Total Synthesis of Gypsetin, Deoxybrevianamide E, Brevianamide E, and Tryprostatin B: Novel Constructions of 2,3-Disubstituted Indoles

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Abstract: A concise and efficient total synthesis of the acyl-CoA:cholesterol acyltransferase inhibitor gypsetin (**1**) is described. The route features a straightforward method for the introduction of a reverse prenyl group into the C2-position of an *N*-phthaloyl-protected tryptophan (**11**). The total synthesis of gypsetin was completed by the dimethyldioxirane-promoted double-oxidative cyclization of a prefashioned diketopiperazine (**19**). Total syntheses of deoxybrevianamide E (**24**) and brevianamide E (**25**) following similar procedures are also described. The reaction of nucleophiles with in situ-generated 3-chloroindolenines provides a route to 2,3-disubstituted indoles from 3-substituted precursors. Indications of the scope and limitations of such reactions are provided. A total synthesis of tryprostatin B (**41**), a diketopiperazine derived from an L-tryptophan derivative (bearing a prenyl group at the α position of the indole) and L-proline, was accomplished. The key step involved the introduction of the prenyl function onto a protected tryptophan congener (**11**). A route for the prenylation of ketones with virtually no competitive reverse prenylation is also provided.

The development of cholesterol-lowering drugs remains an active area of research and development. It is widely accepted that hypercholestemia is one of the major risk factors leading to coronary heart disease.[1] Containment of excessive levels of plasma cholesterol has generally been achieved via controlled dietary absorption of cholesterol-containing foodstuffs as well as with therapeutic agents that interfere with the de novo biosynthesis of cholesterol itself. Indeed, a cornerstone in the treatment of hypercholestemia was the discovery that lovastatin and other compactin analogues are powerful inhibitors of the enzyme HMG-CoA reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway.[2] Agents based on the inhibition of HMG-CoA have effectively lowered LDL and total cholesterol levels in hypercholestemic patients. In this connection, squalene synthase inhibitors such as the zaragozic acids and CP-225,917/263,114 have been identified as possible therapeutic agents; however, their apparent toxicity and difficult availability has hampered their further development.[3]

In recent years, notable attention has been directed to the possibility of inhibition of the enzyme acyl-CoA:cholesterol acyltransferase (ACAT). ACAT is the rate-limiting enzyme in the absorption of cholesterol. Accordingly, inhibition of ACAT-catalyzed cholesterol esterification could result in blocking the accumulation of intracellular cholesterol esters in macrophages.[4,5] It is postulated that build-up of these cholesterol esters

ultimately leads to foam cell formation and presumptively to myocardial infarction.[5] Thus, an ACAT inhibitor might be useful in lowering cholesterol levels and attenuating the risk of coronary heart disease.

Given these considerations, the reports concerning gypsetin (**1**, Figure 1) evoked particular interest. The compound was isolated from the fungal source *N. gypsea var. incurvata* IFO 9228. It was found to be a promising competitive inhibitor of ACAT with respect to oleoyl-CoA, with a K_i value of 5.5 μM. Furthermore, inhibition of cholesterol ester formation in cultured macrophages with an IC$_{50}$ of 0.65 μM was observed.[6] In light of the novel structure of gypsetin, its structural relationship to the ardeemins, brevianamide, and tryprostatin systems (vide infra) as well as its potential as a lead in drug discovery,[7] this alkaloid emerged as a target structure for total synthesis.

Upon inspection, it is seen that the structure of gypsetin (**1**) embodies reverse prenyl groups at C_{5a} and C_{13a} of the hexahydropyrroloindole nucleus. It seemed not improbable that a simple and direct method for the incorporation of the reverse prenyl groups at C_{5a} and C_{13a} could be helpful in completing total syntheses of gypsetin as well as the brevianamides (vide infra). This capability could also be helpful in a drug lead discovery

(1) Kannel, W. B.; Castelli, W. P.; Gordon, T.; McNamara, P. M. *Ann. Intern. Med.* **1971**, *74*, 1. Brown, M. S.; Goldstein, J. L. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 583.

(2) (a) Grundy, S. M. *Cholesterol and Atherosclerosis, Diagnosis and Treatment*; Tower Medical,: New York, 1990; p 4. (b) Grundy, S. M. *New Engl. J. Med.* **1988**, *319*, 24. (c) Spector, A. A.; Mathur, S. N.; Kaduce, T. L. *Prog. Lipid Res.* **1979**, *18*, 31. (d) Suckling, K. E.; Stange, F. *J. Lipid Res.* **1985**, *26*, 647.

(3) Abe, I.; Tomesch, J. C.; Wattanasin, S.; Prestwich, G. D. *Nat. Prod. Rep.* **1994**, *11*, 279 and references therein.

(4) Sliskovic, D. R.; White, A. D. *Trends Pharm. Sci.* **1991**, *12*, 194.

(5) Kimura, T.; Takase, Y.; Hayashi, K.; Tanaka, H.; Ohtsuka, I.; Takao, S.; Kogushi, M.; Yamada, T.; Fujimori, T.; Saitou, I.; Akasaka, K. *J. Med. Chem.* **1993**, *36*, 1630 and references therein.

(6) (a) 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) Fukuyama, T. F.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127 and references therein.

(7) (a) For a preliminary communication on gypsetin, see: Schkeryantz, J. M.; Woo, J. C. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 7025. (b) For a preliminary account of the synthesis of tryprostatin B, see: Depew, K. M.; Danishefsky, S. J.; Rosen, N.; Sepp-Lorenzino, L. *J. Am. Chem. Soc.* **1996**, *118*, 12463. (c) For the total syntheses of amauromine and 5-*N*-acetylardeemin, see: Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953−11963 and references therein.

1 gypsetin

(C15a-C16a-*syn*; C7a-C8a-*anti*)

Figure 1.

context. Moreover, a comprehensive strategy to accomplish the total synthesis goals must also offer provision for incorporating the required oxygen functionality at the bridgehead positions (see C_{8a} and C_{16a}) of the pyrroloindole system.

Closer examination of the gypsetin structure reveals an interesting duality governing the stereochemical connectivity of the central diketopiperazine ring with the respective junction functionalities of the two pyrroloindole moieties. Not surprisingly, in each case the pyrroloindole linkage is *cis* fused. However, the backbone relationships between these functions and the two hydrogen atoms at the two fusion points of the core pyrrolodiketopiperazine ring are different. For instance, the stereochemical connectivity between the C_{16a} hydroxyl and its nearest junction hydrogen (C_{15a}) is *syn*. By contrast, the connectivity between the C_{8a} hydroxyl and its nearest junction (C_{7a}) hydrogen is *anti*. Put differently but equivalently, the central diketpiperazine ring can be construed as arising from the union of two stereochemically distinct amino acids, **2** and **3**. These structures can, in principle, be derived from the essential amino acid L-tryptohan. However, **2** and **3** differ in the "absolute" configurations of their pyrroloindole sectors. It is readily seen that in compound **2**, the absolute configuration of the carbon bearing the bridgehead hydroxyl group (destined to become C_{8a}) is *R*, whereas in **3**, the corresponding center (destined to become C_{16a}) is *S*.

Analysis of the problem in terms of the hypothetical subunits **2** and **3** suggests, in principle, an obvious (though perhaps difficult to achieve) formal route to gypsetin. The program would call for synthesizing **2** and **3** in differentially protected forms (cf. **2′** and **3′**), which would eventually allow for the hetero coupling of the two constructs en route to **1**. The success of such a program would require, ideally, stereoselective access to the two diastereometrically distinct oxidatively and alkylatively cyclized L-tryptophan derivatives, **2′** and **3′**. The likely course of progression of a hypothetical synthesis along these lines of conjecture would commence with building a suitable reverse prenylated L-tryptophan derivative (cf. **4**). It would then be necessary to devise methodology by which oxidative cyclization of **4** could be used to reach *either* **2** or **3**. This goal can be envisioned in terms of kinetically controlled oxidative cyclizations (see hypothesized pathways **4 → 2′** and **4 → 3′**). The prospects of developing two stereospecific kinetic oxidative cyclization solutions, *each culminating in opposite diastereofacial outcomes*, were daunting.

An alternative possibility would entail inversion of configuration of the tryptophan acyl center, *after* the formation of the kinetic oxidatively cyclized product **2′** or **3′**. For the sake of discussion, we postulate a scenario where the only stereoselective capability which is accomplished with excellent kinetic control allows one to progress stereoselectively from **4 → 2′** (Figure 3). In principle, however, deprotonation at the acyl center of **2′** followed by kinetic quenching could produce a diastereomer different from the direct product of oxidative cyclization (cf. *ent* **2′ → 3′**). An alternative to such a second-stage kinetic
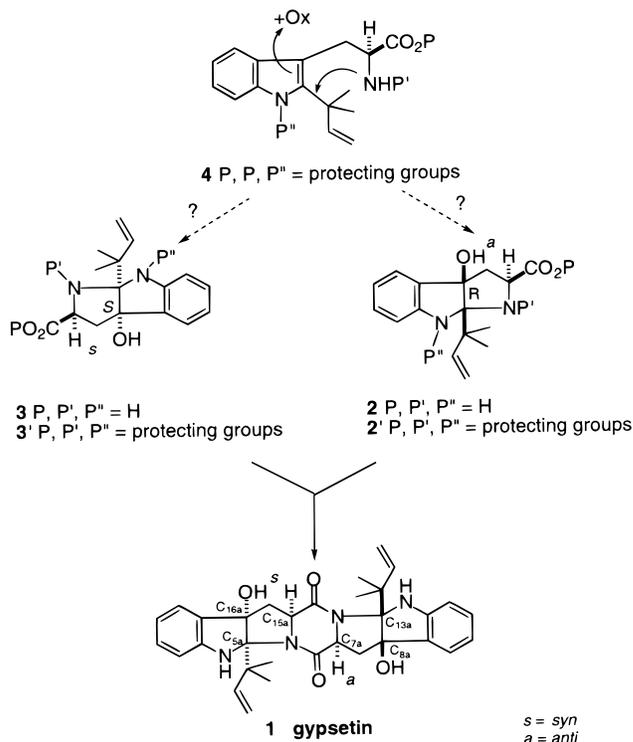
Figure 2.
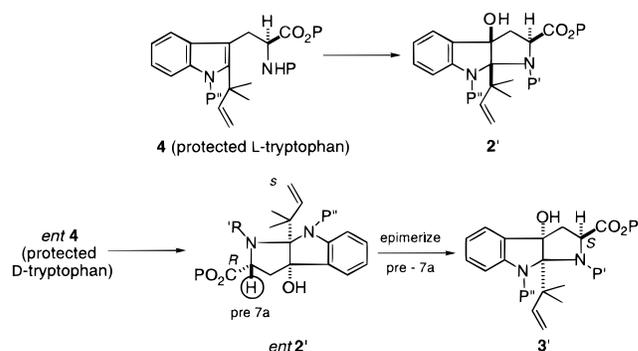
Figure 3.

protonation solution might involve thermodynamic equilibration of one of the kinetic oxidative cyclization products to produce its acyl side chain diastereomer (for the sake of argument, *ent* **2′ → 3′**). It is recognized that, to reach **3′** en route to gypsetin by either a second-stage "corrective" kinetic or thermodynamic solution, the oxidative cyclization would have to have been accomplished in the D-tryptophan series. Epimerization (of *ent* **2′**) at the tryptophan acyl center would transpose the system to the L-amino acid series but with the required stereochemistry at the pyrroloindole junction (i.e., **3′**).

