A Biomimetic Total Synthesis of (−)-Spirotryprostatin B and Related Studies

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The prenylated natural products spirotryprostatin A and B derived from the Trp-Pro diketopiperazine also feature an oxidative rearrangement of the indole to form a spirooxindole. Synthetically, formation of the oxindole ring was stereoselectively accomplished by reaction of the appropriate indole precursor with *N*-bromosuccinimide. For optimum results, the oxidation should be carried out prior to diketopiperazine cyclization. In this manner, we have synthesized the tetrahydro- and dihydro- analogues of spirotryprostatin B in four steps from L-tryptophan methyl ester. The dihydro derivative was then converted to spirotryprostatin B by unsaturation of the pyrrolidine ring to a pyrroline, thus unambiguously confirming the structure of the natural product.

Natural products that affect eukaryotic cell cycle progression are currently attracting attention,[1] both as molecular probes into the process as well as potential antitumor agents. Osada's group in Japan has developed[2] a bioassay for the identification of such compounds, based on the murine temperature-sensitive cell line tsFT210 defective in the cdc2 kinase gene. A number of active fungal metabolites were discovered with this screen, including a series of indole alkaloids[3] from the broth of *Aspergillus fumigatus* BM939. These compounds are related to the previously isolated fumitremorgins[4] as well as the brevianamides, both families originating biosynthetically from prenylation of the L-Trp-L-Pro[5] diketopiperazine.[6]

The most active of these cell cycle inhibitors, demethoxyfumitremorgin C (**1**), has a MIC value of 0.45 μM in the tsFT210 assay. We have completed[7] a three-step total synthesis via *N*-acyliminium Pictet−Spengler condensation, adapted[8] our route to the solid phase, and also prepared analogues[9] that are more potent than the natural product. Two other alkaloids in this series, spirotryprostatin A (**2**) and B (**3**), are less active with MICs of 197.5 and 14.0 μM, respectively, but display an alternative scaffold featuring oxidation of the indole ring. As part of our program to study structure−activity relationships within these alkaloids, we were interested in a route amenable toward preparation of these oxindoles as well as congeners. In addition, we wished to explore a biomimetic approach[10] in which the unusual spirooxindole skeleton is derived by oxidation of tetrahydro-β-carbolines such as **1**. While this work was in progress, the Danishefsky group has also reported[11] a total synthesis of spirotryprostatin A.

Results and Discussion

A model study was carried out with the known[12] *cis*-tetrahydro-β-carboline **4** (Scheme 1), which features a saturated prenyl unit rather than the alkene present in the natural products. Two-phase Schotten−Baumann acylation of the relatively hindered amine provided amide **5**. In the literature, a number of reagents have been used for the oxidative rearrangement of indoles to spiroindolinones, such as *N*-bromosuccinimide (NBS) under aqueous acidic conditions,[13] osmium tetraoxide,[14] lead tetraacetate,[15] and dimethyldioxirane.[16] Subjecting **5** to the NBS

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(3) (a) Cui, C.-B.; Kakeya, H.; Okada, G.; Onose, R.; Ubukata, M.; Takahashi, I.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48*, 1382−1384. (b) Cui, C.-B.; Kakeya, H.; Okada, G.; Onose, R.; Osada, H. *J. Antibiot.* **1996**, *49*, 527−533. (c) Cui, C.-B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832−835. (d) Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651−12666. (e) Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1997**, *53*, 59−72.

(4) For a review of earlier synthetic efforts, see: Hino, T.; Nakagawa, M. *Heterocycles* **1997**, *46*, 673−704.

(5) Abbreviations: APCI = atmospheric pressure chemical ionization; ESI = electrospray ionization; Fmoc = (9*H*-fluoren-9-ylmethoxy)-carbonyl; HMQC = heteronuclear multiple quantum correlation spectroscopy; HMBC = heteronuclear multiple bond correlation spectroscopy; Trp = tryptophan; Pro = proline.

(6) The L-Trp-L-Pro diketopiperazine is itself a fungal natural product, brevianamide F.

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(9) Wang, H.; Usui, T.; Osada, H.; Ganesan, A. *J. Med. Chem.* **2000**, *43*, 1577−1585.

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(11) (a) Edmondson, S. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1138−1140. (b) Edmondson, S. D.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147−2155.

