Total Synthesis of 5-*N*-Acetylardeemin and Amauromine: Practical Routes to Potential MDR Reversal Agents

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Abstract: The total synthesis of the title compounds has been accomplished. The key step involves the kinetic stereoselective conversion of **19** → **20**. The synthesis of **20** represents for the first time a direct method for constructing *exo*-pyrroloindoles from protected tryptophans in a highly diastereoselective manner. This step was followed by reverse prenylation (see conversion of **20** → **27**). Using the methodology worked out for the titled compounds, a practical synthesis of several promising MDR reversal agents was possible. Biological data that provided the basis for selection of candidates for advanced study are presented. Preliminary profiling of the zones of the molecules that are responsive to changes while still retaining MDR reversal ability are described. On the basis of these findings, compounds **2**, **50**, and **51** were selected for more extensive biological follow-up.

Introduction

In 1993, as part of a screening program for biologically active metabolites, McAlpine and co-workers found that extracts of the fungus *Aspergillus fischerii* (var. brasiliensis) demonstrated the ability to restore vinblastine sensitivity to a tumor cell line that was otherwise insensitive.[1a,b] Isolation of the active components from the fermentation mixture led to the characterization of three structurally related agents, which were called the a*rdeem*ins for their ability to reverse drug insensitivity (vide infra). The major and most active constituent was named 5-*N*-acetylardeemin (Figure 1, **2**). Two other constituents isolated from the product mixture were termed ardeemin (**1**) and 15bβ-hydroxy-5-*N*-acetylardeemin (**3**). Structurally, the ardeemins belong to an interesting class of natural products, which we have termed the "reverse prenyl" hexahydropyrrolo[2,3-*b*]indole alkaloids. Another reverse prenyl alkaloid is the potent vasodilator amauromine (**4**), isolated by Takase and co-workers from the Amauroascus sp. 6237.[2]

Our interest in the ardeemins was influenced to no small extent by the method that guided their isolation and purification. The bioassay logic involved the ability of fermentation isolates to restore vinblastine sensitivity to cell lines that had become insensitive (by selection) to this and other cytotoxic agents. Cells manifesting "operational resistance" (i.e., regardless of mechanism) to cytotoxic agents are said to be multidrug resistant (MDR).[3] Thus, 5-*N*-acetylardeemin would be termed a naturally occurring MDR reversal agent.[4] One mechanism widely associated with MDR apparently arises from overexpression of an efflux glycoprotein, Pgp-170.[5] However, MDR is a multifactorial phenomenon.[6] Inhibition of Pgp-170 alone may not suffice to accomplish reversal because cells employ diverse strategies to thwart the action of drugs.

In vitro studies indicated that a 10 μM concentration of **2** enhanced vinblastine sensitivity to the resistant cell line (KBV-1), which dramatically lowered the resistance from 1600- to 6-fold.[1a] Put another way, in this cell line, compound **2** allows for maintenance of vinblastine cytotoxicity, but at a 250-fold reduced dosage. Were this type of capability generalizable and translatable to clinical reality, it could have major ramifications for chemotherapy. In separate experiments, **2** was 10-fold more effective than verapamil in chemosensitizing KBV-1 to vinblastine. These findings were potentially impressive in that increased potency reduces the likelihood of toxic complications from the MDR reversal agent itself. Interestingly, while compound **3** was also found to be active, ardeemin (**1**) was, apparently, rather less potent as an MDR reversal agent in its initial screen against KBV-1 cells.[1a] The presence of the N-5 acetate group in **2** versus **1** and the resulting impact on MDR activity is intriguing.

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(1) (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.

(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.

(3) For a review of this area see: *Molecular and Cellular Biology of Multidrug Resistance in Tumor Cells*; Robinson, I. B., Ed.; Plenum Press: New York, 1991.

(4) For another instance of a naturally occurring MDR reversal agent see: Stratman, K.; Burgoyne, D.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Org. Chem.* **1994**, *59*, 7219.

(5) (a) Georges, E.; Sharom, F. J.; Ling, V. *Adv. Pharmacol.* **1990**, *21*, 185. (b) Pastan, I. H.; Gottesman, M. M. *Important Adv. Oncol.* **1988**, *1*, 13.

(6) *Drug Resistance*; Hait, W. N., Ed.; Kluwer Academic Publishers: Boston, 1996.

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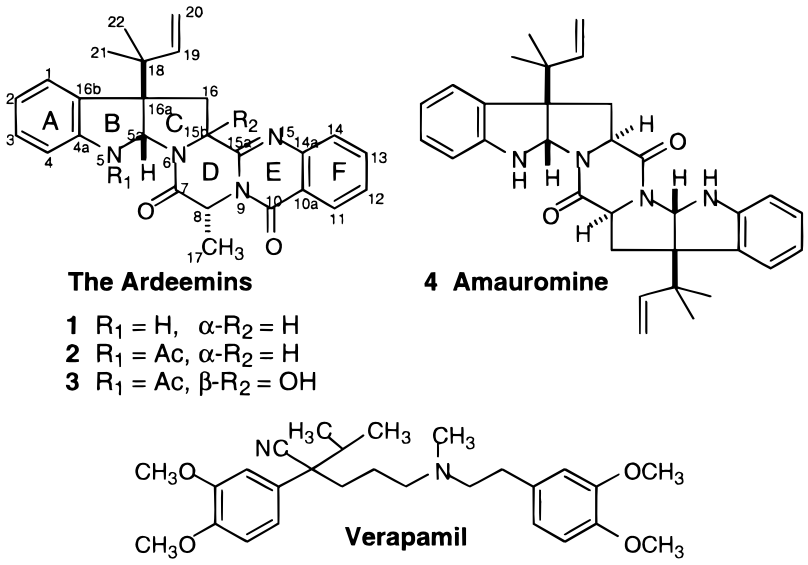


Figure 1.

Inspection of the ardeemin architecture reveals an alkylatively cyclized L-tryptophan residue, linked in a diketopiperazine arrangement to a D-serine residue. Furthermore, the mixed diketopiperazine arrangement in the ardeemin series is fused, through a benzopyrazinone motif, to an anthranilic acid. The related and simplified structure of amauromine is comprised of a C_2-symmetric arrangement, wherein two identical reverse prenylated cyclic tryptophan moieties are united as a diketopiperazine. Not surprisingly, acidic hydrolysis of amauromine leads to cleavage of the linking ring and loss of the angular reverse prenyl group to yield L-tryptophan. By way of comparison we include the structure of the calcium channel blocker verapamil, which is a well-known MDR reversal agent. Unfortunately, the clinical efficacy of verapamil is sharply compromised by attendant cardiotoxicity (vide infra).[7] At this time, there is no information on the question of the degree of mechanistic homology, if any, between verapamil and 5-*N*-acetylardeemin.

A common feature of the ardeemins and amauromine is the presence of a "reverse prenyl" (α,α-dimethallyl) group at the junction of rings B and C of the cyclized tryptophan. Numerous examples of cyclized tryptophan alkaloids, differing in the nature of the substitution at the BC junction, are known, such as in gypsetin,[8] brevianamide E,[9] asperlicin E,[10] himastatin,[11] and the flustramines.[12] Other patterns of cyclized tryptophans that lack the angular prenyl or reverse prenyl feature are hodgkinsine[13] and physostigmine.[14] It is conceivable that in those alkaloids that contain the reverse prenyl group at C3 this function is introduced biosynthetically by alkylation, in an S_N2' sense, via a prenylated cysteine of a prenyl transferase. The latter may, in turn, be generated via the action of prenyl pyrophosphate on a cysteine residue.[15] Subsequent or concurrent 5-*exo* cyclization[16] of the tryptophyl α-amino group onto the intermediate indolenine would complete construction of the pyrroloindole. For thermodynamic and, possibly, kinetic reasons, the fusion of the pyrroloindole moiety is established in a *cis* sense. In the biosynthesis of the ardeemins, the reverse prenyl group emerges *syn* to the tryptophan "carboxyl" function and on the *exo* face of the pendant pyrroloindole system. However, in other related systems, both the *syn* and *anti* (*exo*) dispositions are encountered (Figure 2). The stereochemical relationship of the pyrroloindole junction and the tryptophyl-derived acyl group will be discussed further as the account unfolds.

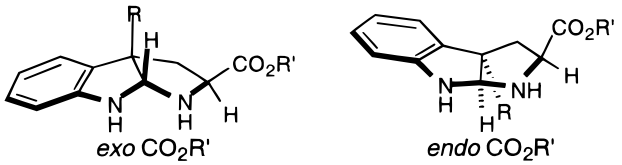


Figure 2.

