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Concise, asymmetric total synthesis of spirotryprostatin A

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Abstract—The structurally intriguing cell-cycle inhibitor spirotryprostatin A has been synthesized utilizing an azomethine ylide dipolar cycloaddition reaction as the key step. This pentacyclic alkaloid contains a prenylated tryptophan-derived oxindole moiety that has been created in a regiocontrolled and stereocontrolled manner in a single step.

1. Introduction

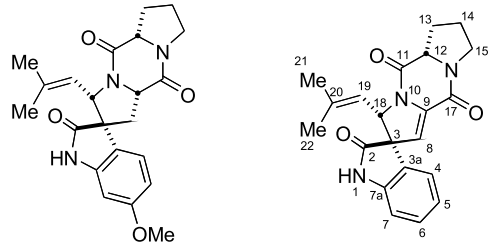
The spirotryprostatins,[1] tryprostatins[2] and cyclotryprostatins[3] represent a promising class of antimitotic arrest agents. Isolated from *Aspergillus fumigatus*, spirotryprostatin A (**1**, Fig. 1) and spirotryprostatin B (**2**) were shown to completely inhibit the progression of cells at concentrations greater than 253 and 34.4 μM, respectively.[1] The spirotryprostatins are characterized by a unique *spiro*-oxindole substituted *cis*-prolyl-prolyl-diketopiperazine that is prenylated at C-18. 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. 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.

Since the isolation of the natural products in 1996, numerous groups have embarked on research programs directed towards the total synthesis of spirotryprostatins A and B. Various research groups have focused their efforts on the development of synthetic methodology of just the *spiro*-oxindole pyrrolidine portion of the natural products. Recent approaches include [5+2]-cycloaddition of enantiomerically pure η^3-pyridinyl molybdenum complexes,[4] directed radical cyclizations,[5] ring expansion of cyclopropanes by aldimines[6] and iodide ion-induced rearrangement of [(*N*-aziridinomethylthio)methylene]-oxindoles.[7] In addition to the generation of the *spiro*-oxindole quaternary carbon, a total synthesis endeavor must contend with the prenyl side-chain, three or four stereogenic centers which pose formidable synthetic challenges, and the enamide moiety in the case of spirotryprostatin B. These issues have been addressed by various strategies and have culminated in the total synthesis of spirotryprostatin B (**2**) by the groups of Williams,[8] Danishefsky,[9] Ganesan,[10] Overman,[11] Fuji[12] and Carreira.[13,14] On the other hand, only one total synthesis of spirotryprostatin A using the classical halohydrin to oxindole *spiro*-ring-forming contraction sequence has been reported thus far by Danishefsky.[15] We previously described the total synthesis of spirotryprostatin B (**2**) using a stereochemically distinct three-component asymmetric azomethine ylide [1,3]-dipolar cycloaddition reaction.[8] Herein, we report a concise asymmetric total synthesis of spirotryprostatin A (**1**).[16]

2. Results and discussion

2.1. Initial synthetic route to spirotryprostatin A

In contemplating the synthesis of spirotryprostatin A (**1**), it was envisioned that the core pyrrolidine ring could be formed through an asymmetric [1,3]-dipolar cycloaddition



1, spirotryprostatin A **2**, spirotryprostatin B

Figure 1. Structures of spirotryprostatins A and B.

Keywords: Spirotryprostatin A; Dipolar cycloaddition; Azomethine ylide.
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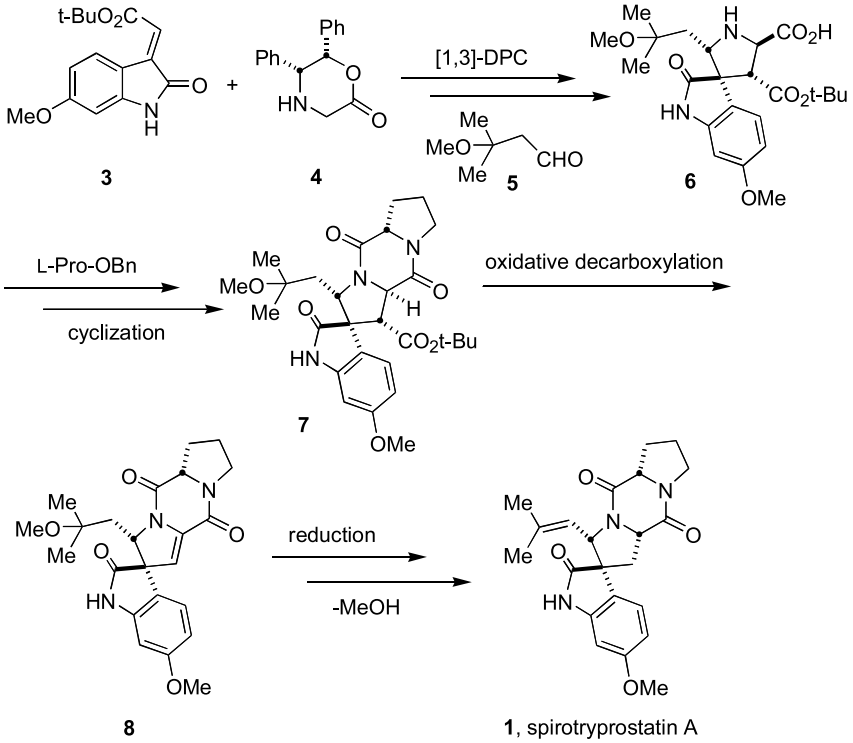
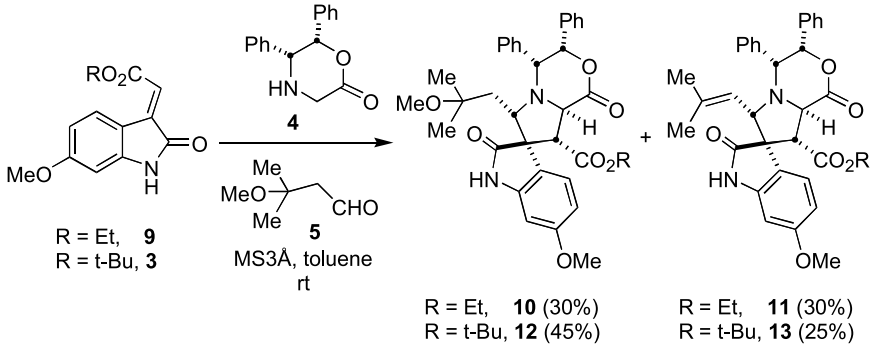
similar to that employed in our spirotryprostatin B synthesis.[8] Spirotryprostatin A (**1**) differs from spirotryprostatin B (**2**) in that it is saturated at C-8 and C-9 and is substituted at C-6 by a methoxy group whereas spirotryprostatin B (**2**) is absent of functionality in the aromatic ring and contains the characteristic C-8, C-9-enamide moiety. The enamide of spirotryprostatin B was installed via a Barton-modified Hunsdiecker reaction through an oxidative decarboxylation of a carboethoxy group that was introduced at C-8 in the initial dipolar cycloaddition reaction. First, we attempted to apply the same strategy, which was developed for spirotryprostatin B, to the total synthesis of spirotryprostatin A (Scheme 1). This approach would have to account for the substitution of the aromatic ring and the formation of the fourth stereogenic center. Thus, [1,3]-dipolar cycloaddition with methoxy-substituted oxindolylidene acetate **3** would yield *spiro*-oxindole pyrrolidine amino acid **6** upon reductive cleavage of the chiral auxiliary. Coupling of **6** to L-proline benzyl ester and concomitant cyclization would afford diketopiperazine **7**. Deprotection of the carboxyl group followed by a Barton-modified Hunsdiecker reaction as deployed previously, would result in the formation of enamide **8**. Palladium-catalyzed reduction of the olefin was reasonably expected to occur from the least hindered face opposite the isopropylidene group and the aromatic ring to *cis*-diketopiperazine. Final acid-catalyzed elimination of methanol would then afford spirotryprostatin A (**1**).

In the synthesis of spirotryprostatin B, ethyl oxindolylidene acetate was synthesized via Wittig reaction of commercially available 1H-indole-2,3-dione (isatin) and the requisite stabilized ylide. For spirotryprostatin A, 6-methoxy-isatin[17] was not commercially available and necessitated preparation from *m*-anisidine by a Sandmeyer reaction.[18] Wittig reaction with (carbethoxymethylene)triphenyl phosphorane then afforded 6-methoxy-ethyl oxindolylidene acetate **9**. Crystallization of the product mixture afforded only the desired *E*-isomer. Addition of dipolarophile **9** to the azomethine ylide derived from morpholinone **4** and aldehyde **5** yielded cycloadducts **10** and **11** (Scheme 2). The reaction proceeded in only modest yields (60%) and afforded the two products as a ~1:1 mixture. It was suspected that the yield and selectivity were a result of the poor solubility of ethyl oxindolylidene acetate (**9**) in toluene at room temperature. It was reasoned that this slowed the cycloaddition down relative to the analogous system used quite successfully in our spirotryprostatin B synthesis, allowing for a competing pathway via formation and cycloaddition of an incipient unsaturated azomethine ylide that results in the formation of the unsaturated cycloadduct (**11**) to prevail.[8] It was speculated that an increase in the lipophilicity of the dipolarophile might aid in the solubility of this species and suppress formation of the unsaturated azomethine ylide. Therefore, the *tert*-butyl ester **3** was synthesized which proved to be readily soluble in toluene at room temperature. Subjecting **3** to the standard reaction conditions for the [1,3]-dipolar cycloaddition resulted in an improved yield (70%) and an increase in the ratio (ca. 2:1) of the desired cycloadduct **12** over the unsaturated cycloadduct **13**.