While it is certainly possible that these generalized concepts could be reduced to practice with suitable study, we also considered a rather more concise strategy although, admittedly, one which was unlikely to produce a stereoselective solution. It is recognized that, in principle, a preformed, suitable diketopiperazine could undergo two-fold oxidative cyclization to furnish gypsetin. We started with the simplifying assumption that the two cyclization events are independent; i.e., the diastereofacial course of the first oxidative cyclization would not influence, in a significant way, the outcome of the second process. Under these circumstances, if the overall oxidative cyclization event is stereospecific in either the *syn* or *anti* sense, such a scheme *could not deliver gypsetin*, since two opposite

Figure 4.

For gypsetin, brevianamide E and tryprostatin B   R = CH$_2$ — CO$_2$Me, NPhth

Figure 5. Preparation of 2,3-disubstituted indoles by addition of nucleophiles to 3-chloroindolenines.

Scheme 1[a]

[a] Reagents and conditions: (a) *tert*-butylhypochlorite, Et$_3$N, THF, −78 °C, 30 min. (b) prenyl 9-BBN (3 equiv), − 78 °C, 6 h, 95%.
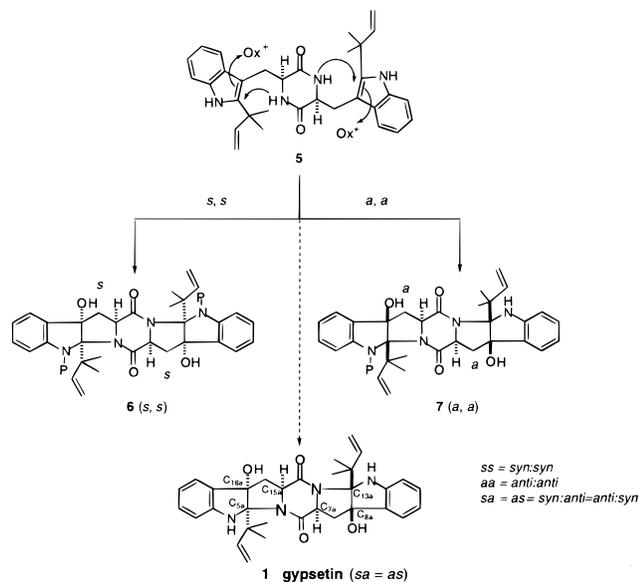
outcomes are required (see discussion above). If, however, each of the disconnected oxidative cyclization reactions is stereorandom, then the prospects for reaching gypsetin are excellent. Toward this end, there would be required one *syn* and one *anti* closure. In the limiting case of stereorandomness in *both* the first and second cyclization steps, the expected ratio would be gypsetin (*syn*:*anti* = *anti*:*syn*, 2):**6** (*syn*:*syn*, 1):**7** (*anti*:*anti*, 1) (Figure 4). The expected preference for reaching gypsetin over either **6** or **7** arises, of course, from the symmetry of the system wherein *syn*:*anti* (*s*,*a*) is identical with *anti*:*syn* (*a*,*s*). Therefore, two of the four equally probable permuted outcomes converge on gypsetin.

In this paper, we describe a remarkably concise total synthesis of gypsetin[7] based on the diketopiperazine double-cyclization concept. In so doing, it was first necessary to learn how to introduce a reverse prenyl group in to the 2-position of a 3-substituted indole. This problem was quite different from the challenge which we faced in the total synthesis of 5-*N*-acetylardeemin, wherein the goal required introduction of a reverse prenyl group into the 3-position of a pyrroloindole.[7c] We will also relate the application of this methodology to the total synthesis of deoxybrevianamide E (**24**) and brevianamide (**25**). We then describe extension of the new method for C$_2$-alkylation of indoles to encompass nucleophiles other than reverse prenyl groups.

During the course of these studies, another natural product, tryprostatin B (**41**), was isolated. This compound was reported to disrupt progression of ts-ft210 cells at the G2/M phase barrier (vide infra). The goal of a total synthesis of tryprostatin B implicitly raised another issue, i.e., that of introduction of a prenyl, rather than a reverse prenyl group, at C$_2$ of an indole and, by extension, to other systems. The attainment of a nucleophilic prenylating protocol and its application to the total synthesis of tryprostatin B is described in the concluding phase of this report.

Results and Discussion

Installation of the Reverse Prenyl Group. At the outset of the program, we focused on an efficient method for introducing the reverse prenyl group at the α-position of the indole moiety of a suitably protected tryptophan. This type of problem had received attention in connection with the synthesis of alkaloids such as austamide, echinulin, and neoechinulin, with the only practical method arising from various Claisen rearrangements.[8] Of the existing methods available for the synthesis of 2,3-disubstituted indoles, none seemed particularly attractive with respect to the particular objective required here.[9]
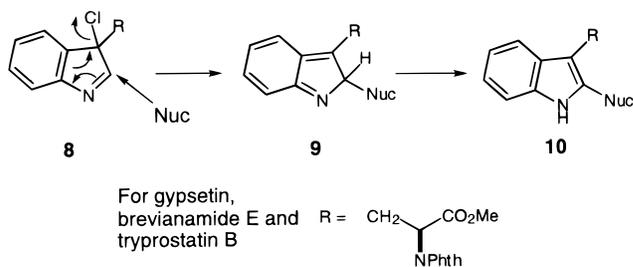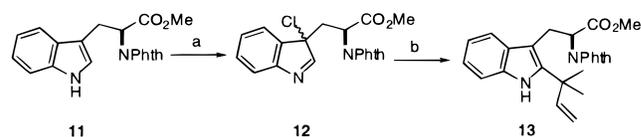
Recalling the oxidative conversion of 2,3-disubstituted indoles to chloroindolenines and the use of such chloroindolenines for functionalization of the carbon benzylic to C$_2$,[10a] we asked whether an intermediate such as **8** might have transient viability even if C$_2$ were unsubstituted.[10b] We hoped that **8** might suffer nucleophilic attack at C$_2$ leading to **9** and thence, after tautomerization, to **10** (Figure 5). Development of this protocol would allow for a rapid and general preparation of 2,3-disubstituted indoles.

Accordingly, the synthesis of gypsetin started with *N*-phthaloyltryptophan methyl ester[11] (**11**). Treatment of this compound with *tert*-butylhypochlorite and triethylamine led to the formation of an unstable 3-chloroindolenine, presumably **12**. Happily, addition of freshly prepared prenyl-9-BBN[12] to this intermediate led to **13** in 95% yield. Thus, the reverse prenyl group had been cleanly incorporated at C$_2$ of the indole ring (Scheme 1). It was particularly gratifying to find that the reverse prenylation reaction at the α-position of the indole in suitably protected tryptophan derivative had been achieved without noticeable racemization.

Interestingly, both prenyl tri(*n*-butyl)stannane and prenyl trimethylsilane failed to react with the chloroindolenine under the influence of several Lewis acid promoters, such as BF$_3$·Et$_2$O, ZnCl$_2$, and SnCl$_4$. Since there are relatively few direct methods for the preparation of 2,3-disubstituted indoles, studies

(8) (a) Tomita, K.; Terada, A.; Tachikawa, R. *Heterocycles* **1976**, *4*, 733. (b) Godtfredsen, W. O.; Vangedal S. *Acta Chem. Scand.* **1956**, *10*, 1414. (c) Owellen, R. J. *J. Org. Chem.* **1974**, *39*, 69. (d) Pleininger, H.; Kraemer, H.-P.; Sirowej, H. *Chem. Ber.* **1974**, *107*, 3915. (e) Takamatsu, N.; Inoue, S.; Kishi, Y. *Tetrahedron Lett.* **1971**, 4661. (f) Takamatsu, N.; Inoue, S.; Kishi, Y. *Tetrahedron Lett.* **1971**, 4665. (g) Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786.

(9) Saulnier, M. G.; Gribble, G. W, *J. Org. Chem.* **1982**, *47*, 2810.

(10) (a) Kuehne, M. E.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3702 and references therein. (b) For the only published example of a carbon-based nucleophilic addition to a C$_2$-unsubstituted chloroindolenine, see: Parsons, R. L.; Berk, J. D.; Kuehne, M. E. *J. Org. Chem.* **1993**, *58*, 7482.

(11) Prepared from L-tryptophan methyl ester by modification of the procedure listed in the following: Bodansky, M.; Bodansky, A. *The Practice of Peptide Synthesis*; Springer-Verlag: Berlin, 1984; p10.

(12) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9.

Scheme 2. Oxidative Ring Closure of Tryptophan Compounds

Scheme 3[a]

[a] Reagents and conditions: (a) NH_2NH_2, EtOH, room temperature, 3 days, 65%. (b) $(Boc)_2O$, Et_3N, THF, 1 h, quantitative. (c) LiOH/THF/MeOH/H_2O, room temperature, 3 h, 100%. (d) **18** (0.91 equiv), BOP-Cl (3 equiv), CH_2Cl_2, $-78 \rightarrow 0$ °C, 1 h. (e) TFA, CH_2Cl_2, room temperature, 1 h. (f) NH_3, MeOH, reflux, 12 h, 73% from **18**.
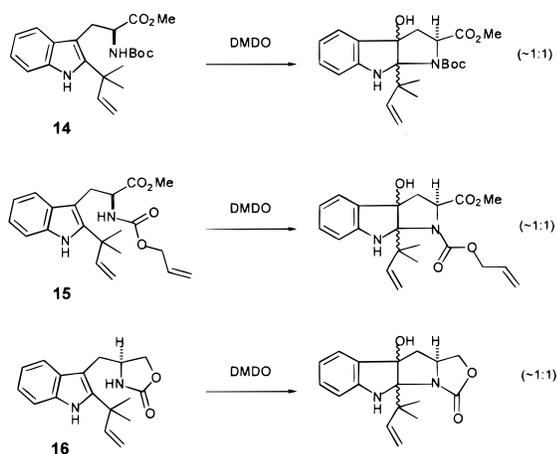
of the reactions of other nucleophiles with transiently generated C2-unsubstituted C3-chloroindolenines were of interest. The results of that investigation are presented later in this disclosure (vide infra).

Oxidative Ring Closure To Form Systems of the Type 2 and 3. With a direct solution for the introduction of a reverse prenyl moiety at C_2 of a tryptophan ring system in hand, our attention turned to the gross feasibility and stereoselectivity in the formation of pyrrolo[2,3-*b*]indoline systems such as **2′** and **3′**. As discussed above, the synthesis of gypsetin would require access to both of these hypothetical amino acids for hetero coupling. The ideal method for obtaining these intermediates would obviously involve kinetically controlled stereoselective oxidative cyclizations of suitably protected tryptophans (cf. **4**), leading specifically to *either* **2′** or **3′**. We envisioned formation of systems such as **2′** and **3′** by oxidative cyclization of N_b of a suitable amino side chain mounted at C_2 of the indole with concomitant hydroxylation at C_3 through the agency of a formal hydroxenium ion ($^+$OH). Oxidative cycloaromatizations of tryptophans are well precedented,[13] but only a few examples of oxidative cyclizations, where the C_3 hydroxyl survives, had been practiced. One such instance involves the use of singlet oxygen[14,15] (vide infra). We chose, instead, the mild oxidant dimethyldioxirane (DMDO)[16] as a possible source of the desired hydroxenium equivalent due to the extensive background of our laboratory in the use of this agent in the epoxidation of sensitive glycals.[14c]

The three substrates **14**, **15**, and **16** had been synthesized by utilization of the reverse prenylation protocol discussed above. In each case, oxidative cyclization[17] via DMDO did occur apparently in high yield, as indicated by rough purification and NMR analyses of the reaction products (Scheme 2). However, NMR analyses of the reaction products indicated the formation of a ca. 1:1 mixture of diastereomers. This result is per se not surprising, since the results of Kametani and Ottenheijm suggested that, at best, only very modest stereoselectivity is achieved in this kind of cyclization[15] (see, for example, the synthesis of brevianamide E below).

