The Total Synthesis of Indolizomycin†

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Abstract: The first total synthesis of racemic indolizomycin (**1**) has been achieved. Initial investigations provided the functionalized indolizidine, **31**, via (i) stereospecific intramolecular vinylsilane/carbinol amide cyclization (**15** → **16**), (ii) rhodium(II) acetate mediated diazoacetate insertion into thioamide **17**, and (iii) epoxide introduction (**25** → **27** → **29**). Although subsequent attempts to fully elaborate **31** into indolizomycin were unsuccessful, these experiments formed the basis of a revised route which did ultimately produce the natural product. Thus, aza-Robinson annulation of diazo ketone **36** afforded dihydropyridone **38**, which underwent vinylogous McCluskey fragmentation to provide azininone **40**. The use of the [2-(trimethylsilyl)ethoxy]carbonyl (TEOC) protecting group (cf. **40e**) was crucial for successful completion of the synthesis. Elaboration of the trienyl side chain was accomplished through $^1O_2$ ene reaction of methyl enol ether **49** followed by Julia olefination of enal **51** with lithio sulfone **52**. Fluoride deprotection of TEOC-amino ketone **57** followed by in situ transannular cyclization gave the highly unstable (±)-indolizomycin.

Background of the Problem

The isolation of medicinally useful antibiotics from the fermentation of various microorganisms has had a major beneficial effect in human health maintenance. The possibility of exploiting the biosynthesizing machinery of mutant microorganisms to provide access to otherwise unavailable natural products, including antibiotics, has been well recognized. Hitherto, mutations have been promoted by thermal means or through the exposure of wild type species to genetically modifying radiation.

A novel strategy for generating mutant precursors of new natural products is implicit in a disclosure by Umezawa and co-workers.[1,2] In this work, two inactive (i.e., non-antibiotic-producing) *Streptomyces* strains, *Streptomyces tenjimariensis* NM16 and *Streptomyces grisline* NP1-1, were co-joined by protoplast fusion. There were thus elaborated various clones, including a particularly active strain (termed SK2-52). It was in this fashion that the bioengineered antibiotic indolizomycin (**1**) was obtained.

It should be recognized that an experiment of this sort does not reveal the genetic origin of **1**. It would be tempting to propose that the biosynthesis of indolizomycin is a consequence of one or more enzymes which have arisen from recombinant genes. Alternatively, the genes in question may have been present in NM16 or NP1-1, and the fusion process may have endowed SK2-52 with the means to express such "silent" genes.

Interesting as the lineage of indolizomycin is, it was primarily its structure which engaged our curiosity and our attentions.[2] The presence of the hemiaminal linkage, wherein the bridgehead hydroxyl group is flanked by fused oxiranyl and cyclopropyl functions, is striking. A successful plan for the total synthesis of indolizomycin must include provision for the elaboration and maintenance of these functions in addition to the triene array. Hopefully the various chirality elements would be introduced with strong margins of stereoselectivity.

There was little in the way of recorded chemistry pertinent to indolizomycin. Therefore, no information which might provide insights as to issues of functional group compatibility with proposed steps was available. The structure of **1** was inferred from a crystallographic determination of **3**. This compound was available from **1** by reduction (sodium borohydride) of the hemiaminal linkage and subsequent reaction of **2** with hydrochloric acid. The possibility that **1**, already bearing the labile triene, could be reconstructed from these transformation products seemed hardly promising.

Adding to the complications awaiting a total synthesis program directed at indolizomycin was the unavailability of the target system itself. Apparently, the compact accommodation of the potentially interactive array of functionalities of **1** leads to very serious instability.[2] Indolizomycin was reported to undergo rapid decomposition after a few hours under neutral conditions at room temperature. Though the progression of reactions which results in this decomposition has not been elucidated, the prospects of obtaining an authentic reference sample from Japan were remote. Only spectral comparisons would be possible.

The antibacterial properties of indolizomycin were hardly sufficient to compel us to undertake its total synthesis.[2] Rather, we were engrossed by the inherent challenge in synthesizing a structure of this degree of complexity and lability without the benefit of any prior leads to its chemical personality. (The closest naturally occurring product was cyclizidine (**4**)).[3] It was anticipated that the difficulty of the indolizomycin problem would serve as a favorable context to stimulate chemically interesting solutions. Hopefully, new insights could be garnered as these proposed solutions were evaluated experimentally. Here we provide an account of the reasoning and experimentation which did indeed lead to the total synthesis of (±)-indolizomycin (**1**).[4a,b]

Synthetic Strategy

A concern in any proposed total synthesis of indolizomycin was its instability. Obviously, it would be well to delay installation of the most labile linkages for as long as possible. Since the desoxy derivatives **2** and **3** were not reported to be unmanageable, we surmised that it was the confluence of the carbinol amine linkage with the remaining functionality which was responsible for the extreme vulnerability of **1**. Accordingly, unveiling of carbinol amine was to be delayed as late as possible, ideally to the very last step of the effort. Two general approaches were entertained (Scheme I). The first plan (plan A) contemplated a very late stage oxidation of C_{8a} of a suitably fashioned indolizidine **9**. An alternative program (plan B) envisioned cyclization of an azoninone structure of the type **11**. By this view the last step of the synthesis would be the deprotection of the unspecified nitrogen

† We dedicate this paper to the accomplishments of Professor Y. Kishi in the mitomycin field.

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§ Yale University Center for Chemical Instrumentation.

(1) Yamashita, F.; Hotta, K.; Kurasawa, S.; Okami, Y.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 58.

(2) Gomi, S.; Ikeda, D.; Nakamura, H.; Naganawa, H.; Yamashita, F.; Hotta, K.; Kondo, S.; Okami, Y.; Umezawa, H.; Iitaka, Y. *J. Antibiot.* **1984**, *37*, 1491.

(3) Freer, A. A.; Gardner, D.; Greatbanks, D.; Poyser, J. P.; Sims, G. A. *J. Chem. Soc., Chem. Commun.* **1982**, 1160.

(4) (a) Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 2003. (b) Kim, G. Ph.D. Dissertation, Yale University, New Haven, CT, 1989.

(5) For a demonstration of this concept in the course of the total synthesis of mitomycin B, see: Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549.

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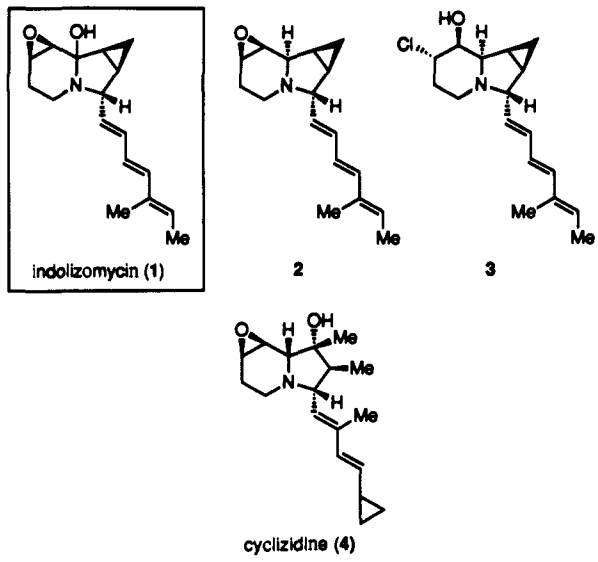
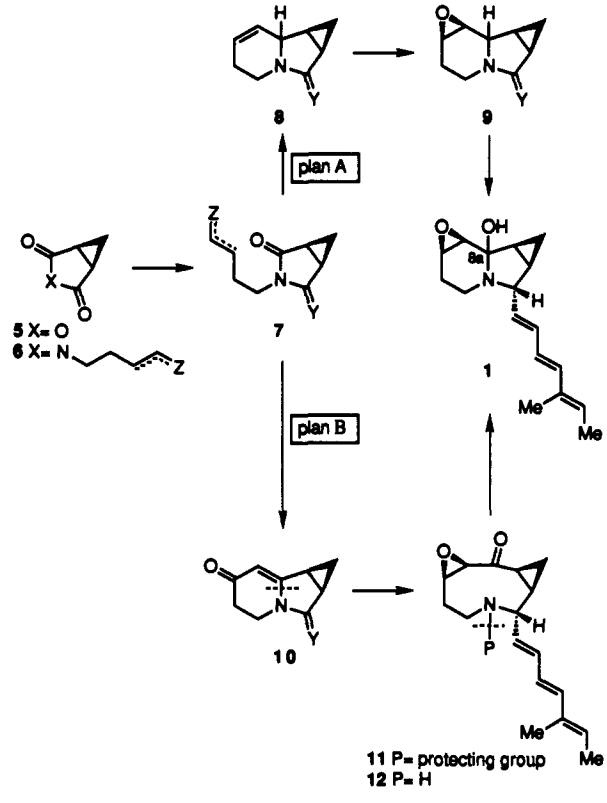


Figure 1.

Scheme I

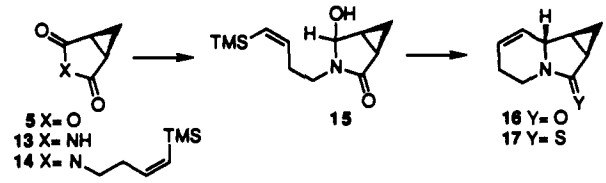


blocking group, thereby generating amino ketone **12** which would undergo cyclization to **1**.

Of course by either scheme a new chiral center bearing the carbinol amine hydroxyl function at C_{8a} would be elaborated. It was hoped that this cyclization would in fact lead to the natural (if unknown) stereochemistry at that center. This hope arose from the supposition that the natural product is configured at C_{8a} in its most stable form and that the fully synthetic product arising from **9** or **12** would emerge as the most stable "anomer". We note in passing that a recent teaching from our own laboratory in the mitomycin field[6] raises uncertainties as to whether such carbinol amine centers in natural products are necessarily the consequence of thermodynamic control. However, in the case at hand we had

(6) (a) Feigelson, G. B.; Danishefsky, S. J. *J. Org. Chem.* **1988**, *53*, 3391. (b) Feigelson, G. B. Ph.D. Dissertation, Yale University, New Haven, CT, 1988.

Scheme II



no real alternative but to proceed on the basis of such an assumption.

An interesting possibility for constructing the azininone required in plan B involved fragmentation of a suitably functionalized indolizidine (cf. **10**). While the chemistry required for this plan (vide infra) was not really developed, it seemed that such an approach would allow us to take advantage of somewhat simpler chemistry in the construction of an indolizidine skeleton while relying on fragmentation to control the oxidation states (particularly C_{8a}) and stereochemistry of the azoninone.

It was further conjectured that the conjugated triene is a contributory factor in the instability of the target system. Accordingly, in the synthetic direction, this functional group would be installed at a very late stage, possibly via Julia coupling.

Since each of the emerging plans was rather vague, it would be particularly useful to have access to readily available intermediates in which the required new chemistry could be developed. It was presumed that anhydride **5**, a well-known compound,[7] could be converted to corresponding N-substituted imides of the type **6**. The nature of the substituents on the nitrogen would hopefully be varied over a wide range. By judicious selection of this imido side chain, one could introduce an arrangement which would lend itself to cyclization to cyclopropylindolizidines of the type **8** or **10** which might be of use in plans A and B, respectively. It was from this rather imprecise planning level that our experiments commenced.

We begin by describing some of our efforts which were directed at implementing plan A. Although, as will be shown, the attempts were not successful, much was learned during this phase. These lessons proved to be very useful in the subsequent investigations (vide infra).

Implementation of Plan A. The program started (Scheme II) with known imide **13**,[8] which served as the nucleophile in a Mitsunobu reaction[9] with (*Z*)-4-(trimethylsilyl)-3-butenol.[10] Coupling occurred uneventfully to give a 77% yield of **14**. The imide linkage was reduced with sodium borohydride in methanol at 0 °C to provide a 12:1 diastereomeric mixture of carbinol amides **15**. The latter was cyclized through the action of trifluoroacetic acid[10] to afford the tricyclic system **16** in 99% yield. Although the substrates for the cyclization were entered as a mixture, the product, **17**, is apparently a single diastereomer. Indeed, the two stereoisomers of **15** could be separated, and each component suffered cyclization to give **16**. On the basis of previous precedents[10,11] it seems reasonable to suppose that the cyclization occurs via an acyliminium species, whose β-face is blocked by the cyclopropane ring. Therefore, cyclization from the α-face would produce the C_{8a}-β proton as shown in **16**.

