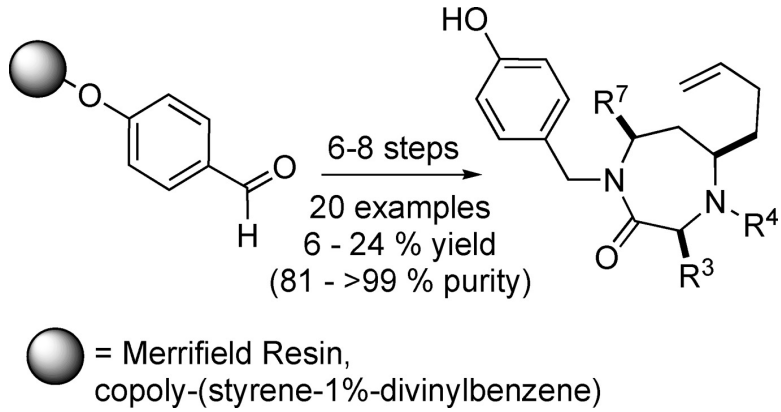
JOURNAL OF combinatorial CHEMISTRY

Article

1,3,5-Tri- and 1,3,4,5-Tetra-Substituted 1,4-Diazepin-2-one Solid-Phase Synthesis

Hassan S. Iden, and William D. Lubell

J. Comb. Chem., **2008**, 10 (5), 691-699• DOI: 10.1021/cc8001052 • Publication Date (Web): 08 August 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

1,3,5-Tri- and 1,3,4,5-Tetra-Substituted 1,4-Diazepin-2-one Solid-Phase Synthesis

Hassan S. Iden and William D. Lubell*

Département de Chimie, Université de Montréal, C.P. 6128, Succursale Centre Ville, Montréal, Québec, Canada H3C 3J7

Received June 23, 2008

Solid-phase syntheses of 1,3,5-tri-substituted and 1,3,4,5-tetra-substituted 1,4-diazepin-2-ones **15**−**18** have been accomplished by employing inexpensive commercially available α- and β-amino acids on Wang resin. Reductive amination of the imine formed by condensation of Wang aldehyde resin respectively with β-alaninate **2** and β- homophenylalaninate **3**, followed by aminoacylation with a set of α-*N*-Boc amino acids (Phe ε-(*Z*)-Lys, and Leu) gave tertiary amide resins **7** and **8**. Exposure of resins **7** and **8** to an excess of vinyl magnesium bromide in the presence of copper cyanide gave the corresponding γ,δ-unsaturated ketone resins **9** and **10** by way of a cascade addition. Diazepinones were made by Boc deprotection and intramolecular reductive amination. To diversify the heterocycle, *N*-alkylation was performed using a series of alkyl halides. Alternatively, diazepinones **15e**−**g** were obtained from treatment of methyl β-alaninate resins **4** and **20** under similar copper-catalyzed cascade conditions to afford the γ,δ-unsaturated ketone **21**, which was acylated using α-*N*-Fmoc-amino acids (Phe, Trp, γ-(*t*-Bu)–Glu). Formation of diazepinones **15** followed a similar protocol, after Fmoc removal with piperidine. Cleavage of the heterocycles with TFA/TES 95:5 gave the N^1-*p*-hydroxybenzyl diazepinones **15**−**18** in overall isolated yields from 6 to 24% after purification in purities ranging from 81 to 100% according to LCMS analysis.

Introduction

1,4-Diazepin-2-ones are a class of privileged structures often used as peptide mimics for the discovery of novel bioactive small molecules.[1] Diazepinones have elicited a wide range of biological activities likely because of their potential to mimic γ- and β-turn peptide secondary structures.[2−4] For example, the 1,4-diazepin-2-one derivatives have been reported to possess anticonvulsant activity,[5] antibacterial activity against multidrug-resistant *Mycobacterium tuberculosis* strains,[6] antitumor properties,[7] and ability to block the lymphocyte function-associated antigen-1 (LFA-1)/immunoglobulin superfamily ICAM-1 receptor interaction[8] (Figure 1).[9−11]

Recently, we have reported solution-phase routes to access enantiopure 3,5-disubstituted and 1,3,5-trisubstituted 1,4-diazepin-2-ones.[4,12] These routes have involved addition of vinyl Grignard reagent to α-aminoacyl β-amino ester starting materials to afford γ,δ-unsaturated ketone precursors to the heterocycle, which was formed by nitrogen deprotection, followed by reductive amination.

Numerous literature reports have concerned the solid-phase synthesis of 1,4-benzodiazepinones.[13] To the best of our knowledge less attention has been devoted to the synthesis of 1,4-diazepin-2-one on solid support. For example, diazepinones were made by lactam formation between N^1 and C^2.[14] Moreover a library of 1,4-diazepin-2-ones was prepared from α-amino acids linked to Rink-amide MBHA resin by a route featuring Michael addition to methyl vinyl ketone, acylation with a second amino acid, and reductive amination between N^4 and C^5 to yield diazepinone.[8]

New solid-phase methodology for making 1,4-diazepin-2-ones is thus desired for creating biologically active peptide mimics. With the goals of adding a variety of pharmacophores at different positions along the diazepinone ring and providing libraries for structure−activity relationship study, we have developed solid-phase processes based on experience from our previous solution-phase syntheses.[12]

Results and Discussion

Resin-bound aldehyde (Wang aldehyde, 1 mmol/g, Scheme 1) **1** was prepared from Merrifield resin as previously described.[15] Conversion of the aldehyde **1** to supported secondary amine resins **4** and **5** was achieved by reductive amination of the imine, produced by treating aldehyde resin **1** with β-alanine and β-homophenylalanine methyl ester hydrochlorides, respectively, using sodium triacetoxyborohydride in DMF containing a catalytic amount of acetic acid.[16] The reductive amination reaction was monitored by a dinitrophenyl hydrazine test,[17] which indicated the disappearance of aldehyde. Moreover, IR spectroscopy could be used to follow the disappearance of the aldehyde stretch at 1681 cm^{-1}. The respective loadings of amine resin **4** and **5** were determined by measurement of the nitrogen content using elemental analysis to be 1.0 and 0.84 mmol/g. The α-amino acid component was then added by coupling Boc-Phe and Boc-Leu to amine resin **4** and α-Boc-(ε-Cbz)Lys and Boc-Leu to resin **5** using HATU and DIEA in DMF.[18]

* To whom correspondence should be addressed. E-mail: lubell@chimie.umontreal.ca.

10.1021/cc8001052 CCC: $40.75
Published on Web 08/08/2008

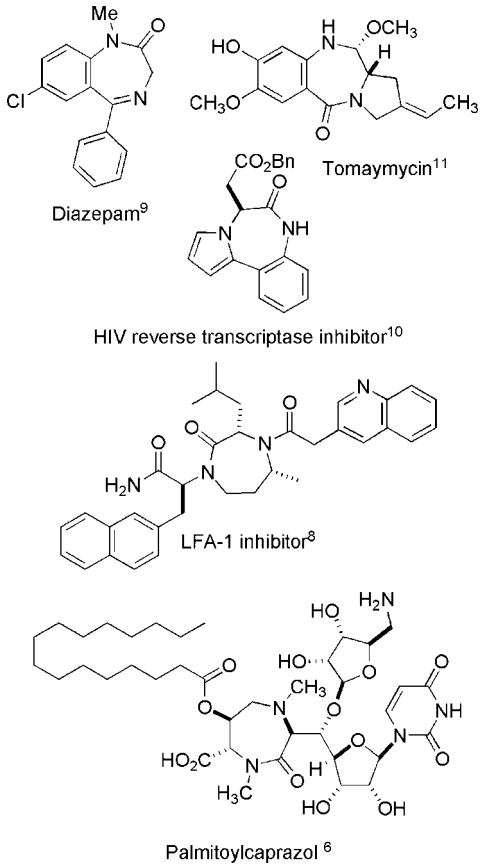


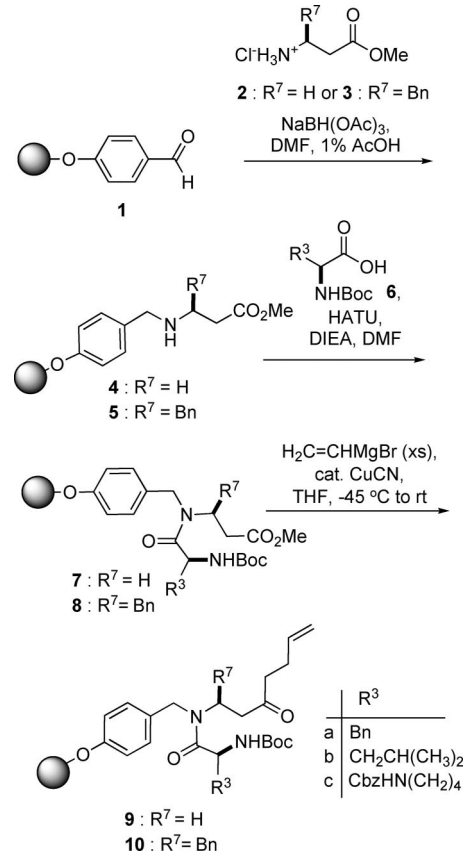
Figure 1. Representative bioactive 1,4-diazepin-2-ones.

