Total Synthesis of Spirotryprostatin A, Leading to the Discovery of Some Biologically Promising Analogues

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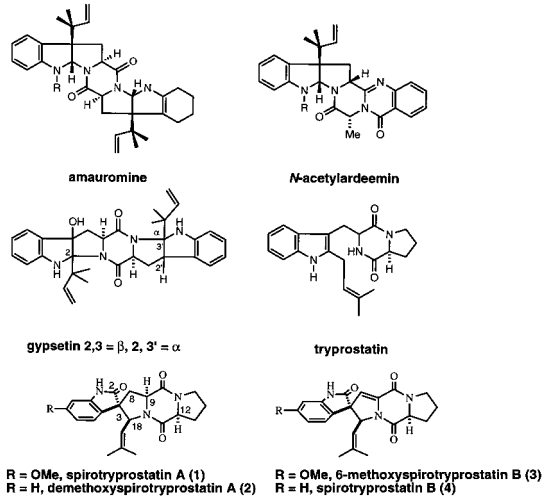
Abstract: The total synthesis of the title compound has been accomplished. A key step involves the oxidative rearrangement of the β-carboline derivative to an oxindole via the action of *N*-bromosuccinimide. From this point, a diketopiperazine was introduced. A thiophenyl group served as a precursor of the isopropylidene function. Implementation of the same sort of chemistry starting with a methoxytryptophan derivative led to the parent structures. Furthermore, it was shown that the difficultly accessible isopropylidene side chain of spirotryprostatin A is not necessary for biological activity. Moreover, three analogues lacking the diketopiperazine system were shown to be quite active as cell cycle inhibitors.

Introduction

A growing number of alkaloids, probably derived from L-tryptophan, which also bear a pyrrolo ring in the context of a diketopiperazine system (or another heterocyclic array), are being discovered. Adding to their interest is the fact that they display a range of biological profiles effecting cell cycle progression.[1] One of these molecules, tryprostatin A, has recently been shown to be a novel inhibitor of microtubule assembly.[1c] Our laboratory has particularly focused on those members of this class that also carry prenyl or "reverse-prenyl" substituents. As a prelude to multidisciplinary investigations addressed to structure−activity relationship and mode of action issues, we have concerned ourselves with the goal of total synthesis. To date, we have described the total syntheses of amauramine, the ardeemins, gypsetin, and tryprostatin B.[2] The ardeemins are currently being pursued in our program as potential MDR reversal agents.

Recently, spirotryprostatins A and B were isolated from the fermentation broth of *Aspergillus fumigatus*.[1] Besides possessing synthetically challenging structural features, these spirooxindoles were shown to inhibit the cell cycle in the G2/M phase with IC_{50}'s of 197.5 (**1**) and 14.0 μm (**4**). Cell cycle inhibitors not only possess the potential to act as antineoplastic agents but could also serve as possible probes to gain information about cell signaling pathways. The difference between the activities in these two cell cycle inhibitors is striking, with **4** being more than an order of magnitude more potent than **1**. Studies in related natural products indicate that the aromatic methoxy group present in **1** and **3** can weaken their activities significantly. When this effect is quantified, however, these related examples underestimate the difference in activity between **1** and **4**.[1b] Analogues **2** and **3** would allow a complete assessment of the importance of the methoxy group relative to the importance of unsaturation at C8/C9. Since 400 L of fermentation broth yielded only 1 mg of **1** and 11 mg of **4**, a total chemical synthesis of these molecules seems at least a competitive way to obtain the compounds in quantities that are ample for launching a thorough biological investigation.



The overall synthesis strategy which we came to favor for reaching the spirotryprostatin targets is illustrated in Scheme 1.[3] Initial formation of the cis-substituted tetrahydro-β-carboline **5** would be accomplished using a Pictet−Spengler reaction between a tryptophan derivative (cf. **8**, vide infra) and a synthetic equivalent of prenyl aldehyde. Spirorearrangement of an indole so derived (cf. **5**) to an oxindole **7** (perhaps via an intermediate of the type **6**) was viewed as the central step in the enterprise, in that it would accomplish installation of the quaternary center at C3 and could provide control over the relative stereochemistry

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(1) (a) Cui, C.-B.; Kakeya, H.; Okada, G.; Onose, R.; Osada, H. *J. Antibiot.* **1996**, *49*, 527. (b) Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1997**, *53*, 59. (c) Usui, T.; Kondoh, M.; Cui, C.-B.; Mayumi, T.; Osada, H. *Biochem. J.* **1998**, *333*, 543.

(2) (a) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143. (b) Schkeryantz, J.; Woo, J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 7025. (c) Depew, K. M.; Danishefsky, S. J.; Rosen, N.; Sepp-Lorenzino, L. *J. Am. Chem. Soc.* **1996**, *118*, 12463.

(3) For an earlier communication of this synthesis, see: Edmondson, S. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1138.

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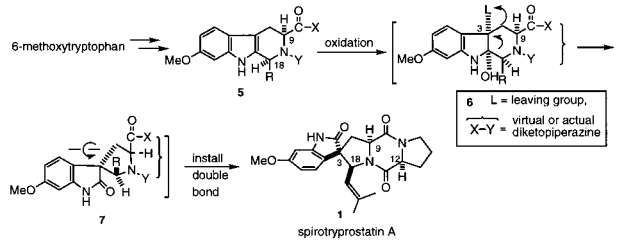
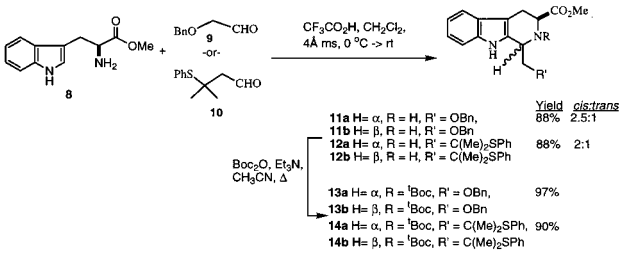
Scheme 1



Scheme 2



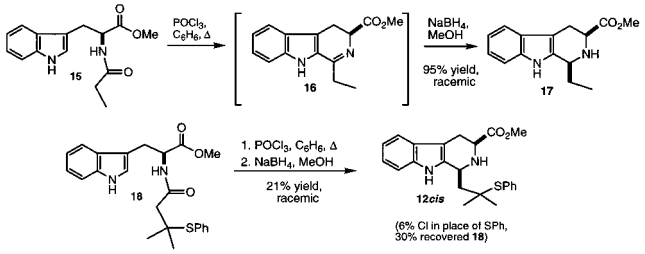
at carbons 3 and 18 in the eventual target **1**. The precise timing of installation of the isopropylidene group and the diketopiperazine ring were issues which would surely merit close attention. However, our primary focus was on the all-critical spirorearrangement step. It was believed that a β-oriented R group at C18 of **5** would direct functionalization of the indole ring to the α-face. It was further anticipated that the rearrangement step would occur with inversion at C3, thereby producing the C3, C18, and C9 stereochemical connectivities shown in **7**.

Synthetic Results

Previous reports concerning attempted Pictet−Spengler reactions between commercially available tryptophan methyl ester (**8**) and prenyl aldehyde per se have been quite discouraging.[4] Moreover, early investigations suggested that the isopropylidene group would be likely to interfere with the maneuvers we had in mind to achieve the overall transformation of **5** → **7**. *We thus came to favor installation of this moiety after the oxidative rearrangement of the indole had been accomplished*. Commercially available benzyloxyacetaldehyde (**9**) or readily available thioaldehyde **10** were evaluated as potential Pictet−Spengler substrates whose functionalities might lend themselves to the eventual incorporation of the isopropylidene linkage. In the event, reaction of these aldehydes with **8** under anhydrous acid conditions provided the desired cis-related tetrahydrocarbolines **11a** and **12a** in excellent yields in the expected marginal selectivities with respect to their trans counterparts, **11b** and **12b** (Scheme 2).[5]

Our results followed the pattern established in the long-term and scholarly studies of Cook and associates[6] as regards the kinetic outcome of the Pictet−Spengler reactions of various tryptophan derivatives. The kinetic outcome favors cis products (cf. **11a**) but only by modest selectivities. By contrast, the trans compounds (cf. **11b**) can often be obtained in high margins by thermodynamic equilibration. Unfortunately, we required intermediates in the cis "family."

Scheme 3



Although the separation of **12a** from **12b** was readily achieved, comparable purification of cis **11a** in the face of trans **11b** proved to be quite difficult. Fortunately, these diastereomers could be more readily separated after suitable protection of the basic nitrogen. Conversion of the sterically crowded secondary amines to their corresponding *tert*-butylcarbamate (Boc) derivatives was sluggish but furnished reasonable yields (based on recovered starting material) of **13a** and **14a**. Deprotection of the Boc group under standard conditions then afforded pure samples of **11a (*cis*)** and **11b (*trans*)**, which were initially identified using Cook's ^{13}C NMR method and later confirmed by NOE methods.[6]

Given this less than ideal situation, additional effort was directed toward improving the synthesis of the desired cis compound. The plan involved use of the Bischler−Napieralski reaction to generate dihydro-β-carbolines (cf. **16**) which might be reduced in the desired sense. A model experiment involved heating amide **15** with phosphorus oxychloride in benzene, followed by treatment of the intermediate imine **16** with sodium borohydride (Scheme 3). This protocol did, indeed, produce the clearly desired cis product **17**. Unfortunately, **17** thus obtained was racemic. It is not clear whether racemization at the "tryptophan" chiral center had occurred on a mechanistic intermediate derived from **15** en route to cyclization or at the stage of **16**. Given this result, we were unable to exploit the fact that simple reduction of the crude intermediate following cyclization (cf. **16**) did, indeed, produce the desired diastereomer **17**. Furthermore, exposure of amide **18** to the above conditions produced the racemic product **12a** in modest yield (21%), with side products resulting from replacement of the thiophenyl group with a chlorine atom. In light of these findings in the context of the Bischler−Napieralski route, the Pictet−Spengler sequence, albeit far from ideal, seemed to be the preferred method for producing the desired cis adducts in enantiomerically homogeneous form.