We next addressed the introduction of the elements necessary for future triene elaboration at position C_3. A variety of attempts to add Grignard reagents to compound **16** were of no avail. In order to activate the carbonyl group at C_3, we turned to the possibility of conversion of the lactam to a thiolactam. This was smoothly accomplished by use of Lawesson's reagent,[12] whereupon the thiolactam was obtained in 85% yield. Indeed the stereo-

(7) (a) McCoy, L. L. *J. Am. Chem. Soc.* **1958**, *80*, 6568. (b) Majchrzak, M. W.; Kotelko, A. *Synthesis* **1983**, 469.

(8) Crockett, G. C.; Swanson, B. J.; Anderson, D. R.; Koch, T. H. *Synth. Commun.* **1981**, *11*, 447.

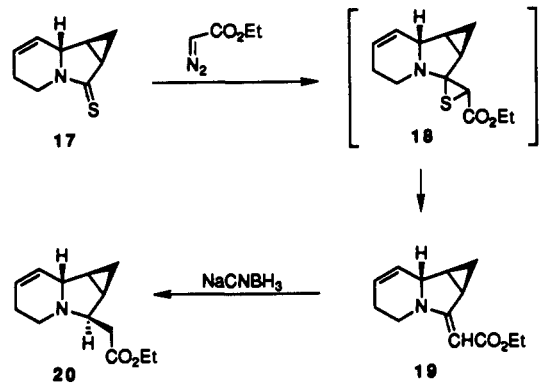
(9) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

(10) Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993.

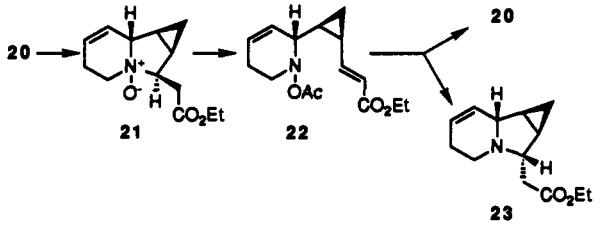
(11) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(12) Pederson, B. S.; Sheibye, S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

Scheme III



Scheme IV



chemistry of the acyliminium cyclization step was subsequently established by a single-crystal determination of **17**, which clearly showed that the C_{8a} hydrogen was cis to the fused cyclopropane. Early attempts to add a variety of Grignard reagents to **17** were also unsuccessful, as were attempts at reduction of either **16** or **17**.

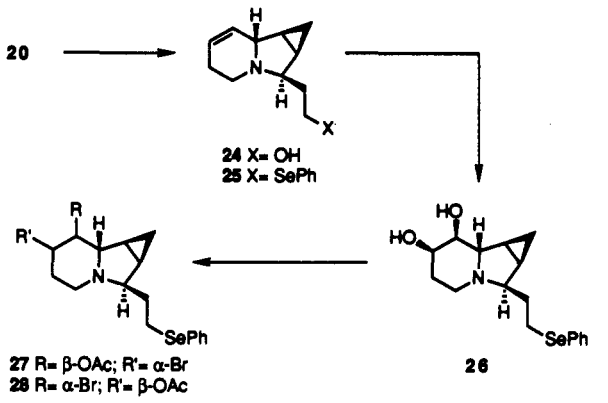
It was at this stage that we investigated the possibility of coupling of the thiolactam function of **17** with ethyl diazoacetate (Scheme III).[13] In the event, rhodium acetate ($Rh_2(OAc)_4$) mediated condensation produced the vinylogous urethane **19** in 49% yield. Our hypothesis was that the intermediate in this reaction was the thiirane **18** which suffered reductive elimination presumably by the reaction of additional diazo ester. This method of direct condensation of a diazo ester with a thioamide bears a mechanistic similarity to the sulfide contraction method of Eschenmoser and co-workers[14] for reaching the same type of functional group. The sulfide contraction reaction method was not successful in the case at hand, possibly due to steric hindrance from the fused cyclopropane.

Reduction of the vinylogous urethane with sodium cyanoborohydride in methanol at pH 4 indeed afforded a dihydro product. It seemed probable that in this compound the carbethoxymethyl group at C_3 would have the β-configuration and that epimerization at C_3 would be necessary for the synthesis of indolizomycin. Thus it was assumed that the "hydride equivalent" would have reduced the iminium species arising from **19**, from its less hindered α-face, to provide amino ester **20**.

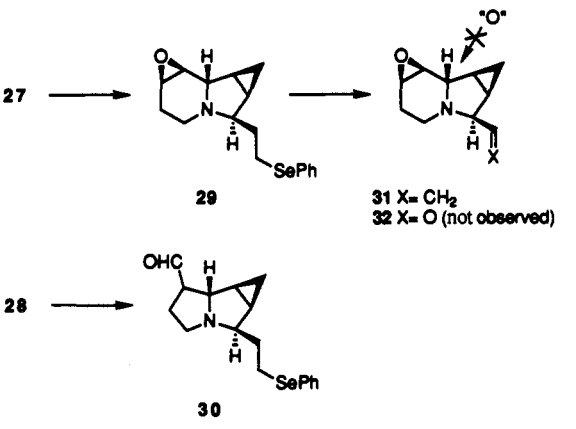
Although the stereochemistry at C_3 was almost certainly opposite to that needed for our purposes, we hoped to gain insight into the synthetic potentialities of plan A by examining the chemistry of compound **20**. We first wondered about the possibility of direct epoxidation of **20** through the action of MCPBA (Scheme IV). In the event, reaction of **20** with this oxidizing agent did lead to the incorporation of one oxygen. However, examination of the spectrum of the product showed it to be *N*-oxide **21** rather than the olefin epoxidation product.

With compound **21** in hand, we investigated the possibility of a Polonovski-like transformation[15] which would be required in the

Scheme V



Scheme VI



very late stage of a plan A based synthesis (see the transformation of compound **9** → **1** in Scheme I). In the event, reaction of **21** with acetic anhydride gave not the desired oxidation product, but a fragmentation product shown by spectral analysis to be compound **22**. The failure of **21** to undergo the desired Polonovski reaction with incorporation of angular acetate (or hydroxyl) was not, per se, alarming since it was rationalized that the activation provided by the ester function enhanced the possibilities for an acylative Cope-like elimination.[16] No such activation would be present when the Polonovski reaction would be necessary in the late stage of a plan A program.

The chemistry of compound **22** was briefly explored. Treatment of this substance with zinc in acetic acid gave rise to a 3:1 mixture of the previously encountered **20** and a new stereoisomer, formulated as **23**. Thus intramolecular Michael addition had produced some of the desired stereoisomer at C_3, albeit only as the minor product. The decisive spectral measurement which defined the stereochemistry of **20** and **23** was that of the C_2–C_3 proton/proton coupling constant. In the case of compound **20** there was a 4.5 Hz coupling constant for the protons noted. On the other hand, in the desired series (cf. **23**), no coupling between those protons could be discerned.

Although small amounts of **23** were in hand, we continued our studies with the more available **20** hoping to transfer useful results to the desired series (Scheme V). Reduction of **20** with lithium aluminum hydride indeed afforded the alcohol **24**, which could be converted into the phenylseleno derivative **25** by standard means.[17] With the ene selenide in hand, we investigated functionalization reactions of the isolated double bond. Treatment of **25** with osmium tetraoxide produced, though only in 27% yield, a single diol which we formulated as containing the β-orientation of the hydroxyl groups at C_7 and C_8. We proceeded to investigate the possibility of fashioning the C_7–C_8 β-epoxide from diol **26**.

(13) For a similar treatment of thiolactones, see: Takano, S.; Tomita, S.; Takahashi, M.; Ogasawara, K. *Synthesis* **1987**, 1116.

(14) (a) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710. (b) Eschenmoser, A. *Q. Rev.* **1970**, *24*, 366.

(15) (a) Polonovski, M.; Polonovski, M. *Bull. Soc. Chim. Fr.* **1927**, *41*, 1190. (b) Grierson, D. *Org. React.* **1990**, *39*, 85.

(16) Cope, A. C.; Trumbull, E. R. *Org. React.* **1960**, *11*, 317.

(17) See, for example: Nakatsuka, S.-i.; Masuda, T.; Goto, T. *Tetrahedron Lett.* **1987**, *28*, 3671.

Toward this end, **26** was subjected to a Moffat-type transformation[18] with 2-acetoxyisobutyryl bromide to produce a mixture of regioisomers in 59% yield (3:2 ratio). Substantial purification of this mixture by silica gel chromatography afforded two vicinal acetoxy bromides.

The major product, formulated as **27** upon treatment with Amberlite IRA-400, provided the desired epoxide **29** in 92% yield (Scheme VI). Although this closure reaction had gone gratifyingly well, the overall yield of epoxide **29** from diol **26** was only 30%. The minor acetoxy bromide, formulated as compound **28**, upon similar treatment gave rise to a crude product which was not properly purified. It was presumed to correspond to structure **30** on the basis of an aldehyde resonance in its ^{1}H NMR spectrum.

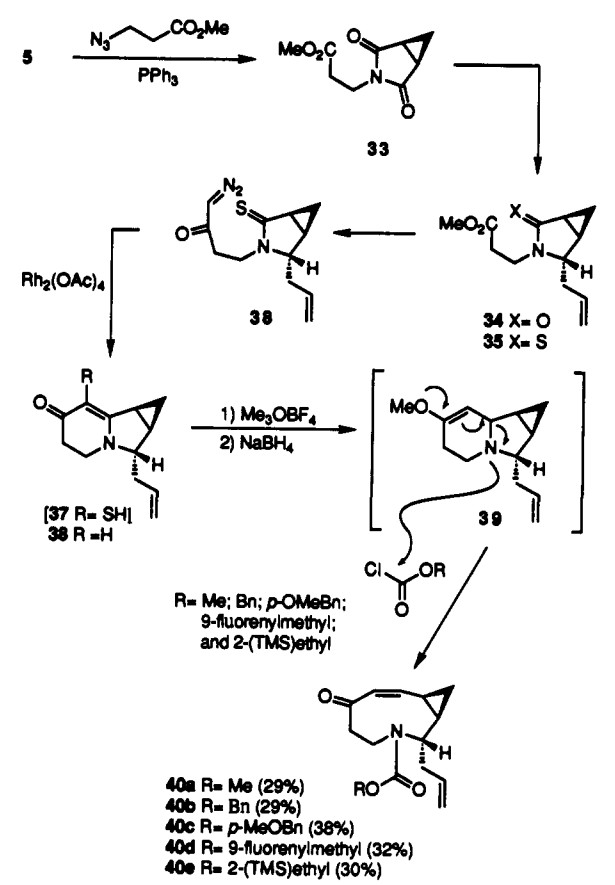
Although epoxide **29** had been obtained in a rather unsatisfactory yield from olefin **20**, it does contain several crucial elements for the implementation of plan A. Toward this end, our next goal became the correction of the stereochemistry at C_3 and the provision for installation of its triene side chain. In the event, the seleno function of **29** was oxidized by MCPBA and the resulting selenoxide thermally eliminated to afford the amino epoxide **31** bearing the vinyl side chain. At this point it was our intention to convert the vinyl group to an aldehyde for the purpose of exploring the controlled epimerization at C_3 and for installation of this triene. Unfortunately, all attempts to cleave the double bond of vinyl compound **31** by ozonolysis or by osmylation followed by periodate fragmentation did not afford any of the desired aldehyde **32**. The failure of this reaction in conjunction with the failure of the Polonovski sequence (as well as other attempts at direct oxidation of C_{8a} in several other intermediates) led us to set aside plan A in favor of plan B.