To accomplish a hetero coupling, in formation of the diketopiperazine moiety, the protecting groups embodied in

these structures would have to be differentiated, and a difficult separation of diastereomers would have to be overcome. Given the absence of stereoselectivity in the reactions with DMDO, and given the gloomy prognosis from literature precedents which documented other related oxidative cyclizations, our hopes to gain stereospecific access to **2′** and **3′** would not be readily achievable and were, for the moment, set aside. The realities of our situation strongly favored the prebuilt diketopiperazine approach (see Figure 4). The advantage of the double cyclization is that the protecting group issues would be much simplified. The predicted stereorandomness of the reaction would have been turned to some advantage from the standpoint of conciseness and could benefit additionally from the stochastic analysis offered above. We therefore embarked on this course.

Total Synthesis of Gypsetin. Fashioning of the diketopiperazine portion of gypsetin required the removal of the phthalimide protecting group from **17**. This result was accomplished via hydrazinolysis in ethanol at ambient temperature for 3 days to provide **17** in 65% yield after chromatography. Attempts to increase the yield and decrease the reaction times by heating **13** with hydrazine in refluxing methanol resulted in concurrent hydrazinolysis of the methyl ester.

A five-step procedure was developed to provide the required diketopiperazine from the amino ester **13** (Scheme 3). First, the BOC derivative (**14**) was prepared from **13** via **17**. Saponification of the methyl ester of **14** gave the acid, **18**. Coupling of this compound to amino ester **17** was accomplished under mediation of BOP-Cl. Removal of the *t*-BOC group with trifluoroacetic acid was followed by ammonia-catalyzed cyclization to provide **19** in 73% yield over the three steps. The

(13) Ohno, M.; Spande, T. F.; Witkop, B. *J. Am. Chem. Soc.* **1968**, *90*, 6521.

(14) (a) Nakagawa, M.; Watanabe, H.; Kodato, S.; Okajima, Y.; Hino, T.; Flippen, J. L.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 4730. (b) Nakagawa, M.; Yokoyama, Y.; Kato, S.; Hino, T. *Tetrahedron* **1985**, *41*, 2125. (c) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.

(15) Kametani and co-workers achieved a 2:1 selectivity in their oxidative cyclization by using singlet oxygen for the synthesis of brevianamide E. The major product was the desired natural product. (a) Kametani, T.; Kanaya, N.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 3974. (b) Kametani, T.; Kanaya, N.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 959. (c) For a report of a 3:2 selectivity ratio in the same reaction, see: Sanz-Cervera, J. F.; Glinka, T.; Williams, R. M. *Tetrahedron*, **1993**, *49*, 8471. (d) Ottenheijm et al. obtained a 1:1 ratio of diastereomers in their approach toward sporidesmin: Plate, R.; Akkerman, M. A. J.; Ottenheijm, H. C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2481.

(16) (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Adam, W.; Curci, R.; Edward, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (c) Adam, W.; Hadjiarapoglou, L. *Top. Curr. Chem.* **1993**, *164*, 45.

(17) For the reaction of N_a-acylated indoles with dimethyldioxirane, see: (a) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867. (b) Adam, W.; Ahrweiler, M.; Peters, K.; Schmiedeskamp, B. *J. Org. Chem.* **1994**, *59*, 2733 and references therein.

Scheme 4. One-Pot Synthesis of Diketopiperazine **19** from **17**
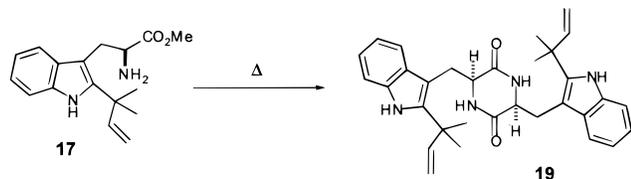
synthesis became especially concise following the finding that diketopiperazine (**19**) can be prepared, albeit only in 30% yield, by pyrolysis of **17** at 140 °C. This capability saved four steps relative to the synthetic sequence described above (Scheme 4).

At this stage in the synthesis, we hoped to effect a culminating *one-step* oxidative conversion of a diketopiperazine to gypsetin (**1**). Indeed, we would attempt the reaction on **19** itself, wherein the indoline amino group was unprotected. As noted above, an approach involving stereochemically random oxidative cyclization, would benefit from the truism that the hypothetical ratio of gypsetin:"*syn*:*syn*" product:"*anti*:*anti*" product would be 2:1:1. In the event, reaction of **19** with 4 equiv of DMDO afforded a 40% isolated yield of fully synthetic gypsetin (**1**). This was accompanied by the formation of two isomers, referred to as **20** and **21**, in 18 and 20% yields, respectively. At the present time, we favor the "*syn*:*syn*" structure for **20** and the "*anti*: *anti*" arrangement in **21**, though these assignments are not definitive. When conducted in large scale (>0.5 g), this cyclization produces essentially the same ratio of products but in only ca. 65% combined yield.

The spectral properties (^{1}H NMR, ^{13}C NMR, MS, and IR) of synthetic gypsetin (**1**) were the same as those of the natural material. The chromatographic properties were also identical, and the melting point (159 °C) was in accord with that reported for the naturally derived material. The optical rotation of synthetic gypsetin was $[\alpha]^{24}_D$ −113.4° (*c* 0.20, CHCl$_3$) was in good agreement with that reported for natural gypsetin, $[\alpha]^{24}_D$ −116.9° (*c* 0.14, CHCl$_3$).

We briefly investigated the use of other potential "oxenium ion" equivalents to achieve two-fold cyclization of **19**. In practice, successful oxidative cyclization on this substrate turned out to be restricted to the set of conditions we tried first. Thus, attempts to utilize mCPBA, Pb(OAc)$_4$, *N*-phenylselenophthalomide, *t*-BuOCl, or Br$_2$ led to substantially decomposed starting material with no indication of formation of either **20**, **21**, or **1** (Scheme 5). Whether these failures reflect a particular nuance of substrate **19**, or whether they are general, was not determined.

Synthesis of the Brevianamides. At this point, it seemed probable that the reactions devised for the synthesis of gypsetin could be applicable toward the synthesis of other reverse prenyl-containing alkaloids, such as deoxybrevianamide (**24**) and brevianamide E (**25**). Deoxybrevianamide E is a metabolite of *Aspergillus ustus* first isolated by Steyn,[19] while brevianamide E had been isolated from the culture medium of *Penicillium brevicompactum* by Birch and Wright.[20] Their syntheses had been the subject of several investigations.[15a,b,18] Our synthesis commenced with coupling of the previously described amino ester **17** to *N*-BOC-protected L-proline to afford **22**. Deprotection of this compound with TFA (see compound **23**), followed by

(18) Ritchie, R.; Saxton, J. E. *J. Chem. Soc., Chem. Comm.* **1975**, 611.
(19) (a) Steyn, P. S. *Tetrahedron Lett.* **1971**, 3331. (b) Steyn, P. S. *Tetrahedron* **1973**, *29*, 107.
(20) (a) Isolation: Birch, A. J.; Wright, J. J. *J. Chem. Soc., Chem. Comm.* **1969**, 644. (b) Structure determination: Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329.
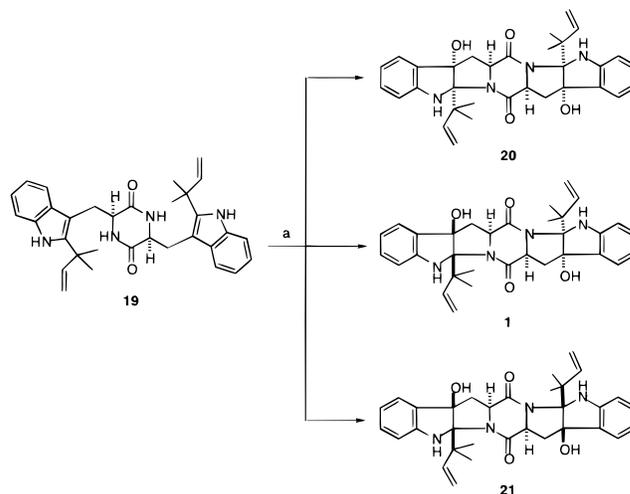
Scheme 5[a]

[a] Reagents and conditions: (a) dimethyldioxyrane (4 equiv), CH$_2$Cl$_2$/acetone, −78 → 0 °C.

Scheme 6[a]

22 R = [t]Boc
23 R = H

24 deoxybrevianamide E

25 brevianamide E

26 bis(*epi*)brevianamide E
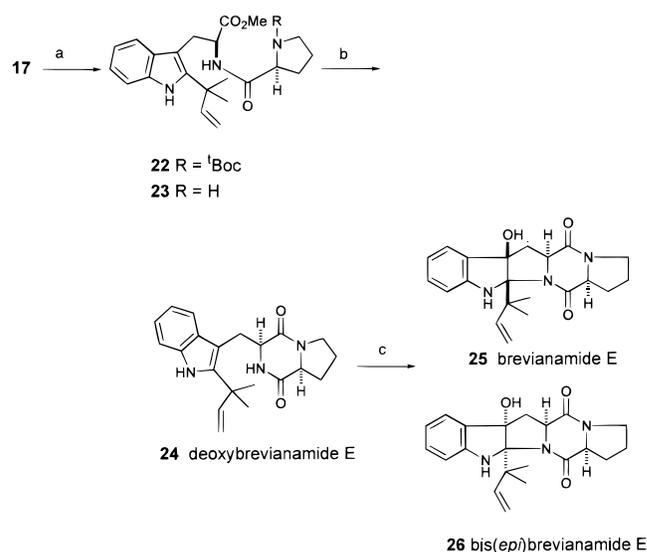
[a] Reagents and conditions: (a) Boc-proline (1.1 equiv), BOP-Cl (3 equiv), CH$_2$Cl$_2$, − 78 → 0 °C, 1 h. (b) TFA, CH$_2$Cl$_2$, room temperature, 2 h then NH$_3$, MeOH, reflux, 12 h, 52% from **17**. (c) Dimethyldioxirane (4 equiv), CH$_2$Cl$_2$/acetone, −78 → 0 °C, 76% for both **25** and **26**.

cyclization, afforded deoxybrevianamide E (**24**) in 52% yield from **17**. To our knowledge, this is the most concise and efficient total synthesis of deoxybrevianamide E of those which have been reported.

Since compound **24** had previously been converted to **25**, a formal total synthesis of brevianamide E had also, in effect, been accomplished. Nonetheless, another opportunity to study the DMDO-induced oxidative cyclization of indolyl-substituted diketopiperazines had presented itself. Hence, the matter was pursued for purposes of learning more about this reaction.

Addition of 4 equiv of DMDO to deoxybrevianamide E (**24**) provided a mixture of compounds in a ratio of ∼5:1 (Scheme 6). Based on ^{1}H NMR and optical rotation data, the major product is bis-*epi*-brevianamide E (**26**), while the minor product is brevianamide E (**25**). This result is in striking contrast to Kametani's reported result, wherein it was claimed that subjection of deoxybrevianamide E to singlet oxygen yielded brevianamide E (**25**) and bis-*epi*-brevianamide E (**26**) in a ratio of ∼2:1.[15]

Figure 6. Proposed pathway of oxidation of deoxybrevianamide E.

By monitoring the consequences of the reaction of DKP (**24**) with dimethyldioxirane by thin-layer chromatography, we were able to note the rapid disappearance of starting material with formation of a minor and a major component as judged by TLC "spot" sizes. Upon continued stirring, the minor product remained seemingly unchanged. Its spectral characteristics, following workup, were consistent with those of brevianamide E (**25**). By contrast, the major TLC-identified product progressed to bis-*epi*-brevianamide E (**26**) only after prolonged reaction time (ca. 12 h).

