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Asymmetric, stereocontrolled total synthesis of (+) and (−)-spirotryprostatin B via a diastereoselective azomethine ylide [1,3]-dipolar cycloaddition reaction

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The authors wish to dedicate this paper to the myriad of impressive accomplishments of Professor Yoshito Kishi of Harvard University and in recognition of his receiving the Tetrahedron Prize

Abstract—The asymmetric, stereocontrolled total syntheses of (+) and (−)-spirotryprostatin B (**2**) are described. Formation of the core pyrrolidine ring was accomplished via a diastereoselective asymmetric [1,3]-dipolar cycloaddition reaction. Addition of 3-methoxy-3-methylbutanal to (5*R*,6*S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one generated an azomethine ylide that reacted with ethyl oxindolylidene acetate to furnish the desired cycloadduct (**11**) that possessed the correct relative and absolute stereochemistry of natural spirotryprostatin B. The key dipolar cycloaddition reaction sets four contiguous stereogenic centers. Reductive cleavage of the oxazinone generated the spiro-oxindole pyrrolidine (**19**) that was coupled to D-proline benzyl ester and cyclized to the pentacyclic diketopiperazine **22**. A Barton-modified Hunsdiecker protocol effected oxidative decarboxylation to yield 12-*epi*-spirotryprostatin B (**30**). Thermodynamic epimerization of the D-proline stereogenic center with sodium methoxide yielded spirotryprostatin B as the major product. The antipode of the natural product, ent-spirotryprostatin B, was prepared from (5*S*,6*R*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one. Several synthetic intermediates and spirotryprostatin analogs were tested for their activity as G2/M phase cell cycle inhibitors and microtuble assembly against 3Y1 and tsFT210 mammalian cells.

1. Introduction

Elucidating the regulatory machinery of the cell cycle is crucial to understanding how defects in the regulatory mechanism of the cell result in uncontrolled growth and differentiation, such as cancer.[1] Small-molecule natural products are proving invaluable in contemporary studies of cellular probes through their ability to specifically bind target proteins that modulate signal transduction cascades. Numerous examples exist in which the biological function of a particular cellular factor have been investigated through the use such compounds.[2] Therefore, the development of new and specific inhibitors of signal transduction cascade pathways will continue to be extremely important in the understanding of the regulatory mechanism of the cell cycle.

Recently, powerful bioassays have been developed to specifically identify new natural products that inhibit the progression of the cell cycle at distinct phases. Using temperature-sensitive mammalian tsFT210 cells and rat normal fibroblast 3Y1 cells, Osada et al., have exploited these screening technologies to identify a wide array of interesting natural products from the fermentation broth of the fungus *Aspergillus fumigatus* and other microbial sources.[3]

Included in the families of fungal metabolites identified in this manner are the fumitremorgins,[4] the tryprostatins,[5] the cyclotryprostatins[4] and the spirotryprostatins (**1** and **2**, Fig. 1).[6] The primary target of tryprostatin A and cyclotryprostatins A and B are microtubules which induce M-phase specific inhibition and microtubule disassembly.[7] This family of prenylated, cyclo-L-Trp-L-Pro-derived polycyclic alkaloids has received considerable attention recently due to their unique biological activities and interesting chemical structures. These substances have therefore attracted considerable synthetic attention and individual total syntheses of each representative class have been reported.[8–10]

The tryprostatin family of secondary metabolites are the consequence of several modes of isoprenylation of the tryptophan moiety of the simple cyclic dipeptide progenitor cyclo-L-Trp-L-Pro.[11] The structurally most interesting and complex members of this family are the spirotryprostatins A and B which, curiously display among the weakest

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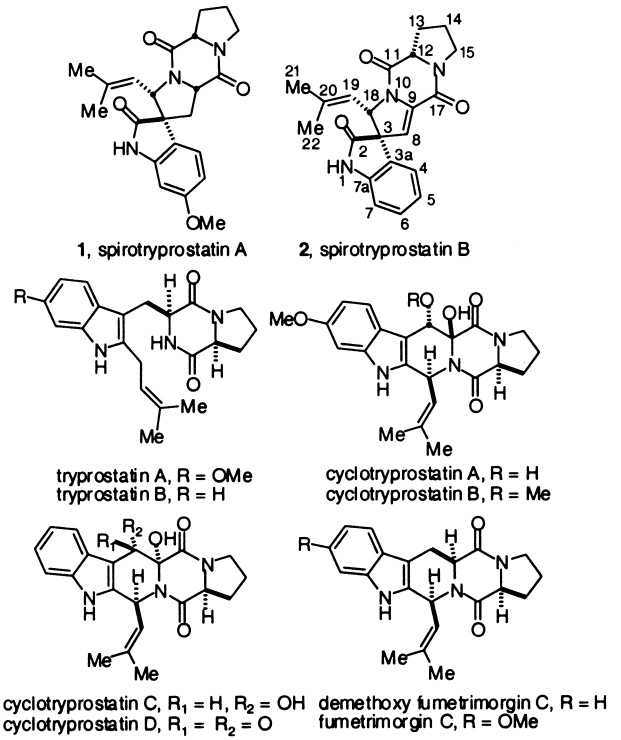
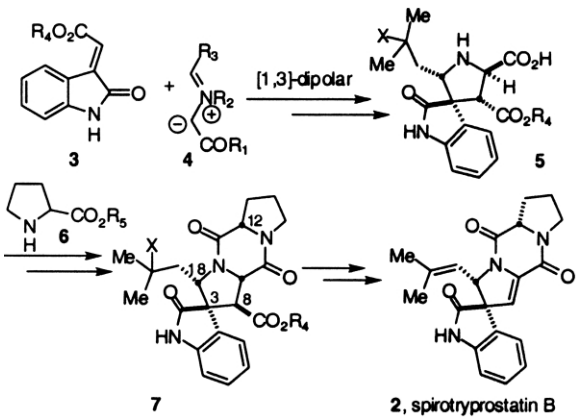


Figure 1. Structures of the spirotryprostatins, tryprostatins, cyclotryprostatins and fumitremorgins.

biological activity of this family of cell cycle inhibitors. Isolated in 1996, from *A. fumigatus*, spirotryprostatin A (**1**) and spirotryprostatin B (**2**) were shown to completely inhibit the progression of cells at concentrations greater than 253 and 34.4 μM, respectively. Despite their relatively modest biological activity relative to other members of this family, the spirotryprostatins have nonetheless garnered the most attention due to their intriguing molecular structures. The detailed mechanism of action by which these substances inhibit microtubule assembly is presently not known and studies to discover the target of these natural products have been hampered by the small quantities of these substances that can be conveniently isolated from the producing organism. Herein, we present a full account of our efforts towards the total synthesis of both antipodes of spirotryprostatin B and analogs.[12]

2. Results and discussion

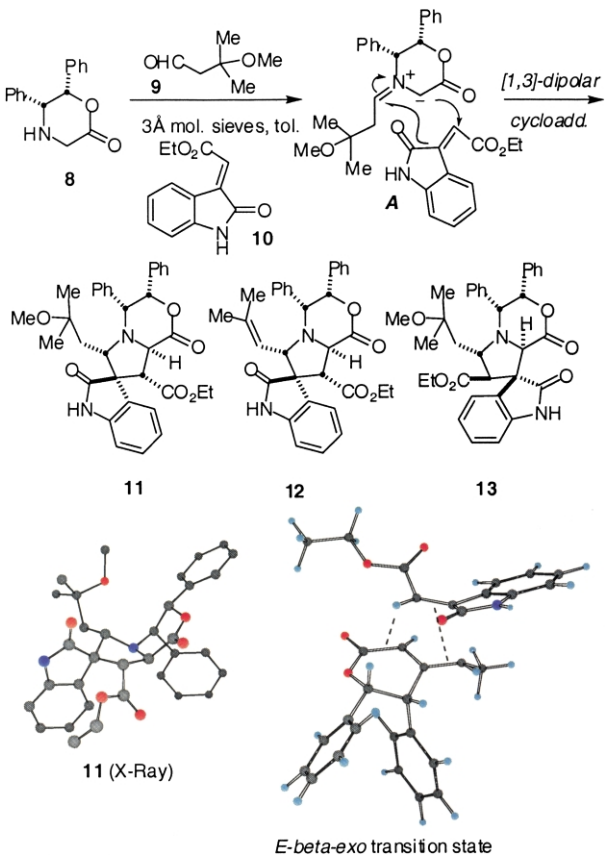
At the outset, we focused on devising an efficient and stereocontrolled method to construct the core spirooxindole-containing pyrrolidine ring as the backbone to our synthetic strategy as shown Scheme 1. It was envisioned that an asymmetric [1,3]-dipolar cycloaddition between a chiral azomethine ylide of the general type **4** and an oxindolylidene acetate (**3**) could, in both a relative and absolute sense, generate the desired spiro-amino acid **5**. If successful, the reaction would generate two of the three necessary stereogenic centers contained in the natural product. Coupling with a suitable proline derivative (**6**) followed by cyclization would yield the diketopiperazine **7**.



Scheme 1. General synthetic plan for the synthesis of **2**.

With the construction of the desired framework represented as in the pentacyclic substance **7**, completion of the synthesis would mandate judiciously timed oxidative decarboxylation and installation of the isoprene-derived unsaturation via elaboration of the pentacyclic substance **7**.