Implementation of Plan B. Two insights gathered from the research described above guided our thinking as to the implementation of plan B. First, the stereochemistry at C_3 should be installed by direct carbon addition to the N–C_3 acyliminium species. Reduction of an iminium species already containing the elements of the future triene side chain would be likely to produce the undesired β-stereochemistry at C_3. Apparently the prospects of inverting the stereochemistry at C_3 via a pendent aldehyde were none too promising. The second teaching centered around use of the diazo carbonyl thioamide condensation to create a vinylogous amide-like structure. In the work shown above, this reaction had been carried out in an intermolecular fashion using a diazo ester to produce a urethane. The possibility of the intramolecular counterpart of this reaction suggested itself. For optimal application to our synthesis, the intramolecular version would be conducted on a diazo ketone, and the product would be a vinylogous amide.

The program started on a very favorable note with the reaction of anhydride **5** with methyl 3-azidopropionate and triphenylphosphine to give rise to the imide **33** (Scheme VII).[19] Reduction[20,21] of **33** with sodium borohydride followed by reaction of the resultant carbinol amide with acidic methanol[21] provided the methoxyaminal, which upon treatment with allyltrimethylsilane and titanium tetrachloride[22,23] produced a single allyl lactam **34**. Treatment of **34** with Lawesson's reagent[12] produced the allyl thiolactam **35** in 85% overall yield from **33**.

We now prepared to test the feasibility of the intramolecular diazo ketone thiolactam coupling which would amount to an aza-Robinson annulation.[24,25] The desired diazo ketone was

Scheme VII



obtained through alkaline hydrolysis of ester **35** followed by treatment of the resultant acid with isobutyl chloroformate in the presence of *N*-methylmorpholine. The mixed anhydride thus produced was reacted with diazomethane[26] to give rise to the desired diazo ketone **36** (77% overall yield) from **35**.

Treatment of **36** with rhodium acetate in benzene led to consumption of starting material, with formation of a new, somewhat unstable product, presumably **37**. As discussed above, it was assumed that in the intermolecular reaction (see **17** → **19**) the intermediate thiirane **18** is cleaved by excess diazo ester. In the intramolecular version studied here, there is no counterpart of excess diazo carbonyl compound to effect reductive desulfurization. Thus, under the assumption that the intermediate is properly formulated as **37**, it was treated with W-2 Raney nickel in acetone,[27] whereupon the desired vinylogous amide **38** was obtained in 66% overall yield from diazo ketone **36**. This two-step version of the aza-Robinson annulation has subsequently been generalized and applied to other objectives in our laboratory.[28]

Having learned how to assemble the indolizine ring system, we now found it necessary to disassemble the structure. The immediate goal systems were represented as the azoninone series **40** differing in the nature of the urethane protecting groups. The plan which evolved is shown in the progression **38** → **39** → **40**. It was hoped that the oxygen function of the vinylogous lactam system could be alkylated with trimethyloxonium tetrafluoroborate.[29] The iminium species would be reduced with a metal

(18) (a) Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4016. (b) Russel, A. F.; Gronberg, S.; Moffat, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4025. (c) Robins, M. J.; Hansske, F.; Low, N. H.; Park, J. I. *Tetrahedron Lett.* **1984**, *25*, 367.

(19) Garcia, J.; Vilarrsa, J.; Bordas, X.; Banaszek, A. *Tetrahedron Lett.* **1986**, *27*, 639.

(20) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653.

(21) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(22) Kraus, G. A.; Neuenschwander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134.

(23) Shono, T.; Matsumura, T.; Uchida, K.; Kobayashi, H. *J. Org. Chem.* **1985**, *50*, 3243.

(24) Fang, F. G.; Prato, M.; Kim, G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 3625.

(25) For an alternate aza-Robinson cyclization strategy using thiolactams, see: Heathcock, C. H.; Davidsen, S. K.; Mills, S. G.; Sanner, M. A. *J. Org. Chem.* **1992**, *57*, 2531.

(26) (a) Leary, R.; Larsen, D.; Watanabe, H.; Shaw, E. *Biochemistry* **1977**, *16*, 5857. (b) For the preparation of diazomethane, see: Arndt, F. *Organic Syntheses*, Wiley: New York, 1943; Collect. Vol. II, p 165.

(27) Petit, G. R.; van Tamelen, E. E. *Org. React.* **1962**, *12*, 356.

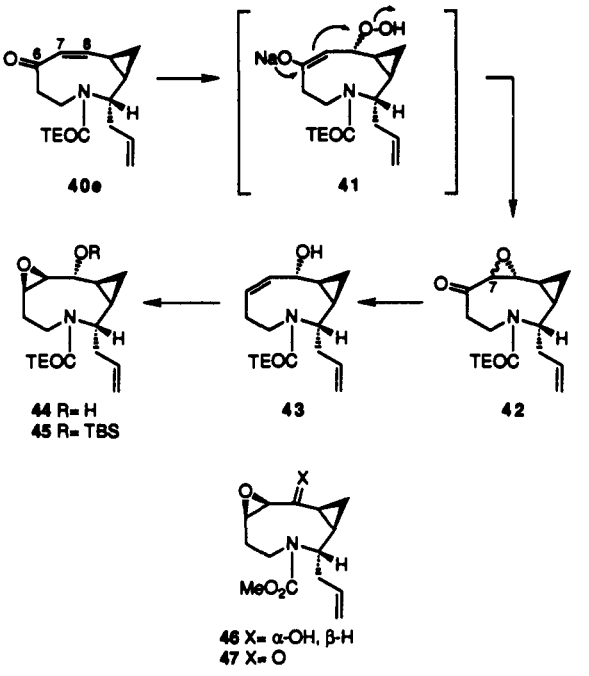
(28) (a) Fang, F. G.; Feigelson, G. B.; Danishefsky, S. J. *Tetrahedron Lett* **1989**, *30*, 2743. (b) Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 2747.

hydride so as to produce an intermediate enol ether of the type **39**.[30] It was further hoped that such a compound would undergo N-alkoxycarboxylation with a suitable chloroformate and that the product of this acylation would suffer fragmentation as shown (see arrows of **39** → **40**). The case where this process was first studied involved cleavage of the enol ether with methyl chloroformate. In practice a 29% yield of the enone carbamate **40a** was obtained. It will be recognized that this transformation constitutes, in overall terms, a special case of nitrogen dealkylation and is mechanistically related to the McCluskey degradation,[31] which accomplishes related amine dealkylations though in much simpler settings. It soon became clear that compound **40a** would not be a suitable intermediate for our synthesis since attempted cleavage of the methyl carbamate protecting group at various stages of the synthesis was uniformly unsuccessful, undoubtedly due to the harsh conditions required in this unveiling. From this case we did learn, however, that the extended McCluskey cleavage process was feasible for azoninone ring formation. Elsewhere[4b] we have related in detail the various travails associated with changing the blocking group of the urethane linkage to allow for exposure of the amine in a fashion which was more compatible with the existing functionality. Here we briefly summarize the results which led to the use of 2-(trimethylsilyl)ethyl chloroformate en route to **40e**.

Our first attempt in this connection utilized benzyl chloroformate as the alkylating agent. Indeed, a 29% yield of compound **40b** was obtained; however, in an attempt to cleave the Cbz function under hydrogenolytic conditions, a compound was produced containing a saturated C_3 side chain. This method of unveiling was, therefore, incompatible with survival of the trienyl linkage (vide infra). In the hope of generating a urethane which would be labile under nonhydrogenolytic conditions, we turned to the use of *p*-methoxybenzyl chlorformate in the cleavage reaction. Once again the process was successful, now leading to compound **40c** in 38% yield. Of all the cases, this one was the most extensively studied. As is reported elsewhere,[4b] contrary to expectation, the *p*-methoxybenzyl group could not be cleaved at a critical stage in the synthesis (i.e., at the *p*-methoxybenzyl urethane version of compound **48**) without incurring various undesired side reactions. Recourse to the FMOC urethane **40d** obtained in 32% yield from the same cleavage reaction was similarly unsuccessful. The FMOC group proved to be unwieldy and too labile for the transformations required (vide infra) to convert the allyl side chain at C_3 to the triene (vide infra). However, compound **40d** was useful in that it lent itself to a single-crystal X-ray determination which confirmed its structure, including the presence of the cis double bond and the trans relationship of the cyclopropane and allyl functions. The final series of experiments led to the TEOC urethane **40e** (in 30% yield). As events unfolded, this group had the right combination of overall stability and "tunable lability" to service the rest of the synthesis.

While the dealkylative fragmentation had provided a row of unsaturation at C_6, C_7, and C_8, it was now necessary to adjust the specific oxidation levels of these centers. Although the chemistry to be described was first developed with other urethanes corresponding to **40**, we focus on **40e** (Scheme VIII). The first step involved the addition of alkaline hydrogen peroxide to the enone system.[32] In the event, a mixture of epoxy ketones was obtained in 97% yield. It was surmised that both components of the mixture (*cis*-**42** + *trans*-**42**) arose from attack of hydroperoxide anion from the α-face at C_8 but that internal bond rotation followed by enolate trapping provided epoxides which were epimeric at C_7. That this interpretation is correct was clearly demonstrated by the subsequent Wharton fragmentation,[33] wherein each component of the diastereomeric mixture of **42** was converted to the same allylic alcohol **43** (overall yield 52%). Had the precursor epoxy ketones differed in configuration at C_8 such an outcome would, of course, not have been possible.

Scheme VIII



We were now in a position to exploit the very interesting finding of Itoh,[34] who demonstrated that in MCPBA-directed epoxidation of medium-ring allylic alcohols the epoxidation occurs anti to the alcohol function.[35] Applying this reaction to the case of **43**, it was found that a single epoxy alcohol **44** was obtained in 84% yield. The resultant C_8 alcohol was protected as its TBS ether pending proper elaboration of the triene side chain.

That the cyclopropane and epoxide functions were in fact cis to one another in this compound was strongly supported by crystallographic determination on compound **47**. This compound had been obtained by Swern oxidation[36] of alcohol **46**, which is identical in all respects to **44** except that the protecting group on nitrogen is a methoxycarbonyl rather than a TEOC. The synthesis of **46** was accomplished in the same manner as shown here for **44**. In fact those experiments provided the protocols to reach **44**.

With the stereochemical assignment of **44** secure, we now turned to installation of the triene side chain. We set as an intermediate goal the enal **51**. On the basis of our findings in the earlier work under plan A, wherein the α-amino aldehyde **32** was not accessible, the prospects for reaching **51** via a similar aldehyde were regarded as bleak. Fortunately, an interesting scheme presented itself when the aldehyde **48** proved to be quite accessible via ozonolysis of **45** (Scheme IX). In generic terms, the problem we now confronted was that of transforming a monosubstituted acetaldehyde (RCH_2CHO) to a monosubstituted acrolein ($RCH{=}CHCHO$). Thus, reaction of **48** with (methoxymethylene)triphenylphosphorane afforded an 80% yield of a 3:2 mixture of enol ethers **49**. Photooxygenation according to Conia[37] provided the uncharacterized allyl methoxy hydroperoxide **50**. Reduction of the latter with triphenylphosphine afforded the enal **51** (69% yield), which is a reasonably stable compound. Reaction of enal **51** with the lithio sulfone **52** gave rise to an adduct which, upon acetylation,

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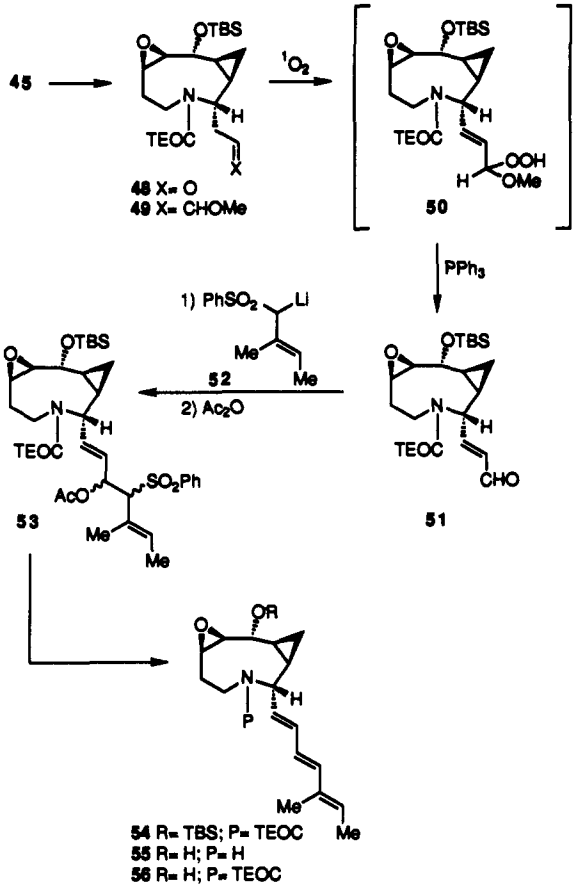
(30) Cf. Kende, A. S.; Bentley, T. J.; Mader, R. A.; Ridge, D. *J. Am. Chem. Soc.* **1974**, *96*, 4332.
(31) Hobson, J. D.; McCluskey, J. G. *J. Chem. Soc. C* **1967**, 2015. For a recent review of amine dealkylations, see: Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1.
(32) House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 2428.
(33) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.
(34) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.
(35) Allylic alcohols constrained in five- and six-membered rings are epoxidized syn to the alcohol function. Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958.
(36) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(37) Rousseau, G.; le Perchec, P.; Conia, J. M. *Synthesis* **1978**, 67.