The α-amino acids were chosen to examine the influence of aromatic, alkyl branched, and linear alkyl side-chains on the reaction sequence, as well as to study the compatibility of a remote carbamate on our methodology. The progress of the reaction was monitored by the chloroanil test.[19] Resin-bound γ,δ-unsaturated ketones **9** and **10** were synthesized by treating tertiary amide methyl ester resins **7** and **8** with freshly prepared vinyl magnesium bromide (2000 mol %) in the presence of copper cyanide (500 mol %) in THF at −45 °C with warming to room temperature.[20] Ketone formation was indicated by the strong carbonyl C═O stretching band at 1706−1709 cm^{-1} in the FT-IR spectrum of resins **9** and **10** compressed in KBr tablets; furthermore, the ester stretch at 1738 cm^{-1} disappeared.

Supported diazepinones **11**−**14** were prepared from linear ketones **9** and **10** by a sequence of reactions initiated by Boc group removal using TFA/DCM (1:1) or $SiCl_4$ (1 M, 2000 mol %) and phenol (3M, 6000 mol %) in DCM,[21] followed by neutralization of the TFA salt using triethylamine and intramolecular imine formation (Scheme 2). Imine reduction was accomplished using sodium cyanoborohydride in THF acidified with 1% acetic acid. The disappearance of the primary amine was monitored by the Kaiser test.[22] The ketone carbonyl stretch at 1708 cm^{-1} was no longer observed in the IR spectra of resins **11** and **12**.

Alkylation of the secondary amines **11** and **12** with a set of reactive alkyl halides was next explored to further diversify the heterocycle. Methyl iodide, benzyl bromide, propargyl bromide, and methyl bromo acetate were chosen to add alkyl, aryl, acetylene, and ester groups, respectively, to diazepinone; furthermore, the acetylene and carboxylate functions were

Scheme 1. γ,δ-Unsaturated Ketone Synthesis Using 4-Alkoxybenzaldehyde Resin **1**

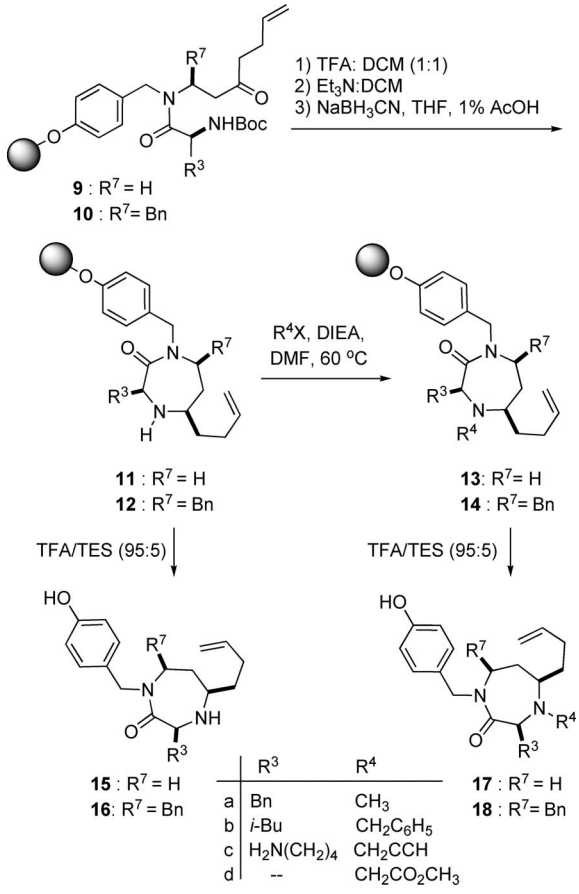


intended for later diversification chemistry by cycloaddition and peptide coupling, repectively. Incorporation of diversity at the N^4 position was initially attempted by exposing resins **11** and **12** to neat alkyl halides at 60 °C,[23] as well as alkyl halides in the presence of *N*, *N*–diisopropylethylamine at room temperature. However, incomplete conversion was observed by LCMS analysis of material after cleavage from resin. Heating resins **11** and **12** in a mixture composed of alkyl halide (1000 mol %) and diisopropylethylamine (1000 mol %) in DMF at 60 °C for 2 days pushed the alkylation to completion.

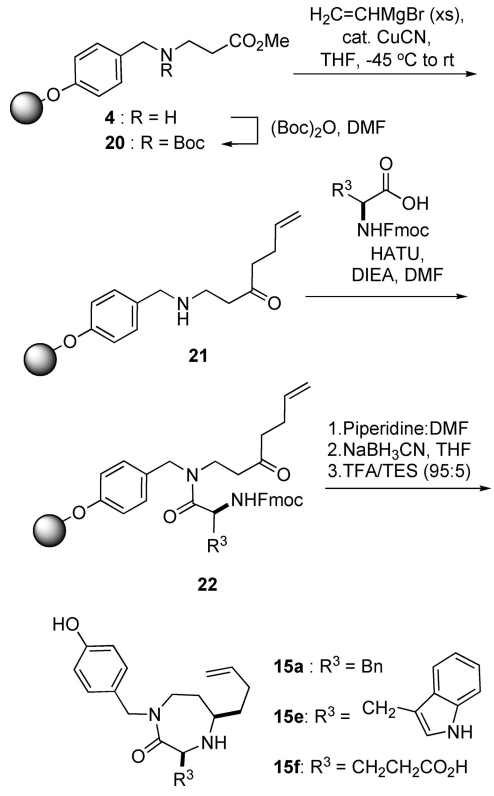
1,4-Diazepin-2-ones **15**−**18** were cleaved from the resin using 95:5 TFA/TES.[24] After resin filtration and washing, the filtrate and washes were evaporated to provide a residue that contained a major component of 50−90% purity as assessed by LCMS analysis, which showed masses corresponding to the *N*′-*p*-hydroxylbenzyl 1,4-diazepin-2-ones **15**−**18**. Crude products were typically purified by chromatography on silica gel to afford the diazepinone **15**−**18** in 6−24% overall yield based on the initial substitution levels of 1.0 and 0.84 mmol/g of resins **4** and **5**, respectively. The *N*-Cbz-protected lysine side-chain was only partially hydrolyzed after 24 h exposure to the conditions described above, and shaking was continued for another 24 h to ensure complete Cbz removal as monitored by TLC and LCMS; lysine-derived 1,4-diazepin-2-ones **16c** and **18(c**, **a**−**d)** were purified by preparative reversed-phase HPLC.

An alternative route for the solid-phase synthesis of 1,4-diazepin-2-one was next pursued to further expand the diversity of the α-amino acid component. Considering that

Scheme 2. 1,4-Diazepin-2-ones Synthesis



Scheme 3. Modified Strategy to Access 1,4-Diazepin-2-one



the cascade addition to ester **7** and **8** had restricted the α-amino acid side-chains to groups tolerant of vinyl Grignard reagent, we envisioned a strategy in which the synthesis of the γ,δ-unsaturated ketone preceded the amino acylation step. The copper-catalyzed cascade addition of vinyl Grignard reagent was thus performed directly on supported β-alanine methyl ester **4,** as well as its *N*-Boc counterpart **20**, which was prepared by treatment of ester **4** preswollen in DMF with a solution of $(Boc)_2O$ and DIEA in DMF (Scheme 3). No significant difference in yield was, however, observed for ketone **21** from both reaction sequences.