We emphasize that the structure of the precursor of compound **26** has not been established. Attempts to purify this compound were not successful. A possible explanation for these qualitative findings is as follows. We postulate that the initial product of dimethyldioxirane oxidation of **24** is the corresponding epoxide, which suffers rapid valance isomerization to the stereoisomeric hydroxyiminium species **27** and **28** (Figure 6). Apparently, stereoisomer **27** cyclizes very rapidly to give rise to the observed **25**. By contrast, the cyclization reaction of presumed **28** is rather slow, allowing this labile intermediate to accumulate and be detected by TLC analysis en route to **26**.

If this line of conjecture has merit, then two conclusions seem to be required. First, in contrast to the singlet oxygen case of Kametani and in contrast to the DMDO-mediated oxidations of diketopiperazine **19** or model compounds **14**−**16**, oxidation of **24** is significantly stereoselective in favor of **28**. Furthermore, it would be necessary to presume that cyclization of **28** is considerably slower than is the case with hypothetical **27**. Conceivably, this differential rate could be the consequence of hindrance to cyclization en route to **26**. Such a cyclization requires forcing the prolyl acyl portion of the diketopiperazine into the endo face of the "cup-shaped" pyrroloindole structure. These matters are the subject of continuing investigations.

Synthesis of 2,3-Disubstituted Indoles. Given the methodology which was implemented for the installation of reverse prenyl groups at the C2-indolic position of substituted tryptophans, we wondered about extensions of the general concept. The thought was that a chloroindolenine of the type **8** should be susceptible to nucleophilic attack by a range of other nucleophiles. As in the case of reverse prenylation, attack would be likely to occur at C₂, with expulsion of chloride ion. Eventual tautomerization would lead to a 2,3-disubstituted indole. As a probe structure for this purpose, we utilized the readily available *N,N*-dibenzyltryptophan methyl ester (**29**). The tertiary nature of the nitrogen precluded cyclization of the required chloroindolenine intermediate. Compound **29** is more conveniently prepared than is **11** and avoids the problem of competitive electrophilicity from

Table 1.[a] Addition of Nucleophiles to 3-Chloroindolenines **30**

Entry	Nucleophile	Product	Yield %
1[b]	prenyl-BBN	**31**	74%
2	allyl-SnBu₃	**32**	79%
3	TMSCN	**33**	69%
4	silyl ketene acetal (OTBS, OEt)	**34**	77%
5	1-pyrrolidino-cyclohexene	**35**	54%
6	1-pyrrolidino-cyclopentene	**36**	50%
7	2-(TMSO)furan	**37**	22%
8	PhC≡C–Li	**38**	56%
9	indole	**39**	68%

[a] Typical procedure: *tert*-butylhypochlorite (1.2 equiv) was added to a cold (−78 °C) solution of starting tryptophan (1 equiv) and Et₃N (1.2 equiv) in 1 mL of THF. After 30 min, the nucleophile was added (2.0 equiv), followed by BF₃·Et₂O (2.0 equiv). The solution was then allowed to warm to ambient temperature over 12 h. [b] A promoter was not used with this nucleophile.

the imide linkage. In the event, compound **29** was treated in several protocols with *tert*-butylhypochlorite to generate the presumed chloroindolenine derivative, **30**. Reaction of **30** with prenyl 9-BBN as described before afforded **31**. Surprisingly, a range of other nucleophiles did not react well with the presumed **30** in the absence of an additional Lewis acid catalyst. However, it was found that, in the presence of BF₃·OEt₂, nucleophilic attack became more general. We first investigated this reaction with allyl trimethylsilane. Curiously, we were unable to obtain the 2-allylated isomer. However, through the use of tri(*n*-butyl) allylstannane, BF₃·OEt₂, a 79% yield of compound **32** was obtained.

Other nucleophiles surveyed in this preliminary inquiry (see Table 1) resulted in the formation of products **33**−**39** as shown. As seen, trimethylsilyl cyanide reacted in good yield to afford the C₂-cyanotryptophan derivative. Trimethlsilyl azide, on the other hand, afforded a complex mixture of unidentified products. A significant extension of the method arose from the finding that the silyl keteneacetals and enamines reacted in serviceable yields to afford the ester and ketones, respectively (see

Scheme 7

Scheme 8
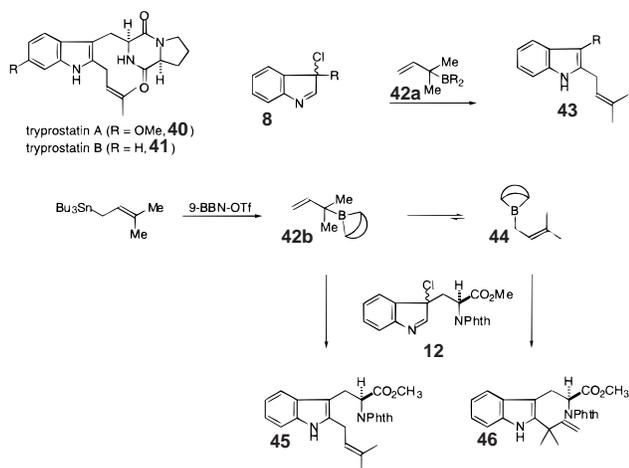
compounds **34−36**). Disappointingly, 2-trimethylsilyloxyfuran afforded only a low yield of the butenolide, although it was interesting that the olefin isomerized into conjugation with the indole ring rather than remain in conjugation with the ester moiety. As seen, the lithium salt of phenylacetylene afforded **38** in moderate yield. The full scope of this kind of reaction with other organolithium derivatives remains to be determined. Thus, in some instances, there is apparent reductive cleavage of **30** to produce **29**. Indeed, indole itself reacted with in situ-generated **30** to produce the 8a-(3′-indolyl)tryptophan methyl ester **39** in 68% yield. We emphasize that these reactions have not been optimized in this survey phase. However, even at this stage, a promising strategy to synthesize tryptophan derivatives that are otherwise difficult to access has emerged.

Synthesis of Tryprostatin B. While these studies were well in progress, we noted a report by Osada and co-workers describing the isolation of two natural products, tryprostatin A (**40**) and B (**41**) from *Aspergillus fumigatus* (Scheme 7).[21] The presence of a diketopiperazine sector and the presence of a prenyl function at the 2-position of the indole are features of the tryprostatins that did not escape our attention. From a synthetic point of view, at the level of the indole substructure, the tryprostatins pose a challenge related to yet different from that faced in the gypsetin and brevianamide targets. In the tryprostatin project, we would be concerned with the introduction of a prenyl group at the C_2-position of a suitable tryptophan derivative. By contrast, a reverse prenyl function was required in the gypsetin and brevianamide programs. Similarly, the key challenge in the 5-*N*-acetylardeemin target[7c] was that of introducing a reverse prenyl function at the 3-position of a pyrroloindole core. In the tryprostatin case, there is no comparable issue of pyrroloindole formation. Our interest in the tryprostatin problem was enhanced by the claims that **40** and **41** are cell cycle progression inhibitors in ts-ft210 cells at the G2/M phase barrier.[21]

At the chemical level, we favored a solution which would adapt the logic already utilized in the gypsetin venture but would now involve attack of a suitable nucleophilic prenylating agent onto a chloroindolenine (e.g., **8**, Scheme 7). We focused on tryprostatin B, because we could start with readily available L-tryptophan. Viewed differently, we sought a methodology

complementary to the Gribble method, wherein suitably N-protected, 3-substituted indoles can be used to fashion 2-lithio derivatives.[9,22] These indolyllithium agents can be alkylated with appropriate electrophiles, thereby producing 2,3-disubstituted indoles. The possibility of successfully extending the published 2-lithioindole method in the context of tryptophan congeners seemed to be remote. Rather, we preferred to explore the possibility of introducing the C_2 group as a nucleophile.

Accordingly, our first approach was directed toward synthesizing a suitable and regioispecific reverse prenylborane nucleophile, generalized as **42**. The thought was that such an agent might react with a chloroindolenine of the type **8**. Following the expected allylic transposition of the nucleophilic moiety, a prenyl group would appear at C_2 of the indole (**43**). The earliest attempts along these lines involved reactions of prenyltri(*n*-butyl)stannane with 9-BBN bromide or triflate. We hoped to generate the 9-BBN version of the reverse prenyl borane derivative (see **42b**). The latter might undergo an "allylic rollover", thereby delivering its prenyl product (see **43**). Preliminary attempts to reduce this method to practice were not satisfying. One interpretation of those early experiments was that **42** (BR₂ = borabicyclononane) was, in fact, generated. However, its allylic transposition leading to **44** is quite rapid, even in the absence of reaction with an electrophile. Species **44** serves to deliver a reverse prenyl function to the chloroindolenine. In practice, reverse prenylation leading to **46** was seriously competitive with formation of the desired prenylation product, **45**, in ca. a 1:1 ratio. Moreover, the combined yields of **45** and **46** were low.

In seeking a workable solution to the goal of prenylating indoles via chloroindolenines, we were much influenced by earlier contributions from the laboratories of Keck,[23] Yamamoto,[24] Denmark,[25] Thomas,[26] and Wardell.[27] These critical background disclosures suggested the possibility of using reactions of allylic organometallic agents with boron trichloride to generate transient allyl boron reagents, possibly structures of the type **42c** (R = Cl, *n* = 2) or -ate versions thereof (**42d**, R = Cl, *n* = 3). With this subgoal in mind, we rapidly treated tri(*n*-butyl)prenylstannane and the chloroindolenine **12** at −78 °C with BCl₃. *Following workup, an 83% yield of the desired compound **45** was obtained* (Scheme 8). Only traces of undesired **46** could be detected. We speculated that, perhaps, the prenyl-

(21) (a) Cui, C.-B.; Kakeya, H.; Okada, G.; Onose, R.; Ubukata, M.; Takahashi, I.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48*, 1382. (b) Cui, C.-B.; Kakeya, H.; Osada, G.; Onose, R.; Osada, H. *J. Antibiot.* **1996**, *49*, 527. (c) Cui, C.-B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 534.

(22) For another preparation of 2-substituted indoles, see: Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127.

(23) (a) Keck, G. E.; Abbot, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927. (b) Keck, G. E.; Andrus, M. B.; Castellino, S. *J. Am. Chem. Soc.* **1989**, *111*, 8136.

(24) Yamamoto, Y.; Maeda, N.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1983**, 742.

(25) Denmark, S. E.; Wilson, T.; Willson, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 984.

(26) McNeill, A. H.; Thomas, E. J. *Synthesis* **1994**, 322.

(27) Harston, P.; Wardell, J. L.; Marton, D.; Tagliavini, G.; Smith, P. J. *Inorg. Chim. Acta* **1989**, *162*, 245.

Table 2. Prenylation of Indoles and Ketones

Scheme 9[a]

[a] Reagents and conditions: (a) hydrazine hydrate (3.5 equiv), 3:1 MeOH/CH$_2$Cl$_2$ (0.1 M), 24 h, 82%; (b) cyanuric fluoride, pyridine, CH$_2$Cl$_2$, -15 °C; (c) CH$_2$Cl$_2$, NaHCO$_3$, H$_2$O 94%; (d) TMSI (1.2 equiv), MeCN, 0 °C; (e) NH$_3$/MeOH, 20 h, 67% from **61**.

stannane reacts with BCl$_3$ to generate, transiently, a reverse prenyl intermediate of the type **42c** or **d**. Transfer of a prenyl function through allylic transposition would provide **45**. It is conceivable, though certainly not proven, that prenyl delivery had occurred via an intramolecular transfer reaction from **47**, in turn generated from **42c** and **12** by ligand exchange.