Construction of the diketopiperazine began with palladium-catalyzed hydrogenolysis of cycloadduct **12** (Scheme 3). The resulting amino acid **6**[19] was coupled without purification to L-proline benzyl ester with BOP as the activating agent. Reduction of the resulting dipeptide-benzyl ester, followed by intramolecular cyclization afforded diketopiperazine **7** in 39% yield over three steps. This is in contrast to the 69% yield observed for the

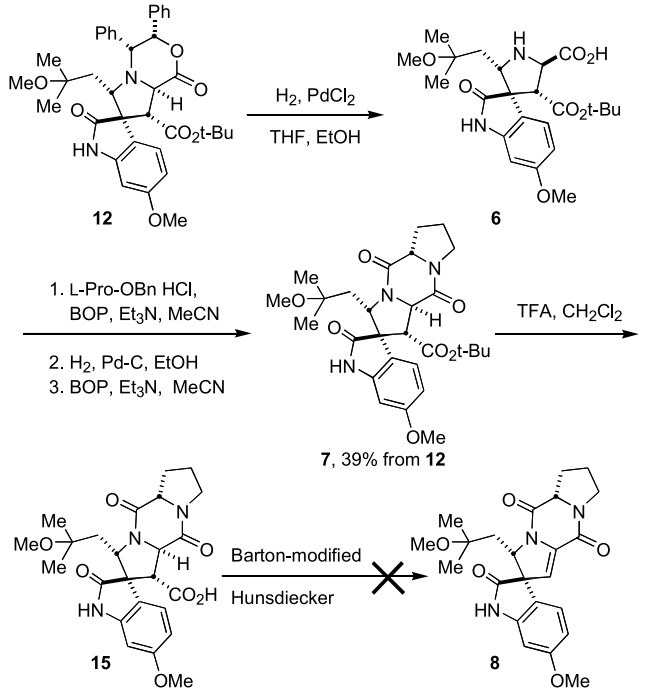


Scheme 1. Initial strategy to spirotryprostatin A (**1**).



Scheme 2. [1,3]-Dipolar cycloaddition with 6-methoxy-alkyl oxindolylidene acetate **9** and **3**.

analogous sequence employed in the spirotryprostatin B synthesis.[8] It is not currently understood why substitution of the aromatic ring or exchange of the ethyl ester for a *tert*-butyl ester caused such a decrease in the overall yield. Completion of the synthesis of spirotryprostatin A required hydrolysis of the ester functionality and the Barton-modified Hunsdiecker reaction to afford enamide **8**. The *tert*-butyl ester **7** was hydrolyzed using trifluoroacetic acid in yields ranging from 42–58%. However, subjecting the resulting carboxylic acid **15** to the same oxidative decarboxylation conditions employed successfully in the spirootryprostatin B synthesis failed to provide enamide **8**. Kochi-type conditions ($Pb(OAc)_4$; and thermal or photolytic cleavage of a benzophenone oxime ester) were also unsuccessful. Attempted reductive decarboxylation conditions resulted in decomposition of the starting material. Attempts to affect either the oxidative or the reductive decarboxylation at an earlier stage in the synthesis were similarly unsuccessful. The complications in the elimination of the carboxyl group and the relatively lower yields observed for the previous steps warranted exploration of a new strategy.



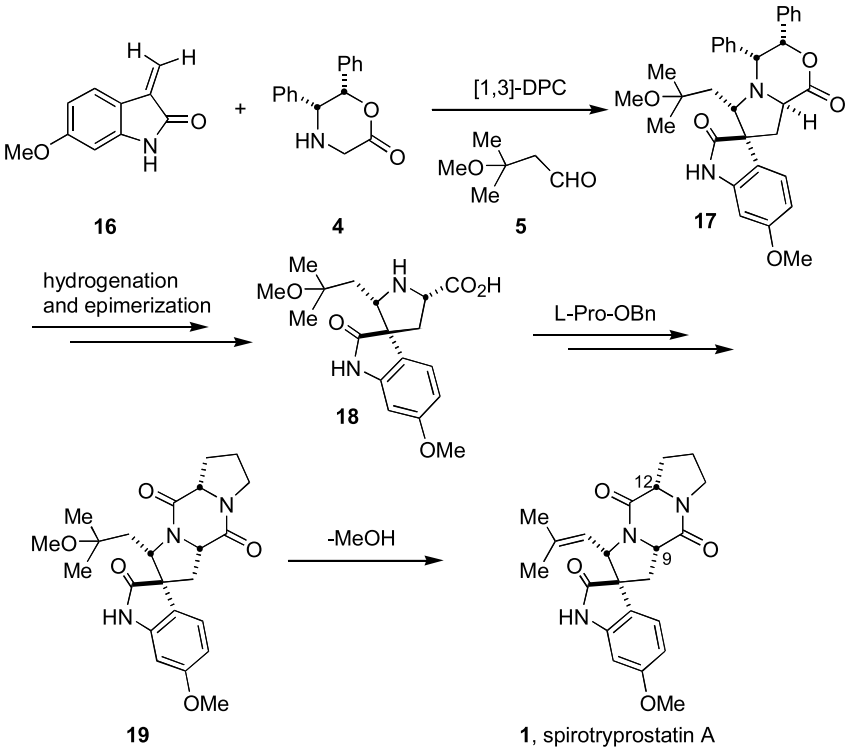
Scheme 3. Elaboration to diketopiperazine **7** and attempted decarboxylation of **15**.

2.2. Revised synthetic route to spirotryprostatin A

A new approach, one that avoided the problematic oxidative decarboxylation step, was eventually devised as outlined in Scheme 4. Since it is not necessary to install a carboxyl group as a precursor for the saturated pyrrolidine moiety, the strategy revolved around formation of 6-methoxy-3-methylene-1,3-dihydro-indol-2-one (**16**). Elimination of the carboalkoxy group from the dipolarophile at the outset would alleviate the problems associated with its ultimate removal. If the synthesis of this dipolarophile could be accomplished, [1,3]-dipolar cycloaddition with **4** and **5** would generate a cycloadduct **17** that would have the correct configuration at the adjacent C-3 quaternary and C-18 stereogenic centers. However, based on the established facial selectivity of azomethine ylide reactions derived from **4**, the α-proton (C-9) would need to be epimerized before elaboration to the diketopiperazine **19**. This was anticipated to be a non-trivial operation since, as our spirotryprostatin B synthesis had shown, the thermodynamic instability of the *trans*-diketopiperazines in this structural family resulted in the facile epimerization of the prolyl-stereogenic center.[8] Finally, elimination of the tertiary methyl ether of **19** would afford the natural product (**1**).

Recently, Horvath and co-workers reported that azomethine ylides generated from silylaminonitriles and 3-methyleneindolin-2-one react to give the corresponding cycloadduct in 70% yield.[20] However, the dipolarophile was generated by flash vacuum pyrolysis and did not seem compatible with the synthesis of the methoxy-substitued derivative we required. After extensive exploration, we found that the Peterson olefination,[21] which has proven to be an efficient method for the generation of terminal olefins, afforded a suitable method for the formation of **16**. As shown in Scheme 5, addition of trimethylsilylmethyllithium to 6-methoxy-isatin[17] (**20**) afforded tertiary alcohol **21** in 85% yield. The *exo*-methylene species **16** could be prepared in situ by the treatment of **21** with trifluoroacetic acid at 0 °C.

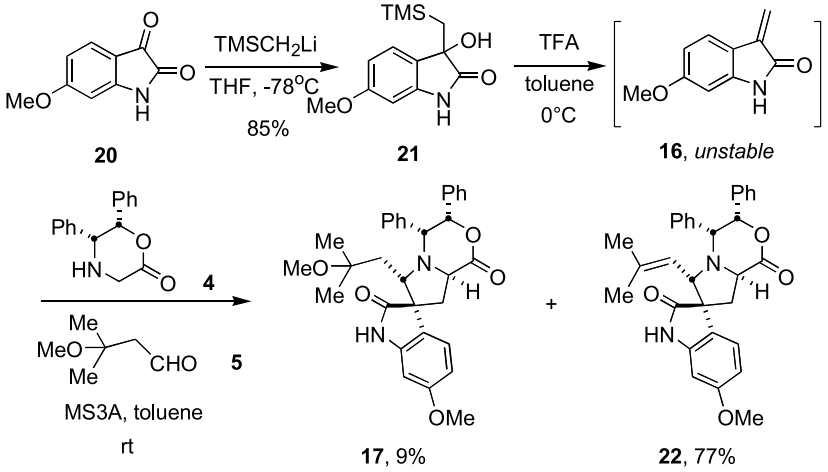
Compound **16** proved to be an unstable species that was not isolable due to polymer formation upon concentration. Thus, after neutralization with triethylamine, the reaction mixture containing crude **16** was directly and rapidly used for the cycloaddition. By the addition of **4** and **5** to the



Scheme 4. Revised strategy to spirotryprostatin A.