Amino acylation of amino ketone resin **21** was next performed using Fmoc-protected Phe, Trp, and (γ-*t*-Bu)Glu to compare and contrast the two methods by (a) synthesis of the same diazepinone that was made in the previously described process and (b) synthesis of analogs that were inaccessible by the previous route. α-(Fmoc)amino acids were coupled to resin **21** using HATU and DIEA in DMF, and the reaction conversion was monitored by the chloranil test. The Fmoc group was removed by treating resin **22** with piperidine/DMF (1:4, v:v). Imine formation, reductive amination, and cleavage of diazepinones **15a** and **15e−f** were performed as previously described. Diazepinone **15a** was made by the two strategies and isolated in 9% by Fmoc stategy and 18% by the Boc strategy. The Trp-derived diazepinone **15e** was isolated in 6% overall yield. Furthermore diazepinone **15f**, which was deemed inaccessible by the Boc strategy, because of the reactivity of the remote ester to the Grignard reaction conditions, was isolated as its TFA salt in 18% overall yield after purification by precipitation from ether.

In accordance with results in solution,[4,12] the diazepinones **15−18** were diastereoselectively prepared as single isomers, and the newly formed chiral center at C^5 was assigned a *cis*-relative stereochemistry with respect to the C^3 center. The cis assignment was confirmed by a NOESY experiment in which strong NOE was observed between the C^3, C^5, and C^7 protons of diazepinones **18(c**, **b**) and **18(c**, **d),** respectively.

In summary, efficient solid-phase syntheses of enantiopure 1,4-diazepin-2-ones have been achieved using two related strategies employing acid-labile 4-alkoxybenzaldehyde resin. The potential to make diazepinones on solid support with greater diversity at the 5−7 positions may be fulfilled by the employment of substituted β-amino esters and vinyl Grignard reagents; moreover, modification of the olefin of the 5-position butenyl chain may provide access to increased diversity.[25] Between the two routes, the Fmoc-protection strategy offers advantages for employing amino acids sensitive to Grignard reagents. γ,δ-Unsaturated ketone **21** and related homoallylic ketones derived from other β-amino esters may serve as common precursors for accessing 1,4-diazepinones, as well as other heterocyclic systems. This chemistry for the synthesis of 1,4-diazepin-2-ones merits further study for making γ-turn mimic libraries and studying peptide chemistry and biology.

General Procedures for the Synthesis of 1,4-Diazepin-2-ones

Anhydrous solvents (DCM, DMF, and THF) were obtained by passage through solvent filtration systems (Glass-Contour, Irvine, CA). Shaking was performed on a reciprocating shaker (SK-300 Jeio Tech). Melting points are

uncorrected. Mass spectral data and HRMS (ES and FAB) were obtained by the Centre Régional de Spectrométrie de Masse de l'Université de Montréal. Unless otherwise noted, ^{1}H (400/700 MHz) and ^{13}C (100/175 MHz) NMR spectra were recorded in $CDCl_3$ and CD_3OD. Chemicals shifts are reported in parts per million; coupling constants, *J*, are reported in hertz. The HPLC analyses of purity were performed on Gemini C18 column (5 μm, 150 × 4.6 mm) using a flow rate of 0.5 mL/min and an eluant of 80:20 A/B over 20 min. Semipreparative HPLC purifications were performed on a Gemini C18 column (5 μm, 250 × 22 mm) using a flow rate of 10.5 mL/min and a solvent system of 60:5 eluants A/B over 20 min. Eluant A and B were H_2O/0.1% formic acid and MeCN/0.1% formic acid, respectively. Analytical thin-layer chromatography (TLC) was performed by using glass-backed silica gel plates coated with a 0.2 mm thickness of silica gel. Flash column chromatography was performed with 230−400 mesh silica gel. Infrared spectra were taken on a PerkinElmer Spectrum apparatus. Unless otherwise noted, resins were swollen in the specified solvent for 15 min prior to the reaction and washed 2 min with each solvent in polyethylene tubes equipped with polyethylene frits and polyethylene stoppers and caps. Glassware was coated with aqua sil film and dried 1 h in the oven at 120 °C before being used for solid-phase reactions.

Synthesis of Secondary Amine Resin 4 and 5. The reductive amination on aldehyde resin **1** was performed as follows: in a polyethylene 20 mL tube charged with 1 g of aldehyde resin **1** (prepared according to ref 15), sodium triacetoxyborohydride (1.272 g, 6 mmol), and β-alanine methyl ester **2** (0.84 g, 6 mmol) or β-homophenylalanine methyl ester **3** (1.38 g, 6 mmol) were dissolved in a minimum volume of DMF buffered with 1% acetic acid. The reaction mixture was shaken by vortex. After 20 min, an aliquot of the resin was removed, rinsed with solvent, and examined by IR spectroscopy, which showed completion of the reaction by loss of the aldehyde band at 1680 cm^{-1} in the IR spectrum. Completion of the reaction was verified by a negative DNPH test. The resin was filtered, washed with DMF (3 × 5 mL), CH_3OH (3 × 5 mL), and DCM (3 × 5 mL) and dried under vaccum.

Resin 4: IR (KBr pellet) 3404, 1731 cm^{-1}; loading of resin **4** 1.0 mmol/g according to nitrogen microanalysis; found C 85.03, H 7.67, N 1.38.

Resin 5: IR (KBr pellet) 3422, 1728 cm^{-1}; loading of resin **5** 0.84 mmol/g according to nitrogen microanalysis; found C 84.47, H 6.88, N 1.16.

Synthesis of Tertiary Amide Resins 7, 8, and 22. The *N*-Boc- and Fmoc-amino acids (400 mol %) were dissolved in a minimum amount of DMF, cooled to 0 °C, treated with DIEA (800 mol %), followed by HATU (400 mol %), stirred for 5 min under argon, and transferred to a polyethylene 20 mL tube containing the swollen secondary amine resin (**4**, **5** or **21**, 1 g) in DMF (6 mL). The reaction mixture was shaken for 24 h at room temperature and filtered, and the resin was washed with DMF (3 × 20 mL), THF (3 × 20 mL), MeOH (3 × 20 mL), and DCM (3 × 20 mL). Completion of the reaction was verified by the chloranil test which showed colorless beads indicating absence of the secondary amine. IR: 3440, 1737 cm^{-1} for resins **7** and **8**; 3412, 1714 cm^{-1} for resin **22**.

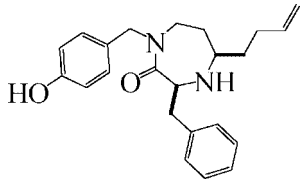
Homoallylic Ketone Resins 9, 10, and 20. A flame-dried, three-neck round-bottom flask with a mechanical stirrer and an argon inlet was charged with copper cyanide (500 mol%) in THF (5 mL), cooled to −45 °C, treated with a freshly prepared solution of vinyl magnesium bromide (2000 mol%, *c* 1 M in THF), stirred for 30 min, and treated portion-wise with resin swollen in THF (1 g, **4**, **7**, **8**, and **20**). The mixture was stirred for 2 h at −45 °C; the bath was removed, and stirring was continued for another 1 h at room temperature. The resin mixture was cooled back to −45 °C and quenched with methanol, followed by 1 N HCl until pH 3. The mixture was allowed to warm to room temperature and was shaken vigorously for 20 min. The resin was filtered and washed with water (3 × 60 mL), DMF (3 × 20 mL), THF (3 × 20 mL), CH_3OH (3 × 20 mL), and DCM (3 × 20 mL) and then dried under under vacuum to give ketone resin. The formation of ketone was confirmed by the IR spectra in which a strong carbonyl stretch at 1709 cm^{-1} was observed for ketones **9** and **10**. A large stretch at 1672 cm^{-1} was noted for resin **21**, and as described below, after acylation with Fmoc-amino acid, the ketone carbonyl stretch was distinctly observed at 1709 cm^{-1}.