Scheme IX

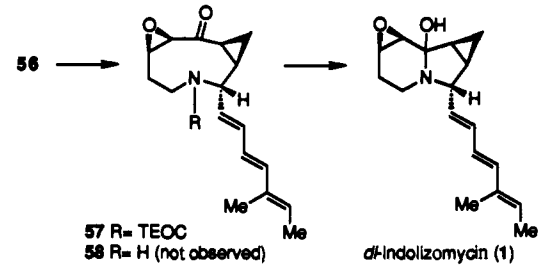


afforded what was presumed to be an epimeric mixture of acetoxy sulfones corresponding to **53**. Treatment of this mixture with sodium amalgam afforded the desired **54** in which the (*E*,*E*,*E*)-triene had been installed stereospecifically.[38]

Our next goal involved liberation of the C_8 alcohol with a view toward its oxidation to the corresponding ketone. It was then hoped that removal of the TEOC blocking group would give rise to indolizomycin. To accomplish deprotection of the C_8 silyl ether, it was necessary to distinguish the deprotection of the TBS ether at C_8 from the unwanted liberation of the secondary amino function. We know that this selection was necessary because the amino alcohol **55**, obtained in crude form from the liberation of both amino and hydroxyl functions, turned out to be unworkable for reaching indolizomycin. Thus several attempts to oxidize the alcohol function of **55** in the presence of the free secondary amine were unrewarding. Accordingly, a major effort was invested toward the objective of liberating the C_8 alcohol while the nitrogen function was still protected as its TEOC urethane derivative. In the end, the problem was solved by a chance discovery. Treatment of **54** with 1 N aqueous periodic acid (95% purity from the Fisher Scientific Company) in THF indeed resulted in selective deprotection of the alcohol function while leaving the secondary nitrogen in the form of its TEOC carbamate derivative.

It was found that oxidation of **56** with tetra-*n*-propylammonium perruthenate[39] produced the desired ketone (Scheme X). At long last we had brought plan B (Scheme I) to near fruition in that compound **57** indeed corresponded to the hypothetical structure **11** of the synthetic construct. We now turn to the final step of the synthesis. This too proved to be quite demanding. In the event, treatment of **57** with TBAF led to removal of the TEOC function. We could not directly observe the formation of the immediate

Scheme X



deprotection product **58**. Rather, in its stead, there could be observed the formation of a compound deemed to be *dl*-indolizomycin. Two chromatographic operations were necessary to obtain this substance in virtually homogeneous form. The first chromatography, through a short column of silica gel, removed debris which, while uncharacterized, clearly had arisen from the TBAF treatment. Additional contaminants arising from the silica gel were removed by prep-plate chromatography. Decomposition of the synthetic indolizomycin was occurring even during these purifications, and the fully synthetic racemic **1** was obtained in 29% yield though not without trace contaminants. The proton NMR spectrum (490 MHz) was in solid agreement with the corresponding spectrum (400 MHz) of the natural product provided by Professor Ikeda. The structure was further confirmed by high-resolution and low-resolution mass spectroscopy as well as by ultraviolet measurements. Of course the stereochemistry of both the allyl and epoxy groups had been demonstrated earlier by crystallographic determinations on congeners of the systems shown above. Though a direct comparison with an authentic sample was, as expected, not feasible, the data that had been amassed allowed us to confidently assert that the total synthesis of indolizomycin had been accomplished. It is interesting to note that this synthesis does not in of itself establish the stereochemistry of the carbinol amine linkage. For this assignment we rely completely on previously published deductions.

Summary

The total synthesis of racemic indolizomycin has been accomplished. This compound is certainly one of the most unstable natural products that has ever been obtained by total synthesis. The key lessons learned in this synthesis are as follows: (i) the feasibility of the aza-Robinson annulation (see **36** → **37** → **38**); (ii) the feasibility of vinylogous McCluskey cleavage (**39** → **40**), which served to provide the vinylogous urethane; (iii) the application of the Conia photooxygenation–hydroperoxide reduction sequence (**49** → **51**) and the application of the Kocienski–Julia olefin synthesis to achieve construction of the difficult trienal side chain (**51** → **53** → **54**); and (iv) the use of the TEOC carbamate function as one which can be maintained through a series of operations, including the cleavage of an OTBS ether, and which can be cleaved at a strategic point through the use of TBAF. It is to be hoped that the lessons garnered in this difficult series of experiments can be fruitfully applied to other goals in synthetic chemistry.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under nitrogen (N_2) atmosphere; benzene (PhH), toluene (PhMe), and dichloromethane (CH_2Cl_2) were distilled from calcium hydride under N_2 atmosphere; and methanol (MeOH) was distilled from magnesium turnings.

Infrared spectra were recorded on a Nicolet 5 SX FT-IR spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker WM-250 or a Bruker WM-500 and are reported in parts per million (δ) relative to $CHCl_3$ (7.24 ppm) as an internal reference, with coupling constants (J) reported in hertz (Hz). Low-resolution mass spectra were obtained on a Hewlett-Packard 5989A mass spectrometer, and high-resolution mass spectra were obtained on a Kratos MS08RFA mass spectrometer. Elemental analyses were determined by Robertson Laboratories, Inc., or Galbraith Laboratories, Inc. Ultraviolet spectra were obtained on a

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Varian CARY 219 spectrophotometer.

Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds which did not absorb UV light were visualized by dipping the plates in a ceric sulfate or anisaldehyde solution followed by heating. Liquid column chromatography was performed using forced flow (flash chromatography) of the indicated solvent on EM Science silica gel 60 (230–400 mesh).

(*Z*)-1-(2,4-Dioxo-3-azabicyclo[3.1.0]hex-3-yl)-4-(trimethylsilyl)-3-butene (14). To a solution of (*Z*)-4-(trimethylsilyl)-3-butenol (4.20 g, 29.2 mmol), cyclopropyl imide **13** (3.00 g, 27.0 mmol), and triphenylphosphine (7.08 g, 27.0 mmol) in THF (15 mL) at room temperature with stirring under N_2 was slowly added a solution of diethyl azodicarboxylate (4.24 mL, 2.70 mmol) in THF (1.5 mL). The resulting solution was stirred at room temperature overnight and concentrated in vacuo. The resulting residue was triturated with EtOAc/hexane (3:7, 100 mL) and filtered. The filtered solid was again triturated (100 mL), and the combined extracts were concentrated and purified by flash column chromatography (1:5 EtOAc/hexane) to give 5.10 g (80%) of imide **14** as a white solid: IR (film) 2940, 1760, 1700, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.86 (dt, J = 18.5, 6.4 Hz, 1 H), 5.64 (dt, J = 18.3, 1.3 Hz, 1 H), 3.45 (t, J = 6.9 Hz, 2 H), 2.42 (dd, J = 8.1, 3.5 Hz, 2 H), 2.31 (q, J = 6.8 Hz, 2 H), 1.45 (td, J = 8.1, 4.5 Hz, 1 H), 1.32 (dt, J = 4.6, 3.6, Hz, 1 H), 0.10 (s, 9 H); MS (EI, 20 eV) m/e 237 (M^+, 27.8), 236 (42.8), 222 (24.3), 168 (30.5), 148 (base).

(*Z*)-(1α,5α)-(±)-1-(2-Hydroxy-4-oxo-3-azabicyclo[3.1.0]hex-3-yl)-4-(trimethylsilyl)-3-butene (15). To a solution of imide **14** (5.47 g, 23.0 mmol) in MeOH (750 mL) at −5 °C with stirring under N_2 was added $NaBH_4$ (4.35 g, 115 mmol) in one portion. After 20 min another portion of $NaBH_4$ (4.35 g, 115 mmol) was added, and again after 20 min, $NaBH_4$ (4.35 g, 115 mmol) was added. After 20 min, this mixture was poured into a cold, vigorously stirring solution of saturated aqueous $NaHCO_3$ (400 mL)/CH_2Cl_2 (400 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (4 × 100 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:2 EtOAc/hexane) to give 5.05 g (92%) of carbinol amides **15** as a mixture (12:1) of diastereomers. Major isomer: IR ($CDCl_3$) 3320, 2960, 2900, 1690, 1610, 1460 cm^{-1}; ^2H NMR ($CDCl_3$, 250 MHz) δ 6.26 (dt, J = 12.7, 6.4 Hz, 1 H), 5.60 (d, J = 18.3 Hz, 1 H), 4.93 (br d, J = 4.2 Hz, 1 H), 3.64 (br s, 1 H), 3.47 (dt, J = 17.1, 6.0 Hz, 1 H), 3.13 (dt, J = 17.5, 6.0 Hz, 1 H), 2.30 (q, J = 6.5 Hz, 2 H), 1.99–1.92 (c, 2 H), 1.08 (ddd, J = 7.9, 7.8, 4.7 Hz, 1 H), 0.48 (td, J = 4.4, 3.3 Hz, 1 H), 0.10 (s, 9 H); MS (EI, 20 eV) m/e 239 (M^+, 3.6), 238 (13.8), 222 (1.6), 184 (4.6), 16 (6.3), 150 (7.2), 126 (base).

(1a*R,7a*S**,7b*R**)-(±)-1,1a,4,5,7a,7b-Hexahydro-2*H*-cycloprop[*a*]indolizin-2-one (16).** A solution of carbinol amides **15** (5.00 g, 20.9 mmol) in trifluoroacetic acid (30 mL) was stirred at 0 °C under N_2 for 45 min, concentrated in vacuo, and purified by flash column chromatography (1:1 EtOAc/hexane) to give 3.10 g (99%) of amide **16**: IR ($CDCl_3$) 2938, 2860, 1680, 1656, 1460, 1450, 1430 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.85 (m, 1 H), 5.68 (m, 1 H), 4.08 (s, 1 H), 4.04 (dd, J = 13.5, 6.8 Hz, 1 H), 2.81 (ddd, J = 16.5, 7.4, 5.0 Hz, 1 H), 2.48 (m, 1 H), 2.00–1.80 (c, 3 H), 1.09 (ddd, J = 8.2, 8.0, 4.5 Hz, 1 H), 0.79 (ddd, J = 7.7, 4.2, 3.5 Hz, 1 H); MS (EI, 20 eV) m/e 149 (M^+, 79.2), 148 (base), 134 (59.8), 126 (11.8), 120 (36.6), 112 (52.2), 97 (35.4), 94 (32.8), 91 (23.7).

(1a*R,7a*S**,7b*R**)-(±)-1,1a,4,5,7a,7b-Hexahydro-2*H*-cycloprop[*a*]indolizine-2-thione (17).** To a solution of amide **16** (2.88 g, 19.3 mmol) in PhMe (20 mL) was added Lawesson's reagent (3.91 g, 9.67 mmol). This mixture was heated at reflux for 2 h, concentrated, and purified by flash column chromatography (1:5 EtOAc/hexane) to give 2.70 g (85%) of thioamide **17** as a white solid: mp 98–99 °C; IR (film) 2920, 2878, 2850, 2810, 1485, 1429 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.85 (m, 1 H), 5.64 (m, 1 H), 4.65 (dd, J = 12.8, 6.6 Hz, 1 H), 4.49 (s, 1 H), 3.05 (ddd, J = 12.5, 11.9, 5.0 Hz, 1 H), 2.61–2.46 (c, 2 H), 2.06 (m, 1 H), 1.85 (m, 1 H), 1.24 (td, J = 8.2, 4.9 Hz, 1 H), 0.74 (ddd, J = 4.5, 3.5, 2.3 Hz, 1 H); MS (EI, 20 eV) m/e 165 (M^+, 98.9), 164 (42.5), 150 (12.1), 132 (23.9), 130 (15.4), 117 (23.7), 94 (20.5), 80 (base).