The utility of [1,3]-dipolar cycloadditions is a well-established synthetic method for the formation of variously substituted pyrrolidine rings.[13] Numerous methods exist, including reaction of azomethine ylides with oxindolylidene acetate dipolarophiles, for the construction of spirooxindole systems related to that present in **1** and **2**.[14] However, the literature contains conflicting evidence as to the regio- and diastereochemical outcome of such reactions.



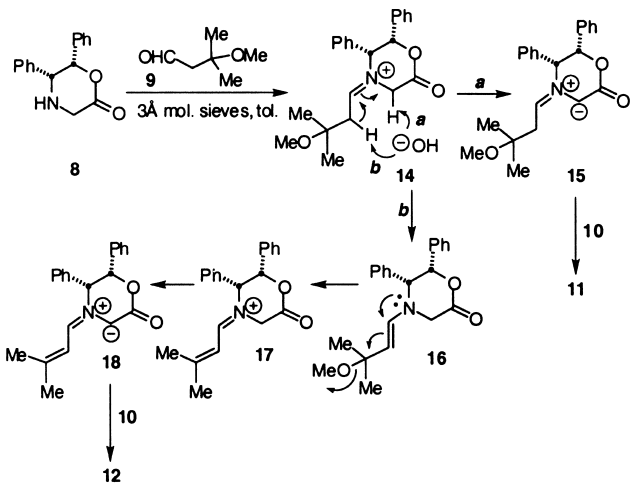
Scheme 2.

Azomethine ylides derived from our diphenyl oxazinone-based glycine template,[15] and related chiral glycine-based azomethine ylide equivalents,[16] reveal that the regio- and stereochemistry of the resulting cycloadducts are dependent upon both the nature of the aldehyde and the dipolarophile. While simple symmetrical alkenyl dipolarophiles (i.e. dimethylmaleate) usually proceed with a high degree of *endo*-selectivity, there are few studies that address the regiochemical aspects of asymmetrically substituted dipolarophiles. It was therefore difficult to predict if the amide or the ester moiety of the oxindolylidene acetate (**3**) would dominate in directing the facial approach of the dipole. In this particular instance, there are thus eight possible diastereomeric transition state structures, and only one of which culminates in the desired spirotryprostatin stereostructure.

With respect to the relative stereochemistry of the prenyl side-chain, the reaction was expected to be diastereoselective in the desired sense since, earlier studies in our laboratories suggested that bulky aliphatic aldehydes preferentially form the *E*-ylide.[15] Assuming that the *E*-ylide geometry would dominate in the present case, four possible diastereomers could be reasonably expected to result from the planned cycloaddition. As shown in Scheme 2, reaction of the azomethine ylide derived from oxazinone **8**[17] and aldehyde **9**[18] with ethyl oxindolylidene acetate **10**[19] in the presence of molecular sieves in hot toluene, resulted in the formation of two cycloadducts **11** and **12** in a 1:2 ratio and 86% combined yield. We were pleased to observe that this initial set of reaction conditions indeed afforded the desired cycloadduct as evidenced by ^{1}H, ^{13}C NMR and nOe experiments.

The relative and absolute stereochemistry of the desired cycloadduct **11** was further secured through single-crystal X-ray analysis as depicted in Scheme 2. This result suggested that approach of the dipolarophile to the azomethine ylide occurs with the carboethoxy group being positioned opposite to the bulky phenyl groups in an *exo*-fashion. The reaction must therefore proceed via an *E*-beta-*exo* transition state[20] and constructs the entire prenylated tryptophyl moiety of spirotryprostatin B in a single, simple operation. However, the yield was far from ideal since **11** was isolated as a 1:2 mixture along with **12**, which results from the elimination of methanol from the desired cycloadduct. Additionally, a small amount of a third product **13** was produced and confirmed to be the reversed regio- and stereoisomer of the desired cycloadduct. Therefore, additional effort was directed at shifting the ratio of cycloadducts towards compound **11**.

We had not foreseen the possible loss of methanol from the aldehyde progenitor as these conditions had heretofore proven to be very mild and tolerated a wide range of aromatic and aliphatic aldehydes.[21] It was not clear whether the elimination was occurring during the reaction or after formation of the cycloadduct. Re-subjecting **11** to refluxing toluene in the presence of molecular sieves did not afford any of the eliminated cycloadduct **12** suggesting that a distinct azomethine ylide was being formed in situ and a proposed mechanism for the formation of **12** is illustrated in Scheme 3.

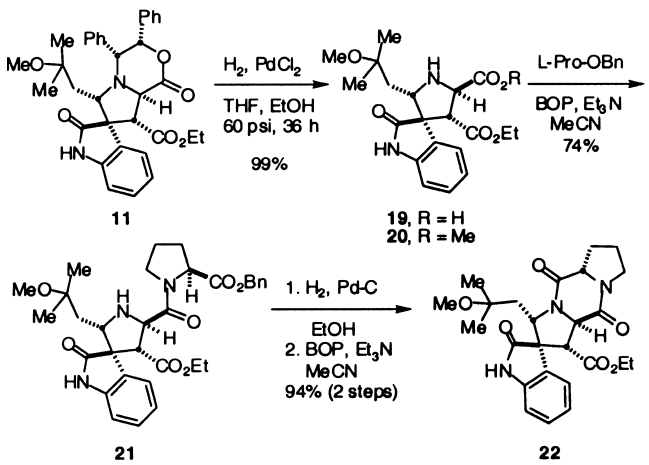


Scheme 3. Mechanism proposed for partitioning of **14** to cycloadducts **11** and **12**.

Addition of the aldehyde **9** to oxazinone **8** should initially generate the salt **14** which can then be deprotonated α- to the lactone carbonyl or β- to the nitrogen atom to give the ylide **15** or the eneamine **16**, respectively. Dipole **15** can then condense with ethyl oxindolylidene acetate (**10**) to generate the desired cycloadduct **11**. If eneamine **16** is formed, then under the thermal conditions of the reaction, nitrogen-assisted extrusion of methoxide furnishes the thermodynamically more stable (relative **14**) conjugated iminium ion species **17**.

Deprotonation α- to the carbonyl would then generate the azomethine ylide **18** that can suffer cycloaddition to yield **12**. To minimize formation of the undesired cycloadduct, the reaction was performed at 60°C instead of at reflux temperature, improving the yield of **11** to 82% with only 6% of **12** being formed.

With the key spiro-tetracyclic intermediate (**11**) in hand, focus shifted to construction of the diketopiperazine as detailed in Scheme 4. Reductive cleavage of the chiral auxiliary afforded acid **19** which was esterified with $TMSCHN_2$ to yield the corresponding methyl ester **20** in 86%. Attempts to acylate the nitrogen of the pyrrolidine ring



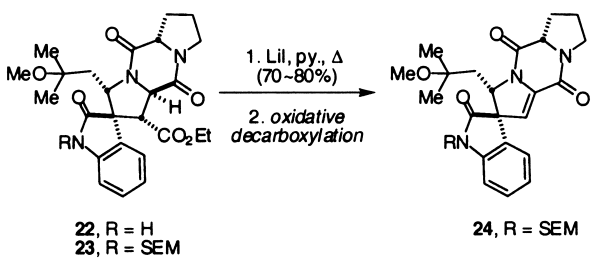
Scheme 4.

of **20** failed under a number of conditions. Only trace amounts of product were ever obtained and were complicated by acylation of the oxindole nitrogen. The decreased nucleophilicity of the pyrrolidine nitrogen can be attributed to the surrounding steric bulk. The ester and propylidene groups which are α- to the amine, are in an *anti*-configuration effectively blocking each face of the nitrogen from electrophilic attack.

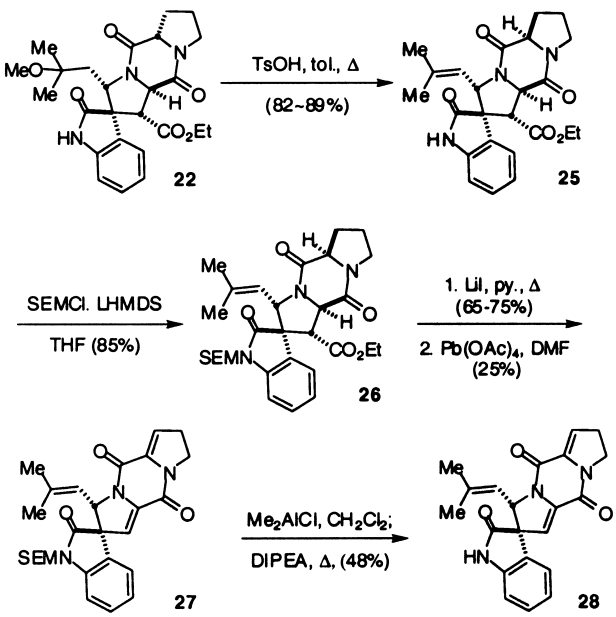
This initially discouraging result was eventually turned into an asset since, it was soon realized that the steric hindrance about the nitrogen might allow for direct coupling on the free, zwitterionic amino acid without concomitant self-condensation with the active ester. Thus, amino acid **19** was taken on crude from the preceeding hydrogenation step and directly coupled with L-proline benzyl ester with BOP[22] as the activating agent to give the dipeptide **21** in 74% for the two steps. Reduction of the benzyl ester followed by BOP-mediated cyclization afforded the desired diketopiperazine (DKP) **22** in excellent yield. The stage was now set for sequential installation of the two olefinic moieties.