The ardeemins and amauromine are available from fermentation only with considerable difficulty and were not *at all* available to our laboratory. Thus, total chemical synthesis would be the only recourse for our laboratory to gain access to significant quantities of these compounds. With synthetically derived material, we would hope to study 5-*N*-acetylardeemin itself, in detail, as to its in vivo and in vitro performances. With synthetic intermediates as well as the natural product at hand, we would also be in a position to generate analogue structures in the context of a SAR evaluation.

In addition to the strong inducements at the biological level for a total synthesis venture, the chemical issues requiring

(7) Ozols, R. F.; Cunnion, R. F.; Klecker, R. W.; Hamiltion, T. C.; Ostchega Y.; Parillo, J. E.; Young, R. C. *J. Clin. Oncol.* **1987** *5*, 641.

(8) a) Isolation: Shinohara, C.; Hasumi, K.; Takei, Y.; Endo, A. *J. Antibiot.* **1994**, *47*, 163. (b) Nuber, B. Hansske, F.; Shinohara, C.; Miura, S.; Hasumi, K.; Endo, A. *J. Antibiot.* **1994**, *47*, 168. (c) Synthesis: Schkeryantz, J. M.; Woo, J. C. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 7025.

(9) (a) Isolation: Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329. (b) Synthesis: Kametani, T.; Kanaya, N.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 3974.

(10) Houck, D. R.; Ondeyka, J.; Zink, D. L.; Inamine, E.; Goetz, M. A.; Hensens, O. D. *J. Antibiot.* **1988**, *41*, 882.

(11) Kamenecka, T. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2995.

(12) Flustramine A: (a) Carlé, J. S.; Christophersen, C. *J. Am. Chem. Soc.* **1979**, *101*, 4012. (b) Carlé, J. S.; Christophersen, C. *J. Org. Chem.* **1980**, *45*, 1586. Flustramine C: (c) Carlé, J. S.; Christophersen, C. *J. Org. Chem.* **1981**, *46*, 3440. Flustramine D: (d) Wright, J. L. C. *J. Nat. Prod.* **1984**, *47*, 893. (e) Laycock, M. V.; Wright, J. L. C.; Findlay, J. A.; Patil, P. D. *Can. J. Chem.* **1986**, *64*, 1312.

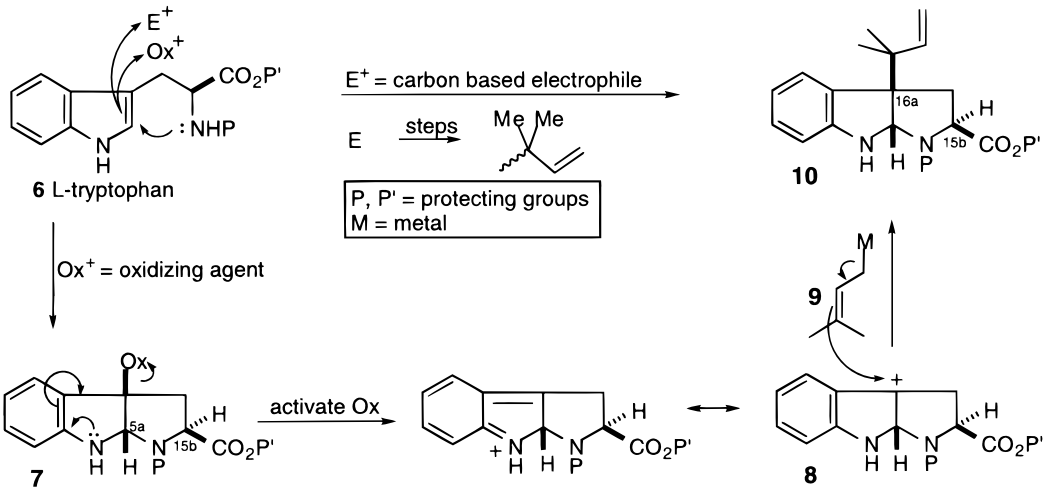
(13) Fridrichsons, J.; Mackay, M. F.; Mathieson, A. M. *Tetrahedron* **1974**, *30*, 85, and references therein.

(14) Takano, S.; Ogasawara, K. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1989; Vol. 36, p 225.

(15) For conjectures concerning the biosynthesis of such natural products see: (a) Bycroft B. W.; Landon, W. *J. Chem. Soc., Chem. Commun.* **1970** 168. (b) Bycroft, B. W.; Landon, W. *J. Chem. Soc., Chem. Commun.* **1970**, 967.

(16) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

Scheme 1



attention in such a project were of inherent interest. Given the range of structures bearing angularly functionalized pyrroloindole systems (vide supra), it seemed probable that solutions to the ardeemin or amauromine assembly problems would find broader applicability. Herein, we present our successful total syntheses of 5-*N*-acetylardeemin (**2**) and amauromine (**4**).[17] We do this in the context of a more general route to the introduction of allyl and reverse prenyl functionality in the angular position of the hexahydropyrroloindole alkaloids. We also describe some potentially informative SAR work, which was enabled by the synthetic advances.

Synthetic Planning

For obvious reasons, we hoped to take advantage of the commercial availability (of L-tryptophan) and its various derivatives (see generalized structure with P and P′ unspecified). Our first subgoal would be pyrroloindole **10**, bearing the angular reverse prenyl group in the required *syn* relationship to the tryptophan carboxyl (Scheme 1). An idealized solution to the problem is seen in the hypothetical construction **6** → **10**. In this perception, reverse prenylation of **6** at position 3 of the indole would set the stage for cyclization via the side chain NH function of a suitably protected tryptophan. This general concept, in various modalities, had been inherent in several previous approaches toward the construction of the pyrroloindoles.[18−20] Its success would depend, in the first instance, on introduction of a functional carbon electrophile, capable in some way of progression to a reverse prenyl group. Included under this formalism would be the special case where the electrophile (E^+) corresponded to the intact reverse prenyl group. Moreover, successful application brings with it the proviso that the chiral center of the tryptophan substrate shall order the sense of pyrroloindole formation such that the acyl group is presented on the convex face of the cup-shaped product.

While all reasonable possibilities for achieving such a direct alkylative cyclization of a suitable tryptophan derivative had certainly not been exhausted,[18−20] another as yet totally untested and, therefore, more interesting possibility presented itself. In this view of the problem, a *cis*-fused pyrrolindole (cf. **7**) would be fashioned by a more precedented oxidative cyclization[21] of **6** via the generalized oxidant "Ox^+". It was further supposed that following appropriate activation, homolysis or heterolysis of the angular leaving group could be induced. Regarding the latter possibility, electronic accession from the indolic nitrogen could greatly facilitate expulsion of the angular hetero group, resulting in cation **8**. It was further supposed that a suitable prenyl-based nucleophile (cf. **9**) would react with **8** via allylic transposition to generate **10**. Given the high preference for *cis* versus *trans* fusion, it seemed likely that the formation of **10** from **7** (via cationoid system **8**) would occur with overall retention of configuration at the junction center corresponding to C16a in ardeemin numbering. An alternate option, involving homolysis of the leaving group and recombination with a functional 1,1-dimethallyl radical, was examined and will be discussed (vide infra).

Viewed in these terms, *the critical stereochemical event in the proposed oxidative cyclization step is the establishment of the relationship of C5a and C15b* (ardeemin numbering) in system **7**. In the ensuing alkylation event (**7** → **8** → **10**), the overall stereochemical outcome at C16a (retention) is, in essence, controlled by the chirality at C5a, given the high predilection for consolidation of the pyrroloindole moiety in a *cis* junction. We assumed that this preference would pertain in either the homolytic or heterolytic alkylation options.

The literature precedents for achieving high degrees of stereoselection in the desired sense and in high yield for the oxidative cyclization reaction of **6** → **7** were not fully encouraging. Detailed studies of Hino[22] and Crich,[23,24] in the protonically induced version of this reaction (Ox = H^+), demonstrated that the product with the *endo* carboxyl is thermodynamically more stable and may also be competitive at the kinetic level. Of course, to reach the ardeemins and amauromine, access to the *exo* (kinetic) product **10** would be necessary. This system

(17) For a preliminary account of this work, see: Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143.

(18) (a) Jackson, A. H.; Smith, A. E. *Tetrahedron* **1965**, *21*, 989. (b) Bocchi, V.; Casnati, G.; Marchelli, R. *Tetrahedron* **1978**, *34*, 929. (c) Muthusubramanian, P.; Carle, J. S.; Christophersen, C. *Acta Chem. Scand.* **1983**, *B37*, 803. For an example in which a protected tryptophan gave C3 and C1 bis(prenylated) products as 1:1 junction isomers in 29 and 22% yield, see: (d) Takase, S.; Kawai, Y.; Uchida, I. *Tetrahedron Lett.* **1984**, *25*, 4673.