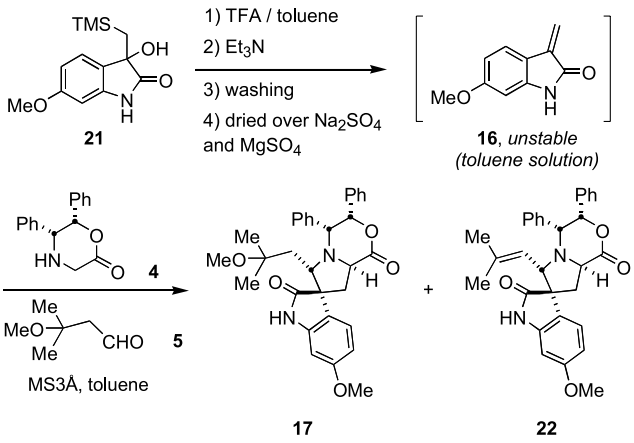
resultant crude mixture of **16** thus prepared, the [1,3]-dipolar cycloaddition proceeded rapidly to give a mixture of cycloadducts (**17** and **22**). We were unable to detect the generation of alternate regio- or diastereoisomers as products in the crude reaction mixture. In initial attempts performed at room temperature, the ratio of products unfortunately heavily favored the methanol elimination product **22**. Although a strategy utilizing **22** as a potential intermediate was explored, the olefin and oxindole functionalities proved incompatible with the conditions required to remove the chiral auxiliary.

This initially discouraging result prompted us to carefully explore the cycloaddition to elucidate crucial factors to control the reaction and suppress formation of **22**. First, the amount of the oxindole **21** was increased from 1.5 to 2 equiv since the yield would be influenced by amount of the unstable intermediate **16**; however, the yield for the desired product **17** was not improved. Next, we evaluated the effect of washing the reaction mixture after neutralization with triethylamine. First, the cycloaddition was performed without washing to give the methanol elimination product **22** exclusively (Table 1). When the reaction mixture was washed with saturated aqueous sodium bicarbonate solution or saturated aqueous citric acid solution, these attempts also afforded **22** exclusively. However, when just water was, the cycloaddition gave the desired compound **17** in 24% yield along with 42% of **22**. ^{1}H NMR studies were then conducted to decipher at what stage during the reaction methanol was being eliminated. After mixing aldehyde **5** and 0.83 equiv of **4** for 5 min in C_6D_6 at room temperature, we observed the generation of a significant amount (>50%) of 3-methyl-2-



Scheme 5. [1,3]-Dipolar cycloaddition with methylene indolinone **16**: an initial attempt.

Table 1. Optimization studies for the azomethine ylide dipolar cycloaddition



Entry	Washing	Temperature (°C)	Yield	
			17	**22**
1	No washing	rt	ND	61
2	H_2O and sat. $NaHCO_3$	rt	ND	40
3	H_2O and sat. citric acid	rt	ND	46
4	H_2O	rt	24	42
5	H_2O	−15–0 °C	44	20

N.D.: not detected (i.e. <trace).

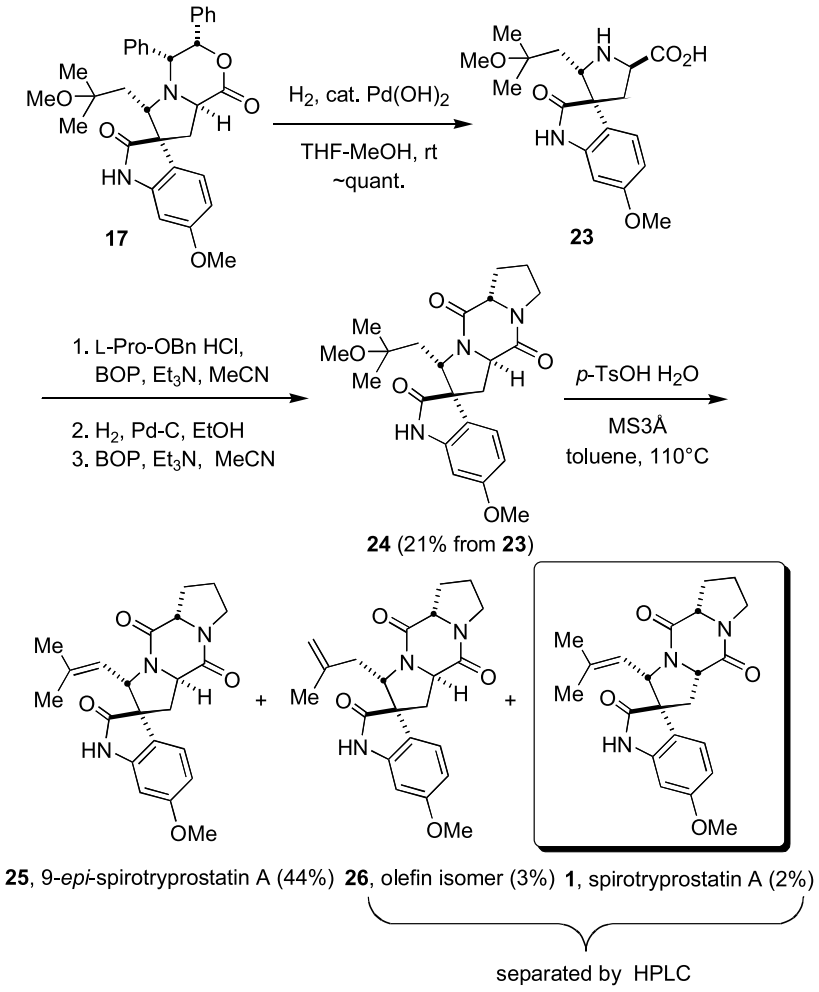
butenal whereas **4** remained intact. This indicated that elimination of methanol from **5** proceeds rapidly at room temperature. In an attempt to obviate the elimination before the dipolar cycloaddition reaction, the cycloaddition was then performed at 0 °C. Under these conditions, the desired cycloadduct **17** was isolated in 44% yield as a major product along with 20% of **22**.

The regiochemistry of **17** was ascertained by the doublet of doublets observed in the ^{1}H NMR spectrum for the α proton (to become C-9) and the relative configuration was confirmed by NOESY. As anticipated, these data indicated that the cycloadduct possesses the incorrect relative stereochemistry at C-9 (spirotryprostatin numbering). However, a strategy utilizing **17** as an intermediate would potentially be warranted for further investigation since catalytic hydrogenation can be used for removal of the chiral auxiliary. Actually, amino acid **23** was cleanly produced from catalytic hydrogenation of **17** using $Pd(OH)_2$ as a catalyst in quantitative yield (Scheme 6). First, we attempted epimerization of the α-proton (C-9) after conversion to the *trans*-diketopiperazine **24** since, during the last methanol elimination step, we anticipated that the prolyl-stereogenic centers (C-9 or C-12) could be epimerized to give a mixture of *cis*-diketopiperazines (i.e. spirotryprostatin A (**1**) and its *bis*-epimer at C-9 and C-12), which are thermodynamically more stable than the corresponding *trans*-diketopiperazines for cyclic anhydrides of proline.[8,22] To obtain diketopiperazine **24**, compound **23** was directly coupled with L-proline benzyl ester and BOP as the activating agent to give the corresponding dipeptide. Reduction of the benzyl ester followed by BOP-mediated cyclization afforded diketopiperazine **24**, a useful precursor of 9-*epi*-spirotryprostatin A, in 21% yield from **23**. The modest yield seemed to be associated with the difficulty of the isolation procedure to remove HMPA (a by-product from BOP-mediated coupling) from the product since diketopiperazine **24** proved to be quite hydrophilic. Additionally, it was observed that some of the product (less than 18%) were partitioned into the aqueous layer in the presence of HMPA.

Next, diketopiperazine **24** was subjected to treatment with *p*-TsOH-H_2O in refluxing toluene to give 9-*epi*-spirotryprostatin A (**25**) in 44% yield along with the olefin isomer of 9-*epi*-spirotryprostatin A (**26**, 3%). The relative configuration of **25** was confirmed by NOESY to be a *trans*-fused diketopiperazine. Unexpectedly, only a trace amount (2%) of the *cis*-fused substance (spirotryprostatin A, **1**), which could be isolated from **26** by HPLC, was generated. We were unable to detect the generation of 9,12-*bis*-*epi*-spirotryprostatin A. This result is in stark contrast to that observed for our spirotryprostatin B synthesis, in which epimerization readily occurred at the prolyl-stereogenic center (C-12) to give the thermodynamically more stable *cis*-fused diketopiperazine.[8]

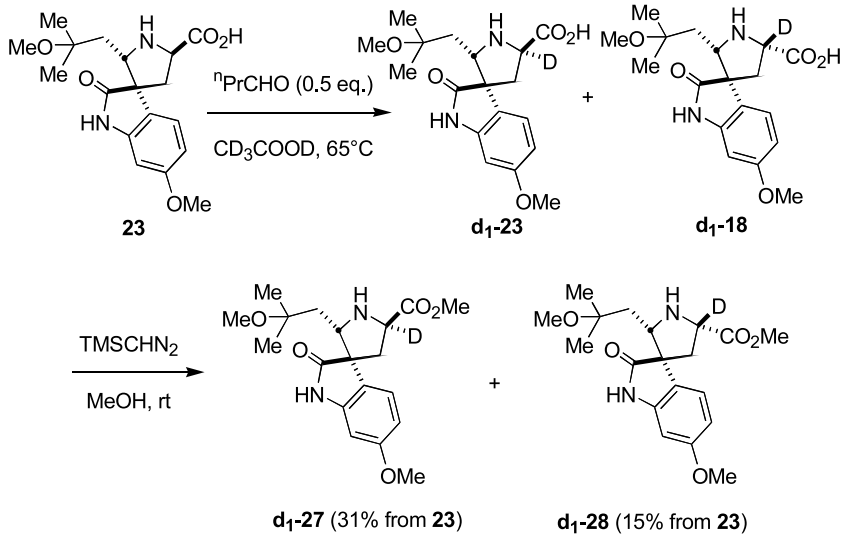
We next turned to examining the epimerization of the α-proton of **23** in the presence of an aldehyde and acid.[23] Butyraldehyde (0.5 equiv) and **23** were dissolved in CD_3COOD and the mixture was heated to 65 °C (Scheme 7). It was observed by ^{1}H NMR that the α-proton of the amino acid was gradually exchanged for deuterium and that thermodynamic epimerization had occurred. After conversion into the corresponding methyl ester by the treatment with $TMSCHN_2$, these diastereomers could be isolated by PTLC.