(1a*R,7a*S**,7b*R**)-(±)-2-(Carbethoxymethylene)-1,1a,4,5,7a,7b-hexahydro-2*H*-cycloprop[*a*]indolizine (19).** To a refluxing solution of thioamide **17** (2.70 g, 16.5 mmol) and rhodium(II) acetate (27 mg, 1 wt %) in PhH (20 mL) with stirring under N_2 was added ethyl diazoacetate (3.47 mL, 33.0 mmol). After 8 h, another portion of ethyl diazoacetate (3.47 mL, 33.0 mmol) was added. After an additional 8 h, this mixture was cooled to room temperature, concentrated, and purified by flash column chromatography (1:30 EtOAc/hexane) to give 800 mg (30%) of recovered starting material **17** and 1.77 g (49%) of vinylogous urethane **19** as a yellow oil: IR ($CDCl_3$) 2970, 2925, 2843, 1683, 1674, 1669, 1652, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.80–5.61 (c, 2 H), 4.76 (br s, 1 H), 4.12 (dq, J = 7.2, 2.2 Hz, 2 H), 4.08 (s, 1 H), 3.56 (dd, J = 14.1, 5.9 Hz, 1 H), 3.27 (m, 1 H), 3.08 (ddd, J = 12.1, 9.7, 4.4 Hz, 1 H), 2.46 (m, 1 H), 1.85 (m, 1 H), 1.73 (ddd, J = 6.9, 4.8, 4.7 Hz, 1 H), 1.27 (t, J = 7.0 Hz, 3 H), 1.17 (ddd, J = 8.2, 8.1, 4.9 Hz, 1 H), 0.63 (dt, J = 4.5, 3.4 Hz, 1 H); MS (EI, 20 eV) m/e 219 (M^+, base), 206 (1.8), 204 (3.9), 198 (1.0), 190 (25.0), 174 (54.7), 172 (15.9), 164 (2.1), 158 (2.2), 152 (3.6), 146 (84.3), 132 (20.6).

(1a*R,2*R**,7a*S**,7b*R**)-(±)-2-(1a,2,4,5,7a,7b-Hexahydro-1*H*-cycloprop[*a*]indolizin-2-yl)ethanoic Acid Ethyl Ester (20).** To a solution of vinylogous urethane **19** (1.77 g, 8.08 mmol) in MeOH (20 mL) was added a trace of bromocresol green followed by sodium cyanoborohydride (508 mg, 8.08 mmol). A solution of 2 M methanolic hydrochloric acid was added dropwise to maintain pH 4 (yellow end point). The mixture was stirred at room temperature under N_2 for 2 h, concentrated, and purified by flash column chromatography (1:2:240 NH_4OH/MeOH/$CHCl_3$) to give 1.44 g (81%) of amino ester **20** as a colorless oil: IR ($CDCl_3$) 2982, 2928, 2844, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.72 (m, 1 H), 5.61 (m, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 3.67 (s, 1 H), 3.42 (dt, J = 9.0, 4.5 Hz, 1 H), 2.87–2.83 (c, 2 H), 2.40 (AB part of ABX, J_{AB} = 8.9 Hz, J_{AX} = 4.1 Hz, J_{BX} = 8.9 Hz, $\Delta\nu$ = 60.4 Hz, 2 H), 2.30–2.15 (c, 2 H), 1.75–1.60 (c, 3 H), 1.25 (t, J = 7.2 Hz, 1 H), 1.25 (buried, 1 H), 0.68 (ddd, J = 7.7, 4.2, 3.5 Hz, 1 H), 0.41 (ddd, J = 8.2, 8.0, 4.5 Hz, 1 H); MS (EI, 20 eV) m/e 221 (M^+, 7.0), 150 (12.1), 134 (base), 132 (10.8), 95 (11.0).

2,4-Dioxo-3-azabicyclo[3.1.0]hexane-3-propanoic Acid Methyl Ester (33). To a solution of cyclopropyl anhydride **5** (15.7 g, 144 mmol) and methyl 3-azidopropionate (20.0 g, 155 mmol) in benzene (120 mL) at 0 °C with stirring under N_2 was added triphenylphosphine (44.3 g, 169 mmol) portionwise over 5 min. After 20 min, tetra-*n*-butylammonium cyanide (3.78 g, 12.1 mmol) was added, and the resulting orangish-brown homogeneous mixture was stirred at 0 °C for 30 min then warmed to room temperature for 4 h, diluted with hexane (200 mL), and filtered. The filtrate was concentrated and purified by flash column chromatography (1:2 EtOAc/hexane) to give 27.5 g (99%) of cyclopropyl imide **33** as a colorless oil: IR ($CDCl_3$) 1734, 1711, 1441 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.69 (s, 3 H), 3.63 (t, J = 6.9 Hz, 2 H), 2.50 (t, J = 6.9 Hz, 2 H), 2.44 (dd, J = 8.0, 3.8 Hz, 2 H), 1.51 (dd, J = 8.0, 4.7 Hz, 1 H), 1.44 (dd, J = 5.4, 4.7 Hz, 1 H); MS (EI, 20 eV) m/e 197 (M^+, 21.4), 165 (73.3), 137 (base). Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.78; H, 5.62; N, 7.57.

(1α,2α,5α)-(±)-2-(2-Propenyl)-4-thioxo-3-azabicyclo[3.1.0]hexane-3-propanoic Acid Methyl Ester (35). To a solution of cyclopropyl imide **33** (30.4 g, 154 mmol) in MeOH (300 mL) at −10 °C with stirring under N_2 was rapidly added $NaBH_4$ (11.6 g, 308 mmol). This mixture was stirred at −10 °C for 45 min and poured into ice-cold saturated aqueous $NaHCO_3$ (500 mL)/CH_2Cl_2 (500 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 200 mL) and 20% isopropyl alcohol/$CHCl_3$ (4 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give a pale yellow oil that was dissolved in MeOH (320 mL). To this solution at room temperature with stirring under N_2 was added 2 N methanolic HCl (1.65 mL). This mixture was stirred for 2 h and then neutralized by addition of 2 N methanolic NaOH, concentrated, redissolved in CH_2Cl_2 (200 mL), and cooled to 0 °C. To this solution was added allyltrimethylsilane (33.0 mL, 208 mmol) followed by $TiCl_4$ (16.7 mL, 152 mmol) dropwise over 5 min. This bright orange homogeneous solution was stirred with warming to room temperature for 16 h, cooled to 0 °C, diluted with CH_2Cl_2 (100 mL), quenched by addition of 1 N HCl (100 mL), and diluted with brine (200 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give 30.2 g of amide **34** as a pale yellow oil. A portion was removed and purified by flash column chromatography (1:2 → 1:1 EtOAc/hexane) to give a colorless oil: IR ($CDCl_3$) 2953, 2928, 1734, 1675, 1475, 1437, 1423 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.76, (m, 1 H), 5.20–5.12 (c, 2 H), 3.78 (dt, J = 12.5, 6.5 Hz, 1 H), 3.66 (s, 3 H), 3.55 (br d, J = 5.9 Hz, 1 H), 3.14 (dt, J = 14.5, 7.0 Hz, 1 H), 2.62–2.36 (c, 3 H), 2.29 (dt, J = 14.2, 8.5 Hz, 1 H), 1.85 (m, 1 H), 1.69 (ddd, J = 7.6, 6.0, 4.2 Hz, 1 H), 1.03 (ddd, J = 8.0, 7.9, 4.7 Hz, 1 H), 0.48 (ddd, J = 4.5, 4.4, 3.3 Hz, 1 H); MS (EI, 20 eV) m/e 192 (M^+ − allyl, 5.3), 182 (base), 96 (21); HRMS (CI, NH_3) exact mass calcd for $C_{12}H_{18}NO_3$ 224.1287 (MH^+), found 224.1288.

A mixture of crude amide **34** and Lawesson's reagent (35.2 g, 87.0 mmol) in benzene (130 mL) was refluxed with stirring under N_2 for 15 min, cooled to room temperature, and filtered. The filtrate was concentrated and purified by flash column chromatography (1:9 → 1:4 EtOAc/hexane) to give 31.5 g (85%) of thioamide **35** as a yellow oil: IR ($CDCl_3$) 2953, 2923, 1731, 1479, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.74 (m, 1 H), 5.20–5.13 (c, 2 H), 4.23 (dt, J = 13.8, 5.8 Hz, 1 H), 3.96 (m, 1 H), 3.65 (s, 3 H), 3.49 (dt, J = 13.8, 5.8 Hz, 1 H), 2.86

(dt, J = 16.6, 6.6 Hz, 1 H), 2.58–2.49 (c, 3 H), 2.38 (dt, J = 14.8, 7.7 Hz, 1 H), 1.78 (ddd, J = 7.6, 5.5, 4.8 Hz, 1 H), 1.20 (ddd, J = 8.0, 7.9, 4.8 Hz, 1 H), 0.39 (ddd, J = 4.7, 4.6, 3.1 Hz, 1 H); MS (EI, 20 eV) m/e 239 (M^+, 57.4), 238 (14.0), 208 (14.3), 206 (19.2), 198 (22.1), 112 (base). Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.50; H, 7.33; N, 5.57.

(1α,2α,5α)-(±)-1-Diazo-4-[2-(2-propenyl)-4-thioxo-3-azabicyclo-[3.1.0]hex-3-yl]-2-butanone (36). To a solution of thioamide **35** (12.2 g, 50.8 mmol) in MeOH (100 mL) at room temperature with stirring under N_2 was added 1 N NaOH (61.0 mL, 61.0 mmol). This yellow homogeneous solution was stirred at room temperature for 13 h, concentrated, and diluted with Et_2O (100 mL)/H_2O (100 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (1 × 25 mL), acidified to pH <1 with 1 N HCl, and extracted with CH_2Cl_2 (10 × 50 mL). The combined organic extracts were washed with brine (1 × 100 mL), dried ($MgSO_4$), filtered, and evaporated to give the desired acid as a yellow oil that was dissolved in THF (200 mL) and cooled to 0 °C. To this solution under N_2 with stirring was added *N*-methylmorpholine (6.70 mL, 61.0 mmol) followed by isobutyl chloroformate (6.59 mL, 50.8 mmol). The resulting white heterogeneous mixture was stirred for 25 min and then rapidly filtered into an ice-cold flask, transferred into an addition funnel, and added to a solution of CH_2N_2 (350 mL, 0.5 M in Et_2O, 175 mmol) at 0 °C in an Erlenmeyer flask. This bright yellow solution was stirred at 0 °C for 45 min and at room temperature for 30 min and then N_2 was bubbled through the solution for 30 min to remove the excess CH_2N_2. The resulting tan solution was concentrated and purified by flash column chromatography (1:5 → 2:3 EtOAc/hexane) to give 9.75 g (77%) of diazo ketone **36** as a bright yellow oil: IR ($CDCl_3$) 2930, 2914, 2224, 1640, 1480 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.72 (m, 1 H), 5.34 (br s, 1 H), 5.20–5.13 (c, 2 H), 4.11 (dt, J = 12.7, 5.5 Hz, 1 H), 3.97 (m, 1 H), 3.60 (dt, J = 15.7, 6.2 Hz, 1 H), 2.94 (m, 1 H), 2.60–2.50 (c, 3 H), 2.36 (dt, J = 14.4, 7.6 Hz, 1 H), 1.77 (dt, J = 7.5, 5.0 Hz, 1 H), 1.20 (dt, J = 8.0, 4.8 Hz, 1 H), 0.36 (td, J = 4.7, 3.2 Hz, 1 H); MS (EI, 20 eV) m/e 221 ($M^+ - N_2$, 14.0), 188 (76.9), 180 (base); HRMS (CI, NH_3) exact mass calcd for $C_{12}H_{16}N_3OS$ 250.1016 (MH^+), found 250.1017.

