yield of **26**). Saponification of the methyl ester with dilute KOH (methyl alcohol/25 °C/2.5 h) gave racemic deoxyfrenolicin (**1**) as a yellow-organge powder of mp 214–214.5 °C (97% yield). It was shown to be identical in spectra and chromatographic properties with a sample of (+)-deoxyfrenolicin (mp 177–179 °C) prepared from (+)-frenolicin.[2a] The melting point of an admixture of synthetic (±)-deoxyfrenolicin with (+)-deoxyfrenolicin is 182–183 °C.

Acknowledgment. We acknowledge generous support of this work under research grant NIH AI 15916.

Registry No. 1, 73804-49-6; **2**, 73804-47-4; **5**, 27436-99-3; **7**, 68280-97-7; **8**, 83153-14-4; **9**, 83153-15-5; **10**, 83153-16-6; **11**, 83159-86-8; **12c**, 83153-18-8; **12T**, 83153-17-7; **13c**, 78340-68-8; **13T**, 78340-69-9; **14**, 83159-85-7; **15**, 83153-19-9; **15** acetate, 83153-26-8; **16**, 83159-70-0; **18**, 83153-20-2; **19**, 83153-21-3; **20**, 83153-22-4; **23**, 83153-23-5; **24**, 83153-24-6; **25a**, 81702-89-8; **25b**, 81702-90-1; **26**, 73804-48-5; *O*-lithioanisole, 31600-86-9; allylacetylene, 871-28-3; acetaldehyde, 75-07-0; 1-hexyn-3-ol THP ether, 829-82-3; allyl bromide, 106-95-6; non-1-en-4-yn-6-ol, 83153-25-7; ethyl bromoacetate, 105-36-2.

Supplementary Material Available: Characterization data for compounds **19**, **20**, **24**, **25**, **26a**, **27a**, and **27b** (1 page). Ordering information is given on any current masthead page.

The Four-Component Condensation: A New Versatile Method for the Synthesis of Substituted Prolyl Peptides

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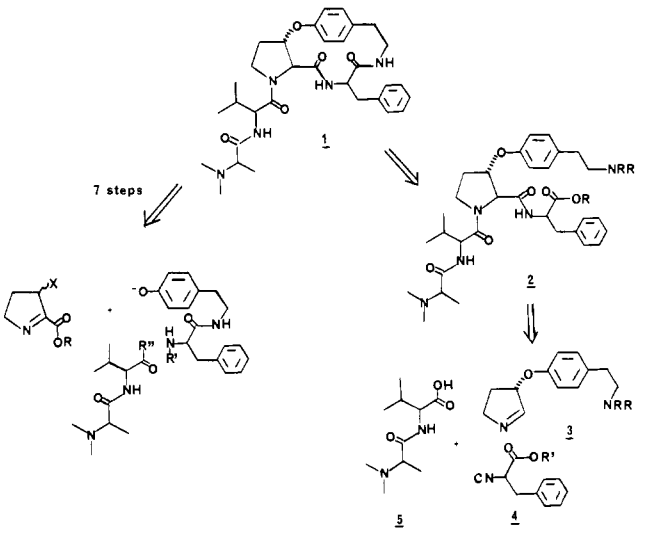
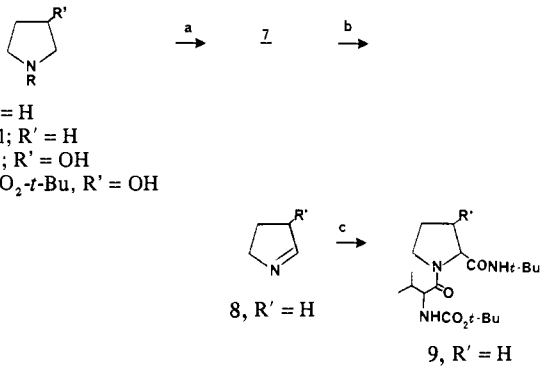
Substituted prolyl peptides are important units in many natural products such as some antibiotic depsipeptides[1] and cyclopeptide alkaloids.[2-4] During our studies directed toward the total synthesis of mauritine A,[2a,3] a cyclopeptide alkaloid, we investigated two approaches for the construction of β-(aryloxy)prolyl peptides. One approach involved the formation of an aryl ether bond via S_N2 displacement on a β-bromopyrroline carboxylate derivative (Scheme I). This method was used in our successful synthesis[3] of dihydromauritine A (**1**) and the recently reported syntheses of two cyclopeptide alkaloids.[4d] Because of our success with the Ugi four-component condensation[5] in the synthesis of the antibiotic furanomycin,[6] we have also investigated this condensation as a totally novel approach for the synthesis of linear precursors of a cyclopeptide alkaloid. This communication describes successful novel studies using the later approach that could potentially afford a linear precursor of a cyclopeptide alkaloid in one step and would be generally applicable to the synthesis of other cyclic secondary amino acid derivatives.

