ORGANIC LETTERS

2006
Vol. 8, No. 16
3425−3428

1,4-Diazepinone and Pyrrolodiazepinone Syntheses via Homoallylic Ketones from Cascade Addition of Vinyl Grignard Reagent to α-Aminoacyl-β-amino Esters

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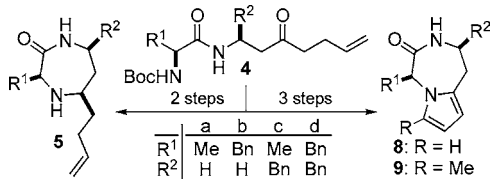
Received April 28, 2006

ABSTRACT



1,4-Diazepinones 5 and pyrrolodiazepinones 8 and 9 were synthesized from common homoallylic ketone precursors 4 prepared by copper-catalyzed cascade addition of a vinyl Grignard reagent to α-aminoacyl β-amino esters 3. Nitrogen deprotection and intramolecular reductive amination yielded 1,4-diazepinones 5. Olefin oxidation, Boc removal, and intramolecular Paal–Knorr condensation gave pyrrolodiazepinones 8 and 9. X-ray structures of diazepinones 5c and 5d depicted dihedral angles about the α-amino acid moiety similar to those of the central residue in an ideal reverse γ-turn.

Among the small molecules employed in drug discovery, molecular scaffolds that mimic peptide secondary structures are particularly useful for lead identification and the development of therapeutic agents. In this respect, 1,4-benzodiazepines display a wide range of pharmacological activities likely due to their potential to mimic peptide turn conformations.[1−3]

1,4-Diazepinones have exhibited activity as high-affinity antagonists of the lymphocyte function-associated antigen-1/immunoglobulin superfamily ICAM-1 interaction.[4] They have shown anticonvulsant activity.[5] The diazepinone system is also present in the liposidomycin nucleoside antibiotics that inhibit bacterial peptidoglycan synthesis (Figure 1).[6]

The pyrrolobenzodiazepine structure is contained in the natural anthramycin family of antitumor antibiotics.[7] Synthetic pyrrolobenzodiazepines have acted as non-nucleoside reverse transcriptase inhibitors[8] and CNS agents;[9] they have also exhibited antiproliferative[10] and antidepressant[11] activity (Figure 1).

The synthesis of diazepinone ring systems has attracted considerable interest. Annulation of the diazepinone ring has been accomplished from linear precursors by reductive amination[12,13] and lactam formation.[14] Ring expansion of N-protected-4-piperidones by azido-Schmidt reactions with