(1a*R,2*S**,7b*R**)-(±)-1,1a,2,4,5,7b-Hexahydro-2-(2-propenyl)-6*H*-cycloprop[*a*]indolizin-6-one (38).** To a solution of rhodium(II) acetate dimer (97.0 mg, 220 μmol) in benzene (500 mL) at vigorous reflux under N_2 with stirring was added a solution of diazo ketone **36** (2.74 g, 11.0 mmol) in benzene (50 mL) rapidly over 1.5 min. The resulting brownish-red mixture was immediately immersed into an ice bath and then concentrated to a dark brown oil that was added as a solution in acetone (2.0 mL) to a suspension of Raney nickel (5 spoonfuls, pretreated by refluxing for 2 h) in acetone (250 mL) at room temperature. This mixture was stirred for 4 h and then filtered. The Raney Ni was washed with acetone repeatedly using a Soxhlet extractor, and both organic solutions were concentrated. The residue was purified by flash column chromatography (EtOAc → 2% MeOH/CH_2Cl_2) to give 1.37 g (66%) of dihydropyridone **38** as a dark yellow oil: IR ($CDCl_3$) 2930, 2900, 1615, 1569, 1497, 1451 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.80 (m, 1 H), 5.25–5.16 (c, 2 H), 5.11 (s, 1 H), 3.54 (m, 1 H), 3.46 (ddd, J = 12.4, 7.0, 6.9 Hz, 1 H), 3.27 (ddd, J = 12.7, 12.5, 5.7 Hz, 1 H), 2.63–2.27 (c, 4 H), 2.15 (m, 1 H), 1.80 (dt, J = 7.5, 5.0 Hz, 1 H), 1.18 (ddd, J = 8.0, 7.9, 4.9 Hz, 1 H), 0.40 (ddd, J = 4.7, 4.4, 3.1 Hz, 1 H); MS (EI, 20 eV) m/e 189 (M^+, 11.2), 148 (M^+ – allyl, base), 120 (21.5); HRMS (CI, NH_3) exact mass calcd for $C_{12}H_{16}NO$ 190.1233 (MH^+), found 190.1242.

(1*R,2*S**,7*Z*,9*R**)-(±)-6-Oxo-2-(2-propenyl)-3-azabicyclo[7.1.0]-dec-7-ene-3-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (40e).** To a tan solution of dihydropyridone **38** (1.00 g, 5.29 mmol) in CH_2Cl_2 at 0 °C with stirring under N_2 was added trimethyloxonium tetrafluoroborate (860 mg, 5.82 mmol). This heterogeneous mixture was stirred at 0 °C for 1 h, concentrated, and redissolved in MeOH (20 mL). To this solution at 0 °C with stirring under N_2 was added $NaBH_4$ (720 mg, 21.2 mmol). This cloudy mixture was stirred at 0 °C for 20 min and at room temperature for 20 min and poured into saturated aqueous $NaHCO_3$ (15 mL)/CH_2Cl_2 (15 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to yield a tan oil, which was dissolved in PhH (15 mL) and treated with 2-(trimethylsilyl)ethyl chloroformate, freshly prepared from 2-(trimethylsilyl)ethanol (1.27 mL, 8.86 mmol) and phosgene (13.8 mL, 1.93 M in toluene, 26.6 mmol) in ether (10 mL). This mixture was stirred for 4 h, evaporated, and purified by flash column chromatography (1:4 EtOAc/hexane) to give 531 mg (30%) of urethane **40e** as a colorless oil: IR ($CDCl_3$) 2952, 2869, 1679, 1652, 1460, 1414 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.30 (br d, J = 10.8 Hz, 1 H), 5.99 (br d, J = 11.5 Hz, 1 H), 5.82 (m, 1 H), 5.12–5.02 (c, 2 H), 4.09 (m, 1 H), 4.05 (dd, J = 10.0, 6.0 Hz, 2 H), 3.65 (m, 1 H), 3.40 (m, 1 H), 2.62–2.40 (c, 2 H), 2.52 (dd, J = 12.6, 6.6 Hz, 1 H), 1.90–1.79 (c, 2 H), 1.40–1.25 (c, 2 H), 0.96 (dd, J = 10.8, 7.7 Hz, 2 H), 0.59 (m, 1 H), 0.17 (s, 9 H); MS (EI, 20 eV) m/e 335 (M^+, 0.2), 294 (M^+ – allyl, 19.2), 292 (13.8), 264 (4.2), 250 (17.0), 222 (87.1), 208 (7.9); HRMS (CI, NH_3) exact mass calcd for $C_{18}H_{30}NO_3Si$ 336.1996 (MH^+), found 336.1995. Anal. Calcd for $C_{18}H_{29}NO_3Si$: C, 64.44; H, 8.71; N, 4.17. Found: C, 64.31; H, 8.88; N, 4.11.

Urethanes **40a–d** were prepared from dihydropyridone **38** using the corresponding chloroformates following the general procedure given for urethane **40e**.

40a, R = Me (29%): IR ($CDCl_3$) 3024, 2976, 1693, 1661, 1469, 1459, 1438, 1411 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.30 (br d, J = 10.8 Hz, 1 H), 6.12 and 6.01 (two br d, J = 11.7 Hz, 1 H, rotamers), 5.80 (m, 1 H), 5.11–5.03 (c, 2 H), 4.06 (m, 1 H), 3.80–3.35 (c, 2 H), 3.61 and 3.56 (two s, 3 H, rotamers), 2.61–2.40 (c, 2 H), 2.50 (dd, J = 12.5, 6.7 Hz, 1 H), 1.90–1.78 (c, 2 H), 1.40–1.23 (c, 2 H), 0.54 (m, 1 H); MS (EI, 20 eV) m/e 208 (M^+ – allyl, base), 180 (2.1), 166 (12.5), 152 (15.6), 140 (22.6); HRMS (CI, NH_3) exact mass calcd for $C_{14}H_{20}NO_3$ 250.1445 (MH^+), found 250.1437.

40b, R = Bn (29%): IR (film) 3078, 3027, 3000, 2941, 1697, 1661, 1458, 1425 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.40–7.31 (c, 5 H), 6.28 (br d, J = 10.8 Hz, 1 H), 6.08 and 5.93 (two br d, J = 11.4 Hz, 1 H, rotamers), 5.85 (m, 1 H), 5.12–5.02 (c, 2 H), 4.98 (AB q, J = 10.9 Hz, Δν = 12.9 Hz, 2 H), 4.18 (m, 1 H), 3.79–3.35 (c, 3 H), 2.65–2.40 (c, 2 H), 2.52 (dd, J = 12.5, 6.7 Hz, 1 H), 1.90–1.79 (c, 2 H), 1.40–1.25 (c, 2 H), 0.56 (m, 1 H); MS (EI, 20 eV) m/e 284 (M^+ – allyl, 2.7), 240 (10.8), 198 (1.2), 190 (1.0), 148 (16.8), 13.6 (2.7), 122 (1.9), 91 (base); HRMS (CI, NH_3) exact mass calcd for $C_{20}H_{24}NO_3$ 326.1757 (MH^+), found 326.1754.

40c, R = *p*-OMeBn (38%): IR ($CDCl_3$) 2958, 1688, 1661, 1613, 1515, 1462, 1442, 1423 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.30 (d, J = 8.3 Hz, 2 H), 6.90 (d, J = 8.3 Hz, 2 H), 6.28 (br d, J = 10.8 Hz, 1 H), 6.10 and 5.90 (two br d, J = 11.0 Hz, 1 H, rotamers), 5.87 (m, 1 H), 5.12–5.00 (c, 2 H), 4.92 (AB q, J = 10.4 Hz, Δν = 17.1 Hz, 2 H), 3.80 (s, 3 H), 3.80–3.35 (c, 3 H), 2.63–2.41 (c, 2 H), 2.50 (dd, J = 11.7, 6.3 Hz, 1 H), 1.90–1.80 (c, 2 H), 1.41–1.28 (c, 2 H), 0.58 (m, 1 H); MS (EI, 20 eV) m/e 355 (M^+, 0.1), 314 (0.3), 283 (1.0), 270 (20.3), 192 (2.6), 121 (base); HRMS (CI, NH_3) exact mass calcd for $C_{21}H_{26}NO_4$ 356.1863 (MH^+), found 356.1867.

40d, R = 9-fluorenylmethyl (32%): mp 139–141 °C; IR (film) 3051, 2958, 2919, 2902, 1683, 1659, 1478, 1445, 1422 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.76 (d, J = 7.4 Hz, 2 H), 8.26–7.28 (c, 6 H), 6.28 and 6.05 (two br d, J = 15.5 Hz, 1 H, rotamers), 5.73 and 5.60 (two br d, J = 13.8 Hz, 1 H, rotamers), 5.75 and 5.16 (two m, 1 H, rotamers), 5.15–4.65 (c, 2 H), 4.79 and 4.49 (two m, 1 H, rotamers), 4.30–4.10 (c, 2 H), 3.55–3.40 (c, 2 H), 3.18 and 2.65 (two br s, 1 H, rotamers), 2.55–2.40 (c, 2 H), 2.08–1.80 (c, 2 H), 1.63 and 1.26 (two m, 1 H, rotamers), 1.20–0.90 (c, 2 H), 0.55 and 0.05 (two m, 1 H, rotamers); MS (EI, 20 eV) m/e 413 (M^+, 0.2), 372 (2.0), 179 (base), 150 (2.6); HRMS (CI, NH_3) exact mass calcd for $C_{27}H_{28}NO_3$ 414.2070 (MH^+), found 414.2085.

(1*R,2*S**,9*R**,10*S**)-(±)-5-Oxo-9-(2-propenyl)-3-oxa-8-azatricyclo[8.1.0.0^{2,4}]undecane-8-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (42).** To a pale yellow solution of enone **40e** (2.04 g, 6.09 mmol) in MeOH (43 mL) at room temperature with stirring under N_2 was added H_2O_2 (1.86 mL, 30 wt % in H_2O, 18.3 mmol). This mixture was cooled to 0 °C, and 3 N NaOH (1.01 mL, 3.04 mmol) was added dropwise. This mixture was stirred with warming to room temperature for 5 h, concentrated, diluted with EtOAc (50 mL), washed with saturated aqueous NH_4Cl (2 × 10 mL) and brine (1 × 10 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:1 EtOAc/hexane) to give 2.07 g (97%) of epoxy ketones **42** as a pale yellow oil. The two diastereomers were separated by HPLC for characterization. Major isomer: IR ($CDCl_3$) 2950, 2915, 1703, 1675, 1464, 1400 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.78 (m, 1 H), 5.11–5.03 (c, 2 H), 4.29 (m, 1 H), 4.21 (dd, J = 9.8, 7.7 Hz, 1 H), 3.80–3.42 (c, 2 H), 3.67 and 3.37 (two d, J = 5.0 Hz, 1 H, rotamers), 3.12 (m, 1 H), 3.01 (dt, J = 19.3, 6.2 Hz, 1 H), 2.68–2.30 (c, 3 H), 1.23–0.95 (c, 5 H), 0.88 (m, 1 H), 0.68 (m, 1 H), 0.10 (s, 9 H); MS (EI, 20 eV) m/e 310 (M^+ – allyl, 8.0), 282 (3.8), 266 (17.7), 209 (4.0), 167 (7.1), 120 (3.2), 101 (34.7), 73 (base); HRMS (CI, NH_3) exact mass calcd for $C_{18}H_{30}NO_4Si$ 352.1945 (MH^+), found 352.1948. Minor isomer: IR ($CDCl_3$) 2959, 1710, 1682, 1470, 1420 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.70 (m, 1 H), 5.12–5.00 (c, 2 H), 4.31–4.20 (c, 2 H), 4.10 (m, 1 H), 3.60 and 3.40 (two td, J = 16.5, 2.3 Hz, 1 H, rotamers), 3.51 (s, 1 H), 2.90 and 2.68 (two dt, J = 13.5, 9.2 Hz, 1 H, rotamers), 2.52 (m, 1 H), 2.50 (d, J = 6.4, 1 H), 2.28 (m, 1 H), 2.15 (m, 1 H), 1.78 (m, 1 H), 1.28 (sextet, J = 7.8 Hz, 1 H), 1.10–1.00 (c, 4 H), 0.45 (dt, J = 4.8, 4.7 Hz, 1 H), 0.07 and 0.05 (two s, 9 H, rotamers); MS (EI, 20 eV) m/e 310 (M^+ – allyl, 32.4), 282 (4.3), 266 (5.9), 252 (4.3), 238 (11.6), 208 (74.8), 196 (22.4), 148 (17.1), 101 (base).