Several strategies were examined for the installation of the enamide functionality and the prenyl side-chain. The initial plan was to first form the C-8/C-9 unsaturation and subsequently secure the C-19/C-20 olefinic group since the planned oxidative decarboxylation would involve an alkyl radical that might react with a proximal prenyl group. However, it was recognized that if an undesired intramolecular radical cyclization process were to occur, it would have to occur via a stereoelectronically disfavored 5-*endo-trig* cyclization.[23] With these considerations in mind attempts to effect a radical-based oxidative decarboxylation were pursued. Saponification of the ethyl ester of **22** was attempted using LiOH in THF/MeOH/H_2O, but failed to give any of the desired carboxylic acid. After some exploration, it was found that LiI in refluxing pyridine[24] furnished the desired carboxylic acid (Scheme 5). However, attempts to affect the oxidative decarboxylation either through the use of $Pb(OAc)_4$[25] or iodosobenzene diacetate[26] were unsuccessful, apparently due to the lability of the oxindole 2° amide. The oxindole nitrogen atom of **22** was protected as the corresponding SEM derivative **23**. Cleavage of the ethyl ester with LiI in refluxing pyridine furnished the corresponding acid that was subjected to Kochi-type conditions generating the eneamide **24**, albeit only in poor yields (10–25%).

Unfortunately, all attempts to install the C-19/C-20 unsaturation with **24** as a substrate were uniformly unsuccessful under a range of acidic elimination conditions. While the enamide proved to be stable to both mildly basic



Scheme 5.

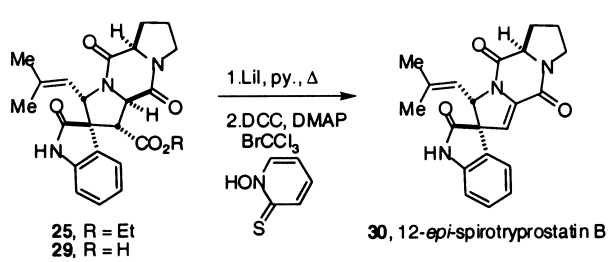


Scheme 6.

and acidic conditions, more vigorous conditions resulted in decomposition. These results suggested that the isopropylidene group needed to be in place prior to installation of the C-8/C-9 unsaturation. To this end, diketopiperazine **22** was subjected to treatment with TsOH in refluxing toluene resulting in the formation of the desired olefin **25** in good yield with only trace amounts of the isomeric disubstituted olefin present (Scheme 6). As before, the SEM group was used to protect the oxindole nitrogen (**26**).

Subjecting the carboxylic acid, resulting from saponification of the ethyl ester **26**, to a classical Kochi-type oxidative decarboxylation protocol produced the over-oxidized triene **27**. Despite extensive effort, we were unable to obviate oxidation of the proline residue under a wide range of Kochi-type conditions. Triene **27** provided an intriguing analog of spirotryprostatin B once the protecting group was removed. The free oxindole **28** was thus obtained using dimethyl aluminum chloride followed by heating in diisopropylethyl amine.[27]

We next turned to examining a Barton-modified Hunsdiecker reaction as a possible solution to the oxidative decarboxylation problem.[28] This reaction has found utility in a number of applications for the generation of alkyl halides, however the application of this method for the formation of α,β-unsaturated amino acid derivatives has seldom been reported. The ethyl ester was converted to the acid as above with lithium iodide in hot pyridine yielding



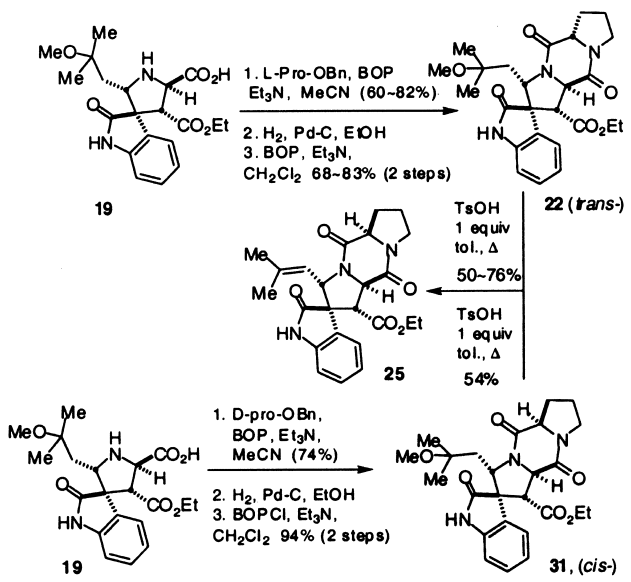
Scheme 7.

carboxylic acid **29**, (Scheme 7). Treatment of **29** with DCC, DMAP and *N*-hydroxy pyridine-2-thione yielded a product **30** whose ^{1}H NMR spectroscopic signatures closely resembled those of the natural product with the exception of some slight variations in the chemical shifts of several resonances.

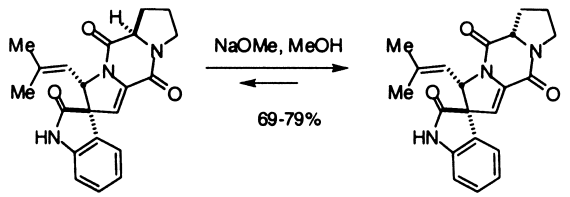
The Barton-modified Hunsdiecker protocol converts the carboxylic acid, via radical decarboxylation of the *N*-hydroxy pyridine-2-thione ester, into a secondary alkyl radical that is quenched by the solvent, $BrCCl_3$, into the corresponding alkyl bromides, which under thermal conditions, eliminate HBr to form the olefin. The overall yield for this process was far from exceptional (34–43%) and, it is possible that the formation and relative rates of elimination of the two diastereomeric bromides, might have contributed to the recovery of only moderate amounts of the desired product. We suspect that only the bromide that is positioned *trans*, antiperiplanar to the α-hydrogen, suffers facile elimination to give 12-*epi*-spirotryprostatin B. Our excitement that the reaction had occurred as planned was tempered by the discrepancies observed in the ^{1}H NMR data between the natural spirotryprostatin B and product **30**.

The absolute stereochemistry of the L-proline residue was not in doubt in the initial stages of the synthesis and both the relative and absolute stereochemistry of the spiro-oxindole moiety had been secured by X-ray crystallographic analysis of **11**. Thus, we suspected that an epimerization had occurred in the proline ring either at the stage of the elimination of methanol from **22**, or during the ethyl ester cleavage to ultimately give 12-*epi*-spirotryprostain B **30**.

To decipher at what stage the suspected epimerization reaction was occurring, the complementary D-proline-derived *cis*-diketopiperazine **31**, was constructed as shown in Scheme 8. This was accomplished in a similar fashion to that utilized for the formation of the *trans*-diketopiperazine **22**. Thus, coupling of amino acid **19** with D-proline benzyl ester (74%) followed by hydrogenation of the benzyl ester and cyclization (94% over two steps) afforded **31**.



Scheme 8.



Scheme 9. Thermodynamic epimerization of **32** to **2**.

If the dehydration step was the culprit in the loss of stereochemical integrity of **22**, then subjecting the two substrates (**22** and **31**) separately to the elimination conditions would yield the same product. This indeed proved to be the case wherein it was observed that the pentacyclic product **25** was formed exclusively from either substrate when treated with TsOH in hot toluene. It is well-known that *cis*-diketopiperazines are thermodynamically more stable than the corresponding *trans*-isomers for cyclic anhydrides of proline.[29] In contrast, reported syntheses of the fumetrimorgins have demonstrated the ability of substrates with the 6-6-5-ring system to undergo epimerization from the *cis*-configuration to the *trans*-configuration.[30]

With the stereochemical issues clarified, we returned to the task of converting 12-*epi*-spirotryprostatin B (**30**) into the natural stereoisomer as shown in Scheme 9. Addition of NaOMe in MeOH at 0°C to **30** yielded an equilibrium mixture of spirotryprostatin B (2): 12-*epi*-spirotryprostatin B (**30**) in a 2:1 ratio. These diastereomers were easily separated by chromatography and the recovered **30** could be re-subjected to the epimerization protocol giving **2** in 62% overall yield for the two cycles. The synthetic and natural specimens of (−)-spirotryprostatin B displayed identical spectroscopic data including optical rotation. In like fashion, (+)-*ent*-spirotryprostatin B was synthesized starting with the opposite antipode of **8**.[17]

3. Biological activity

The effects of compounds **11**, **19**, **20**, **21**, **22**, **25**, **28**, **29**, **30**, their enantiomers, and *ent*-spirotryprostatin B on cell cycle control and microtubule assembly were examined. Given the moderate activities of the title compounds (IC_{50}=14.0 μM for spirotryprostatin B), it was not surprising to find that all of the spirotryprostatin analogs prepared in this study that were tested had no effect on in vitro microtubule assembly and had little or no effect on in vitro cell cycle inhibition. Three compounds (**30**, *ent*-**30**, and *ent*-**2**) did however, provide some intriguing results.