The reaction was extended to two other indole cases. Once again, the starting 3-substituted indoles **48** and **49** were converted (by chloroindolenine formation and prenylation at C2) to **50** and **51**, respectively (Table 2). It was also of interest to probe the applicability of the prenylation method to ketonic electrophiles. In so doing, we would be addressing the problem of avoiding the formation of mixtures of prenyl and reverse prenyl products provided by other allylic metal systems.[28] In this very preliminary phase, we examined three substrates, **52**–**54**. As before, the ketone and tri(*n*-butyl)prenylstannane at -78 °C were treated with BCl$_3$. This step was followed by quenching and standard workup. In this way, cyclohexanone (**52**) itself gave rise to **55**, while its 4,4-dimethyl derivative (**53**) afforded **56**. The impact of a preexisting chiral center on this reaction was examined in only one case. Thus, 2-phenylcyclohexanone (**54**), when subjected to this protocol, reacted smoothly to provide an 80% yield of **57**. No other products were obtained.

At the interpretive level, it can be argued that our protocol simply generates a de facto equivalent of **42c** or **42d** which transfers a prenyl group to the keto group in a bimolecular reaction. An alternative, more interesting, but certainly unproven interpretation envisions ligand exchange leading to **58**. This step is followed by intramolecular transfer prenylation.

With a sound and seemingly broadly applicable method developed for the nucleophilic prenylation of indoles accomplished, we turned our attention to completion of the total synthesis of tryprostatin B. This program started with hydrazinolysis of **45**, thereby giving rise to **59** (Scheme 9). Its coupling partner was generated by conversion of *N*-Boc-L-proline to its *N*-Boc acid fluoride derivative **60**, using cyanuric fluoride, following the tenets laid down by Carpino *et al.*[29] Coupling of **59** and **60** was conducted under essentially Shotten–Baumann conditions, giving rise to seco derivative **61**.

Attempted acidic cleavage of the Boc function through the agency of trifluoroacetic acid was surprisingly complicated.
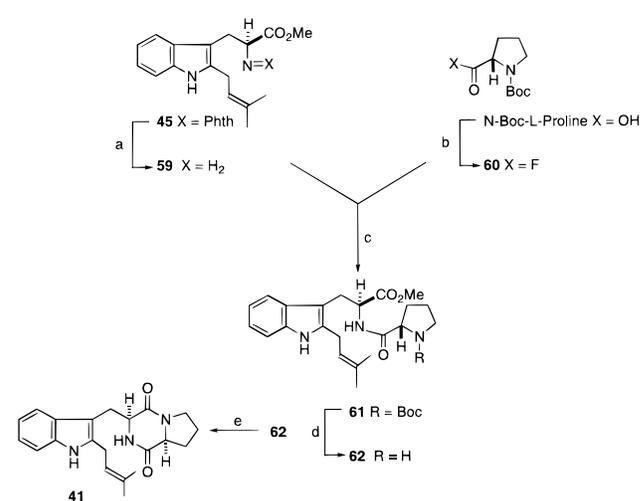
Though the matter has not been sorted out in detail, these conditions apparently triggered significant and unproductive chemistry at the double bond of the prenyl function. Success, however, was achieved through the action of TMSI on **61**. This treatment gave rise to the N-deprotected prolyl tryptophan derivative **62** (Scheme 9). Finally, cyclization was achieved by reaction of **62** with methanolic ammonia. There was thus produced tryprostatin B (**41**). The high-field NMR spectrum of fully synthetic tryprostatin B was identical to that provided by Professor H. Osada.[30] The optical rotation of fully synthetic tryprostatin was substantially the same ([α]$^{27.5}_D$ $-74.6°$ (*c* 0.64, CHCl$_3$) vs lit. [α]$^{27}_D$ $-71.1°$ (*c* 0.63, CHCl$_3$)) as that reported. The overall yield of tryprostatin B from N-phthalolyl tryptophan methyl ester was a gratifying 46%.

Elsewhere, we have described the results of investigations into the biological profile of tryprostatin B.[7b] While the cytotoxicity reported in the original disclosure could be nicely duplicated in a collaborator's laboratory, cell proliferation inhibition by the agent in our assays occurred only at higher concentrations (50 µg/mL) than those reported. Proper analysis of the matter was further complicated by the finding of some shelf instability for tryprostatin B. These findings raised the question as to whether part of the discrepancy in the assays may, in fact, be the consequence of transformation products of **41**, rather than the compound itself. Clarification of these issues would require careful side-by-side evaluation of natural and fully synthetic **41**, in addition to transformation products of **41** of as yet undetermined structure.

Summary

Several new synthetic methods have been developed and applied to interesting problems in alkaloid total synthesis. A key unifying factor in the investigation was the finding that 2-unsubstituted chloroindolenines can be used, rather broadly, in reactions with various nucleophiles to generate 2,3-disubsti-

(28) We note recent examples of prenylation via a prenylbarium species: (a) Yanagisawa, A.; Ogasawara, K.; Yasue, K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* **1996**, 367. (b) Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130.

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

(30) We thank Professor Osada for furnishing us with the spectra of authentic tryprostatin B.

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tuted indole derivatives. This general concept allowed for introduction of a reverse prenyl function at C_2 in substituted tryptophans. This chemistry was used in a total synthesis of gypsetin. The final cyclization step in that total synthesis involved two-fold DMDO-induced oxidative ring closure of a diketopiperazine derivative (see **19** → **1**, Scheme 5). The stereochemistry of this induced cyclization reaction seemed to be governed largely by stochastic considerations. Extension of the logic of the gypsetin synthesis was attempted in the total syntheses of deoxybrevianamide E (**24**) and brevianamide E (**25**). In the latter case, DMDO-induced cyclization led, in a moderately stereoselective fashion, to the bis-*epi* derivative of the natural agent as the major product (see **26**). The chloroindolenine method was generalized to produce a range of 2-substituted tryptophan congeners, not easily obtained by other means. Finally, extension of the method involving introduction of a prenyl function led to a total synthesis of tryprostatin B (**41**). Undoubtedly, the concise access provided by this new methodology to novel indole derivatives, including substituted tryptophans, will find application in other synthetic undertakings.

Experimental Section

General. All melting points were determined using a Hoover capillary melting point apparatus and are uncorrected. Reagents and starting materials were obtained from commercial suppliers and used without further purification unless otherwise indicated. Unless specified otherwise, solvents were freshly distilled prior to use: tetrahydrofuran (THF) and diethyl ether were distilled under nitrogen from sodium metal utilizing benzophenone as an indicator; benzene, toluene, pyridine, dichloromethane, diisopropylamine, tetramethylethylenediamine (TMEDA), and chloroform were distilled from powdered calcium hydride; dimethyl formamide was distilled at reduced pressure from barium oxide. Flash column chromatography was carried out on silica gel obtained from EM Science (230−400 mesh). HPLC grade solvents were used for all chromatography. Analytical thin-layer chromatography (TLC) was conducted on precoated plates: silica gel 60 F-254, 0.25 mm thickness, manufactured by E. Merck & Co., Germany. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of dry nitrogen in oven-dried glassware equipped with a tightly fitted rubber septum. All syringes and needles were oven-dried and transferred to a desiccator for cooling immediately before use. A Bruker AM-400 spectrometer was used to obtain proton (400 MHz) and carbon (100 MHz) nuclear magnetic resonance spectra in deuteriochloroform unless otherwise indicated. The chemical shifts are reported as δ values in ppm relative to deuteriochloroform (7.26 for ^{1}H, 77.0 for ^{13}C). *J*-Modulated spin−echo Fourier transform (JMOD) ^{13}C NMR experiments are reported as (+) for CH$_3$ and CH or (−) for CH$_2$ and C and are used as an alternative to off-resonance decoupling. Mass spectra were determined on a Finnigan spectrometer. Reactions at 0 °C were carried out in an ice/water bath. Reactions at −78 °C were carried out in a dry ice/acetone bath. The term "concentrated in vacuo" refers to the removal of volatile materials on a rotary evaporator at reduced pressure (30−80 Torr).

Methyl (2S)-2-(Dibenzylamino)-3-[1H-indol-3-yl]propanoate (29). Benzyl bromide (2.4 g, 13.7 mmol) was added dropwise to a cool (0 °C) solution of tryptophan methyl ester hydrochloride (1.0 g, 6.2 mmol) and Hünig's base (2.8 g, 3.83 mL, 21.8 mmol) in 10 mL of CH$_2$Cl$_2$. The ice-bath was removed, and the solution was stirred for 48 h, after which water (20 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The organics were combined and dried (MgSO$_4$), filtered, and concentrated in vacuo. Chromatography (10 → 25% EtOAc/Hex) of the residue afforded 1.6 g (65%) of pure **29**, R_f = 0.65 (25% EtOAc/Hex): [α]^{25}$_D$ −104.4° (*c* = 3.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.91 (s, 1 H), 7.23−7.35 (m, 11 H), 7.13−7.17 (m, 2 H), 6.97 (dd, *J* = 7.1, 7.9 Hz, 1 H), 6.90 (d, *J* = 2.1 Hz, 1 H), 4.04 (d *J* = 13.9 Hz, 2 H), 3.83 (dd, *J* = 5.6, 9.0 Hz, 1 H), 3.71 (s, 3 H), 3.57 (d, *J* = 13.9 Hz, 2 H), 3.41 (dd,

J = 11.2, 16.3 Hz, 1 H), 3.11 (dd, *J* = 14.2, 8.6 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 172.9, 139.5, 136.1, 128.8, 128.2, 127.4, 126.9, 122.7, 121.8, 119.2, 118.7, 112.1, 61.4, 54.7, 51.0, 26.2; IR (CHCl$_3$) 3420, 1729, 1455 cm^{-1}; MS (DCI, NH$_3$) *m/v* 399 (M$^+$ + H), 268, 198; HRMS calculated for C$_{26}$H$_{27}$N$_2$O$_2$ 399.2072, found 399.2065.

Methyl (2S)-3-[2-(1,1-Dimethyl-2-propenyl)-1H-indol-3-yl]-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoate (13). To a cold (−78 °C) solution of **11** (1.99 g, 5.70 mmol) and Et$_3$N (0.95 mL, 6.84 mmol) in 20 mL of THF was added *tert*-butyl hypochlorite (0.83 mL, 6.84 mmol). After the solution was stirred for 0.5 h at −78 °C, a 1.0 M solution of prenyl-9-BBN[12] (11.4 mL, 11.4 mmol) in THF was added dropwise. The solution was allowed to warm slowly over 6 h to ambient temperature, after which 5 mL of a saturated solution of K$_2$CO$_3$(aq) was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organics were combined and dried (MgSO$_4$), filtered, and concentrated in vacuo. Chromatography (10% EtOAc/Hex) of the residue afforded 2.26 g (95%) of pure **13** as a pale yellow foam, R_f = 0.70 (50% EtOAc/Hex): [α]^{25}$_D$ −180.8° (*c* = 3.9, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.93 (s, 1 H), 7.68 (m, 2 H), 7.60 (m, 2 H), 7.26 (d, *J* = 7.9 Hz, 1 H), 7.12 (d, *J* = 8.1 Hz, 1 H), 6.9 (t, *J* = 7.1 Hz, 1 H), 6.71 (t, *J* = 7.1 Hz, 1 H), 6.19 (dd, *J* = 10.5, 17.5 Hz, 1 H), 5.18 (m, 3 H), 3.87 (dd, *J* = 3.8, 15.2 Hz, 1 H), 3.77 (s, 3 H), 3.67 (dd, *J* = 11.3, 15.2 Hz, 1 H), 1.57 (s, 6 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 169.9, 167.7, 145.8, 140.1, 133.9, 133.8, 131.8, 129.7, 123.2, 121.1, 119.1, 117.7, 112.1, 110.2, 106.2, 53.5, 52.7, 39.2, 27.6, 27.5, 24.4; IR (CHCl$_3$) 3416, 1742, 1713, 1391 cm^{-1}; MS (DCI, NH$_3$) *m/v* 417 (M$^+$ + H), 386, 324, 309; HRMS calculated for C$_{25}$H$_{24}$N$_2$O$_4$ 416.1736, found 416.1733.