Diazepinone Resins 11 and 12. Ketone resins **9** and **10** (500 mg) were exposed for 5 min to a solution of TFA/DCM 1:1 to cause Boc deprotection, which was qualitatively indicated by a positive blue color Kaiser test. The resin was then rinsed with DCM/Et_3N 9:1 (3 × 20 mL), DCM (3 × 20 mL), and THF (3 × 20 mL). The deprotected resin was swollen in THF (4 mL), acidified with 40 μL of acetic acid, and treated with sodium cyanoborohydride (1000 mol %). The reaction was continued until the Kaiser Test showed colorless beads. The resin was rinsed with THF (3 × 20 mL), DMF (3 × 20 mL), and DCM (3 × 20 mL). In the IR spectra of resins **11** and **12**, the ketone stretch was no longer observed at 1711 cm^{-1}.

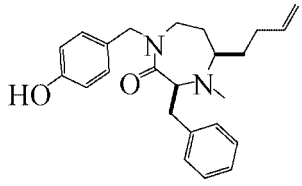
Diazepinones 15a, 15e and 15f. Ketone resin **22** (500 mg) was first exposed for 15 min to a piperidine/DMF solution (1:4, v:v) to cause Fmoc deprotection, which was qualitatively indicated by a positive blue color Kaiser test. The resin was rinsed with DMF (3 × 20 mL), DCM (3 × 20 mL), and THF (3 × 20 mL). The deprotected resin was swollen in THF (4 mL), acidified with 40 μL acetic acid, and treated with sodium cyanoborohydride (600 mol %). The reaction was continued until the Kaiser test showed colorless beads. The resin was rinsed with THF (3 × 20 mL), DMF (3 × 20 mL), and DCM (3 × 20 mL). In the IR spectra of resins the ketone stretch was no longer observed at 1711 cm^{-1}. Diazepinones **15e−g** were then cleaved with TFA as described below.

Cleavage from the Resin. Resins **11−14** (125 mg) were treated with a TFA/TES solution (19:1) at room temperature for 16 h. The resin was filtered, washed once with TFA, and the combined filtrates were concentrated under vacuum to dryness. The residue was purified as described below by flash column chromatography, precipitation as a TFA salt, or by preparative HPLC to yield 1,4-diazepin-2-ones **15−18**.

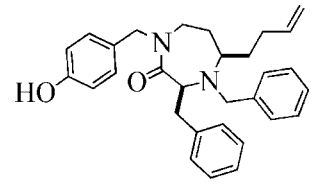
N^4-Alkylated Diazepin-2-one Resins 13 and 14. Diazepinone resins **11** and **12**(125 mg) were placed in four separate glass tubes equipped with stopcocks. The resins were swollen in dry DMF (3 mL) and treated with alkyl halides (1000 mol %) and Hünig's base (1000 mol %) at 60 °C for 2 days. The resins were then filtered and washed with DMF (3 × 5 mL), THF (3 × 5 mL), CH_3OH (3 × 5 mL), and DCM (3 × 5 mL) and then dried under vacuum to yield the N_4-alkylated diazepin-2-one resins. Completion of the reaction was monitored by LCMS after cleavage of a resin aliquot from the reaction mixture using the conditions described above.



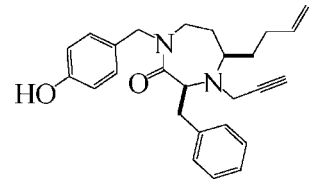
(3*S*,5*S*)-3-Benzyl-5-but-3-enyl-1-(4-hydroxybenzyl)-[1,4]diazepin-2-one 15a. Diazepinone resin (125 mg) was swollen in DCM (4 mL) in a 10 mL polyethylene tube and treated with 4 mL of a mixture of TFA/TES (95:5) at room temperature for 24 h. The resin was filtered and washed with TFA (2 × 5 mL) and DCM (2 × 5 mL). The filtrate and washings were concentrated under vacuum to a residue that was purified by flash column chromatography using 50% EtOAc/hexane as eluent to afford diazepinone **15a** (8 mg, 18% overall yield) in 85% purity as colorless oil: R_f 0.25 (50% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29−1.47 (m, 2H), 1.6−1.93 (m, 4H), 2.02−2.22 (m, 4H), 3.20−3.24 (br d, 1H), 3.75−3.82 (br q, 1H), 4.50−4.62 (m, 2 H), 5.02−5.10 (m, 2H), 5.75−5.83 (m, 1H), 6.70−7.39 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 165.7, 156.5, 135.8, 135.6, 129.0, 128.8, 127.8, 126.5, 126.2, 114.8, 114.6, 60.4, 58.6, 43.9, 34.7, 32.0, 30.1, 28.6; HRMS (EI) *m/z* 365.2228 $[M + H]^+$, calcd for $C_{23}H_{28}N_2O_2$ 365.2224; $[\alpha]_D^{20}$ −7.0 (*c* 1.4, $CHCl_3$).



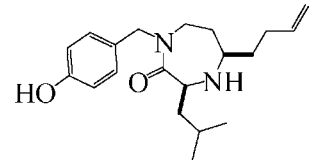
(3*S*,5*S*)-3-Benzyl-4-methyl-5-but-3-enyl-1-(4-hydroxybenzyl)-[1,4]diazepin-2-one 17(a, a). After purification by column chromatography using 40% EtOAc/hexane, **17**(**a**, **a**) was isolated in 93% purity as a colorless oil (10 mg, 19% overall yield): R_f 0.4 (40% EtOAc/petroleum ether); ^{1}H NMR (700 MHz, $CDCl_3$) δ 1.89−2.10(m, 4H), 2.54(s, 3H), 3.32−3.38(m,2H),3.63−3.68(m,2H),3.93(br,1H),4.49−4.93(dd, J = 14.7, 2H), 4.50(d, J = 10.5, 1H), 5.00−5.03(m, 2H), 5.68(m, 1H), 6.80−7.43(m, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) 164.5, 156.2, 135.7, 135.5, 130.1, 128.6, 127.9, 127.1, 116.9, 116.0, 67.1, 66.7, 33.4, 31.9, 31.2, 30.3, 29.7, 29.3, 26.7; HRMS (EI) *m/z* 379.2380 $[M + H]^+$, calcd for $C_{24}H_{30}N_2O_2$ 379.2374; $[\alpha]_D^{20}$ 12.3 (*c* 0.7, $CHCl_3$).



(3*S*,5*S*)-1-(4-Hydroxybenzyl)-3,4-dibenzyl-5-butyl-3-enyl-1-[1,4]-diazepin-2-one 17(a, b). Diazepinone **17**(**a**, **b**) was isolated as a colorless oil (13 mg, 24% overall yield) in 92% purity after purification by column chromatography using 40% EtOAc/hexane: R_f 0.47 (40% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30−1.36(m, 2H),1.41−1.52(m, 2H), 1.85−1.91(q, J = 7.2, 2H), 2.79−2.96(m, 2H), 3.13−3.33(m, 2H), 3.49−3.70(m, 3H), 4.03(t, J = 6.9, 1H), 4.37−4.41(br d, 1H), 4.71−4.82(m, 3H), 5.45−5.54(m, 1H), 6.80−7.29(m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 156.4, 142.8, 141.2, 139.1, 130.7, 130.3, 130.1, 129.2, 128.9, 127.3, 126.6, 116.4, 115.4, 69.3, 68.8, 54.3, 52.0, 49.0, 48.7, 38.5, 35.1, 31.6, 28.7; HRMS (EI) *m/z* 455.2693 $[M + H]^+$, calcd for $C_{30}H_{34}NO$ 455.2686; $[\alpha]_D^{20}$ −20.5 (*c* 0.8, $CHCl_3$).

