.5, 114.1, 70.4, 55.2, 54.9, 28.1, 19.6, 19.3; HRMS (EI) m/z (M^+) calcd 383.1481, found 383.1480.

(*R*,*S*)-1-Methyl-3-(4-methylphenyl)-4-(2-phenylethyl)-1,4-benzodiazepine-2,5-dione (11). See procedure A: yield 17%; IR (neat) 2924, 1669, 1642, 1476 cm^{-1}; ^1H NMR (400 MHz) δ 7.59 (dd, 1, J = 7.8, 1.5), 7.31 (d, 4, J = 4.4), 7.23 (m, 1), 7.18 (td, 1, J = 8.1, 1.5), 6.97 (t, 1, J = 7.8), 6.83 (d, 3, J = 8.0), 6.78 (d, 2, J = 8.0), 5.51 (s, 1), 4.29 (ddd, 1, J = 13.5, 10.5, 6.1), 3.89 (ddd, 1, J = 13.5, 10.5, 5.4), 3.43 (s, 3), 3.16 (ddd, 1, J = 13.2, 10.5, 5.3), 3.03 (ddd, 1, J = 13.3, 10.5, 6.1), 2.14 (s, 3); HRMS (EI) m/z (M^+) calcd 384.1838, found 384.1827.

(*R*,*S*)-3-(4-(3-Isopropyl-1-methyl-1,4-benzodiazepine-2,5-dione) propanoic Acid Ethyl Ester (12). See procedure B: yield 50%; IR (neat) 2965, 2928, 1734, 1669, 1642, 1478 cm^{-1}; ^1H NMR (400 MHz) δ 7.81 (dd, 1, J = 7.8, 1.6), 7.51 (td, 1, J = 7.8, 1.6), 7.28−7.25 (m, 1), 7.14 (d, 1, J = 8.0), 4.45 (m, 1), 4.15 (q, 2, J = 7.0), 3.71 (d, 1, J = 11.5), 3.40 (m, 1), 3.40 (s, 3), 2.72 (t, 2, J = 7.5), 1.26 (t, 3, J = 7.2), 1.35 (m, 1), 0.81 (d, 3, J = 6.5), 0.77 (d, 3, J = 6.6); HRMS (EI) m/z (M^+) calcd 332.1736, found 332.1740.

(*R*,*S*)-3-(4-Methyl phenyl)-4-(2-phenylethyl)-1-phenyl-1,4-benzodiazepine-2,5-dione (13). See procedure B: yield 53%; IR (neat) 3029, 2924, 1678, 1644, 1455, 1352 cm^{-1}; ^1H NMR (400 MHz) δ 7.64 (dd, 1, J = 7.1, 2.4), 7.48−7.20 (m, 10), 6.98−6.90 (m, 6), 6.38 (dd, 1, J = 8.0, 1.9), 5.63 (s, 1), 4.39 (ddd, 1, J = 13.4, 9.9, 6.8), 3.93 (ddd, 1, J = 13.5, 10.0, 5.1), 3.17 (ddd, 1, J = 13.4, 9.9, 5.1), 3.06 (ddd, 1, J = 13.3, 10.0, 6.8), 2.17 (s, 3). ^{13}C NMR (101 MHz) δ 169.1, 166.8, 140.8, 139.1, 138.0, 137.2, 131.3, 130.6, 130.4, 130.2, 129.4, 129.1, 128.9, 128.5, 128.4, 127.8, 126.5, 125.3, 124.0, 123.8, 68.1, 52.3, 34.3, 20.9; HRMS (EI) m/z (M^+) calcd 446.1994, found 446.1992.

(*R*,*S*)-3-(4-(7-Nitro-3-phenyl-1,4-benzodiazepine-2,5-dione) propanoic acid ethyl ester (14). See procedure B: yield 54%; IR (neat) 3349, 1686, 1624, 1318 cm^{-1}; ^1H NMR (500 MHz) δ 8.11 (d, 1, J = 2.6), 8.07 (dd, 1, J = 9.0, 2.6), 7.49−7.44 (m, 5), 6.66 (d, 1, J = 9.0), 5.85 (s, 1), 3.91 (q, 2, J = 7.0), 3.64−3.56 (m, 2), 2.19 (m, 1), 2.00 (m, 1), 1.09 (t, 3, J = 7.1). ^{13}C NMR (126 MHz) δ 171.8, 170.7, 169.6, 149.8, 137.9, 133.8, 129.9, 129.6, 129.5, 126.9, 124.4, 119.2, 114.6, 60.7, 34.0, 29.7, 13.9, 9.8; HRMS (EI) m/z [$(M + H)^+$] calcd 398.1352, found 398.1349.