By substituting acetic acid for CD_3COOD, **23** was epimerized to give an inseparable diastereomeric mixture of amino acids (**29**, Scheme 8). Separation by PTLC was possible only after conversion to the pentacyclic substances **24** and **19** by the following three-step sequence.[8] Coupling

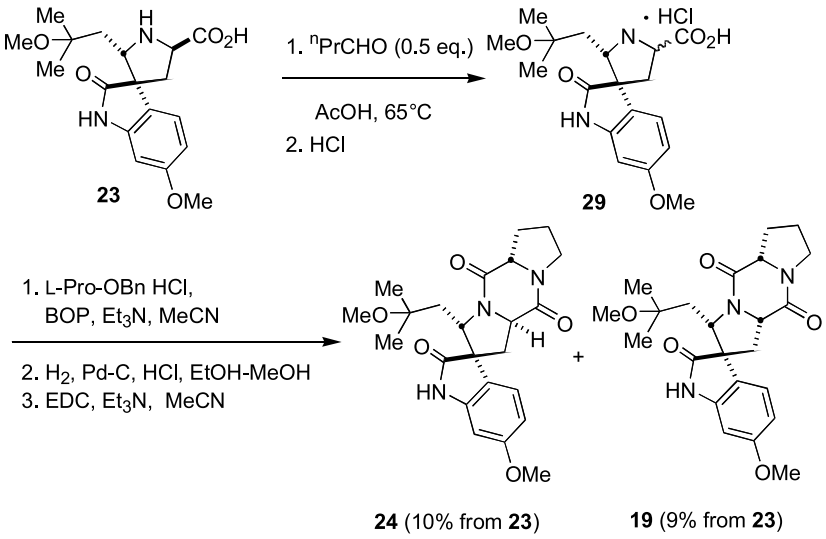


Scheme 6. Synthesis of 9-*epi*-spirotryprostatin A (**25**).

of **29** with L-proline benzyl ester in the presence of BOP afforded a diastereomeric mixture of dipeptides that was used without purification for the next reaction. Reduction of the benzyl ester followed by WSC-mediated cyclization afforded the *cis*-fused product **19** (9% from **23**), which has the correct relative and absolute configuration for the synthesis of spirotryprostatin A, plus the *trans*-fused substance (**24**, 10% from **23**), which was converted into 9-*epi*-spirotryprostatin A as shown in Scheme 6. The highly hydrophilic character of compounds **19** and **24** have resulted in lower yields due to loss of material in the aqueous work-up procedure.



Scheme 7. Epimerization of the α-proton of **23** in the presence of butyraldehyde and acetic acid.



Scheme 8. Elaboration to *cis*-fused diketopiperazine **19**.

Finally, **19** was subjected to treatment with *p*-TsOH-H_2O in refluxing toluene to give spirotryprostatin A (**1**) in 43% yield along with tertiary alcohol **30** (31%) (Scheme 9). Aiming to improve the yield, anhydrous camphorsulfonic acid, was used instead as a protic acid; however, elimination of methanol was not observed under these conditions.

3. Conclusion

In summary, a concise asymmetric total synthesis of spirotryprostatin A utilizing the asymmetric azomethine ylide [1,3]-dipolar cycloaddition reaction of methylene indolinone **16** has been achieved. The synthesis recorded herein requires only twelve steps (seven steps in the longest linear sequence) from commercially available reagents. The effects of compound **25**, 9-*epi*-spirotryprostatin A, on the cell cycle and microtubule assembly will be reported separately.

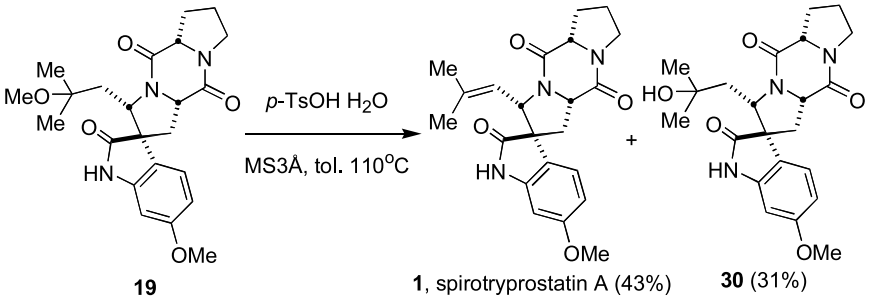
4. Experimental

4.1. General

Unless otherwise noted, materials were obtained from commercially available sources and used without purification. Toluene was freshly distilled from calcium hydride. Diethyl ether and tetrahydrofuran were freshly distilled from sodium benzophenone ketyl. 3 Å Molecular sieves were activated by heating for three minutes at the highest setting in a microwave followed by cooling under argon. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (120 °C) that was cooled in a dessicator, unless stated otherwise. Column chromatography was performed on Merck silica gel Kiesel 60 (230–400 mesh).

Mass spectra were obtained on Fisons VG Autospec. ^{1}H NMR, ^{13}C NMR, HSQC and NOE experiments were recorded on a Varian 300 or 400 MHz spectrometer. Spectra were recorded in $CDCl_3$ and chemical shifts (δ) were given in ppm and were relative to $CHCl_3$. Proton ^{1}H NMR were tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant in hertz, and number of protons. When appropriate, the multiplicity of a signal is denoted as 'br' to indicate the signal was broad. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrometer. Optical rotations were determined with a Rudolph Research Autopol III automatic polarimeter referenced to the D-line of sodium.

4.1.1. *tert*-Butyl (6-methoxy-2-oxo-1,2-dihydroindol-3-ylidene)acetate (3). To an oven-dried 25 mL round bottom flask with stir bar was added 6-methoxy isatin (0.50 g, 2.8 mmol) and carbo-*tert*-butoxy triphenylphosphylidene (1.15 g, 3.1 mmol). An oven-dried condensor was attached and the system flushed with argon. Dimethoxyethane (30 mL) was added via syringe and the system heated to



Scheme 9. The final stage: elimination of methanol to give spirotryprostatin A (**1**).

reflux with stirring. Heating continued for 14 h followed by filtering through a pad of celite. The solution was then evaporated to dryness and recrystallized from methanol to yield **3** (0.42 g, 54%) as an orange solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ $CHCl_3$: 1.56 (s, 9H), 3.84 (s, 3H), 4.30 (q, J=7.5 Hz, 2H), 6.43 (d, J=2.1 Hz, 1H), 6.53 (dd, J=2.1, 8.7 Hz, 1H), 6.65 (s, 1H), 8.50 (d, J=8.7 Hz, 1H), 9.25 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ $CHCl_3$: 28.5, 55.9, 81.7, 97.1, 108.0, 113.7, 121.6, 130.9, 137.3, 145.5, 163.4, 165.5, 171.0; IR (NaCl/neat) 3219, 1726, 1700; HRMS (FAB+) calcd for $C_{15}H_{17}O_4N$ (*m*/*z*) 275.1157, found (*m*/*z*) 275.1156.

4.1.2. Spiro[3H-indole-3,7′(6′H)-[1H]pyrrolo[2,1-*c*][1,4]oxazine]-8′-carboxylic acid, 1,2,3′,4′,8′,8′a-hexahydro-6-methoxy-6′-(2-methoxy-2-methylpropyl)-1′,2-dioxo-3′-4′-diphenyl-, *tert*-butyl ester, (3*S*,3′*S*,4′*R*,6′*S*,8′*R*,8′a*R*) (12) and Spiro[3H-indole-3,7′(6′H)-[1H]pyrrolo[2,1-*c*][1,4]oxazine]-8′-carboxylic acid, 1,2,3′,4′,8′,8′a-hexahydro-6-methoxy-6′-(2-methyl-1-propenyl)-1′,2-dioxo-3′-4′-diphenyl-, *tert*-butyl ester, (3*S*,3′*S*,4′*R*,6′*S*,8′*R*,8′a*R*) (13). To a flame-dried 100 mL round bottom flask with stir bar was added **3** (0.60 g, 2.2 mmol), (5*R*,6*S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (0.40 g, 1.5 mmol) and 3 Å molecular sieves (2.5 g). An oven-dried condensor was attached and the system flushed with argon. Distilled toluene (25 mL) was added via syringe followed by the addition of 3-methoxy-3-methyl butanal (0.22 g, 1.8 mmol) via syringe. The reaction mixture was kept at room temperature for 14 h while stirring. The reaction was then filtered through a pad of celite with toluene as the eluent and the resulting solution was evaporated under reduced pressure. Column chromatography with 3:1 hexane/AcOEt furnished cycloadduct **12** (0.44 g, 45%) and cycloadduct **13** (0.25 g, 25%).

