diisopropylamine has been shown to influence reaction product distributions,[10h,i] to the best of our knowledge, this is the first systematic study proving that HMDS is free in solution *prior to* and *after* completion of an aldol reaction. Previously, it had been *assumed* that the steric bulk of HMDS prevented it from interacting with the enolate.

The influence of counterion effects was probed by the reaction of sodium, potassium, and cryptated-potassium pincolonates with pivalaldehyde. The non-lithium aldolate products were found to undergo elimination after several seconds, making the analogous structural and calorimetric investigations impossible, and emphasizing yet again the important role of lithium in these reactions.

Conclusions

In order to study even the simplest aldol reaction in nonpolar media systematically, it is necessary to apply a methodology that employs a variety of methods to elucidate the structures of the reactants and products, thermochemical measurements, and, ultimately, kinetic studies. Excluding kinetics, we have successfully applied this methodology to yield the first concrete structure–energy analysis of the reactants and products for an aldol reaction. It was found that the enthalpy of reaction for the hexameric enolate was approximately 5–6 kcal/mol more exothermic than for the tetrameric enolate complexed with THF. The reaction of the hexameric enolate was also ~2 kcal/mol more exothermic than were the dimeric enolates (complexed with TMEDA and DME).

Enolates complexed with DME and TMEDA were seen to have nearly identical ΔH_{rxn}s. However, TMEDA was found to complex lithiopinacolonate to a slightly greater degree than DME in cyclohexane by VPO and ^{6}Li NMR. THF was more efficient than either TMEDA or DME in this respect, since no equilibrium effects were observed. It is hoped that these studies will be the first in a series which will ultimately lead to a thoroughly documented mechanism for the modern aldol reaction under synthetic conditions.

Acknowledgment. This work was supported by NSF Grant CHE-8709249 to E.M.A. and by funding from NSF, NIH, the North Carolina Biotechnology Center, and Duke University to the Duke NMR Center, for which we are most appreciative.

Supplementary Material Available: Spectra and experimental conditions including proton assignments made from 1D ^{1}H decoupling, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HETCOR, and ^{1}H–^{6}Li HOESY experiments and descriptions of the error analyses used in the various techniques (9 pages). Ordering information is given on any current masthead page.

Asymmetric, Stereocontrolled Total Synthesis of (−)-Brevianamide B†

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Abstract: The asymmetric, stereocontrolled total synthesis of (−)-brevianamide B (**2**) is described. The synthesis features a stereocontrolled intramolecular S_N2' cyclization to construct the central bicyclo[2.2.2] nucleus. A synthetic route to C-10-epibrevianamide A (**49**) is also described. A synthetic sample of a shunt metabolite (**9**) proposed by Birch in 1972 has been prepared and its oxidation chemistry in the context of the proposed biosynthetic schemes is discussed.

In 1969, the yellow culture extract of *Penicillium brevicompactum* was observed by Birch and Wright[1] to produce in very low yield several neutral, toxic metabolites that were named brevianamides A–E. Based primarily on spectroscopic evidence, chemical degradation, and biogenetic considerations, the structure **1** was proposed[1b] and later shown in 1974[2] to be correct by single-crystal X-ray analysis of a bromination product, 5-bromobrevianamide A. The X-ray structure also established the relative and absolute configuration of **1**. Brevianamide A was subsequently isolated from *Penicillium viridicatum*[3] and *Penicillium ochraceum*.[4] Birch and Russell[1c] also isolated brevianamides C (**3**) and D (**4**) from the same culture filtrates, but these are thought to be artifacts since white light irradiation of **1** in MeOH efficiently produces **3** and **4**. It was also shown that brevianamide F [**6**, *cyclo*(L-tryptophyl-L-proline)] is biosynthetically incorporated into brevianamide A. From these observations, Birch postulated a biosynthetic pathway involving prenylation of **6** to the dioxopiperazine **7** (deoxybrevianamide E)[6]. However, deoxybrevianamide E (**7**) has not been detected in culture filtrates that produce **1** and **2** and thus must still be considered a hypothetical shunt metabolite. Formation of the bicyclo[2.2.2]dioxopiperazine nucleus is then thought to arise via oxidation of the tryptophanyl moiety **8** and a unique intramolecular [4 + 2] cycloaddition reaction[7] to furnish the hexacyclic indole **9**; oxidative spiro re-

† Dedicated to the late Professor John K. Stille.

‡ Fellow of the Alfred P. Sloan Foundation 1986–1990. NIH Research Career Development Awardee 1984–1989. Eli Lilly Grantee 1986–1988.

(1) (a) Birch, A. J.; Wright, J. J. *J. Chem. Soc., Chem. Commun.* **1969**, 644. (b) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329. (c) Birch, A. J.; Russell, R. A. *Ibid.* **1972**, *28*, 2999.

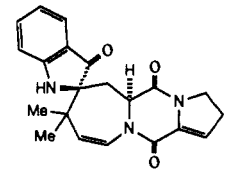
(2) Coetzer, J. *Acta Crystallogr.* **1974**, *B30*, 2254. The absolute configuration of natural brevianamide A is *opposite* to that depicted throughout this manuscript.

(3) Wilson, B. J.; Yang, D. T. C.; Harris, T. M. *Appl. Microbiol.* **1973**, 633.

(4) Robbers, J. E.; Straus, J. W. *Lloydia* **1975**, *38*, 355.

(5) Baldas, J.; Birch, A. J.; Russell, R. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 50.

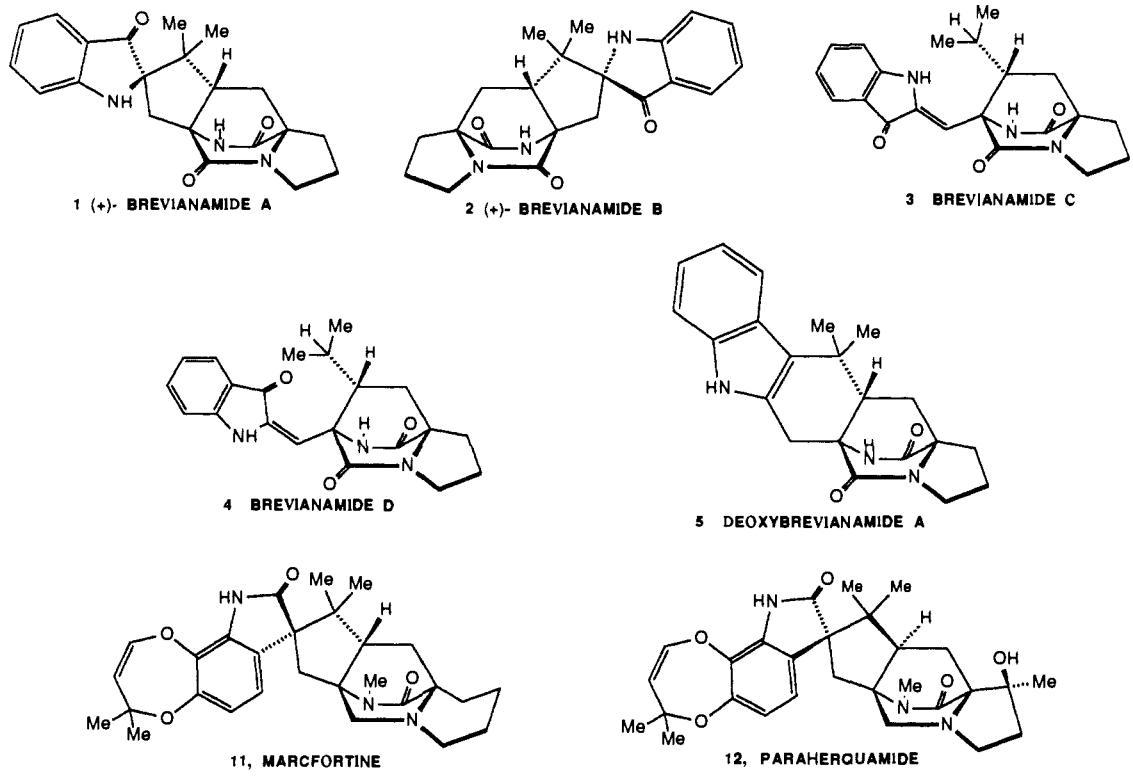
(6) Compound **8** has subsequently been isolated from *Aspergillus ustus* and serves as the biosynthetic precursor to a product of alternative ring closure, austamide i: Steyn, P. S. *Tetrahedron Lett.* **1971**, 3331.



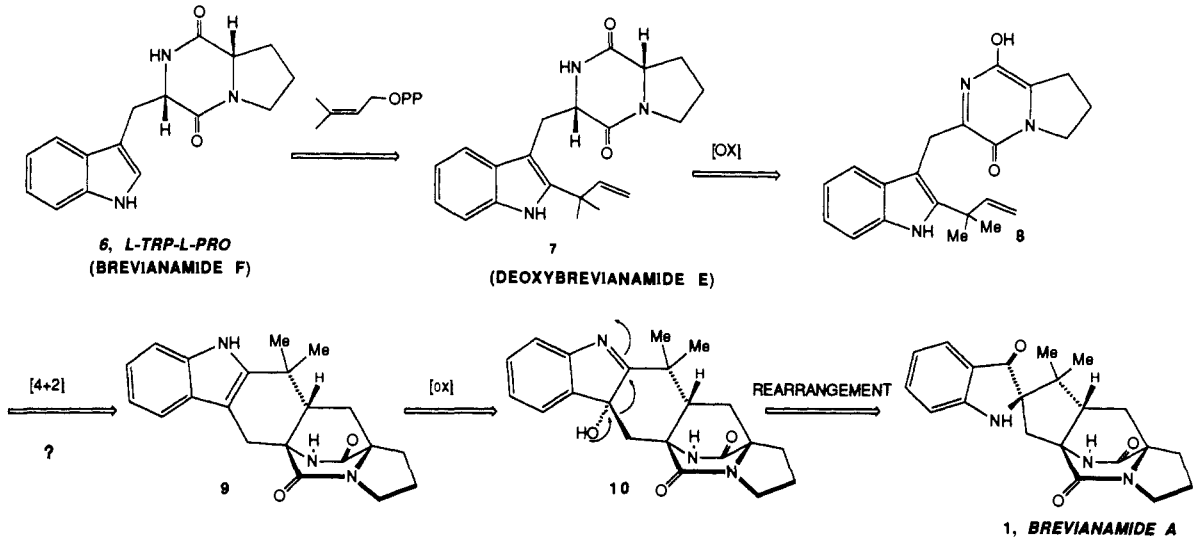
I, AUSTAMIDE

0002-7863/90/1512-808$02.50/0

Chart I



Scheme I



arrangement of **9** is well-precedented[8] to afford the spiro indoxyl system, via the 3-hydroxyindolenine **10** (Scheme I).

The brevianamides are members of a curious, yet growing, small class of mycotoxins that has recently been joined by marcfortine[9] (**11**) and paraherquamide[10] (**12**), which has now been shown to possess potent antiparasitic properties.[10] It is significant to note that, in spite of the structural differences between **1**/**2** and **11**/**12**, such as the presence of a diketopiperazine in **1**/**2** and a monoketopiperazine in **11**/**12** and the spiro indoxyl in **1**/**2** and the oxygenated dioxepin spiro oxindole in **11**/**12**, the structural similarities bespeak a unified biogenesis for all of these compounds. If one accepts the biogenetic proposal of Birch[1] (Scheme I), it is also reasonable that **11** and **12** could arise via a related pathway resulting from intramolecular Diels–Alder cyclization of the generic indole **13** (Scheme II). Subsequent reduction to the monoketopiperazine, oxidation at the 2-position of the indole **14** and ring-contractive rearrangement would furnish the spiro oxindoles. It is further significant to note that marcfortine has the same *relative* stereochemistry as brevianamide B with respect to both the indole oxidation and the stereogenic center set in the proposed Diels–Alder cyclization. Paraherquamide, on the other hand, has the *opposite relative stereochemistry* at the key stereogenic center set in the hypothetical [4 + 2] cycloaddition. The facial selectivity of the indole oxidation for **2**, **11**, and **12** seems

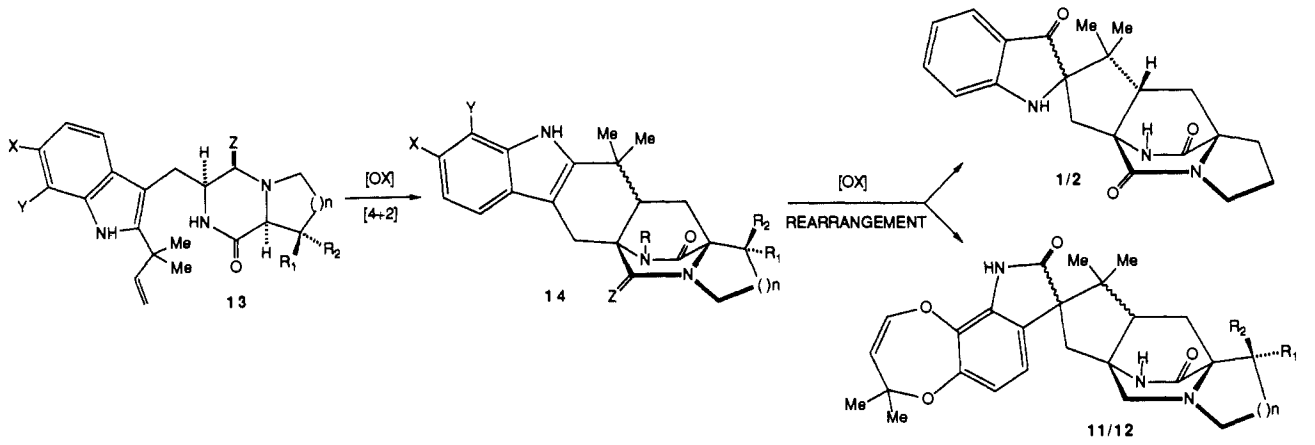
(7) Experimental support for this hypothesis has been realized in a model reaction: (a) Porter, A. E. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1970**, 1103. See also: (b) Fabre, J. L.; Farge, D.; James, C.; Lave, D. *Tetrahedron Lett.* **1985**, *26*, 5447. For an approach to the Diels–Alder precursor, see: (c) Dunkerton, L. V.; Chen, H.; McKillican, B. P. *Tetrahedron Lett.* **1988**, *29*, 2539.

(8) For an elegant example of this transformation, see: (a) Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786. (b) Hutchison, A. J.; Kishi, Y. *Tetrahedron Lett.* **1978**, 539. (c) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 2188.

(9) Polonsky, J.; Merrien, M.-A.; Prange, T.; Pascard, C. *J. Chem. Soc., Chem. Commun.* **1980**, 601.

(10) (a) Yamazaki, M.; Okuyama, E. *Tetrahedron Lett.* **1981**, *22*, 135. (b) Blizzard, T. A.; Marino, G.; Mrozik, H.; Fisher, M. H.; Hoogsteen, K.; Springer, J. P. *J. Org. Chem.* **1989**, *54*, 2657. (c) European patent 301742A, Merck and Co., July 28, 1987.

Scheme II



to be from the less hindered face of the indole (**9** or **14**); brevianamide A, on the other hand, is produced by oxidation from the more hindered face of the indole **9** (to **10**). This is quite interesting, since brevianamide A is produced as the most abundant metabolite, and raises numerous interesting questions with regard to the validity of **9** as a biosynthetic precursor and, if so, whether the oxidation of this hypothetical species to **1** and **2** is an enzyme-catalyzed process, an autoxidation, or a combination of enzymatic oxidation (presumably for **1**) and autoxidation (presumably for **2**) of indole **9**. In fact, brevianamide B is produced in such small quantities from the microorganism that sufficient spectroscopic, analytical, and structural data could not be readily collected to secure the proposed structure **2**. The complete structure of brevianamide B (**2**) has recently been rigorously confirmed in a relative and absolute sense by total synthesis.[11a] The results of chiroptical studies[11b] have demonstrated that brevianamides A and B obtained directly from cultures of *P. brevicompactum* are diastereomers that are enantiomorphic with respect to the bicyclo[2.2.2]piperazinedione nucleus. The absolute configuration of each natural product is that depicted in Chart I.