Assembly of a diketopiperazine starting from **11a,b** was achieved. The first step involved acylation of the mixture with the proline-derived acid chloride **19.** The crude *seco* compound was subjected to the action of zinc metal. This treatment accomplished the desired deprotection of the carbamate, thereby setting into motion the required cyclization (see **20**, in 54% overall yield) (Scheme 4).[7]

Compound **20** was subjected to the action of *N*-bromosuccinimide (NBS) in aqueous acetic acid.[8] This exposure sufficed to bring about oxidative rearrangement as originally planned. Surprisingly extensive NMR analysis of the resultant product, particularly its NOESY spectrum, revealed it to be oxindole **23**. Thus, the stereosense of the formation of the spirorearrangement product had occurred opposite to our expectation.

(4) (a) Harrison, D. M. *Tetrahedron Lett.* **1981**, *22*, 2501. (b) O'Malley, G. J.; Cava, M. P. *Tetrahedron Lett.* **1987**, *28*, 1131.

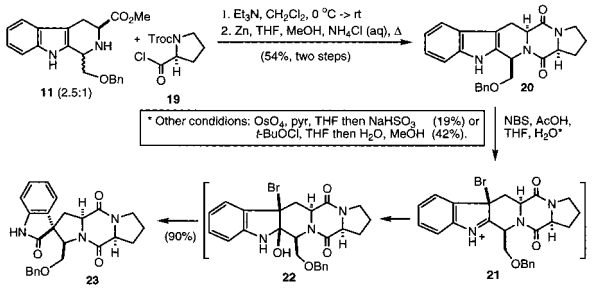
(5) The Pictet−Spengler reaction of **8** and **38** with **10** has been reported: (a) Harrison, D. M.; Sharma, R. B. *Tetrahedron Lett.* **1986**, *27*, 521. (b) Kodato, S.; Nakagawa, M.; Hongu, M.; Kawate, T.; Hino, T. *Tetrahedron* **1988**, *44*, 359.

(6) For lead references of the Pictet−Spengler reaction to synthesize cis and trans tetrahydrocarbolines, see: (a) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng., L.; Bennett, D. W.; Cook, J. M.; Watson, W. H.; Krawlec, M. *J. Org. Chem.* **1997**, *62*, 44. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.

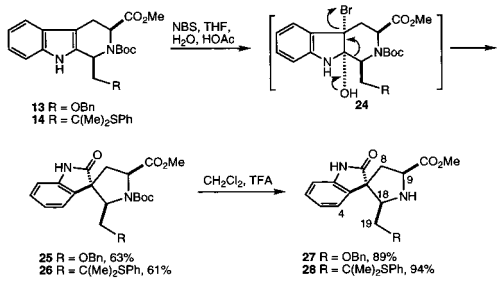
(7) Boyd, S. A.; Thompson, W. J. *J. Org. Chem.* **1987**, *52*, 1790.

(8) VanTamelen, E. E.; Yardley, J. P.; Miyano, M.; Hinshaw, W. B. *J. Am. Chem. Soc.* **1969**, *91*, 7333.

Scheme 4



Scheme 5

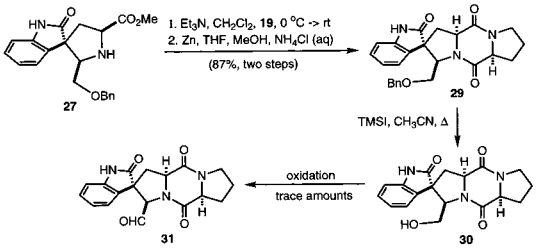


The use of some alternative oxidants such as osmium tetraoxide or ^{t}BuOCl resulted in diminished yields of **23** (19% and 42%, respectively).[10] The use of other agents such as dimethyl dioxirane[11] or lead tetraacetate[12] led to complicated mixtures which did not lend themselves to separation. Replacement of the benzyl group with a *tert*-butyldimethylsilyl group also failed to correct the problem.[13] *Apparently, the diketopiperazine ring enforces a poorly understood conformational preference on the fused pyrrolo ring which favors electrophilic attack at the β-face of the indole syn to the benzyloxymethylene group*. The intermediate bromoindolenine **21** is then solvolyzed to form hemiaminal **22**. The latter proceeds to rearrange to **23**.[14]

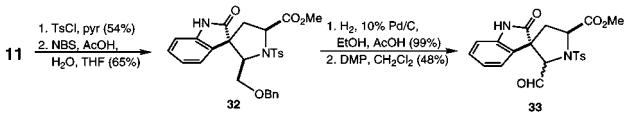
Since the precise factors which favored attack of the oxidant syn to the benzyloxymethyl group remain somewhat mysterious, we were obliged to survey other substrates without the benefit of a guiding rationale, hoping to find one where attack of the oxidant anti to the resident C3 group was favored. An obvious possibility was to conduct spirorearrangement *before* diketopiperazene formation.

With this subgoal in mind, indoles **13a** and **14a** were exposed to the aforementioned NBS-mediated rearrangement conditions to afford oxindoles **25** and **26** (Scheme 5). Since the proton NMR spectra of these molecules were complicated by carbamate rotamers, deprotection of the Boc groups was necessary before the stereochemistry of these products could be confirmed. The appropriate NOE enhancements of amines **27** and **28** indeed

Scheme 6



Scheme 7



showed that the desired stereochemistry had now been obtained following the spirorearrangement step. Irradiation of H4 typically showed NOE enhancements at H8β and H19, while irradiation of H18 showed enhancements at H8α, H9, and H19. The reverse enhancements were also observed.

Rearrangements of this type had been studied extensively by Borschberg et al., and a detailed conformational analysis can be found in that work.[15] Also to be noted is the resistance of the phenyl sulfide to oxidation under the spirorearrangement conditions. Care must be taken to employ appropriate amounts of NBS since excess reagent induces electrophilic aromatic bromination of the oxindole products.

Amine **27** was next converted to the corresponding diketopiperazine **29**, under conditions similar to those employed above (Scheme 6). However, deprotection of the benzyl group from **29** proved to be problematic, affording low yields of the corresponding alcohol. Furthermore, oxidation of the resulting alcohol to the corresponding aldehyde was a low-yielding and incomplete process.[16]

In a model system, oxindole **32** was generated by spirorearrangement of the cis N-tosyl derivative of **11a** (Scheme 7). Deprotection of the benzyl group was easily accomplished by hydrogenolysis. Although oxidation of this alcohol proved to be difficult, the pure aldehyde was finally obtained only after repeated exposure of partially oxidized mixtures to Dess−Martin's periodinane. Proton and carbon NMR analysis of this aldehyde indicated that it was actually a 1:1 mixture of two products. This suggested the occurrence of a rapid enolization and epimerization of the "α-chiral aldehyde". In any case, the mixture of **33** was resistant to olefination procedures, however, and this route was abandoned.

Attention was next directed to sulfide **26**. Oxidation of this compound to a mixture of sulfoxides was followed by thermal elimination and nitrogen deprotection to give a 1:1.5 mixture of external olefin **34** and enamine **35**, respectively (Scheme 8). When sulfoxide elimination was induced after carbamate deprotection, **34** was obtained. Apparently, the acidic conditions required to achieve Boc deprotection also had induced isomerization of the trisubstituted double bond to form the stable enamine **35**. By contrast, the undesired alternate elimination product, **34**, is stable to the reaction conditions. Presumably, **35** benefits from nitrogen resonance with the double bond.

(9) (a) Takayama, H.; Kitajima, M.; Okata, K.; Sakai, S. *J. Org. Chem.* **1992**, *57*, 4583. (b) Peterson, A. C.; Cook, J. M. *Tetrahedron Lett.* **1994**, *35*, 2651.

(10) (a) Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S.-i. *Tetrahedron* **1989**, *45*, 1327. (b) Hollinshead, S. P.; Grubisha, D. S.; Bennett, D. W.; Cook, J. M. *Heterocycles* **1989**, *29*, 529.

(11) (a) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867. (b) Adam, W.; Ahrweiler, M.; Peters, K.; Schmeideskamp, B. *J. Org. Chem.* **1994**, *59*, 2733.

(12) Finch, N.; Gemenden, C. W.; Hsu, I. H.-C.; Kerr, A.; Simm, G. A.; Tayer, W. I. *J. Am. Chem. Soc.* **1965**, *87*, 2229.

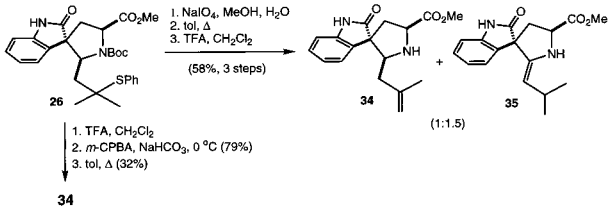
(13) The synthesis of the TBS analogue of **20** is achieved easily in two steps: TMSI, CH_3CN/CH_2Cl_2; then TBSCl, imid, DMF. Attempts to oxidatively rearrange this molecule resulted in complicated mixtures and loss of silicon.

(14) An observation of molecular models reveals that the corresponding trans ring fusion, resulting from attack of water on the α-face of **21**, would be a highly strained molecule and, thus, less likely to form.

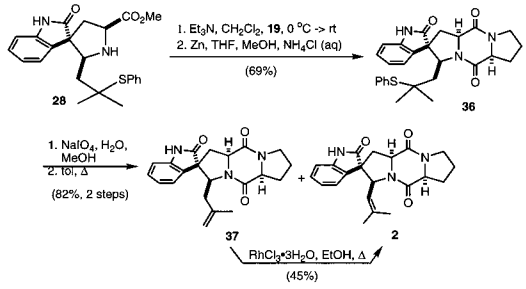
(15) (a) Pelligrini, C.; Strassler, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979. (b) Pelligrini, C.; Weber, M.; Borschberg, H.-J. *Helv. Chim. Acta* **1996**, *79*, 151.

(16) In part, the difficulty in oxidizing of **30** is due to the poor solubility of this molecule in organic solvents. Advantage was taken in the model system (Scheme 7) of the more desirable solubility properties that these molecules possess prior to diketopiperazine formation.