Methyl (2S)-2-Amino-3-[2-(1,1-dimethyl-2-propenyl)-1H-indol-3-yl]propanoate (17). Hydrazine monohydrate (2.44 g, 48.3 mmol, 3.0 equiv) was added to a solution of **13** (5.92 g, 14.2 mmol) in 120 mL of ethanol. The solution was stirred at ambient temperature for 3 days, after which the ethanol and hydrazine were removed in vacuo. The residue was taken up in 5 mL of H$_2$O/EtOAc (1:1), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the organics were combined, washed with H$_2$O (10 mL) and brine (10 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Chromatography (20% EtOAc/Hex, hexamethyldisilazane treated silica) of the residue afforded 4.06 g (69%) of pure **17** as a pale yellow foam, R_f = 0.20 (50% EtOAc/Hex). This reaction was also run on a 5.66 mmol scale for only 12 h. An identical workup and purification procedure afforded **17** in 56% yield: [α]^{25}$_D$ 12.4° (*c* 1.9, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.04 (s, 1 H), 7.57 (d, *J* = 7.7 Hz, 1 H), 7.31 (m, 1 H), 7.11 (m, 2 H), 6.17 (dd, *J* = 5.1, 10.2, 1 H), 5.20 (m, 3 H), 3.90 (m, 1 H), 3.69 (s, 3 H), 3.36 (dd, *J* = 5.0, 14.5 Hz, 1 H), 3.09 (dd, *J* = 9.4, 14.4 Hz, 1 H), 1.62 (br s, 2 H), 1.58 (s, 6 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 175.8, 145.9, 140.4, 134.1, 129.7, 121.5, 119.3, 118.5, 112.1, 110.4, 106.8, 55.7, 51.9, 39.1, 31.1, 27.8, 27.7; IR (CHCl$_3$) 3405, 1730, 1202 cm^{-1}; MS (DCI, NH$_3$) *m/v* 287 (M + H)$^+$, 272, 198; HRMS calculated for C$_{17}$H$_{23}$N$_2$O$_2$ 287.1760, found 287.1771.

Methyl (2S)-2-[(tert-Butoxycarbonyl)amino]-3-[2-(1,1-dimethyl-2-propenyl)-1H-indol-3-yl]propanoate (14). Di-*tert*-butyl dicarbonate (2.14 g, 9.80 mmol) was added to a solution of **17** (1.4 g, 4.90 mmol) in 25 mL of THF. The solution was stirred at ambient temperature for 2 h, after which H$_2$O (25 mL) was added. The aqueous layer was extracted with EtOAc (3 × 25 mL). The organics were washed with H$_2$O (10 mL) and brine (10 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Chromatography (25% EtOAc/Hex) of the residue afforded 1.43 g (76%) of pure **14** as white solid, R_f = 0.30 (25% EtOAc/Hex): [α]^{25}$_D$ 11.3° (*c* = 0.8, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.03 (s, 1 H), 7.49 (d, *J* = 7.4 Hz, 1 H), 7.27 (m, 1 H), 7.09 (m, 2 H), 6.14 (dd, *J* = 10.5, 17.4 Hz, 1 H), 5.20 (m, 2 H), 5.09 (d, *J* = 7.4 Hz, 1 H), 4.57 (app. q, *J* = 7.5 Hz, 1 H), 3.57 (s, 3 H), 3.30 (m, 1 H), 3.24 (m, 1 H), 1.56 (s, 3 H), 1.55 (s, 3 H), 1.53 (s, 9 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ (rotamers) 173.5, 155.0, 146.7, 146.0, 140.5, 134.2, 129.7, 121.5, 119.4, 118.2, 112.2, 110.4, 105.6, 85.2, 79.6, 54.5, 52.1, 39.1, 28.5, 28.2, 27.7, 27.4; IR (CHCl$_3$) 3379, 1699, 1366, 1167 cm^{-1}; MS (DCI, NH$_3$) *m/v* 387 (M + H)$^+$, 369, 331; HRMS calculated for C$_{22}$H$_{30}$N$_2$O$_4$ 386.2209, found 386.2206.

(2S)-2-[(tert-Butoxycarbonyl)amino]-3-[2-(1,1-dimethyl-2-propenyl)-1H-indol-3-yl]propanoic Acid (18). Solid LiOH monohydrate

(0.77 g, 18.5 mmol) was added to a solution of **14** (1.43 g, 3.7 mmol) in 38 mL of a THF/MeOH/H$_2$O (8/1/1) solution. The solution was stirred at ambient temperature for 3 h, after which 1 N HCl was added to neutralize the solution. The aqueous layer was extracted with ether (3 × 50 mL). The organics were washed with H$_2$O (2 × 25 mL) and brine (25 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo to afford 1.38 g (100%) of pure **18** as a white foam, R_f = 0.26 (75% EtOAc/Hex): [α]$^{25}_D$ 4.5° (*c* = 1.15, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.95 (m, 1 H), 7.60 (m, 1 H), 7.27 (d, *J* = 7.5 Hz, 1 H), 7.10 (m, 2 H), 6.15 (dd, *J* = 10.5, 17.4 Hz, 1 H), 5.21 (m, 2 H), 5.18 (m, 1 H), 4.61 (m, 1 H), 3.44 (m, 1 H), 3.23 (dd, *J* = 9.6, 14.7 Hz, 1 H), 1.57 (s, 6 H), 1.49, 0.94 (singlets, rotomers, 9 H); IR (CHCl$_3$) 3384, 1716, 1699, 1367, 1165 cm^{-1}; MS (DCI, NH$_3$) *m/v* 373 (M$^+$ + H), 333, 317, 257, 198; HRMS calculated for C$_{21}$H$_{28}$N$_2$O$_4$ 372.2049, found 372.2050.

(3S,6S)-3,6-Bis{[2-(1,1-dimethyl-2-propenyl)-1H-indol-3-yl]methyl}-2,5-piperazinedione (Pre-Gypsetin Diketopiperazine) (19). Bis-(2-oxo-3-oxazolidinyl)phosphonic chloride (BOP-Cl) (2.92 g, 11.1 mmol) was added to a cool (0 °C) solution of Et$_3$N (1.49 g, 2.06 mL, 14.8 mmol), acid **18** (1.34 g, 3.70 mmol), and amine **17** (1.16 g, 4.07 mmol) in 18.5 mL of THF. The solution was stirred at ambient temperature for 12 h, after which H$_2$O (50 mL) was added. The aqueous layer was extracted with EtOAc (3 × 25 mL). The organics were combined and washed with H$_2$O (50 mL) and brine (50 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo to afford a light yellow solid. The solid was suspended in 6 mL of CH$_2$Cl$_2$. The suspension was cooled to 0 °C, and 34 mL of TFA was added. The ice bath was removed and the clear orange solution allowed to warm to ambient temperature. After the solution was stirred for 1 h, the volatiles were removed in vacuo, a 7 M solution of NH$_3$ in MeOH (50 mL) was added, and the solution brought to reflux. The reaction was complete after 3 h. It was best to monitor the final cyclization reaction by ^{1}H NMR. The volatiles were removed in vacuo, and the residue was dissolved in 25% EtOAC/Hex and a couple of drops of THF and loaded onto a silica gel column. Chromatography (25 → 33 → 50% EtOAc/Hex) afforded 0.85 g (73%) of pure **19** as a white amorphous solid, R_f = 0.49 (75% EtOAc/Hex): [α]$^{25}_D$ −39.6° (*c* = 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.17 (s, 1 H), 7.47 (d, *J* = 7.7 Hz, 1 H), 7.27 (d, *J* = 7.9 Hz, 1 H), 7.09 (m, 2 H), 6.10 (dd, *J* = 10.4, 17.5 Hz, 1 H), 5.78 (s, 1 H), 5.16 (m, 2 H), 4.34 (d, *J* = 10.2 Hz, 1 H), 3.70 (dd, *J* = 3.2, 14.5 Hz, 1 H), 3.22 (dd, *J* = 11.8, 14.5 Hz, 1 H), 1.54 (s, 3 H), 1.52 (s, 3 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 167.2, 145.6, 141.6, 134.2, 128.7, 122.0, 120.0, 118.0, 112.4, 110.8, 104.4, 54.8, 39.0, 29.9, 28.0, 27.8; MS (FAB) *m/v* 509 (M + H)$^+$, 386, 373, 315, 301, 287; HRMS calculated for C$_{32}$H$_{37}$N$_4$O$_2$ 509.2917, found 509.2913.

Gypsetin (1). An acetone solution of dimethyldioxirane (DMDO) (53 mL, ∼3.9 mmol, ∼4 equiv) was added to a cold (−78 °C) solution of diketopiperazine **19** (500 mg, 0.98 mmol) in 20 mL of THF. The resultant yellow solution was warmed to −30 °C over 1 h, and the volatiles were removed in vacuo. The residue was dissolved in 50 mL of THF and stirred for 24 h at ambient temperature. The volatiles were again removed in vacuo. Chromatography (TLC grade silica, 15% EtOAc/Hex) of the residue afforded three compounds.

The first compound to elute was the *cis,cis* isomer, **(5aR,7aS,8aS,-13aR,15aS,16aS)-5a,13a-bis(1,1-dimethyl-2-propenyl)-8a,16a-dihydroxy-5a,8,8a,13,13a,15a,16,16a-octahydroindolo[3‴,2‴:4′,5′]pyrrolo-[1″,2″:4′,5′]pyrazino[2′,1′:5,1]pyrrolo[2,3-b]indole-7,15(5H,7aH)-dione (20).** After chromatography, the residue was triturated with hexane to afford 75 mg (15%) of pure **20** as a white solid, R_f = 0.36 (15% EtOAc/Hex, plate eluted twice): [α]$^{25}_D$ 246.5° (*c* = 0.2, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.17 (d, *J* = 7.4, 1 H), 6.96 (t, *J* = 6.7 Hz, 1 H), 6.71 (t, *J* = 7.3 Hz, 1 H), 6.31 (dd, *J* = 10.8, 17.6 Hz, 1 H), 6.05 (d, *J* = 7.8 Hz, 1 H), 5.90 (br s, 1 H), 5.09 (dd, *J* = 10.9, 17.7 Hz, 1 H), 4.22 (d, *J* = 10.4 Hz, 1 H), 3.42 (d, *J* = 13.7 Hz, 1 H), 2.55 (dd, *J* = 10.5, 13.6 Hz, 1 H), 1.85 (s, 1 H), 1.28 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 161.4, 142.5, 139.5, 126.2, 124.4, 119.3, 114.6, 108.2, 106.2, 89.0, 83.5, 54.5, 40.3, 29.7, 21.2, 18.1; IR (CHCl$_3$) 3372, 1663, 1611, 1469, 1375, 1320, 1091, 913 cm^{-1}; MS (DCI, NH$_3$) *m/v* 541 (M$^+$ + H), 471, 401, 331, 313, 261; HRMS calculated for C$_{32}$H$_{37}$N$_4$O$_4$ 541.2815, found 541.2803.

