of **9a** (Scheme II).[11] Treatment of **9a** with methanolic potassium fluoride gave 75% of **10a**. When **10a** was treated with a catalytic amount of palladium chloride[12] (0.8 mol %), an 80% yield of **11a** was obtained. In an analogous series of reactions **8b** gave 74% of **9b**; **9b** yielded 81% of **10b**; and **10b** gave 75% of **11b**. Spectroscopic and/or chromatographic comparisons of **9a** and **9b**, **10a** and **10b**, and **11a** and **11b** showed that in each case the isomers were uncontaminated by the epimer. Thus, very epimerically pure $\beta$-amino alcohols and oxazolines can be synthesized from the isonitriles prepared by our method.

In summary, we have shown that the addition of trimethylsilyl cyanide to epoxides is extremely dependent on the nature of the Lewis acid catalyst. With zinc iodide, a new synthetic route to isonitriles has been developed. These isonitriles are extremely useful intermediates for the synthesis of $\beta$-amino alcohols and oxazolines.

**Acknowledgment.** We are indebted to the National Science Foundation for Grant CHE81-14772, which supported this investigation.

**Registry No. 1a**, 286-20-4; **1b**, 1713-33-3; **2a**, 83152-87-8; **2b**, 83152-88-9; **3a**, 83152-97-0; **3b**, 83152-89-0; **4a**, 5456-63-3; **4b**, 5456-63-3; **5**, 285-67-6; **6**, 83152-90-3; **7**, 83152-98-1; **8a**, 36611-94-6; **8b**, 36611-93-5; **9a**, 83152-91-4; **9b**, 83152-94-7; **10a**, 83152-92-5; **10b**, 83152-95-8; **11a**, 83152-93-6; **11b**, 83152-96-9; $(CH_3)_3SiCN$, 7677-24-9; $ZnI_2$, 10139-47-6; *trans*-$\beta$-amino alcohol hydrochloride salt, 31775-67-4.

(11) The stereochemistry of the ring opening of **8a** and **8b** has not been rigorously established. The assignments of the stereochemistry of **9a** and **9b** were made by analogy to the stereochemistry of the ring opening of **1** and **5**.

(12) Bartel, K.; Fehlhammer, W. P. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 599.

## Synthesis of Nanaomycin A and Deoxyfrenolicin by Alkyne Cycloaddition to Chromium–Carbene Complexes

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*Received July 6, 1982*

Deoxyfrenolicin (**1**)[2] and nanaomycin A (**2**)[3] are members of a group of naphthoquinone antibiotics based on the isochroman skeleton. The significant antibiotic activity[2,4] and potential antitumor activity[5] of members of this group have prompted numerous recent synthesis efforts.[6] As part of a general study in naphthoquinone synthesis directed toward granaticin (**3**), we have developed a strategy (Scheme I) that relies on two key steps: cycloaddition of an alkyne (ideally **4**) with a carbene–chromium

Scheme I. Strategy

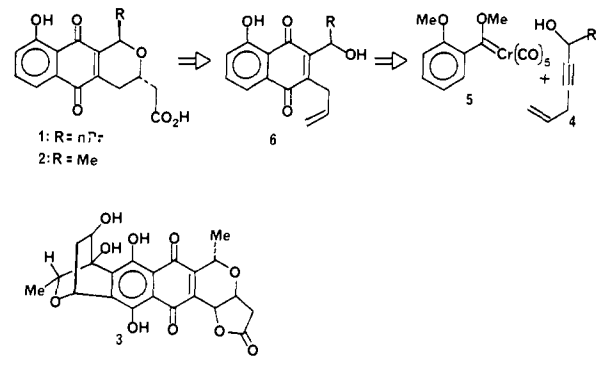
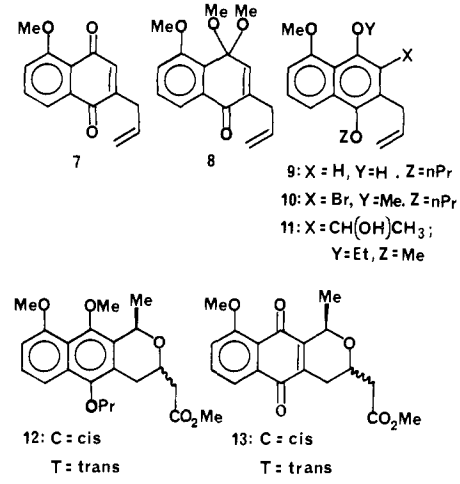