Compound **12**. A white solid: $[\alpha]_D^{25}$=86.3 ($CHCl_3$, c=0.63); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.97 (s, 9H), 1.03 (s, 3H), 1.05 (s, 3H), 1.14 (dd, J=1.6, 16.4 Hz, 1H), 1.63 (dd, J=1.6, 16.4 Hz, 1H), 3.03 (s, 3H), 3.76 (s, 3H), 3.80 (d, J=7.2 Hz, 1H), 3.92 (d, J=1.6 Hz, 1H), 4.50 (d, J=7.2 Hz, 1H), 4.99 (d, J=3.2 Hz, 1H), 6.34 (d, J=3.2 Hz, 1H), 6.45–6.49 (m, 2H), 7.00 (d, J=8.8 Hz, 1H), 7.12–7.38 (m, 8H), 7.39 (d, J=8.8 Hz, 1H), 8.10 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 22.6, 26.0, 27.5, 44.3, 49.7, 55.2, 55.7, 56.0, 56.2, 60.0, 64.8, 73.5, 75.9, 82.0, 97.1, 107.2, 119.9, 125.1, 127.3, 127.4, 128.4, 128.5, 129.5, 136.7, 137.5, 142.6, 160.8, 167.7, 172.1, 178.2; IR (NaCl/neat) 1733, 1628; HRMS (FAB+) calcd for $C_{37}H_{43}O_7N_2$ (*m*/*z*) 627.3070, found (*m*/*z*) 627.3074; NOE data: irradiation of H_7 enhanced H_5 (1.12%) and H_9 (2.21%).

Compound **13**. White amorphous solid: $[\alpha]_D^{25}$=−12.7 ($CHCl_3$, c=0.29); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.99 (s, 9H), 1.44 (s, 3H), 1.67 (s, 3H), 3.76 (s, 3H), 3.93 (d, J=7.2 Hz, 1H), 4.33 (d, J=3.2 Hz, 1H), 4.41 (d, J=9.2 Hz, 1H), 4.48 (d, J=9.2 Hz, 1H), 4.76 (d, J=7.2 Hz, 1H), 6.03 (d, J=3.2 Hz, 1H), 6.42 (d, J=2.0 Hz, 1H), 6.49 (dd, J=2.0, 8.2 Hz, 1H), 7.08 (d, J=7.2 Hz, 1H), 7.15–7.24 (m, 10H), 7.52 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 18.9, 26.3, 27.5, 54.7, 55.7, 57.0, 59.3, 60.2, 68.8, 77.9, 82.1, 97.1, 106.8, 119.3, 119.9, 126.1, 126.9, 127.7, 128.0, 128.3, 128.6, 129.3, 136.2, 136.6, 140.8, 142.4, 160.6, 167.7, 171.9, 177.6; IR (NaCl/neat) 1730, 1632 cm^{-1}; HRMS (FAB+) calcd for $C_{36}H_{39}O_6N_2$ (*m*/*z*) 595.2808, found (*m*/*z*) 595.2804; NOE data: irradiation of H_9 enhanced H_7 (2.02%) and H_6 (1.31%).

4.1.3. Spiro[3H-indole-3,3′-pyrrolidine]-4′,5′-dicarboxylic acid, 1,2-dihydro-6-methoxy-2′-(2-methoxy-2-methylpropyl)-2-oxo, 4′-*tert*-butyl ester, 5′-metyl ester, (2′*S*,3*S*,4′*R*,5′*R*) (14). Cycloadduct **12** was added to a sealable pressure tube and dissolved in 1:1 THF/EtOH. The solvent was purged with argon for 5 min and palladium dichloride (1.0 equiv) 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 freshly distilled diethyl ether to afford the crude amino acid **6** as a white solid. For characterization purposes, a small amount of **6** was converted to the methyl ester. The carboxylic acid **6** was dissolved in 1:1 CH_2Cl_2/MeOH. To the solution was added 2 M (trimethylsilyl)diazomethane in hexane until a yellow color persisted. The reaction was stirred 5 min and then concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (silica gel, 1:1 hexane/AcOEt) to give **14** as a white amorphous solid.

$[\alpha]_D^{25}$=−17.2 ($CHCl_3$, c=0.64); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.89 (d, J=13.6 Hz, 1H), 0.98 (s, 9H), 1.00 (s, 3H), 1.10 (s, 3H), 1.17–1.21 (m, 1H), 3.09 (s, 4H), 3.64 (d, J=6.4 Hz, 2H), 3.76 (s, 6H), 4.49 (brs, 1H), 6.43 (d, J=2.0 Hz, 1H), 6.48 (d, J=8.4 Hz, 1H), 7.25 (s, 1H), 7.78 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 21.8, 24.0, 24.9, 28.0, 30.1, 39.8, 44.8, 48.9, 55.7, 57.0, 60.4, 60.5, 61.6, 74.5, 82.6, 97.4, 106.9, 116.6, 129.2, 143.1, 160.9, 162.9, 166.2, 168.7, 181.1; IR (NaCl/neat) 1724, 1662 cm^{-1}; HRMS (FAB+) calcd for $C_{24}H_{35}O_7N_2$ (*m*/*z*) 463.2444, found (*m*/*z*) 463.2444.

4.1.4. Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole]-1-carboxylic acid, 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methoxy-2-methylpropyl)-2′,5,10-trioxo-, *tert*-butyl ester, (1*R*,2*S*,3*S*,5a*S*,10a*R*) (7). Cycloadduct **12** (389 mg, 0.62 mmol) was added to a sealable pressure tube and dissolved in 1:1 THF/EtOH (7.8 mL). The solvent was purged with argon for 5 min and palladium dichloride (109 mg, 0.62 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 freshly distilled diethyl ether to afford the crude amino acid **6** as a white amorphous solid. To a 50 mL round-bottom flask that contained the crude amino acid **6** was added BOP reagent (0.30 g, 0.68 mmol) and L-proline benzyl ester hydrochloride (0.16 g, 0.68 mmol). The flask was flushed with argon, 15 mL of acetonitrile was added and the reaction mixture cooled to 0 °C. With stirring, triethylamine (0.19 mL, 1.3 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

10 mL of ethyl acetate, washed with 1 M HCl (2×2.5 mL), H_2O (1×2.5 mL), 5% $NaHCO_3$ (2×2.5 mL), sat. brine sol. (1×1 mL), dried over Na_2SO_4, filtered and evaporated to yield the crude dipeptide as a brown foam which was taken on crude. To the foam was added a stir bar and ethanol (10 mL). Argon was bubbled through for 5 min and 10% Pd/C (0.04 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 reagent (0.27 g, 0.62 mmol) and acetonitrile (5 mL). Triethylamine (0.086 mL, 0.62 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/AcOEt/^{i}PrOH afforded **7** (127 mg, 39%) as a white amorphous solid.

$[\alpha]_D^{25}=-57.3$ (CH_2Cl_2, $c=1.1$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.05 (s, 3H), 1.15 (s, 3H), 1.21 (s, 9H), 1.70 (dd, $J=4.0$, 18.4 Hz, 2H), 1.78 (quint, $J=8.4$ Hz, 1H), 1.85–1.96 (m, 1H), 1.96–2.08 (m, 1H), 2.15 (dd, $J=9.6$, 14.0 Hz, 1H), 2.49 (quint, $J=6.0$ Hz, 1H), 2.95 (s, 3H), 3.43 (d, $J=9.6$ Hz, 1H), 3.39 (ddd, $J=3.6$, 10.0, 13.6 Hz, 1H), 3.76 (s, 3H), 3.89 (dt, $J=8.0$, 12.4 Hz, 1H), 4.24 (dd, $J=6.0$, 11.6 Hz, 1H), 4.80 (dd, $J=4.4$, 9.6 Hz, 1H), 4.96 (d, $J=10.0$ Hz, 1H), 6.45 (d, $J=2.0$ Hz, 1H), 6.47 (dd, $J=2.0$, 8.4 Hz, 1H), 7.13 (d, $J=8.4$ Hz, 1H), 8.01 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ $CHCl_3$: 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 $C_{28}H_{38}O_7N_3$ (*m/z*) 528.2710, found (*m/z*) 528.2714.

4.1.5. 3-Hydroxy-6-methoxy-3-trimethylsilyl-1,3-dihydroindole-2-one (21). To a suspension of 6-methoxy-1H-indole-2,3-dione (3.22 g, 20 mmol) in tetrahydrofuran (200 mL) was gradually added a 1.0 M solution of (trimethylsilyl)methyllithium in pentane (50 mL, 50 mmol) at −78 °C. After stirring for 3 h at −78 °C, saturated aqueous ammonium chloride solution was added. The product was extracted with ethyl acetate and dichloromethane. The combined organic layer was dried over anhydrous sulfate and concentrated to give **21** (4.49 g, 85%) as a white solid. The compound **21** was used for the next reaction without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: −0.22 (s, 9H), 1.49 (d, $J=10.2$ Hz, 1H), 1.53 (d, $J=10.2$ Hz, 1H), 2.65 (s, 1H), 3.79 (s, 3H), 6.45 (d, $J=1.8$ Hz, 1H), 6.56 (dd, $J=1.8$, 6.3 Hz, 1H), 7.23 (d, $J=6.3$ Hz, 1H), 7.88 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: −1.1, 28.3, 55.5, 75.5, 97.5, 107.5, 123.4, 125.4, 141.1, 161.2, 180.6; IR (NaCl/neat) 3388, 1714, 1634, 1507, 1351, 1251, 1151, 1125, 840 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{19}O_3NSi$ (*m/z*) 265.1134, found (*m/z*) 265.1132.