The second compound to elute was **(5aR,7aS,8aR,13aS,15aS,16aS)-5a,13a-bis(1,1-dimethyl-2-propenyl)-8a,16a-dihydroxy-5a,8,8a,13,- 13a,15a,16,16a-octahydroindolo[3‴,2‴:4′,5′]pyrrolo[1″,2″:4′,5′]-pyrazino[2′,1′:5,1]pyrrolo[2,3-b]indole-7,15(5H,7aH)-dione (Gypsetin, 1).** After chromatography, the residue was triturated with hexane to afford 163 mg (32%) of pure gypsetin as a white solid, R_f = 0.27 (15% EtOAc/Hex, plate eluted twice): [α]$^{25}_D$ −113.4° (*c* = 0.2, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.28 (d, *J* = 7.3 Hz, 1 H), 7.21 (d, *J* = 7.5 Hz, 1 H), 7.13 (app. q, *J* = 7.4 Hz, 2 H), 6.79 (m, 2 H), 6.73 (d, *J* = 7.9 Hz, 1 H), 6.64 (d, *J* = 7.9 Hz, 1 H), 6.4 (br s, 1 H), 6.35 (dd, *J* = 10.8, 17.6 Hz, 1 H), 5.95 (dd, *J* = 10.8, 17.6 Hz, 1 H), 5.12 (dd, *J* = 10.8, 17.7 Hz, 2 H), 4.92 (m, 2 H), 4.04 (d, *J* = 10.9 Hz, 1 H), 3.59 (dd, *J* = 7.4, 11.0 Hz, 1 H), 3.35 (d, *J* = 13.7 Hz, 1 H), 2.71 (m, 2 H), 2.51 (dd, *J* = 7.4, 13.1 Hz, 1 H), 2.25 (br s, 1 H), 2.06 (br s, 1 H), 1.33 (s, 3 H), 1.31 (s, 3 H), 0.67 (s, 3 H), 0.60 (s, 3 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 170.5 (−), 168.1 (−), 148.6 (−), 148.4 (−), 144.2 (+), 144.1 (+), 130.8 (+), 130.7 (+), 130.2 (−), 130.1 (−), 124.6 (+), 123.6 (+), 120.5 (+), 120.0 (+), 113.4 (−), 112.9 (−), 111.3 (+), 111.2 (+), 93.72 (−), 90.9 (−), 88.8 (−), 87.8 (−), 61.2 (+), 59.2 (+), 44.7 (−), 44.0 (−), 35.8 (−), 35.1 (−), 27.2 (+), 25.9 (+), 23.1 (+), 22.0 (+); IR (CHCl$_3$) 3365, 1672, 1609, 1468, 1366, 1109, 1090, 894 cm^{-1}; MS (DCI, NH$_3$) *m/v* 541 (M + H)$^+$, 471, 388, 279; HRMS calculated for C$_{32}$H$_{37}$N$_4$O$_4$ 541.2815, found 541.2818.

The third compound to elute was the *trans,trans* isomer, **(5aS,7aS,-8aR,13aS,15aS,16aR)-5a,13a-bis(1,1-dimethyl-2-propenyl)-8a,16a-dihydroxy-5a,8,8a,13,13a,15a,16,16a-octahydroindolo[3‴,2‴:4′,5′]-pyrrolo-[1″,2″:4′,5′]pyrazino[2′,1′:5,1]pyrrolo[2,3-b]indole-7,15(5H,7aH)-dione (21).** After chromatography, the residue was triturated with hexane to afford 83 mg (16%) of pure *trans,trans* isomer **21** as a white solid, R_f = 0.20 (15% EtOAc/Hex, plate eluted twice): [α]$^{25}_D$ −400° (*c* = 0.2, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.23 (d, *J* = 7.4 Hz, 1 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 6.76 (t, *J* = 7.5 Hz, 1 H), 6.62 (d, *J* = 7.8 Hz, 1 H), 6.36 (dd, *J* = 10.8, 7.6 Hz, 1 H), 6.16 (s, 1 H), 5.16 (d, *J* = 17.7 Hz, 1 H), 5.09 (d, *J* = 10.9 Hz, 1 H), 3.43 (dd, *J* = 7.5, 11.2 Hz, 1 H), 2.76 (dd, *J* = 11.5, 12.9 Hz, 1 H), 2.62 (dd, *J* = 7.6, 13.1 Hz, 1 H), 2.25 (s, 1 H), 1.36 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 171.4, 166.0, 148.7, 144.2, 130.9, 129.8, 123.7, 120.1, 113.3, 90.0, 89.0, 61.3, 45.1, 35.5, 27.1, 23.0; IR (CHCl$_3$) 3375, 1679, 1608, 1469, 1361, 1318, 1109, 1082, 911 cm^{-1}; MS (DCI, NH$_3$) *m/v* 541 (M + H)$^+$, 471, 401, 340, 270; HRMS calculated for C$_{32}$H$_{37}$N$_4$O$_4$ 541.2815, found 541.2803.

Methyl N-Phthaloyl-2-(3-methyl-2-butenyl)-L-tryptophan (45). To a 0 °C solution of **11** (101 mg, 0.290 mmol) and Et$_3$N (0.040 mL, 0.290 mmol) in CH$_2$Cl$_2$ (2.9 mL) was added *tert*-butylhypochlorite (0.696 mL, 0.5 M in CCl$_4$) via syringe pump over a 20 min period. The solution was then chilled to −78 °C. Tri(*n*-butyl)prenylstannane (0.423 mL, 1.16 mmol) was added, followed by rapid addition of BCl$_3$ (0.580 mL, 1.0 M in CH$_2$Cl$_2$). After 3 min, the solution was poured into saturated NaHCO$_3$ to quench and extracted with CH$_2$Cl$_2$. The organic layer was washed successively with saturated NaHCO$_3$ and saturated KF. Both layers were filtered through Celite with CH$_2$Cl$_2$. The organic layer was separated and washed again with saturated KF, dried (Na$_2$SO$_4$), filtered, concentrated, and chromatographed (silica gel, 95/5 to 60/40 Hex/EtOAc) to give a yellow-green amorphous solid weighing 100.1 mg (83%): R_f = 0.64 (60/40 Hex/EtOAc); [α]$_D$ −253° (*c* = 4.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73 (m, 2 H), 7.71 (br d, *J* = 1.2 Hz, 1 H), 7.64 (m, 2 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.17 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.01 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1 H), 6.95 (ddd, *J* = 7.6, 7.2, 1.2 Hz, 1 H), 5.20 (dd, *J* = 10.2, 5.4 Hz, 1 H), 5.12 (tquin, *J* = 7.2, 1.4 Hz, 1 H), 3.79 (s, 3 H), 3.69 (dd, *J* = 14.8, 5.4 Hz, 1 H), 3.63 (dd, *J* = 14.8, 10.4 Hz, 1 H), 3.40 (ddd, *v* = 52 Hz, *J* = 16.4, 7.2 Hz, 2 H), 1.67 (s, 6 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.6, 167.4, 135.7, 135.0, 134.7, 133.8, 131.7, 128.4, 123.2, 121.0, 120.1, 119.2, 117.7, 110.3, 105.8, 52.7, 52.4, 25.6, 24.9, 24.0, 17.7; FTIR (film) 3398, 3058, 3028, 2954, 2916, 2852, 1774, 1743, 1714, 1615, 1462, 1438, 1390, 1255, 1206, 1116, 1100, 1028, 920, 868, 746, 719, 666, 608, 581, 530; HRMS (FAB) calculated for C$_{25}$H$_{24}$N$_2$O$_4$ M$^+$ 416.1736, found 416.1730.

Ethyl 2-(3-Methyl-2-butenyl)-3-indoleacetate (50). To a −78 °C solution of ethyl 3-indoleacetate (**48**, 149 mg, 0.733 mmol) and Et$_3$N (0.102 mL, 0.733 mmol) in CH$_2$Cl$_2$ (7.3 mL) under argon was added via syringe pump over a 20 min period a *tert*-butyl hypochlorite solution (1.8 mL, 0.5 M in CCl$_4$). Tri(*n*-butyl)prenylstannane (1.07 mL, 2.93

mmol) was then added, followed by rapid addition of BCl_3 solution (1.45 mL, 1.0 M in CH_2Cl_2), which produced a deep orange solution color. After 3 min, the reaction was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ and then with saturated KF, filtered over Celite and then washed again with saturated KF, dried (Na_2SO_4), filtered, concentrated, and chromatographed on silica gel (90/10 to 70/30 Hex/EtOAc) to recover a clear oil (130 mg, 65%), which turns a bright yellow color upon exposure to air. The product was stored neat at −20 °C under argon to prevent further air oxidation, R_f = 0.67 (70/30 Hex/EtOAc): ^{1}H NMR (400 MHz, C_6D_6) δ 7.79 (dd, J = 7.0, 1.6 Hz, 1 H), 7.24−7.18 (m, 2 H, H5), 7.01−6.99 (m, 2 H, NH), 5.18 (dquin, J = 7.1 1.3 Hz, 1 H), 3.88 (q, J = 7.2 Hz, 2 H), 3.64 (s, 3 H), 3.29 (d, 2 H), 1.61 (br d, J = 1.2 Hz, 3 H), 1.52 (s, 3 H), 0.87 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6); δ 171.5, 135.6, 135.5, 133.6, 129.4, 121.5, 121.1, 119.9, 118.9, 110.8, 104.7, 60.4, 30.7, 25.6, 25.5, 17.7, 14.2; FTIR (C_6D_6) 3434, 3059, 2980, 2930, 1916, 1879, 1733, 1587, 1568, 1461, 1443, 1368, 1342, 1300, 1263, 1239, 1158, 1098, 1036, 1014, 910, 741; HRMS (FAB) calculated for $C_{17}H_{21}NO_2$ M$^+$ 271.1572, found 271.1564.

2-(3-Methyl-2-butenyl)-*O-tert*-butyldiphenylsilyltryptophol (51). To a −48 °C solution of tryptophol TBDPS ether (**49**, 204 mg, 0.512 mmol) and Et_3N (0.071 mL, 0.512 mmol) in CH_2Cl_2 (5.0 mL) under argon was added over a 20 min period via syringe pump a *tert*-butyl hypochlorite solution (1.23 mL, 0.5 M in CCl_4). The solution was chilled to −78 °C, and tri(*n*-butyl)prenylstannane (0.784 mL, 2.05 mmol) was then added, followed by rapid addition of BCl_3 solution (1.00 mL, 1.0 M in CH_2Cl_2). After 3 min, the reaction was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2 (two times). The organic layers were combined and washed with saturated $NaHCO_3$ and then with saturated KF. The emulsion thus formed was filtered over Celite, rinsed with CH_2Cl_2, washed again with saturated KF, dried (Na_2SO_4), filtered, concentrated, and chromatographed on silica gel (100/0 to 80/20 Hex/EtOAc) to recover a clear viscous oil (195 mg, 81%) which turns bright yellow on exposure to air or upon standing for extended periods of time (1−2 h) in halogenated solvents, R_f = 0.62 (80/20 Hex/EtOAc): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 5 H), 7.54 (m, 2 H), 7.47 (m, 4 H), 7.39 (d, J = 7.7 Hz, 1 H), 7.34 (d, J = 8.0 Hz, 1 H), 7.21 (dt, J = 6.9, 1.1 Hz, 1 H), 7.12 (dt, J = 6.9, 6.9, 1.0 Hz, 1 H), 5.36 (b t, J = 7.3 Ha, 1 H), 4.00 (t, J = 7.8, 7.6 Hz, 1 H), 3.48 (d, J = 7.3 Hz, 1 H), 3.15 (t, J = 7.8, 7.6 Hz), 1.89 (s, 3 H), 1.85 (s, 3 H), 1.22 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 135.0, 134.9, 134.2, 134.0, 129.5, 128.9, 127.6, 120.8, 120.5, 119.0, 118.2, 110.2, 107.4, 64.4, 27.7, 26.9, 25.7, 25.0, 19.1, 17.8; FTIR (film) 3411, 3070, 3051, 2930, 2857, 2737, 1960, 1888, 1827, 1667, 1621, 1589, 1568, 1487, 1462, 1428, 1384, 1361, 1338, 1307, 1285, 1244, 1210, 1189, 1111, 1065, 1030, 1010, 940, 823, 739, 702, 614, 505; HRMS (FAB) calculated for $C_{31}H_{37}NOSi$ M$^+$ 467.2644, found 467.2642.