Indeed, in the original structural elucidation work on **1**; Birch[1] demonstrated that sodium borohydride reduction and acid dehydration of brevianamide A yielded a single indole assigned the structure **5** (Chart I, deoxybrevianamide A); this compound is isomeric to the proposed biogenetic intermediate **9**. Further treatment of **5** with O_2 on Pt or air autoxidation in MeOH stereoselectively furnished brevianamide B (**2**). This redox process of obtaining **2** from **1** is more efficient in terms of producing quantities of **2** than repeated fermentation and direct isolation of **2**. The complete facial selectivity of the oxidation of **5** for the production of **2** to the complete exclusion of **1** supports the contention stated above concerning steric effects from **9** or **14** governing the relative stereochemistry of the oxidized indole moiety. These observations also played a significant role in our synthetic planning (vide infra).

In this article, we disclose the results of our studies on the total synthesis of brevianamide B.[11] Our objectives were to design a general, flexible strategy that could embrace both brevianamides A and B as well as provide a framework from which to tackle the more complex alkaloids marcfortine (**11**) and paraherquamide (**12**). These aspirations mandate the following: (1) a means to control the relative stereochemistry of the bicyclo[2.2.2]-piperazinedione nucleus, (2) a method to control both the regio- and stereochemistry of the indole oxidation, and (3) a protocol for addressing the absolute stereochemistry in the context of the above criteria. Our approach to the brevianamides was designed to converge on the hypothetical biogenetic intermediate **9** and was attempted via two, related routes as outlined in Scheme III. We decided to explore a nonbiogenetically (i.e., Birch; cf. Scheme I) patterned construction of the bicyclo[2.2.2] nucleus that would employ an intramolecular S_N2' cyclization. These two approaches only differ in the timing of the introduction of the indole moiety to reach the key derivative **18**. It was reasoned that such a structure upon protonation with mineral acid would form the incipient carbocation **19** and cyclize in a precedented fashion[9] at the indole 2-position to furnish **20**. Indole **20** is expected to display facial selectivity upon oxidation with *m*-CPBA to furnish the 3-hydroxyindolenine **21**; subsequent rearrangement of diastereomer **21** to the spiro indoxyl and deprotection of the amide would provide brevianamide B.

Results

We previously reported[13] on a successful synthesis of the tricycle **17** in racemic form beginning with (±)-homoserine. This route, along with a more efficient enantioselective synthesis from L-proline is described herein. The experimental details for the preparation of racemic **32** (and thus, **17**) previously communicated are available as supplemental material. The route previously described,[13] effected the intramolecular S_N2' cyclization of **15** (R = *p*-methoxybenzyl; X = Cl) to **17** and the epimer **23** in a 10:1 ratio (60%) by reaction of **15** with NaH in DMF. The relative configuration of the major product was unambiguously determined by single-crystal X-ray analysis. The results clearly indicate that of the two possible reactive conformers **22a** and **22b** (Scheme IV) that precede formation of **17** and **23**, respectively, it is the "exo" conformer **22a** that is the predominant reactive conformer. This is somewhat surprising, since molecular models reveal that conformer **22a** should experience significant steric compression between the allylic chloride moiety and the *p*-methoxybenzyl residue. It appears that there is a fundamentally interesting and, as yet, poorly understood stereoelectronic effect[17] that prefers the "exo" cyclization mode (**22a**) over the "endo" cyclization mode (**22b**). This phenomenon will be discussed in depth, below. With the successful obtention of target **17**, efforts were now directed at devising an enantioselective synthesis of this system and functionalizing the bridgehead position of **17**.

It was found that after treatment of **15** with excess NaH at ambient temperature for a prolonged period of time, the initially formed product **17** isomerized to the tetrasubstituted isopropylidene derivative **24** (54%; Scheme V).

(11) (a) For a preliminary account of this work, see: Williams, R. M.; Glinka, T.; Kwast, E. *J. Am. Chem. Soc.* **1988**, *110*, 5927. (b) Williams, R. M.; Kwast, E.; Coffman, H.; Glinka, T. *J. Am. Chem. Soc.* **1989**, *111*, 3064.

(12) A similar transformation was utilized in the synthesis of (−)-hobartine: Darbre, T.; Nussbaumer, C.; Borschberg, H.-J. *Helv. Chim. Acta* **1984**, *67*, 1040.

(13) Williams, R. M.; Glinka, T. *Tetrahedron Lett.* **1986**, *27*, 3581.

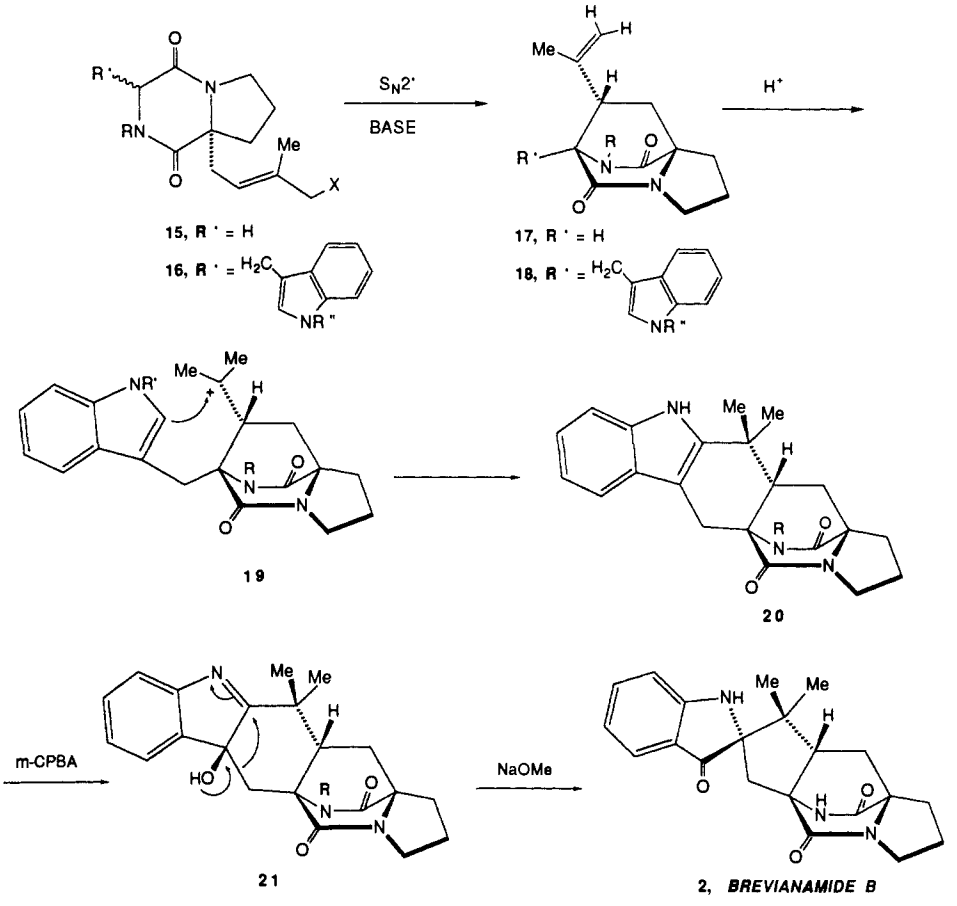
(14) Bottin-Strzalko, T. *Tetrahedron* **1973**, *29*, 4199.

(15) Schlessinger, R. H.; Poss, M. A.; Richardson, S.; Lin, P. *Tetrahedron Lett.* **1985**, *28*, 2391.

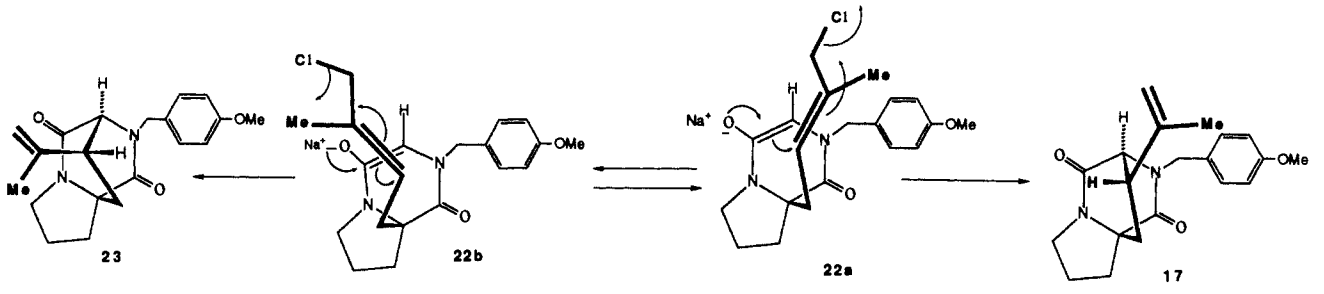
(16) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

(17) Baldwin has pointed to the preference of six-ring closures for "exo" mode over "endo" mode: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. However, these distinctions differ considerably from the present case since the reacting olefin is (in the Baldwin sense) exo in both cases and must be regarded as two alternative 6-exo-trigonal ring closures.

Scheme III



Scheme IV

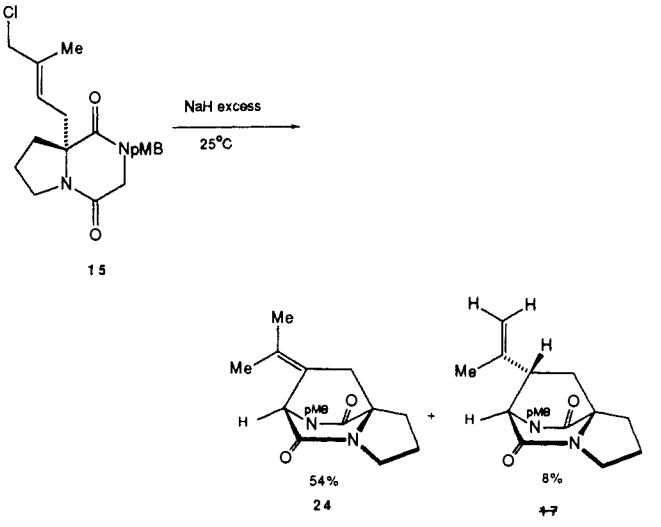


As a model to probe the feasibility of alkylating the bridgehead position of **17** with a suitably activated indole derivative, treatment of **17** with *n*-BuLi in THF followed by quenching with benzyl bromide afforded two benzylated products identified as the desired compound **25** and the *unwelcome* product **26**. Unfortunately, the product (**26**) resulting from deprotonation of the *p*-methoxybenzyl protecting group was the major product and the desired bridgehead carbanion product **25** was produced in amounts so small relative to **26** as to render this approach on this substrate as synthetically useless.

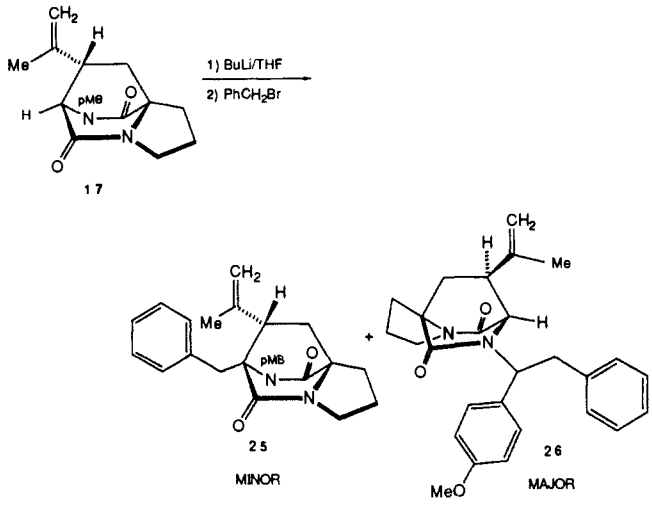
In a final (desperate) attempt to improve the efficiency of functionalization of the bridgehead position, it was reasoned that the tetrasubstituted olefin **24** might possess a sufficiently acidic bridgehead methine (due to the adjacent sp^2 system) to favor bridgehead carbanion formation over benzylic deprotonation. Interestingly, **24** underwent an unusual ring expansion/rearrangement when treated with strong base to furnish the tricyclic isomer **28** as the sole identifiable product. As in the case of **17**, benzylic deprotonation followed by ring opening produces a highly delocalized enolate **27** that suffers a 7-endo-trigonal closure on the amidine **27** to provide **28** (relative stereochemistry not assigned).

While it may still be possible, in principle, to effect a synthetically successful bridgehead carbanion route to **18** (Scheme III) by a more judicious choice of amide protection, our simultaneous investigations of the alternate route to **18** via **16** were

Scheme V



Scheme VI

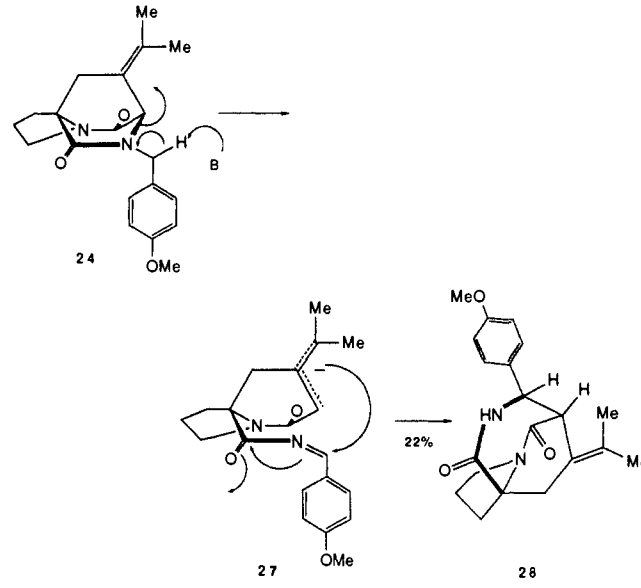


emerging as a more promising route; the bridgehead carbanion investigations were thus put aside.

An efficient and enantioselective synthesis of the key aldehyde **32** was achieved starting with L-proline. Formation of the known[18] pivaldehyde acetal from L-proline followed by enolate alkylation with allyl bromide according to Seebach, furnished the known[18] allylated heterocycle **29**. Reaction of **29** with the lithium salt of *p*-methoxybenzylamine cleanly provided the amide **30** (ca. quantitative). Acylation of **30** with bromoacetyl bromide (CH_2Cl_2, K_2CO_3) followed by ring closure (50% aqueous $NaOH/CH_2Cl_2$) furnished the enantiomerically pure piperazinedione **31** (79–85% from **30**). Ozonolysis of **31** in methanol followed by quenching with dimethyl sulfide furnished the optically pure aldehyde **32**, which was identical in every respect (except melting point and optical rotation) with the racemic aldehyde.[13] This route proved to be much more convenient than that described above in the racemic series and was easily carried out on a large scale. The optical purity of this series was determined by examination of the MTPA ester[19] of allylic alcohol **33**. Protection of the allylic alcohol as the corresponding *tert*-butyldimethylsilyl ether **34** furnished an appropriate substrate for examining introduction of the indole nucleus.

As an unambiguous stereochemical model, we chose to alkylate the enolate of **34** with benzyl bromide; this furnished a 10:1 ratio of phenylalanine products **35**. Removal of the silyl group and conversion to the allylic chloride **36** followed by NaH-induced cyclization furnished two cyclic products (65% yield; 2:3 ratio) **25** and **37**. The relative stereochemistry of the minor product **25** was unambiguously correlated to the authentic sample prepared from bridgehead carbanion benzylation of **17** (Scheme VI). Thus, S_N2' cyclization proceeds to favor the undesired stereoisomer, and the level of selectivity (2:3) is significantly poorer than that from **15** (10:1). The reasons for this difference in selectivity were not obvious and was not probed further with **36**. Instead, introduction of the indole moiety was immediately pursued with a measure of foreboding inflicted by the poor performance of **36**.