12-*epi*-Spirotryprostatin B (**30**) was shown to cause partial accumulation of cells at the G_2/M phase at concentrations of 125 μM but were toxic to 3Y1 and tsFT210 cells at 250 μM or higher concentrations. The enantiomer of **30** was however, neither toxic to the cells nor showed any activity for cell cycle proliferation and microtubule assembly. Similar results were seen in the testing of spirotryprostatin (**2**) and *ent*-**2**. Spirotryprostatin B has been reported to inhibit tubulin polymerization and to be cytotoxic to mammalian cells[6] whereas *ent*-**2** had no effect on in vitro microtubule

assembly or in vitro cell cycle inhibition but was toxic to 3Y1 and tsFT210 cells at 31.3 and 15.6 μM concentrations, respectively. These data suggest that the molecular target of *ent*-spirotryprostatin B is different from that of the natural product. Further studies aimed at elucidating the cellular target of these substances and the molecular mechanism by which they arrest the cell cycle are currently under investigation in these laboratories.

4. Conclusion

In summary, the synthesis of both antipodes of spirotryprostatin B (**2**) has been achieved utilizing a diastereoselective, asymmetric [1,3]-dipolar cycloaddition reaction as the key step. This strategy, which sets four contiguous stereogenic centers in one step, also appears to be adaptable to the synthesis of spirotryprostatin A and efforts are underway in this regard. In addition, a tertiary methyl ether was demonstrated to serve as a suitable progenitor of the prenyl group providing an alternative method for the introduction of the isopropylidene functionality. Moreover, the inherent thermodynamic stability of diketopiperazines with the 5-6-5 ring system have been shown to preferentially favor the *cis*-configuration. Application of the methodology developed in this work is being applied to the synthesis of other potentially biologically useful members of the spirotryprostatin structural class.

5. Experimental

5.1. Cell culture and proliferation assay

Rat normal fibroblast 3Y1 cells[31] were grown in Dulbecco's modified MEM culture medium supplemented with 10% fetal calf serum under a humidified atmosphere containing 5% CO_2. Exponentially growing 3Y1 cells were treated with the test compounds for 24 h. The distribution of DNA content was determined by flow cytometry and relative cell numbers (cell number at 24 h per initial cell number at 0 h×100) were counted. MTT assay is a colorimetric assay using 3(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide. The cell viability was determined by this assay with minor modifications.[32]

5.2. Preparation of microtubule and turbidity assay (in vitro microtubule assembly assay)

Calf brain microtubule protein was prepared by two cycles of assembly-disassembly[33] and stored at −80°C in Mes buffer (100 mM 2-(*N*-morpholino)ethanesulfonic acid (Mes), 1 mM EGTA and 0.5 mM $MgCl_2$) at pH 6.8. Protein concentrations were determined by using the Dc Protein Assay (BioRad, Hercules, CA). Microtubule assembly was monitored by the turbidity assay as described previously.[34,35]

5.2.1. 3-Methyl-3-methoxybutanal (9). To an oven-dried 2000 mL three-neck round-bottom flask with stir bar was added DMSO (15.8 mL, 22.3 mmol) in 50 mL of CH_2Cl_2. The solution was cooled to −78°C under argon and oxalyl chloride (10 mL, 112 mmol) in 250 mL of CH_2Cl_2 was added dropwise over 15 min. 3-Methyl-3-methoxybutan-1-ol (12.0 g, 100 mmol) along with pyridine (16.5 mL, 200 mmol) in 100 mL of CH_2Cl_2 was added dropwise over 15 min. The reaction was stirred 15 min. more at −78°C and then Et_3N (75 mL, 0.5 mol) in 75 mL of CH_2Cl_2 was added over 15 min with vigourous stirring. The solution was kept at 78°C for 15 min and then warmed to 4°C and stirred for another 15 min. 1N HCl was used to acidify to pH −4 and the layers separated. The aqueous layers were extracted with three 50 mL portions of CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered and evaporated. The crude product could be obtained by column chromatography with 2:1 CH_2Cl_2/Et_2O as the eluent to yield 11.5 g (97%). The product was further purified by distillation to remove any impurities. For **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ $CHCl_3$: 1.31 (s, 6H), 2.53 (d, J=3.3 Hz, 2H), 3.26, (s, 3H), 9.84 (t, J=3.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ $CDCl_3$: 18.6, 42.7, 46.6, 67.1, 195.4; IR (NaCl/neat) 2974, 2937, 2828, 1732 cm^{-1}; LRMS (EI+) calcd for $C_6H_{13}O_2$ (*m/z*) 117.1, found (*m/z*) 117.1.

5.3. Cycloaddition

To a 500 mL round-bottom flask with stir bar was added (5*R*,6*S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (5.0 g, 19.8 mmol), ethyl oxindolylidene acetate (**10**) (6.4 g, 29.6 mmol) and 5.0 g of activated 3 Å molecular sieves. An oven-dried condenser was attached and the system was flushed with argon. Freshly distilled toluene (250 mL) was added followed by 3-methyl-3-methoxybutanal (**9**, 2.75 g, 23.7 mmol). The reaction was then heated to 60°C and kept at that temperature for 1 h at which time the heating mantle was turned off. The reaction was allowed to cool to room temperature and filtered through Celite to remove the sieves. Concentration afforded an orange solid which was chromatographed (SiO_2, 4:1 hexanes/EtOAC→1:1 hexanes/EtOAc) to afford 9.2 g of **11** (82%) and 0.70 g of **12** (6.3%) and 0.12 g of **13** (1.1%). Analytical samples of **11** were generated by recrystallization from EtOH.

5.3.1. Spiro[3*H*-indole-3,7′ (6′*H*)-[1*H*]pyrrolo[2,1-*c*][1,4]oxazine]-8′-carboxylic acid, 1,2,3′,4′,8′,8′a-hexahydro-6′-(2-methoxy-2-methylpropyl)-1′,2-dioxo-3′,4′-diphenyl, ethyl ester, (3*S*,3′*S*,4′*R*,6′*S*,8′*R*,8′a*R*) (11). $[\alpha]_D^{25}$=−88.8 (*c* 1.0, CH_2Cl_2); melting point: 225–227°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ $CHCl_3$: 0.68 (t, J=6.9 Hz, 3H), 1.09 (s, 6H), 1.14 (dd, J=3.6, 16.2 Hz, 2H), 1.70 (d, J=3.3, 15.9 Hz, 2H), 3.08 (s, 3H), 3.63–3.85 (m, 2H), 3.95 (d, J=7.5 Hz, 1H), 4.04 (t, J=3.3 Hz, 1H), 4.65 (d, J=7.5 Hz, 1H), 5.07 (d, J=3.3 Hz, 1H), 6.40 (d, J=3.3 Hz, 1H), 6.91 (d, J=7.5 Hz, 1H), 7.00 (dt, J=0.9, 7.5 Hz, 1H), 7.15 (d, J=7.5 Hz, 1H), 7.18–7.33 (m, 10H), 7.44 (d, J=7.5 Hz, 1H), 8.09 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ $CDCl_3$: 23.6, 26.9, 45.4, 50.6, 53.3, 56.0, 57.1, 57.5, 61.5, 65.5, 74.5, 77.1, 110.8, 124.0, 126.2, 127.2, 128.3, 128.4, 128.5, 129.4, 129.5, 130.2, 130.4, 137.5, 138.3, 142.3, 170.1, 173.0, 178.9; IR (NaCl/neat) 3308, 1734, 1618 cm^{-1}.

ent-**11**: $[\alpha]_D^{25}$=91.7 (*c* 1.0, CH_2Cl_2).

5.3.2. Spiro[3*H*-indole-3,7′ (6′*H*)-[1*H*]pyrrolo[2,1-*c*][1,4]oxazine]-8′-carboxylic acid, 1,2,3′,4′,8′,8′a-hexahydro-6′-(2-methyl-2-prop-ene-yl)-1′,2-dioxo-3′,4′-

diphenyl-, ethyl ester, (3*S*,3′*S*,4′*R*,6′*S*,8′*R*,8′a*R*) (12). $[\alpha]_D^{25}=52.8$ (*c* 0.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.11 (t, $J=6.8$ Hz, 3H), 1.16 (s, 3H), 1.19 (s, 3H), 1.80–1.94 (m, 2H), 3.18 (s, 3H), 3.41 (d, $J=6.0$ Hz, 1H), 4.00–4.14 (m, 2H), 4.53 (m, 1H), 4.69 (d, $J=7.6$ Hz, 1H), 5.0 (s, 1H), 6.41 (d, $J=2.8$ Hz, 1H), 6.84 (d, $J=7.6$ Hz, 2H), 7.01–7.35 (m, 12H), 7.62 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CDCl_3$: 13.5, 18.8, 26.2, 54.1, 57.3, 59.8, 60.2, 61.4, 68.7, 78.0, 109.8, 119.8, 122.7, 125.9, 126.1, 126.9, 127.8, 128.1, 128.3, 128.6, 129.0, 129.2, 136.0, 136.4, 141.1, 141.4, 168.6, 171.8, 177.6; IR (NaCl/neat) 3305, 1730, 1618 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{33}O_5N_2$ (*m*/*z*) 537.2389, found (*m*/*z*) 537.2383.