(*R*,*S*)-3-(4-(7-Iodo-3-phenyl-1,4-benzodiazepine-2,5-dione)propanoic Acid Ethyl Ester (15). See procedure B: yield 50%; IR (neat) 3222, 1730, 1688, 1636, 1476 cm^{-1}; ^1H NMR (400 MHz) δ 8.57 (s, 1), 8.03 (d, 1, J = 1.8), 7.45 (dd, 1, J = 8.3, 1.7), 7.18−7.03 (m, 5), 6.47 (d, 1, J = 8.4), 5.52 (s, 1), 4.30 (m, 1), 4.09 (q, 2, J = 6.5), 4.04−3.97 (m, 1), 3.84 (t, 2, J = 6.5), 1.21 (t, 3, J = 7.1); ^{13}C NMR (101 MHz) δ 171.3, 171.0, 165.7, 140.9, 139.5, 133.7, 132.7, 129.0, 128.7, 128.2, 124.4, 121.5, 88.1, 67.8, 61.0, 48.0, 33.3, 14.1; HRMS (EI) m/z (M^+) calcd 478.0390, found 478.0393.

(*R*,*S*)-4-Benzyl-3-(2-pyridyl)-1,4-benzodiazepine-2,5-dione (16). See procedure B. Yield: 55%; IR (neat) 3225, 3063, 1694, 1636, 1485 cm^{-1}; ^1H NMR (500 MHz) δ 9.27 (s, 1), 8.23 (d, 1, J = 4.3), 7.73 (dd, 1, J = 7.9, 1.3), 7.58 (d, 2, J = 7.3), 7.39−7.28 (m, 4), 7.18 (dt, 1, J = 7.2, 1.4), 6.98 (t, 1, J = 7.3), 6.91 (dd, 1, J = 7.4, 4.9), 6.83 (d, 1, J = 8.0), 6.79 (d, 1, J = 7.8), 5.50 (s, 1), 5.27 (d, 1, J = 14.4), J = 5.02 (d, 1, J = 14.4); ^{13}C NMR (126 MHz) δ 171.8, 167.2, 154.0, 148.6, 136.4, 136.2, 134.8, 132.0, 130.9, 129.1, 128.9, 128.1, 127.1, 124.4, 122.4, 120.3, 119.6, 67.5, 54.1; HRMS (EI) m/z [$(M + H)^+$] calcd 344.1399, found 344.1399.

(*R*,*S*)-3-ethyl-4-hexyl-1,4-benzodiazepine-2,5-dione (17). See procedure B: yield 83% of a 1.8:1 mixture of conformational isomers; IR (neat) 3222, 3957, 2930, 1690, 1636, 1485. NMR data are listed for each isomer, when resonances from each can be identified. ^1H NMR (400 MHz) (major) δ 9.30 (s, 1), 7.94 (t, 1, J = 6.6), 7.43 (m, 1), 7.27−7.19 (m, 1), 6.99 (t, 1, J = 8.0), 4.12−3.98 (m, 1), 3.94 (t, 1, J = 8.4), 3.34−3.27 (m, 1), 1.66−1.47 (m, 4), 1.30−1.25 (m, 6), 0.89 (t, 3, J = 7.5), 0.85 (m, 3); (minor) δ 9.05 (s, 1), 7.94 (t, 1, J = 6.6), 7.43 (m, 1), 7.27−7.19 (m, 1), 6.99 (t, 1, J = 8.0), 4.12−3.98 (m, 1), 3.86 (t, 1, J = 7.3), 3.14 (m, 1), 2.19 (m, 1), 1.90 (m, 1), 1.66−1.47 (m, 3), 1.30−1.25 (m, 5), 0.98 (t, 3, J = 7.2), 0.91−0.83 (m, 3); ^{13}C NMR (101 MHz) (major) δ 172.8, 165.6, 134.6, 132.3, 131.6, 127.0, 124.7, 119.8, 66.4, 51.7, 31.5, 28.0, 26.4, 22.5, 14.0, 10.8;

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(minor) δ 172.1, 168.2, 135.7, 132.1, 131.3, 127.8, 125.1, 120.3, 57.0, 42.5, 31.4, 28.5, 26.6, 22.6, 19.5, 11.2; HRMS (EI) *m/z* (M^+) calcd 288.1838, found 288.1840.