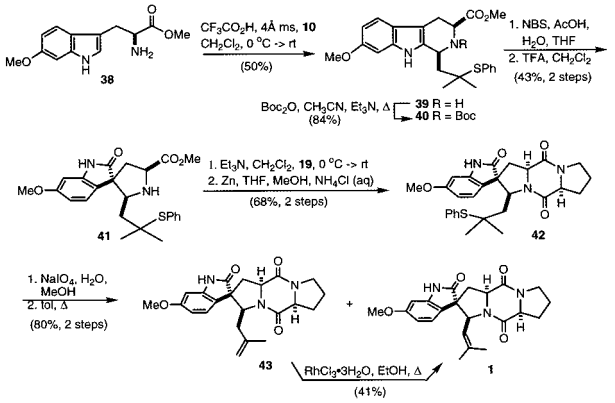
Scheme 8



Scheme 9



Scheme 10



Although, in principle, **34** could be converted to the desired target, a late-stage sulfoxide elimination was investigated with the hope that introduction of the diketopiperazine ring might modulate regioselectivity in the desired sense. Formation of the diketopiperazine from **28** proceeded without event to give **36** (Scheme 9). Careful oxidation of **36** with 1 equiv of sodium periodate afforded a 1:1 mixture of the two diastereomeric sulfoxides in nearly quantitative yield (97%). A reaction designed to achieve elimination of the sulfoxides in refluxing toluene then afforded a mixture of the external and internal olefins in 93% yield and 2.6:1 selectivity, favoring the internal olefin. HPLC separation of the double bond isomers then afforded pure samples of **37** and **2**. A comparison of ^{1}H and ^{13}C NMR spectral data between **2** and naturally occurring **1** revealed striking similarities in all respects except the aromatic regions (which was to be expected). An extensive series of NOE enhancements further supported the relative stereochemistry of C3, C9, C12, and C18. We were pleased to find that we could further increase the efficiency of our route by transforming **37** to **2** using rhodium chloride catalysis. The first total synthesis of spirotryprostatin **2** was now complete.

With a workable route to spirotryprostatin A accomplished, we set about to apply this chemistry to the real system (Scheme 10). Pictet−Spengler reaction of **38** with **9** was followed by protection of the amine as its Boc derivative to give **40**. Spirorearrangement of **40** to the oxindole **41** was followed by deprotection of the carbamate under standard conditions to afford amine **42**. A detrimental effect on the yield of the spirorearrangement was observed, apparently due to the increased susceptibility of the methoxy-bearing oxindole to electrophilic aromatic bromination.

Conversion of **42** to the diketopiperazine was followed by sulfide oxidation and sulfoxide elimination to afford a 2.5:1 mixture of **1** and **43**, respectively. HPLC separation of these isomers afforded pure natural product. External olefin **43** could then be converted to spirotryprostatin A by treatment with rhodium chloride in refluxing ethanol. The ^{1}H and ^{13}C NMR spectra and mass spectrum of **1** matched those of the naturally occurring material in all respects.[17] The optical rotation of synthetic **1** ($[\alpha]^{21.4}_D$ −116.2°), however, was significantly different from that of naturally occurring **1** ($[\alpha]^{26}_D$ −34.0°). Since, in principle, every chiral center of **1** is susceptible to epimerization, it is conceivable that, during its isolation, naturally occurring **1** had undergone substantial racemization. Alternatively, and more likely, the discrepancy reflects the fact that only small, inhomogeneous samples of **1** were isolated from natural sources. By contrast, chemical synthesis, even in the face of some difficulties described above, provides ample amounts of optically pure material.

In summary, the total synthesis of spirotryprostatin A (**1**) and its demethoxy congener (**2**) were each achieved in a total of eight steps in 10% and 14% yields, respectively. Highlighted in this synthesis is the ability to control the stereochemical relationship between C3 and C18 during the stereodefining spirorearrangement step. The late-stage regioselective sulfoxide elimination that favors formation of the internal olefin over the external olefin (despite a 3:1 statistical bias) also merits attention.

Biological Results

We now describe the biological evaluation of spirotryprostatin and some of its analogues available by total synthesis. We started with the fully synthetic spirotryprostatin A. Cell cycle inhibition of mouse tsFT210 cell lines in the G2/M phase had been reported for **1** (IC_{50} = 197.5 μM) and **3** (IC_{50} = 14.0 μM) by Osada et al.[1] With access to substantial quantities of **1** and selected analogues of **1** at our disposal, we explored the activity of six molecules (**1**, **2**, **23**, **25**, **29**, and **43**) on MCF-7 and MDA MB-468 human breast cancer cells (Figure 1).[2c]

Given the low activity of **1** with the tsFT210 cell line, it was not surprising that it shows little activity in the anchorage-dependent growth assay. MCF7 cells were not inhibited in terms of growth with concentrations as high as 300 μM (Figure 1 and Table 1), and high micromolar concentrations were necessary to inhibit the growth of MDA MB-468 cells (IC_{50} = 110 μM). Similar values were obtained for demethoxyspirotryprostatin A (**2**) and isospirotryprostatin A (**43**). These compounds showed no significant activity in MCF7 cells, whereas micromolar concentrations of both compounds inhibited MDA MB-468 cell growth (Figure 1 and Table 1).

By contrast, **23**, **25**, and **29** were active in both cells lines (Figure 1 and Table 1). As seen most remarkably for MDA MB-468 cells, **23**, **25**, and **29** were 3−4 orders of magnitude more potent than the natural product in inhibiting cancer cell growth (Figure 1 and Table 1). It should be noted that one of these active compounds, **25**, is also the simplest of the molecules, since it lacks the proline-containing diketopiperazine ring. Oxindole **25** had been easily synthesized in only three steps from commercially available starting materials. Moreover, the synthesis of **23** is also both shorter and higher yielding (four steps, 43% yield) than is the synthesis of the natural product itself.

(17) Spectral data of naturally occurring **1** were kindly provided by Professor Osada.

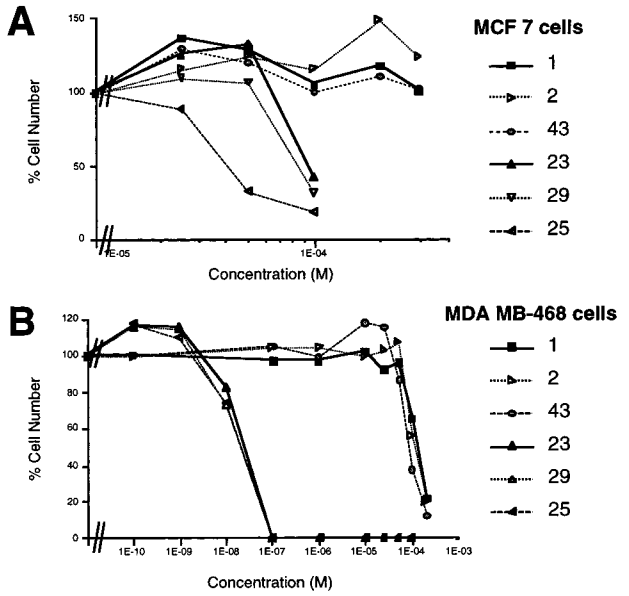


Figure 1. Effect of spirotryprostatin A and derivatives on anchorage-dependent tumor cell growth. MCF7 (A) and MDA MB-468 (B) human breast cancer cells were plated at 10 000 cells/well on six-well plates and treated with increasing concentrations of spirotryprostatin A and analogues. Drugs were added from 1000× stock solutions dissolved in dimethyl sulfoxide. Control cultures received an equivalent volume of dimethyl sulfoxide. Cultures were refed with drug-containing medium at day 3, and cultures were trypsinized and cell number determined at day 6. Results are the averages of two independent experiments.

Table 1. IC_{50} for Inhibition of Anchorage-Dependent Growth of MDA MB-468 and MCF7 Human Breast Cancer Cells

	IC_{50} (M)	
compound	MDA MB-468	MCF7
spirotryprostatin A (**1**)	1.1×10^{-4}	$\gg 3 \times 10^{-4}$
demethoxyspirotryprostatin A (**2**)	1×10^{-4}	$\gg 3 \times 10^{-4}$
isospirotryprostatin A (**43**)	8.5×10^{-5}	$\gg 3 \times 10^{-4}$
benzyl spiroisomer (**23**)	2.5×10^{-8}	1×10^{-4}
benzyl analogue (**29**)	2×10^{-8}	8×10^{-5}
spirooxindole (**25**)	2×10^{-8}	4×10^{-5}

In conclusion, the synthetic studies directed at spirotryprostatin A have yielded three analogues which show much greater activity than the natural product itself. It appears that the structure−activity relationships among spirotryprostatins are multifaceted and go beyond the presence or absence of a methoxy group on the aromatic ring in the fully developed structure. Further studies concerning the nature of these structure−activity relationships, as well as a search for more optimal development candidates, are currently underway.

Experimental Section

Benzyloxytetrahydro-β-carbolines 11. To L-tryptophan methyl ester (4.417 g, 20.2 mmol), powdered 4-Å molecular sieves (300 mg), and benzyloxyacetaldehyde (3.75 g, 25 mmol) in 50 mL of CH_2Cl_2 at 0 °C was added 1.7 mL (22 mmol) of trifluroroacetic acid, and the reaction mixture was stirred at 0 °C for 1 h. Then, an additional 3.0 mL (60.6 mmol total) of trifluoroacetic acid was added to the reaction mixture, and the solution was stirred at 0 °C for an additional 4 h before the mixture was filtered, dissolved into 500 mL of CH_2Cl_2, washed with saturate $NaHCO_3$ (2 × 200 mL) and brine (100 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, 20% EtOAc/hexanes) to afford 6.155 g (87%) of the cis/trans diastereomers **11** (2.3:1). For **11a**: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.52$ (s, 1 H), 7.52 (d, $J = 8.3$ Hz, 1 H), 7.18 (t, $J = 7.8$ Hz, 1 H), 7.12 (t, $J = 7.5$ Hz, 1 H), 4.66 (s, 2 H), 4.42−4.41 (m, 1 H), 3.84 (s, 3 H), 3.86−3.81 (m, 3 H), 3.68 (t, $J = 9.3$ Hz, 1 H), 3.18 (dd, $J = 16.0$, 12.0 Hz, 1 H), 2.86 (m, 1 H), 2.22 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 173.4$, 137.5, 135.8, 134.5, 128.6 (2 C), 128.1, 128.0 (2 C), 126.7, 121.7, 119.3, 118.0, 110.9, 107.5, 73.8, 73.5, 56.3, 52.2, 52.1, 25.6.

