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ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · OCTOBER 1998

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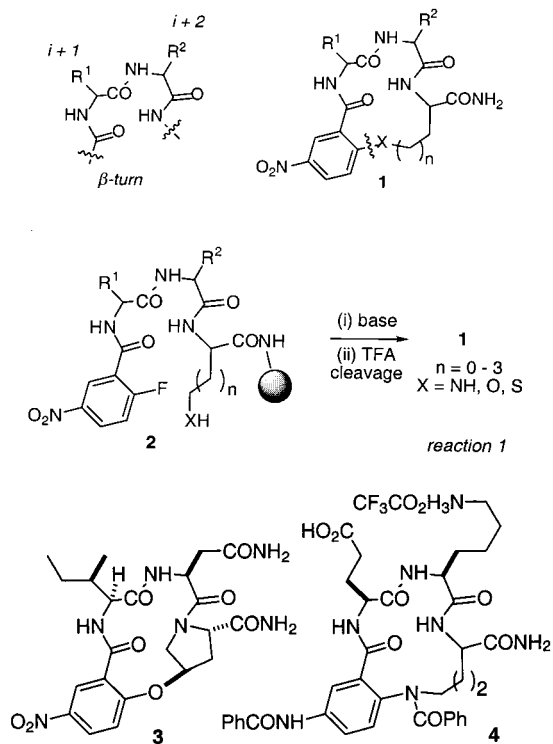
# S<sub>N</sub>Ar Cyclizations To Form Cyclic Peptidomimetics of $\beta$ -Turns

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Received May 7, 1998

Turn motifs feature prominently in many protein–protein and protein–peptide contacts.<sup>1</sup> Such interactions can be exploited in medicinal chemistry and biotechnology; hence small molecules that incorporate  $\beta$ -turns have a multitude of applications. Combinatorial and high-throughput parallel syntheses of  $\beta$ -turn mimic libraries, however, present some challenging synthetic issues. Foremost among these are requirements for efficient macrocyclizations on a solid phase to give molecules with preferred  $\beta$ -turn conformations.<sup>2</sup> This paper describes S<sub>N</sub>Ar cyclizations on a support that are useful for syntheses of  $\beta$ -turn libraries.



Structures **1** were selected as targets for this study for two reasons. First, it was envisaged that the aryl component linked to an amino acid side chain would form a ring that would induce a  $\beta$ -turn in the peptidic fragment. In this respect, the systems resemble cyclic hexapeptides except that only one possible turn–extended-turn arrangement exists. Conversely, cyclic hexapeptides from L-amino acids exist in several alternative turn–extended-turn conformers with different amino acids at the  $i$  to  $i + 3$  positions.<sup>3</sup> Second, macrocyclizations via the disconnection indicated could be facile.<sup>4</sup> In summary, the target molecules could be relatively rigid macrocycles, be accessible by solid-phase

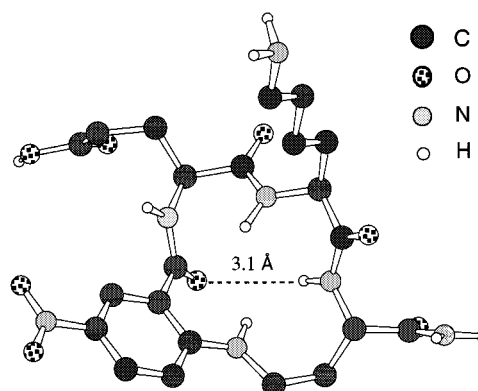


Figure 1. Simulated low-energy conformer for compound **1f**.

syntheses, and differ in significant ways from cyclic peptides,<sup>5,6</sup> Ellman's medium ring-size turn analogues,<sup>7–9</sup> and nonpeptidic turn mimetics.<sup>2</sup>

Reaction 1 demonstrates the key solid-phase S<sub>N</sub>Ar macrocyclization used in our protocol. Substrates **2** were formed on resins functionalized with Rink's amide handle.<sup>10</sup> Where appropriate, the side chains were protected as *tert*-butyl esters or BOC-amides as is conventional for the Fmoc approach. Cyclization was performed via an S<sub>N</sub>Ar reaction, as indicated. Products **1** isolated after cleavage were reasonably pure as assessed by HPLC/MS, and no racemization was observed under the conditions shown as evidenced by analytical HPLC (see Supporting Information). Generally, the yields of isolated purified materials obtained after preparative HPLC were good, considering that the synthesis consisted of nine steps and a chromatographic separation. More than nine steps were involved for **1e** and **1f** because a solid-phase Hoffmann rearrangement was used to generate the 2,4-diaminobutyric acid (Dbu) residue; consequently, the overall yields for these syntheses were good.<sup>11</sup> Similarly, synthesis of **4** also involved additional steps (reduction of the nitro group and benzoylation). These reactions were performed to illustrate how diversity could be increased in a library synthesis. Compounds **1j**, **1k**, and **3**, the 13-membered ring products, gave the lowest yields in the series, and HPLC/MS evidence indicated that significant amounts of cyclic dimers form in these reactions.