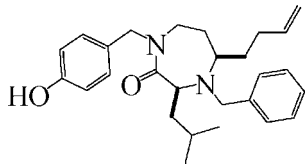


(3*S*,5*S*)-1-(4-Hydroxybenzyl)-3-benzyl-4-(propargyl)-5-(butyl-3-enyl)-[1,4]-diazepin-2-one 17(a, c). Alkyne **17**(**a**, **c**) was isolated as a colorless oil (6.5 mg, 13% overall yield) in 100% purity; the title compound was purified by column chromatography using 40% EtOAc/hexane: R_f 0.4 (40% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61−2.13(m, 4H), 2.71(br m, 1H), 3.07−3.35(m, 4H), 3.48−3.53(br q, 1H), 3.72−3.77(m, 1H), 4.70−4.83(m, 2H), 5.3(s, 2H), 6.01(m, 1H), 6.80−7.61(m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 175.0, 156.3, 140.9, 139.3, 130.61, 130.1, 128.8, 126.7, 116.5, 115.4, 84.4, 71.6, 68.4, 67.1, 54.3, 51.9, 48.7, 36.9, 34.1, 32.0, 31.1, 29.2; HRMS (EI) *m/z* 403.2380 $[M + H]^+$, calcd for $C_{26}H_{30}N_2O_2$ 403.2369; $[\alpha]_D^{20}$ −45.6 (*c* 0.5, $CHCl_3$).

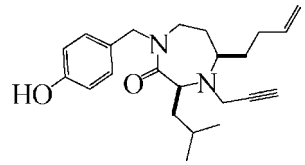


(3*S*,5*S*)-1-(4-Hydroxybenzyl)-5-(but-3-enyl)-3-isobutyl-[1,4]-diazepin-2-one 15b. Diazepinone **15b** was isolated as a colorless oil (9 mg, 21% overall yield) in 96% purity after purification by column chromatography using 20% EtOAc/petroleum ether: R_f 0.11 (20% EtOAc/ petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91−0.93 (d, J = 8.2, 3H), 0.95−0.97(d, J = 8.2, 3H), 1.38(m, 2H), 1.53−1.75(m, 4H), 1.78−1.85(m, 2H), 2.06−2.12(q, J = 8.0, 2H), 2.82(m, 1H), 3.31(m, 1H), 3.53(m, 2H), 4.56(s, 2H), 4.98(brq, 2H), 5.31(s, 1H), 5.74(m, 1H), 6.78(d, J = 9,0, 2H), 7.10(d, J = 9.0, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 156.4, 138.6, 130.5,

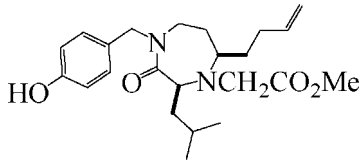
129.8, 116.5, 116.1, 61.0, 58.4, 54.3, 51.8, 47.3, 41.6, 36.4, 31.0, 25.6, 24.0, 23.1; HRMS (EI) *m/z* 331.2378 $[M + H]^+$, calcd for $C_{20}H_{31}N_2O_2$ 331.238; $[\alpha]_D^{20}$ −15 (*c* 0.4, $CHCl_3$).



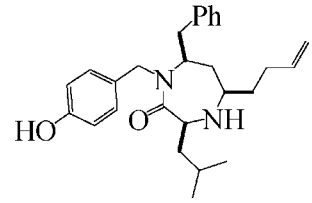
(3*S*,5*S*)-1-(4-Hydroxybenzyl)-4-benzyl-5-(but-3-enyl)-3-isobutyl-[1,4]-diazepin-2-one 17(b, b). Diazepinone **17(b, b)** was isolated as a colorless oil (10 mg, 19% overall yield) in 88% purity after purification by column chromatography using 20% EtOAc/petroleum ether: R_f 0.21(20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80−0.81 (d, J = 3.88, 3H), 0.82−0.83(d, J = 3.88, 3H), 1.26−1.55(m, 2H), 1.58−1.79(m, 6H), 1.97(m, 2H), 3.4(m, 1H), 3.76(m, 4H), 4.36 (d, J = 18.8, 1H), 4.83−4.91(m, 3H), 5.57(m, 1H), 6.85−7.91(m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 157.2, 137.4, 130.8, 130.3, 129.9, 129.5, 129.4, 129.1, 116.8, 116.6, 70.2, 66.4, 52.5, 50.2, 47.6, 39.0, 34.2, 31.6, 28.6, 26.3, 23.6, 22.7; HRMS (EI) *m/z* 421.2849 $[M + H]^+$, calcd for $C_{27}H_{36}N_2O_2$ 421.2843; $[\alpha]_D^{20}$ 16.5 (*c* 0.7, $CHCl_3$).



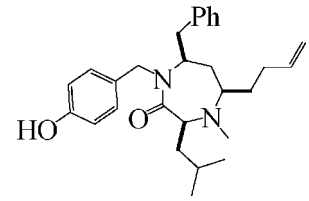
(3*S*,5*S*)-1-(4-Hydroxybenzyl)-5-(but-3-enyl)-3-isobutyl-4-(prop-2-ynyl)-[1,4]-diazepan-2-one 17(b, c). Alkyne **17(b, c)** was isolated as a colorless oil (8 mg, 18% overall yield) in 98% purity after purification by column chromatography using 20% EtOAc/petroleum ether: R_f 0.11 (20% EtOAc/ petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87−0.90 (d, J = 8, 3H), 0.82−0.83 (d, J = 8, 3H), 1.26(s, 2H), 1.66−1.96(m, 4H), 2.11(s, 2H), 2.15(m, 1H), 3.23(s, 2H), 3.29(br s, 1H), 3.51−3.56(m, 2H), 4.38−4.61(m, 2H), 5.80 (br q, 2H), 5.0(m, 2H), 5.81(m, 1H), 6.8(d, J = 11.2, 2H), 7.10(d, J = 11.2, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 156.4, 139.2, 130.5, 130.0, 116.5, 115.7, 71.5, 67.4, 63.8, 51.9, 48.6, 39.4, 34.2, 32.0, 31.6, 30.5, 29.5, 25.1, 24.3, 22.8; HRMS (EI) *m/z* 369.2536 $[M + H]^+$, calcd for $C_{23}H_{32}N_2O_2$ 369.2529; $[\alpha]_D^{20}$ −22.5 (*c* 0.6, $CHCl_3$).



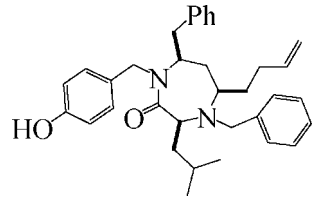
4-Methyl Acetate-(2*S*,7*S*)-4-(4-hydroxybenzyl)-7-3(butyl)-2-isobutyl-3-[1,4]-diazepin-2-one 17(b, d). Ester **17(b, d)** was isolated as a colorless oil (11 mg, 23% overall yield) in 97% purity after purification by column chromatography using 20% EtOAc/petroleum ether: R_f 0.21 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88−0.90(d, J = 8.0, 3H), 0.93−0.95(d, J = 8.0, 3H), 1.18−1.67(m, 8H), 2.05−2.18(m, 3H), 3.07−3.12(d, J = 20, 1H), 3.17−3.29(m, 1H), 3.64(m, 2H), 3.67(s, 3H), 4.31−4.71(m, 2H), 5.0(m, 2H), 5.73(m, 1H), 6.79−6.82(d, J = 12, 2H), 7.11−7.14(d, J = 12, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 174.1, 156.5, 139.1, 130.6, 130.0, 116.5, 115.7, 67.5, 64.6, 52.7, 51.9, 48.6, 45.9, 40.3, 34.3, 31.3, 28.9, 24.7, 24.3, 22.8; HRMS (EI) *m/z* 403.2591 $[M + H]^+$, calcd for $C_{23}H_{34}N_2O_2$ 403.2586; $[\alpha]_D^{20}$ −7.3 (*c* 0.7,$CHCl_3$).