For **11b**: ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 174.0$, 137.8, 135.9, 133.5, 128.6 (2 C), 128.0, 127.9 (2 C), 126.7, 121.7, 119.3, 118.0, 110.9, 107.0, 73.6, 73.6, 56.3, 53.3, 49.5, 24.8.

cis-Benzyloxycarbamate 13. To the mixture **11a,b** (4.72 g, 13.5 mmol) in 60 mL of 5:1 MeOH/Et_3N was added the Boc_2O (8.84 g, 40.5 mmol), and the mixture was stirred at 50 °C for 14 h and then cooled to room temperature. The crude mixture was concentrated and chromatographed (SiO_2, 10% EtOAc/hexanes) to afford 1.07 g of **13a**, 0.571 g of **13b** (27% yield, 1.9:1 cis/trans), and 3.42 g of recovered starting material (97% adjusted yield). For **13a**: $[\alpha]^{21.0}_D$ +141.9° ($c = 1.812$, $CHCl_3$); IR ($CHCl_3$) 3420, 2986, 2960, 2932, 2908, 2840, 1730, 1678, 1618, 1448, 1390 cm^{-1}; HRMS (FAB) *m*/*z* (M^+) calcd 450.2156, obsd 450.2142.

Carbamate Sulfide 14. To the amine **12a**[5] (2.49 g, 6.3 mmol) in 100 mL of 9:1 CH_3CN/Et_3N was added the Boc_2O (4.10 g, 18.9 mmol), and the mixture was stirred at 50 °C for 14 h and then cooled to room temperature. The crude mixture was concentrated and chromatographed (SiO_2, 15% EtOAc/hexanes) to afford 1.02 g of the desired product **14a** (33%) and 1.59 g of recovered starting material (90% adjusted yield). For **14a**: $[\alpha]^{21.6}_D$ −14.6° ($c = 2.17$, $CDCl_3$); IR ($CDCl_3$) 3434, 3292, 3057, 2981, 2934, 2858, 1741, 1684, 1623, 1391, 1368, 1165 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 8.94-8.84$ (br s, 1 H), 7.56−7.13 (series of m, 9 H), 5.75−4.98 (m, 2 H), 3.68−3.62 (m, 3 H), 3.40−3.10 (m, 2 H), 2.35−2.11 (m, 2 H), 1.62−1.23 (m, 15 H); HRMS *m*/*z* (M^+) calcd 494.2241, obsd 494.2239.

Bischler−Napieralski Reaction of 15. Amide **15**[18] (303 mg, 1.10 mmol) in 5 mL of benzene and 1 mL of $POCl_3$ was heated to reflux for 40 min, cooled to room temperature, and then concentrated. After the orange viscous oil was taken up in 10 mL of methanol, $NaBH_4$ (285 mg, 7.54 mmol) was added to the mixture at room temperature, and the yellow slurry was stirred for an additional 30 min, quenched with 5 mL of 5% HCl, diluted with 100 mL of saturated $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were then washed with saturated $NaHCO_3$ (2 × 20 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, 30% EtOAc/hexanes) to afford 282 mg (99%) of the racemic product **17**.[19]

Amide 18. Readily available 3-methyl-3-phenylsulfonylbutyric acid[20] (4.70 g, 22.4 mmol) in 50 mL of benzene and 10 mL of $SOCl_2$ was heated to reflux for 90 min and then concentrated to form the corresponding acid chloride. To tryprophan methyl ester hydrochloride (4.58 g, 18 mmol) and Et_3N (5.0 mL, 36 mmol) in 100 mL of CH_2Cl_2 at 0 °C was added the acid chloride (dropwise in 60 mL of CH_2Cl_2) over 30 min. The reaction mixture was then allowed to stir for 60 min at 0 °C and for 60 min at room temperature before being quenched with 50 mL of water and extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were then washed with 5% HCl (3 × 100 mL), saturated $NaHCO_3$ (2 × 200 mL), and brine (100 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, 30% EtOAc/hexanes → 70% EtOAc/hexanes) to afford 6.91 g (94%) of amide **18**: $[\alpha]^{20.0}_D$ +33.9° ($c = 1.42$, $CHCl_3$); IR ($CHCl_3$) 3458, 3407, 3285, 2996, 2950, 2908, 1730, 1656, 1502, 1430 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.82$ (s, 1 H), 7.58 (d, $J = 7.9$ Hz, 1 H), 7.38−7.07 (m, 7 H), 7.02 (d, $J = 2.2$ Hz, 1 H), 5.01 (dd, $J = 12.9$, 6.7 Hz, 1 H), 3.68 (s, 3 H), 3.39 (dd, $J = 14.9$, 5.4 Hz, 1 H), 3.32 (dd, $J = 14.9$, 6.7 Hz, 1 H), 2.36 (s, 2 H), 1.35 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 172.4$, 170.1, 137.2 (2 C), 136.1, 130.6, 129.0,

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128.6 (2 C), 127.3, 122.9, 121.9, 119.3, 118.2, 111.3, 109.4, 52.9, 52.1, 48.0, 47.0, 28.8, 28.2, 27.4; HRMS *m/z* ($M^+ + 1$) calcd 411.17, obsd 411.18.

Bischler−Napieralski Reaction of 18. Amide **18** (210 mg, 0.513 mmol) in 5 mL of benzene and 4 mL of $POCl_3$ was heated to reflux for 2.5 h, cooled to room temperature, and then concentrated. After the orange viscous oil was then taken up in 15 mL of methanol, $NaBH_4$ (700 mg, 18.5 mmol) was added to the mixture at 0 °C, and the yellow slurry was stirred for an additional 30 min at this temperature, quenched with 3 mL of 10% HCl, diluted with 50 mL of saturated $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were then washed with saturated $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, 20% EtOAc/hexanes) to afford 43.4 mg (21%) of the racemic product **12a**,[5] 12.0 mg of the chloride, and 63.7 mg of recovered starting material.

Diketopiperazine 20. To the amine mixture **11** (386 mg, 1.10 mmol) and Et_3N (0.307 mL, 2.20 mmol) in 4 mL of CH_2Cl_2 at 0 °C was added acid chloride **19**[7] (583 mg, 1.88 mmol) in 10 mL of CH_2Cl_2 dropwise. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for 5 h before being quenched with 10 mL of water. Extraction of the aqueous layer with CH_2Cl_2 (3 × 40 mL) was followed by washing with 10% HCl and saturated $NaHCO_3$ (50 mL each), drying over $MgSO_4$, filtration, concentration, and chromatography (SiO_2, 30% EtOAc/hexanes) to afford 434 mg of the desired cis diastereomer and 167 mg of the trans diastereomer (87% total yield, 2.6:1).

To the above cis amide (343 mg, 0.549 mmol) in 35 mL of 2:2:1 THF/MeOH/saturated NH_4Cl was added zinc dust (3 g), and the gray slurry was stirred at reflux for 6 h. After cooling to room temperature, the slurry was filtered, concentrated, dissolved into 20 mL of water, and then washed with saturated $NaHCO_3$ and brine (50 mL each), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, 80% EtOAc, hexanes) to afford 198 mg (86%) of diketopiperazine **20**: $[\alpha]^{21.7}_D$ −5.3° (c = 2.35, CH_2Cl_2); IR ($CHCl_3$) 3679, 3453, 3011, 2863, 1663, 1520, 1420, 1212 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.19 (s, 1 H), 7.60 (d, J = 7.7 Hz, 1 H), 7.36 (d, J = 7.9 Hz, 1 H), 7.28−7.15 (m, 7 H), 5.47 (dd, J = 9.8, 4.0 Hz, 1 H), 4.47 (d, J = 9.9 Hz, 1 H), 4.39 (d, J = 9.9 Hz, 1 H), 4.18−4.11 (m, 2 H), 3.94 (dd, J = 9.2, 3.9 Hz, 1 H), 3.66−3.63 (m, 2 H), 3.56 (dd, J = 15.9, 4.9 Hz, 1 H), 3.33 (t, J = 8.5 Hz, 1 H), 3.08 (dd, J = 15.8, 11.8 Hz, 1 H), 2.48−1.94 (series of m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.4, 165.5, 137.8, 136.1, 132.5, 128.4 (2 C), 127.7, 127.0 (2 C), 126.0, 122.1, 119.1, 118.3, 111.3, 106.8, 73.3, 72.4, 59.2, 58.5, 51.8, 45.4, 28.0, 23.1, 21.8; HRMS *m/z* ($M^+ + 1$) calcd 416.1976, obsd 416.1981.

Deprotection of 20. To the ether **20** (222 mg, 0.535 mmol) in 150 mL of CH_3CN/CH_2Cl_2 (1.5:1) was added TMSI (0.304 mL, 2.14 mmol) at 0 °C, the reaction mixture was stirred at 0 °C for 90 min, and then MeOH (5 mL) was added and the resulting mixture was stirred for an additional 30 min. This mixture was then quenched with saturated $NaHSO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine (50 mL each), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, EtOAc → 5% MeOH in CH_2Cl_2) to afford 134 mg (77%) of the pure alcohol as a colorless solid: $[\alpha]^{20.6}_D$ −76.2° (c = 0.803, MeOH); IR ($CHCl_3$) 3457, 3050, 2986, 1676, 1452, 1401, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.77 (s, 1 H), 7.59 (d, J = 7.7 Hz, 1 H), 7.35 (d, J = 7.7 Hz, 1 H), 7.21−7.14 (m, 2 H), 5.51 (t, J = 5.8 Hz, 1 H), 4.16−4.09 (m, 2 H), 3.91 (m, 1 H), 3.70−3.55 (m, 4 H), 3.15−3.05 (m, 2 H), 2.47−1.94 (series of m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.4, 165.2, 136.3, 131.0, 125.9, 122.3, 120.0, 118.4, 111.4, 107.4, 68.9, 59.2, 58.9, 54.9, 54.8, 45.4, 28.8, 23.0; HRMS *m/z* ($M^+ + 1$) calcd 326.1505, obsd 326.1491.

***tert*-Butyldimethylsilyl Analogue of 20.** To the above alcohol (81 mg, 0.249 mmol) in 2 mL of DMF were added the TBSCl (301 mg, 2.0 mmol) and imidazole (170 mg, 2.5 mmol), and the reaction mixture was stirred at room temperature for 12 h. This solution was quenched with 10 mL of water and extracted with CH_2Cl_2 (3 × 50 mL), and the organic layers were washed with brine (5 × 20 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, EtOAc) to afford 89 mg (82%) of the desired silyl ether: $[\alpha]^{21.6}_D$ −17.6° (c = 0.944, $CHCl_3$); IR (CH_2Cl_2) 3432, 3030, 2963, 2938, 2910, 2840, 1659, 1440, 1390 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.13 (s, 1 H), 7.59 (d, J = 7.7 Hz, 1 H), 7.36 (d, J = 7.9 Hz, 1 H), 7.20 (t, J = 7.5 Hz, 1 H), 7.15 (t, J = 7.4 Hz, 1 H), 5.33 (dd, J = 8.3, 4.0 Hz, 1 H), 4.17−4.12 (m, 2 H), 4.05 (dd, J = 8.0, 4.0 Hz, 1 H), 3.66−3.63 (m, 2 H), 3.53 (dd, J = 15.8, 5.0 Hz, 1 H), 3.45 (t, J = 8.5 Hz, 1 H), 3.10 (dd, J = 15.8, 11.7 Hz, 1 H), 2.48−1.93 (series of m, 4 H), 0.82 (s, 9 H), −0.07 (s, 3 H), −0.14 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.4, 165.6, 136.1, 132.6, 126.1, 122.0, 119.8, 118.3, 111.1, 106.8, 65.4, 59.2, 56.5, 53.7, 45.4, 28.6, 25.8 (3 C), 23.1, 21.8, 18.2, −5.7 (2 C); HRMS *m/z* ($M^+ + K$) calcd 478.1928, obsd 478.1939.