4.1.6. Spiro[3H-indole-3,7′(6′H)-[1H]pyrrolo[2,1-*c*][1,4]oxazine], 1,2,3′,4′,8′,8′a-hexahydro-6-methoxy-6′-(2-methoxy-2-methylpropyl)-1′,2-dioxo-3′-4′-diphenyl-, (3*S*,3′*S*,4′*R*,6′*S*,8′a*R*) (17) and Spiro[3H-indole-3,7′(6′H)-[1H]pyrrolo[2,1-*c*][1,4]oxazine], 1,2,3′,4′,8′,8′a-hexahydro-6-methoxy-6′-(2-methyl-1-propenyl)-1′,2-dioxo-3′-4′-diphenyl-, (3*S*,3′*S*,4′*R*,6′*S*,8′a*R*) (22). To a suspension of oxyindole **21** (199 mg, 0.750 mmol) in toluene (10 mL) was added trifluoroacetic acid (97 μl, 1.25 mmol) at once at 0 °C. After stirring for 15 min at 0 °C, triethylamine (174 μl, 1.25 mmol) was added at once. After stirring for additional 5 min at 0 °C, water (6.1 mL) and toluene (10 mL) were added and the mixture was filtrated through celite. The residue was washed by toluene (2.5 mL). The organic layer was separated by phase separation and was dried over anhydrous sodium sulfate (2.5 g) and anhydrous magnesium sulfate (2.5 g) for 20 min. The drying reagents were removed by filtration and the residue was washed with toluene (1 mL). To the combined toluene solution were added 0.5 g of activated 3 Å molecular sieves, (5*R*,6*S*)-2,3,5,6-tetrahydro-5,6-diphenyl-1,4-oxazin-2-one (127 mg, 0.5 mmol), 3-methyl-3-methoxybutanal (70 mg, 0.6 mmol) and toluene (4 mL) at −15 °C. After stirring for 25 h at 0 °C, the mixture was filtrated through celite to remove the sieves and concentrated in vacuo. The product was purified by thin layer chromatography (eluted with 1:2 hexane/AcOEt) to give **17** (115 mg, 44%) and **22** (51 mg, 20%).

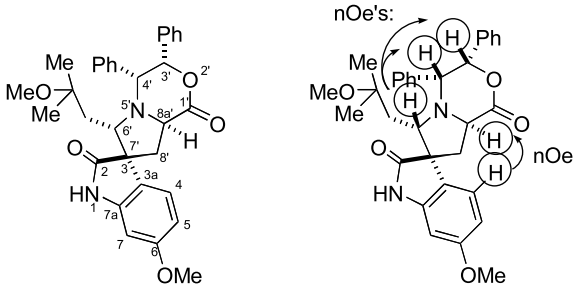
Compound **17**. A pale yellow amorphous solid: $[\alpha]_D^{24}=-46.0$ ($CHCl_3$, $c=1$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.02 (s, 3H), 1.09 (s, 3H), 1.36 (dd, $J=5.6$, 15.6 Hz, 1H), 1.61 (dd, $J=2.1$, 15.6 Hz, 1H), 2.44 (dd, $J=8.0$, 12.6 Hz, 1H), 2.69 (dd, $J=10.4$, 12.6 Hz, 1H), 3.04 (s, 3H), 3.81 (s, 3H), 4.01 (dd, $J=2.1$, 5.6 Hz, 1H), 4.46 (dd, $J=8.0$, 10.4 Hz, 1H), 4.85 (d, $J=2.6$ Hz, 1H), 6.29 (d, $J=2.6$ Hz, 1H), 6.55 (d, $J=2.1$ Hz, 1H), 6.57 (dd, $J=2.1$, 8.4 Hz, 1H), 6.99–7.05 (m, 2H), 7.13–7.33 (m, 9H), 8.35 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 23.5, 25.0, 41.4, 44.5, 49.1, 55.5, 56.5, 56.7, 59.2, 64.6, 73.3, 76.4, 97.3, 107.4, 122.6, 125.5, 125.7, 127.2, 127.6, 128.0, 128.3, 128.8, 136.8, 136.8, 141.6, 160.2, 172.2, 179.2; IR (NaCl/neat) 1726, 1631, 1505, 1271, 1238, 1193, 1148, 755, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{32}H_{35}O_5N_2$ (*m/z*) 527.2546, found (*m/z*) 527.2540.

Compound **22**. A pale yellow amorphous solid: $[\alpha]_D^{24}=-36.4$ ($CHCl_3$, $c=0.55$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.54 (s, 3H), 1.74 (s, 3H), 2.48 (dd, $J=8.4$, 13.0 Hz, 1H), 2.75 (dd, $J=9.6$, 13.0 Hz, 1H), 3.80 (s, 3H), 4.27 (d, $J=3.0$ Hz, 1H), 4.52 (d, $J=9.4$ Hz, 1H), 4.54 (dd, $J=8.4$, 9.6 Hz, 1H), 4.70 (d, $J=9.4$ Hz, 1H), 6.18 (d, $J=3.0$ Hz, 1H), 6.48 (d, $J=2.3$ Hz, 1H), 6.56 (dd, $J=2.3$, 8.4 Hz, 1H), 7.02–7.07 (m, 2H), 7.15–7.33 (m, 9H), 7.75 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 18.6, 26.2, 40.0, 55.5, 56.3, 56.6, 60.2, 67.5, 97.2, 107.2, 120.8, 122.1, 125.6, 125.7, 127.4, 127.9, 128.0, 128.4, 128.9, 136.2, 136.4, 139.9, 141.2, 160.1, 168.5, 171.9, 178.3; IR (NaCl/neat) 3261, 1723, 1631, 1504, 1453, 1193, 1153, 755, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{31}H_{31}O_4N_2$ (*m/z*) 495.2284, found (*m/z*) 495.2267.

4.2. Confirmation of the relative configuration of 17 by NOESY

NOE's were obrserved between the proton at position 4 of the oxyindole and the proton at 8′a, between the proton at 6′

and the proton at 3′, and between the proton at 6′ and the proton at 4′.



4.2.1. Spiro[3H-indole-3,3′-pyrrolidine]-5′-carboxylic acid, 1,2-dihydro-6-methoxy-2′-(2-methoxy-2-methylpropyl)-2-oxo, (2′*S*,3*S*,5′*R*) (23). To a solution of compound **17** (640 mg, 1.22 mmol) in dry tetrahydrofuran (6.2 mL) and methanol (6.2 mL) was added 20 wt% palladium hydroxide on carbon (215 mg). After stirring for 77 h at room temperature under H_2 atmosphere, the reaction mixture was filtrated through celite and concentrated in vacuo. The residue was washed by ethyl acetate (6 mL, 3 times) to give **23** (424 mg, 100%) as an off-white solid.

$[\alpha]_D^{23} = -18.4$ (MeOH, $c=1$); ^{1}H NMR (400 MHz, CD_3OD) δ MeOH: 1.17 (s, 3H), 1.20 (s, 3H), 1.29 (dd, $J=2.0$, 14.8 Hz, 1H), 1.72 (dd, $J=9.9$, 14.8 Hz, 1H), 2.49 (dd, $J=9.0$, 13.1 Hz, 1H), 2.57 (dd, $J=9.0$, 13.1 Hz, 1H), 3.24 (s, 3H), 3.85 (s, 3H), 4.19 (dd, $J=2.0$, 9.9 Hz, 1H), 4.51 (t, $J=9.0$ Hz, 1H), 6.62 (d, $J=2.0$ Hz, 1H), 6.70 (dd, $J=2.0$, 8.4 Hz, 1H), 7.32 (d, $J=8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ MeOH: 22.2, 25.0, 40.8, 42.6, 49.6, 56.0, 59.1, 61.3, 63.7, 75.1, 98.9, 108.4, 121.3, 125.8, 144.2, 162.5, 172.3, 178.6; IR (NaCl/neat) 2968, 1716, 1633, 1600, 1507, 1456, 1346, 1193, 1156 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{25}O_5N_2$ (*m*/*z*) 349.1764, found (*m*/*z*) 349.1778.

4.2.2. Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methoxy-2-methylpropyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*R*) (24). To a solution of **23** (143 mg, 0.291 mmol), L-proline benzyl ester hydrochloride (84.5 mg, 0.349 mmol) and triethylamine (97.3 μl, 0.698 mmol) in acetonitrile (2.9 mL) was added BOP (153 mg, 0.349 mmol) at 0 °C. After stirring for 11 h at room temperature, the mixture was concentrated in vacuo. After the addition of 1 M hydrochloric acid, the product was extracted with ethyl acetate. The organic layer was washed by sat. $NaHCO_3$ aq. and brine, and was dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was dissolved in ethanol (7.4 mL) and methanol (3.7 mL). To a solution was added 10 wt% palladium on carbon (20 mg). After stirring for 5 h at room temperature under H_2 atmosphere, the reaction mixture was filtrated through celite and concentrated in vacuo. To the residue were added triethylamine (31.8 μl, 0.228 mmol) and acetonitrile (3.4 mL). To the mixture was added BOP (90.7 mg, 0.207 mmol). After stirring for 10 h at room temperature, the mixture was concentrated in vacuo. After the addition of 1 M hydrochloric acid, the product was extracted with ethyl acetate and was purified by preparative thin layer chromatography (silica gel, 10:1 CH_2Cl_2/MeOH) to give **24** (25.6 mg, 21%) as a colorless amorphous solid.

$[\alpha]_D^{25} = -77.0$ ($CHCl_3$, $c=0.2$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.02 (s, 3H), 1.19 (s, 3H), 1.76–1.86 (m, 2H), 1.87–2.08 (m, 3H), 2.41–2.53 (m, 3H), 2.93 (s, 3H), 3.40 (ddd, $J=3.6$, 9.4, 12.4 Hz, 1H), 3.80 (s, 3H), 3.94 (dt, $J=12.4$, 8.3 Hz, 1H), 4.22 (dd, $J=5.4$, 11.4 Hz, 1H), 4.61 (t, $J=8.8$ Hz, 1H), 4.81 (t, $J=6.8$ Hz, 1H), 6.47 (s, 1H), 6.54 (d, $J=8.2$ Hz, 1H), 7.09 (d, $J=8.2$ Hz, 1H), 7.58 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 21.7, 23.2, 24.7, 30.0, 40.6, 40.7, 44.7, 48.5, 54.8, 55.5, 58.8, 60.7, 61.0, 74.4, 97.5, 106.7, 121.3, 125.9, 142.0, 160.3, 163.6, 165.8, 181.0; IR (NaCl/neat) 2927, 1718, 1653, 1506, 1456, 1343, 1303, 1194, 1157 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{30}O_5N_3$ (*m*/*z*) 428.2185, found (*m*/*z*) 428.2193.