Several years ago, Ugi proposed the four-component method as an alternative to conventional approaches to peptide synthesis.[5]

Scheme I



Scheme II



6, R, R′ = H
7, R = Cl; R′ = H
10, R = H; R′ = OH
11, R = CO_2-*t*-Bu, R′ = OH

[a] *t*-BuOCl. [b] $^-OCH_3$. [c] *t*-BuNC, *t*-BuO_2C-Val-OH.

By controlling conditions, this investigator was able to obtain a high degree of stereoselectivity, thereby making this procedure a valuable tool for an asymmetric synthesis. The four-component condensation generates an N-acylated amino acid amide from an aldehyde, an amine, a carboxylic acid, and an isonitrile. In our system, visualizing the linear precursor of dihydromauritine A (**2**) as an acylated cyclic secondary amino acid amide, a retrosynthetic analysis shows that compounds **3**–**5** are the components needed for carrying out a four-component condensation (Scheme I). Compound **3**, an (aryloxy)pyrroline, represents an intramolecular condensation product of the amine and aldehyde components. This key intermediate can then react with **4**, the isonitrile of the desired amino acid, L-phenylalanine in this case, and a carboxylic acid, the appropriate dipeptide side chain of the cyclopeptide alkaloid, *N*,*N*-dimethyl-L-alanyl-L-valine (**5**), to afford the desired acylated β-(aryloxy)prolyl peptide **2**. The four-component condensation approach would generate the N-acyl bond, the bond to the α carbon of proline, the prolyl amide, and the trans stereochemistry of the proline derivative *all* in one reaction step. The success of such an approach depends mainly on the availability of the key intermediate **3** and on the feasibility of preparing cyclic secondary amino acid peptides by the four-component condensation, a feature with no precedent in the literature. The condensation of an unsymmetrically substituted pyrroline requires both regioselective and stereochemical control. To ascertain the versatility of this novel approach, we designed and carried out several model studies.

The feasibility of synthesizing prolyl peptides by the four-component condensation was demonstrated by the reactions shown in Scheme II. Pyrrolidine (**6**) was treated with *tert*-butyl hypochlorite to afford the corresponding *N*-chloro derivative **7** which was immediately dehydrohalogenated with freshly prepared so-

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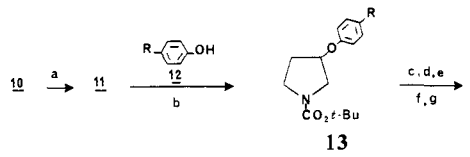
Scheme III



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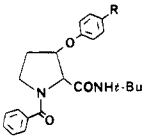

α,β-*trans*-**14**
α,β-*cis*-15

a, R = H
b, R = CH_2CH_2NPhth

[a] *t*-BuOCO$_2$N=C(CN)Ph. [b] NCO_2Et / NCO_2Et, Ph_3P. [c] TFA. [d] K_2CO_3.
[e] *t*-CuOCl. [f] $^-OCH_3$ or DBU. [g] *t*-BuNC, $PhCO_2H$.

dium methoxide to afford the unstable pyrroline **8** which was trapped with *tert*-butyl isonitrile in the presence of Boc-L-valine to afford the *tert*-butylamide of Boc-valylproline (**9**) in 56% yield as a diastereomeric mixture with DL stereochemistry at proline. The product was isolated by extraction and characterized by NMR, HPLC, amino acid analysis, and high-resolution mass spectroscopy.

