Stereoselective Total Syntheses of Amauromine and 5-*N*-Acetylardeemin. A Concise Route to the Family of "Reverse-Prenylated" Hexahydropyrroloindole Alkaloids

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Amauromine (**1**),[2] ardeemin (**2**),[3] and 5-*N*-acetylardeemin (**3**)[3] are members of a burgeoning class of biologically active indole alkaloids (including aszonalenin,[4] roquefortine,[5] and the flustramines[6]) featuring a hexahydropyrrolo[2,3-*b*]indole nucleus, substituted at the benzylic ring junction with a 1,1-dimethylallyl ("reverse-prenyl") group.[7] Amauromine is a vasodilator, apparently operating through calcium antagonism.[2a] Compound **3** is one of the most potent known agents for reversal of multiple drug resistance (MDR), as measured against KBV-1 (vinblastine resistant) tumor cell lines.[3] The novel structures of these compounds, as well as the goal of studying structure–activity relationships, prompted an exploration of their total synthesis. A route to amauromine had been reported,[2c] via a thio-Claisen rearrangement. However, that pathway was low-yielding, lacked usable stereocontrol, and was not necessarily applicable to preparing **3**.

We noted that, in principle, **1**, **2**, and **3** could be obtained from the hypothetical tricyclic amino acid **4** which is formally derived from a tryptophan precursor **5** by alkylative cyclization (Figure 1; protection states of **4** and **5** are unspecified). As our study began, no method for achieving a transformation of the type **5** to **4** was known in the tryptophan series. We were not optimistic about the prospects for introduction of a 1,1-dimethallyl moiety at the *gem*-dimethyl carbon in the required series, in serviceable yield, via direct alkylative cyclization (path a).[8,9] A more promising possibility seemed to be that contemplated in path b, wherein a heteroatom-mediated oxidative cyclization of **5** leads to **6**.[10] Following suitable activation, a resultant cationoid species would serve to alkylate a reverse-prenyl nucleophile. This strategy relies on an expected strong preference for a cis interlocked 5,5-ring system to enforce cis stereochemistry in both the oxidative cyclization and alkylation steps. Furthermore, it requires that efficient transmission of stereochemical information from the tryptophan stereogenic center to the emerging junction occur in the heteroatom-mediated cyclization. *Indeed, these concepts have been realized and are reported in this communication in the context of total syntheses of 1, 2, and 3.*

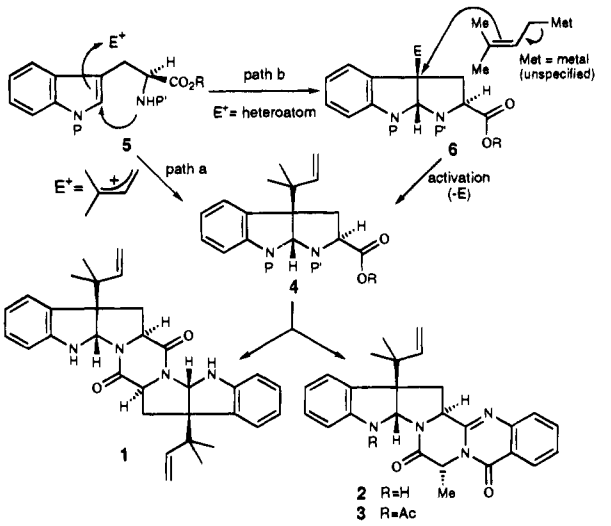

Figure 1.

Our starting material was bis(Boc)tryptophan methyl ester **7** (Scheme 1).[11] This compound reacted with *N*-phenylselenophthalimide[12] and catalytic *p*-toluenesulfonic acid to give a 78% yield of 3-selenenylated pyrroloindole **8** as an inseparable 9:1 mixture of diastereomers, following the equilibration of an initial 1:1 mixture. Happily, treatment of **8** with methyl triflate and prenyl tributylstannane[13] (in the presence of 2,6-di-*tert*-butylpyridine) gave a 60% yield of **9**, bearing the reverse prenyl group at the desired position as an unchanged 9:1 diastereomeric mixture. Remarkably, no products due to simple proton loss in the presumed benzylic cation intermediate were observed.[14] After saponification of **9** to acid **10**, chromatographic separation of the diastereomers was possible. In addition, the Boc groups could be simultaneously removed to give the aminal **11**, which was again isolated as a single diastereomer.

With our subgoal attained, we first proceeded toward the total synthesis of **1**. BOP chloride-mediated coupling of **10** and the

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(2) (a) Isolation: Takase, S.; Iwami, M.; Ando, T.; Okamoto, M.; Yoshida, K.; Horiai, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1984**, *37*, 1320. (b) Structure: Takase, S.; Kawai, Y.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron* **1985**, *41*, 3037. (c) Synthesis: Takase, S.; Itoh, Y.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron* **1986**, *42*, 5887.