Scheme VII



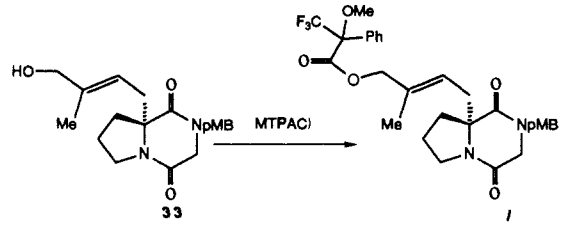
Direct introduction of the indole nucleus to **34**, however, proved more difficult. Treatment of **34** with LDA in THF followed by quenching with *N*-(*tert*-butyloxycarbonyl)-3-(bromomethyl)-indole[20] gave none of the desired substrate corresponding to **16**. Aldol condensation of **34** with *N*-(*tert*-butyloxycarbonyl)-3-formylindole gave synthetically useful yields of aldol products. However, the difficulties associated with separation of the isomers (three diastereomers were produced) and the attendant extra steps required for removal of the secondary alcohol also forced abandonment of this route.

Fortunately, the methodology devised by Kametani and Somei[21] for the synthesis of brevianamide E proved to work extremely well. Thus, carbomethoxylation of **34** (*n*-BuLi/THF/$ClCO_2Me$) afforded a 4:1 diastereomeric mixture of **38**, which was directly treated with gramine in the presence of tri-*n*-butylphosphine[21] in acetonitrile to furnish a single diastereoisomer **39**. The relative configuration of **39** (shown, Scheme X) was quite easy to assign based on ^1H NMR behavior.[22] Conversion to the desired pentacyclic olefin could be accomplished two ways. Most directly, **39** was protected as the *N*-*t*-BOC derivative and desilylated to furnish the corresponding allylic alcohol. Conversion to the allylic chloride, as above, followed by warming in the presence of LiCl in HMPA resulted in concomitant decarbomethoxylation, incipient enolate formation, and intramolecular S_N2' cyclization to afford the desired tricyclic compound **42** and a stereoisomer **43** in a 2:1 ratio favoring the desired compound **42**.

A less direct but more efficient route involving removal of the carbomethoxy group (of **39**) to the corresponding carboxylic acid with concomitant thermal decarboxylation was realized with LiCl in wet HMPA at 100 °C. Protection of the indole nitrogen as the *t*-BOC derivative and removal of the silyl group furnished **40**

(18) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.

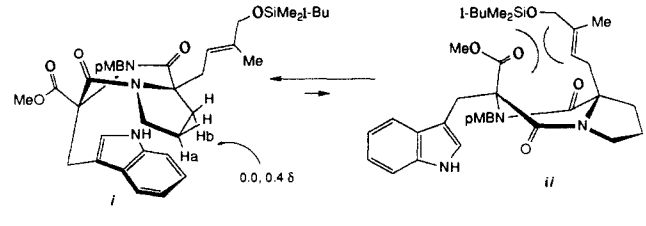
(19) The stereochemical purity of this series was established by conversion of the allylic alcohol **33** into the MTPA ester i and examination by ^{19}F NMR (compared against an authentic sample).



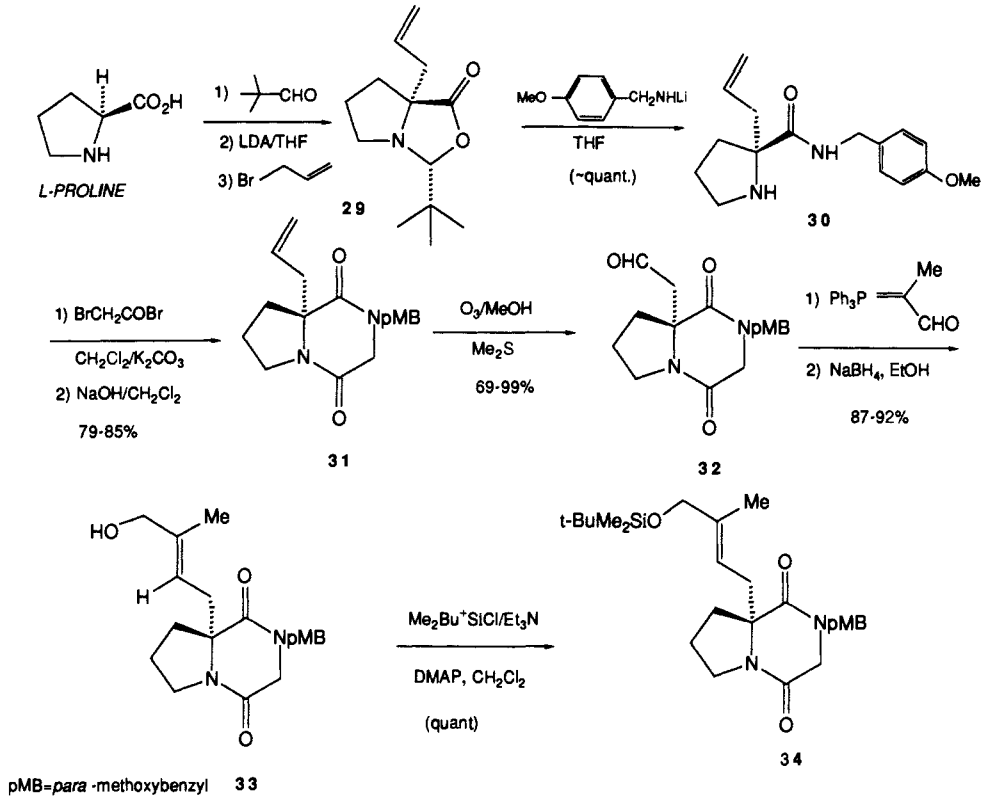
(20) Schollkopf, U.; Lonsky, R.; Lehr, P. *Liebigs Ann. Chem.* **1985**, 413.

(21) (a) Somei, M.; Karasawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*, 941. (b) Kametani, T.; Kanaya, N.; Ihara, M. *J. Am. Chem. Soc.* **1980**, 102, 3974.

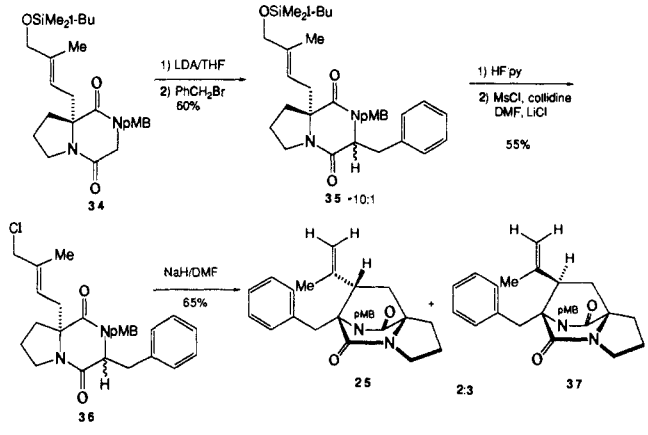
(22) The ^1H NMR spectrum reveals an anomalously high upfield shift for two coupled protons on the proline residue (H_aH_b at δ 0.0, 0.45). Steric compression (ii) between the carbomethoxy group and the C_5 moiety should favor conformation i; this places the shielding portion of the indole ring directly over these two protons. The alternative diastereomer is not capable of such shielding of these protons.



Scheme VIII



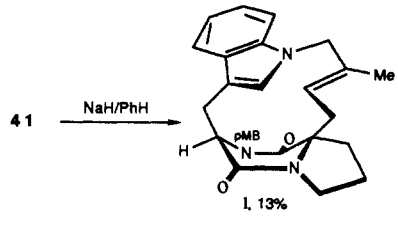
Scheme IX



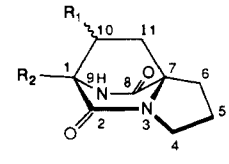
in good overall yield. Standard conversion to the allylic chloride **41** followed by treatment with NaH in DMF resulted in the same two pentacyclic olefins **42** and **43** (2:1 ratio) as shown in Scheme X. In an effort to improve the stereoselectivity of this critical cyclization reaction, a variety of solvents and additives were examined. Simply changing the solvent for cyclization from DMF to benzene (NaH, reflux) resulted in a highly stereoselective S_N2' cyclization resulting in a 3:97 ratio of **42** to **43** in 82% yield.[23]

To examine if this was a general solvent effect, all three substrates **15**, **36**, and **41** were compared for stereoselectivity under the same conditions as shown in Table I. The change in stereoselectivity in going from DMF to benzene can be rationalized by considering the environments of the two possible conformers of the putative enolate generated from, for example, **41**. It is quite reasonable that, in a good cation-solvating solvent such as DMF, the sodium cation is surrounded by a solvent shell of ligated DMF molecules. This would create a sterically demanding environment for the allylic chloride moiety to fold over the enolate ("endo") and achieve the proper transition-state geometry for cyclization. In this situation, the alternative ("exo") conformer leading to the desired stereochemistry is favored on steric grounds. On the other hand, in a nonpolar, poor ligating solvent such as benzene, the allylic group would be expected to fold over the enolate to bring the sodium cation and the developing chloride anion proximal in the transition state, since solvation of the individual ions from the alternative ("exo") conformer in such a nonpolar environment would be very poorly accommodated and have a much higher activation energy (**45**, "endo"; Scheme XI). On the basis of this hypothesis, it was anticipated that, if a bulkier solvent shell could be created around the metal cation, an improvement in the stereoselective formation of **42** should result. By simply adding several equivalents of 18-crown-6 to the reaction done in benzene with sodium hydride as the base, the stereoselectivity *reversed*, giving **42**/**43** in a 3.8:1 ratio (56% combined yield). As depicted in Scheme XI, it is postulated that the crown ether loosely associates with the sodium cation (**44**, "exo") thus creating a large, sterically demanding environment in the vicinity of the enolate oxygen and favoring cyclization from this conformer. It is quite

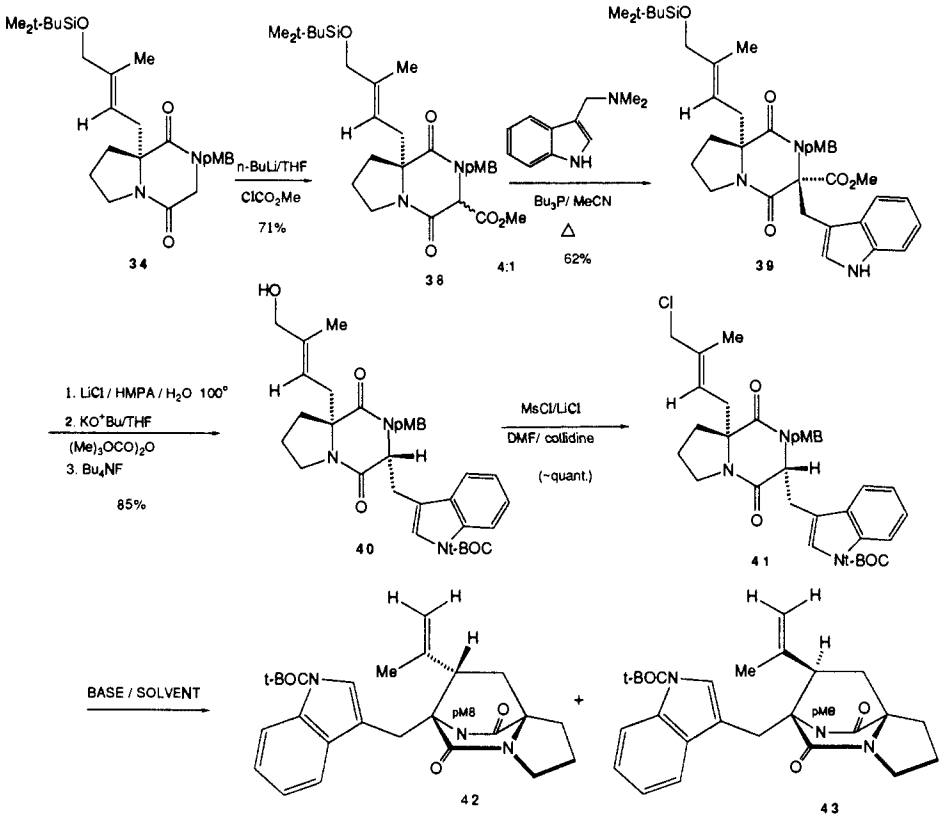
(23) A minor byproduct (i) is obtained in 13% yield from this reaction and has been assigned the interesting macrocyclic structure based on spectroscopic evidence.



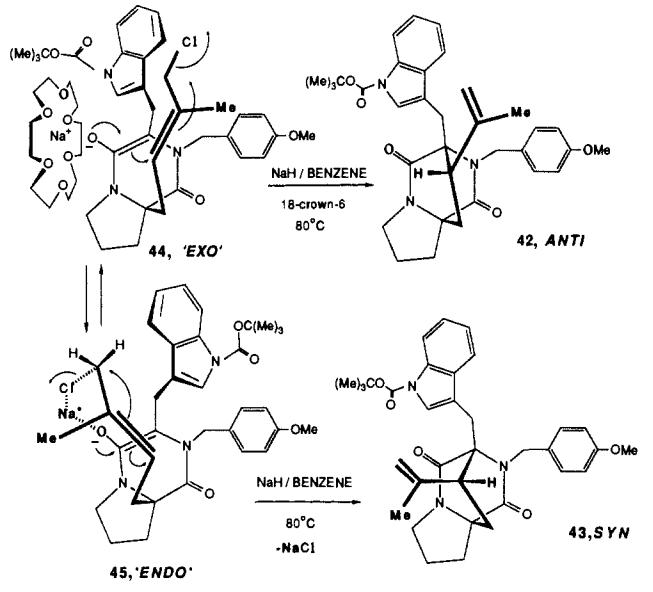
(24) The numbering system of the brevianamide ring system is based on the following nucleus: 2,8-diketo-3,9-diazatricyclo[5.2.2.$0^{3,7}$]undecane.



Scheme X



Scheme XI



curious that similar reactions carried out with 18-crown-6/KH and 15-crown-5/NaH in benzene at reflux temperature gave essentially a 1:1 ratio of **42**:**43**. A slightly improved procedure was found involving the reaction of **41** with 10 equiv of NaH in warm THF containing 5 equiv of 18-crown-6, resulting in a 3–4.9:1 ratio of **42**:**43** in 64–77% combined yield.

With the stereoselective obtention of **42**, the stage was now set to examine the final, crucial carbon–carbon bond construction via the olefin/cation cyclization approach proposed in Scheme III to access the hexacyclic indole structure **9**. We chose to first examine the remaining synthetic transformations to the indoxyl on the unnatural stereoisomer **43**. We were gratified to discover that isomer **43** underwent clean, regiospecific cyclization/*t*-BOC deprotection to afford the crystalline hexacyclic compound **46** (Scheme XII) in the presence of aqueous HCl in dioxane. Oxidation of the indole **46** with *m*-CPBA in CH_2Cl_2 provided the stable hydroxyindolenine **47** as a single isomer. Treatment of this material with NaOMe in MeOH resulted in a clean, stereospecific rearrangement to give the expected yellow, crystalline indoxyl **48**. The relative stereochemistry of **48** was unambiguously established by single-crystal X-ray analysis as shown in Figure 1. This structure elucidation served to confirm the stereochemical outcome of the S_N2' cyclization reactions as well as that of the indole oxidation. As expected (vide supra), the facial selectivity of the indole oxidation is controlled by the stereogenic center at C-10[24] of the bicyclo[2.2.2] nucleus; the peracid is directed to the least hindered face of the indole.