5.3.3. Spiro[3*H*-indole-3,7′ (6′*H*)-[1*H*]pyrrolo[2,1-*c*][1,4]oxazine]-8′-carboxylic acid, 1,2,3′,4′,8′,8′a-hexahydro-6′-(2-methoxy-2-methylpropyl)-1′,2-dioxo-3′,4′-diphenyl-, ethyl ester, (3*S*,3′*S*,4′*R*,6′*S*,8′*R*,8′a*R*) (13). $[\alpha]_D^{25}=118.1$ (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.64 (t, $J=6.8$ Hz, 3H), 1.42 (s, 3H), 1.67 (s, 3H), 3.46–3.68 (m, 1H), 3.78–3.83 (m, 1H), 4.04 (d, $J=7.6$ Hz, 1H), 4.36 (d, $J=3.6$ Hz, 1H), 4.50 (t, $J=7.6$ Hz, 1H), 4.51 (s, 1H), 4.87 (d, $J=7.6$ Hz, 1H), 5.0 (s, 1H), 6.08 (d, $J=3.6$ Hz, 2H), 6.97, (t, $J=6.8$ Hz, 1H), 6.84, (d, $J=6.8$ Hz, 1H), 7.16–7.28 (m, 12H), 7.62 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CDCl_3$: 14.2, 24.7, 24.8, 43.0, 49.5, 56.1, 59.8, 60.4, 60.5, 60.7, 65.6, 73.7, 79.2, 110.3, 123.1, 124.7, 126.5, 127.4, 127.7, 127.8, 128.0, 128.3, 129.2, 129.4, 137.0, 137.1, 141.1, 169.5, 170.4, 179.4; IR (NaCl/neat) 3288, 1718, 1621 cm^{-1}; HRMS (FAB+) calcd for $C_{24}H_{36}O_6N_2$ (*m*/*z*) 569.2651, found (*m*/*z*) 569.2640.

5.3.4. Spiro[3*H*-indole-3,3′-pyrrolidine]-4′,5′-dicarboxylic acid, 1,2-dihydro-2′-(2-methoxy-2-methylpropyl)-2-oxo-, 4′-ethyl ester, monohydrochloride, (2′*S*,3*S*,4′*R*,5′*R*) (19). Recrystallized cycloadduct **11** (5.0 g, 8.8 mmol) was added to a sealable pressure tube and dissolved in 200 mL of 1:1 THF/EtOH. The solvent was purged with argon for 5 min and $PdCl_2$ (1.55 g, 8.80 mmol) was added. The tube was sealed and flushed with H_2 before finally pressurizing to 70 Psi. The reaction was stirred for 36 h and then filtered through Celite to remove the palladium catalyst. Concentration afforded a viscous oil which was triturated with 1×25 mL Et_2O, 1×25 mL EtOAc, and 1×25 mL Et_2O to give 3.75 g (quant. yield) of a white solid **19** upon drying under high vaccum. $[\alpha]_D^{25}=-14.0$ (*c* 1.0, MeOH); ^1H NMR (300 MHz, DMSO d_6) δ HOD: 0.64 (t, $J=6.9$ Hz, 3H), 0.96 (s, 3H), 1.02 (s, 3H), 1.14 (dd, $J=3.6$, 14.7 Hz, 1H), 1.80 (dd, $J=8.4$, 15.0 Hz, 2H), 2.93 (s, 3H), 3.61–3.73 (m, 3H), 4.22 (dd, $J=4.2$, 8.1 Hz, 1H), 4.85 (d, $J=11.4$ Hz, 1H), 6.96 (t, $J=7.5$ Hz, 1H), 7.00 (d, $J=7.5$ Hz, 1H), 7.27 (d, $J=7.5$ Hz, 1H), 7.62 (d, $J=7.5$ Hz, 1H), 11.1 (br s, 1H); ^{13}C NMR (75 MHz, DMSO d_6) δ HOD: 15.0, 24.8, 25.6, 41.9, 50.5, 55.0, 60.2, 61.1, 63.1, 63.9, 75.0, 112.3, 120.2, 123.6, 124.6, 125.2, 125.7, 127.7, 129.9, 130.9, 131.7, 144.3, 168.2, 169.3, 176.3; IR (NaCl/neat) 3444, 3098, 3058, 2977, 1746, 1771, 1634, 1568 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{27}O_6N_2$ (*m*/*z*) 391.1869, found (*m*/*z*) 391.1866.

ent-Amino acid **19**: $[\alpha]_D^{25}=10.0$ (*c* 1.0, MeOH).

5.3.5. Spiro[3*H*-indole-3,3′-pyrrolidine]-4′,5′-dicarboxylic acid, 1,2-dihydro-2′-(2-methoxy-2-methylpropyl)-2-oxo-, 4′-ethyl ester, 5′-methyl ester, (2′*S*,3*S*,4′*R*,5′*R*) (20). Recrystallized cycloadduct **11** (0.50 g, 0.88 mmol) was added to a sealable pressure tube and dissolved in 10 mL of 1:1 THF/EtOH. The solvent was purged with argon for 5 min and $PdCl_2$ (155 mg, 0.88 mmol) was added. The tube was sealed and flushed with H_2 before finally pressurizing to 70 Psi. The reaction was stirred for 36 h and then filtered through Celite to remove the palladium catalyst. Concentration afforded a viscous oil which was taken up 5 mL of 1:1 CH_2Cl_2/MeOH. $TMSCHN_2$ (−1.0 mL of a 2.0 M solution in hexanes) was added until a yellow color persisted. The reaction was stirred 5 min. and then concentrated under reduced pressure. Column Chromatography with 1:1 hexanes/EtOAc affored 325 mg (91%) of white solid **20**. $[\alpha]^{25}=-27.3$ (*c* 0.97, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.63 (t, $J=6.8$ Hz, 3H), 0.90 (dd, $J=1.6$, 14.4 Hz, 1H), 0.99 (s, 3H), 1.10 (s, 3H), 1.19 (dd, $J=9.6$, 14.4 Hz, 1H), 3.08 (s, 3H), 3.17 (br s, 1H), 3.58–3.66 (m, 1H), 3.70 (d, $J=8.8$ Hz, 1H), 3.72–3.80 (m, 2H), 3.76 (s, 3H), 4.58 (d, $J=8.8$ Hz, 1H), 6.82 (d, $J=7.6$ Hz, 1H), 6.96 (dt, $J=0.8$, 7.6 Hz, 1H), 7.18 (dt, $J=0.8$, 7.6 Hz, 1H), 7.36 (d, $J=7.6$ Hz, 1H), 7.98 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CDCl_3$: 1.53, 24.4, 25.8, 40.6, 49.4, 52.8, 54.9, 59.1, 61.0, 61.1, 63.7, 74.4, 109.4, 122.7, 126.2, 127.8, 128.6, 140.9, 169.4, 175.2, 178.0; IR (NaCl/neat) 3244, 1734 cm^{-1}; HRMS (FAB+) calcd for $C_{21}H_{29}O_6N_2$ (*m*/*z*) 405.2025, found (*m*/*z*) 405.2024.

5.3.6. Spiro[3*H*-indole-3,3′-pyrrolidine]-4′-carboxylic acid, 1,2-dihydro-2′-(2-methoxy-2-methylpropyl)-2-oxo-5′-[[(2*S*)-2-[(phenylmethoxy)carbonyl]-1-pyrrolidinyl]-carbonyl]-, ethyl ester, (2′*S*,3*S*,4′*R*,5′*R*) 21. To a 200 mL round-bottom flask that contained amino acid **19** (3.75 g, 8.8 mmol) and was placed under high vacuum for 24 h was added BOP[22] (4.25 g, 9.7 mmol) and L-proline benzyl ester hydrochloride (2.35 g, 9.7 mmol). The flask was flushed with argon, 100 mL of CH_3CN was added and the reaction mixture cooled to 0°C. With stirring, triethylamine (2.70 mL, 19.3 mmol) was added dropwise and the solution allowed to warm to room temperature and stir for 8 h. The solvent was then evaporated, replaced with 100 mL of EtOAc, washed with 2×15 mL, 1N HCl, 1×15 mL H_2O, 2×15 mL 5% $NaHCO_3$, 1×10 mL sat. brine sol., dried over Na_2SO_4, filtered and evaporated to yield 5.0 g of a brown foam **21** which was taken on crude. An analytical sample of **21** was generated by column chromatography with 1:1 hexanes/EtOAc: $[\alpha]_D^{25}=-75.3$ (*c* 1.0, CH_2Cl_2); ^1H NMR (300 MHz, 120°C, DMSO) δ DMSO: 0.60 (t, $J=7.2$ Hz, 3H), 0.88 (d, $J=3.9$ Hz, 2H), 0.90 (s, 6H), 1.84 (br s, 1H), 2.05–2.16 (m, 1H), 2.75 (br s, 2H), 2.85 (s, 3H), 3.47–3.66 (m, 3H), 4.00 (d, $J=7.2$ Hz, 1H), 4.51 (d, $J=7.5$ Hz, 1H), 5.06 (s, 1H), 6.77 (t, $J=7.5$ Hz, 1H), 6.81 (d, $J=7.5$ Hz, 1H), 7.08 (dt, $J=1.2$, 7.5 Hz, 1H), 7.15–7.28 (m, 6H), 9.97 (br s, 1H); ^{13}C NMR (75 MHz, DMSO d_6) δ DMSO d_6: 13.8, 25.6, 25.7, 47.4, 48.7, 49.0, 55.9, 59.9, 60.2, 60.6, 60.8, 62.7, 64.5, 66.6, 74.2, 109.9, 121.5, 122.2, 1222.6, 125.5, 128.2, 128.3, 128.4, 128.5, 129.0, 143.4, 170.2, 171.2, 172.3, 177.8; IR (NaCl/neat) 3239, 1731, 1725, 1645, 1618 cm^{-1}; HRMS (FAB+) calcd for $C_{32}H_{40}O_7N_3$ (*m*/*z*) 578.2866, found (*m*/*z*) 578.2862.

ent-**21**: $[\alpha]_D^{25}=81.5$ (*c* 1.0, CH_2Cl_2).