Oxindole 23. To the indole **20** (167 mg, 0.401 mmol) in 30 mL of 1:1:1 THF/AcOH/H_2O at 0 °C was added NBS (93 mg, 0.52 mmol), and the resulting mixture was stirred at room temperature for 8 h. The mixture was then carefully quenched with 200 mL of saturated Na_2CO_3 and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were then washed with saturated $NaHCO_3$ (2 × 80 mL) and brine (80 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, EtOAc → 5% MeOH/CH_2Cl_2) to afford 155 mg (90%) of oxindole **23**: $[\alpha]^{20.4}_D$ −33.5° (c = 0.822, CH_2Cl_2); IR ($CHCl_3$) 3404, 3310, 2957, 2926, 2843, 1736, 1664, 1524, 1420, 1233 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 10.11 (s, 1 H), 7.81 (d, J = 8.2 Hz, 1 H), 7.43−7.29 (m, 7 H), 7.17 (t, J = 7.4 Hz, 1 H), 6.60 (s, 1 H), 4.72 (s, 2 H), 4.56 (d, J = 1.9 Hz, 2 H), 4.47−4.40 (m, 1 H), 3.98−3.95 (m, 2 H), 3.62−3.44 (m, 3 H), 2.24−1.80 (series of m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.8, 169.4, 165.6, 136.3, 131.2, 129.1, 128.8 (2 C), 128.6, 128.3 (2 C), 127.3, 121.3, 121.2, 120.8, 112.4, 74.2, 59.0, 56.6, 45.8, 45.4, 29.4, 28.1, 25.6, 22.5.; HRMS *m/z* ($M^+ + 1$) calcd 432.1923, obsd 432.1935.

Oxindole Amine 27. To the indole **13** (750 mg, 1.60 mmol) in 45 mL of 1:1:1 THF/AcOH/H_2O at 0 °C was added NBS (322 mg, 1.80 mmol) portionwise over 20 min, and then the resulting mixture was stirred for an additional 90 min at 0 °C. The mixture was then carefully quenched with 100 mL of saturated Na_2CO_3 and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were then washed with saturated $NaHCO_3$ (2 × 80 mL) and brine (80 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, 25% EtOAc/hexanes) to afford 473 mg (63%) of oxindole **25**: $[\alpha]^{20.6}_D$ +2.1° (c = 0.908, $CHCl_3$); IR ($CHCl_3$) 3400, 2995, 2953, 2930, 2835, 1745, 1702, 1684, 1608, 1460, 1380, 1357 cm^{-1}; HRMS (CI) *m/z* ($M^+ + K$) calcd 505.1741, obsd 505.1751.

The carbamate **25** (58 mg, 0.123 mmol) was stirred with 10 mL of 1:1 CH_2Cl_2/TFA at room temperature for 30 min and then concentrated, dissolved into 50 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered, concentrated, and filtered through a plug of SiO_2 (25% EtOAc/hexanes) to afford 40 mg (89%) of amine **27**: $[\alpha]^{20.9}_D$ +11.2° (c = 2.32, $CHCl_3$); IR ($CHCl_3$) 3630, 3400, 3000, 2980, 2832, 1712, 1700, 1600, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.85 (s, 1 H), 7.32 (d, J = 7.5 Hz, 1 H), 7.24−7.20 (m, 5 H), 7.07−7.00 (m, 2 H), 6.85 (d, J = 7.7 Hz, 1 H), 4.26−4.22 (m, 1 H), 4.24 (d, J = 11.9 Hz, 1 H), 4.10 (d, J = 11.6 Hz, 1 H), 3.81−3.78 (m, 1 H), 3.77 (s, 3 H), 3.41 (dd, J = 9.4, 5.7 Hz, 1 H), 3.17 (dd, J = 9.4, 6.8 Hz, 1 H), 2.84 (dd, J = 13.7, 10.1 Hz, 1 H), 2.24 (dd, J = 13.7, 6.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 180.6, 173.9, 140.6, 137.7, 131.4, 128.2 (2 C), 128.0, 127.4 (2 C), 127.2, 124.8, 122.4, 109.7, 73.2, 69.7, 67.2, 58.8, 56.2, 52.3, 41.8; HRMS *m/z* ($M^+ + 1$) calcd 367.1658, obsd 367.1653; NOE data, irradiated proton (enhancements), H4 (H5, H19 (2 H), H8b), H8a (H8b, H9, H18), H8b (H4, H8a), H19 (H4, H18, H19), H19′ (H4, H18, H19).

Oxindole Amine 28. To indole **14** (970 mg, 1.96 mmol) in 60 mL of 1:1:1 THF/AcOH/H_2O at 0 °C was added NBS (454 mg, 2.50 mmol) in 20 mL of THF dropwise over 10 min, and the resulting mixture was stirred for 90 min at 0 °C and for 3 h at room temperature. The mixture was then carefully quenched with 100 mL of saturated Na_2CO_3 and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were then washed with saturated $NaHCO_3$ (2 × 80 mL) and brine (80 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, 20% EtOAc/hexanes) to afford 429 mg (43%) of oxindole **26** and 283 mg of recovered starting material (61% adjusted yield): $[\alpha]^{26.3}_D$ −47.3° (c = 2.38, $CDCl_3$); IR ($CDCl_3$) 3436, 3191, 3075, 2979, 1710, 1617, 1474, 1382, 1368, 1176 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 9.26−8.95 (two br s, 1 H), 7.54−7.14 (m, 6 H), 7.02 (d, J = 7.4 Hz, 1 H),

6.92 (t, $J = 7.1$ Hz, 1 H), 6.86 (d, $J = 7.7$ Hz, 1 H), 5.03−4.85 (br m, 1 H), 4.54 (br s, 1 H), 3.75 (s, 3 H), 2.50−2.38 (m, 2 H), 2.05−1.81 (m, 2 H), 1.49 (s, 9 H), 1.36−1.23 (m, 6 H); HRMS *m*/*z* ($M^+ + 1$) calcd 511.2269, obsd 511.2267.

The carbamate **26** (61 mg, 0.119 mmol) was stirred with 9 mL of 2:1 CH_2Cl_2/TFA at room temperature for 45 min and then concentrated, dissolved into 50 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, concentrated, and filtered through a plug of SiO_2 (50% EtOAc/hexanes) to afford 46 mg (94%) of amine **28**: $[\alpha]^{25.3}_D$ −35.4° ($c = 1.22$, $CHCl_3$); IR ($CHCl_3$) 3426, 3298, 3192, 3064, 3011, 2958, 2928, 2853, 1728, 1709, 1619, 1471, 1222 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) $\delta = 8.77$ (s, 1 H), 7.39−7.19 (m, 7 H), 7.02 (t, $J = 7.2$ Hz, 1 H), 6.89 (d, $J = 7.7$ Hz, 1 H), 4.21 (dd, $J = 10.5$, 5.8 Hz, 1 H), 3.79 (s, 3 H), 3.71 (d, $J = 9.0$ Hz, 1 H), 3.00−2.40 (br s, 1 H), 2.85 (dd, $J = 13.7$, 10.5 Hz, 1 H), 1.26−1.09 (m, 2 H), 1.20 (s, 3 H), 1.17 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 180.2$, 174.2, 140.0, 137.6 (2 C), 132.1, 131.5, 128.7, 128.4 (2 C), 127.9, 124.4, 122.8, 109.8, 66.3, 59.1, 59.0, 52.4, 48.0, 43.0, 41.1, 29.1, 29.0; HRMS *m*/*z* ($M^+ + 1$) calcd 411.1744, obsd 411.1748.

Diketopiperazine 29 (Representative Procedure for Diketopiperazine Formation). To the amine **27** (171 mg, 0.470 mmol) and Et_3N (0.40 mL, 2.76 mmol) in 5 mL of CH_2Cl_2 at 0 °C was added the acid chloride **19** (492 mg, 1.69 mmol) in 20 mL of CH_2Cl_2 dropwise. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for 12 h before being quenched with 10 mL of water. Extraction of the aqueous layer with CH_2Cl_2 (3 × 80 mL) was followed by washing with 10% HCl and saturated $NaHCO_3$ (50 mL each), drying over $MgSO_4$, filtration, concentration, and chromatography (SiO_2, 30% EtOAc/hexanes) to afford 384 mg of the crude amide.

To the crude amide in 30 mL of 1:1:1 THF/MeOH/saturated NH_4Cl was added zinc dust (2 g), and the gray slurry was stirred at room temperature for 12 h. The slurry was then filtered, concentrated, dissolved into 200 mL of CH_2Cl_2, and then washed with 10% HCl, saturated $NaHCO_3$, and brine (50 mL each), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, 80% EtOAc, hexanes → EtOAc) to afford 175 mg (87%) of diketopiperazine **29**: $[\alpha]^{20.5}_D$ −27.1° ($c = 1.594$, CH_2Cl_2); IR ($CDCl_3$) 3398, 3168, 3052, 3032, 3000, 2923, 2892, 2850, 1690, 1650, 1608, 1590, 1456, 1408 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 9.14$ (s, 1 H), 7.41 (d, $J = 7.4$ Hz, 1 H), 7.33−7.18 (m, 6 H), 6.97 (t, $J = 7.7$ Hz, 1 H), 6.87 (d, $J = 7.7$ Hz, 1 H), 4.94 (dd, $J = 9.6$, 7.7 Hz, 1 H), 4.54 (d, $J = 12.1$ Hz, 1 H), 4.37 (d, $J = 12.1$ Hz, 1 H), 4.27 (t, $J = 8.1$ Hz, 1 H), 4.16 (m, 2 H), 3.74 (t, $J = 6.7$ Hz, 1 H), 3.59−3.49 (m, 2 H), 3.40 (d, $J = 9.4$ Hz, 1 H), 2.99 (dd, $J = 13.5$, 10.6 Hz, 1 H), 2.33−1.82 (series of m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 181.3$, 167.3, 166.9, 141.5, 137.6, 129.0, 128.3 (2 C), 127.6, 127.2 (2 C), 126.8, 125.9, 122.7, 110.0, 73.1, 66.2, 61.1, 60.9, 58.7, 55.3, 45.0, 35.3, 27.5, 23.6; HRMS *m*/*z* ($M^+ + 1$) calcd 432.1923, obsd 432.1935.