(19) Wenkert, E.; Sliwa, H. *Bioorg. Chem.* **1977**, *6*, 443.

(20) Cf.: (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.

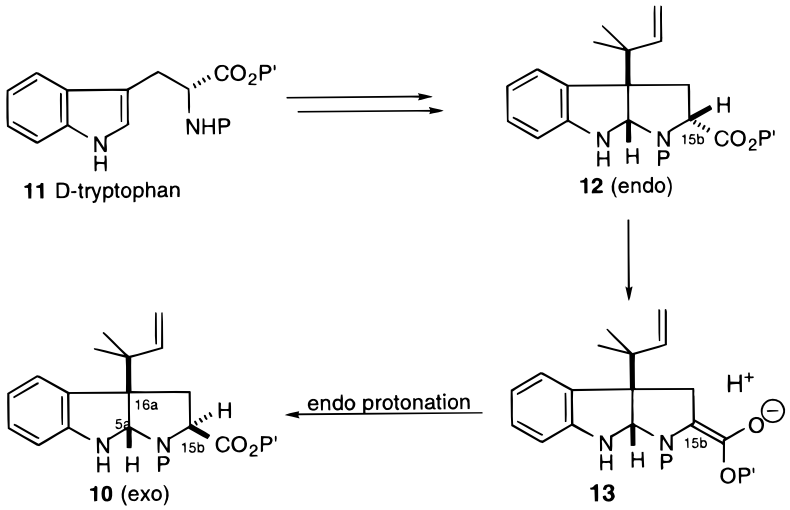
(21) Ohno, M.; Spande, T. F.; Witkop, B. *J. Am. Chem. Soc.* **1968**, *90*, 6521. For a recent application of this oxidative closure logic see: Kamenecka, T. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1998,** *37*, 2993.

(22) Taniguchi, M.; Hino, T. *Tetrahedron* **1981**, *37*, 1487.

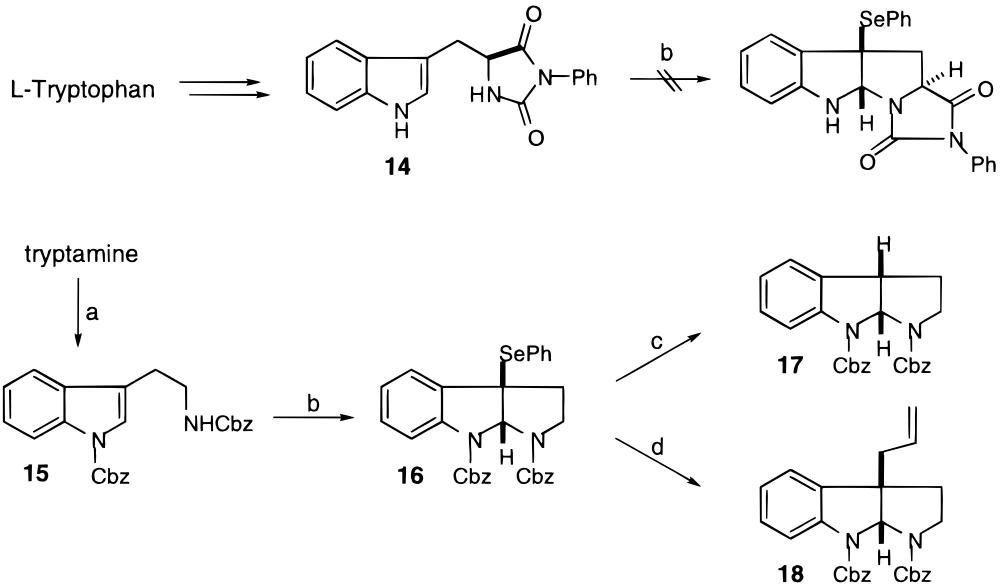
(23) Crich, D.; Davies, J. W. *J. Chem. Soc., Chem. Commun*. **1989**, 1418.

(24) Bourne, G. T.; Crich, D.; Davies, J. W.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1693.

Scheme 2



Scheme 3[a]



[a] Reaction conditions: (a) NaOH, Cbz-Cl, cat. $(n\text{-Bu})_4NHSO_4$, CH_2Cl_2, 83%; (b) *N*-PSP, cat. *p*-TSA, CH_2Cl_2, 84%; (c) methyl acrylate, $(n\text{-Bu})_3SnH$, AIBN, TolH, reflux, 55%; (d) allyl-Sn$(n\text{-Bu})_3$, AIBN, toluene, reflux, 56%.

corresponds to the *exo* configuration for the tryptophyl-derived acyl function with respect to the cup-shaped pyrroloindole system. Given the logic of the projected route discussed above, which anticipated oxidative cyclization followed by alkylation, the former step must be such as to present the acyl function *exo* at the stage of **7**. The work of Crich[23,24] cited above and that of Hino[22] in the context of variously related cyclizations suggested the likelihood of mixtures at the kinetic level if the reaction is driven to completion prior to equilibration. Given the studies of the Crich group, thermodynamic equilibration would unlikely afford the desired *exo* product.[25] In principle, a solution to our problem might be achieved by kinetic protonation of a C15a enolate (cf. **13**), possibly derived from the *endo* series system **12** (Scheme 2). Such a "kinetic" protonation might provide access to the desired **7**. Clearly, if we were to follow a course based on such a prospectus, it would be necessary to start with D-tryptophan (**11**) en route to *endo* **12**. The latter would contain the pyrroloindole version of **7**, but would be epimeric at C15a. The success of such an enterprise could also not be anticipated with confidence.

Discussion and Results

Since a great deal of research had already been conducted by previous workers[21] into oxidative cyclizations of tryptophan derivatives using oxygen-based electrophiles, we decided on a newer type of venture. Inspired by an earlier success in our lab with selenocyclization as a means of fashioning a pyrrolo ring (via concurrent formation of carbon−selenium and nitrogen−carbon bonds),[26,27] we turned to this approach for the problem at hand.

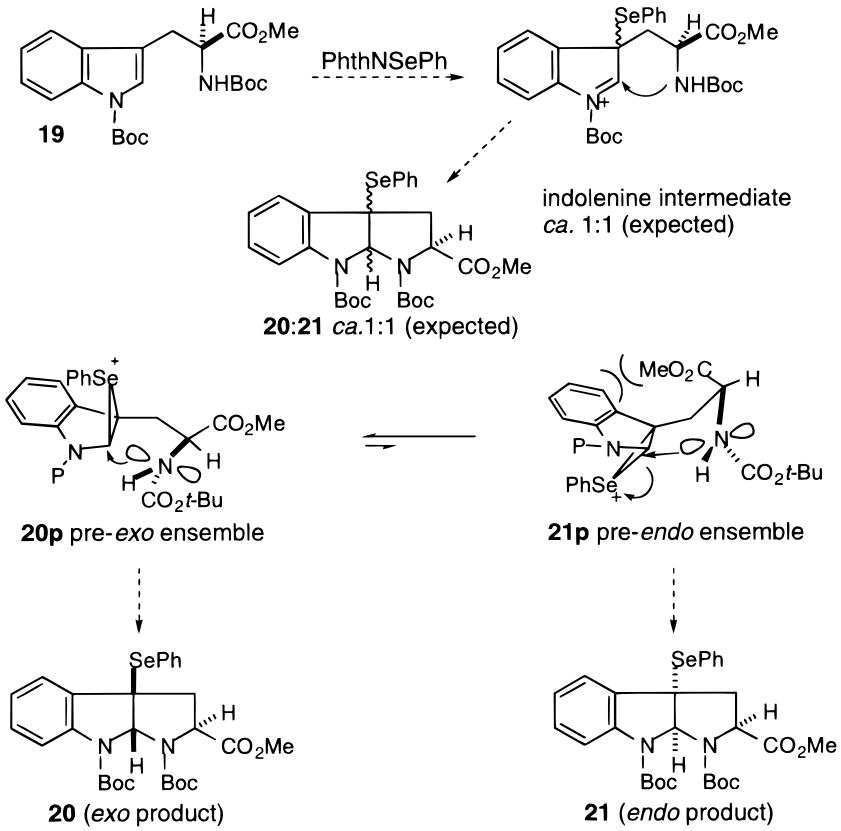
In our first attempt at the reduction of Scheme 1 to practice, we protected L-tryptophan in the form of phenylhydantoin **14** (Scheme 3). A few attempts at selenocyclization of **14** were unsuccessful. Before exhausting a variety of possibilities for

(25) For a detailed analysis of the issues inherent in this puzzling result see: Crich, D.; Bruncko, M.; Natarajan, S.; Teo, B. K.; Tocheri, D.-A. *Tetrahedron* **1995**, *51*, 2215.