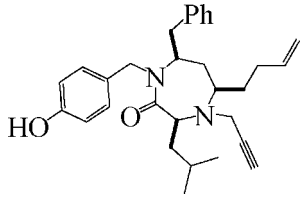
(3*S*,5*S*,7*S*)-1-(4-Hydroxybenzyl)-7-benzyl-5-(butyl)3-3-isobutyl-[1,4]-diazepin-2-one 16b. Diazepinone **16b** was isolated as a colorless oil (9 mg, 19% overall yield) in 83% purity after purification by column chromatography using 40% EtOAc/hexane: R_f 0.28 (40% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94−096(d, J = 8.0, 3H), 0.98(d, J = 8.0, 3H), 1.26−1.35(br q, 2H), 1.09−1.17(m, 1H), 1.55−1.59(m, 2H), 1.79−1.83(br t, 2H) 2.0−2.06(m, 2H), 2.8(m, 2H), 3.19−3.21(m, 3H), 3.67(dd, J = 6,7, 1H), 4.59(s, 2H), 4.85−4.90(m, 2H), 5.30(m, 1H), 6.73−7.34(m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 155.9, 139.2, 138.8, 131.7, 129.8, 129.6, 127.5, 116.4, 115.8, 60.5, 59.1, 57.9, 46.8, 42.3, 41.0, 39.2, 36.9, 31.0, 30.5, 25.4, 24.3, 29.1; HRMS (EI) *m/z* 421.2849 $[M + H]^+$, calcd for $C_{27}H_{36}N_2O_2$ 421.2846; $[\alpha]_D^{20}$ −38.5 (*c* 0.9, $CHCl_3$).



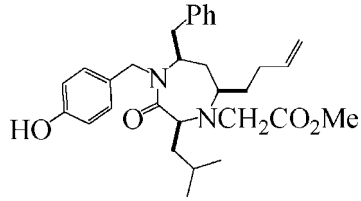
(3*S*,5*S*,7*S*)-1-(4-Hydroxybenzyl)-7-benzyl-5-3(butyl)-3-isobutyl-4-methyl-[1,4]-diazepin-2-one 18(b, a). Diazepinone **18(b, a)** was isolated as a colorless oil (4 mg, 9% overall yield) in 84% purity after purification by column chromatography using 20% EtOAc/petroleum ether: R_f 0.11 (20% EtOAc/ petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.88(d, J = 9.1, 3H), 0.92−0.94(d, J = 9.1, 3H), 1.06−1.61(m, 6H), 1.74−1.86(m, 2H), 1.90(s, 3H), 1.84−2.01(m, 1H), 2.65−2.80(m, 2H), 3,14−3,16(br q, 1H), 3.79−3.89(m, 1H), 4.16−4.21(d t, J = 2.4, 6, 1H), 4.12−4.77(m, 2H), 4.90−4.98(m, 2H), 5.64−5.80(m, 1H), 6.62−7.29(m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 154.9, 138.7, 138.6, 131.7, 129.4, 129.1, 126.7, 115.3, 114.5, 65.8, 62.2, 59.6, 45.3, 42.5, 39.9, 38.0, 33.2, 30.4, 29.7, 26.6, 24.5, 24.1, 22.2; HRMS (EI) *m/z* 435.3006 $[M + H]^+$, calcd for $C_{28}H_{38}N_2O_2$ 435.3000; $[\alpha]_D^{20}$ −74.7 (*c* 0.4,$CHCl_3$).



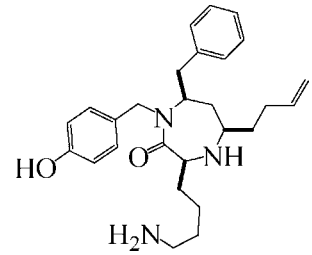
(3*S*,5*S*,7*S*)-1-(4-Hydroxybenzyl)-4-benzyl-5-(but-3-enyl)-3-isobutyl-[1,4]-diazepin-2-one 18(b, b). Diazepinone **18**(**b**, **b**) was isolated as a colorless oil (11 mg, 21% overall yield) in 92% purity after purification by column chromatography using 40% EtOAc/petroleum ether: R_f 0.17 (40% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ. 0.86−0.90(d, J = 8,7, 3H), 0.92−0.94(d, J = 8,7, 3H), 1.27(m, 2H), 1.39(m, 2H), 1.52−1.58(m, 4H), 1.76(q, J = 9.32, 2H), 1,92(m, 1H), 2.80(br d, 2H), 3.40−3.55(m, 2H), 3.89−4.30(m, 2H), 4.50−4.73(m, 3H), 5.57(m, 1H), 6.76−7.61(m, 14H); δ ^{13}C NMR (100 MHz, $CDCl_3$) 176.5, 156.0, 139.0, 138.8, 132.2, 130.2, 129.9, 129.6, 129.6, 128.8, 128.7, 127.6, 127.2, 116.4, 115.4, 68.7, 64.8, 60.4, 48.7, 46.7, 40.8, 35.2, 31.7, 30.5, 25.3, 24.1, 23.2; HRMS (EI) m/z 511.3319 $[M + H]^+$, calcd for $C_{34}H_{42}N_2O_2$ 511,3321; $[\alpha]_D^{20}$ −46.6 (c 0.9, $CHCl_3$).



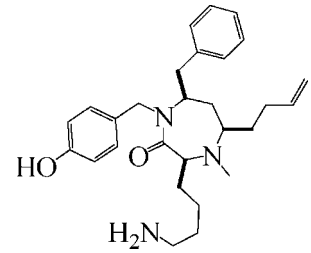
(3*S*,5*S*,7*S*)-1-(4-Hydroxybenzyl)-7-benzyl-5-(but-3-enyl)-3-isobutyl-4-propargyl-[1,4]-diazepin-2-one 18(b, c). Alkyne **18**(**b**, **c**) was isolated as a colorless oil (6 mg, 14% overall yield) in 97% purity after purification by column chromatography using 20% EtOAc/petroleum ether: R_f 0.17 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89−0.891 (d, J = 8.5, 3H), 0.82−0.83(d, J = 8.5, 3H), 1.26−1.36(m, 4H), 1.77−2.13 (m, 6H), 2.86 (m, 3H), 3.16(br, 2H), 3.88−4.36(m, 3H), 4.31−4.37(brd, 1H), 4.82−4.85(m, 1H), 4.88(s, 2H), 5.69(m, 1H), 6.72−7.33(m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 175.93, 155.8, 139.0, 132.2, 130.0, 129.8. 129.6, 129.3, 127.6, 116.4, 115.6, 84.2, 71.5, 67.3, 62.7, 60.5, 46.8, 40.7, 39.2, 34.0, 32.8, 31.6, 25.3, 29.2, 24.3, 22.9; HRMS (EI) m/z 459.3006 $[M + H]^+$, calcd for $C_{30}H_{38}N_2O_2$ 459.2998; $[\alpha]_D^{20}$ −57 (c 0.7, $CHCl_3$).



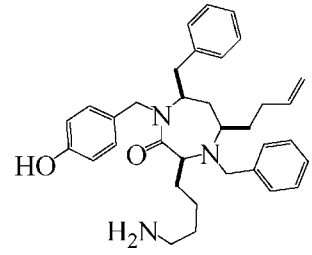
4-Methyl Acetate-(2*S*,5*S*,7*S*)-4-(4-hydroxybenzyl)-5-benzyl-7-(but-3-enyl)-2-isobutyl-3−1,4-diazepin-2-one 18(b, d). Ester **18**(**b**, **d**) was isolated as a colorless oil (6 mg, 14% overall yield) in 95% purity after purification by column chromatography using 20% EtOAc/petroleum ether: R_f 0.1 (20% EtOAc/PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94−0.99(br dd, 6H), 1.28−1.39(m, 4H), 1.68−2.0(m, 6H), 2.73−2.78(m, 2H), 3.0−3.22(dd, J = 8.0, 2H), 3.68(s, 3H), 3.90−3.93(q, J = 4.0, 1H), 4.64(m, 1H), 4.72−4.73(br q, 2H), 4.72−4.77(m, 2H), 5.61(m, 1H), 6.78(d, J = 8.5, 2H), 7.15−7.35(m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 173.4, 155.2, 138.0, 137.8, 131.0, 129.1, 128.9, 128.7, 115.6, 115.2, 114.8, 66.6, 62.9, 59.4, 51.7, 45.4, 44.9, 39.7, 39.4, 33.2, 31.1, 30.3, 24.0, 23.3, 22.1; HRMS (EI) m/z 493.3061 $[M + H]^+$, calcd for $C_{30}H_{40}N_2O_2$ 493.3053; $[\alpha]_D^{20}$ −52.3 (c 0.8, $CHCl_3$).