Alcohol 30. To the ether **29** (60 mg, 0.139 mmol) in 6 mL of 1:1 CH_3CN/CH_2Cl_2 was added the TMSI (0.5 mL, 1.27 mmol), and the mixture was stirred at room temperature for 7 h and then diluted with MeOH and saturated $NaHSO_3$ (4 mL each). The reaction mixture was then diluted with $NaHCO_3$ (30 mL), extracted with CH_2Cl_2 (3 × 40 mL), then washed with saturated $NaHCO_3$ and brine (20 mL each), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, EtOAc → 3% MeOH/CH_2Cl_2) to afford 33 mg of **29** and 22 mg (34% adjusted) of **30**.

Tosylation of 11. To the amine mixture **11** (1.08 g, 3.08 mmol) in 30 mL of pyridine was added TsCl (5.88 g, 30.8 mmol), and the reaction mixture was stirred at room temperature for 20 h, diluted with 10% HCl (100 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were then washed with 5% HCl (2 × 200 mL) and brine (100 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, 15% EtOAc/hexanes) to afford 790 mg of the desired cis diastereomer and 327 mg of the trans diastereomer (77% yield, 2.4:1 ratio). For the cis tosylate: $[\alpha]^{20.7}_D$ +109.4° ($c = 0.622$, $CHCl_3$); IR ($CHCl_3$) 3410, 3005, 2932, 2900, 2820, 1737, 1730, 1585, 1340, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.64$ (s, 1 H), 7.71 (d, $J = 8.4$ Hz, 2 H), 7.42−7.23 (m, 9 H), 7.16 (t, $J = 7.0$ Hz, 1 H), 7.08 (t, $J = 7.0$ Hz, 1 H), 5.14 (d, $J = 6.6$ Hz, 1 H), 4.74 (d, $J = 11.3$ Hz, 1 H), 4.65 (d, $J = 11.3$ Hz, 1 H), 4.25 (dd, $J = 8.5$, 3.7 Hz, 1 H), 4.01 (dd, $J = 10.3$, 8.8 Hz, 1 H), 3.60 (s, 3 H), 3.35 (d, $J = 15.7$ Hz, 1 H), 2.62 (m, 1 H), 2.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 171.4$, 143.9, 137.8, 137.0, 135.9, 131.2, 130.0 (2 C), 128.7 (2 C), 128.1, 128.0 (2 C), 126.8 (2 C), 125.9, 122.1, 119.4, 118.2, 111.0, 104.7, 74.6, 73.7, 54.1, 52.6, 51.3, 22.4, 21.5; HRMS (CI) *m*/*z* ($M^+ + K$) calcd 543.1356, obsd 543.1352.

For the trans tosylate: $[\alpha]^{21.3}_D$ −26.4° ($c = 0.652$, $CHCl_3$); IR ($CHCl_3$) 3410, 3040, 2966, 2930, 2840, 1742, 1443, 1323, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.32$ (s, 1 H), 7.74 (d, $J = 8.4$ Hz, 2 H), 7.46 (d, $J = 7.8$ Hz, 1 H), 7.44−7.07 (m, 11 H), 5.23 (dd, $J = 8.4$, 4.5 Hz, 1 H), 4.68 (dd, $J = 8.7$, 4.8 Hz, 1 H), 4.47 (s, 2 H), 4.00 (dd, $J = 9.0$, 4.5 Hz, 1 H), 3.74 (s, 3 H), 3.55 (t, $J = 8.8$ Hz, 1 H), 3.31 (m, 1 H), 3.10 (dd, $J = 15.1$, 4.5 Hz, 1 H), 2.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 170.8$, 143.7, 138.0, 137.4, 136.2, 132.1, 129.4 (2 C), 128.5 (2 C), 128.0, 127.8 (2 C), 127.2 (2 C), 126.3, 122.1, 119.5, 118.2, 111.0, 107.2, 73.5, 72.1, 57.5, 53.8, 52.5, 24.0, 21.5; HRMS (CI) *m*/*z* ($M^+ + K$) calcd 543.1356, obsd 543.1344.

Spiro Tosylate 32. To the above cis tosylate (2.35 g, 4.66 mmol) in 60 mL of 1:1:1 THF/AcOH/H_2O at 0 °C was added NBS (1.08 g, 6.1 mmol) portionwise over 20 min, and and then the resulting mixture was allowed to warm to room temperature and stirred for an additional 90 min. The mixture was then carefully quenched with 200 mL of saturated Na_2CO_3 and extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were then washed with saturated $NaHCO_3$ (2 × 200 mL) and brine (100 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, 25% EtOAc/hexanes) to afford 1.58 g (65%) of oxindole **32** and 230 mg of recovered starting material (72% adjusted yield). For **32**: $[\alpha]^{20.9}_D$ +31.9° ($c = 1.376$, $CHCl_3$); IR ($CHCl_3$) 3400, 3000, 2928, 2905, 2830, 2800, 1718, 1710, 1608, 1583, 1347, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.31$ (s, 1 H), 7.83 (d, $J = 8.3$ Hz, 2 H), 7.53 (d, $J = 7.7$ Hz, 1 H), 7.31 (d, $J = 8.3$ Hz, 2 H), 7.26−6.99 (m, 7 H), 6.80 (d, $J = 7.9$ Hz, 1 H), 4.71 (dd, $J = 8.3$, 7.0 Hz, 1 H), 4.27−4.09 (m, 4 H), 3.95 (m, 1 H), 3.81−3.74 (m, 1 H), 3.76 (s, 3 H), 3.55 (dd, $J = 10.0$, 8.0 Hz, 1 H), 2.40 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 179.3$, 171.9, 144.0, 140.9, 137.7, 134.3, 129.6 (2 C), 128.6, 128.3 (2 C), 128.1 (2 C), 128.0, 127.5, 127.3 (2 C), 125.6, 122.4, 109.9, 73.3, 70.0, 65.0, 60.8, 55.9, 52.5, 38.8, 21.6; HRMS (CI) *m*/*z* ($M^+ + K$) calcd 559.1305, obsd 559.1324.

Aldehydes 33. The benzyl ether **32** (700 mg, 1.34 mmol) in 50 mL of EtOH and 3 mL of AcOH was carefully added to a flask containing 10% Pd/C (50 mg) under hydrogen gas. After the addition, the reaction mixture was stirred under a hydrogen atmosphere for 24 h and then filtered through Celite and taken up in 200 mL of CH_2Cl_2. The organic layer was then washed with saturated $NaHCO_3$ (2 × 60 mL) and brine (60 mL), dried over $MgSO_4$, filtered, and concentrated to afford 575 mg (99%) of the desired alcohol: $[\alpha]^{20.3}_D$ +12.6° ($c = 1.10$, $CHCl_3$); IR ($CHCl_3$) 3420, 2992, 2930, 1710, 1609, 1586, 1345, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 8.07$ (s, 1 H), 7.80 (d, $J = 8.2$ Hz, 2 H), 7.77 (d, $J = 7.7$ Hz, 1 H), 7.34 (d, $J = 8.1$ Hz, 2 H), 7.27 (dt, $J = 7.7$, 0.9 Hz, 1 H), 7.09 (dt, $J = 7.6$, 0.5 Hz, 1 H), 6.82 (d, $J = 7.7$ Hz, 1 H), 4.75 (dd, $J = 9.6$, 7.8 Hz, 1 H), 4.11 (dd, $J = 12.4$, 2.7 Hz, 1 H), 3.97 (br s, 1 H), 3.90 (s, 3 H), 3.82 (d, $J = 2.0$ Hz, 1 H), 3.64 (d, $J = 12.3$ Hz, 1 H), 2.73 (dd, $J = 12.7$, 9.8 Hz, 1 H), 2.41 (dd, $J = 12.8$, 7.8 Hz, 1 H), 2.38 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 180.1$, 174.7, 143.9, 141.0, 134.7, 129.4 (2 C), 129.2, 128.2 (2 C), 126.8, 125.9, 123.1, 109.7, 65.7, 63.6, 59.5, 55.7, 53.2, 39.5, 21.6; HRMS (CI) *m*/*z* ($M^+ + K$) calcd 469.0836, obsd 469.0816.

To this alcohol (106 mg, 0.246 mmol) in 10 mL of CH_2Cl_2 was added Dess−Martin's periodinane (1.06 g, 2.5 mmol), and the resulting mixture was stirred at room temperature for 3 h, quenched with saturated $NaHCO_3$ (50 mL), extracted with CH_2Cl_2 (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated. Crude NMR showed a 1:1.5 mixture of product:starting material, so the crude product was reexposed to the reaction conditions and worked up in the same manner. After chromatography (SiO_2, 40% EtOAc/hexanes), 49.5 mg (48%) was obtained of the pure aldehyde mixture **33**: ^1H NMR (500 MHz, $CDCl_3$) $\delta = 9.57$ (d, $J = 3.6$ Hz, 1 H), 7.74 (d, $J = 8.3$ Hz, 2 H), 7.57 (d, $J = 7.7$ Hz, 1 H), 7.40 (d, $J = 8.0$ Hz, 2 H), 7.24 (dt, $J = 7.7$, 0.9 Hz, 1 H), 7.06 (dt, $J = 7.7$, 0.8 Hz, 1 H), 6.83 (d, $J = 7.8$ Hz, 1 H), 4.46 (dd, $J = 9.9$, 5.4 Hz, 1 H), 3.94 (d, $J = 3.6$ Hz, 1 H), 3.88 (s, 3 H), 2.62 (dd, $J = 13.6$, 9.9 Hz, 1 H), 2.47 (s, 3 H), 2.37 (dd, $J = 13.6$, 5.4 Hz, 1 H);

^{13}C NMR (75 MHz, $CDCl_3$) δ = 197.5 (0.5 C), 197.4 (0.5 C), 176.7, 171.2, 145.2, 140.3, 131.8, 130.1 (2 C), 129.7, 128.5 (0.5 C), 128.4 (0.5 C), 126.2, 125.8, 123.2, 110.5, 72.0 (0.5 C), 71.9 (0.5 C), 60.9 (0.5 C), 60.8 (0.5 C), 60.5, 55.6, 52.8, 39.7, 21.7.