(26) Cf.: (a) Nicolaou, K. C.; Lysenko, Z. *J. Am. Chem. Soc.* **1977**, *99*, 3185. (b) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049.

(27) Danishefsky, S. J.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891.

Scheme 4. Proposed Transition Ensembles for the Selenocyclization Reaction



using **14**, we backed off the idealized version of the synthesis and investigated the concept in the tryptamine rather than tryptophan series. Specifically, we prepared the bis(Cbz) derivative **15**. Indeed, in this case, treatment with *N*-phenylselenophthalimide (*N*-PSP)[28] in methylene chloride in the presence of catalytic *p*-toluenesulfonic acid (*p*-TSA) afforded **16** in 84% yield. Thus, an important element of the basic plan for the total synthesis had been reduced to practice.

Fresh from this success, we investigated the feasibility of angular allylation, prenylation, and reverse prenylation at C3 (indole numbering). Our first initiative involved attempted applications of the elegant free radical chemistry pioneered by Keck[29] (and subsequently practiced in our own lab)[30] for the introduction of an allylic functionality via carbon-bound halogen. Treatment of selenide **16** with tri(*n*-butyl)tin hydride in the presence of allyltri(*n*-butyl)tin led to reduction rather than reductive alkylation. Apparently the tertiary pyrroloindolyl free radical, at least under these conditions, is more adept at hydrogen atom abstraction than at de-stannylative allylation (see formation of **17**). Success was realized, albeit at a modest level, through the reaction of **16** under photolytic conditions with hexa(*n*-butyl)distannane[31] in the presence of allyltri(*n*-butyl)stannane to afford **18** in 56% yield.

Encouraged by these successes, we returned to the tryptophan series. At this stage we were particularly interested in pursuing a kinetic solution to the problem of the C5a−C15b−C16a stereochemical connectivity, even in the absence of fully supportive precedents (vide supra). We first turned our attentions to a feasible protection of L-tryptophan, which still provides an opportunity for achieving the gross cyclization goal. In the event, L-tryptophan methyl ester was converted to its bis(Boc) derivative **19** using Boc anhydride under phase transfer conditions, as shown (Scheme 4). Reaction of compound **19** with *N*-PSP in the presence of *p*-TSA occurred smoothly. Early in our studies,[17] when reaction was carried out in the presence of excess sodium sulfate and *p*-TSA as catalyst (10 mol %), wherein we were monitoring the progress of the reaction by NMR analysis, the appearance of two isomers was indicated. The rough ratio of these products seemed to be ca. 1:1. It further appeared that as the reaction progressed, the ratio of the two compounds changed to the point where there was a clear major and a minor product (ca. 6−9:1). Since the NMR signals due to the two compounds were similar and since the concentration of one *seemed* to grow at the expense of the other, we assumed that the two products corresponded to the *endo* versus *exo* acyl systems.

As we continued to examine the selenocyclization reaction, we could not repeat this curious observation pertaining to a change in ratio as the reaction progresses. In these follow-up studies, using again *p*-TSA, there was produced *from the outset* a mixture of cyclization products in a ratio of ca. 8−10:1. Indeed, we found that this apparently kinetic ratio could be improved still further by modification of the cyclization method. The heterogeneous conditions associated with the use of *p*-TSA in our first attempts were not very well suited for scale-up. We used sodium sulfate to dry the hydrated form of *p*-TSA, which by itself is a poor catalyst for this particular substrate. Also, under these conditions, our *exo*:*endo* product ratios varied from 9:1 to 16:1. To correct both problems, we turned to anhydrous

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

(29) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829. Coincident with our report[17] Crich reported related chemistry with a 3a-bromopyrroloindole (see: Bruncko, M.; Crich D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543.

(30) Webb, R.; Danishefsky, S. J. *Tetrahedron Lett.* **1983**, *24*, 1357.

(31) cf. Keck, G. E.; Enholm. E. J.; Yates, J. B.; Wiley, M. R. *Tetrahdron* **1985**, *41*, 4079.

pyridinium *p*-toluenesulfonate (PPTS). In the presence of an equimolar amount of PPTS, reaction of **19** with *N*-PSP occurred remarkably smoothly to deliver the selenocyclization product in 93% yield as an 18:1 mixture of **20**:**21**. Under these conditions, the ratio of the two stereoisomers **20**(*exo*):**21**(*endo*) as judged by the integrated levels of the methyl ester resonance in ^{1}H NMR spectra did not materially change throughout the course of the reaction. Given these findings and given the fact that the apparent equilibration of **20** in favor of **21** could not be duplicated, we now believe that the high preference in the reaction in favor of **21** is a kinetic effect.

We also note that the initial report, which implied that the *endo* product was being equilibrated in favor of the *exo* product, was evaluated by Crich and co-workers.[32] Their research demonstrated that, as is usual in related systems, the *endo* isomer (cf. **21**) is actually more stable than the *exo* isomer (**20**). Although the Crich conditions for base-induced equilibration were radically different from ours, we can only assume that the thermodynamic relationship of **20** and **21**, even in the setting of our experiment, is not materially different.

Attempts to account for the high degree of stereoselection in the intramolecular selenoamination reaction are complicated by the fact that, at present, there is no fully understandable theory as to the central observation from earlier workers[25] that the *endo* product is thermodynamically more stable than the *exo* product in related systems. The extent of the kinetic level of stereocontrol in the phenylselenocyclization[26−28] may well rest on the degree to which cyclization corresponds to *anti*-addition to the 2,3-indolic double bond by the electrophilic oxidant and the nucleophilic tryptophan nitrogen (Scheme 4, see structures **20p** and **21p**). This "S_N2-like" mode of cyclization should be contrasted with another cyclization pathway, which progresses through a discreet iminium species en route to pyrroloindole formation. In the latter case, the stereochemical outcome had, in substance, been determined by the sense of attack at C3 of the indole. Thus, it seems unlikely that the formation of the indolenine cyclization intermediate could manifest a high degree of kinetic stereoselection. By contrast, in the more "S_N2-like" variation, kinetic stereoselection seems more probable. Thus it is possible that formation of the selenonium species **20p** and **21p** en route to the S_N2-type of cyclization is reversible and that the kinetic ratio of **20**:**21** may reflect the relative ease of cyclization of the pre-*exo* and pre-*endo* intermediates **20p** and **21p**, respectively. In each instance, we position the carbomethoxy function antiperiplanar to the N-Boc function as the urethane nitrogen prepares to displace the carbon−selenonium bond with inversion. While the final *endo* product **21** is apparently more stable than the *exo* product **20**, judging by the base-induced equilibration reaction described by Crich,[32] the pre-*exo* cycling ensemble **20p** could well be more stable than the pre-*endo* ensemble **21p**. In the latter situation, the carbomethoxy group is possibly drawn more deeply into the concave pocket of the pyrroloindole than is the case in the final product **20**. *In summary, the stability order of the two precyclization ensembles may be quite different from that of the energy-minimized version of the products **20** and **21**.*[33]

Returning to the syntheses, separation at the stage of the methyl esters **20** and **21** could not be accomplished in our hands. Moreover, the assignment of stereochemistry at C5a and C16a of the major product could not be established in a convincing way. Nonetheless, we proceeded to address the all-critical introduction of a reverse prenyl function. On the basis of our experiences in the tryptamine series described above, we began with an experiment directed to free radical allylation.

Photolysis of the **20**:**21** mixture, enriched in the former, with allyltri(*n*-butyl)tin in the presence of hexa(*n*-butyl)distannane gave rise, in 95% yield, to a mixture, which by NMR anaylsis was comprised of a major and a minor allylation product (see structures **22** and **23**) in much the same ratio as was operative in the precursor phenylseleno series (**20** and **21**). With these compounds in hand, the stereochemistry at C5a could be surmised. One-dimensional NOE experiments on the major product revealed that irradiation of the allylic protons caused an enhancement of one of the H16 protons. Irradiation of this proton enhanced the other H16 proton and H15b. Irradiation of the H15b proton strongly enhanced the latter H16 proton and weakly enhanced the former. Hence, the allyl group seemed to be on the opposite plane, i.e., *trans* to H15b. If the assignment is correct, compound **22** corresponds to the desired diastereomer. Accordingly, by the logic discussed above, **20** is in the required *exo* series. However, because we had noted some H15b enhancement by both H16 protons, the decision was not clear-cut. A total synthesis of amauromine or one of the ardeemins would hopefully confirm the assignment.