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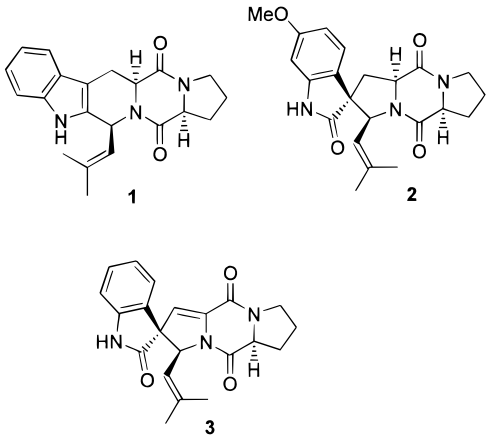
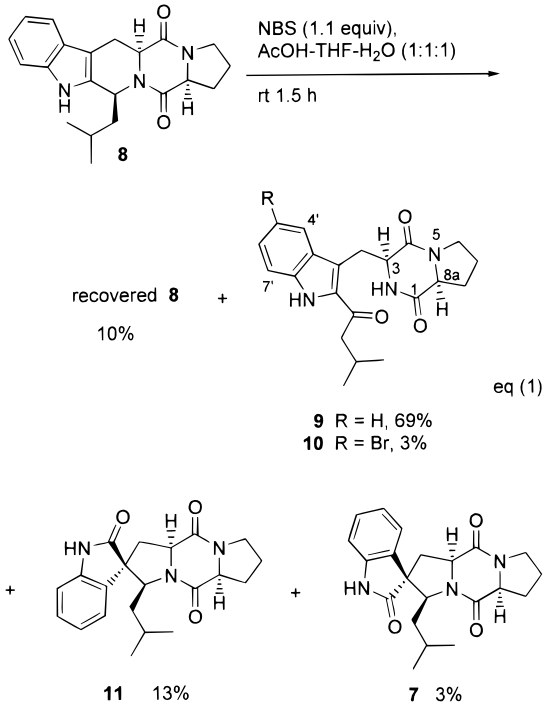


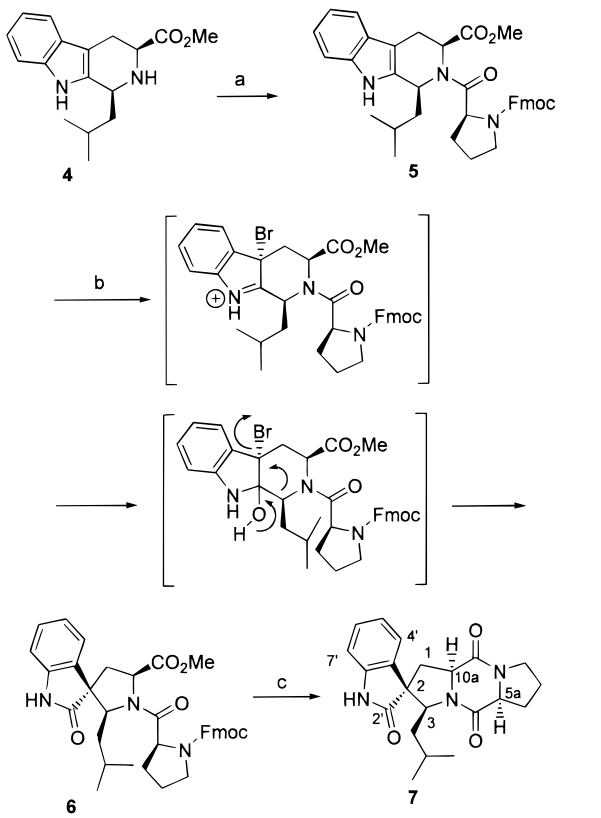
Figure 1.

protocol introduced by van Tamelen afforded in good yield a single product **6**. Deprotection of the Fmoc group in **6** triggered diketopiperazine cyclization to give tetrahydrospirotryprostatin B **7** [$[\alpha]^{33}_D = -93$ (*c* 1.18, $CHCl_3$)].[17] NOE measurements indicated that the spiro chiral center had been formed exclusively in the same sense as the natural product. This favorable result was consistent with the expectation that the bromonium ion would be formed from the less hindered α face of **5**, away from the alkyl side-chain, and that the subsequent pinacol-like rearrangement would occur with inversion at the spiro center and retention at the migrating carbon.

Albeit the deceptive simplicity of the above successful result, the relative timing of oxidative rearrangement and diketopiperazine cyclization proved to be crucial. *Thus, the NBS oxidation of diketopiperazine **8** (eq 1) predominantly afforded 2-acylindole **9***. This compound had previ-

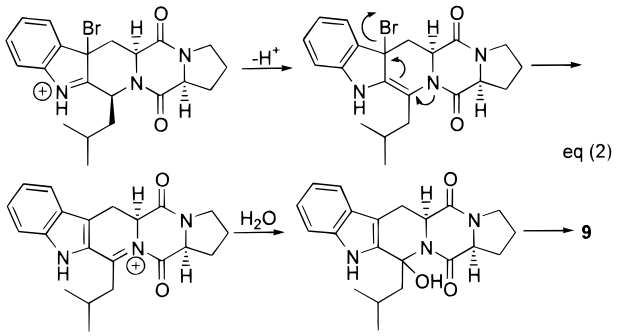


Scheme 1[a]