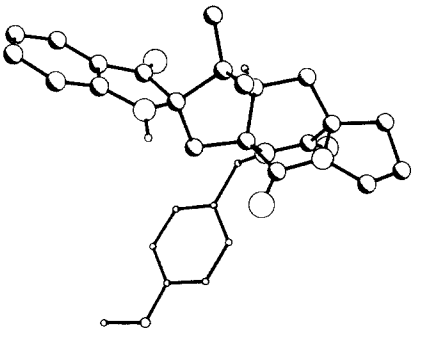
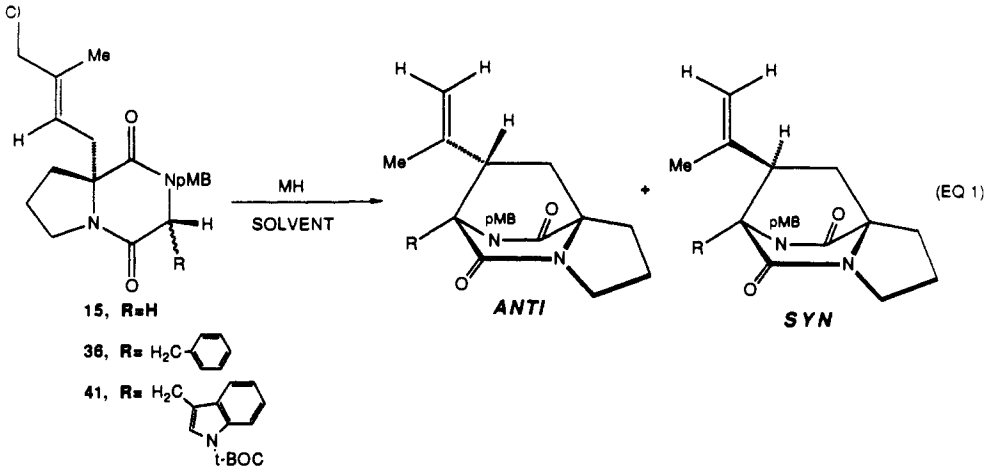


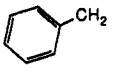
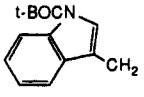
Figure 1. Molecular structure of compound **48**. Atoms are shown as spheres of fixed, arbitrary radius. The *p*-methoxybenzyl group has been diminished for clarity.

By utilization of the unnatural isomer **48**, it was found that removal of the *p*-methoxybenzyl protecting group proved extremely difficult under the standard oxidative conditions employing ceric ammonium nitrate.[25] While these conditions were found to effect deprotection on the simple, unsubstituted compound **17**, the presence of the electron-rich indoxyl of **48** apparently predicated reaction much faster with the oxidizing reagent than did the

(25) (a) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001. (b) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1985**, *107*, 3253.

Table I. Stereoselectivity of Intramolecular S_N2' Cyclizations



substrate (R)	solvent	T, °C	base	ratio (anti:syn)	yield, %
H	DMF	25	NaH	10:1	60
	benzene	80	NaH	~0:1	10
	DMF	25	NaH	2:3	65
	benzene	80	NaH	~0:1	20
	DMF	25	NaH	2:1	63
	benzene	80	NaH	3:97	82
	benzene	80	NaH/18-crown-6	3.9:1	56
	benzene	80	KH/18-crown-6	1.1:1	38
	benzene	80	NaH/15-crown-5	1.42:1	40
	benzene	25	NaH/18-crown-6	6:1	14
	THF	67	NaH/18-crown-6	4.9:1	64

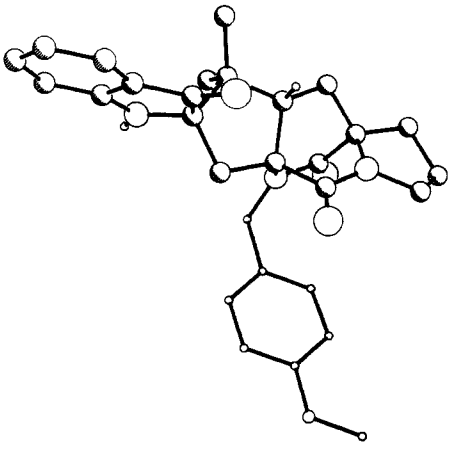


Figure 2. Molecular structure of compound **52**. Atoms are shown as spheres of fixed, arbitrary radius. The *p*-methoxybenzyl group has been diminished for clarity.

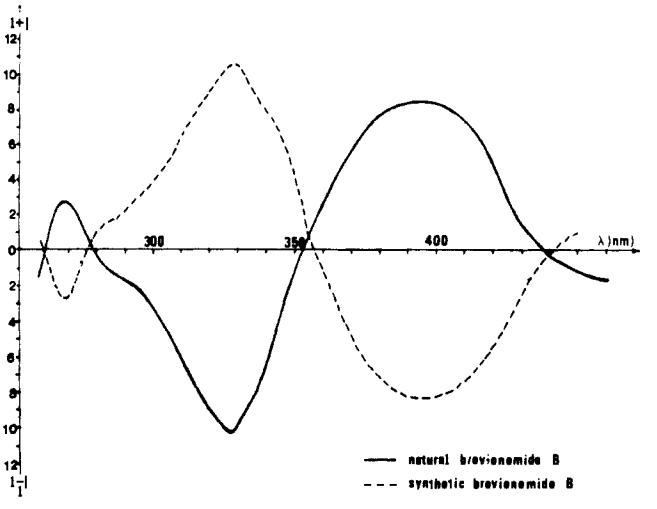


Figure 3. CD spectra of natural (from *P. brevicompactum*) and synthetic brevianamide B. Spectra were recorded in 2.5% formic acid in methylene chloride between 200 and 450 nm.

p-methoxybenzyl group. Under many sets of conditions, we were not able to isolate any of the desired material **49**; only extensive decomposition and destruction of the indoxyl chromophore were evident. Similar attempts to effect deprotection of the indole **46** were equally unsuccessful. Additional attempts to deprotect both **46** and **48** by dissolving-metal reduction, catalytic hydrogenation, acidic solvolysis, boron tribromide, boron trichloride, DDQ oxidation, and photooxidation all met with complete failure to provide even a trace of the desired deprotected compounds. Recalling our earlier, frustrating experiences to metalate the bridgehead position of **17**, the somewhat efficient metalation of the *p*-methoxybenzyl group (cf. Schemes VI and VII) indicated that a selective carbanionic oxidative deprotection may provide a reprieve. In the event, treatment of **48** with excess *tert*-butyllithium in THF at low temperature, followed by quenching with MoOPH[26] and aqueous extractive isolation, afforded **49** (C-10-epibrevianamide A) in 33% yield[27,28].

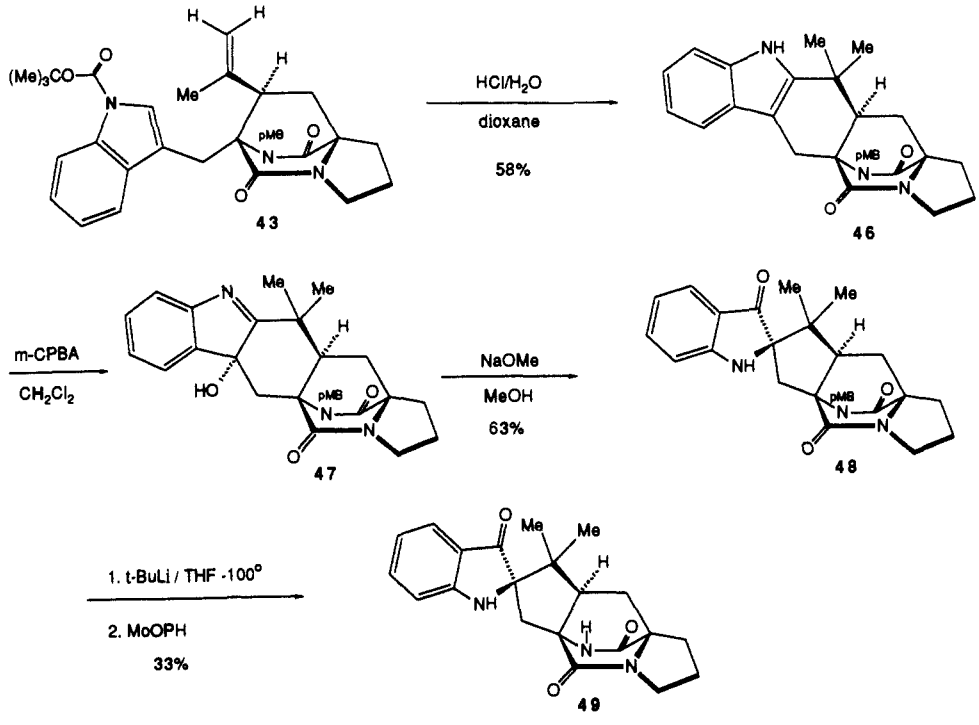
With the same protocol as that deployed for **43**, the naturally configured isomer **42** was smoothly cyclized to the crystalline hexacycle **50** in 72% yield (Scheme XIII). As in the case of **46**, the peracid oxidation of **50** proceeded in an entirely stereocontrolled manner giving a single 3-hydroxyindolenine (**51**) that could either be isolated by silica gel chromatography or be subjected crude to the base-induced rearrangement to the crystalline, bright yellow indoxyl **52** (67% yield overall from **50**). X-ray crystallo-

(26) MoOPH = oxodiperoxymolybdenum(hexamethylphosphoric triamide)(pyridine): Vedejs, E.; Telschow, E. *J. Org. Chem.* **1976**, *41*, 740.

(27) Williams, R. M.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 451.

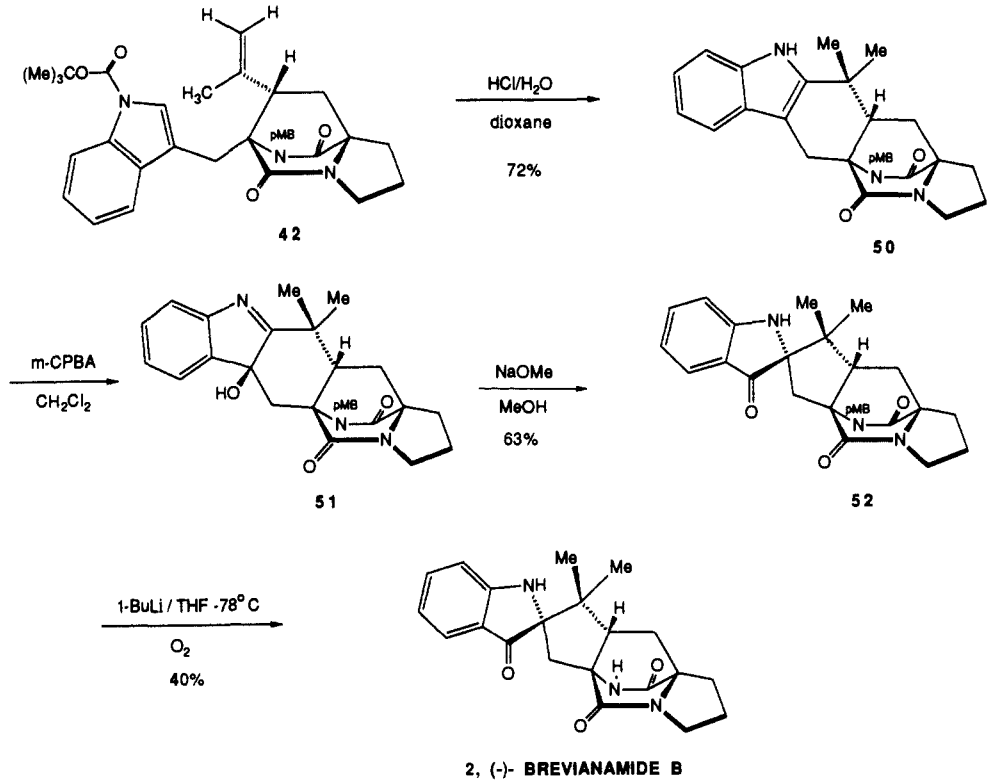
(28) For related reports detailing benzylic carbanion oxidations, see: (a) Gigg, R.; Conant, R. *Carbohydr. Res.* **1982**, *100*, C5–C9. (b) Gigg, R.; Conant, R. *J. Chem. Soc., Chem. Commun.* **1983**, 465. (c) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1985**, *107*, 3253. (d) Photooxidation: Barbier, M. *Heterocycles* **1985**, *23*, 345.

Scheme XII



43 46 47 48 49

Scheme XIII



42 50 51 52

2, (-)- BREVIANAMIDE B

graphic analysis of **52** (Figure 2) rigorously proved the structure and again clearly demonstrated that the stereogenic center at C-10 controls the facial selectivity of the indole oxidation from the less hindered face. Subjecting this compound to the benzylic carbanion oxidation protocol (*t*-BuLi/THF/O_2) furnished brevianamide B (**2**) in 40% yield. This compound was identical with an authentic sample of brevianamide B obtained in our laboratories from harvesting cultures of *P. brevicompactum* by TLC and ^{1}H NMR, IR, and UV spectroscopy. However, the specific rotation of the natural and synthetic samples were of opposite sign and of equal magnitude, indicating that the synthetic material is the enantiomorph of the natural product. This was further corroborated by examination of the mirror image CD curves of both samples shown in Figure 3. These data have been further corroborated by comparison of synthetic brevianamide B and semisynthetic brevianamide B derived from **1** by the redox scheme developed by Birch involving deoxybrevianamide A (**5**). The conversion of natural brevianamide A (from *P. brevicompactum*) to **5** and then into (-)-**2** proceeded as exactly as described.[1] The brevianamide B obtained from **1** was identical in every respect with the synthetic substance, including the sign and magnitude of the specific optical rotation and CD spectra; these materials have the absolute con-

figuration depicted in Scheme XIII.

In an attempt to prepare a synthetic sample of brevianamide A, it was reasoned that removal of the *p*-methoxybenzyl group from **50** would allow greater access to the α side of the indole during oxidation. This would also provide an authentic sample of the hypothetical indole **9** postulated by Birch as the direct biosynthetic precursor to **1**/**2**. Treatment of **50** with *n*-BuLi in THF at −78 °C, followed by quenching with MoOPH, gave in 35% yield the desired compound **9**. Simply allowing **9** to stand in ethyl acetate solution in the air led to a variety of unidentified oxidation products; not a trace, however, of either **1** or **2** could be detected in this mixture. Oxidation of **9** with *m*-CPBA in CH_2Cl_2 followed by treatment with NaOMe in MeOH gave, in good yield, brevianamide B with no detectable trace of brevianamide A. These results are significant for several reasons: (1) The fact that **9** does *not* undergo autoxidation with molecular oxygen strongly implies that if **9** is indeed the precursor to **1**/**2**, the conversion of the indole to the indoxyl is most likely an enzyme-mediated process; (2) even though **2** is the very minor metabolite produced, it also is likely produced enzymatically from **9** and is, therefore, not an artifact of small amounts of propitious **9** in the culture medium being oxidized from the less hindered face by oxygen; (3) the complete stereochemical preference of the indole to be oxidized from the less hindered face (to the B series) by chemical oxidants clearly suggests that nature has evolved as a major pathway a means to deliver oxygen from the more hindered face and as a minor pathway, from the less hindered face. These questions are only relevant if it can be demonstrated that **9** is indeed the biosynthetic precursor to the brevianamides. We have carefully examined the fermentation extracts of *P. brevicompactum* at varying growth intervals for production of trace amounts of **9**, this search being greatly facilitated by the possession of the authentic, synthetic sample. Despite intense effort, we were not able to detect even trace quantities of this compound being produced by the organism. Although this does not rule out the possible intermediacy of **9** as a tightly enzyme bound, short-lived species, the failure to detect any amount of this compound raises a series of new speculations concerning the biogenesis of these compounds. Efforts are presently underway to prepare a racemic sample of ^{13}C-enriched **9** for feeding experiments with the producing organism.

We have similarly deprotected **46** to the corresponding C-10-epi-**9** and have examined the fermentation extracts of *P. brevicompactum* for production of this material as well as for **49**. To the limits of detection, neither compound is produced.

The above facts lead to the conclusion that brevianamides A and B produced by *P. brevicompactum* are secondary metabolites that arise via enantio- and diastereodivergent biosynthetic pathways. A provocative hypothesis to embrace this rare stereochemical biogenesis involves considering that the planar, achiral intermediate **8** (Scheme I) is kinetically resolved by distinct enzymes that differ in both their enantioselectivity and diastereoselectivity. Alternatively, a single oxidase that only recognizes the binding orientation of the indole and thus, displays complete *S*-facial selectivity in the oxidation of racemic or partially racemic **9** would similarly resolve this substance into the optically pure indoxyls **1** and **2**. If the Birch hypothesis is correct regarding the intermediacy of **9**, this compound should be produced in racemic or partially racemic form and is then resolved by distinct oxidases that are genetically encoded to produce **1** and **2** in optically pure form. Experiments aimed at validating the intermediacy of **8** and **9** are in progress in these laboratories.