Attention was now directed toward installation of the reverse prenyl group via photolysis. Irradiation of the **20**/**21** mixture (rich in the former) in the presence of prenyltri(*n*-butyl)tin and hexa(*n*-butyl)distannane[31] led to complete reductive cleavage of the phenylseleno function (see formation of **24**). Irradiation of the mixture in the presence of other potential radical acceptors (e.g., methyl acrylate and methyl 2-butynoate) resulted in either no reaction or reductive cleavage. In one case, however, we could install an acrylate group to give **25** by reaction with ethyl β-tri(*n*-butyl)stannylacrylate,[34] albeit in 21% yield. In this product mixture, we saw evidence of a dimeric product (HRMS), which could only have resulted from the coupling of two tertiary radicals. Photolysis of the **20**/**21** mixture with hexa(*n*-butyl)-distannane produced this dimer (**26**) in 10−15% yield. Compound **26** represents a potential solution toward natural products of the dimeric tryptamine and tryptophan class of indole alkaloids.[35] In principle, photolysis of tryptamine **16** could allow direct access to the Calycanthaceous class of plant natural products.

We next attempted to activate the **20**/**21** mixture (highly enriched in favor of the former) toward reverse prenylation in a cationic sense. Exposure of the selenides to Lewis acids such as $TiCl_4$, $BF_3{\cdot}OEt_2$, and AgOTf in the presence of prenyltri(*n*-butyl)tin brought forth a complex mixture of products, probably associated with cleavage of the phenyl selenide function.

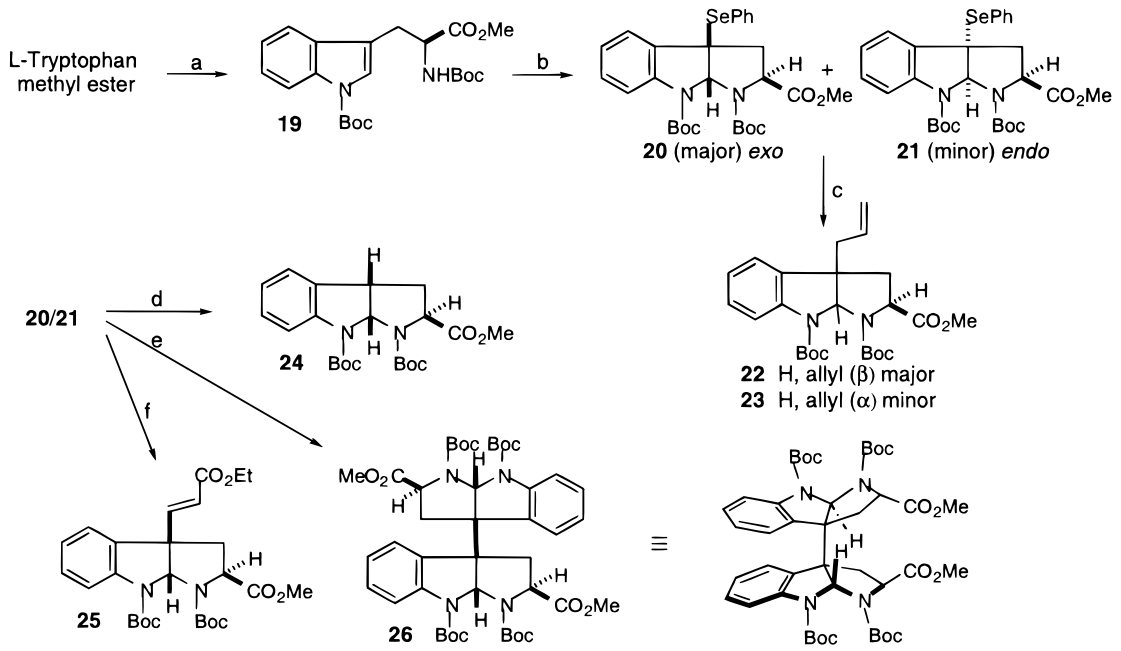
(32) Crich, D.; Huang, X.; Manuscript submitted. That the ratio of **20**:**21** was not changing during the course of the reaction of **19** with *N*-PSP had already been described in the dissertation of Kristopher Depew, Columbia University, 1998 (vide infra ref 42).

(33) The extent to which the critical carbomethoxy is drawn into the cavity is a function of the precise bond angles of the selenonium species and the requirement of collinearity in the displacement process.

(34) (a) Russell, G. A.; Tashtoush, H.; Ngoviwatchai, P. *J. Am. Chem. Soc.* **1984**, *106*, 4622. (b) Baldwin, J. E.; Kelly, D. R. *J. Chem. Soc., Chem. Commun.* **1985**, 682. (c) Barrett, A. G. M.; Pilipauskas, D. *J. Org. Chem.* **1991**, *56*, 2787.

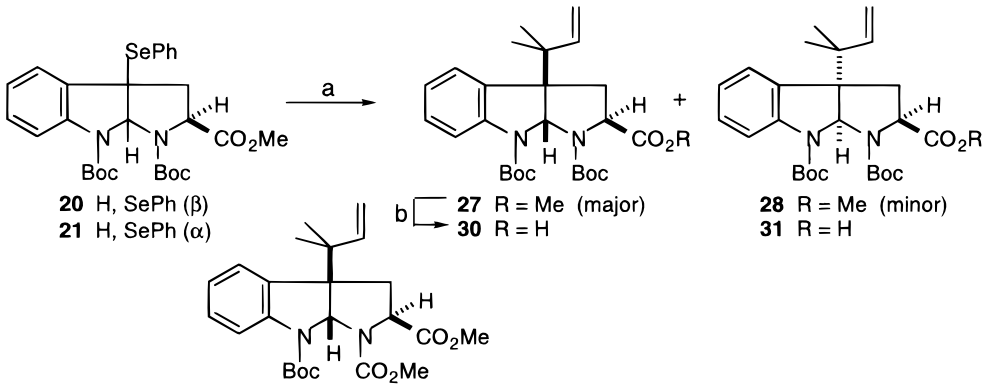
(35) We attribute the formation of **26** to result from the simple coupling of two free tertiary radicals. NMR experiments of **26** at room temperature gave broad peaks, which sharpened at 55 °C to one set of pyrroloindole peaks, which suggests a dimeric structure of C_2-symmetry. This product potentially represents a very direct solution to the problem of constructing fungal natural products of the C3a-bis(pyrroloindole) alkaloid class such as (a) the leptosins: Takahashi, C.; Takai, Y.; Kimura, Y.; Numata, A.; Shigematsu, N.; Tanaka, H. *Phytochemistry* **1995**, *38*, 155. (b) Chaetocin: Weber, H. P. *Acta Crystallogr. B* **1972**, *28*, 2945. (c) Ditryptophenaline: Springer, J. P.; Buchi, G.; Clardy, J. *Tetrahedron Lett.* **1977**, *18*, 2403. (d) WIN 64821: Barrow, C. J.; Cai, P.; Snyder, J. K.; Sedlock, D. M.; Sun, H. H.; Cooper, R. *J. Org. Chem.* **1993**, *58*, 6016. See Supporting Information for details.

Scheme 5[a]



[a] Reaction conditions: (a) NaOH, cat. $(n\text{-Bu})_4NHSO_4$, BOC_2O, CH_2Cl_2, 91%; (b) *N*-PSP, CH_2Cl_2, PPTS, 93%; (c) allyl-Sn(*n*-Bu)$_3$, $(n\text{-Bu})_6Sn_2$, toluene, *hν*, 23 °C, 94%; (d) $(n\text{-Bu})_3SnH$, AIBN, methyl acrylate, toluene, reflux, 55%; (e) $(n\text{-Bu})_6Sn_2$, toluene, *hν*, 23 °C, 10−15%; (f) $(n\text{-Bu})_6Sn_2$, ethyl *β*-tri(*n*-butyl)stannylacrylate, toluene, *hν*, 23 °C, 21%.

Scheme 6[a]



[a] Reaction conditions: (a) MeOTf, 2,6-di-(*tert*-butyl)pyridine, prenyltri(*n*-butyl)stannane, CH_2Cl_2, −78 °C to reflux, 60% (9:1 **27**:**28**); (b) NaOH, THF/MeOH/H_2O, reflux, 98%.