Conversion of 26 to Olefins 34 and 35. To the carbamate **26** (165 mg, 0.323 mmol) in 15 mL MeOH and 2 mL of water was added $NaIO_4$ (77 mg, 0.36 mmol), and the resulting white slurry was stirred at room temperature for 18 h, diluted with 50 mL of water, and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were then dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, 40% EtOAc/hexanes) to afford 117 mg (69%) of sulfoxide mixture.

This mixture was then heated to reflux in 10 mL of toluene for 45 min, cooled to room temperature, and chromatographed (SiO_2, 30% EtOAc/hexanes) to afford 78.9 mg (96%) of pure product. The material was stirred with 15 mL of 2:1 CH_2Cl_2/TFA at room temperature for 30 min and then concentrated, dissolved into 50 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered, concentrated, and then chromatographed (SiO_2, 40% EtOAc/hexanes) to afford 21.9 mg of the less polar **34** and 34.0 mg of **35** (1:1.5, 58% from **26**). For **34**: $[\alpha]^{20.9}_D$ −42.3° (c = 0.438, $CHCl_3$); IR ($CHCl_3$) 3436, 2958, 2935, 2898, 2855, 1725, 1621, 1468 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.67 (s, 1 H), 7.30 (dd, J = 7.5, 0.5 Hz, 1 H), 7.22 (td, J = 7.7, 1.2 Hz, 1 H), 7.05 (td, J = 7.6, 1.0 Hz, 2 H), 6.89 (dd, J = 7.5, 0.3 Hz, 1 H), 4.60 (s, 1 H), 4.39 (d, J = 1.2 Hz, 1 H), 4.18 (dd, J = 10.4, 5.8 Hz, 1 H), 3.78 (s, 3 H), 3.66 (dd, J = 8.3, 5.7 Hz, 1 H), 2.89 (dd, J = 13.7, 10.5 Hz, 1 H), 2.60−2.20 (br s, 1 H), 2.20 (dd, J = 13.7, 5.8 Hz, 1 H), 1.91 (dd, J = 14.0, 8.3 Hz, 1 H), 1.77 (dd, J = 14.1, 5.5 Hz, 1 H), 1.63 (d, J = 0.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 180.6, 174.2, 141.7, 140.4, 131.8, 128.0, 124.6, 122.7, 112.7, 109.8, 66.3, 58.6, 57.7, 52.4, 42.6, 38.7, 22.2; HRMS m/z (M^+) calcd 300.1474, obsd 300.1469.

For **35**: $[\alpha]^{20.9}_D$ −42.3° (c = 0.438, $CHCl_3$); IR ($CHCl_3$) 3390, 3160, 2958, 2923, 1690, 1672, 1603 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01 (s, 1 H), 7.86 (d, J = 7.7 Hz, 1 H), 7.27 (t, J = 7.7 Hz, 1 H), 7.12 (t, J = 7.7 Hz, 1 H), 6.93 (d, J = 7.7 Hz, 1 H), 4.66 (dd, J = 11.2, 2.9 Hz, 1 H), 4.15 (dd, J = 12.0, 3.7 Hz, 1 H), 3.80 (s, 3 H), 3.00 (dd, J = 14.0, 11.3 Hz, 1 H), 2.23 (dd, J = 14.0, 3.0 Hz, 1 H), 1.55−1.39 (m, 2 H), 1.37 (d, J = 13.0 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.9, 170.8, 151.8, 140.3, 129.1, 128.8, 126.5, 123.2, 110.3, 80.4, 60.7, 58.2, 56.7, 52.5, 38.5, 29.7, 27.2; HRMS m/z (M^+) calcd 300.1474, obsd 300.1464.

Conversion of 26 to 34. To the thioether **26** (165 mg, 0.402 mg) in 10 mL of CH_2Cl_2 were added $NaHCO_3$ (168 mg, 2.0 mmol) and *m*-CPBA (65 mg, 0.402 mmol) at −78 °C. The mixture was then stirred at 0 °C for 40 min and at room temperature for 10 min, quenched with 20 mL of water, extracted with CH_2Cl_2 (2 × 25 mL), washed with saturated $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, concentrated, and then chromatographed (SiO_2, 40% EtOAc/hexanes) to afford 54 mg of **26** and 91 mg of the sulfoxides (79%).

This sulfoxide mixture was then heated to reflux in 5 mL of toluene for 30 min, cooled to room temperature, and chromatographed (SiO_2, 50% EtOAc/hexanes) to afford 24 mg (34%) of pure **34**.

Diketopiperazine 36. See the above representative procedure for diketopiperazine **29**. After chromatographic purification, amine **28** (98 mg, 0.238 mmol) afforded 77.7 mg (69%) of diketopiperazine **36**: $[\alpha]^{25.2}_D$ −147.7° (c = 1.06, $CHCl_3$); IR ($CHCl_3$) 3435, 3196, 3009, 2884, 1711, 1675, 1617, 1467, 1415, 1218 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.56 (s, 1 H), 7.43−7.31 (m, 5 H), 7.12 (t, J = 7.7 Hz, 1 H), 6.79 (d, J = 7.8 Hz, 1 H), 6.69 (d, J = 7.8 Hz, 1 H), 6.64 (t, J = 7.5 Hz, 1 H), 4.87 (dd, J = 10.8, 7.0 Hz, 1 H), 4.27 (t, J = 8.1 Hz, 1 H), 4.15 (d, J = 6.8 Hz, 1 H), 3.60−3.55 (m, 2 H), 2.55 (dd, J = 13.3, 10.9 Hz, 1 H), 2.38−1.93 (series of m, 7 H), 1.31 (s, 3 H), 0.43 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 181.1, 167.5, 166.8, 141.1, 138.1 (2 C), 131.5, 128.8 (2 C), 128.6 (2 C), 127.4, 125.9, 122.3, 109.9, 61.4, 58.8, 58.1, 55.4, 48.2, 45.1, 42.6, 34.5, 28.0, 27.8, 26.4, 23.7; HRMS m/z (M^+) calcd 476.2010, obsd 476.1989.

Oxidation of 36 (Representative Procedure). To the sulfide **36** (50.0 mg, 0.105 mmol) in 3 mL of MeOH were added the $NaIO_4$ (25 mg, 0.115 mmol) and 0.1 mL of water. After being stirred at room temperature for 12 h, the reaction mixture was diluted with 60 mL of CH_2Cl_2 and then washed with saturated $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, CH_2Cl_2 → 3% MeOH/CH_2Cl_2) to afford 50.2 mg (97%) of the 1:1 sulfoxide mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.94 (s, 1 H), 8.86 (s, 1 H), 7.52−7.42 (m, 10 H), 7.19−7.14 (m, 2 H), 6.90−6.77 (m, 6 H), 4.92−4.84 (m, 2 H), 4.29−4.18 (m, 4 H), 3.59−3.56 (m, 4 H), 2.63−2.56 (m, 2 H), 2.38−1.90 (m, 14 H), 1.25 (s, 3 H), 1.24 (s, 3 H), 0.30 (s, 3 H), 0.27 (s, 3 H).

Alkenes 37 and 2 (Representative Procedure). The above sulfoxides (56 mg, 0.114 mmol) were dissolved into 5 mL of toluene and heated to reflux for 60 min. After cooling to room temperature, the reaction mixture was concentrated and chromatographed (SiO_2, CH_2Cl_2 → 5% MeOH/CH_2Cl_2) to afford 38.8 mg (93%) of the olefin mixture (2.5:1, **2**:**37**). This mixture was further purified by HPLC (90% EtOAc/hexanes) to afford 28 mg of **2** and 10 mg of **37**. For **37**: $[\alpha]^{22.4}_D$ −72.1° (c = 0.117, $CHCl_3$); IR (CH_2Cl_2) 3225, 3000, 2979, 2942, 2900, 2885, 1740, 1674, 1625, 1425 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.58 (s, 1 H), 7.22 (td, J = 7.7, 0.8 Hz, 1 H), 7.16 (d, J = 7.5 Hz, 1 H), 6.99 (t, J = 7.3 Hz, 1 H), 6.86 (d, J = 7.7 Hz, 1 H), 4.86 (t, J = 9.2 Hz, 1 H), 4.46 (d, J = 8.5 Hz, 1 H), 4.45 (d, J = 1.5 Hz, 1 H), 4.26 (t, J = 8.0 Hz, 1 H), 4.21 (s, 1 H), 3.61−3.56 (m, 2 H) 2.77−2.69 (m, 2 H), 2.42−1.93 (series of m, 7 H), 1.59 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 180.4, 168.4, 166.9, 141.4, 140.8, 129.0, 127.4, 125.5, 122.4, 112.0, 109.8, 61.5, 60.0, 58.4, 55.1, 45.1, 39.8, 33.7, 28.0, 23.7, 22.6; HRMS m/z (M^+) calcd 365.1739, obsd 365.1627.

For **2**: $[\alpha]^{20.1}_D$ −79.2° (c = 0.171, $CHCl_3$); IR ($CHCl_3$) 3424, 2996, 2954, 2937, 2886, 1722, 1670, 1653, 1623, 1469, 1414 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.44 (s, 1 H), 7.20 (t, J = 7.5 Hz, 1 H), 7.03 (d, J = 7.4 Hz, 1 H), 6.96 (t, J = 7.5 Hz, 1 H), 6.85 (d, J = 7.7 Hz, 1 H), 5.06−5.02 (m, 2 H), 4.82 (d, J = 9.1 Hz, 1 H), 4.30 (t, J = 8.0 Hz, 1 H), 3.65−3.54 (m, 2 H), 2.65 (dd, J = 13.4, 10.8 Hz, 1 H), 2.42 (dd, J = 13.4, 7.0 Hz, 1 H), 2.36−1.92 (series of m, 4 H), 1.62 (s, 3 H), 1.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 180.5, 167.03, 166.95, 140.8, 138.3, 128.6, 127.1, 126.5, 122.0, 121.4, 109.4, 61.1, 60.4, 58.6, 56.0, 45.2, 34.3, 27.5, 25.4, 23.7, 17.9; HRMS m/z (M^+ + 1) calcd 366.1812, obsd 366.1819; NOE data H4 (H8b, H19, H20, H21), H8a (H8b, H9), H8b (H4, H8a, H19), H12 (H9, H13, H13), H20 (H4, H19, H21), H21 (H19, H20).