1-(3-Methyl-2-butenyl)cyclohexan-1-ol (55). To a −78 °C solution of cyclohexanone (215 mg, 2.19 mmol) and tri(*n*-butyl)prenylstannane (1.6 mL, 8.8 mmol) in CH_2Cl_2 (14.6 mL) was added rapidly BCl_3 solution (2.4 mL, 1.0 M in CH_2Cl_2). After 5 min, the reaction was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2 (two times). The combined organic layers were washed with saturated KF (two times), dried (Na_2SO_4), filtered, concentrated, and chromatographed (95/5 to 80/20 Hex/EtOAc) to recover a clear oil (287 mg, 78%), R_f = 0.39 (90/10 Hex/EtOAc): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 (tquin, J = 8.1, 1.5 Hz, 1 H), 2.13 (d, J = 8.1 Hz, 1 H), 1.73 (d, J = 1.1 Hz, 3 H), 1.62 (s, 3 H), 1.60−1.35 (m, 10 H), 1.28−1.18 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 118.9, 71.8, 40.8, 37.3, 26.05, 25.8, 22.2, 17.9; FTIR (film) 3385, 2933, 2858, 2727, 2666, 1672, 1448, 1376, 1356, 1318, 1297, 1264, 1169, 1148, 1115, 1067, 1036, 972, 914, 888, 845, 779, 726; HRMS (FAB) calculated for $C_{11}H_{20}O$ M$^+$ 168.1514, found 168.1519.

1-(3-Methyl-2-butenyl)-4,4-dimethylcyclohexan-1-ol (56). To a −78 °C solution of 4,4-dimethylcyclohexanone (201 mg, 1.58 mmol) and tri(*n*-butyl)prenylstannane (1.16 mL, 6.34 mmol) in CH_2Cl_2 (16 mL) was added rapidly BCl_3 solution (1.7 mL, 1.0 M in CH_2Cl_2). After 5 min, the reaction was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2 (two times). The combined organic layers were washed with saturated KF (two times), dried (Na_2SO_4), filtered, concentrated

and chromatographed (95/5 to 80/20 Hex/EtOAc) to recover a clear oil (276.2 mg, 88%), R_f = 0.40 (90/10 Hex/EtOAc): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (tquin, J = 8.1, 1.5 Hz, 1 H), 2.15 (d, J = 7.8 Hz, 1 H), 1.75 (s, 3 H), 1.65 (s, 3 H), 1.53−1.44 (m, 4 H), 1.20−1.18 (m, 4 H), 0.93 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0, 119.0, 71.4, 40.7, 34.8, 33.2, 30.8, 29.5, 26.0, 25.3, 17.9; FTIR ($CHCl_3$) 3694, 3604, 3010, 2932, 2855, 1668, 1602, 1453, 1378, 1365, 1260, 1235, 1174, 1118, 1103, 1065, 1048, 990, 967, 879, 849; HRMS (FAB) calculated for $C_{13}H_{24}O$ M$^+$ 196.1827, found 196.1820.

(±)-*trans*-1-(3-Methyl-2-butenyl)-2-phenylcyclohexan-1-ol (57). To a −78 °C solution of 2-phenylcyclohexanone (100 mg, 0.574 mmol) and tri(*n*-butyl)prenylstannane (0.419 mL, 2.30 mmol) in CH_2Cl_2 (5.7 mL) was added rapidly BCl_3 solution (0.631 mL, 1.0 M in CH_2Cl_2). After 5 min, the reaction was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2 (two times). The combined organic layers were washed with saturated KF (two times), dried (Na_2SO_4), filtered, concentrated, and chromatographed (95/5 to 80/20 hexane/EtOAc) to recover a clear oil (112.6 mg, 80%), R_f = 0.46 (90/10 Hex/EtOAc): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.23 (m, 4 H), 7.20−7.15 (m, 1 H), 5.07 (tquin, J = 7.7, 1.5 Hz), 2.52 (dd, J = 12.9, 3.5 Hz, 1 H), 2.03 (dq, J = 13.1, 3.6 Hz, 1 H), 1.92−1.81 (AB-dd, J = 18.8, 7.6 Hz, 2 H), 1.79−1.74 (m, 1 H), 1.73−1.67 (m, 2 H, H5), 1.65 (br d, J = 1.1 Hz, 3 H), 1.60−1.55 (m, 2 H, H3e), 1.40 (s, 3 H, H4), 1.40 (m, 1 H), 1.31 (qt, J = 13.2, 3.7 Hz, 1 H); NOE (H2′) H2, H4a, 4't-CH_3, H6a; NOE (H2) H2′, H3e, H6a; ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 134.9, 129.1, 128.0, 126.3, 119.1, 73.3, 51.9, 40.3, 37.0, 29.2, 26.5, 26.1, 21.6, 17.9; FTIR (film) 3563, 3488, 3084, 3060, 3025, 2931, 2856, 2727, 2669, 1946, 1879, 1808, 1729, 1602, 1492, 1446, 1376, 1271, 1234, 1184, 1131, 1088, 1070, 1032, 979, 958, 894, 860, 830, 765, 702, 516; HRMS (FAB) calculated for $C_{17}H_{24}O$ M$^+$ 244.1829, found 244.1827.

Methyl 2-(3-Methyl-2-butenyl)-L-tryptophan (59). To a solution of **45** (437 mg, 1.05 mmol) in 3:1 MeOH/CH_2Cl_2 (7.9:2.6 mL) was added hydrazine hydrate 0.178 mL, 3.67 mmol). The flask was capped and the solution stirred at ambient temperature for 24 h, during which time a white precipitate formed. The solution was poured into water (50 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated, and chromatographed (silica gel treated with $(TMS)_2NH$, 90/10 to 20/80 Hex/EtOAc) to yield **59** as an opaque syrup weighing 248 mg (83%), R_f = 0.37 (95/5 $CHCl_3$/MeOH): [α]$_D$ +9.5° (c = 1.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br s, 1 H), 7.54 (d, J = 7.2 Hz, 1 H), 7.27 (d, J = 7.8 Hz, 1 H), 7.10 (m, 2 H), 5.30 (tquin, J = 7.6, 1.4 Hz, 1 H), 3.82 (dd, J = 8.2, 5.0 Hz, 1 H), 3.71 (s, 3 H), 3.49 (d, J = 7.2 Hz, 2 H,), 3.25 (dd, J = 14.4, 5.0 Hz, 1 H), 2.98 (dd, J = 14.4, 8.2 Hz, 1 H), 1.79 (s, 3 H), 1.76 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 135.9, 135.2, 134.7, 128.7, 121.1, 120.2, 119.3, 119.1, 110.4, 106.2, 55.3, 51.9, 30.0, 25.7, 26.1, 17.9; FTIR (film) 3387, 3180, 3055, 2950, 2925, 2854, 1736, 1578, 1461, 1438, 1376, 1343, 1308, 1285, 1202, 1175, 1098, 1034, 1010, 916, 845, 742; HRMS (FAB) calculated for $C_{17}H_{22}N_2O_2$ 286.1681, found 286.1688.

Methyl *N-tert*-Butoxycarbonyl-L-proline-L-2′-(3-methyl-2-butenyl)tryptophan (61). To a −30 °C solution of *N*-Boc-L-proline (279 mg, 1.30 mmol) and pyridine (0.104 mL, 1.30 mmol) in CH_2Cl_2 (13 mL) was added cyanuric fluoride (0.350 mL, 3.89 mmol). The solution was stirred for 1 h between −30 and −5 °C and then poured onto ice. The emulsion was extracted quickly with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to afford crude **60**. The concentrate was redissolved in CH_2Cl_2 (2 × 5 mL) and transferred to a vigorously stirring biphasic solution of **59** (248 mg, 0.864 mmol) in CH_2Cl_2 (10 mL) containing $NaHCO_3$ (145 mg, 1.73 mmol) in water (10 mL). The reaction was stirred for 10 h before the layers were separated. The aqueous layer was washed with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and chromatographed (silica gel, 85/15 to 30/70 Hex/EtOAc) to give 391 mg (94%) of **61** as a white amorphous solid, R_f = 0.19 (60/40 Hex/EtOAc): [α]$^{30}_D$ −38.3° (c = 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.80 (br s, 1 H), 7.47 (d, J = 7.4 Hz, 1 H), 7.24 (m, 1 H), 7.09 (m, 2 H), 5.31 (tt, 1 H), 4.82 (dd, 1 H), 4.18 (br s, 1 H), 3.64 (s, 3 H), 3.46 (d, 1 H), 3.30 (m, 1 H), 3.21 (ddd, ν = 32 Hz, J = 14.7, 6.8 Hz, 2 H), 3.12 (br s, 1 H),

1.94 (br s, 1H), 1.80 (s, 3 H), 1.77 (s, 3 H), 1.66 (bm, 1 H), 1.48 (m, 1 H), 1.41 (s, 9 H), 1.27 (m, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$, 50 °C) δ 172.3, 172.2, 154.9, 135.9, 135.2, 134.8, 129.2, 121.2, 120.1, 119.6, 117.7, 110.4, 105.3, 80.3, 60.7, 53.0, 52.0, 46.9, 28.2, 27.2, 25.6, 25.1, 23.7, 17.8; FTIR (film) 3393, 3314, 2975, 2928, 2880, 1743, 1676, 1512, 1458, 1439, 1391, 1366, 1247, 1215, 1163, 1124, 744; HRMS (FAB) calculated for C$_{27}$H$_{37}$N$_3$O$_5$ M$^+$ 483.2733, found 483.2730.

Tryprostatin B (41). To a 0 °C solution of **61** (50.0 mg, 0.103 mmol) in freshly distilled MeCN (2.0 mL) under argon was added TMSI (0.018 mL, 0.126 mmol). After 45 min, the reaction was quenched with a few drops of methanol. The solvent was removed, and the orange-brown concentrate (crude **62**) was redissolved in ammonia-saturated methanol. The light yellow solution was stirred for 20 h, concentrated, and chromatographed on (TMS)$_2$NH-treated silica gel (90/ 10 to 0/100 Hex/EtOAc) to obtain 24.1 mg (67%) of tryprostatin B (**41**) as a white amorphous solid: [α]$^{27.5}_D$ −74.6° (c = 0.64, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94 (s, 1 H), 7.48 (d, J = 7.7 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.16 (ddd, J = 8.1, 7.1, 1.0 Hz, 1 H), 7.10 (ddd, J = 7.9, 7.1, 0.9 Hz, 1 H), 5.61 (br s, 1 H), 5.32 (m, 1 H), 4.37 (dd, J = 11.0, 2.6 Hz, 1 H), 4.06 (t, J = 8.0 Hz, 1 H), 3.69 (m, 1 H), 3.67 (m, 1 H), 3.59 (ddd, J = 9.3, 8.7, 3.3 Hz, 1 H), 3.49 (m, 2 H), 2.96 (dd, J = 15.1, 11.4 Hz, 1 H), 2.34 (m, 1 H), 2.03 (m, 2 H), 1.91 (m, 1 H), 1.79 (s, 3 H), 1.75 (s, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.3, 165.8, 136.4, 135.4, 135.4, 127.9, 121.8, 119.9, 119.7, 117.7, 110.8, 104.6, 59.2, 54.5, 45.4, 45.4, 28.3, 25.7, 25.6, 25.1, 22.6, 18.0; FTIR (film) 3295, 2959, 2925, 2854, 1666, 1461, 1429, 1305, 1216, 1114, 1099, 1012, 919, 753, 666; HRMS (FAB) calculated for C$_{21}$H$_{26}$N$_3$O$_2$ (M + H)$^+$ 352.2025, found 352.2021.

Supporting Information Available: Experimental details relative to the syntheses of deoxybrevianamide E and brevianamide E (**24**−**26**), as well as experimental details relative to the syntheses and characterizations of 2,3-disubstituted indoles, listed in Table 1 (**31**−**39**) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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