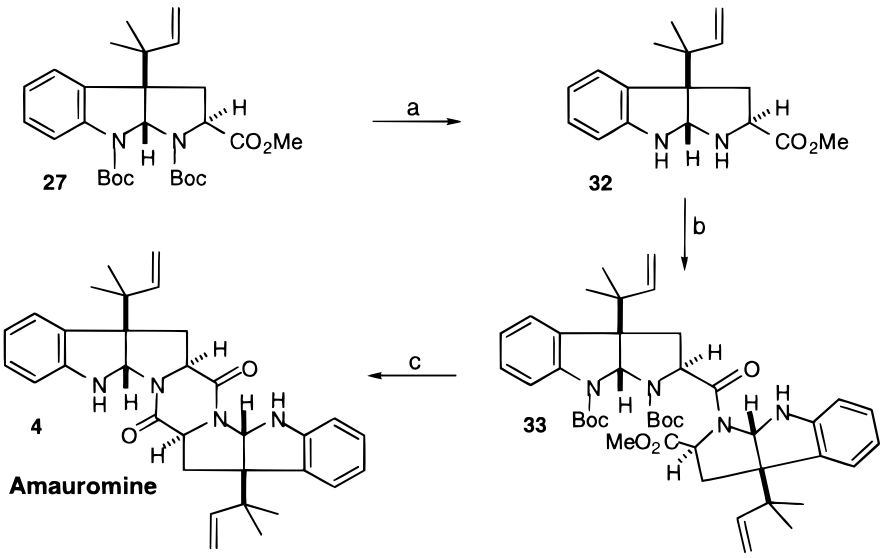
However, activation of a 9:1 mixture of **20**/**21** with methyl trifluoromethanesulfonate (MeOTf) in the presence of 2,6-di-(*tert*-butyl)pyridine and prenyltri(*n*-butyl)tin, beginning from −78 °C and proceeding to reflux in CH_2Cl_2 under argon, led to a 60% yield of the desired angular reverse prenyl products **27** and **28** (not separated, Scheme 5). The ratio of these products was essentially the same as that of the starting mixture. In addition, in some instances, up to 15% of a monomethyl carbamate byproduct **29** was produced.[36] The overall yield of reverse prenylation was 75%. Again, we assumed the alkylation reaction would produce the *cis*-fused 5,5-ring junction, even though this course would have involved net retention in the displacement step.

The methyl esters were cleanly hydrolyzed, as shown, to provide the tricyclic acids **30** and **31** in quantitative yield, with no apparent loss of stereochemical integrity. Having in hand a highly enriched (18:1) mixture of methyl esters **27** and **28** in essentially the same ratio as the starting **20**/**21** mixture allowed us to avoid laborious chromatography of acids **30** and **31**, which we used earlier to enable full purification of the major diastereomer **30**. Happily, simple crystallization from hexane now delivered the major diastereomer methyl ester **27** in ca. 57% overall yield from **20**/**21**. We note that this key intermediate for the total synthesis of the ardeemins is available in three steps from **19**. In principle, it can service syntheses of the ardeemins, of amauromine, or many of the other reverse prenyl hexahydropyrroloindole alkaloids.

We first turned our attention to the amauromine problem. Cleavage of the two Boc functions of **27**, using iodotrimethylsilane (TMSI), gave rise to the doubly deprotected ester, **32** (Scheme 6). Coupling of **32** with acid **30** under mediation by BOP chloride gave the amide **33**. There seemed to be no complication from competitive acylation at the anilino nitrogen. Treatment of product **33** with TMSI produced amauromine. Undoubtedly, this welcome result had come about by cleavage of the two Boc groups accompanied by cyclization of the carbomethoxy function onto the proximal NH group. *That the total synthesis of amauromine (4) had, in fact, been ac-*

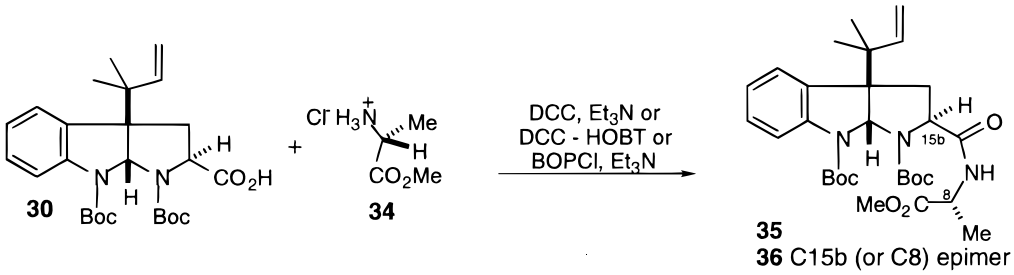
(36) Presumably, **29** arises by methylation of the carbonyl group of the more exposed t-Boc group accompanied by de-*tert*-butylation.

Scheme 7[a]



[a] Reaction conditions: (a) TMSI, MeCN, 0 °C, 83%; (b) **30**, BOP-Cl, Et_3N, CH_2Cl_2, 58%; (c) TMSI, MeCN, 0 °C, 58%.

Scheme 8



complished was vouchsafed by full spectral, chromatographic, and optical rotation comparisons of the fully synthetic material with an authentic sample provided by the Fujisawa pharmaceutical company.

With the total synthesis of amauromine achieved, we next focused on the synthesis of the ardeemins. Building blocks **27**, **30**, and **32** had already been prepared in homogeneous form, from the amauromine program. The next subgoal for reaching the ardeemins was that of amide bond formation between modified amino acid **30** and the amino group of D-alanine methyl ester (**34**).

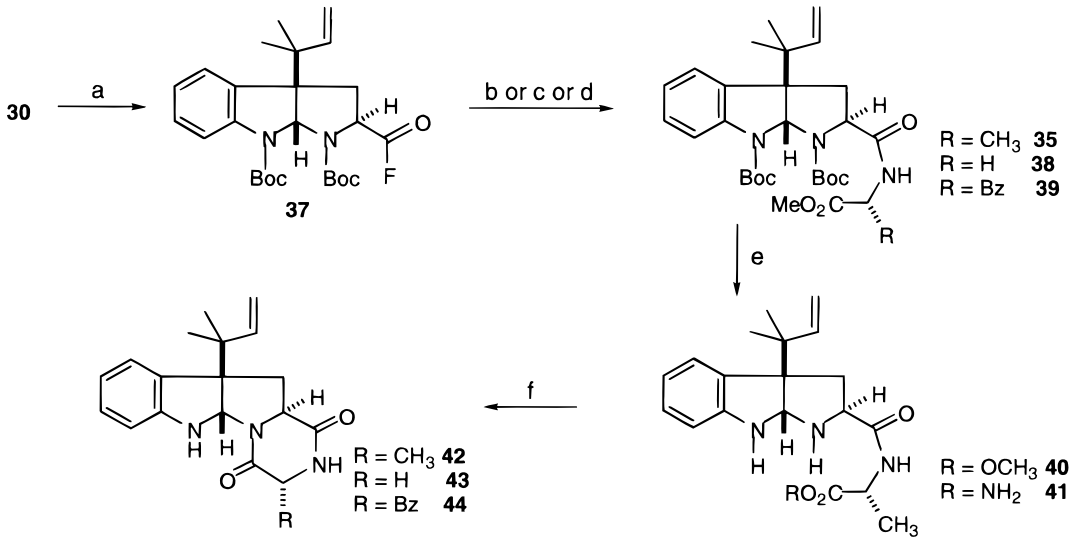
Surprisingly, during this attempted coupling, under conditions very similar to those used to prepare **33**, substantial difficulties were encountered. In the event, a variety of coupling agents (DCC, DMAP; triethylamine, DCC, HOBT; and BOPCl) all led to the production of protected dipeptide **35** (Scheme 7). However, in each case, NMR analysis revealed the production of two very closely related compounds. We took the formation of this mixture to suggest the partial racemization of one of the amino acid components in the synthesis of **35** (see structure **36**). Actually, it was not clear whether this epimerization had been sustained during the carboxyl activation process en route to coupling or after the coupling. While we did not rigorously establish whether the racemization had occurred in the tryptophan- or the alanine-derived moieties, however, it can be argued, based on the lack of a corresponding difficulty in the virtual homo coupling leading to **33** en route to amauromine, that the stereochemical vulnerability in the pre-ardeemin case was lodged in the alanine.

Fortunately this problem lent itself to a solution. The key to progress lay in the work of Carpino[37] which indicated that amino acid derived carboxyl groups can be converted to acid fluorides without epimerization under mild, nonacidic conditions. Furthermore, Carpino demonstrated that such acid fluorides couple smoothly to amines to generate peptide bonds, again without racemization. In the event, the action of compound **30** with cyanuric fluoride and pyridine in the presence of methylene chloride at −15 °C generated the acid fluoride **37** (Scheme 8). Reaction of this substance under Schotten−Baumann-like conditions with D-alanine methyl ester (**34**) resulted in amide bond formation yielding the protected peptide **35** in 71% overall yield. Only a single product seemed to have been produced. The partial racemization problem had thus been overcome. In like fashion, glycine methyl ester and D-phenylalanine methyl ester coupled to **37** to give peptides **38** and **39**, respectively.