In summary, the stereocontrolled total synthesis of the enantiomorph of brevianamide B has been achieved in 17 chemical steps and provides unambiguous evidence for the structure originally proposed by Birch. In addition, the biosynthetic precursor **9** proposed by Birch has been synthesized; the intermediacy of this compound in the biosynthesis of **1**/**2**, however, remains to be verified. The discovery of means to control the facial selectivity of the intramolecular S_N2' cyclization provides a firm foundation from which to tackle the more challenging mycotoxins marcfortine and paraherquamide. The fundamental significance of these findings as applied to other synthetic operations as well as efforts to construct **11** and **12** are under study.

Experimental Section

6-[(2*E*)-4-Keto-3-methylbut-2-enyl]-2,5-diketo-4-(4-methoxybenzyl)-1,4-diazabicyclo[4.3.0]nonane. A suspension of aldehyde **32** (1.57 g, 4.96 mmol, 1.0 equiv) and $Ph_3P{=}C(CH_3)CHO$ (1.66 g, 5.21 mmol, 1.05 equiv) in 1,2-dichlorobenzene (13.0 mL) was heated under N_2 at 115 °C for 3 h (upon heating, both substrates dissolve). The mixture was cooled to O °C, diluted with hexane (20 mL), and stirred for a few minutes. The crystalline product was filtered off and recrystallized from ethanol to furnish 1.43 g of pure aldehyde (81%). The mother liquors were combined with the hexane/1,2-dichlorobenzene filtrates, and after evaporation of the solvent, a second crop of the product was obtained by separation on silica gel by radial chromatography (EtOAc): 0.25 g, 14%; ^1H NMR (270 MHz, $CDCl_3$) δ TMS 1.69 (3 H, s), 1.95–2.10 (2 H, m), 2.18–2.30 (2 H, m), 2.68 (1 H, dd, J = 14.5, 8.2 Hz), 2.88 (1 H, dd, J = 14.5, 8.2 Hz), 3.45–3.60 (1 H, m), 3.76 (1 H, $^1/_2$ AB q, J = 17.5 Hz), 3.80 (3 H, s), 3.75–3.90 (1 H, m), 3.89 (1 H, $^1/_2$ AB q, J = 17.5 Hz), 4.12 (1 H, $^1/_2$ AB q, J = 14.0 Hz), 4.88 (1 H, $^1/_2$ AB q, J = 14.0 Hz), 6.26–6.36 (1 H, m), 6.84 (2 H, d, J = 8.5 Hz), 7.16 (2 H, d, J = 8.5 Hz), 9.19 (1 H, s); Anal. ($C_{20}H_{24}N_2O_4$) C, H, N; mp 150–152 °C (recrystallized from EtOH); $[\alpha]^{25}_D$ = −94.7° (c = 1.1, $CHCl_3$).

6-[(2*E*)-4-Hydroxy-3-methylbut-2-enyl]-2,5-diketo-4-(4-methoxybenzyl)-1,4-diazabicyclo[4.3.0]nonane (33). To a stirred solution of the aldehyde obtained above (1.69 g, 4.75 mmol, 1.0 equiv) in EtOH (80 mL) at 50 °C was added $NaBH_4$ (0.92 g, 24.3 mmol, 5 equiv) in one portion. After 20 min of stirring (temperature dropped to ~35 °C), the mixture was poured on water and the excessive $NaBH_4$ was decomposed by the dropwise addition of 3 N HCl (20.5 mL). After 15 min of stirring, the product was extracted with CH_2Cl_2 and the organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent furnished **33** as a colorless oil, which solidified on standing (1.64 g, 96.5%). An analytical sample was crystallized from EtOAc: mp 135–136 °C; $[\alpha]^{25}_D$ = −56.3° (c = 1.65, $CHCl_3$).

33: ^1H NMR (270 MHz, $CDCl_3$) δ TMS 1.56 (3 H, s), 1.98–2.04 (2 H, m), 2.17–2.25 (2 H, m), 2.45 (1 H, dd, J = 8.1, 14.0 Hz), 2.61 (1 H, dd, J = 7.8, 14.0 Hz), 2.85 (1 H, br s), 3.40–3.60 (1 H, m), 3.69 (1 H, $^1/_2$ AB q, J = 17.1 Hz), 3.79 (3 H, s), 3.83 (2 H, br s), 3.90–4.10 (1 H, m), 3.95 (1 H, $^1/_2$ AB q, J = 17.1 Hz), 4.24 (1 H, $^1/_2$ AB q, J = 14.2 Hz), 4.75 (1 H, $^1/_2$ AB q, J = 14.2 Hz), 5.29 (1 H, m), 6.86 (2 H, d, J = 8.6 Hz), 7.20 (2 H, d, J = 8.6 Hz); IR (NaCl, neat) 3440, 1665, 1610, 1510, 1450, 1245, 1170, 1030, 810 cm^{-1}; mass spectrum, m/e (rel intensity) 358 (M^+, 0.5), 340 (0.8), 273 (21.3), 121 (100); Anal. ($C_{20}H_{26}N_2O_4$) C, H, N.

6-[(2*E*)-4-Chloro-3-methylbut-2-enyl]-2,5-diketo-4-(4-methoxybenzyl)-1,4-diazabicyclo[4.3.0]nonene (15). To a solution of alcohol **33** (0.762 g, 2.13 mmol, 1.0 equiv), collidine (0.34 mL, 2.61 mmol, 1.23 equiv), and LiCl (0.11 g, 2.61 mmol, 1.23 equiv) in DMF (6 mL) cooled to 0 °C was added methanesulfonyl chloride (0.20 mL, 2.61 mmol, 1.23 equiv) in one portion. The reaction mixture was allowed to warm to 25 °C and then stirred for 4 h. The mixture was poured on water, acidified with 3 N HCl (1.0 mL), and extracted with CH_2Cl_2. The organic extract was dried over anhydrous Na_2SO_4 and evaporated in vacuo to yield crude **15** as a colorless oil (0.83 g), which was dissolved in EtOH (~10 mL) and after addition of hexane (20 mL) left overnight for crystallization; white crystals (0.39 g, 49%) mp 85–95 °C, were collected. Chromatography of the mother liquors (EtOAc) yielded the second crop of **15** as a colorless oil, which solidified on standing (0.31 g, 39%). The analytical sample was recrystallized from EtOAc/hexane (1:1): mp 94–97 °C.

15: ^1H NMR (270 MHz, $CDCl_3$) δ TMS 1.68 (3 H, s), 1.94–2.06 (2 H, m), 2.11–2.24 (2 H, m), 2.42 (1 H, dd, J = 14.1, 8.1 Hz), 2.55 (1 H, dd, J = 14.1, 8.0 Hz), 3.41–3.56 (1 H, m), 3.70 (1 H, $^1/_2$ AB q, J = 17.2 Hz), 3.75–3.90 (1 H, m), 3.79 (2 H, d, J = 3.3 Hz), 3.80 (3 H, s), 3.98 (1 H, $^1/_2$ AB q, J = 17.2 Hz), 4.34 (1 H, $^1/_2$ AB q, J = 14.0 Hz), 4.70 (1 H, $^1/_2$ AB q, J = 14.0 Hz), 5.37 (1 H, br t, J = 8.0 Hz), 6.87 (2 H, d, J = 8.6 Hz), 7.20 (2 H, d, J = 8.6 Hz); IR (NaCl, neat) 1670, 1620, 1460, 1250, 1180, 1035, 820, 755, 670 cm^{-1}; mass spectrum (CI-NH_3), m/e (rel intensity) 377 (M^+ 1, 46.5), 343 (75.9), 341 (40.7), 275 (37.1), 273 (34.3), 136 (100).

2,8-Diketo-10-(1-methylethenyl)-9-(4-methoxybenzyl)-3,9-diazatricyclo[5.2.2.0^{3,7}]undecane (17). To a small flask containing NaH (79 mg, 1.53 mmol, 6.0 equiv, 50% oil suspension washed with hexanes) was added a solution of allylic chloride **15** (96 mg, 0.25 mmol, 1.0 equiv) in DMF (5 mL) at 25 °C. The mixture was stirred for 8 h, poured on water, acidified with 3 M HCl (0.5 mL), and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4, filtered, evaporated, and separated by PTLC silica gel (eluted with EtOAc/hexanes, 2:1) to afford a mixture of **17** and the syn epimer **23** (52

mg, 60.5%) from which the major isomer (**17**) could be crystallized. GLC analysis of the reaction mixture before chromatography indicated a 10:1 anti:syn ratio. Recrystallization of **17** from EtOAc/hexanes afforded an analytical sample for X-ray analysis, mp 128.5–129.5 °C.

17: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.70 (3 H, s), 1.78–1.93 (1 H, m), 1.93–2.11 (4 H, m), 2.68–2.80 (1 H, m), 2.80–2.90 (1 H, m), 3.45 (2 H, br t, J = 6.7 Hz), 3.78 (3 H, s), 3.90 (1 H, s), 3.98 (1 H, $^1/_2$ AB q, J = 14.8 Hz), 4.76 (1 H, s), 4.87 (1 H, $^1/_2$ AB q, J = 15.3 Hz), 4.91 (1 H, s), 6.83 (2 H, d, J = 8.5 Hz), 7.08 (2 H, d, J = 8.5 Hz); IR (NaCl, neat) 1685, 1610, 1245, 1175, 1030, 810 cm^{-1}; mass spectrum, m/e (rel intensity) 340 (M^+, 2.3), 272 (4.6), 219 (3.3), 121 (100); Anal. ($C_{20}H_{24}N_2O_3$) C, H, N.

2,8-Diketo-10-isopropylidene-9-(4-methoxybenzyl)-3,9-diazatricyclo-[5.2.2.0^{3,7}]undecane (24). To a suspension of sodium hydride (0.878 g, 18.3 mmol, 10 equiv, 50% in oil) (washed with hexane) in DMF (5.0 mL) was added a solution of allylic chloride **15** (0.69 g, 1.83 mmol, 1.0 equiv) in DMF (5 mL) in one portion at 25 °C, and the mixture was stirred for 11 h. The reaction mixture was poured portionwise into water (100 mL), acidified with 3 M HCl (6 mL), and extracted with CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4, filtered, evaporated, and separated on silica by radial chromatography to yield the 87:13 mixture of **24** and **17** (0.38 g, 62%). Crystallization from EtOAc/hexanes (2:1) yielded pure **24**: 0.23 g, 37%; mp 145–146 °C.

24: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.37 (3 H, s), 1.52 (3 H, s), 1.83–1.95 (1 H, m), 1.96–2.08 (2 H, m), 2.41 (1 H, $^1/_2$ AB q, J = 16.0 Hz), 2.48 (1 H, $^1/_2$ AB q, J = 16.0 Hz), 2.78–2.90 (1 H, m), 3.40–3.50 (2 H, m), 3.79 (3 H, s), 4.24 (1 H, $^1/_2$ AB q, J = 14.7 Hz), 4.49 (1 H, s), 4.80 (1 H, $^1/_2$ AB q, J = 14.7 Hz), 6.82 (2 H, d, J = 8.1 Hz), 7.11 (2 H, d, J = 8.5 Hz); mass spectrum (CI-NH_3), m/e (rel intensity) 340 (M^+, 100), 179 (8.3), 136 (12.5), 121 (25.2); IR (KBr, disk) 1680, 1615, 1515, 1410, 1235, 1020 cm^{-1}.

2,8-Diketo-9-(4-methoxybenzyl)-10-(1-methylethenyl)-1-benzyl-3,9-diazatricyclo[5.2.2.0^{3,7}]undecane (25) and 2,8-Diketo-9-[1-(4-methoxyphenyl)-2-phenylethyl]-10-(1-methylethenyl)-3,9-diazatricyclo-[5.2.2.0^{3,7}]undecane (26). To a stirred solution of **17** (18.4 mg, 0.063 mmol, 1.0 equiv) in THF (2 mL) was added a solution of n-butyllithium (1.1 equiv of a 1.65 M solution) at −78 °C. The mixture was stirred for 15 min at −78 °C and benzyl bromide (0.025 mL, 0.2 mmol, 3.0 equiv) was added. The reaction was stirred for 1 h at −78 °C and allowed to come to room temperature over a 1.5-h period. The mixture was concentrated and the residue separated by PTLC silica gel (eluted with EtOAc/hexanes, 2:1) to afford **26** (2.4 mg, 9%) and **25** (<1 mg) that was identical with that obtained from **36**.

26: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.04 (3 H, s), 1.35–2.10 (5 H, m), 2.48–2.63 (2 H, m), 3.05–3.30 (4 H, m), 3.81 (3 H, s), 4.01 (1 H, d, J = 1.5 Hz), 4.49 (2 H, s), 5.84 (1 H, dd, J = 5.5, 10.0 Hz), 6.82 (2 H, d, J = 8.5 Hz), 7.12–7.30 (7 H, m); IR (KBr, disk) 1675, 1510, 1410, 1260, 1240, 1170, 1025 cm^{-1}; mass spectrum m/e (rel intensity) (NH_3-CI) 431 (M^+ + 1, 100), 340 (10.3), 211 (62.5), 178 (18.5), 136 (24.7).

25: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.46 (3 H, s), 1.72 (1 H, dd, J = 5.5, 13.0 Hz), 1.77–1.86 (1 H, m), 1.96–2.07 (2 H, m), 2.20 (1 H, dd, J = 10.5, 13.0 Hz), 2.57 (1 H, dd, J = 5.5, 10.5 Hz), 2.84–2.93 (1 H, m), 3.16 (1 H, $^1/_2$ AB q, J = 16.0 Hz), 3.45–3.60 (2 H, m), 3.59 (1 H, $^1/_2$ AB q, J = 16.0 Hz), 3.77 (3 H, s), 4.28 (1 H, $^1/_2$ AB q, J = 16.0 Hz), 4.48 (1 H, s), 4.78 (1 H, s), 5.26 (1 H, $^1/_2$ AB q, J = 16.0 Hz), 6.79 (2 H, d, J = 8.5 Hz), 7.00 (2 H, d, J = 8.5 Hz), 7.12–7.20 (3 H, m), 7.42–7.49 (2 H, m), mass spectrum (CI-NH_3), m/e (rel intensity) 430 (M^+, 93.8), 136 (41.4), 121 (100); IR (NaCl, neat) 1685, 1615, 1510, 1385, 1245, 1175, 1030 cm^{-1}.

2,8-Diketo-11-isopropylidene-10-(4-methoxyphenyl)-3,9-diazatricyclo[5.3.2.0^{3,7}]dodecane (28). To a stirred solution of **24** (32 mg, 0.09 mmol, 1.0 equiv) in THF (1 mL) at −78 °C was added a solution of n-BuLi in hexane (1 equiv of a 1.95 M solution). After stirring 20 min at −78 °C, DMF (0.05 mL, 0.68 mmol, 7.6 equiv) was added and the mixture was stirred for an additional 30 min at −78 °C and allowed to warm to room temperature. The mixture was partitioned between water and methylene chloride and thoroughly extracted with methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with EtOAc/hexanes, 2:1) to afford 7 mg (22%) of **28** as a clear oil.

28: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.70–2.10 (4 H, m), 1.70 (3 H, s), 1.85 (3 H, s), 2.42 (1 H, d, J = 17.0 Hz), 3.00 (1 H, d, J = 17.0 Hz), 3.07–3.18 (1 H, m), 3.42–3.55 (1 H, m), 3.58–3.70 (1 H, m), 3.79 (3 H, s), 4.53–4.59 (1 H, m), 5.82 (1 H, s, D_2O exchange), 6.89 (2 H, d, J = 8.5 Hz), 7.12 (2 H, d, J = 8.5 Hz); mass spectrum (CI-NH_3), m/e (rel intensity) 340 (M^+, 18.1), 177 (100), 162 (29.8), 149 (18.5), 133 (88), 121 (26.6); IR (KBr, disk) 3280, 1660, 1510, 1250, 1170, 1035 cm^{-1}.