(3*S*,5*S*,7*S*)-1-(4-Hydroxybenzyl)-3-(4-aminobutyl)-7-benzyl-5-(but-3-enyl)-[1,4]-diazepin-2-one 16c. Amine **16c** was isolated as a solid (3 mg, 8% overall yield) in 93% purity after purification by HPLC (Gemini 5 μm C18 110A, 250 × 21.20 mm 5 μm) using 5−40% acetonitrile/H_2O: mp 80−82 °C; ^{1}H NMR (700 MHz, CD_3OD) δ 1.12−1.34(m, 2H), 1.42−1.61(m, 6H), 1.66−1.69(dd, J = 2.8, 1H), 1.75(m, 2H), 1.95−2.0(m, 2H), 2.67(m, 1H), 2.85(m, 2H), 2.98−3.01(m, 2H), 3.15−3.18(m, 1H), 3.83(t, J = 7.0, 1H), 4.4(m, 1H), 4.65(m, 3H) 4.78−4.87(m, 2H), 5.66(m, 1H), 6.75−7.32(m, 9H); ^{13}C NMR (175 MHz, CD_3OD) δ 177.5, 157.7, 140.2, 131.4, 130.6, 130.3, 129.8, 129.6, 127.8, 116.3, 115.5, 79.5, 61.0, 59.7, 59.5, 54.8, 40.4, 38.2, 36.8, 33.0, 31.1, 28.5, 24.3; HRMS (EI) m/z 436.2958 $[M + H]^+$, calcd for $C_{27}H_{37}N_3O_2$ 436.2951; $[\alpha]_D^{20}$ −24° (c 0.1, MeOH).

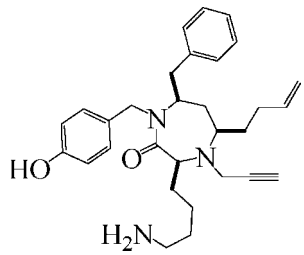


(3*S*,5*S*,7*S*)-1-(4-Hydroxybenzyl)-3-(4-aminobutyl)-7-benzyl-5-(butyl-3-enyl)-4-methyl-[1,4]-diazepin-2-one 18(c, a). Amine **18**(**c**, **a**) was isolated as a solid (5 mg, 10% overall yield) in 92% purity after purification by HPLC using a gradient of 5−40% acetonitrile/H_2O: mp 105−107 °C; ^{1}H NMR (700 MHz, CD_3OD) δ 1.2−1.51(m, 4H), 1.57−1.62(m, 2H), 1.68−1.74(m, 4H), 1.76−1.78(m, 2H), 1.89−1.95(m, 1H), 1.96(s, 3H), 1.97−2.03(m, 1H), 2.77−2.80(m, 1H), 2.81−2.85(q, J = 10.5, 1H), 2.93−2.99(m, 2H), 3.12(brq, 1H), 4.01(q, J = 5.6, 1H), 4.38(dt, J = 4.2, 10.5, 1H), 4.52−4.55(br d, 1H), 4.8(s, 1H), 4.48−4.80(m, 2H), 5.66−5.73(m, 1H), 6.74−7.36(m, 9H); ^{13}C NMR (175 MHz, CD_3OD) δ 175.7, 156.1, 138.5, 138.1, 130.4, 128.9, 128.3, 128.1, 126.1, 114.8, 113.8, 65.4, 63.9, 59.4, 44.7, 39.2, 39.0, 33.0, 30.0, 29.2, 28.6, 27.2, 26.3, 22.9; HRMS (EI) m/z 450.3115 $[M + H]^+$, calcd for $C_{28}H_{39}N_3O_2$ 450.3103; $[\alpha]_D^{20}$ −53.5 (c 0.3, MeOH).

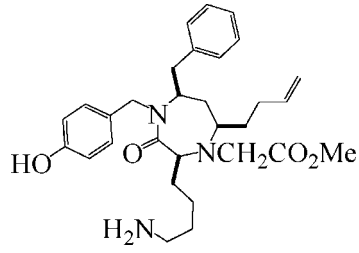


(3*S*,5*S*,7*S*)-1-(4-Hydroxybenzyl)-3-(4-aminobutyl)-4,7-dibenzyl-5-(butyl)3-[1,4]-diazepin-2-one 18(c, b). Amine **18**(**c**, **b**) was isolated as a solid (4 mg, 8% overall yield) in

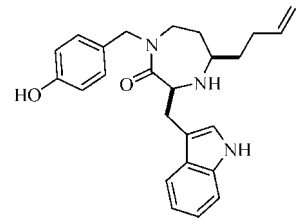
97% purity after purification by HPLC using a gradient of 5−40% acetonitrile/H_2O: mp 112−115 °C; ^{1}H NMR (700 MHz, CD_3OD) δ 1.41−1.47(m, 2H), 1.60−1.79(m, 8H), 2.85(t, J = 7, 2H), 2.90−2.94(q, J = 11.2, 2H), 3.21−3.23(m, 2H), 3.44−3.47(m, 3H), 4.06(m, 1H), 4.42−4.55(m, 3H), 4.65−4.80(m, 4H), 5.4(m, 1H), 6.79(m, 14H); ^{13}C NMR (175 MHz, CD_3OD) δ 176.0, 156.2, 138.5, 137.8, 130.3, 128.9, 128.8, 128.6, 128.4, 128.2, 128.0, 127.6, 126.3, 126.1, 114.8, 113.7, 65.9, 60.9, 59.5, 53.8, 45.0, 39.2, 34.3, 30.7, 30.3, 29.4, 27.3, 23.1; HRMS (EI) *m*/*z* 526.3428 $[M + H]^+$, calcd for $C_{34}H_{43}N_3O_2$ 526.3411; $[\alpha]_D^{20}$ −16.5 (*c* 0.2, MeOH).



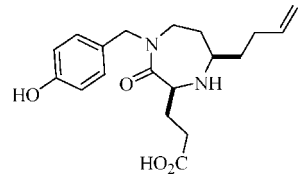
(3*S*,5*S*,7*S*)-1-(4-Hydroxybenzyl)-3-(4-aminobutyl)-7-benzyl-5-(butyl-3-enyl)-4-(propargyl)-[1,4]-diazepin-2-one 18(c, c). Amine **18**(**c**, **c**) was isolated as a solid (4 mg, 6% overall yield) in 98% purity after purification by HPLC using a gradient of 5−40% acetonitrile/H_2O: mp 84−87 °C; ^{1}H NMR (700 MHz, CD_3OD) δ 1.27−1.35(m, 2H), 1.46(m, 2H), 1.69−1.82(m, 8H), 2.02−2.17(m, 2H), 2.50(t, J = 2.1, 1H), 2.79−2.85(m, 2H), 2.96−2.98(oct, J = 8.4, 2H), 3.10−3.13(dd, J = 4.2, 1H), 3.15−3.23(m, 2H), 4.00−4.02(br q, 1H), 4.36−4.46(m, 2H), 4.81−4.87(m, 3H), 5.64−5.73(m, 1H), 6.70−7.33(m, 9H); ^{13}C NMR (175 MHz, CD_3OD) δ 175.8, 156.0, 138.5, 138.1, 130.4, 128.9, 128.3, 128.0, 126.3, 114.8, 113.8, 83.4, 70.4, 66.0, 63.9, 59.5, 45.4, 39.3, 39.1, 33.3, 31.0, 30.6, 30.5, 29.3, 27.2, 22.8; HRMS (EI) *m*/*z* 474.31150 $[M + H]^+$, calcd for $C_{30}H_{39}N_3O_2$ 474.30996; $[\alpha]_D^{20}$ −69 (*c* 0.2, MeOH).