Chart I




complex (**5**)[7] and intramolecular alkoxycarbonylation of an hydroxy alkene (**6**) to form the pyran ring. High regioselectivity and functional group compatibility are required in the alkyne cycloaddition. Since regioselectivity in the alkyne cycloaddition appears to be strongly influenced by steric effects of the alkyne substituents and since the few *di*substituted alkynes that have been tested show poor regioselectivity,[7,8] we studied intermolecular reaction with a very simple *mono*substituted alkyne, allylacetylene.[9]

The first target was nanaomycin A (**2**). Reaction of *o*-lithioanisole[10] with $Cr(CO)_6$ (equimolar) in ether at 25 °C for 2 h followed by addition of methyl fluorosulfonate (3-fold excess) gave the known[11] complex, **5**, as red crystals in 77% yield overall from *o*-bromoanisole. Heating a solution of complex **5** (10 mmol) and allylacetylene (15 mmol) in THF at 45 °C for 36 h led to a red solution. After removal of the volatiles at reduced pressure, the residue was oxidized with ceric ammonium nitrate (aqueous acetonitrile; 25 °C/0.5 h) to give a mixture which was partitioned between ether and water. From the ether was isolated 2-allyl-5-methoxy-1,4-naphthoquinone (**7**, 52% (Chart I)).[12] Alternatively, oxidation of the crude product in methyl alcohol led directly to the monoketal **8** (54% yield). Only one regioisomer was de-

(1) Recipient of an NIH Postdoctoral Fellowship: (a) 1978–1981; (b) 1980–1982.

(2) Deoxyfrenolicin (**1**) is a degradation product of a natural epoxy naphthoquinone, frenolicin: Ellestad, G. Z.; Kunstmann, M. P.; Whaley, H. A.; Patterson, E. L. *J. Am. Chem. Soc.* **1968**, *90*, 1325.

(3) (a) Omura, S.; Tanaka, H.; Koyana, Y.; Oiwa, R.; Katagiri, M. *J. Antibiot.* **1974**, *25*, 363. (b) Tanaka, H.; Koyama, Y.; Marumo, H.; Oiwa, R.; Katagiri, M.; Nagai, T.; Omura, S. *Ibid.* **1975**, *28*, 860. (c) Tanaka, H.; Koyama, Y.; Nagai, T.; Marumo, H.; Omura, S. *Ibid.* **1975**, *78*, 868.

(4) Deoxyfrenolicin shows antibacterial activity in vitro and antifungal activity against a variety of fungi in vivo: (a) van Meter, J. C.; Cann, M.; Bohonos, N. "Antibacterial Agents Annual, 1960"; Plenum Press: New York, 1961; p 77. (b) Iwai, Y.; Kora, A.; Takahashi, Y.; Awaya, T.; Masuma, R.; Oiwa, R.; Omura, S. *J. Antibiot.* **1978**, *31*, 959

(5) For a discussion and leading references, see: Moore, H. W. *Science (Washington, D.C.)* **1977**, *197*, 527.

(6) (a) Naruta, Y.; Uno, H.; Maruyama, K. *Chem. Lett.* **1982**, 609–612. (b) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Chem. Soc., Perkin Trans 1* **1981**, 1197–1202. (c) Ichihara, A.; Ubukata, M.; Oikawa, H.; Murakami, K.; Sakamura, S. *Tetrahedron Lett.* **1980**, *22*, 4469–4477. (d) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1978**, *43*, 4923–4924. (e) Li, T.; Ellison, R. H. *J. Am. Chem. Soc.* **1978** *100*, 6263–6265. (f) Pyrek, J. St.; Achmatowica, O.; Jr.; Zamojski, A. *Tetrahedron* **1977**, *33*, 673–680.

(7) (a) Dotz, K. H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 644–645. (b) Dötz, K. H.; Fügen-Köster, B. *Chem. Ber.* **1980**, *113*, 1449–1457. (c) Dötz, K. H.; Pruskil, I. *J. Organomet. Chem.* **1981**, *209*, C4–C6 and references therein.

(8) Wulff, W. D.; Tang, T. C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677–7678.

(9) While this work was in progress, Dr. Dötz reported a series of similar reactions with allylacetylene and other enynes; see ref 7b.

(10) This compound can be prepared either by bromine–lithium exchange with *n*-butyllithium in hexane [according to the procedure: Glaze, W. H.; Ranade, A. C. *J. Org. Chem.* **1971**, *36*, 3331] or by direct metalation of anisole with *n*-butyllithium in ether [see: Ronald, R. C. *Tetrahedron Lett.* **1975**, 3973–3977 and references therein].

(11) Fischer, E. O.; Kreiter, C. G.; Kollmeier, H. J.; Muller, J.; Fischer, R. D. *J. Organomet. Chem.* **1971**, *28*, 237.