(3) (a) Biological activity: Karwowski, J. P.; Jackson, M.; Rasmussen, R. R.; Humphrey, P. E.; Poddig, J. B.; Kohl, W. L.; Scherr, M. H.; Kadam, S.; McAlpine, J. B. *J. Antibiot.* 1993, *46*, 374. (b) Isolation and structure: Hochlowski, J. E.; Mullally, M. M.; Spanton, S. G.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J. Antibiot.* **1993**, *46*, 380.

(4) Kimura, Y.; Hamasaki, T.; Nakajima, H.; Isogai, A. *Tetrahedron Lett.* **1982**, *23*, 225.

(5) (a) Scott, P. M.; Merrien, M.-A.; Polonsky, J. *Experientia* **1976**, *32*, 140. (b) Scott, P. M.; Polonsky, J.; Merrien, M.-A. *J. Agric. Food Chem.* **1979**, *27*, 201.

(6) Flustramine A: Carlé, J. S.; Christophersen, C. *J. Am. Chem. Soc.* **1979**, *101*, 4012. Flustramine C: Carlé, J. S.; Christophersen, C. *J. Org. Chem* **1981**, *46*, 3440.

(7) There are also examples of a complementary family of alkaloids wherein the reverse-prenyl group is found at the 2-position of the indoline. (a) Gypsetin: Shinohara, C.; Hasumi, K.; Takei, Y.; Endo, A. *J. Antibiot.* **1994**, *47*, 163. (b) Brevianamide E: Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329.

(8) In the corresponding tryptamine series, where the issue of stereochemical information transfer does not exist, two methods for the direct introduction of a 1,1–dimethyl*propynyl* group have been reported to give a modest yield: (a) Hino, T.; Hasumi, K.; Yamaguchi, H.; Taniguchi, M.; Nakagawa, M. *Chem. Pharm. Bull.* **1985**, *33*, 5202. (b) Nakagawa, M.; Ma, J.; Hino, T. *Heterocycles* **1990**, *30*, 451.

(9) Direct alkylative cyclization of tryptamine derivatives with prenyl halides occurs exclusively at the primary carbon to give the undesired 3,3-dimethylallyl regioisomer. Bocchi, V.; Casnati, G.; Marchelli, R. *Tetrahedron* **1978**, *34*, 929.

(10) Numerous examples of protonic or oxidative cyclizations of the type **5** to **6** are known in both the tryptamine and tryptophan series. However, these methods did not fulfill our criteria for efficient stereocontrol during cyclization (**5** to **6**) nor for subsequent activation in the substitution by the reverse-prenyl nucleophile (**6** to **4**). (a) For a review, see: Hino, T.; Nakagawa, M. In *The Alkaloids*; Brossi, A., Ed.; Academic Press, Inc.: New York, 1988; Vol. 34, p 1. (b) See also: Bruncko, M.; Crich, D. *J. Org. Chem.* **1994**, *59*, 4239 and related references therein.

(11) Prepared in two steps from L-tryptophan: Franzen, H.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Chem. Commun.* **1984**, 1699. However, we chose to prepare **7** from L-tryptophan methyl ester by treatment with BOC_2O (3 equiv), NaOH (5 equiv), and NBu_4HSO_4 (10 mol %) in CH_2Cl_2 (91% yield).

(12) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

(13) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Chem. Lett.* **1986**, 1857.

(14) This stability possibly arises from the reluctance of the ring system to approach planarity, wherein the bulky Boc groups would be forced into close proximity.

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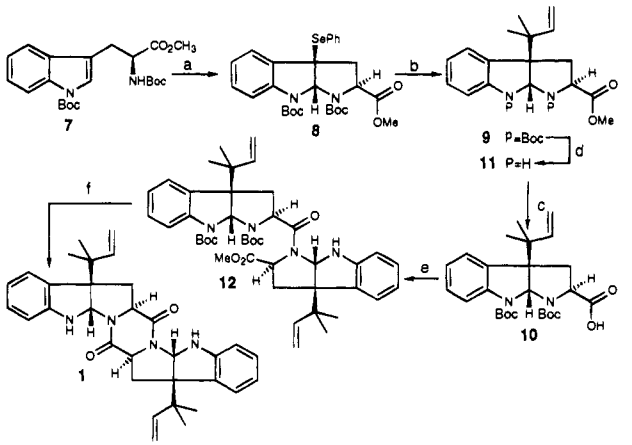
Scheme 1[a]