4.2.3. Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methyl-1-propenyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*R*) (25; 9-*epi*-spirotryprostatin A), Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methyl-2-propenyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*R*) (26) and Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methyl-1-propenyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*S*) (1; spirotryprostatin A). To a solution of compound **24** (33.9 mg, 0.0793 mmol) in toluene (2.4 mL) were added *p*-toluenesulfonic acid (15.1 mg, 0.0793 mmol) and 144 mg of activated 3 Å molecular sieves. After stirring for 5 h at 110 °C, the mixture was allowed to cool to room temperature. After the addition of sodium bicarbonate, the product was extracted with ethyl acetate and was purified by preparative thin layer chromatography (silica gel, 18:5:2 CH_2Cl_2/AcOEt/^{i}PrOH) to give **25** (13.8 mg, 44%) and a mixture of **26** and **1**. Both compounds could be isolated by reversed-phase high performance liquid chromatography eluting with a gradient of 25% MeCN in H_2O to give **26** (0.9 mg, 3%) and **1** (0.6 mg, 2%).

Compound **25**. A colorless amorphous solid: $[\alpha]_D^{25} = +30.0$ ($CHCl_3$, $c=0.4$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.42 (s, 3H), 1.67 (s, 3H), 1.85–2.10 (m, 2H), 2.30 (dt, $J=5.5$, 8.2 Hz, 2H), 2.51 (dd, $J=9.0$, 13.4 Hz, 1H), 2.94 (dd, 5.2, 13.4 Hz, 1H), 3.57 (ddd, $J=3.5$, 8.2, 11.6 Hz, 1H), 3.68 (dt, $J=11.6$, 8.2 Hz, 1H), 3.79 (s, 3H), 4.24 (t, $J=8.2$ Hz, 1H), 4.62 (dd, $J=5.2$, 9.0 Hz, 1H), 5.11 (s, 2H), 6.46 (d, $J=2.3$ Hz, 1H), 6.51 (dd, $J=2.3$, 8.3 Hz, 1H), 7.01 (d, $J=8.3$ Hz, 1H), 7.88 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 18.1, 23.3, 25.7, 27.8, 35.9, 45.7, 54.2, 55.5, 58.9, 60.0, 61.6, 97.0, 106.9, 119.1, 119.6, 125.7, 138.4, 142.1, 160.3, 165.6, 166.1, 179.7; IR (NaCl/neat) 1720, 1662, 1598, 1506, 1426, 1342, 1310, 1278, 1193, 1156 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{26}O_4N_3$ (*m*/*z*) 396.1923, found (*m*/*z*) 396.1915.

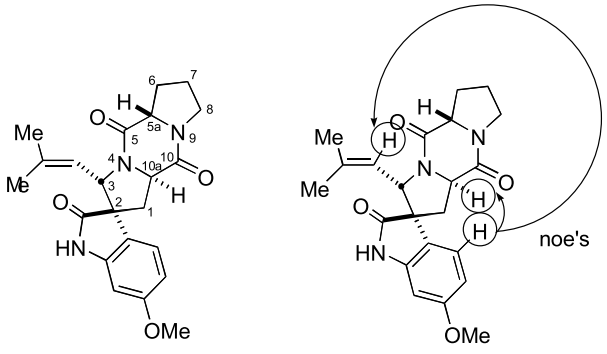
Compound **26**. A colorless amorphous solid: $[\alpha]_D^{25} = +38.8$ ($CHCl_3$, $c=0.08$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.65 (s, 3H), 1.85–2.09 (m, 2H), 2.13 (dd, $J=7.7$, 13.1 Hz, 1H), 2.19–2.35 (m, 2H), 2.43 (dd, $J=7.8$, 13.2 Hz, 1H),

2.79 (dd, J=7.8, 13.2 Hz, 1H), 2.85 (dd, J=7.7, 13.1 Hz, 1H), 3.51–3.69 (m, 2H), 3.80 (s, 3H), 4.18 (s, 1H), 4.25 (t, J=8.0 Hz, 1H), 4.55 (s, 1H), 4.60 (t, J=7.8 Hz, 1H), 4.65 (t, J=7.7 Hz, 1H), 6.46 (d, J=2.4 Hz, 1H), 6.56 (dd, J=2.4, 8.4 Hz, 1H), 7.09 (d, J=8.4 Hz, 1H), 7.40 (brs, 1H); IR (NaCl/neat) 2924, 1718, 1662, 1507, 1457, 1429, 1341, 1310, 1157 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{26}O_4N_3$ (m/z) 396.1923, found (m/z) 396.1919.

Compound **1**. A colorless amorphous solid: see below.

4.3. Confirmation of the relative configuration of 25 by NOESY

A NOE was obrserved between the proton at position 4 of the oxyindole and the olefinic proton of the 2-methyl-1-propenyl group. A NOE was also obrserved between the proton at position 9 of the oxyindole and the proton at position 9.



4.3.1. Spiro[3H-indole-3,3′-pyrrolidine]-5′-carboxylic acid, 1,2-dihydro-6-methoxy-2′-(2-methoxy-2-methylpropyl)-2-oxo, methyl ester, (2′*S*,3*S*,5′*R*) (27).

To a solution of compound **17** (101 mg, 0.193 mmol) in dry tetrahydrofuran (1 mL) and methanol (1 mL) was added palladium dichloride (34.2 mg, 0.193 mmol). After stirring for 54 h at room temperature under H_2 atmosphere, the reaction mixture was filtrated and concentrated in vacuo. The residue was dissolved in methanol (1.9 mL) and to the solution was added 2 M (trimethylsilyl)diazomethane in hexane (483 μl, 0.965 mmol). After stirring for 2 h at room temperature, a few drops of acetic acid were added and the reaction mixture was concentrated in vacuo. After the addition of aqueous sodium bicarbonate solution, the product was extracted with ethyl acetate and was purified by preparative thin layer chromatography (silica gel, 1:2 hexane/AcOEt) to give **27** (26.2 mg, 37% (2 steps)) as a pale yellow solid.

$[\alpha]_D^{25}=-32.0$ ($CHCl_3$, c=1); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.96 (dd, J=2.0, 14.3 Hz, 1H), 1.05 (s, 3H), 1.13 (s, 3H), 1.28 (dd, J=9.7, 14.3 Hz, 1H), 2.30 (dd, J=9.0, 13.1 Hz, 1H), 2.50 (dd, J=6.8, 13.1 Hz, 1H), 3.11 (s, 3H), 3.72 (dd, J=2.0, 9.7 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 4.12 (dd, J=6.8, 9.0 Hz, 1H), 6.46 (d, J=2.1 Hz, 1H), 6.54 (dd, J=2.1, 8.1 Hz, 1H), 7.32 (d, J=8.1 Hz, 1H), 7.80 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 24.3, 25.6, 39.8, 41.2, 49.2, 52.3, 55.5, 57.4, 57.7, 62.4, 74.3, 96.9, 107.0, 124.0, 125.7, 141.0, 159.8, 175.8, 179.7; IR (NaCl/neat) 2972, 2359, 1711, 1633, 1558, 1506, 1457, 1341, 1194, 1153, 1020, 771 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{27}O_5N_2$ (m/z) 363.1920, found (m/z) 363.1923.

4.3.2. 5′-d$_1$-Spiro[3H-indole-3,3′-pyrrolidine]-5′-carboxylic acid, 1,2-dihydro-6-methoxy-2′-(2-methoxy-2-methylpropyl)-2-oxo, methyl ester, (2′*S*,3*S*,5′*R*), (d$_1$-27) and 5′-d$_1$-Spiro[3H-indole-3,3′-pyrrolidine]-5′-carboxylic acid, 1,2-dihydro-6-methoxy-2′-(2-methoxy-2-methylpropyl)-2-oxo, methyl ester, (2′*S*,3*S*,5′*S*), (d$_1$-28).

Amino acid **23** (20.3 mg, 0.0583 mmol) and butyraldehyde (2.60 μl, 0.0292 mmol) were dissolved in d_4-acetic acid (0.7 mL). After stirring for several hours at 65 °C, it was obrserved by NMR that α-proton of the amino acid was converted to deuterium and that epimerization of the wrong chiral center proceeded. After stirring for 31 h at 65 °C, the mixture was concentrated in vacuo. The residue was dissolved in methanol (0.7 mL) and 2 M (trimethylsilyl)-diazomethane in hexane (146 μl, 0.292 mmol) was added. After stirring for 5 h at room temperature, the mixture was concentrated in vacuo. After the addition of aqueous sodium bicarbonate solution, the product was extracted with ethyl acetate and was purified by preparative thin layer chromatography (silica gel, 1:3 hexane/AcOEt) to give d$_1$-**27** (6.6 mg, 31% (2 steps)) and d$_1$-**28** (3.2 mg, 15% (2 steps)).