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Published on Web 07/12/2006

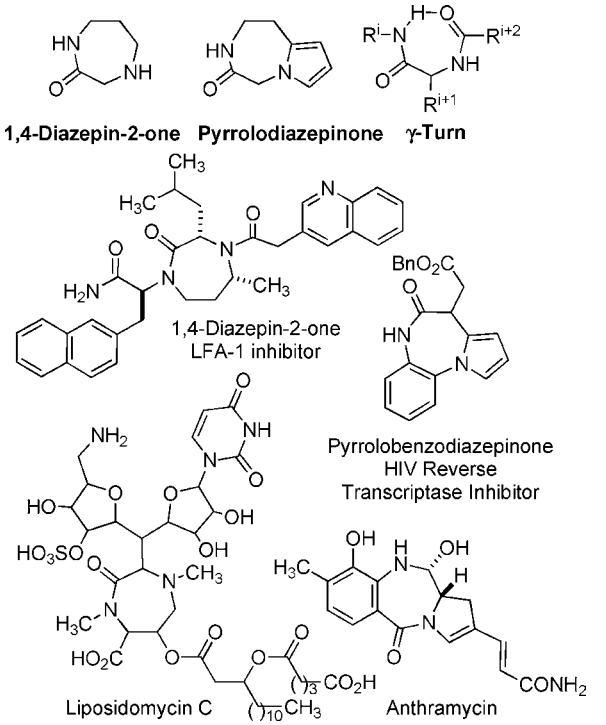


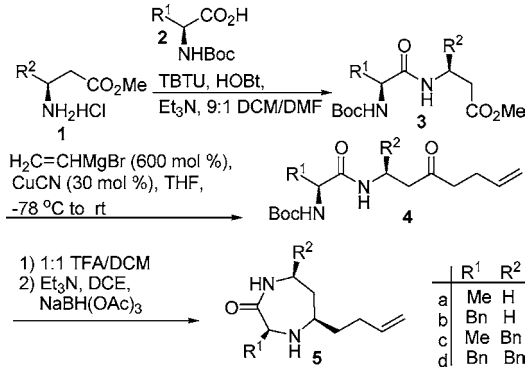
Figure 1. Representative 1,4-diazepin-2-one and pyrrolodiazepinone systems and related biologically active structures.

2-hydroxyalkyl azides has given N-substituted diazepinones.[3] 1,4-Diazepin-5-ones have been recently made by acid-catalyzed hydrolysis of azeto[1,2-*a*]imidazoles.[15] In addition, a combinatorial library of 1,4-diazepinone derivatives was synthesized by a solid-phase approach.[16]

Syntheses of the pyrrolobenzodiazepine structures were reviewed in a recent note on pyrroloaryldiazepine construction by modification of the four-component Ugi condensation.[17] To the best of our knowledge, only one synthesis of the parent pyrrolodiazepinone has been described featuring a Paal−Knorr condensation/lactam cyclization sequence to form sequentially the pyrrole and diazepinone rings.[18]

Their remarkable biological activity has inspired the development of new synthesis methodology for making diazepinone and fused aryl- and heteroaryldiazepinone structures. Present methods employ often expensive starting materials, give low to moderate yields, and provide compounds of limited diversity. Employing inexpensive amino

Scheme 1. Synthesis of Diazepinones **5**



acids as chiral educts, we conceived efficient synthetic approaches for making diazepinone and pyrrolodiazepinone heterocycles that use a common homoallylic ketone **4**. Four diazepinones **5** and eight pyrrolodiazepinones **8** and **9** (Schemes and Tables 1 and 2) were synthesized starting from combinations of Ala, Phe, β-Ala, and β-homophenylalanine to provide α-aminoacyl-β-amino esters **3**. Homoallylic ketones **4** were then made by Cu-catalyzed cascade addition of a vinyl Grignard reagent to esters **3**.[19]

α-Aminoacyl-β-amino esters **3** were synthesized by coupling β-amino ester **1** to the respective *N*-Boc-α-amino acid **2** using TBTU and HOBt in dichloromethane (Scheme 1).[20] Dipeptides **3** were isolated by chromatography on silica gel in 85−92% yields. Homoallylic ketones **4** were synthesized by treating α-aminoacyl-β-amino esters **3** with an excess of freshly prepared vinylmagnesium bromide (600 mol %) in the presence of copper cyanide (30−40 mol %) in THF at −78 °C to room temperature.[19] After quenching the Grignard reaction at 0 °C, workup, and solvent removal under vacuum, homoallylic ketones **4a**−**c** were isolated by chromatography on silica gel in 60−75% yields (Table 1). Isolation of ketone

Table 1. Yields of Isolated Products in the Synthesis of **5**

entry	R^1	R^2	**3** (%)	**4** (%)	**5** (%)
a	CH_3	H	85	75	45
b	CH_2Ph	H	90	60	40
c	CH_3	CH_2Ph	90	65	50
d	CH_2Ph	CH_2Ph	92	45	50

4d was best accomplished by chromatography over silica gel impregnated with silver nitrate in 45% yield.[21]

Diazepinones **5** were synthesized from homoallylic ketones **4** by a route featuring nitrogen deprotection with TFA/DCM (1:1), treatment of the trifluoroacetate salt with triethylamine at 0 °C, and reduction of the imine intermediate with sodium

(12) Knapp, S.; Nandan, S.; Resnick, L. *Tetrahedron Lett.* **1992**, *33*, 5485−5486.
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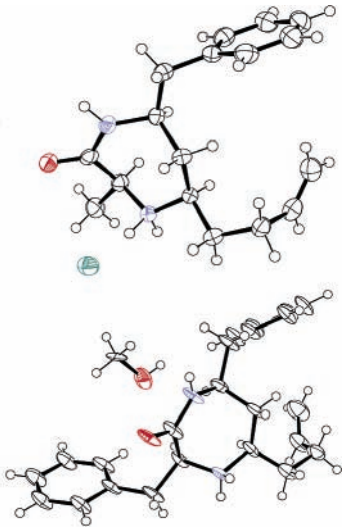