4-Methyl Acetate-(2*S*,5*S*,7*S*)-1-(4-hydroxybenzyl)-3-(4-aminobutyl)-5-(butyl-3-enyl)-[1,4]-diazepin2-one 18(c, d). Amine **18**(**c**, **d**) was isolated as a solid (5 mg, 9% overall yield) in 95% purity after purification by HPLC using a gradient of 5−40% acetonitrile/H_2O: mp 80−84 °C; ^{1}H NMR (700 MHz, CD_3OD) δ 1.38−1.76(m, 9H), 1.92−1.99(m, 3H), 2.84−2.87(m, 2H), 2.98(d, J = 7.7, 2H), 3.03−3.13(m, 2H), 3.16−3.18(dd, J = 4.2, 1H), 3.67(s, 3H), 4.02−4.04(q, J = 4.9, 1H), 4.37−4.41(m, 1H), 4.65(s, 2H), 4.67(s, 1H), 4.71−4.80(m, 2H), 5.58−5.62(m, 1H), 6.76−7.32(m, 9H), 8.85(s, 1H); ^{13}C NMR (175 MHz, CD_3OD) δ 175.5, 174.2, 156.2, 138.1, 137.8, 130.2, 128.9, 128.4, 126.3, 114.8, 113.9, 66.3, 64.8, 59.3, 51.0, 44.8, 44.3, 39.1, 39.0, 33.2, 30.4, 30.2, 29.8, 27.2, 22.5; HRMS (EI) *m*/*z* 508.3170 $[M + H]^+$, calcd for $C_{30}H_{41}N_3O_2$ 508.3163; $[\alpha]_D^{20}$ −27.3 (*c* 0.3, MeOH).



(3*S*,5*S*)-3-Methyl-(1*H*-indolyl)-1-(4-hydroxybenzyl)-5-(butyl-3-enyl)-[1,4]-diazepin-2-one 15e. Indole **15e** was isolated as a colorless oil (2 mg, 6% overall yield) in 89% purity after purification by column chromatography using 20% EtOAc/petroleum ether: R_f 0.3 (40% EtOAc/petroleum ether); ^{1}H NMR (700 MHz, $CDCl_3$) δ 1.34−1.46(m, 2H), 1.39−1.50(s, J = 11.2, 2H), 1.68−1.82(m, 2H), 2.04(m, 2H), 2.48−2.50(br m, 1H), 3.14−3.29(m, 2H), 3.44−3.58(m, 2H), 3.74(br dd, 1H), 4.51−4.73(m, 4H), 5.43−4.49(m, 1H), 6.75−7.76(d, J = 17,5, 2H), 7.08−7.12(m, 3H), 7.16(t, J = 7, 1H), 7.23(s, 1H), 7.39−7.40(d, J = 7.7, 1H), 7.69−7,70(d, J = 7.7, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 167.6, 156.9, 136.7, 136.0, 129.5, 128.5, 127.4, 124.1, 121.5, 118.9, 117.7, 115.2, 107.9, 78.1, 61.0, 58.6, 50.5, 48.2, 44.5, 32.6, 31.7, 29.4, 28.8, 25.3; HRMS (EI) *m*/*z* 403.2380 $[M + H]^+$, calcd for $C_{26}H_{30}N_2O_2$ 403.23693; $[\alpha]_D^{20}$ −14 (*c* 0.1, MeCN).



3-Propanoate-(2*S*,7*S*)-4-(4-hydroxybenzyl)-5-(butyl-3-enyl)-[1,4]-diazepin-2-one 15f. The TFA salt of **15f** was isolated as a solid (8 mg, 18% overall yield) in 95% purity after precipitation from ether: mp 112−115 °C; ^{1}H NMR (700 MHz, CD_3OD) δ 1.30−1.90(m, 4H), 2.09−2.21(m, 4H), 2.42(sex, J = 7.0, 2H), 2.56−2.71(m, 2H), 3.48−3.53(m, 2H), 3.74−3.78(q, J = 11.2, 1H), 4.38−4.40(q, J = 4.9, 1H), 4.42−4.71(m, 2H), 5.04−5.15(br dd, 2H), 5.79−5.85(m, 1H), 6.77−6.78(d, J = 7, 2H), 7.16−7.19(d, J = 7, 2H); ^{13}C NMR (175 MHz, CD_3OD) δ 176.3, 166.9, 157.0, 136.3, 129.5, 129.4, 126.9, 115.4, 115.0, 61.0, 57.6, 44.5, 32.6, 30.4, 29.1, 26.2, 24.3; HRMS (EI) *m*/*z* 347.19653 $[M + H]^+$, calcd for $C_{19}H_{26}N_2O_2$ 347.19572; $[\alpha]_D^{20}$ 18.8 (*c* 0.4, MeOH).

Acknowledgment. This research was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Fonds Québecois de la Recherche sur la Nature et les Technologies (FQRNT), and the Canadian Institutes of Health Research (CIP-79848). We thank Dalbir Sekhon (UdeM) for performing HPLC analyses and Sylvie Bilodeau from the Centre Régional de RMN (UdeM) for NMR spectral analyses.

Supporting Information Available. Proton and carbon NMR spectra of final diazepinone products. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235.

(2) Weitz, I, S.; Pellegrini, M.; Mierke, D. F.; Chorev, M. *J. Org. Chem.* **1997**, *62*, 2527–2534.

(3) Ramanathan, S. K.; Keeler, J.; Lee, H.-L.; Reddy, D. S.; Lushington, G.; Aubé, J. *Org. Lett.* **2005**, *7*, 1059–1062.

(4) Iden, H.; Lubell, W. D. *Org. Lett.* **2006**, *8*, 3425–3428.

(5) Kesheva Murthy, K. S.; Knaus, E. E. *Drug Dev. Res.* **1999**, *46*, 155–162.

(6) Hirano, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2008**, *73*, 569–577.

(7) Isono, K. *J. Antibiot.* **1988**, *41*, 1711–1739.

(8) Wattanasin, S.; Albert, R.; Ehrhardt, C.; Roche, D.; Sabio, M.; Hommel, U.; Welzenbach, K.; Weitz-Schmidt, G. *Biorg. Med. Chem. Lett.* **2003**, *13*, 499–502.

(9) Gates, M. *J. Org. Chem.* **1980**, *45*, 1675–1681 and ref. 1 therein.

(10) De Lucca, G. V.; Otto, M. J. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1639–1644.

(11) Kaneko, T.; Wong, H.; Doyle, T. W.; Rose, W. C.; Bradner, W. T. *J. Med. Chem.* **1985**, *28*, 388–392 and ref. 1 therein.

(12) Iden, H.; Lubell, W. D. *J. Org. Chem.* **2007**, *72*, 8980–8983.

(13) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.

(14) Weitz, I, S.; Pellegrini, M.; Royo, M.; Mierke, D. F.; Chorev, M. *Lett. Pep. Sci.* **1998**, *5*, 83–86.

(15) Kobayashi, S.; Akiyama, R. *Tetrahedron Lett.* **1998**, *39*, 9211–9214.

(16) Boojamra, C. G.; Burow, K. M.; Thompson, L. A.; Ellman, J. *J. Org. Chem.* **1997**, *62*, 1240–1256.

(17) Shannon, S. K.; Peacock, M. J.; Kates, S. A.; Barany, G. *J. Comb. Chem.* **2003**, *5*, 860–868.

(18) Fader, L. D.; Boyd, M.; Tsantrizos, Y. S. *J. Org. Chem.* **2001**, *66*, 3372–3379.

(19) Vojkovsky, T. *Pept. Res.* **1995**, *8*, 236–237.

(20) Hansford, K. A.; Dettwiler, J. E.; Lubell, W. D. *Org. Lett.* **2003**, *5*, 4887–4890.

(21) Sivanandaiah, K. M.; Suresh Babu, V. V.; Gangadhar, B. P. *Tetrahedron Lett.* **1996**, *37*, 5989–5990.

(22) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595–598.

(23) Schwarz, M. K.; Tumelty, D.; Gallop, M. A. *Tetrahedron Lett.* **1998**, *39*, 8397–8400.

(24) Müller-Hartweig, J. D.; Akyel, K. G.; Zimmermann, J. *J. Peptide Sci.* **2003**, *9*, 187–199.

(25) Dörr, A; Lubell, W. D. *Can. J. Chem.* **2007**, *85*, 1006–1017.

CC8001052