5.3.7. Spiro[1*H*,5*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-1-carboxylic acid, 1′,2′,5a,6,7,8,10,10a-octahydro-3-(2-methoxy-2-methylpropyl)-2′,5,10-trioxo-, ethyl ester, (1*R*,2*S*,3*S*,5a*S*,10a*R*) 22. To a 100 mL round-bottom flask that contained **21** (5.0 g, 8.7 mmol) was added a stir bar and 20 mL of EtOH. Argon was bubbled through for 5 min. and 10% Pd/C (0.5 g) was added. The system was flushed with H_2 and a balloon of H_2 was attached. The solution was stirred vigorously for 1.5 h and then filtered through Celite, evaporated and placed on high vacuum overnight. To the crude mixture was added a stir bar, BOP[22] (3.83 g, 8.6 mmol) and 80 mL of CH_3CN. Triethylamine (1.2 mL, 8.6 mmol) was added dropwise and the reaction was allowed to stir for 8 h at which time the solvent was evaporated. Purification via column chromatography with 75:20:5 CH_2Cl_2/EtOAc/*i*-PrOH afforded 2.75 g (68%) of **22** as a white solid. For **22**: $[\alpha]_D^{25}=-92.0$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ $CHCl_3$: 0.92 (t, *J*=7.2 Hz, 3H), 1.11 (s, 3H), 1.19 (s, 3H), 1.72 (dd, *J*=4.2, 14.4 Hz, 1H), 1.75–2.08 (m, 3H), 2.21 (dd, *J*=10.5, 14.4 Hz, 1H), 2.49 (h, *J*=6.0 Hz, 1H), 3.0 (s, 3H), 3.42 (ddd, *J*=3.9, 7.5, 9.9 Hz, 1H), 3.49 (d, *J*=9.3 Hz, 1H), 4.67 (d, *J*=9.9 Hz, 1H), 3.84–4.07 (m, 3H), 4.31 (dd, *J*=5.4, 9.9 Hz, 1H), 4.89 (dd, *J*=3.9, 10.5 Hz, 1H), 5.13 (dd, *J*=1.2, 9.6 Hz, 1H), 6.96 (t, *J*=7.5 Hz, 1H), 6.99 (d, *J*=7.5 Hz, 1H), 7.17 (d, *J*=7.5 Hz, 1H), 7.25 (dt, *J*=1.9, 7.5 Hz, 1H), 8.42 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ $CDCl_3$: 12.9, 20.7, 23.1, 23.7, 29.1, 38.4, 43.8, 47.9, 53.3, 56.1, 59.3, 59.6, 60.1, 60.6, 73.5, 109.6, 121.1, 123.6, 126.3, 128.5, 141.0, 161.8, 165.2, 168.8, 179.5; IR (NaCl/neat) 3244, 1763, 1667, 1665 cm^{-1}; HRMS (FAB+) calcd for $C_{25}H_{32}O_6N_3$ (*m*/*z*) 470.2291, found (*m*/*z*) 470.2280.

ent-**22**: $[\alpha]_D^{25}=95.8$ (*c* 1.2, CH_2Cl_2).

5.3.8. *N*-SEM diketopiperazine 23. To a flame-dried 10 mL round-bottom flask with stir bar was added diketopiperazine **22** (65 mg, 0.14 mmol). The system was flushed with Ar, THF added and cooled to −78°C. KHMDS (0.33 mL of a 0.5 M sol., 0.16 mmol) was added and stirred for 15 min. SEMCl (0.03 mL, 0.16 mmol) was added dropwise and the reaction allowed to warm to room temperature and stirred for 8 h. Sat. NH_4Cl was added and the reaction mixture poured into 10 mL EtOAc. The aq. layer was extracted 3×5 mL with EtOAc, the organic layers combine, dried over Na_2SO_4, filtered, evaporated and chromatographed with 75:20:5 CH_2Cl_2/EtOAc/*i*-PrOH to yield 60 mg (72%) of the white solid **23**: $[\alpha]_D^{25}=-2.4$ (*c* 0.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: −0.04 (s, 9H), 0.8 (t, *J*=6.8 Hz, 6H), 1.12 (s, 3H), 1.18 (s, 3H), 1.70 (dd, *J*=4.0, 14.4 Hz, 1H), 1.81 (dt, *J*=3.2, 11.6 Hz, 1H), 1.88–2.01 (m, 1H), 2.02–2.12 (m, 1H), 2.21 (dd, *J*=10.8, 14.4 Hz, 1H), 2.50 (quint, *J*=6.0 Hz, 1H), 3.01 (s, 3H), 3.40–3.48 (m, 1H), 3.47 (d, *J*=9.2 Hz, 1H), 3.54 (t, *J*=8.8 Hz, 2H), 3.83–3.90 (m, 1H), 3.92–3.96 (m, 1H), 3.97–4.04 (m, 1H), 4.32 (dd, *J*=5.6, 11.6 Hz, 1H), 4.85 (dd, *J*=4.0, 10.8 Hz, 1H), 5.05 (1/2 Abq, *J*=11.2 Hz, 1H), 5.13, (dd, *J*=1.2, 9.2 Hz, 1H), 5.20 (1/2 Abq, *J*=11.2 Hz, 1H), 7.06–7.09 (m, 2H), 7.22 (d, *J*=7.6 Hz, 1H), 7.33 (t, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CDCl_3$: −2.09, 13.0, 17.1, 20.9, 23.2, 23.8, 29.2, 38.8, 44.0, 48.2, 54.2, 56.2, 59.7, 60.2, 60.8, 65.6, 69.0, 73.7, 109.5, 121.9, 123.0, 126.4, 128.7, 142.1, 161.9, 164.9, 168.8, 178.6; IR (NaCl/neat) 2971, 1724, 1668 cm^{-1}; HRMS (FAB+) calcd for $C_{31}H_{46}O_7N_3Si_1$ (*m*/*z*) 600.3105, found (*m*/*z*) 600.3109.

5.3.9. Eneamide 24. To a flame-dried 10 mL round-bottom flask with stir bar was added SEM protected diketopiperazine **23** (70 mg, 0.08 mmol) and LiI (110 mg, 0.80 mmol). An oven dried condensor was attached and the system was flushed with argon, freshly distilled pyridine (5 mL) was added and the system heated to reflux for 48 h. The solvent was evaporated and replaced with 10 mL of EtOAc, extracted with 5×2 mL 5% $NaHCO_3$ and the aqueous layers combined. The solution was then saturated with NaCl, acidified to pH 4 with 1N HCl and extracted with 5×5 mL EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered and evaporated to yield a white solid, which was used without further purification. To the flask which contained the crude carboxylic acid was added $Cu(OAc)_2$ (1 mg, 0.006 mmol) and an oven dried condensor was attached. The system was flushed with Ar and distilled DMF (1 mL) was added. The reaction was wrapped in tin foil and stirred for 15 min. at which time $Pb(OAc)_4$ (55 mg, 0.12 mmol) was added. The mixture was stirred (still in the dark) for 15 min more and then heated to reflux for 1.5 h. Evaporation of the solvent and purification via column chromatography with 75:20:5 CH_2Cl_2/EtOAc/*i*-PrOH to yielded 5 mg (11%) of a clear oil. For **24**: $[\alpha]^{25}=-6.2$ (*c* 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: −0.04 (s, 9H), 0.79 (s, 3H), 0.91 (t, *J*=7.6 Hz, 3H), 1.15 (s, 3H), 1.22 (d, *J*=8.4 Hz, 1H), 1.92–2.00 (m, 2H), 2.10–2.1 (m, 1H), 2.18 (dd, *J*=10.8, 13.6 Hz, 1H), 2.40–2.50 (m, 1H), 2.62 (s, 3H), 3.40–3.48 (m, 1H), 3.49–3.54 (m, 1H), 3.60 (t, *J*=8.8 Hz, 1H), 4.21–4.25 (m, 1H), 3.78–3.81 (m, 1H), 4.97 (d, *J*=10.0 Hz, 1H), 5.02 (1/2 ABq, *J*=10.8 Hz, 1H), 5.24 (1/2 ABq, *J*=10.8 Hz, 1H), 5.63 (s, 1H), 6.99–7.09 (m, H), 7.2 (d, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CDCl_3$: −1.23, 18.0, 22.2, 22.9, 25.4, 29.7, 39.7, 44.7, 48.4, 61.9, 63.8, 66.5, 70.1, 70.6, 109.7, 110.3, 118.0, 122.7, 126.6, 128.8, 137.2, 142.3, 161.3, 164.6, 169.0; IR (NaCl/neat) 2952, 1727, 1683, 1650 cm^{-1}; HRMS (FAB+) calcd for $C_{28}H_{40}O_5N_3Si_1$ (*m*/*z*) 526.2737, found (*m*/*z*) 527.2727.