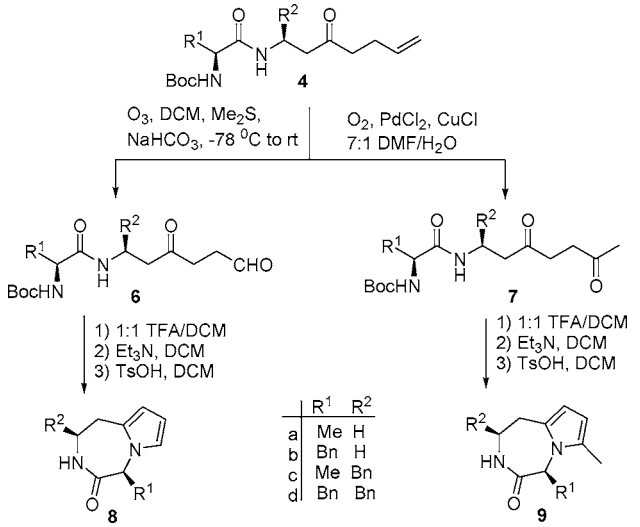
Figure 2. X-ray diffraction structures of compounds **5c** (upper) and **5d** (lower).

triacetoxyborohydride in dilute dichloroethane.[22] The progress of the imine reduction was followed by LCMS analysis, which showed only one diastereoisomer in the crude product as confirmed by ^{1}H NMR spectroscopy. After workup, diazepinone **5a** was isolated after this sequence from **4a** in 45% yield by preparative HPLC, and **5b**−**d** were purified by precipitation as hydrochloride salts and isolated in 40−50% overall yields from ketones **4b**−**d** (Scheme 1, Table 1).

The hydrochloride salts of diazepinones **5c** and **5d** were recrystallized from methanol in ethyl acetate to furnish crystals for X-ray analysis. The newly formed stereocenter at the 5-position of diazepinones **5** was found to have a cis relationship with respect to the 3-position substituent as expected on the basis of the literature precedent in which reduction of the cyclic iminium intermediate occurred with hydride attack on the face opposite of the ring substituents.[16,23] A survey of the Cambridge structural database indicated that the X-ray structures of **5c** and **5d** represent the first 1,4-diazepin-2-one examples. On comparison of the dihedral angle geometry of the α-amino acid portion of diazepinones **5c** ($\psi = 70$, $\phi = -80$) and **5d** ($\psi = 67$, $\phi = -83$) with ideal values of turn conformations, we noted the close resemblance to the dihedral angle geometry of the central residue in a reverse γ-turn conformation ($\psi = 60-70$, $\phi = -70-85$; Figure 2). [24]

Pyrrolodiazepinones **8** and **9** were made next from the common homoallylic ketone intermediate **4**. First, 4-keto aldehydes **6** and 1,4-diketones **7** were obtained from oxidation of olefin **4** using either ozonolysis or periodate/osmium tetraoxide and by Tsuji−Wacker oxidation, respectively (Scheme 2).

Scheme 2. Synthesis of Pyrrolodiazepinones **8** and **9**



4-Keto aldehydes **6** were isolated in 80−85% yields by chromatographic purification after ozonolysis of homoallylic ketones **4** in CH_2Cl_2/MeOH (1:1) at −78 °C and treatment with excess dimethyl sulfide in the presence of $NaHCO_3$.[25] Alternatively, oxidative cleavage of the double bond of homoallylic ketones **4** was performed with sodium periodate in the presence of catalytic amounts of OsO_4[26] to afford aldehydes **6** in 65−85% yield after chromatography. Comparing the two methods for making aldehyde **6**, we found the ozonolysis to be more advantageous because the crude product was obtained in suitable purity for the subsequent Paal−Knorr reaction.