(*R*,*S*)-3-hexyl-4-decyl-1,4-benzodiazepine-2,5-dione (18). See procedure B: yield 56% of a 1.8:1 mixture of conformational isomers; IR (neat) 3222, 2926, 2855, 1686, 1640, 1622. NMR data are listed for each isomer, when resonances from each can be identified. ^{1}H NMR (400 MHz) (major) δ 8.62 (s, 1), 7.94 (t, 1, J = 6.3), 7.47−7.41 (m, 1), 7.28−7.21 (m, 1), 6.94 (d, 1, J = 8.1), 4.10−4.01 (m, 1), 4.00 (t, 1, J = 8.2), 3.33−3.26 (m, 1), 1.9−1.1 (m, 26), 0.88−0.79 (m, 6); (minor) δ 8.41 (s, 1), 7.94 (t, 1, J = 6.3), 7.47−7.41 (m, 1), 7.28−7.21 (m, 1), 6.96 (d, 1, J = 8.1), 4.10−4.01 (m, 1), 3.92 (t, 1, J = 7.3), 3.16−3.09 (m, 1), 2.12 (m, 1), 1.9−1.1 (m, 25), 0.88−0.79 (m, 6); ^{13}C NMR (101 MHz) (major) δ 172.6, 165.6, 134.5, 132.3, 131.6, 127.1, 124.8, 119.6, 65.0, 51.6, 31.9, 31.3, 29.5, 29.3, 29.2, 28.1, 26.8, 26.1, 22.7, 22.3, 14.1, 13.9; (minor) δ 171.9, 168.1, 135.5, 132.1, 131.4, 127.9, 125.2, 120.2, 55.5, 42.6, 31.9, 31.5, 29.5, 29.3, 29.1, 28.6, 27.0, 26.6, 26.2, 22.7, 22.5, 14.1, 14.0; HRMS (EI) *m/z* (M^+) calcd 400.3090, found 400.3090.

(*R*,*S*)-4-Isobutyl-3-(2-phenylethyl)-1,4-benzodiazepine-2,5-dione (19). See procedure B: yield 71% of a 2:1 mixture of conformational isomers; IR (neat) 3221, 2961, 1686, 1624, 1485. NMR data are listed for each isomer, when resonances from each can be identified. ^{1}H NMR (400 MHz) (major) δ 9.38 (s, 1), 7.98 (t, 1, J = 8.9), 7.44 (m, 1), 7.27−7.14 (m, 5), 7.01 (m, 2), 4.05−3.98 (m, 2), 2.92 (dd, 1, J = 13.3, 6.5), 2.59 (m, 2), 2.03−1.78 (m, 3), 0.94 (d, 3, J = 6.2), 0.89 (d, 3, J = 6.5); (minor) δ 9.26 (s, 1), 7.98 (t, 1, J = 8.9), 7.44 (m, 1), 7.27−7.14 (m, 5), 7.01 (m, 2), 4.13−4.07 (m, 2), 2.97 (dd, 1, J = 15.2, 4.9), 2.78−2.65 (m, 1), 2.49−2.37 (m, 1), 2.21−2.11 (m, 1), 2.03−1.78 (m, 2), 0.90 (d, 3, J = 6.2), 0.82 (d, 3, J = 6.5); ^{13}C NMR (101 MHz) (major) δ 172.6, 166.1, 139.6, 134.6, 132.4, 131.6, 128.5, 128.2, 126.9, 126.3, 124.9, 119.8, 64.5, 58.6, 32.2, 30.9, 27.2, 20.1, 19.7; (minor) δ 172.1, 168.5, 140.4, 135.7, 132.2, 131.5, 128.5, 128.3, 127.6, 126.3, 125.1, 120.4, 54.8, 49.4, 32.7, 28.1, 27.6, 20.2, 19.7; HRMS (EI) *m/z* $(M)^+$ calcd 336.1838, found 336.1837.

Spirobenzodiazepinedione (20). See procedure B: yield 54%; IR (neat) 3227, 2957, 1676, 1615, 1512, 1246 cm^{-1}; ^{1}H NMR (400 MHz) δ 8.37 (s, 1), 7.99 (dd, 1, J = 7.8, 1.0), 7.46 (td, 1, J = 7.6, 1.1), 7.24 (t, 1, J = 7.5), 7.19 (d, 2, J = 8.5), 6.90 (d, 1, J = 8.0), 6.83 (d, 2, J = 8.6), 4.99 (d, 1, J = 15.8), 4.72 (d, 1, J = 16.3), 3.76 (s, 3), 2.77 (d, 1, J = 9.8), 1.99−1.51 (m, 7); ^{13}C NMR (101 MHz) δ 173.1, 169.0, 158.5, 135.3, 132.5, 131.5, 130.8, 128.4, 127.7, 124.7, 119.2, 113.9, 69.4, 55.2, 49.8, 38.0, 34.4, 24.1, 23.7; HRMS (EI) *m/z* $(M)^+$ calcd 350.1630, found 350.1627.

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Supporting Information Available: ^{1}H NMR spectra of **9**-**20** (12 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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