Compound d$_1$-**27**. A pale yellow amorphous solid: $[\alpha]_D^{25}=-17.6$ ($CHCl_3$, c=0.25); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.96 (d, J=14.0 Hz, 1H), 1.05 (s, 3H), 1.13 (s, 3H), 1.28 (dd, J=8.8, 14.0 Hz, 1H), 2.31 (d, J=12.6 Hz, 1H), 2.50 (d, J=12.6 Hz, 1H), 3.12 (s, 3H), 3.73 (d, J=8.8 Hz, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 6.45 (d, J=2.3 Hz, 1H), 6.55 (dd, J=2.3, 8.2 Hz, 1H), 7.35 (d, J=8.2 Hz, 1H), 7.54 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 24.2, 25.6, 39.7, 41.2, 49.3, 52.4, 55.5, 57.3, 57.7, 62.4, 74.3, 97.0, 107.0, 123.9, 125.8, 140.9, 159.9, 175.7, 179.5; IR (NaCl/neat) 1710, 1630, 1505, 1461, 1270, 1244, 1193, 1153, 1122 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{25}DO_5N_2$ (m/z) 363.1904, found (m/z) 363.1906.

Compound d$_1$-**28**. A pale yellow amorphous solid: $[\alpha]_D^{25}=-18.6$ ($CHCl_3$, c=0.167); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.02 (d, J=14.4 Hz, 1H), 1.08 (s, 3H), 1.10 (s, 3H), 1.31 (dd, J=9.2, 14.4 Hz, 1H), 2.13 (d, J=13.8 Hz, 1H), 2.76 (d, J=13.8 Hz, 1H), 3.09 (s, 3H), 3.54 (d, J=9.2 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 6.44 (d, J=2.4 Hz, 1H), 6.54 (dd, J=2.4, 8.0 Hz, 1H), 7.24 (brs, 1H), 7.41 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 24.3, 25.4, 38.0, 40.6, 41.2, 49.2, 52.3, 55.5, 57.4, 65.0, 74.1, 97.0, 107.1, 123.4, 125.7, 140.9, 159.8, 175.7, 180.1; IR (NaCl/neat) 1722, 1630, 1506, 1463, 1275, 1194, 1155, 1123, 1077 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{25}DO_5N_2$ (m/z) 363.1904, found (m/z) 363.1910.

4.3.3. Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methoxy-2-methylpropyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*R*) (24) and Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methoxy-2-methylpropyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*S*) (19).

To a solution of compound **23** (58.2 mg, 0.167 mmol) in acetic acid (1.7 mL) was added n-butyraldehyde (7.4 μL, 0.083 mmol).

After stirring for 6 h at 60 °C, the reaction mixture was concentrated in vacuo. The residue was dissolved in methanol (1.7 mL) and 37% hydrochloric acid (17 μl, 0.20 mmol) was added. The mixture was concentrated to give a pale yellow solid. To the solid were added L-proline benzyl ester hydrochloride (61 mg, 0.251 mmol), triethylamine (88.5 μl, 0.635 mmol) and acetonitrile (1.7 mL). To the mixture was added BOP (95 mg, 0.216 mmol) at 0 °C. After stirring for 55 h at room temperature, the mixture was concentrated in vacuo. After the addition of 1 M hydrochloric acid (7.5 mL), the product was extracted with ethyl acetate (15 mL, 3 times). The organic layer was washed by sat. $NaHCO_3$ aq. (15 mL) and brine (15 mL), and was dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was dissolved in ethanol (3 mL), methanol (1.5 mL) and 37% hydrochloric acid (15 μl, 0.18 mmol). To a solution was added 10 wt% palladium on carbon (33 mg). After stirring for 34 h at room temperature under H_2 atmosphere, the reaction mixture was filtrated through celite and concentrated in vacuo. To the residue were added triethylamine (51.2 μl, 0.368 mmol) and acetonitrile (3.4 mL). To the mixture was added 1-(3-dimethylpropyl)-3-ethylcarbodiimide hydrochloride (38.4 mg, 0.200 mmol). After stirring for 123 h at room temperature, the mixture was concentrated in vacuo. After the addition of 1 M hydrochloric acid (10 mL), the product was extracted with ethyl acetate (20 mL, 3 times) and was purified by preparative thin layer chromatography (silica gel, 100:7.5 CH_2Cl_2/MeOH) to give **24** (7.2 mg, 10%) and **19** (6.3 mg, 9%).

Compound **24**. A colorless amorphous solid: see above.

Compound **19**. A colorless amorphous solid: $[\alpha]_D^{25} = -60.0$ ($CHCl_3$, $c=0.33$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.93 (s, 6H), 1.86–2.24 (m, 5H), 2.30–2.66 (m, 3H), 2.83 (s, 3H), 3.57 (dd, $J=5.4$, 8.2 Hz, 2H), 3.79 (s, 3H), 4.20–4.27 (m, 2H), 4.77 (t, $J=8.8$ Hz, 1H), 6.43 (s, 1H), 6.54 (d, $J=8.4$ Hz, 1H), 7.04 (d, $J=8.4$ Hz, 1H), 7.64 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 23.3, 23.6, 24.9, 27.9, 30.0, 34.9, 40.8, 45.0, 48.7, 55.5, 58.4, 59.8, 61.4, 74.0, 97.1, 106.5, 121.4, 126.3, 142.0, 160.2, 166.7, 168.1, 181.4; IR (NaCl/neat) 1716, 1665, 1633, 1506, 1461, 1343, 1193, 1157, 732 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{30}O_5N_3$ (*m*/*z*) 428.2185, found (*m*/*z*) 428.2193.

4.3.4. Spiro[1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-methyl-1-propenyl)-2′,5,10-trioxo-, (2*S*, 3*S*,5a*S*,10a*S*) (1; spirotryprostatin A) and Spiro [1H,5H-dipyrrolo[1,2-a:1′,2′-*d*]pyrazine-2(3H),3′-[3H]indole], 1′,2′,5a,6,7,8,10,10a-octahydro-6′-methoxy-3-(2-hydroxy-2-methylpropyl)-2′,5,10-trioxo-, (2*S*,3*S*,5a*S*,10a*S*) (30). To a solution of compound **19** (6.3 mg, 0.0147 mmol) in toluene (0.5 mL) were added *p*-toluenesulfonic acid (2.8 mg, 0.0147 mmol) and 75 mg of activated 3 Å molecular sieves. After stirring for 5 h at 110 °C, the mixture was allowed to cool to room temperature. After the addition of sodium bicarbonate, the product was extracted with ethyl acetate and was purified by preparative thin layer chromatography (silica gel, 73:20:7 CH_2Cl_2/AcOEt/^{i}PrOH) to give **1** (2.5 mg, 43%) and **30** (1.9 mg, 31%).

Compound **1**. A colorless amorphous solid: $[\alpha]_D^{25} = -30.5$ ($CHCl_3$, $c=0.2$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 1.17 (s, 3H), 1.64 (s, 3H), 1.86–2.08 (m, 2H), 2.20–2.39 (m, 2H), 2.38 (dd, $J=7.2$, 13.5 Hz, 1H), 2.60 (dd, $J=10.7$, 13.5 Hz, 1H), 3.50–3.68 (m, 2H), 3.79 (s, 3H), 4.27 (t, 8.4 Hz, 1H), 4.77 (d, $J=9.0$ Hz, 1H), 4.99 (dd, $J=7.2$, 10.7 Hz, 1H), 5.02 (d, $J=9.0$ Hz, 1H), 6.41 (d, $J=2.4$ Hz, 1H), 6.49 (dd, $J=2.4$, 8.5 Hz, 1H), 6.92 (d, $J=8.5$ Hz, 1H), 7.48 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 18.0, 23.7, 25.5, 27.4, 34.4, 45.2, 55.5, 58.5, 60.2, 60.2, 61.0, 96.6, 106.7, 118.7, 121.4, 127.3, 138.4, 141.6, 160.4, 167.1, 168.2, 180.5; IR (NaCl/neat) 2924, 1716, 1669, 1653, 1635, 1507, 1457, 1419, 1340, 1157 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{26}O_4N_3$ (*m*/*z*) 396.1923, found (*m*/*z*) 396.1909.

Compound **30**. A colorless amorphous solid: $[\alpha]_D^{25} = -25.0$ ($CHCl_3$, $c=0.1$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$: 0.62 (s, 3H), 1.11 (s, 3H), 1.79 (dd, $J=4.3$, 15.4 Hz, 1H), 1.92 (dd, $J=4.3$, 15.4 Hz, 1H), 1.89–2.10 (m, 2H), 2.16–2.40 (m, 2H), 2.46 (dd, $J=8.7$, 13.6 Hz, 1H), 2.65 (dd, $J=8.7$, 13.6 Hz, 1H), 3.60 (dd, $J=5.4$, 8.2 Hz, 2H), 3.79 (s, 3H), 4.29 (t, $J=8.2$ Hz, 1H), 4.36 (t, $J=4.3$ Hz, 1H), 4.45 (brs, 1H), 4.87 (t, $J=8.7$ Hz, 1H), 6.46 (d, $J=2.4$ Hz, 1H), 6.56 (dd, $J=2.4$, 8.4 Hz, 1H), 6.97 (d, $J=8.4$ Hz, 1H), 7.40 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 23.6, 27.0, 27.7, 31.5, 33.9, 43.3, 45.2, 55.5, 59.0, 59.4, 61.0, 68.7, 77.2, 97.5, 107.1, 120.4, 126.3, 142.0, 160.7, 168.1, 168.3, 181.4; IR (NaCl/neat) 2923, 2850, 1717, 1683, 1652, 1636, 1507, 1456, 1433, 1158 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{28}O_5N_3$ (*m*/*z*) 414.2029, found (*m*/*z*) 414.2020.

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