1,4-Diketones **7** were produced by Tsuji−Wacker oxidation[27] employing $PdCl_2$ (0.2 equiv) and CuCl (2 equiv), in DMF/H_2O (9:1) at room temperature under an atmosphere of oxygen. After workup and chromatography on silica gel, 1,4-diketones **7** were isolated in 80−85% yields (Scheme 2, Table 2). Yields were improved for olefins **4c** and **4d** by using more $PdCl_2$ (40 mol %) and 2 equiv of CuCl in THF/H_2O (4:1) at room temperature under an oxygen atmosphere and agitation in a sonicator.

Pyrrolodiazepinones **8** and **9** were, respectively, prepared from 4-keto aldehydes **6** and 1,4-diketones **7** by a generally effective albeit moderate yielding route featuring nitrogen deprotection and Paal−Knorr condensation.[28] Acid-induced Boc group removal was accomplished using either HCl gas or TFA in CH_2Cl_2, with better success on keto aldehyde **6**

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(23) The footnote of ref 16 notes: Compounds without the R2 substituents show a 1:1 mixture of two diastereomers. Moreover, a discerning referee pointed out that "seven-membered rings containing an amide bond usually adopt chairlike conformations; in this analysis, the observed product can be seen to arise from axial attack. This is borne out by the crystal structures of the products".

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Table 2. Yields of Isolated Products in the Synthesis of **8** and **9**

entry	R^1	R^2	**6** (%)	**7** (%)	**8** (%)	**9** (%)
a	CH_3	H	85	85	30	65
b	CH_2Ph	H	85	80	40	45
c	CH_3	CH_2Ph	80	80	55	50
d	CH_2Ph	CH_2Ph	85	80	60	50

using TFA instead of the HCl conditions. Paal−Knorr cyclization occurred on treatment with triethylamine and a catalytic amount of toluenesulfonic acid in dilute DCM at 0 °C. After quenching with saturated $NaHCO_3$ solution, pyrrolodiazepinones **9** were isolated by chromatography on silica gel in 45−65% overall yield from **7**. An improved Paal−Knorr condensation was then developed using basic Amberlyst A-21 ion-exchange resin for generating the free amine after Boc deprotection with TFA in DCM.[29]

The use of higher concentrations of keto aldehydes **6** and diketones **7** in the Paal−Knorr annulation to form pyrrolodiazepinones **8** and **9** provided mixtures of monomers and dimers as observed by LCMS analyses. Dimer **10** was isolated by preparative HPLC and identified by its doubling in mass and relatively simple ^1H and ^{13}C NMR spectra due to C_2 symmetry (Figure 3) .

A practical, diversity-oriented methodology for the synthesis of diazepinone structures has been developed that features treatment of α-aminoacyl-*β*-amino esters **3** with excess vinyl Grignard reagent to yield a common homoallylic ketone intermediate. Diazepinones **5a**−**d**, pyrrolo-, and

(29) Natarajan, S.; Yurek-George, A.; Ganesan, A. *Mol. Diversity* **2005**, *9*, 291−293.

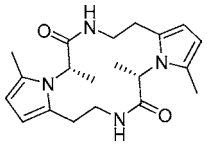

Figure 3. Dimer **10**.

methylpyrrolodiazepinones **8a**−**d** and **9a**−**d** all were made in four to six steps and 16−31% overall yields from inexpensive amino acid building blocks **1** and **2**. Considering the tolerance of the Cu-catalyzed cascade additions of vinyl Grignard reagent to a variety of *N*-(acyl)-amino esters possessing different side chains,[19] a wealth of peptide-based diazepinone and pyrrolodiazepinone structures may now be obtained by this practical approach.

Acknowledgment. The authors would like to acknowledge Françine Bélanger-Gariépy from the Regional Laboratory of X-ray Analysis, Dalbir Sekhon from the Regional Laboratory of Mass Spectrometry, and Dr. Ramesh Kaul, Simon Suprenant, and Dr. Susan Seaman, at the Université de Montréal, for their helpful assistance as well as the Natural Sciences and Engineering Research Council of Canada (NSERC) and Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT), for financial support.

Supporting Information Available: Experimental details, spectroscopic characterization for all compounds, and X-ray crystallographic data of **5c** and **5d.** This material is available free of charge via the Internet at http://pubs.acs.org.

OL061036K