(−)-2-(*R*)-Allyl-2-[(4-methoxybenzyl)carboxamido]pyrrolidine (30). To a stirred solution of 4-methoxybenzylamine (6.77 g, 49.5 mmol, 2.0 equiv) in THF (100 mL) was added n-butyllithium (32.1 mL, 49.5 mmol, 2.0 equiv, 1.54 M in hexane) at −78 °C. After stirring 30 min at −78 °C, a solution of **29** (5.40 g, 24.7 mmol, 1.0 equiv) in THF (20 mL) was added via cannula. The mixture was stirred for 1.5 h at −78 °C, warmed to room temperature, and concentrated under reduced pressure. The residue was partitioned between water and CH_2Cl_2 and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated and the excess 4-methoxybenzylamine removed via Kugelrohr distillation [100 °C (0.5 Torr)], leaving the crude amide **30** as an oil (6.8 g). This material was directly used in the next step without additional purification. An analytical sample was obtained by radial chromatography on silica gel, (eluted with EtOAc/MeOH, 50:1): ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.58–1.78 (3 H, m), 1.86 (1 H, br s), 2.06–2.30 (2 H, m), 2.72–2.82 (2 H, m), 2.92–3.01 (1 H, m), 3.75 (3 H, s), 4.30 (2 H, d, J = 4.3 Hz), 5.00–5.11 (2 H, m), 5.57–5.75 (1 H, m), 6.82 (2 H, d, J = 8.7 Hz), 7.14 (2 H, d, J = 8.7 Hz), 8.17 (1 H, br s); IR (NaCl, neat) 3330, 1655, 1605, 1500, 1240, 1165, 1025 cm^{-1}; mass spectrum, m/e (rel intensity) 275 (M + I$^+$, 100), 233 (14.9), 136 (33.9), 121 (50.6); $[\alpha]^{25}_D$ = −3.0° (c = 7.2, $CHCl_3$).

(−)-2,5-Diketo-6-(*R*)-allyl-4-(4-methoxybenzyl)-1,4-diazabicyclo-[4.3.0]nonane (31). To a solution of crude amide **30** (6.70 g, 24.45 mmol, 1.0 equiv) in methylene chloride (80 mL) was added an aqueous solution of 0.5 M K_2CO_3 (51.3 mL, 25.67 mmol, 1.05 equiv), and the mixture was cooled to 0 °C. To the vigorously stirred mixture was added bromoacetyl bromide (5.43 g, 26.90 mmol, 1.1 equiv) in one portion. The starting material disappearance was followed by TLC (eluted with EtOAc/Et_3N, 100:1). After ca. 1 h (when no more starting material was present) the organic layer was separated and then stirred vigorously with 50% aqueous NaOH (8.0 mL) until the intermediate formed in the first step was consumed (by TLC; approximately 8 h). The mixture was diluted with water, and the organic layer was separated, washed with dilute HCl, dried over Na_2SO_4, and concentrated under reduced pressure. Silica gel chromatography of the oily residue (eluted with EtOAc) yields diketopiperazine **31** as a colorless solidifying oil (6.05 g, 79%). An analytical sample was obtained by recrystallization from EtOAc/hexanes (1:2): mp 89–90 °C; $[\alpha]^{25}_D$ = −71.2° (c = 1.46, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.74–2.00 (2 H, m), 2.05–2.14 (2 H, m), 2.32 (1 H, dd, J = 13.7, 7.5 Hz), 2.49 (1 H, dd, J = 13.7, 7.5 Hz), 3.34–3.46 (1 H, m), 3.63 (1 H, $^1/_2$ AB q, J = 17.1 Hz), 3.66–3.81 (1 H, m), 3.72 (3 H, s), 3.87 (1 H, $^1/_2$ AB q, J = 17.1 Hz), 4.19 (1 H, $^1/_2$ AB q, J = 14.2 Hz), 4.70 (1 H, $^1/_2$ AB q, J = 14.2 Hz), 4.96–5.10 (2 H, m), 5.50–5.67 (1 H, m), 6.78 (2 H, d, J = 8.6 Hz), 7.12 (2 H, d, J = 8.6 Hz); IR (KBr, disk) 1660, 1610, 1510, 1450, 1235, 1170, 1025 cm^{-1}; Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

(−)-2,5-Diketo-6-(*R*)-(formylmethyl)-4-(4-methoxybenzyl)-1,4-diazabicyclo[4.3.0]nonane (32). A stirred solution of olefin **31** (6.0 g, 19.1 mmol, 1.0 equiv) in MeOH (450 mL) at −78 °C was charged with a constant stream of ozone. After 1 h, the solution turned the characteristic pale blue color and was purged with oxygen. Dimethyl sulfide (3 mL) was added in one portion and the mixture was warmed to ambient temperature. Evaporation of the solvent was followed by partitioning the residue between CH_2Cl_2 and water and thoroughly extracting with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated, and separated by silica gel chromatography (eluted with EtOAc) to afford the aldehyde **32**: 4.17 g, 69%; mp 119–120 °C (recrystallized from EtOAc/hexanes); $[\alpha]^{25}_D$ = −119.5° (c = 0.8, $CHCl_3$); Anal. ($C_{17}H_{20}N_2O_4$) C, H, N; ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.78–2.36 (4 H, m), 2.85 (1 H, $^1/_2$ AB q, J = 16.8 Hz), 3.05 (1 H, $^1/_2$ AB q, J = 16.8 Hz), 3.32–3.47 (1 H, m), 3.77 (1 H, $^1/_2$ AB q, J = 17.1 Hz), 3.80 (3 H, s), 3.85–3.95 (1 H, m), 4.20 (1 H, $^1/_2$ AB q, J = 17.1 Hz), 4.46 (1 H, $^1/_2$ AB q, J = 14.3 Hz), 4.63 (1 H, $^1/_2$ AB q, J = 14.3 Hz), 6.87 (2 H, d, J = 8.5 Hz), 7.23 (2 H, d, J = 8.5 Hz), 9.68 (1 H, s); IR (KBr, disk) 1720, 1665, 1240, 1110, 1030, 810 cm^{-1}.

(−)-6-(*R*)-[(2*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbut-2-enyl]-2,5-diketo-4-(4-methoxybenzyl)-1,4-diazabicyclo[4.3.0]nonane (34). To a stirred solution of allylic alcohol **33** (0.59 g, 1.65 mmol, 1.0 equiv) in DMF (5.0 mL) at 0 °C were added *tert*-butyldimethylchlorosilane (0.37 g, 2.47 mmol, 1.5 equiv) and triethylamine (0.35 mL, 2.47 mmol, 1.5 equiv) over a 5-min period. The cooling bath was removed and the mixture was stirred for 1 h at room temperature. The mixture was partitioned between CH_2Cl_2 and water, and the aqueous layer was thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated, and the residual DMF removed under reduced pressure at 50 °C. The crude silyl ether **34** (yield ca. quantitative) was used directly for the next step without further purification. An analytical sample was purified by silica gel

chromatography (eluted with AcOEt/MeOH, 10:1): ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.00 (3 H, s), 0.03 (3 H, s), 0.89 (9 H, s), 1.53 (3 H, s), 1.93–2.09 (2 H, m), 2.15–2.29 (2 H, m), 2.45 (1 H, dd, J = 14.0, 8.0 Hz), 2.65 (1 H, dd, J = 14.0, 8.0 Hz), 3.45–3.55 (1 H, m), 3.65 (1 H, $^1/_2$ AB q, J = 17.0 Hz), 3.79 (3 H, s), 3.75–3.90 (1 H, m), 3.82 (2 H, s), 3.95 (1 H, $^1/_2$ AB q, J = 17.0 Hz), 4.47 (2 H, br s), 5.33 (1 H, m), 6.85 (2 H, d, J = 8.5 Hz), 7.16 (2 H, d, J = 8.5 Hz); IR (NaCl, neat) 1665, 1510, 1445, 1245, 1165, 830 cm^{-1}; mass spectrum, m/e (rel intensity) 472 (M^+, 37.3), 341 (63.5), 273 (32.9), 199 (100), 121 (43.7); $[\alpha]^{25}_D$ = −26.0° (c = 1.25, $CHCl_3$).

3-Benzyl-6-[(2*E*)-[(*tert*-butyldimethylsilyl)oxy]-3-methylbut-2-enyl]-2,5-diketo-4-(4-methoxybenzyl)-1,4-diazabicyclo[4.3.0]nonane (35). To a stirred solution of (racemic) **34** (89 mg, 0.188 mmol, 1.0 equiv) in THF (1.0 mL) at −78 °C was added a solution of LDA in THF/hexanes (0.51 mL, 0.224 mmol, 1.2 equiv) dropwise. The enolate solution was stirred 30 min at −78 °C, benzyl bromide (0.067 mL, 0.564 mmol, 3.0 equiv) was added, and the cooling bath was removed. When the mixture reached ambient temperature, the solvent was removed under reduced pressure and the residue was separated by PTLC silica gel chromatography (eluted with EtOAc/hexanes, 3:1) to afford a ~10:1 diastereomeric mixture of the benzylated products **35**:**35**-anti (51 mg, 55%), **35**-syn (5 mg, 5%) as colorless oils together with **34** (11 mg, 12%).

35-anti: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.00 (6 H, s), 0.58–0.7 (1 H, m), 0.85 (9 H, s), 1.32–1.45 (1 H, m), 1.50 (3 H, s), 1.56–1.82 (2 H, m), 2.20 (1 H, dd, J = 14.0, 8.0 Hz), 2.51 (1 H, dd, J = 14.0, 8.0 Hz), 3.10–3.34 (3 H, m), 3.60–3.75 (1 H, m), 3.77 (2 H, s), 3.80 (3 H, s), 3.96 (1 H, $^1/_2$ AB q, J = 14.5 Hz), 4.12–4.15 (1 H, m), 5.03 (1 H, m), 5.59 (1 H, $^1/_2$ AB q, J = 14.5 Hz), 6.87 (2 H, d, J = 8.5 Hz), 7.01–7.09 (2 H, m), 7.18–7.31 (5 H, m); IR (NaCl, neat) 1665, 1615, 1510, 1440, 1245, 1065, 830 cm^{-1}.

35-syn: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.06 (6 H, s), 0.90 (9 H, s), 1.60 (3 H, s), 1.82–2.11 (4 H, m), 2.20–2.32 (2 H, m), 3.14 (1 H, dd, J = 14.0, 7.1 Hz), 3.27–3.45 (3 H, m), 3.77 (3 H, s), 3.82–3.96 (1 H, m), 4.04 (2 H, s), 4.11 (1 H, dd, J = 7.1, 4.7 Hz), 5.27 (1 H, $^1/_2$ AB q, J = 17.5 Hz), 5.42–5.52 (1 H, m), 6.78 (2 H, d, J = 8.5 Hz), 6.91 (2 H, d, J = 8.5 Hz), 7.15–7.40 (5 H, m); IR (NaCl, neat) 1660, 1615, 1510, 1445, 1250, 1110, 1065, 835 cm^{-1}; mass spectrum, m/e (rel intensity) 562 (M^+, 14.9), 430 (24), 364 (26.3), 362 (23.5), 199 (100), 121 (53.6).

6-[(2*E*)-4-Chloro-3-methylbut-2-enyl]-2,5-diketo-4-(4-methoxybenzyl)-3-benzyl-1,4-diazabicyclo[4.3.0]nonane (36). To a stirred solution of **35**-anti (51 mg, 0.091 mmol) in THF (2.0 mL) in a plastic bottle was added HF–pyridine complex (0.1 mL) at room temperature. The mixture was stirred for 2 h, neutralized with 1 N NaOH solution, and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated to yield a colorless oil (allylic alcohol): 37 mg, 91%; ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.54–0.71 (1 H, m), 1.42–1.60 (1 H, m), 1.53 (3 H, s), 1.60–1.80 (2 H, m), 2.21 (1 H, dd, J = 14.4, 7.3 Hz), 2.50 (1 H, dd, J = 14.4, 7.2 Hz), 3.08–3.33 (3 H, m), 3.58–3.79 (1 H, m), 3.77 (2 H, s), 3.81 (3 H, s), 3.95 (1 H, $^1/_2$ AB q, J = 14.5 Hz), 4.11–4.25 (1 H, m), 4.97–5.08 (1 H, m), 5.63 (1 H, $^1/_2$ AB q, J = 14.5 Hz), 6.90 (2 H, d, J = 8.5 Hz), 7.03–7.11 (2 H, m), 7.20–7.40 (5 H, m); IR (NaCl, neat) 3410, 1630, 1435, 1240, 1025, 835 cm^{-1}; mass spectrum, m/e (rel intensity) 449 (M^+ + 1, 35.4), 433 (24.1), 431 (23.6), 365 (38.0), 363 (59.3), 121 (100).

To a stirred solution of the crude allylic alcohol (37 mg, 0.083 mmol, 1.0 equiv), lithium chloride (4.2 mg, 0.1 mmol, 1.2 equiv), and collidine (0.0132 mL, 0.1 mmol, 1.2 equiv) in DMF (0.3 mL) was added methanesulfonyl chloride (0.0077 mL, 0.1 mmol, 1.2 equiv) at 0 °C. The mixture was allowed to come to room temperature and was stirred overnight. The solution was diluted with water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, evaporated, and separated by PTLC silica gel (eluted with EtOAc) to furnish the allylic chloride **36** (14 mg, 61% based on recovered alcohol, 16 mg, 43%).

36: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.51–0.69 (1 H, m), 1.33–1.50 (1 H, m), 1.61 (3 H, s), 1.60–1.76 (2 H, m), 2.19 (1 H, dd, J = 14.4, 8.2 Hz), 2.47 (1 H, dd, J = 14.4, 7.0 Hz), 3.08–3.38 (3 H, m), 3.65 (2 H, s), 3.65–3.70 (1 H, m), 3.82 (3 H, s), 3.96 (1 H, $^1/_2$ AB q, J = 14.3 Hz), 4.21–4.29 (1 H, m), 4.96–5.06 (1 H, m), 5.60 (1 H, $^1/_2$ AB q, J = 14.3 Hz), 6.91 (2 H, d, J = 8.5 Hz), 7.05–7.12 (2 H, m), 7.20–7.35 (5 H, m); mass spectrum, m/e (rel intensity) 467 (M^+, 30.2), 431 (28.9), 363 (85.8), 121 (100).

Cyclization of 36 to 25 and 37. A solution of allylic chloride **36** (12.3 mg, 0.026 mmol, 1.0 equiv) in DMF (0.5 mL) was transferred via cannula into a flask containing NaH (7.8 mg of a 50% oil dispersion, 0.158 mmol, 6.0 equiv, washed with n-hexane). The mixture was vigorously stirred at room temperature overnight. The mixture was diluted with water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and analyzed by ^{1}H NMR. NMR analysis indicated that the ratio of **25**:**37** was ca. 2:3. Separation of this mixture by PTLC on silica gel (eluted with EtOAc/hexanes, 2:1) yields **25** (3.4 mg, 29%) and **37** (4.0 mg, 36%). The **25** obtained was identical in every respect with that obtained from benzylation of **17** (see above).

37: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.53 (3 H, s), 1.78 (1 H, dd, J = 13.5, 5.4 Hz), 1.84–2.11 (4 H, m), 2.73 (1 H, dd, J = 10.3, 5.4 Hz), 2.81–2.97 (1 H, m), 3.16 (1 H, $^1/_2$ AB q, J = 18.0 Hz), 3.51–3.66 (3 H, m), 3.78 (3 H, s), 4.15 (1 H, $^1/_2$ AB q, J = 15.4 Hz), 4.41 (1 H, br s), 4.72 (1 H, br s), 4.89 (1 H, $^1/_2$ AB q, J = 15.4 Hz), 6.79 (2 H, d, J = 8.7 Hz), 7.04 (2 H, d, J = 8.7 Hz), 7.16–7.22 (5 H, m); IR (NaCl, neat) 1685, 1615, 1510, 1390, 1250, 1175, 1030 cm^{-1}; mass spectrum, m/e (rel intensity) 430 (M^+, 100), 361 (7.9), 121 (73.9).

6-[(2*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]but-2-enyl]-3-(carbomethoxy)-4-(4-methoxybenzyl)-1,4-diazabicyclo[4.3.0]nonane (38). To the stirred solution of **34** (2.14 g, 4.53 mmol, 1.0 equiv) in THF (50 mL) was added n-butyllithium in hexane (1.05 equiv of a 1.54 M solution) at −78 °C over a 5-min period. Methyl chloroformate (1.76 mL, 22.6 mmol, 5.0 equiv) was added rapidly in one portion. After stirring for 20 min at −78 °C, the reaction mixture was allowed to warm to room temperature, concentrated under reduced pressure, diluted with CH_2Cl_2, and washed with water. The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated. (^{1}H NMR of the crude mixture shows almost exclusively one isomer of the product.) The product was isolated from the crude mixture by silica gel radial chromatography (eluted with EtOAc/hexane, 1:1) as a colorless oil (1.70 g, 71%), which indicates the presence of two diastereoisomers (^{1}H NMR analysis) in a 4:1 ratio. Both isomers could not be separated by chromatography and were used as a mixture for the next step.