(1R*,2S*,6Z,8R*,9R*)-(±)-8-Hydroxy-2-(2-propenyl)-3-azabicyclo[7.1.0]dec-6-ene-3-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (43). To a pale yellow solution of epoxy ketone **42** (2.07 g, 5.89 mmol) in MeOH (200 mL) at room temperature with stirring was added hydrazine hydrate (1.00 mL, 85% in H_2O, 17.7 mmol) followed by glacial AcOH (10 drops from a Pasteur pipet). This mixture was stirred for 45 min and then quenched by addition of saturated aqueous $NaHCO_3$ (50 mL), concentrated, diluted with EtOAc (100 mL), washed with saturated aqueous $NaHCO_3$ (1 × 20 mL) and brine (1 × 20 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:2 EtOAc/hexane) to give 1.03 g (52%) of allylic alcohol **43** as a yellow oil: IR ($CDCl_3$) 3591, 2950, 2922, 1668, 1457, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.81 (m, 1 H), 5.75 (dd, J = 10.8, 8.8 Hz, 1 H), 5.50 and 5.40 (two ddd, J = 11.3, 10.2, 6.7 Hz, 1 H, rotamers), 5.12–5.00 (c, 2 H), 4.22–3.75 (c, 4 H), 2.93–2.40 (c, 5 H), 2.09 (m, 1 H), 1.71 (s, 1 H), 1.20–0.90 (c, 5 H), 0.35 (m, 1 H), 0.04 (s, 9 H); MS (EI, 20 eV) m/e 296 (M^+ − allyl, 4.0), 268 (2.2), 252 (9.9), 224 (2.4), 176 (1.0), 152 (2.0), 134 (10.7), 101 (39.9); HRMS (CI, NH_3) exact mass calcd for $C_{18}H_{32}NO_3Si$ 338.2153 (MH^+), found 338.2155. Anal. Calcd for $C_{18}H_{31}NO_3Si$: C, 64.05; H, 9.26; N, 4.15. Found: C, 63.97; H, 9.31; N, 4.12.

(1R*,2S*,3R*,5S*,9R*,10S*)-(±)-2-Hydroxy-9-(2-propenyl)-4-oxa-8-azatricyclo[8.1.0.0^{3,5}]undecane-8-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (44). To a yellow solution of allylic alcohol **43** (1.03 g, 3.06 mmol) in CH_2Cl_2 (40 mL) at 0 °C with stirring under N_2 was added MCPBA (580 mg, 3.37 mmol). This homogeneous mixture was stirred at 0 °C for 24 h and diluted with saturated aqueous $Na_2S_2O_3$ (10 mL)/saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 20 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:2 → 2:3 EtOAc/hexane) to give 911 mg (84%) of epoxy alcohol **44** as a colorless oil: IR ($CDCl_3$) 3584, 2950, 2925, 1675, 1457, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.78 (m, 1 H), 5.12–5.00 (c, 2 H), 4.32 and 4.17 (two td, J = 12.9, 5.4 Hz, 1 H, rotamers), 4.25–4.10 (c, 2 H), 3.19 (m, 1 H), 3.10 (d, J = 3.6 Hz, 1 H), 2.92 and 2.86 (t and dd, J = 6.7 Hz and J = 8.3, 3.3 Hz, 1 H, rotamers), 2.55 (m, 1 H), 2.35–2.05 (c, 3 H), 1.89 and 1.84 (two td, J = 8.7, 6.7 Hz, 1 H, rotamers), 1.53 and 1.48 (two td, J = 12.5, 7.1 Hz, 1 H, rotamers), 1.12–0.85 (c, 5 H), 0.32–0.29 (m, 1 H), 0.02 (s, 9 H); MS (EI, 20 eV) m/e 312 (M^+ − allyl, 22.2), 268 (24.4), 240 (21.6), 150 (21.4), 101 (68.8), 73 (base); HRMS (CI, NH_3) exact mass calcd for $C_{18}H_{32}NO_4Si$ 354.2102 (MH^+), found 354.2129. Anal. Calcd for $C_{18}H_{31}NO_4Si$: C, 61.15; H, 8.84; N, 3.96. Found: C, 60.70; H, 9.03; N, 3.85.

(1R*,2S*,3R*,5S*,9R*,10S*)-(±)-2-[(*tert*-Butyldimethylsilyl)oxy]-9-(2-propenyl)-4-oxa-8-azatricyclo[8.1.0.0^{3,5}]undecane-8-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (45). To a colorless solution of epoxy alcohol **44** (737 mg, 2.09 mmol) in CH_2Cl_2 (30 mL) at 0 °C with stirring under N_2 was added Et_3N (582 μL, 4.18 mmol) followed by TBSOTf (575 μL, 2.51 mmol). This mixture was allowed to stir for 5 min and then quenched by addition of saturated aqueous $NaHCO_3$ (5 mL) and diluted with CH_2Cl_2 (20 mL). The layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 10 mL) and brine (1 × 10 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (hexane → 1:19 EtOAc/hexane) to give 929 mg (95%) of silyl ether **45** as a colorless oil: IR ($CDCl_3$) 2950, 2922, 1844, 1675, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.80 (m, 1 H), 5.18–5.00 (c, 2 H), 4.32 and 4.17 (two td, J = 13.0, 4.6 Hz, 1 H, rotamers), 4.25–4.12 (c, 2 H), 3.16–3.00 (c, 2 H), 3.05 (d, J = 6.6 Hz, 1 H), 2.89 and 2.87 (two dd, J = 8.3, 6.2 Hz and J = 8.4, 7.1 Hz, 1 H, rotamers), 2.60 (m, 1 H), 2.30–2.00 (c, 2 H), 1.83 (m, 1 H), 1.46 (m, 1 H), 1.40 (m, 1 H), 1.10–0.90 (c, 4 H), 0.92 (s, 9 H), 0.12 (m, 1 H), 0.11 (s, 3 H), 0.08 (s, 3 H), 0.05 (s, 9 H); MS (EI, 20 eV) m/e 426 (M^+ − allyl, 15.7), 382 (85.0), 354 (28.2), 340 (15.8), 326 (13.3), 260 (10.2), 253 (18.6), 172 (24.1), 147 (33.7), 129 (12.9), 101 (base); HRMS (CI, NH_3) exact mass calcd for $C_{24}H_{46}NO_4Si_2$ 468.2967 (MH^+), found 468.2955. Anal. Calcd for $C_{24}H_{45}NO_4Si_2$: C, 61.62; H, 9.70; N, 2.99. Found: C, 61.63; H, 9.56; N, 2.89.

(1R*,2S*,3R*,5S*,9R*,10S*)-(±)-2-[(*tert*-Butyldimethylsilyl)oxy]-9-(2-oxoethyl)-4-oxa-8-azatricyclo[8.1.0.0^{3,5}]undecane-8-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (48). Ozone (from a Welsbach Ozonator) was bubbled through a mixture of silyl ether **45** (435 mg, 930 μmol) and $NaHCO_3$ (220 mg) in CH_2Cl_2 (22 mL)/MeOH (22 mL) at −78 °C with stirring until a light purple color appeared. The excess ozone was removed via N_2 purge to give a colorless solution that was immediately treated with excess dimethyl sulfide (3.75 mL). This mixture was allowed to stir with warming to room temperature for 19 h, concentrated, diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:9 → 1:7 EtOAc/hexane) to give 396 mg (91%) of aldehyde **48** as a colorless oil: IR ($CDCl_3$) 2950, 2922, 2887, 2812, 1717, 1675, 1464, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.80 (s, 1 H), 4.30–4.03 (c, 3 H), 3.43 (dd, J = 17.9, 7.6 Hz, 1 H), 3.18–3.00 (c, 5 H), 2.90 (m, 1 H), 2.23–2.08 (c, 2 H), 2.16 and 1.88 (two m, 1 H, rotamers), 1.55 and 1.50 (two ddd, J = 14.3, 14.1, 5.9 Hz, 1 H, rotamers), 1.18–0.90 (c, 4 H), 0.92 (s, 9 H), 0.12–0.04 (c, 15 H); MS (EI, 20 eV) m/e 469 (M^+, 0.6), 384 (22.1), 294 (3.6), 250 (3.4), 224 (50.8), 186 (6.9), 155 (11.8), 101 (base); HRMS (CI, NH_3) exact mass calcd for $C_{23}H_{43}NO_5Si_2$ 470.2759 (MH^+), found 470.2740. Anal. Calcd for $C_{23}H_{44}NO_5Si_2$: C, 58.81; H, 9.23; N, 2.98. Found: C, 58.96; H, 8.93; N, 2.90.

(1R*,2S*,3R*,5S*,9R*(E),10S*)-(±)-2-[(*tert*-Butyldimethylsilyl)oxy]-9-(3-methoxy-2-propenyl)-4-oxa-8-azatricyclo[8.1.0.0^{3,5}]undecane-8-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (49E) and (1R*,2S*,3R*,5S*,9R*(Z),10S*)-(±)-2-[(*tert*-Butyldimethylsilyl)oxy]-9-(3-methoxy-2-propenyl)-4-oxa-8-azatricyclo[8.1.0.0^{3,5}]undecane-8-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (49Z). To a heterogeneous mixture of (methoxymethyl)triphenylphosphonium chloride (433 mg, 1.26 mmol) in THF (1.5 mL) at 0 °C with stirring under N_2 was added sodium bis(trimethylsilyl)amide (1.0 M in THF) until a faint red color persisted, and then the requisite amount (1.35 mL, 1.0 M in THF, 1.35 mmol) was delivered. This red mixture was warmed to room temperature, stirred for 20 min, and recooled to 0 °C. To this solution was added aldehyde **48** (396 mg, 843 μmol) in THF (3.0 mL), and this mixture was warmed to room temperature. After 20 min, EtOAc (15 mL) was added and this mixture was washed with saturated aqueous NH_4Cl (2 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:9 EtOAc/hexane) to give 335 mg (80%) of methyl enol ethers **49E/49Z** (3:2 mixture) as a pale yellow oil. A portion was removed and the isomers were separated. **49E**: IR ($CDCl_3$) 2950, 2922, 2887, 2844, 1675, 1647, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.31 and 7.30 (two d, J = 12.4 Hz, 1 H, rotamers), 4.69 (m, 1 H), 4.36 and 4.20 (two td, J = 13.8, 5.6 Hz, 1 H, rotamers), 4.20–4.12 (c, 2 H), 3.51 and 3.50 (two s, 3 H, rotamers), 3.19–3.00 (c, 3 H), 2.90 (dt, J = 14.5, 7.6 Hz, 1 H), 2.70 (m, 1 H), 2.36 (m, 1 H), 2.20–1.70 (c, 3 H), 1.49 and 1.42 (two dt, J = 12.9, 6.7 Hz, 1 H, rotamers), 1.08–0.85 (c, 4 H), 0.92 (s, 9 H), 0.12 (m, 1 H), 0.11 (s, 3 H), 0.08 (s, 3 H), 0.05 (s, 9 H); MS (EI, 20 eV) m/e 426 (5.3), 382 (9.8), 354 (8.6), 276 (2.0), 266 (2.9), 238 (9.4); HRMS (CI, NH_3) exact mass calcd for $C_{25}H_{48}NO_5Si_2$ 498.3072 (MH^+), found 498.3094. **49Z**: IR ($CDCl_3$) 2950, 2922, 2887, 2852, 1675, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.91 (d, J = 6.8 Hz, 1 H), 4.34 (m, 1 H), 4.25–4.10 (c, 3 H), 3.58 (s, 3 H), 3.15–2.90 (c, 4 H), 2.51 (m, 1 H), 2.30–2.10 (c, 3 H), 2.12 and 1.82 (two m, 1 H, rotamers), 1.50 (m, 1 H), 1.10–0.90 (c, 4 H), 0.90 (s, 9 H), 0.10 (m, 1 H), 0.09 (s, 3 H), 0.06 (s, 3 H), 0.02 (s, 9 H); MS (EI, 20 eV) m/e 426 (16.2), 412 (16.8), 382 (29.7), 354 (25.3), 312 (7.8), 253 (18.5), 238 (18.6), 172 (16.0), 101 (92.7), 73 (base); HRMS (CI, NH_3) exact mass calcd for $C_{25}H_{48}NO_5Si_2$ 498.3072 (MH^+), found 498.3084.