Rearrangement of 37 to 2 (Representative Procedure). To the external olefin **37** (10.0 mg, 0.027 mmol) in 4 mL of EtOH was added $RhCl_3 \cdot 3H_2O$ (17.0 mg, 0.081 mmol) under Ar, and the reaction mixture was heated to reflux for 3 h, cooled to room temperature, filtered through a pipet column (SiO_2, CH_2Cl_2), concentrated, and then chromatographed (SiO_2, EtOAc → 5% MeOH/CH_2Cl_2) to give 4.5 mg (45%) of pure **2**.

Methoxycarbamate Sulfide 40. To the amine **39**[5] (1.54 g, 3.6 mmol) in 50 mL of 4:1 CH_3CN/Et_3N was added the Boc_2O (3.17 g, 14.5 mmol), and the mixture was stirred at 50 °C for 10 h and then cooled to room temperature. The crude mixture was concentrated and chromatographed (SiO_2, 15% EtOAc/hexanes) to afford 590 mg of the desired product **40** (31%) and 970 mg of recovered starting material (84% adjusted yield). For **40**: $[\alpha]^{20.9}_D$ −26.9° (c = 1.25, $CHCl_3$); IR ($CHCl_3$) 3450, 3430, 3307, 3004, 2975, 2947, 2852, 1739, 1735, 1683, 1630, 1501, 1473, 1393, 1369 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.85 (s, 1 H), 7.71−7.28 (m, 6 H), 6.84−6.77 (m, 2 H), 5.67−4.95 (m, 2 H), 3.83 (s, 3 H), 3.64−3.59 (m, 3 H), 3.28−3.00 (m, 2 H), 2.25−2.03 (m, 2 H), 1.66−0.89 (m, 15 H); HRMS m/z (M^+) calcd 524.2347, obsd 524.2345.

Methoxyoxindole Amine 41. To indole **40** (166 mg, 0.316 mmol) in 25 mL of 2:2:1 AcOH/H_2O/THF at 0 °C was added NBS (68 mg, 0.380 mmol) in 5 mL of THF dropwise over 5 min, and the resulting mixture was stirred for 10 min at 0 °C and 90 min at room temperature. The mixture was then carefully quenched with 100 mL of saturated Na_2CO_3 and extracted with CH_2Cl_2 (3 × 80 mL). The organic layers were then washed with saturated $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed (SiO_2, 20% EtOAc/hexanes) to afford 53 mg (31%) of oxindole and 55 mg of recovered starting material (46% adjusted yield). For the oxindole: $[\alpha]^{24.0}_D$ −13.1° (c = 0.788, $CHCl_3$); IR ($CHCl_3$) 3433, 2993, 2930, 2861, 1724, 1710, 1637, 1628, 1368 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.17−8.74 (m, 1 H), 7.53−7.16 (m, 5 H), 6.88 (d, J = 8.3 Hz, 1 H), 6.46 (d, J = 1.7 Hz, 1 H), 6.43 (dd, J = 8.3, 1.9 Hz, 1

H), 5.09−4.49 (m, 2 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 2.47−1.89 (m, 4 H), 1.48 (s, 9 H), 1.35−1.25 (m, 6 H); HRMS *m*/*z* ($M^+ + 1$) calcd 541.2374, obsd 541.2373.

The above carbamate (45 mg, 0.083 mmol) was stirred with 5 mL of 3:2 CH_2Cl_2/TFA and a few drops of 1,3-dimethoxybenzene at room temperature for 30 min and then concentrated, dissolved into 50 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, concentrated, and filtered through a plug of SiO_2 (50% EtOAc/hexanes) to afford 34 mg (93%) of amine **41**: $[\alpha]^{21.5}_D$ −41.4° (*c* = 0.269, $CHCl_3$); IR ($CDCl_3$) 3438, 3189, 3065, 2961, 2908, 1728, 1707, 1629, 1598, 1505 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.54 (s, 1 H), 7.40 (d, *J* = 2.3 Hz, 1 H), 7.31−7.16 (m, 5 H), 6.54 (dd, *J* = 8.3, 2.3 Hz, 1 H), 6.47 (d, *J* = 2.3 Hz, 1 H), 4.18 (dd, *J* = 10.6, 5.6 Hz, 1 H), 3.78 (s, 3 H), 3.78 (s, 3 H), 3.64 (d, *J* = 9.5 Hz, 1 H), 2.83 (dd, *J* = 13.7, 10.6 Hz, 1 H), 2.68 (br s, 1 H), 2.11 (dd, *J* = 13.7, 5.6 Hz, 1 H), 1.27−1.09 (m, 2 H), 1.21 (s, 3 H), 1.18 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 180.8, 174.4, 159.9, 141.2, 137.6 (2 C), 131.7, 128.7, 128.3 (2 C), 125.1, 124.2, 107.4, 97.2, 66.2, 59.1, 58.6, 55.5, 52.3, 48.0, 43.3, 41.3, 29.2, 29.1; HRMS *m*/*z* ($M^+ + 1$) calcd 441.1848, obsd 441.1832; NOE data, irradiated proton (enhancements), H4 (H8b, H19), H8a (H8b, H9, H18), H8b (H4, H8a, H19), H9 (H8a, H8b, H18), H18 (H8a, H9), H19 (H4, H5, H18).

Methoxydiketopiperazine 42. See the above representative procedure for diketopiperazine **29**. After chromatographic purification, amine **41** (59.5 mg, 0.135 mmol) afforded 46.3 mg (68%) of diketopiperazine **42**: $[\alpha]^{20.9}_D$ −109.5° (*c* = 0.731, CH_2Cl_2); IR (CH_2Cl_2) 3421, 3055, 2985, 2890, 1723, 1675, 1631, 1597, 1418 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 9.02 (s, 1 H), 7.41−7.30 (m, 5 H), 6.53 (d, *J* = 8.4 Hz, 1 H), 6.36 (d, *J* = 2.3 Hz, 1 H), 6.08 (dd, *J* = 8.4, 2.3 Hz, 1 H), 4.84 (dd, *J* = 10.7, 5.7 Hz, 1 H), 4.25 (dd, *J* = 8.0, 8.0 Hz, 1 H), 4.09 (dd, *J* = 6.7, 6.3 Hz, 1 H), 3.72 (s, 3 H), 3.55 (m, 1 H), 2.49 (dd, *J* = 13.4, 11.1 Hz, 1 H), 2.36−1.92 (m, 8 H), 1.31 (s, 3 H), 0.45 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 181.7, 167.5, 166.8, 160.4, 142.4, 138.1 (2 C), 131.7, 128.7, 128.5 (2 C), 126.5, 119.2, 106.6, 97.6, 61.3, 58.7, 58.0, 55.4, 55.1, 48.3, 45.0, 42.8, 34.5, 27.9, 27.7, 26.5, 23.6; HRMS *m*/*z* (M^+) calcd 506.2116, obsd 506.2102.

Oxidation of 42. See the representative procedure for oxidation of **36**. Sulfide **42** (68.0 mg, 0.134 mmol) afforded 57.7 mg (82%) of the corresponding 1:1 sulfoxide mixture: ^1H NMR (500 MHz, $CDCl_3$) δ = 9.20 (s, 1 H), 9.11 (s, 1 H), 7.49−7.41 (m, 10 H), 6.74−6.69 (m, 2 H), 6.38−6.24 (m, 4 H), 4.84−4.82 (m, 2 H), 4.25−4.11 (m, 4 H), 3.71 (s, 6 H), 3.54 (br s, 4 H), 2.52−1.85 (m, 16 H), 1.25 (s, 6 H), 0.31 (6 H).

Alkenes 43 and 1. See the representative procedure for **37** and **2** above. The above sulfoxides (83 mg, 0.159 mmol) afforded 61.6 mg (98%) of the olefin mixture (2.5:1, **1**:**43**). This mixture was further purified by HPLC (90% EtOAc/hexanes) to afford 31.2 mg of **1**, 15.9 mg of **43**, and 14.6 mg of the mixture enriched in **1**. For **43**: $[\alpha]^{22.0}_D$ −67.0° (*c* = 0.100, $CHCl_3$); IR ($CDCl_3$) 3436, 3207, 3072, 2958, 2886, 1722, 1711, 1670, 1597, 1504, 1410 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.20 (s, 1 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 6.51 (dd, *J* = 8.4, 2.3 Hz, 1 H), 6.44 (d, *J* = 2.3 Hz, 1 H), 4.84 (t, *J* = 8.2 Hz, 1 H), 4.49 (s, 1 H), 4.42 (t, *J* = 7.2 Hz, 1 H), 4.26 (m, 1 H), 4.25 (s, 1 H), 3.79 (s, 3 H), 3.61−3.55 (m, 2 H), 2.72 (dd, *J* = 13.5, 10.1 Hz, 1 H), 2.68 (dd, *J* = 14.7, 6.2 Hz, 1 H), 2.39−1.93 (series of m, 6 H), 1.61 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 181.0, 168.4, 167.0, 160.7, 142.1, 141.5, 126.3, 119.2, 112.1, 107.0, 97.3, 61.5, 59.7, 58.3, 55.5, 54.9, 45.2, 40.0, 33.8, 28.0, 23.7, 22.5; HRMS *m*/*z* (M^+) calcd 434.1482, obsd 434.1487.

For **1**: $[\alpha]^{21.4}_D$ −111.3° (*c* = 0.088, $CHCl_3$); $[\alpha]^{19.0}_D$ −117.0° (*c* = 0.314, CH_2Cl_2).

Rearrangement of 43 to 1. See the representative procedure for rearrangement of **37**. The external olefin **43** (8.3 mg, 0.021 mmol) gave 3.4 mg (41%) of pure **1**.

Cell Proliferation Assay. To investigate the effect of spirotryprostatin A and analogues on the proliferation of MDA MB-468 and MCF7 human tumor cells, six-well plates were seeded at 10 000 cells/well, and duplicate wells were treated with increasing drug concentrations. Drugs were dissolved in dimethyl sulfoxide, and 1000× stock solutions were made for each concentration to be tested. Control cultures received an equivalent volume of dimethyl sulfoxide. Cultures were fed medium and drug at days 1 and 3, and cell number was determined on day 6. Attached cells were trypsinized, and samples were counted on a Coulter counter.

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