38-anti: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.00 (6 H, s), 0.86 (9 H, s), 1.49 (3 H, s), 1.87–2.04 (2 H, m), 2.12–2.22 (2 H, m), 2.35 (1 H, dd), 2.51 (1 H, dd), 3.32–3.46 (1 H, m), 3.51–3.98 (10 H, m), 4.58 (10 H, s), 5.06 (1 H, m), 5.22 (1 H, $^1/_2$ AB q, J = 14.7 Hz), 6.82 (2 H, d, J = 8.5 Hz), 7.17 (2 H, d, J = 8.5 Hz); IR (NaCl, neat) 1760, 1675, 1515, 1450, 1435, 1250, 1175, 835 cm^{-1}; mass spectrum, m/e (rel intensity) 529 (M^+, 18.9), 472 (7.1), 399 (100), 331 (22.2), 199 (46.7), 121 (48.0). From the ^{1}H NMR spectrum of the mixture of diastereoisomers some of the peaks corresponding to **38**-syn could be discerned (corresponding peaks of **38**-anti in brackets: 0.06/0.00/ (3 H, s), 0.90/0.86/ (9 H, s), 1.58/1.49/ (3 H, s), 5.47/5.06/ (1 H, m).

(+)-6-(*R*)-[(2*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbut-2-enyl]-3-(*R*)(carbomethoxy)-2,5-diketo-3-[(3-indolyl)methyl]-4-(4-methoxybenzyl)-1,4-diazabicyclo[4.3.0]nonane (39). A solution of **38** (mixture of epimers, 1.52 g, 2.87 mmol, 1.0 equiv), gramine (0.52 g, 3.01 mmol, 1.05 equiv), and tri-n-butylphosphine (0.28 mL, 1.15 mmol, 0.4 equiv) in acetonitrile (50 mL) was gently refluxed under N_2 for 7 h. The solvent was evaporated under reduced pressure, and from the oily residue the product **39** was isolated on silica gel by radial chromatography (eluted with EtOAc/hexanes, 1:1) as a colorless glass (1.17 g, 62%).

39: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.02 (7 H, m), 0.33–0.47 (1 H, m), 0.87 (9 H, m), 1.22–1.38 (1 H, m), 1.47–1.65 (1 H, m), 1.56 (3 H, s), 2.23 (1 H, dd, J = 14.9, 3.8 Hz), 2.59 (1 H, dd, J = 14.9, 3.8 Hz), 2.95 (1 H, m), 3.31 (3 H, s), 3.35–3.52 (1 H, m), 3.63–4.03 (8 H, m), 5.33 (1 H, m), 5.45 (1 H, $^1/_2$ AB q, J = 14.7 Hz), 6.73–6.89 (3 H, m), 7.05–7.32 (5 H, m), 7.67 (1 H, d, J = 7 Hz), 9.03 (1 H, br s); IR (KBr, disk) 3330, 1750, 1655, 1510, 1455, 1440, 1245, 1055, 830, 736 cm^{-1}; mass spectrum m/e (rel intensity) 527 (1.1), 461 (3), 399 (3.2), 333 (8.8), 275 (8.8), 199 (56.1), 132 (100), 130 (70.8), 121 (26.6); $[\alpha]^{25}_D$ = +9.3° (c = 1.76, $CHCl_3$).

(−)-6-(*R*)-[(2*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbut-2-enyl]-2,5-diketo-3-(*R*)-[(3-indolyl)methyl]-4-(4-methoxybenzyl)-1,4-diazabicyclo[4.3.0]nonane. A solution of **39** (0.850 g, 1.29 mmol, 1.0 equiv), lithium chloride (0.273 g, 6.45 mmol, 5.0 equiv), and water (0.035 mL, 1.92 mmol, 1.5 equiv) in HMPA (5.0 mL) was heated at 100–105 °C under N_2 for 2 h. The reaction mixture was diluted with EtOAc/hexanes (1:1) and thoroughly washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to furnish an oily residue. Separation by silica gel column chromatography (EtOAc/hexanes, 1:2) yields the isomeric decarbomethoxylated products syn (0.565 g, 78%) and anti (0.076 g, 10%).

Anti: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.01 (6 H, s), 0.20–0.35 (1 H, m), 0.48–0.62 (1 H, m), 0.87 (9 H, s), 1.33–1.60 (2 H, m), 1.52 (3 H, s), 2.16 (1 H, dd, J = 14.3, 6.9 Hz), 2.54 (1 H, dd, J = 14.3, 7.9 Hz), 2.93–3.03 (1 H, m), 3.29–3.48 (2 H, m), 3.61 (1 H, dd, J = 14.7, 2.0 Hz), 3.81 (3 H, s), 3.84 (2 H, s), 3.97 (1 H, $^1/_2$ AB q, J = 14.4 Hz), 4.12–4.17 (1 H, m), 5.05–5.15 (1 H, m), 5.64 (1 H, $^1/_2$ AB q, J = 14.4 Hz), 6.85–6.97 (3 H, m), 7.04–7.18 (2 H, m), 7.25–7.36 (3 H, m), 7.36 (3 H, m), 7.65 (1 H, d, J = 7.8 Hz), 9.10 (1 H, br s); IR (KBr, disk) 3280, 1645, 1510, 1450, 1245, 825, 730 cm^{-1}; mass spectrum, m/e (rel intensity) 601 (M^+, 3.0), 469 (4.2), 403 (6.9), 401 (5.3), 273 (3.7), 199

(100), 132 (51.0), 130 (30.2), 121 (19.4); $[\alpha]^{25}_D$ = −20.0° (c = 1.44, $CHCl_3$).

Syn: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.03 (5 H, s), 0.89 (9 H, s), 1.49 (3 H, s), 1.70–2.03 (5 H, m), 2.12–2.25 (1 H, m), 3.20–3.47 (3 H, m), 3.53 (1 H, $^1/_2$ AB q, J = 14.4 Hz), 3.78 (3 H, s), 3.80–3.95 (1 H, m), 3.96 (2 H, s), 4.15–4.25 (1 H, m), 5.18 (1 H, $^1/_2$ AB q, J = 14.4 Hz), 5.21–5.30 (1 H, m), 6.71 (2 H, d, J = 8.6 Hz), 6.87 (2 H, d, J = 8.6 Hz), 6.95 (1 H, br s), 7.08–7.22 (2 H, m), 7.32 (1 H, d, J = 78.7 Hz), 7.63 (1 H, d, J = 7.6 Hz), 8.09 (1 H, br s); IR (KBr, disk) 3290, 1650, 1515, 1455, 1245, 830, 735 cm^{-1}; mass spectrum, m/e (rel intensity) 601 (M^+, 3.3), 469 (5.3), 403 (7.7), 401 (5.5), 273 (3.5), 199 (100), 132 (39.1), 130 (26.7), 121 (19.1); $[\alpha]^{25}_D$ = +48.9° (c = 1.56, $CHCl_3$).

(−)-6-(*R*)-[[*N*-(*tert*-Butyloxycarbonyl)-3-indolyl]methyl]-2,5-diketo-4-(4-methoxybenzyl)-6-(*R*)-[(2*E*)-4-hydroxy-3-methylbut-2-enyl]-1,4-diazabicyclo[4.3.0]nonane (40). To a solution of the syn isomer obtained above (0.320 g, 0.53 mmol, 1.0 equiv) in THF (5.0 mL) cooled to 0 °C was added a solution of potassium *tert*-butoxide (0.066 g, 0.59 mmol, 1.1 equiv) in THF (1 mL). After 5 min, a solution of *t*-BOC anhydride (0.129 g, 0.59 mmol, 1.1 equiv) in THF (1 mL) was added, the cooling bath was removed, and the mixture was allowed to warm to room temperature. A solution of *n*-$Bu_4NF{\cdot}3H_2O$ (0.2 M, 4 mL, 0.8 mmol, 1.6 equiv) in THF was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, extracted with EtOAc, and dried over anhydrous Na_2SO_4. Evaporation of the solvent yields **40**-syn as a colorless foam (0.30 g, 97%).

40-syn: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.50–2.30 (7 H, m), 1.58 (3 H, s), 1.68 (9 H, s), 2.25–2.45 (3 H, m), 3.59 (1 H, $^1/_2$ AB q, J = 14.5 Hz), 3.76 (3 H, s), 3.80–4.03 (3 H, m), 4.24–4.32 (1 H, m), 5.24 (1 H, $^1/_2$ AB q, J = 14.5 Hz), 5.30–5.40 (1 H, m), 6.74 (2 H, d, J = 8.7 Hz), 6.87 (2 H, d, J = 8.7 Hz), 7.20–7.40 (2 H, m), 7.42 (1 H, s), 7.61 (1 H, d, J = 7.1 Hz), 8.13 (1 H, d, J = 6.9 Hz); IR (KBr, disk) 3430, 1735, 1515, 1450, 1370, 1255, 1105, 1085 cm^{-1}; $[\alpha]^{25}_D$ = +39.7° (c = 1.62, $CHCl_3$).

(−)-3-(*R*)-[[*N*-(*tert*-Butyloxycarbonyl)-3-indolyl]methyl]-6-(*R*)-[(2*E*)-4-chloro-3-methylbut-2-enyl]-2,5-diketo-4-(4-methoxybenzyl)-1,4-diazabicyclo[4.3.0]nonane (41). The allylic alcohol **40**-syn (0.470 g) was converted into the corresponding allylic chloride as described above with LiCl (2.0 equiv), collidine (2.0 equiv), and mesyl chloride (2.0 equiv). The usual workup yielded the crude **41**-syn in quantitative yield (0.480 g, 100%) as a colorless glass.

41-syn: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.64 (3 H, s), 1.67 (9 H, s), 1.70–2.00 (5 H, m), 2.11–2.25 (1 H, m), 3.21–3.45 (3 H, m), 3.66 (1 H, $^1/_2$ AB q, J = 14.5 Hz), 3.76 (3 H, s), 3.80–3.90 (1 H, m), 3.96 (2 H, s), 4.21–4.29 (1 H, m), 5.24 (1 H, $^1/_2$ AB q, J = 14.5 Hz), 5.28–5.38 (1 H, m), 6.75 (2 H, d, J = 8.5 Hz), 6.91 (2 H, d, J = 8.5 Hz), 7.20–7.43 (3 H, m), 7.60 (1 H, d, J = 7.4 Hz), 8.12 (1 H, d, J = 7.9 Hz); IR (KBr, disk) 1735, 1660, 1515, 1455, 1370, 1255, 1170, 1085 cm^{-1}; $[\alpha]^{25}_D$ = +69.7° (c = 1.04, $CHCl_3$).

1-(*R*)-[(*N*-(*tert*-Butoxycarbonyl)-3-indolyl]methyl]-2,8-diketo-10-(*R*)-(1-methylethenyl)-9-(4-methoxybenzyl)-3,9-diazatricyclo-[5.2.2.0^{3,7}]undecane (42) and 1-(*R*)-[[*N*-(*tert*-Butoxycarbonyl)-3-indolyl]methyl]-2,8-diketo-10-(*S*)-1-(1-methylethenyl)-9-(4-methoxybenzyl)-3,9-diazatricyclo[5.2.2.0^{3,7}]undecane (43) from 41. To a solution of allylic chloride **41** (0.49 g, 0.80 mmol, 1.0 equiv) in dry DMF (8.0 mL) was added a 50% suspension of NaH in oil (0.230 g, 4.8 mmol, 6.0 equiv) and the resulting mixture was stirred under N_2 at room temperature for 15 h. The reaction mixture was poured on water, neutralized with an equimolar amount of dilute HCl, and extracted with ethyl acetate/hexanes. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure and the residue was separated on a silica gel column (EtOAc/hexane, 2:1) to furnish a mixture of **42** and **43** (0.051 g, 11.5%, 84:16 ratio), macrocyclic byproduct (see i, ref 23) (0.028 g, 7.5%), and the tricyclic materials corresponding to **42** and **43** (0.193 g, 51.5%, 56:44 ratio) that had lost the indole *N*-*t*-BOC protecting group (**42a** and **43a**). The fractions containing **42**, **43**, and the *N*-*t*-BOC-deprotected materials (**42a**/**43a**) were combined for the subsequent cyclization.

42: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.54 (3 H, s), 1.60 (9 H, s), 1.75–1.90 (2 H, m), 1.90–2.10 (2 H, m), 2.23 (1 H, dd, J = 13.5, 10.5 Hz), 2.81–2.98 (2 H, m), 3.27 (2 H, s), 3.52–3.60 (2 H, m), 3.70 (3 H, s), 4.00 (1 H, $^1/_2$ AB q, J = 16.0 Hz), 4.56 (1 H, s), 4.85 (1 H, s), 5.08 (1 H, $^1/_2$ AB q, J = 16.0 Hz), 6.60 (4 H, s), 7.15–7.30 (2 H, m), 7.39–7.46 (1 H, m), 7.52 (1 H, s), 7.90–7.98 (1 H, m).

43: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.61 (3 H, s), 1.67 (9 H, s), 1.76–1.96 (2 H, m), 2.03–2.12 (2 H, m), 2.26 (1 H, dd, J = 13.4, 10.4 Hz), 2.86–3.02 (2 H, m), 3.20 (1 H, $^1/_2$ AB q, J = 17.8 Hz), 3.37 (1 H, $^1/_2$ AB q, J = 17.8 Hz), 3.57–3.66 (2 H, m), 3.75 (3 H, s), 4.36 (1 H, $^1/_2$ AB q, J = 15.7 Hz), 4.61 (1 H, s), 4.63 (1 H, $^1/_2$ AB q, J = 15.7 Hz), 4.76 (1 H, s), 6.67 (2 H, d, J = 8.6 Hz), 7.22–7.36 (2 H, m), 7.45 (1 H, s), 7.52 (1 H, d, J = 7.7 Hz), 8.04 (1 H, d, J = 7.5 Hz).

42a: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.54 (3 H, s), 1.75–1.90 (2 H, m), 1.98–2.08 (2 H, m), 2.20 (1 H, dd, J = 13.5 Hz, J = 10.5 Hz), 2.38 (2 H, s), 2.81–2.92 (2 H, m), 3.55–3.60 (2 H, m), 3.71 (3 H, s), 4.13 (1 H, $^1/_2$ AB q, J = 15.8 Hz), 4.46 (1 H, s), 4.80 (1 H, s), 5.07 (1 H, $^1/_2$ AB q, J = 15.8 Hz), 6.62 (4 H, s), 7.06–7.12 (2 H, m), 7.18–7.30 (2 H, m), 7.45–7.51 (1 H, m), 7.76 (1 H, br s).

43a: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.55 (3 H, s), 1.74–1.96 (2 H, m), 2.01–2.09 (2 H, m), 2.13–2.24 (1 H, m), 2.80–2.92 (2 H, m), 3.27 (1 H, $^1/_2$ AB q, J = 16.7 Hz), 3.43 (1 H, $^1/_2$ AB q, J = 16.7 Hz), 3.54–3.63 (2 H, m), 3.74 (3 H, s), 4.26 (1 H, $^1/_2$ AB q, J = 15.4 Hz), 4.52 (1 H, s), 4.69 (1 H, $^1/_2$ AB q, J = 15.4 Hz), 4.72 (1 H, s), 6.67 (2 H, $^1/_2$ AB q, J = 8.4 Hz), 6.82 (2 H, $^1/_2$ AB q, J = 8.4 Hz), 7.05–7.35 (4 H, m), 7.56–7.60 (1 H, m), 7.96 (1 H, br s).