The synthesis of key intermediate **3** and the feasibility of using (aryloxy)pyrrolidines in the four-component condensation was first examined in a model system using phenol (**12a**) as the aryloxy group (Scheme III). Commercially available 3-hydroxypyrrolidine (**10**) was quantitatively converted into the corresponding *N*-butyloxycarbonyl derivative **11** by using either 2-((*tert*-butylcarbonyloxyimino))-2-phenylacetonitrile (Boc-ON)[7] or di-*tert*-butyl dicarbonate. The aryl ether **13a** was prepared in 82% yield by using equimolar ratios of **11** and **12a** and a 10% excess of both diethyl azodicarboxylate and triphenylphosphine, according to procedures developed by Mitsunobu.[8] Removal of the nitrogen blocking group by treatment with trifluoroacetic acid for a short period of time afforded the protonated phenoxypyrrolidine as the trifluoroacetate salt (99% yield). The free base was generated in situ by stirring an ether suspension of this compound with sodium carbonate. Subsequent treatment of the base with *tert*-butyl hypochlorite at 0 °C gave the *N*-chloro derivative, which was extracted with ether and dehydrohalogenated either with sodium methoxide or diazabicycloundecene to afford the highly unstable pyrroline derivative, which was subjected immediately to the four-component condensation conditions by rapid evaporation of the solvent and addition of methanol, benzoic acid, and *tert*-butyl isonitrile to afford two products (**14a** and **15a**). These products were readily separated by silica gel chromatography and identified as the α,β-cis and -trans isomers of benzamido-β-phenoxyproline *tert*-butyl amide. The cis:trans isomeric ratio was 55:45. Configurational assignments were easily made from the NMR spectra of the two isomers, as the trans isomer exhibits a characteristic singlet for the α proton of the substituted proline, while the α,β-proton coupling constant of the cis isomer is 6 Hz in CD_3OD.

The total yield for the five-step reaction scheme starting with **13a** was 58%. The major side reaction that occurred during the dehydrohalogenation step was the β elimination of phenol. No condensation product derived from dehydrohalogenation in the direction of the δ carbon of the pyrrolidine derivative was observed.

Another model study incorporating a blocked tyramine derivative was also carried out as the reagents resembled more closely those that would be used in a cyclopeptide alkaloid synthesis (Scheme III). The amino group of tyramine was blocked by the phthalimido group by using commercially available (ethoxycarbonyl)phthalimide. Compound **12b** was obtained in 79% yield. Ether formation with Boc-β-hydroxypyrrolidine was accomplished by using 1.1 equiv of triphenylphosphine and diethyl azodicarboxylate to afford **13b** in 75% yield. The *N*-(butyloxy)carbonyl group was removed with trifluoroacetic acid to yield the corresponding trifluoroacetate salt. Deprotonation was carried out by using potassium carbonate in tetrahydrofuran–ether, and dehydrohalogenation was accomplished with diazabicycloundecene to give the desired pyrroline, which was dissolved in methanol and treated immediately with benzoic acid and *tert*-butyl isonitrile to afford a mixture of cis and trans isomers in a 56:44 ratio (**14b** and **15b**). The total yield for the five-step reaction sequence was 56%, with β elimination being again the major side reaction. The spectroscopic properties of **14b** and **15b** were again consistent with their assigned structures, and they showed structural features similar to the other model discussed.

Our model studies clearly show that the four-component condensation can serve as an alternate, novel, and short approach for the synthesis of substituted prolyl peptides. This methodology can also be extended to other cyclic secondary amino acids. We plan to use the four-component condenstion approach for the synthesis of cyclopeptide alkaloids of the amphibine B family. These studies represent the first application of the four-component condensation to the synthesis of cyclic secondary amino acids.

Acknowledgment. We thank Merck Sharp & Dohme Research Laboratories for their help in the determination of elemental analyses, amino acid analyses, HPLC, and ^1H NMR and mass spectral determinations.

Supplementary Material Available: Experimental details, analytical data, R_f, and IR and ^1H NMR spectra for compounds **9**, **11**, **13a**, **14a**, **15a**, **12b**, **13b**, **14b**, and **15b** (2 pages). Ordering information is given on any current masthead page.

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Cyclodextrin Catalysis in the Intramolecular Diels–Alder Reaction with the Furan Diene[1]

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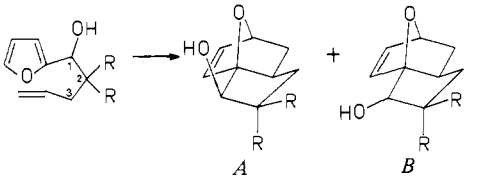
In the course of a broad project directed toward the total syntheses of prostaglandins and tiglianes we needed to investigate the intramolecular Diels–Alder reaction with a substituted furan as the diene component. Our findings[2] indicated that for systems in which the diene (furan ring) and the dienophile were separated by a three-atom chain, substituents on carbon-2 were extremely important. For example, the reaction (eq 1) failed when R = H



(1)

1, R = H
2, R = CH_3
3, R = $-S(CH_2)_3S-$
4, R = OEt

5
6
7
8

or R = CH_3[3a] (**1** and **2**); however, excellent yields were obtained

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