5.3.10. Spiro[1*H*,5*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-1-carboxylic acid, 1′,2′,5a,6,7,8,10,10a-octahydro-3-(2-methyl-1-propenyl)-2′,5,10-trioxo-, ethyl ester, (1*R*,2*S*,3*S*,5a*R*,10a*R*-25). To a flame-dried 250 mL round-bottom flask with stir bar was added diketopiperazine **22** (2.70 g, 5.75 mmol), 4 Å molecular sieves (5.0 g) and TsOH (1.0 g, 5.75 mmol). An oven-dried condensor was attached, the system was flushed with argon, freshly distilled toluene (200 mL) was added and the system heated to reflux temperature for 8 h. The solvent was evaporated and replaced with 100 mL of EtOAc, washed with 2×15 mL 5% $NaHCO_3$, 1×10 mL sat. brine sol., dried over Na_2SO_4, filtered, evaporated and chromatographed with 75:20:5 CH_2Cl_2/EtOAc/*i*-PrOH to yield 1.75 g (70%) of **25**: $[\alpha]_D^{25}=78.5$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ $CHCl_3$: 0.79 (t, *J*=7.5 Hz, 3H) 1.48 (d, *J*=1.5 Hz, 3H), 1.61 (d, *J*=1.5 Hz, 3H), 1.90–2.10 (m,

2H), 2.20–2.40 (m, 2H), 3.50–3.70 (m, 2H), 3.74–3.92 (m, 2H), 3.97 (d, $J=10.2$ Hz, 1H), 4.33 (t, $J=7.5$ Hz, 1H), 4.78 (dt, $J=1.5$, 9.6 Hz, 1H), 5.12 (d, $J=9.6$ Hz, 1H), 5.21 (d, $J=10.2$ Hz, 1H), 6.86 (d, $J=7.5$ Hz, 1H), 7.03 (dt, $J=1.9$, 7.5 Hz, 1H), 7.13 (d, $J=7.5$ Hz, 1H), 7.24 (dt, $J=1.9$, 7.5 Hz, 1H), 7.97 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ $CDCl_3$: 7.27, 11.9, 17.4, 19.4, 20.8, 39.3, 45.2, 52.8, 54.3, 54.9, 55.3, 57.2, 103.8, 113.1, 116.0, 119.2, 119.3, 122.8, 130.8, 134.8, 158.5, 160.3, 161.5, 171.0; IR (NaCl/neat) 3219, 1723, 1663, 1648 cm^{-1}; HRMS (FAB+) calcd for $C_{24}H_{28}O_5N_3$ (*m/z*) 438.2029, found (*m/z*) 438.2017.

ent-**25**: $[\alpha]_D^{25}=-74.0$ (*c* 1.0, CH_2Cl_2).

5.3.11. *N*-SEM diketopiperazine 26. To a flame-dried 10 mL round-bottom flask with stir bar was added **25** (65 mg, 0.15 mmol). The system was flushed with Ar, THF added and cooled to −78°C. KHMDS (0.35 mL of a 0.5 M sol., 0.18 mmol) was added and stirred for 15 min. SEMCl (0.035 mL, 0.18 mmol) was added dropwise and the reaction allowed to warm to room temperature and stirred for 8 h. Sat. NH_4Cl was added and the reaction mixture poured into 10 mL EtOAc. The aq. layer was extracted 3×5 mL with EtOAC, the organic layers combine, dried over Na_2SO_4, filtered, evaporated and chromatographed with 75:20:5 CH_2Cl_2/EtOAc/*i*-PrOH to yield 70 mg (84%) of the white solid **26**: $[\alpha]_D^{25}=-63.5$ (*c* 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: −0.04 (s, 9H), 0.71 (t, $J=7.2$ Hz, 3H), 0.86–1.00 (m, 2H), (1.46 (s, 3H), 1.55 (s, 3H), 1.95 – 2.02 (m, 2H), 2.24–2.40 (m, 2H), 3.52–3.65 (m, 3H), 3.68–3.76 (m, H), 3.82–3.90 (m, 1H), 3.97 (d, $J=10.0$ Hz, 1H), 4.32 (t, $J=8.0$ Hz, 1H), 4.78 (d, $J=14.8$ Hz, 1H), 5.09 (1/2 ABq, $J=11.2$ Hz, 1H), 5.10 (d, $J=10.0$ Hz, 1H), 5.20 (1/2 ABq, $J=11.2$ Hz, 1H), 7.04 (d, $J=8.0$ Hz, 1H), 7.07 (t, $J=8.0$ Hz, 1H), 7.15 (d, $J=8.0$ Hz, 1H), 7.30 (t, $J=8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CDCl_3$: −1.16, 13.7, 17.9, 18.5, 23.8, 25.9, 27.2, 45.7, 51.9, 59.0, 60.7, 61.3, 61.8, 63.7, 66.4, 70.1, 110.0, 119.4, 122.9, 125.1, 125.5, 129.4, 137.5, 142.8, 165.0, 166.8, 167.9, 175.9; IR (NaCl/neat) 1728, 1678 cm^{-1}; HRMS (FAB+) calcd for $C_{30}H_{42}O_6N_3Si_1$ (*m/z*) 568.2843, found (*m/z*) 568.2827.

5.3.12. *N*-SEM triene 27. To a flame-dried 10 mL round-bottom flask with stir bar was added **26** (70 mg, 0.12 mmol) and LiI (165 mg, 1.2 mmol). An oven dried condensor was attached and the system was flushed with argon, freshly distilled pyridine (5 mL) was added and the system heated to reflux for 48 h. The solvent was evaporated and replaced with 10 mL of EtOAc, extracted with 5×2 mL 5% $NaHCO_3$ and the aqueous layers combined. The solution was then saturated with NaCl, acidified to pH 4 with 1N HCl and extracted with 5×5 mL EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered and evaporated to yield 45 mg (68%) a white solid, which was used without further purification. To the flask which contained the crude carboxylic acid was added $Cu(OAc)_2$ (1.5 mg, 0.008 mmol) and an oven dried condensor was attached. The system was flushed with Ar and distilled DMF (1 mL) was added. The reaction was wrapped in tin foil and stirred for 15 min. at which time $Pb(OAc)_4$ (55 mg, 0.12 mmol) was added. The mixture was stirred (still in the dark) for 15 min. more and then heated to reflux for 1.5 h. Evaporation of the solvent and purification via column chromatography with 75:20:5 CH_2Cl_2/EtOAc/*i*-PrOH to yielded 8 mg (20%) of **26** as a clear oil. For **26**: $[\alpha]^{25}=-60.0$ (*c* 0.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: −0.02 (s, 9H), 0.93 (t, $J=7.6$ Hz, 3H), (1.34 (s, 3H), 1.56 (s, 3H), 2.89 (dt, $J=2.4$, 8.0 Hz, 2H), 3.57 (t, $J=7.6$ Hz, 2H), 4.12 (t, $J=8.8$ Hz, 2H), 5.13 (d, $J=10.8$ Hz, 1H), 5.21 (t, $J=11.2$ Hz, 2H), 5.20 (d, $J=8.0$ Hz, 1H), 5.75 (s, 1H), 6.22 (t, $J=3.2$ Hz, 1H), 7.04–7.11 (m, 3H), 7.31 (t, $J=7.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CDCl_3$: −1.2, 18.0, 18.5, 25.4, 28.7, 29.9, 45.4, 62.1, 64.5, 66.6, 70.2, 110.1, 116.2, 119.7, 119.9, 123.0, 126.7, 127.4, 129.4, 135.5, 138.1, 138.5, 142.0, 152.2, 152.7, 177.0; IR (NaCl/neat) 1727, 1683 cm^{-1}; HRMS (FAB+) calcd for $C_{27}H_{33}O_4N_3Si_1$ (*m/z*) 491.2240, found (*m/z*) 491.2226.

5.3.13. Triene 28. To a flame-dried 10 mL round-bottom flask with stir bar was added **27** (8 mg, 0.017 mmol) dissolved in CH_2Cl_2 (2 mL) and cooled to −78°C. A 1.0 M hexane solution of Me_2AlCl (0.086 mL, 0.086 mmol) was added dropwise under Ar. The mixture was warmed to room temperature and stirred for 15 min. The solution was cooled to 0°C and poured into a sat. Na/K tartrate solution (2 mL) also at 0°C. The mixture was allowed to warm to room temperature and stirred vigorously for 1 h. The aq. layer was then extracted 3×5 mL with EtOAc, the organic layers combined, dried over Na_2SO_4, filtered and evaporated. Purification was accomplished by PTLC (1/2 of a 250 μm plate) with 75:20:5 CH_2Cl_2/EtOAc/*i*-PrOH as the eluent to yield 3 mg (48%) of **28** as a clear oil. For **28**: ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.22 (s, 3H), 1.35 (s, 3H), 2.85 (dt, $J=3.2$, 8.0 Hz, 2H), 4.09 (t, $J=8.8$ Hz, 2H), 5.17 (d, $J=8.8$ Hz, 1H), 5.51 (d, $J=8.8$ Hz, 1H), 5.75 (s, 1H), 6.19 (t, $J=3.2$ Hz, 1H), 6.82 (d, $J=7.6$ Hz, 1H), 6.97–7.05 (m, 2H), 7.37 (t, $J=7.6$ Hz, 1H), 7.85 (br s, 1H); IR (NaCl/neat) 1763, 1667 cm^{-1}; HRMS (FAB+) calcd for $C_{21}H_{20}O_3N_3$ (*m/z*) 362.1504, found (*m/z*) 362.1484.