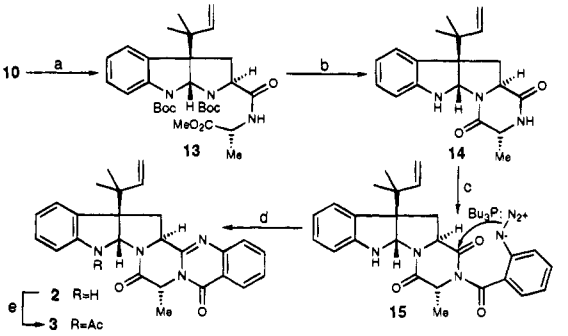
[a] Reagents and conditions: (a) *N*-phenylselenophthalimide (1.5 equiv), *p*-toluenesulfonic acid (0.1 equiv), Na_2SO_4, CH_2Cl_2, 78%; (b) MeOTf (4.5 equiv), prenyl tributylstannane (4.5 equiv), 2,6-di-*tert*-butylpyridine (4.5 equiv), CH_2Cl_2, −78 °C to reflux, 60%; (c) NaOH, THF, methanol, reflux, 98%; (d) TMSI (2.4 equiv), CH_3CN, 0 °C to room temperature, 83%; (e) **11** (1.1 equiv), **10** (1 equiv), BOP-Cl (1.2 equiv), Et_3N (2.3 equiv), CH_2Cl_2, 78%; (f) TMSI (4 equiv), CH_3CN, 0 °C to room temperature 58%.

hindered amine **11** proceeded in 78% yield to give peptide **12**.[15] Removal of the remaining Boc groups with iodotrimethylsilane was accompanied by spontaneous cyclization to furnish, directly, amauromine[16] (**1**) in only five linear steps from bis(Boc)-tryptophan methyl ester and an overall yield of 16%.

Coupling of **10** with D-alanine methyl ester (Scheme 2), using standard agents[17] afforded, in addition to the expected **13**, considerable amounts of a minor product, presumably arising through epimerization of the "α-tryptophan" stereogenic center. However, *in situ* generation of the acyl fluoride of **10** followed by its condensation with D-alanine methyl ester resulted in clean conversion (71%) to peptide **13**.[18] The diketopiperazine **14** was obtained in 76% yield upon deprotection of **13** and ammonia-DMAP-induced cyclization.

An intramolecular variant of the aza-Wittig reaction[19] was used for efficient fusion of the (3*H*)-quinazolin-4-one sector. Following acylation of **14** with *o*-azidobenzoyl chloride, the resultant **15** reacted with tributylphosphine in benzene to afford ardeemin (**2**) in 56% yield from **14**. Finally, acylation of **2** provided 5-*N*-acetylardeemin[20] (**3**) in 11% overall yield for the total synthesis.

Scheme 2[a]



[a] Reagents and conditions: (a) cyanuric fluoride (4 equiv), pyridine (1 equiv), CH_2Cl_2, −15 °C, and then D-Ala-OMe·HCl (1 equiv), $NaHCO_3$ (2 equiv), H_2O, CH_2Cl_2, 71%; (b) TMSI (3 equiv), CH_3CN, 0 °C, and then NH_3, methanol, DMAP, 76%; (c) KHMDS (1.1 equiv), *o*-azidobenzoyl chloride (2.4 equiv), THF, −78 °C, 80%; (d) PBu_3 (1.2 equiv), PhH, 72%; (e) LDA (2.5 equiv), THF, -78 °C to room temperature, and then AcCl, reflux, 82%.

In summary, *the core structure of the three reverse prenylated hexahydropyrroloindole alkaloids was assembled rapidly and stereoselectively (through thermodynamic control) from a suitably protected tryptophan in two steps.* The value of this approach was demonstrated by concise and efficient syntheses of **1**, **2**, and **3**. Applications to related natural products as well as SAR studies in the anti-MDR properties of the ardeemins will be pursued.

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(15) Attempted couplings with other reagents were uniformly unsuccessful. For an additional example of a BOP chloride-mediated coupling of a hindered secondary amine where other reagents failed, see: Danishefsky, S. J.; Harrison, P. J.; Webb, R. R., II; O'Neill, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1421.

(16) Identical in all respects with an authentic sample of the natural material, kindly provided by the Fujisawa Pharmaceutical Co., Japan.

(17) Attempted activating agents include DCC/DMAP, DCC/HOBT, isobutyl chloroformate, and BOP chloride.

(18) Carpino, L. A.; Mansour, E-S. M. E.; Sadat-Aalaee, D. *J. Org. Chem.* **1991**, *56*, 2611.

(19) Takeuchi, H.; Hagiwara, S.; Eguchi, S. *Tetrahedron* **1989**, *45*, 6375.

(20) Identical in all respects with an authentic sample of the natural material, kindly provided by Abbott Laboratories.