(12) Eisenhuth, W.; Schmid, H. *Helv. Chim. Acta* **1958**, *41*, 2021.

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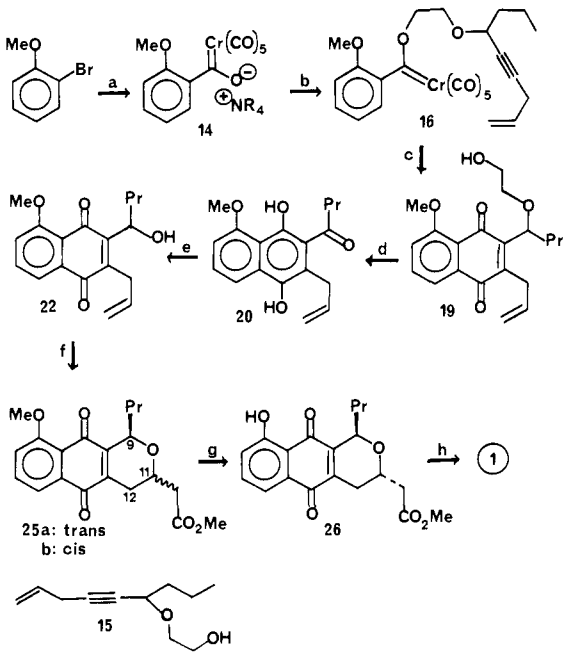
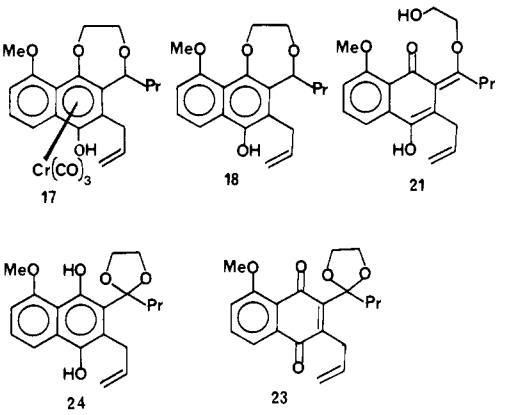
Scheme II. Synthesis of Deoxyfrenolicin (1)



[a] *n*-BuLi, ether, −78 °C; $Cr(CO)_6$, ether, 25 °C; $Me_4N^+Br^-$, $H_2O$. [b] AcCl, −20 °C, $CH_2Cl_2$, alcohol **15** (1.0 mol equiv), $CH_2Cl_2$, 25 °C, 6 h. [c] 35 °C, 64 h, ether; DDQ, $CH_3CN$, 1 h. [d] 5 N $H_2SO_4$, MeOH, 6 days. [e] $NaBH_4$, THF, 25 °C, 24 h; DDQ, MeOH, 0 °C, 1 h. [f] $CuCl_2$ (3 mol equiv), $PdCl_2(CH_3CN)_2$ (0.1 mol equiv), MeOH, CO (1.1 atm), 25 °C, 3.3 h. [g] 10 mol equiv $BBr_3$, $CH_2Cl_2$, −78 to 0 °C, 10 min. [h] KOH, MeOH, 25 °C, 2.5 h.

tected, and the orientation is consistent with previous observations.[7,8] Addition of a carbon substituent at C-3 in **7** or **8** proved difficult. Direct 1,4-addition of carbonyl anion equivalents to **8** failed. A multistep procedure was developed starting with reduction of **7** ($Na_2S_2O_4$) and monoalkylation (*n*-propyl iodide, $K_2CO_3$) to give **9** (76% yield). Then bromination (*N*-bromosuccinimide, $CH_3CN$, −30 °C) followed by methylation provided **10** (70% yield). Lithiation (*n*-BuLi, ether, −78 °C) followed by quenching with acetaldehyde (−100 °C) gave **11** (90% yield).[13] Following our general development of intramolecular alkoxycarbonylation,[14] **11** was treated with $PdCl_2$ (1.1 mol equiv) and $CuCl_2$ (3.0 mol equiv) in methyl alcohol at 25 °C for 4 h under 1.1 atm of CO. The major products were the isomers **12T** (30%) and **12C** (45%).[15] Oxidation [Ce(IV), acetonitrile, $H_2O$] of **12T** produced **13T** in 79% yield, while **13C** was obtained from **12C** (75%) under the same conditions.[16] Since **13C** can be epimerized to **13T** in a favorable process[6a] and **13T** has been converted to nanaomycin A (**2**),[6a,b] a formal synthesis of racemic **2** was complete. However, while high regioselectivity in the acetylene cyclization was obtained, the modest yields and long sequence to introduce the C-3 substituent led us to consider alternatives.