A conformational analysis of peptidomimetic **1f** was undertaken. NMR studies of the compound in DMSO indicated one conformer predominated. NOE data from ROESY experiments, and coupling constants, compared well with parameters for a dominant conformer generated via the quenched molecular technique (i.e., without constraints, Figure 1; see Supporting Information for details).<sup>12,13</sup> Temperature coefficient measurements indicated the endocyclic Dbu-NH is involved in a hydrogen bond (−2.04 ppb/K).<sup>14–16</sup> These data support the assertion that

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**Table 1.** Turn Analogues **1**, **3**, and **4**

<b>1</b>	compound				ring size	S <sub>N</sub> Ar cond <sup>a</sup>	yields (%)	
	R <sup>1</sup>	R <sup>2</sup>	<i>n</i>	X			HPLC <sup>b</sup>	isolated <sup>c</sup>
<b>1a</b>	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	3	NH	16	A	89	52
<b>1b</b>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> (OH)CH <sub>3</sub>	2	NH	15	A	90	89
<b>1c</b>	CH(CH <sub>3</sub> ) <sub>2</sub>	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	2	NH	15	A	91	74
<b>1d</b>	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	(CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	2	NH	15	A	93	56
<b>1e</b>	CH <sub>2</sub> OH	(CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	1	NH	14	A	82	40 <sup>d</sup>
<b>1f</b>	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	(CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	1	NH	14	A	90	30 <sup>d</sup>
<b>1g</b>	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	1	O	14	A	80	37
<b>1h</b>	CH <sub>2</sub> OH	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	1	O	14	A	94	65
<b>1i</b>	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	(CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	1	O	14	A	89	43
<b>1j</b>	(CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	H	0	S	13	A	85	38
<b>1k</b>	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	0	S	13	A	67	23
<b>3</b>	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CONH <sub>2</sub>		O	13/14	B	67	21
<b>4</b>	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	(CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	2	N	15	C	71	49

<sup>a</sup> Conditions: (A) K<sub>2</sub>CO<sub>3</sub>, DMF, 25 °C, 30 h (strictly under N<sub>2</sub> for **1j** and **1k**); (B), (i) Bu<sub>4</sub>NF, THF, 25 °C, 24 h, then (ii) K<sub>2</sub>CO<sub>3</sub>, DMF, 25 °C, 24 h; (C) as for (A), then (i) SnCl<sub>2</sub>·2H<sub>2</sub>O, DMF/EtOH (10:1.0), 25 °C, 16 h, and (ii) ClCOC<sub>6</sub>H<sub>4</sub>-4-Me, <sup>t</sup>Pr<sub>2</sub>NEt CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 2 h. All amino acids used were protein amino acids having the L-configuration. The resin was Rink amide AM (0.66 mmol/g) for X = NH, and TentaGel S RAM (0.30 mmol/g) for X = O, S. <sup>b</sup> Percentage areas of peaks corresponding to the desired product relative to all other peaks in the HPLC trace (average of values monitored by UV at 215 and 254 nm). <sup>c</sup> Yields were calculated on the basis of the resin loads and the mass obtained after preparative HPLC separation. For those compounds with side-chain free amines, the yields were based on the TFA salts; NMR results showed that the secondary aniline does not exist in the form of TFA salt. <sup>d</sup> Bis(trifluoroacetoxy)iodobenzene was used to generate the intermediate 2,4-diaminobutyric acid derivative on the resin; this may have caused some premature cleavage from the support and reduced the isolated yield.

**1f** can adopt a turn—extended-turn(mimic) conformation with the CO···HN hydrogen bond being the ring fusion point for 10-membered rings formed by the β-turn and by the β-turn analogue. Variation of the turn mimic and/or the configuration of the natural amino acids could be used to generate analogues of a variety of turn types. Studies are in progress to explore this issue and to relate the products to a target of medicinal significance.

**Acknowledgment.** This research was supported by Boehringer-Ingelheim Pharmaceuticals Inc., the National Institutes of Health (Grant

DA 09358-01), the Texas Advanced Research program, and the Robert A. Welch Foundation. K.B. thanks the NIH for a Research Career Development Award and the Alfred P. Sloan Foundation for a fellowship.

**Supporting Information Available:** Experimental procedures **A**, **B**, and **C** with data for all compounds; NMR (crude and pure compounds) spectra for **1a** and **1d**; illustrative analytical HPLC profiles for samples of crude and purified materials; tables of NMR and QMD data, and tabulated comparison of simulated and observed values (16 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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JA981589T