Proceeding toward our ardeemin goal, the two Boc groups of compounds **35** were cleaved with TMSI in freshly distilled acetonitrile at 0 °C. There was thus generated the diamine **40** in 86% yield. When this compound was subjected to the action of methanolic ammonia, containing catalytic quantities of DMAP, the diketopiperazine **42** (R = Me) was obtained in 70% yield. Under these conditions the *seco*-amide **41** was generated in approximately 10−15% yield. However, this compound could easily be removed by chromatography. Unlike the *seco*-amauromine case (cf. **33** → **4**), the diamine **40** did not spontaneously cyclize. Smooth cyclization to **42** required the presence of *N*,*N*-dimethylaminopyridine (DMAP), without which reaction was slow. In a similar way, diketopiperazines **43** and **44** were generated from *seco* systems **38** and **39**, respectively.

(37) Carpino, L. A.; Mansous, E.-S. M. E.; Sadat-Aalee, D. *J. Org. Chem.* **1991**, *56*, 2611.

Scheme 9[a]



[a] Reaction conditions: (a) cyanuric fluoride, pyridine, CH_2Cl_2, −15 °C, 93%; (b) D-Ala-OMe·HCl, $NaHCO_3$, H_2O, CH_2Cl_2; (c) Gly-OMe, $NaHCO_3$, H_2O, CH_2Cl_2, 71% from **30**; (d) D-Phe-OMe, $NaHCO_3$, H_2O, CH_2Cl_2; (e) TMSI, MeCN, 0 °C, 86%; (f) NH_3 sat. in MeOH, cat. DMAP, 86%.

The stage for completing the total synthesis of 5-*N*-acetylardeemin was now well set. Our strategy for accomplishing fusion of an anthranilic acid onto ring D was based on work by Eguchi,[38] who developed an elegant synthesis of benzoquinazolinones utilizing an aza-Wittig-like reaction. To benzoylate **42** with *o*-azidobenzoyl chloride (**45**), we required a base stronger than Et_3N, which had been used by Eguchi (Scheme 9). We found that KHMDS worked well to give imide **46** in 50−80% yield. The yields were variable, and we found it hard to completely convert all of **42** to **46**. On larger scales, we preferred to use *o*-azidobenzoic anhydride (**47**) as the acylating agent for technical reasons. With this reagent, compound **48** was reliably delivered in high yield. For example, during our analogue synthesis, we found that *n*-BuLi (diluted with THF) as a base was superior to KHMDS. When the lithium anion of the 8-demethyl analogue **43** was quenched with a THF solution of **47**, compound **48** was obtained in 96% yield.

When compound **46** was stirred with P(*n*-Bu)$_3$ in benzene, ardeemin (**1**) was isolated in 90% yield.[39] In a similar way, treatment of **48** with P(*n*-Bu)$_3$ gives **49** (8-desmethylardeemin) in 86% yield. Finally, acetylation of **1** was effected with acetyl chloride under the conditions shown to give 5-*N*-acetylardeemin (**2**) in 82% yield. For larger scale work, we have found that simply warming ardeemin in a 9:1 solution of acetic anhydride/Hünig's base for 36 h at 60 °C causes precipitation of **2** during the reaction. Filtration and chromatography of the mother liquor leads to an overall yield of 85% for **2**. *The fully synthetic 5-N-acetylardeemin (mp 229−231 °C) was identical in all respects to naturally derived material furnished by the Abbott Pharmaceutical Company*. In a similar way, compound **49** was converted to the nor analogue of **2** (**50**) and by trifluoroacetylation to **51**.

With the total synthesis accomplished, we undertook a brief survey of the regions of the ardeemins, which could be structurally modified in a straightforward way. The activities of such accessible analogues would be investigated first in cell culture. One important question was the importance of the *N*-acetyl group at the indoline nitrogen. As noted above, ardeemin (**1**) itself was reported to be "inactive" as a reversal agent with respect to KBV-1 cells. Was there, indeed, some kind of profound electronic or steric property that the acetyl group imparted to **2** to influence its activity relative to **1**? What effect would there be in deleting rings E and F, which are nonexistent in most of the members of this natural product class? If such compounds were still active, the synthesis of a viable reversal agent would be substantially simplified. We also wondered about the effect of modifying the character of C8 and the consequences of modifying the angular substituent at C16a.

Our analogues were prepared along the following lines. The allyl analogue (**52**) of 5-*N*-acetylardeemin (**2**) was synthesized in seven steps from **22** following the same set of conditions as described for **2** (Scheme 10). Truncated versions of the ardeemins addressed to test the requirement of the quinazolinone portion of **2** were made via synthetic intermediate **42**. Trifluoroacetylation of **42** under the conditions shown gives a bis(trifluoroacetylated) product. The latter via de-trifluoroacetylation at N9, as shown, leads to **53**. Attempted monoacetylation of **43** leads to acetylation of the alanyl NH group of the diketopiperazine ring (see compound **54**).

The synthesis of the C8 benzyl compound **55** was accomplished in an interesting way. In principle, it would have been possible to reach this goal via the previously described diketopiperazine **44** following the three-step sequence practiced in the synthesis of **2** (from **42**) and **49** (from **43**). A more pleasing possibility started with the previously described nor compound **50**. The benzyl group was introduced in 43% yield by deprotonation at C8 (following a Seebach type of protocol)[40] followed by reaction with benzyl bromide.

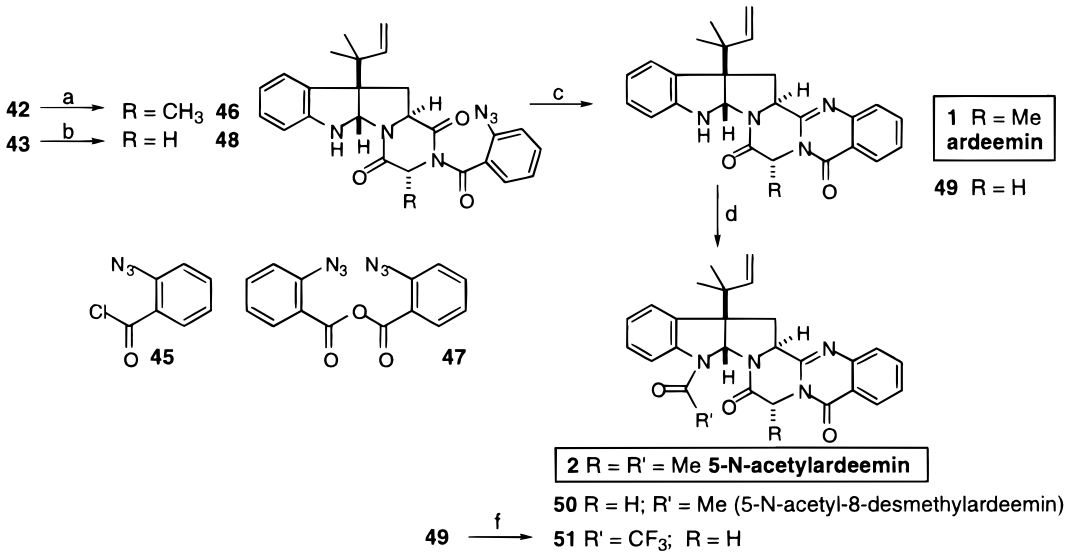
We are confident that the stereochemistry is indeed as shown in **55**. Thus, no NOE was observed between H8 and H15b, which indicated a *trans* relationship between these two hydrogens. Also, H15b was shifted far upfield (2.53 vs 4.41 ppm for **2**) due to shielding by the benzyl group. Late stage alkylation of C8 streamlines the route to analogues of the central amino

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

(39) On occasion, this reaction is accompanied by the formation of **42** (in ca. 15% yield). Conceivably, this compound arises from attack of the phosphine−imine nucleophile on the adjacent imide carbonyl group. This would lead, formally, to a benzoazetidene en route to the observed **42**. More likely, an adventitious external nucleophile cleaves the labile exocyclic imide.

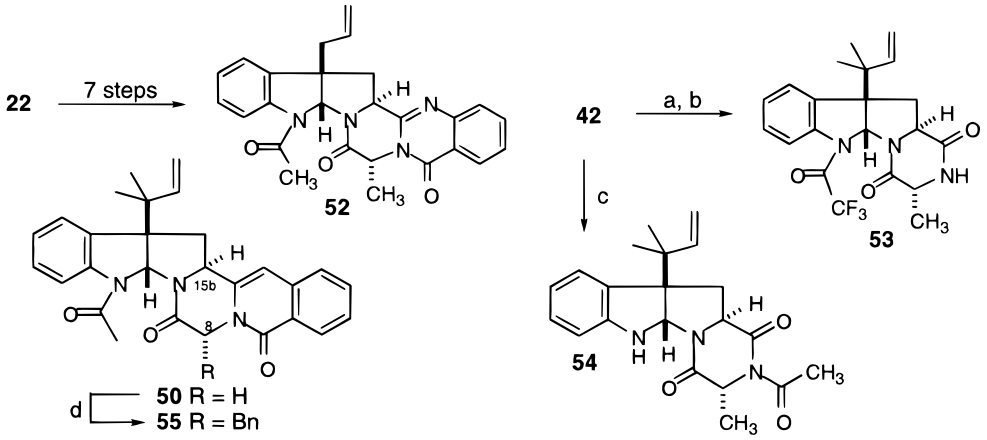
(40) Seebach, D.; Bossler, H.; Gründler, H.; Shoda, S.-I. *Helv. Chim. Acta* **1991**, *74*, 197.