5.3.14. Spiro[1*H*,5*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-1-carboxylic acid, 1′,2′,5a,6,7,8,10,10a-octahydro-3-(2-methyl-1-propenyl)-2′,5,10-trioxo-, (1*R*,2*S*,3*S*,5a*R*,10a*R*) 29. To a flame dried 100 mL round-bottom flask with stir bar was added olefin **25** (0.87 g, 2.0 mmol) and LiI (2.66 g, 20.0 mmol). An oven-dried condensor was attached and the system was flushed with argon, freshly distilled pyridine (50 mL) was added and the system heated to reflux for 48 h. The solvent was evaporated and replaced with 50 mL of EtOAc, extracted with 5×10 mL 5% $NaHCO_3$ and the aqueous layers combined. The solution was then saturated with NaCl, acidified to pH 4 with 1N HCl and extracted with 5×10 mL EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered and evaporated to yield 0.58 g (71%) of **29**. The organic layer from the first extraction was dried over Na_2SO_4, filtered, evaporated and purified via column chromatography with 75:20:5 CH_2Cl_2/EtOAc/*i*-PrOH to recover 80 mg of unreacted starting material **25**. For **29**: $[\alpha]_D^{25}=73.0$ (*c* 0.8, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ MeOH: 1.27 (s, 3H), 1.29 (s, 3H), 1.98–2.04 (m, 2H), 2.18–2.30 (m, 2H), 3.50–3.70 (m, 2H), 3.37–3.46 (m, 1H), 3.51–3.58 (m, 2H), 3.74 (d, $J=10.2$ Hz, 1H), 4.52 (t, $J=7.5$ Hz, 1H), 4.96 (d, $J=5.1$ Hz), 5.32 (d, $J=9.3$ Hz, 1H), 6.84 (d, $J=7.5$ Hz, 1H), 6.98 (dt, $J=1.9$, 7.5 Hz, 1H),

7.19 (dt, J=1.9, 7.5 Hz, 1H), 7.24 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ CD_3OD: 12.5, 18.7, 19.9, 22.3, 40.7, 47.0, 54.8, 55.9, 57.1, 58.8, 105.2, 115.8, 117.1, 121.3, 121.5, 124.2, 131.1, 137.7, 161.3, 163.0, 164.9, 173.1; IR (NaCl/neat 3248, 1731, 1678, 1668 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{24}O_5N_3$ (*m/z*) 410.1716, found (*m/z*) 410.1698.

ent-**29**: $[\alpha]_D^{25}=-75.0$ (*c* 1.0, MeOH).

5.3.15. Spiro[1*H*,5*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-1-carboxylic acid, 5a,6,7,8,10,10a-hexahydro-3-(2-methoxy-2-methylpropyl)-2′,5,10-trioxo-, ethyl ester, (1*R*,2*S*,3*S*,5a*R*,10a*R*-31). Compound **31** was generated in an identical fashion to diketopiperazine **22** yet afforded a higher yield (94%). For **31**: $[\alpha]_D^{25}=81.7$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ $CHCl_3$: 0.85 (s, 3H), 0.87 (t, J=7.2 Hz, 3H), 1.24, (s, 3H), 1.77 (dd, J=9.9, 14.1 Hz, 1H), 1.90–2.11 (m, 2H), 2.25–2.33 (m, 2H), 2.52 (d, J=13.8 Hz, 1H), 2.79 (s, 3H), 3.56–3.65 (m, 2H), 3.73–3.81 (m, 3H), 4.31 (t, J=7.5 Hz, 1H), 4.67 (d, J=9.9 Hz, 1H), 5.09 (d, J=9.9 Hz, 1H), 6.86 (d, J=7.5 Hz, 1H), 7.01 (t, J=7.5 Hz, 1H), 7.09 (d, J=7.5 Hz, 1H), 7.23 (t, J=7.5 Hz, 1H), 8.26 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ $CDCl_3$: 7.27, 15.8, 17.0, 19.2, 21.0, 33.5, 39.1, 41.3, 48.1, 52.7, 54.1, 54.7, 55.0, 55.5, 67.3, 103.2, 115.2, 119.8, 120.2, 122.3, 135.3, 158.0, 159.7, 161.0, 171.5; IR (NaCl/neat) 3268, 1729, 1671, 1669 cm^{-1}; HRMS (FAB+) calcd for $C_{25}H_{32}O_6N_3$ (*m/z*) 470.2291, found (*m/z*) 470.2296.

ent-Diketopiperazine **31**: $[\alpha]_D^{25}=-81.2$ (*c* 1.0, CH_2Cl_2).

5.3.16. Spiro[3*H*,5*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(10*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione, 5a,6,7,8-tetrahydro-3-(2-methyl-1-propenyl)-, (2*S*,3*S*,5a*R*) (12-*epi*-spirotyprostatin B) (30). To a flame-dried 100 mL round-bottom flask with stir bar was added carboxylic acid **31** (0.29 g, 0.26 mmol), DCC (0.22 g, 1.06 mmol), DMAP (0.13 g, 1.06 mmol) and 2-mercaptopyridine *N*-oxide (0.112 g, 0.88 mmol). An oven-dried condenser was attached and the system was flushed with argon and wrapped in tin foil. Freshly distilled $BrCCl_3$ (25 mL) was added and the system was heated to 60°C for 1 h. The foil was then removed and the reaction heated to reflux for 1.5 h. The solvent was evaporated and the resulting oil was purified by chromatography (silica gel, eluted with 75:20:5 CH_2Cl_2/EtOAc/*i*-PrOH) to yield 0.095 g (37%) of **32**. $[\alpha]_D^{25}=41.3$ (*c* 0.8, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ $CHCl_3$: 1.50 (d, J=1.5 Hz, 3H), 1.54 (d, J=1.5 Hz, 3H), 1.90–2.16 (m, 3H), 2.18–2.30 (m, 2H), 3.40–3.48 (m, 1H), 3.52–3.60 (m, 1H), 3.81–3.92 (m, 2H), 4.36 (dd, J=6.9, 10.5 Hz, 1H), 5.13 (dt, J=1.5, 8.1 Hz, 1H), 5.54 (d, J=9.3 Hz), 5.83 (s, 1H), 6.87 (d, J=7.5 Hz, 1H), 7.01–7.09 (m, 2H), 7.19 (dt, J=1.9, 7.5 Hz, 1H), 7.22–7.27 (m, 1H) 7.69 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CDCl_3$: 18.6, 22.2, 25.7, 29.3, 45.3, 62.0, 62.1, 64.8, 110.1, 115.8, 119.3, 121.8, 122.8, 127.2, 128.6, 129.3, 155.7, 162.5, 178.2; IR (NaCl/neat) 3196, 1724, 1676, 1639 cm^{-1}; HRMS (FAB+) calcd for $C_{21}H_{21}O_3N_3$ (*m/z*) 364.1661, found (*m/z*) 364.1658.

epi-ent-Spirotyprostatin B: $[\alpha]_D^{25}=-42.5$ (*c* 0.8, CH_2Cl_2).

5.3.17. Spirotyprostatin B (2). To a flame-dried 10 mL round-bottom flask with stir bar was added 12-*epi*-spirotyprostatin B (**32**) (0.95 g, 0.26 mmol), MeOH (2 mL) was added and the system cooled to 0°C. A 1 M solution of NaOMe in MeOH (0.26 mL) was added dropwise and the mixture was stirred at 0°C for 2 h at which time 5 mL of saturated aqueous NH_4Cl was added along with 5 mL of EtOAc. The aqueous layer was extracted with EtOAc (3×5 mL) and the organic layers combined, dried over Na_2SO_4, filtered, evaporated and purifed by chromatography (silica gel, eluted with 75:20:5 CH_2Cl_2/EtOAc/*i*-PrOH) to yield 0.044 g (46%) of **2** and 0.28 g (30%) of **32**. For **2**: $[\alpha]_D^{25}=-151.1$ (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.28 (d, J=0.9 Hz, 3H), 1.57 (d, J=0.9 Hz, 3H), 1.94–2.05 (m, 2H), 2.08–2.16 (m, 1H), 2.46–2.53 (m, 1H), 3.58 (ddd, J=2.9, 9.3, 12.2 Hz, 1H), 3.84 (dt, J=8.3, 12.2 Hz, 1H), 4.35 (dd, J=6.1, 10.5 Hz, 1H), 5.22 (dt, J=1.2, 8.8 Hz, 1H), 5.4 (d, J=8.8), 5.79 (s, 1H), 6.89 (d, J=7.6 Hz, 1H), 6.99 (dt, J=1.0, 7.6 Hz, 2H), 7.06 (dt, J=1.0, 7.6 Hz, 1H), 7.23 (dt, J=1.0, 7.6 Hz, 1H) 7.77 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ $CDCl_3$: 18.4, 22.3, 25.5, 29.5, 45.0, 61.8, 61.9, 64.3, 110.0, 116.4, 120.7, 122.5, 127.4, 128.1, 129.3, 138.4, 138.5, 140.6, 155.2, 162.7, 178.1; IR (NaCl/neat) 3235, 1718, 1677, 1690 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{21}O_3N_3$ (*m/z*) 363.1583, found (*m/z*) 363.1584.

ent-Spirotryprostatin B: $[\alpha]_D^{25}=155.1$ (*c* 0.33, CH_2Cl_2).

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18. Aldehyde **9** is obtained from inexpensive, commercially available 3-methoxy-3-methyl-1-butanol (Aldrich Chemical Co.) by Swern oxidation in 89% yield (see Section 5).
19. The unsaturated oxindolylidene acetate **10** is readily prepared from isatin (Aldrich Chemical Co.) by condensation with $(Ph)_3PCHCO_2Et$ (Aldrich Chemical Co.) in refluxing diglyme in 84% yield (see Ref. 14c).
20. Beta refers to approach of the dipolarophile from the top face as drawn in Scheme 2.
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