Chart II



Using intramolecular reaction to control regioselectivity, we can report a short, convergent pathway for the synthesis of deoxyfrenolicin (**1**) as outlined in Scheme II, starting again from *o*-bromoanisole. Reaction of *o*-lithioanisole with chromium hexacarbonyl gave a lithium salt that could be exchanged with tetramethylammonium ion and precipitated from water as **14**.[17] Formation of the acetate and immediate displacement of acetate by the primary hydroxyl group of alcohol **15**[18,19] gave carbene complex **16**[20] as a red oil (88% yield from **14**). When heated at 35–37 °C in ether, complex **16** began to cyclize; after 64 h, the volatile material was removed at reduced pressure to leave a crude product expected to be complex **17** (Chart II). The free ligand (**18**) was obtained by treatment with excess triphenylphosphine in acetone at 25 °C, but more efficiently, treatment of the crude complex **17** with 2,3-dichloro-5,6-dicyanoquinone in aqueous acetonitrile caused removal of chromium and conversion to quinone **19**. Chromatography of the product from oxidation provided **19** as a yellow oil in 51% yield.[21] By simple treatment with aqueous acid, the hydroxyethyl side chain was lost and the keto hydroquinone **20** was obtained in 95% yield.[21] Presumably enolization produced the *o*-quinomethide **21**; ring closure gives ketal **22**, which is hydrolyzed. The quinone ketal **23** is obtained from **19** simply on standing in air for several weeks, presumably by a similar process and air oxidation. Hydride reduction followed by oxidation back to the quinone converts **20** into **24** (78% yield),[21] the substrate for alkoxycarbonylation.

Quinone **24** underwent alkoxycarbonylation promoted by Pd(II) in methyl alcohol under a positive pressure of CO (1.1 atm). After 3.3 h at 25 °C, the crude product was obtained and chromatographed to provide a mixture of **25a** and **25b** (70% yield). Analytical HPLC indicated a 3:1 ratio of **25a**:**25b**. The major component was obtained by crystallization as orange needles, mp 134–136 °C.[21] The minor product was also obtained by crystallization from the mother liquor (mp 144–148.5 °C) and identified as the cis isomer **25b**.[2] Treatment of the phenol ethers (separately or as a mixture) with $BBr_3$ causes demethylation to the phenol for both **25a** and **25b**, and complete isomerization of the cis arrangement in **25b** into the natural trans series, **26** (84%

(13) The formation of **1** is based on an essentially identical procedure used in a somewhat different overall strategy; see ref 6b.

(14) (a) Zask, A. Ph.D. Thesis, Princeton University, Princeton, NJ, 1982. (b) Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.*, in press. (c) For a discussion of this general reaction, see: Stille, J. K.; Hines, L. F.; Fries, R. W. Wong, P. K.; James, D. E.; Lau, K. *Adv. Chem. Ser.* **1974**, *No. 132*, 90. Collman, J. P.; Hegedus, L. S. "Principles and Applications of Organotransition Metal Chemistry", University Science Books: Mill Valley, CA, 1980; pp 585, 604. James, D. E.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810. The problems associated with Pd-promoted addition of nucleophiles to alkenes followed by carbonylation have been discussed recently; the same work describes examples of intramolecular addition of amine nucleophiles with CO trapping that are efficient in a limited number of examples: Hegedus, L. S.; Allen, G.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583.

(15) The isomers **12** were separated by multidevelopment layer chromatography (hexane:ether, 2:1; $SiO_2$). The colorless oils were characterized by comparison of spectral data with the closely related analogues (OPr replaced by OMe) reported in detail in ref 6b. The stereochemical assignment is clear only after oxidation to **13C** and **13T**.

(16) The isomers **13C** and **13T** were prepared by the same oxidation procedure, fully characterized, and converted to (±)-nanaomycin A (**2**) by Kometani, ref 6b.

(17) Fischer, E.; Maasböl, A. *Chem. Ber.* **1967**, *100*, 2445–2456.

(18) For examples of the general procedure, see: (a) Fischer, E. O.; Selmayr, T.; Kreissl, F. R. *Chem. Ber.* **1977**, *110*, 2947–2955. (b) Semmelhack, M. F.; Bozell, J. J. *Tetrahedron Lett.* **1982**, *23*, 2931–2934.