Cyclization of 41 in Benzene (Formation of 42 and 43). To a solution of allylic chloride **41** (0.24 g, 0.39 mmol, 1 equiv) in dry benzene (20 mL) was added a 50% suspension of NaH in oil (0.190 g, 3.96 mmol, 10 equiv) and the mixture was stirred at reflux temperature for 30 h. The reaction mixture was poured on an equimolar amount of dilute HCl(aq) and thoroughly extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was separated by radial silica gel chromatography (eluted with EtOAc/hexanes, 1:1) to afford **42** and **43** (0.184 g, 82%) as a 3:97 mixture.

Cyclization of 41 in THF in the Presence of 18-Crown-6 (Formation of 42 and 43). To a stirred suspension of NaH (10 mg, 0.41 mmol, 10 equiv, washed with pentane) in THF (2 mL) was added a solution of 18-crown-6 (55 mg, 0.21 mmol, 5 equiv) in THF (0.3 mL) at room temperature, followed by the addition of **41** (25 mg, 0.041 mmol, 1 equiv) in THF (0.4 mL). The mixture was stirred under N_2 at reflux temperature for 5 h, then cooled, and diluted with dry benzene (10 mL). The suspension was filtered through a thin layer of silica gel and concentrated under reduced pressure, and the residue was separated by PTLC on silica gel (EtOAc/hexanes, 2:1) to furnish a mixture of **42** and **43** (15 mg, 64%, 4.9:1 ratio).

Cyclization of 42/43 (Formation of 50/46). A solution of the mixture of **42** and **43** (~3:1 ratio) (17.5 mg, 0.03 mmol) in 1:1 dioxane/concentrated HCl (2.4 mL) was left under N_2 at 3 °C for 24 h and 16 °C for 24 h. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The oily residue was separated by PTLC on silica gel (CH_2Cl_2/acetone, 10:1) to afford **50** (9 mg, 62%) and **46** (3.5 mg, 24%). The average yield for this reaction using mixtures ranging from 3:1 to 4.9:1 of **42**:**43** was ca. 72%.

50: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.22 (3 H, s), 1.37 (3 H, s), 1.90–2.22 (5 H, m), 2.44 (1 H, dd, J = 9.8, 4.3 Hz), 2.89–3.01 (1 H, m), 3.26 (1 H, $^1/_2$ AB q, J = 18.4 Hz), 3.55–3.66 (4 H, m), 3.79 (3 H, s), 5.01 (1 H, $^1/_2$ AB q, J = 15.8 Hz), 6.81 (2 H, d, J = 8.7 Hz), 6.88 (2 H, d, J = 8.7 Hz), 7.10–7.25 (2 H, m), 7.38 (1 H, d, J = 7.8 Hz), 7.50 (1 H, d, J = 7.5 Hz), 7.92 (1 H, br s); IR (KBr, disk) 3330, 1675, 1510, 1385, 1240, 1170, 1020, 730 cm^{-1}; mass spectrum, m/e (rel intensity) 469 (M^+, 64.5), 454 (5.4), 362 (17.6), 348 (5.0), 306 (84.5), 208 (52.7), 121 (100); $[\alpha]^{25}_D$ = −7.8° (c = 1.1, $CHCl_3$); mp 251–252 °C (recrystallized from EtOAc); Anal. $C_{29}H_{31}N_3O_3$: C, H, N.

46: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.10 (3 H, s), 1.24 (3 H, s), 1.90–2.12 (4 H, m), 2.24 (1 H, dd, J = 13.3, 10.4 Hz), 2.46 (1 H, dd, J = 10.4, 4.0 Hz), 2.90–3.01 (1 H, m), 3.17 (1 H, $^1/_2$ AB q, J = 15.0 Hz), 3.34–3.45 (1 H, m), 3.51–3.62 (1 H, m), 3.73 (1 H, $^1/_2$ AB q, J = 15.0 Hz), 3.76 (3 H, s), 4.41 (1 H, $^1/_2$ AB q, J = 16.0 Hz), 5.03 (1 H, $^1/_2$ AB q, J = 16.0 Hz), 6.82 (2 H, d, J = 8.5 Hz), 7.04–7.28 (5 H, m), 7.49 (1 H, d, J = 7.4 Hz), 7.68 (1 H, br s); IR (KBr, disk) 3300, 1675, 1510, 1390, 1240, 1175, 1020, 740 cm^{-1}; mass spectrum, m/e (rel intensity) 469 (M^+, 19.1), 363 (4.3), 349 (2.9), 306 (17.9), 289 (11.6), 136 (87.6), 121 (66.9); $[\alpha]^{25}_D$ = −49.6° (c = 0.80, $CHCl_3$); mp 294–295 °C (recrystallized from EtOAc/benzene); Anal. $C_{29}H_{31}N_3O_3$: C, H, N.

By utilization of exactly the same procedure as above, **43** (as a 97:3 ratio with **42**) (184 mg, 0.32 mmol) was cyclized in dioxane (12 mL) with concentrated HCl (12 mL) to afford 80 mg (58%) of **46**; traces of **63** were not isolated.

Oxidation and Rearrangement of 50 to 3-Indoxyl Derivative 52. To a stirred solution of **50** (10 mg, 0.021 mmol, 1 equiv) in THF (1 mL) was added *m*-CPBA (4.8 mg, 0.028 mmol, 1.3 equiv) at room temperature. Formation of **51** was observed by TLC (CH_2Cl_2/methanol, 15:1). After 30 min, the mixture was quenched with a drop of Me_2S and concentrated under reduced pressure (by using cold water bath). The residue was dissolved in 1 M MeONa/MeOH (4.5 mL), refluxed for 40 min, and cooled to room temperature; 3 N HCl (3 mL) was added to the mixture. After most of the alcohol was removed under reduced pressure, the mixture was poured into water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. PTLC separation on silica gel (CH_2Cl_2/methanol, 20:1) furnished **52** (6.5 mg,

63%). (Compound **51** could be purified and isolated by PTLC silica gel prior to rearrangement.)

51: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.24 (3 H, s), 1.38 (3 H, s), 1.84 (1 H, d, J = 15.7 Hz), 1.89–2.20 (4 H, m), 2.84–2.97 (1 H, m), 3.41 (1 H, d, J = 16.1 Hz), 3.44–3.78 (5 H, m), 3.73 (3 H, s), 5.28 (1 H, d, J = 16.1 Hz), 6.73 (4 H, s), 7.18–7.28 (2 H, m), 7.32–7.41 (2 H, m), 7.52 (1 H, d, J = 7.5 Hz).

52: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.79 (3 H, s), 0.90 (3 H, s), 1.76 (1 H, dd, J = 7.8, 12.8 Hz), 1.85–2.07 (4 H, m), 2.29 (1 H, $^1/_2$ AB q, J = 16.3 Hz), 2.86–2.98 (1 H, m), 3.10 (1 H, $^1/_2$ AB q, J = 16.3 Hz), 3.23 (1 H, dd, J = 7.8, 10.5 Hz), 3.37–3.52 (2 H, m), 3.75 (3 H, s), 4.24 (1 H, $^1/_2$ AB q, J = 15.5 Hz), 4.69 (1 H, br s), 5.09 (1 H, $^1/_2$ AB q, J = 15.5 Hz), 6.72–6.85 (4 H, m), 7.05 (2 H, d, J = 8.6 Hz), 7.34–7.44 (1 H, m), 7.51 (1 H, d, J = 7.9 Hz); IR (KBr, disk) 3350, 1685, 1515, 1385, 1245, 1025, 745 cm^{-1}; UV, λ_{max}, nm (ϵ_{max}) (EtOH) 238 (13 500), 285 (1500), 405 (2900); $[\alpha]^{25}_D$ = −138.6° (c = 1.32, $CHCl_3$); mp (MeOH) 243–246 °C; X-ray analysis.

The same procedure as above was applied for the oxidation and rearrangement of **46** (10 mg, 0.02 mmol) to **48** (via stable intermediate **47**) using *m*-CPBA (4.8 mg) in THF (1 mL) to afford 6.5 mg (63%) of **48**. (Compound **47** could be purified and isolated prior to rearrangement.)

47: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.11 (3 H, s), 1.30 (3 H, s), 1.78–2.17 (5 H, m), 2.60 (1 H, $^1/_2$ AB q, J = 17.0 Hz), 2.78–2.92 (2 H, m), 3.03 (1 H, br s), 3.43–3.60 (2 H, m), 3.70 (1 H, dd, J = 10.3, 7.5 Hz), 3.76 (3 H, s), 4.78 (1 H, $^1/_2$ AB q, J = 16.6 Hz), 5.25 (1 H, $^1/_2$ AB q, J = 16.6 Hz), 6.84 (2 H, d, J = 8.6 Hz), 7.02 (2 H, d, J = 8.6 Hz), 7.10–7.18 (1 H, m), 7.25–7.35 (2 H, m), 7.41 (1 H, d, J = 7.4 Hz); IR (NaCl, neat) 3330, 1680, 1510, 1390, 1240, 1170, 1020 cm^{-1}.

48: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.85 (3 H, s), 0.87 (3 H, s), 1.73 (1 H, dd, J = 12.9, 7.7 Hz), 1.83–1.95 (1 H, m), 2.02–2.15 (3 H, m), 2.41 (1 H, $^1/_2$ AB q, J = 14.6 Hz), 2.63 (1 H, $^1/_2$ AB q, J = 14.6 Hz), 2.85–2.96 (1 H, m), 3.10 (1 H, dd, J = 7.8, 10.0 Hz), 3.45–3.65 (2 H, m), 3.72 (3 H, s), 4.29 (1 H, $^1/_2$ AB q, J = 16.0 Hz), 5.14 (1 H, $^1/_2$ AB q, J = 16.0 Hz), 5.31 (1 H, s), 6.68–6.80 (4 H, m), 6.96 (2 H, d, J = 8.6 Hz), 7.35–7.42 (1 H, m), 7.51 (1 H, d, J = 7.7 Hz); IR (KBr, disk) 3375, 1680, 1620, 1515, 1385, 1240, 1025, 760 cm^{-1}; UV, λ_{max}, nm (ϵ_{max}) (EtOH) 244 (13 600), 285 (1550), 408 (3540); $[\alpha]^{25}_D$ = +221° (c = 1.0, $CHCl_3$); X-ray analysis.

Synthetic (−)-Brevianamide B (2). To a stirred solution of **52** (2.6 mg, 0.0055 mmol, 1 equiv) in THF (3 mL) cooled to −78 °C was added under N_2 0.03 mL of *t*-BuLi (0.055 mmol, 10 equiv, 1.78 M solution in pentane). After 10 min of stirring at −78 °C, a stream of dry oxygen was passed through the bright purple solution for 15 min; 20 mg of solid NH_4Cl was added, followed by 10 mL of CH_2Cl_2 and a drop of water. The mixture was filtered, concentrated under reduced pressure, and separated by PTLC on silica gel (toluene/EtOAc/formic acid, 5:4:1) to furnish **2** (0.8 mg, 40%) as an amorphous yellow solid.

2: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.81 (3 H, s), 1.11 (3 H, s), 1.71 (1 H, $^1/_2$ AB q, J = 15.6 Hz), 1.70–2.11 (4 H, m), 2.65–2.78 (2 H, m), 3.23–3.33 (1 H, m), 3.24 (1 H, $^1/_2$ AB q, J = 15.6 Hz), 3.46 (2 H, tr, J = 6.7 Hz), 4.77 (1 H, br s), 5.99 (1 H, s), 6.70–6.85 (2 H, m), 7.35–7.45 (1 H, m), 7.53 (1 H, d, J = 7.8 Hz); IR (NaCl, neat) 3325, 2925, 1690, 1615, 1470, 1320, 1020, 815 cm^{-1}; UV (MeOH) λ_{max}, nm 400, 256, 230, 198; $[\alpha]^{25}_D$ = −124° (c = 0.81, 2.5% HCOOH in CH_2Cl_2); exact mass calcd for $C_{21}H_{23}N_3O_3$ 365.17409, found 365.1745. This substance was found to be identical in every respect with semisynthetic **2** derived from **1** and enantiomorphic to natural **2**.

Essentially the same procedure was applied for removing the pMB group from **48**. (Formation of **49**.) From 6.4 mg (0.013 mmol) of **48**, 6 equiv of *t*-BuLi in THF (0.3 mL), and MoOPH as the oxidant (17.4 mg, 0.04 mmol) was obtained 1.6 mg (33%) of **49** (isolated by silica gel PTLC, CH_2Cl_2/acetone, 7:1).

49: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 0.84 (3 H, s), 0.90 (3 H, s), 1.68–2.20 (5 H, m), 2.14 (1 H, $^1/_2$ AB q, J = 14.1 Hz), 2.72–2.85 (1 H, m), 2.89 (1 H, $^1/_2$ AB q, J = 14.1 Hz), 3.13 (1 H, dd, J = 8.0, 10.2 Hz), 3.45–3.65 (2 H, m), 6.39 (1 H, br s), 6.71–6.83 (2 H, m), 7.38–7.43 (1 H, m), 7.51 (1 H, d, J = 7.7 Hz), 8.46 (1 H, br s); IR (NaCl, neat) 3300, 2925, 1685, 1615, 1475, 1330 cm^{-1}; UV (MeOH) λ_{max}, nm 404, 253, 232, 201.

***p*-Methoxybenzyl Group Removal from 50 (Formation of 9).** To a stirred solution of **50** (2 mg, 0.004 mmol, 1 equiv) in 1 mL of THF cooled to −78 °C was added 0.027 mL of *n*-BuLi (0.04 mmol, 10 equiv, 1.59 M solution in hexane) under N_2. After 10 min of stirring, 19 mg of MoOPH (0.04 mmol, 10 equiv) was added to the bright yellow solution. The mixture was stirred at −78 °C for 5 min, and the cooling bath was removed. Two drops of Me_2S were added, followed by solid NH_4Cl (10 mg), CH_2Cl_2 (5 mL), and one drop of water. The mixture was passed through a thin layer of silica gel, concentrated under reduced pressure, and separated by PTLC on silica (CH_2Cl_2/acetone, 10:1) furnishing 0.52 mg of **9** (35%).

9: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.23 (3 H, s), 1.28 (3 H, s), 1.80–1.92 (1 H, m), 2.0–2.15 (3 H, m), 2.33–2.39 (1 H, m), 2.75–2.87 (2 H, m), 2.83 (1 H, $^1/_2$ AB q, J = 18.0 Hz), 3.54 (2 H, tr, J = 6.8 Hz), 3.92 (1 H, $^1/_2$ AB q, J = 18 Hz), 5.74 (1 H, br s), 7.08–7.19 (2 H, m), 7.31 (1 H, d, J = 7.7 Hz), 7.51 (1 H, d, J = 7.7 Hz), 7.82 (1 H, br s); IR (NaCl, neat) 3305, 2925, 1675, 1450, 1410, 1260 cm^{-1}; exact mass calcd for $C_{21}H_{23}N_3O_2$ 349.17919, found 349.1795.

The same procedure as above was applied for removal of the *p*-methoxybenzyl group from **46**. (Formation of C-10-epi-**9**.)

From 1 mg (0.002 mmol) of **59**, 10 equiv of *n*-BuLi in THF (1 mL), and 9.1 mg of MoOPH (0.02 mmol) was obtained 0.2 mg (30%) of C-10-epi-**9** (isolated by PTLC silica gel, CH_2Cl_2/acetone, 10:1).

C-10-epi-9: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS 1.11 (3 H, s), 1.30 (3 H, s), 1.79–2.11 (4 H, m), 2.14–2.26 (1 H, m), 2.55–2.66 (1 H, m), 2.63 (1 H, $^1/_2$ AB q, J = 15.3 Hz), 2.76–2.83 (1 H, m), 3.32–3.43 (1 H, m), 3.46–3.60 (1 H, m), 3.87 (1 H, $^1/_2$ AB q, J = 15.3 Hz), 6.08 (1 H, br s), 7.06–7.17 (2 H, m), 7.50 (1 H, d, J = 7.6 Hz), 7.76 (1 H, br s), 8.49 (1 H, d, J = 8.6 Hz); IR (NaCl, neat) 3325, 2920, 1690, 1455, 1395, 1260, 1020 cm^{-1}.

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Supplementary Material Available: Experimental details for the preparation of racemic **32** from D,L-homoserine, and structures and tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atom positions for four crystal structures (**52**, **48**, **13a**, and **17**) (61 pages); tables of observed and calculated structure factors (66 pages). Ordering information is given on any current masthead page.