(1R*,2S*,3R*,5S*,9R*(E),10S*)-(±)-2-[(*tert*-Butyldimethylsilyl)oxy]-9-(3-oxo-1-propenyl)-4-oxa-8-azatricyclo[8.1.0.0^{3,5}]undecane-8-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (51). To a colorless solution of enol ethers **49** (370 mg, 715 μmol) in benzene (32 mL) at room temperature with stirring was added pyridine (~1 μL, catalytic) followed by 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (4.4 mg, 7.15 μmol). The resulting reddish-brown mixture was irradiated with a tungsten–iodine lamp while bubbling O_2 through the solution at room temperature for 8 h. Triphenylphosphine (187 mg, 715 μmol) was added, and this mixture was stirred for 1 h, concentrated, and purified by flash column chromatography (1:10 EtOAc/hexane) to give 200 mg (69%) of α,β-unsaturated aldehyde **51** as a tan oil: IR ($CDCl_3$) 2950, 2922, 2852, 1682, 1675, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.60 (d, J = 7.7 Hz, 1 H), 7.07 and 6.91 (two dd, J = 16.1, 5.6 Hz, 1 H, rotamers), 6.19 and 6.16 (two dd, J = 15.8, 7.9 Hz, 1 H, rotamers), 4.40 and 4.22 (two m, 1 H, rotamers), 4.25–4.18 (c, 2 H), 3.20–3.00 (c, 3 H), 2.95–2.85 (c, 2 H), 2.31–2.15 and 2.03–1.90 (two c, 2 H, rotamers), 1.50 (m, 1 H), 1.25 (m, 1 H), 1.17–0.90 (c, 3 H), 0.90 (s, 9 H), 0.21 (m, 1 H), 0.13 (s, 3 H), 0.10 (s, 3 H), 0.05 (s, 9 H); MS (EI, 20 eV) m/e 438 (4.2), 396 (28.5), 352 (24.3), 278 (5.4), 260 (7.4), 186 (14.2), 170 (5.8), 129 (21.0); HRMS (CI, NH_3) exact mass calcd for $C_{24}H_{44}O_5Si_2$ 482.2759 (MH^+), found 482.2729.

(1R*,2S*,3R*,5S*,9R*(1E,5E),10S*)-(±)-9-[3-(Acetyloxy)-5-methyl-4-(phenylsulfonyl)-1,5-heptadienyl]-2-[(*tert*-butyldimethylsilyl)oxy]-4-oxa-8-azatricyclo[8.1.0.0^{3,5}]undecane-8-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (53). To a solution of (*E*)-2-methyl-2-butenyl phenyl sulfone[40] (99.4 mg, 473 μmol) in THF (3.0 mL) at −78 °C with

(40) Julia, M.; Saussine, L. *Tetrahedron Lett.* **1974**, *38*, 3443. We synthesized this compound starting from (*E*)-2-methyl-2-buten-1-ol via conversion to its corresponding bromide followed by displacement with sodium sulfinate.

stirring under N_2 was added *n*-BuLi (1.6 M in hexane) until a yellow color persisted, and then the requisite amount (296 μL, 1.6 M in hexane, 473 μmol) was delivered. The resulting dark yellow mixture was stirred for 10 min and then a solution of enal **51** (190 mg, 394 μmol) in THF (3.5 mL) was added followed by, after 25 min, Ac_2O (112 μL, 1.18 mmol). This colorless mixture was warmed to room temperature, stirred for 75 min, and then poured into saturated aqueous $NaHCO_3$ (20 mL)/EtOAc (20 mL). The layers were separated, and the organic phase was washed with brine (1 × 20 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:5 → 1:3 EtOAc/hexane) to give 249 mg (86%) of a diastereomeric mixture of acetoxy sulfones **53** as a white foam. Major isomer: mp 64–66 °C; IR ($CDCl_3$) 2950, 2922, 2894, 2852, 1738, 1675, 1457, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.85–7.50 (c, 5 H), 6.20–5.85 (c, 3 H), 5.40 (m, 1 H), 5.43 (q, *J* = 6.6 Hz, 1 H), 4.30–4.05 (c, 3 H), 3.95 (dd, *J* = 9.1, 5.1 Hz, 1 H), 3.15–3.00 (c, 3 H), 2.80 (m, 1 H), 2.58 (m, 1 H), 2.10 (m, 1 H), 1.84 (s, 3 H), 1.62 (s, 3 H), 1.51 (d, *J* = 6.3 Hz, 3 H), 1.42 (m, 1 H), 1.10 (m, 1 H), 1.00–0.80 (c, 3 H), 0.90 (s, 9 H), 0.12 (m, 1 H), 0.09 (s, 3 H), 0.04 (s, 3 H), 0.01 (s, 9 H); HRMS (FAB, thioglycerol) exact mass calcd for $C_{37}H_{60}NO_8SSi_2$ 734.3580 (MH^+), found 734.3592.

(1*R,2*S**,3*R**,5*S**,9*R**(1*E*,3*E*,5*E*),10*S**)-(±)-2-[(*tert*-Butyldimethylsilyl)oxy]-9-(5-methyl-1,3,5-heptatrienyl)-4-oxa-8-azatricyclo[8.1.0.0^{3,5}]undecane-8-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (54).** To a colorless solution of acetoxy sulfones **53** (71.0 mg, 96.9 μmol) in THF (3.0 mL) and MeOH (1.0 mL) at −20 °C with stirring under N_2 was added 5% sodium amalgam (240 mg, 522 μmol). This mixture was stirred for 8 h and then poured into H_2O (15 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:5 EtOAc/hexane) to give 46 mg (89%) of triene **54** as a tan oil: IR ($CDCl_3$) 2950, 2922, 2852, 1675, 1457, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.30–6.10 (c, 3 H), 5.95–5.85 and 5.65–5.42 (two c, 2 H, rotamers), 4.40–4.10 (c, 3 H), 3.20–3.01 (c, 3 H), 2.93 (m, 1 H), 2.66 (m, 1 H), 2.32–2.10 (c, 2 H), 1.75 (s, 3 H), 1.74 (d, *J* = 5.7 Hz, 3 H), 1.50 (m, 1 H), 1.20–0.90 (c, 4 H), 0.93 (s, 9 H), 0.15 (s, 3 H), 0.13 (buried, 1 H), 0.12 (s, 3 H), 0.10 (s, 9 H); HRMS (CI, NH_3) exact mass calcd for $C_{29}H_{52}NO_4Si_2$ 534.3436 (MH^+), found 534.3412; UV λ_{max}^{MeOH} (nm) (ε) 258 (34 759), 268 (45 720), 279 (35 455).

(1*R,2*S**,3*R**,5*S**,9*R**(1*E*,3*E*,5*E*),10*S**)-(±)-2-Hydroxy-9-(5-methyl-1,3,5-heptatrienyl)-4-oxa-8-azatricyclo[8.1.0.0^{3,5}]undecane-8-carboxylic Acid 2-(Trimethylsilyl)ethyl Ester (56).** To a tan solution of silyl ether **54** (28.0 mg, 52.4 μmol) in THF (2.8 mL) at room temperature with stirring under N_2 was added 1 M HIO_4 (11 drops from a Pasteur pipet). After 8 h, the mixture was diluted with EtOAc (10 mL), washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (2 × 5 mL), dried ($MgSO_4$), filtered, and evaporated. The above procedure was repeated on the same scale two additional times, and the crude mixtures were combined and purified by flash column chromatography (1:2 → 1:1 EtOAc/hexane) to give 57.0 mg (86%) of alcohol **56** as a colorless oil: IR ($CDCl_3$) 3584, 2950, 2915, 2852, 1675, 1457, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.30–6.10 (c, 3 H), 5.91–5.43 (c, 2 H), 4.40–4.10 (c, 3 H), 3.30–3.10 (c, 3 H), 2.94 (m, 1 H), 2.68 (m, 1 H), 2.40–2.00 (c, 2 H), 1.79 (d, *J* = 15.7 Hz, 3 H), 1.73 (s, 3 H), 1.62 (m, 1 H), 1.20–1.08 (c, 4 H), 0.35 (m, 1 H), 0.05 (s, 9 H); MS (EI, 20 eV) *m/e* 419 (M^+, 2.0), 391 (15.1), 362 (1.0), 347 (2.1), 332 (4.7), 318 (2.6), 274 (25.3), 160 (10.5); HRMS (CI, NH_3) exact mass calcd for $C_{23}H_{38}NO_4Si$ 420.2571 (MH^+), found 420.2566; UV λ_{max}^{MeOH} (nm) (ε) 258 (31 000), 279 (31 316), 268 (40 421).

(1*R,2*S**,3*R**,5*S**,9*R**(1*E*,3*E*,5*E*),10*S**)-(±)-9-(5-Methyl-1,3,5-heptatrienyl)-2-oxo-4-oxa-8-azatricyclo[8.1.0.0^{3,5}]undecane-8-carboxylic Acid 2-(Trimethylsilyl)ethyl Ether (57).** To a colorless solution of alcohol **56** (77.2 mg, 184 μmol) in CH_2Cl_2 (5.0 mL) at room temperature with stirring under N_2 was added tetra-*n*-propylammonium perruthenate (70.5 mg, 200 μmol). This mixture was stirred for 10 min and then filtered through a pad of Celite. The filtrate was concentrated and purified by flash column chromatography (1:4 EtOAc/hexane) to give 64.5 mg (84%) of ketone **57** as a colorless oil: IR ($CDCl_3$) 2950, 2922, 2852, 1696, 1675, 1457, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.30–6.00 (c, 3 H), 5.86 and 5.46 (two m, 1 H, rotamers), 5.56 (m, 1 H), 4.30–3.98 (c, 3 H), 5.06 (d, *J* = 4.8 Hz, 1 H), 3.40 (m, 1 H), 2.82–2.70 and 2.48–2.30 (two c, 4 H, rotamers), 2.06 (m, 1 H), 1.75 (d, *J* = 6.8 Hz, 3 H), 1.73 (s, 3 H), 1.56 (m, 1 H), 1.38 (dt, *J* = 5.0, 4.1 Hz, 1 H), 1.10–1.00 (c, 3 H), 0.07 (s, 9 H); MS (EI, 20 eV) *m/e* 417 (M^+, 3.6), 389 (18.2), 374 (9.1), 272 (85.7), 254 (6.2); HRMS (CI, NH_3) exact mass calcd for $C_{23}H_{36}NO_4Si$ 418.2415 (MH^+), found 418.2413; UV λ_{max}^{MeOH} (nm) (ε) 259 (27 917), 269 (37 292), 278 (28 542).

(±)-Indolizomycin (1). To a colorless solution of ketone **57** (17.0 mg, 40.7 μmol) in THF (1.7 mL) at 0 °C with stirring under N_2 was added TBAF (122 μL, 1.0 M in THF, 122 μmol). The resulting brown solution was stirred for 1.5 h, concentrated, and purified by flash column chromatography (15% MeOH/$CHCl_3$) followed by preparatory TLC (200 μm, 1:1 MeOH/$CHCl_3$) to give 3.2 mg (29%) of synthetic indolizomycin (**1**) as a brown oil, whose spectral properties were identical with the published data[2] for natural indolizomycin (**1**) except for optical rotation.

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Supplementary Material Available: Listings of experimental procedures and analytical data for compounds **21–26, 29, 31, 46,** and **47**, X-ray structures and listings of parameters for **17, 40d,** and **47**, and ^1H NMR spectra of synthetic and natural **1** (31 pages). Ordering information is given on any current masthead page.