(19) The alcohol **15** was prepared by the following path. Sequential treatment of the tetrahydropyranyl ether of 1-hexyn-3-ol with *n*-BuLi, CuI, and allyl bromide produced non-1-en-4-yn-6-ol after cleavage of the THP-ether. Alkylation of this alcohol with ethyl bromoacetate (NaI, NaH, THF) produced an ester that was reduced with $LiAlH_4$ to give **15**.

(20) The carbene complex **16** was isolated by concentration of the reaction mixture at 25 °C, trituration of the residue with pentane, filtration, and removal of the pentane. The pentane-soluble material was used directly in the next stage. In this and related cases,[18b] spectral analysis of the crude carbene complex indicated relatively high (90–95%) purity.

(21) For characterization data for **19**, **20**, **24**, **25a**, and **25b**, see the Supplementary Material.

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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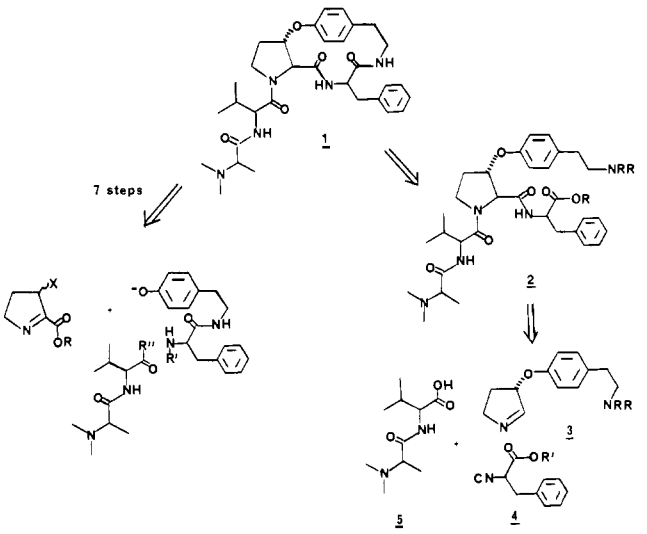
*Received July 19, 1982*

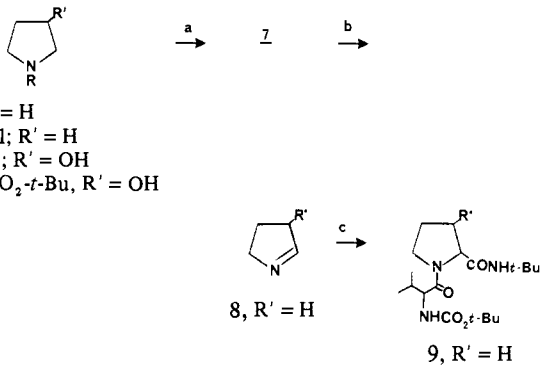
Substituted prolyl peptides are important units in many natural products such as some antibiotic depsipeptides[1] and cyclopeptide alkaloids.[2-4] During our studies directed toward the total synthesis of mauritine A,[2a,3] a cyclopeptide alkaloid, we investigated two approaches for the construction 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

**8**, R′ = H

**9**, R′ = H

[a] *t*-BuOCl. [b] $^-OCH_3$. [c] *t*-BuNC, *t*-Bu$O_2$C-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-

(1) (a) Smirnova, I. G.; Katnkha, G. S.; Silaev, A. B. *Khim. Brir. Soedin.* **1974**, *10*, 532. (b) Crooy, P.; DeNeys, R. *J. Antibiot.* **1972**, *25*, 371. (c) Kingston, D. G. I.; Kolpak, M. X. *J. Am. Chem. Soc.* **1980**, *102*, 5964.

(2) (a) Tschesche, R.; Wilhelm, H.; Fehlhaber, H. W., *Tetrahedron Lett.* **1972**, 2609. (b) Tschesche, R.; Kaussmann, E. U. In "The Alkaloids"; Manske, R. H., Ed.; Academic Press: New York, 1975; Vol. 15, Chapter 4, p 193.

(3) Nutt, R. Ph.D. Dissertation, University of Pennsylvania, Philadelphia, PA, 1981.

(4) (a) Schmidt, U.; Griesser, H.; Lieberknecht, A.; Talbiersky, J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 280. (b) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Hausler, J. *Ibid.* **1981**, *20*, 281. (c) Schmidt, U.; Bokens, H.; Lieberknecht, A.; Griesser, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1026.

(5) (a) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8. (b) Ugi, I. In "The Peptides"; Meienhofer, J., Gross, E., Ed.; Academic Press: New York, 1980; Chapter IV, p 365. (c) Ugi, I.; Marquarding, D.; Urban, R. In "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins"; Weinstein, B., Ed.; Marcel Dekker: New York, 1982; Vol. 6, p 245.

(6) Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullié, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505.

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