Scheme 10. Synthesis of **1**, **2**, and Analogues[a]



[a] Reaction conditions: (a) KHMDS, THF, −78 °C, **45**, 80%; (b) n-BuLi, THF, −78 °C, **47**, 96%; (c) P(*n*-Bu)$_3$, benzene, 72%; (d) Hünig's base, acetic anhydride, 60 °C, 36 h, 85%; (e) trifluoroacetic anhydride, pyridine, 60 °C.

Scheme 11. Synthesis of 16a-Allyl-5-*N*-acetylardeemin, 8α-Benzylardeemin, and Two Truncated Analogues[a]



[a] Reaction conditions: (a) trifluoroacetic anhydride, pyridine, 60 °C; (b) K_2CO_3, MeOH; (c) acetic anhydride, pyridine; (d) LDA, *n*-BuLi, THF, −78 °C; benzyl bromide, 33%.

acid, bypassing the need to synthesize a fresh diketopiperazine at the stage of precursor **30** for each projected C8 derivative (Scheme 11).[41]

Compounds **42**, **50**, **51**, **52**, **53**,and **55** were examined, particularly in comparison with **1**, **2,** and verapamil, as the latter is a widely discussed reversal agent. Since we did not prepare each of these materials in amounts required for in vivo evaluation, we used in vitro screens to orient our efforts. We hoped that these initial experiments would identify the consequences of our structural modifications relative to the parent **2**. We would then advance the most effective compound(s) to in vivo studies. General cytotoxicity screens were conducted against two wild-type tumor cell lines (DC-3F, CCRF-CEM) and their MDR counterparts (DC-3F/ADII, CCRF-CEM/VBL$_{100}$) to develop a basic sense of each compound's relative toxicity to the sensitive wild type. From there, we examined the effects of these agents in conjunction with vinblastine in a cell line, which was 760-fold resistant to vinblastine. The results have been published elsewhere[42,43] and are detailed in the Supporting Information. We summarize here the most salient findings.

Ardeemin (**1**) and 5-*N*-acetylardeemin (**2**) display comparable cytotoxicity, while the 16a-allyl analogue (**52**) is 2- to 3-fold less cytotoxic than **2** against these cell lines. As is the case with **1** and **2**, **52** is more cytotoxic to resistant lines than to their respective parent cell lines (collaterally sensitive). The exceptions were the 5-*N*-trifluoroacetyl analogue **51** and the 8α-benzyl analogue (**55**), which were less cytotoxic to the resistant cell line than to the parent (CCRF-CEM). Addressing deletion of the acetyl group, we found that **1** was somewhat more cytotoxic than **2** in the above sensitive cell lines. However, the reversal power of **1** and its 8-desmethyl analogue (**49**) were slightly less potent than **2**, when studied in conjunction with vinblastine.

(41) For some additional studies in the ardeemin area see: (a) Martin-Santamaria, S.; Espada, M.; Avendaño, C. *Tetrahedron* **1997**, *53*, 16795. (b) Bartolome, M. T.; Buenadicha, F. L.; Avendaño, C.; Sollhuber, M. *Tetrahedron-Asym.* **1998**, *9*, 249. (c) Buenadicha, F. L.; Bartolome, M. T.; Aguirre, M. J.; Avendaño, C.; Sollhuber, M. *Tetrahedron-Asym.* **1998**, *9*, 483. (d) Madrigal, A.; Grande, M.; Avendaño, C. *J. Org. Chem.* **1998**, *63*, 2724. (e) Fernandez, M.; Heredia, M. L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **1998**, *54*, 2777. (f) Sanchez, J. D.; Ramos, M. T.; Avendaño, C. *Tetrahedron* **1998**, *54*, 969. (g) Caballero, E.; Avendano, C.; Menendez, J. C. *Tetrahedron Asymmetry* **1998**, *9*, 3025.

(42) Chou, T. C.; Depew, K. M.; Zheng, Y.-H.; Safer, M. L.; Chan, D.; Helfrich, B. Zatorska, D.; Zatorski, A.; Bornmann, W.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 8369.

(43) Depew, K. M., Ph.D. Dissertation, Columbia University, 1998.

Thus, while the 5-*N*-acetyl group is not essential for reversal power, it seems to help. Hence, the nonacylated **1** and **49** were not advanced further. The trifluoroacetyl derivative **51** did seem to have some advantage over **2** in the vinblastine combination study. This compound is being considered for future development. We note that the reversal power of verapamil could equal that of **2** only when administered at 5 times the concentration of **2**. Given the peripheral toxicity problems of verapamil, such an increase could not even be considered.

We also found that the *hexa*cyclic compounds (**2**, **50**, and **51**) were much more efficacious than their tetracyclic analogues (**42**, **53**). For example, the latter two performed poorly in a vinblastine combination study by being >400-fold weaker than **2** at re-sensitizing the CCRF-CEM/VBL_{100} cells. Thus, the truncation of rings E and F vastly reduces reversal potential. Hence, neither compound was advanced.

Following a preliminary round of in vitro screening, we selected our parent structure **2** and the 8-desmethyl analogue **50** for more in-depth analyses involving other chemotherapeutic agents (vinblastine, doxorubicin, Taxol) and several in vivo studies using two separate mouse lines ($B6D2F_1$ and Swiss nude). The results of this study were also reported earlier.[42,43] Both of these ardeemins (i) reversed drug resistance to vinblastine and Taxol by >700-fold in the CCRF-CEM/VBL_{100} cell line, (ii) killed MDR cells more efficaciously than wild-type cells, and (iii) exhibited strong synergistic effects with doxorubicin and vinblastine against the growth of MDR neoplastic cells.

In vivo studies indicated that nontoxic doses of doxorubicin and **2** significantly increased the life span of $B6D2F_1$ mice inoculated with wild-type and doxorubicin-resistant P388 tumor cells. In separate experiments, using nude mice bearing human MX-1 mammary carcinoma xenografts, one particular dose combination regimen of doxorubicin with **2** produced two tumor-free mice (out of eight in the group) by the 49th day after the tumor was introduced.[37] The ardeemins also demonstrated remarkably low toxicity in mice. *Quantities of **2** as high as 300 mg/kg per day for 3 days or 150 mg/kg per day for 8 days were tolerated without noticeable weight loss. This is in sharp contrast to verapamil, which is far more toxic*. Presently then, we are at the stage of a detailed assessment of the relative advantages of 5-*N*-acetylardeemin relative to several of the most promising analogues with respect to further development.

Summary

We have presented an efficient total synthesis of 5-*N*-acetylardeemin (**2**) (nine steps in 12.5% overall yield from **19**) in the context of a stereoselective solution to the construction of reverse-prenylated hexahydropyrroloindole alkaloids. A key step is the *N*-PSP-induced phenyl selenocyclization of a suitable tryptophan derivative.[28] Remarkably, this reaction gives rise to very high stereoselection favoring the *exo* product **20**. This result is, apparently, not the result of equilibration. Rather, it must reflect a largely kinetic selection. The phenylseleno function is then replaced with retention of configuration by methyl triflate-induced alkylation via prenyl tri(*n*-butyl)stannane. The remaining steps require the formation of three amide bonds, an aza-Wittig reaction to complete the ardeemin backbone, and the insertion of an acetate group onto the hindered N5 nitrogen.

Using the strategy outlined for **2**, several analogues containing singular modifications all around the backbone of **2** were synthesized. This chemistry enabled the production of multigram quantities of the more promising compounds for further biological analysis. We also note that this technology was practiced recently by Joullié and co-workers in a total synthesis of roquefortine.[44] Studies related to the bioefficacy of the ardeemins will be described in due course.

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Supporting Information Available: Experimental procedures and spectral data for compounds **1**, **2**, **4**, **16**−**23**, **25**−**27**, **30**, **32**, **33**, **35**, **37**, **40**, **42**−**44**, **46**−**50**, and **52** as well as a table listing cytotoxicity and reversal data for **2** and its analogues (PDF). This information is available free of charge via the Internet at http://pubs.acs.org.

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