[a] Reagents and conditions: (a) Fmoc-L-ProCl (1.30 equiv), aqueous Na_2CO_3/CH_2Cl_2, rt, 2 h, 55% overall from L-Trp-OMe; (b) NBS (1.16 equiv), THF−AcOH−H_2O(1:1:1), 0 °C, 5 min, rt 30 min, 85%; (c) 20% piperidine in CH_2Cl_2, rt, 12 min, 100%.

ously been reported[12] as the major product when **8** was subjected to DDQ oxidation. A plausible mechanism for acylindole formation is due to the intermediate iminium species undergoing loss of a proton rather than hydration (eq 2). The subsequent 1,4-elimination of bromide gener-

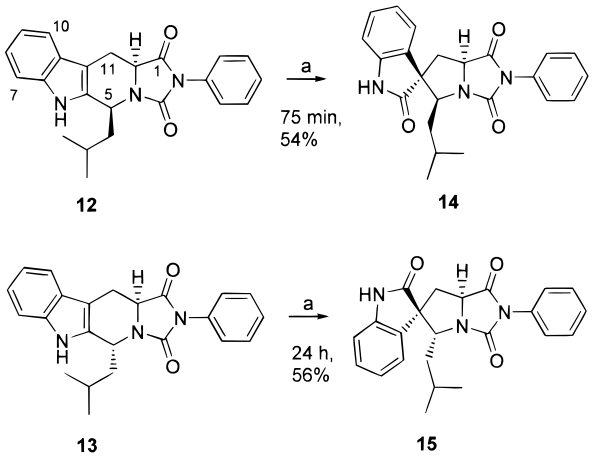


ates a new iminium ion, which is captured by water and hydrolyzed to **9**. In addition to **9** and a trace of the brominated indole **10**, we also isolated a small amount of the expected oxindole **7** and the epimeric **11**. Surprisingly, NMR analysis revealed that the major oxindole **11** arose by electrophilic attack from the *β*-face, unlike the situation with **5**. The Danishefsky group has performed[11b] the NBS oxidation of a compound analogous to **8**, bearing a benzyl ether in place of our saturated prenyl group. In their case, no acylindole was formed, although a similar shift to *β*-face bromination by NBS was observed in the oxindole product.

(16) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867−8868.

(17) The synthesis of **7** was presented at the 214th ACS National Meeting, Las Vegas, 7−11 Sep 1997, abstract ORGN 282.

Scheme 2[a]



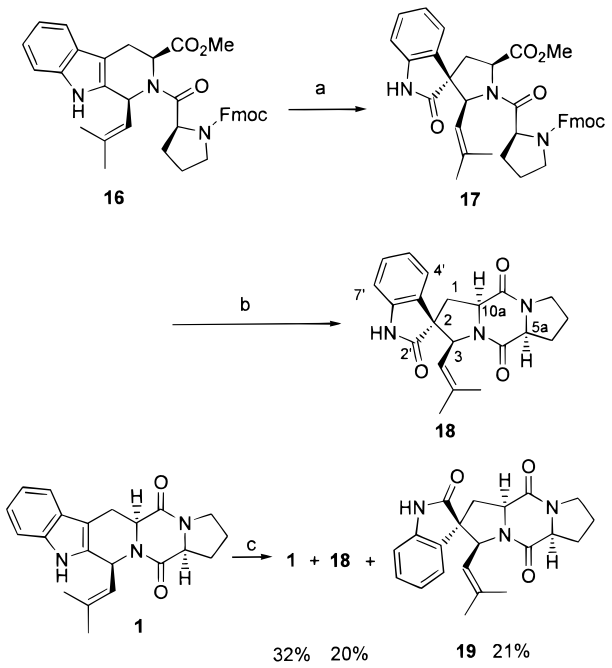
12 14 13 15

[a] Reagents and conditions: (a) NBS, THF−AcOH−H_2O (1:1:1), rt.

We also investigated the oxidative rearrangement of compounds where N-2 and C-3 (tetrahydro-*β*-carboline numbering) were connected, but not as a diketopiperazine. Reaction of **4** and its trans epimer with phenyl isocyanate gave substituted ureas, which cyclized spontaneously[18] to hydantoins **12** and **13** respectively. These hydantoins yielded oxindoles **14** and **15** upon NBS oxidation (Scheme 2). As with **5**, NOE measurements indicated that the oxidation took place from the less hindered face of the indole. Taken together, our studies (and those of the Danishefsky group) imply that the result with **8** is an exception to the general outcome of these NBS reactions. Apparently, the diketopiperazine exerts an unusual conformational bias that can affect both the reaction pathway and stereoselectivity.

For a synthesis of the natural products, the compatibility of the alkenyl side-chain with these electrophilic oxidations was of significant concern. Nevertheless, the NBS oxidation of tetrahydro-*β*-carboline **16** (Scheme 3) afforded a major product **17**, which upon Fmoc deprotection furnished dihydrospirotryprostatin B, **18**. *Thus, provided a large excess of reagent is not used and the reaction time carefully controlled, the NBS oxidations can be performed with alkene containing substrates.* The ability to do so, combined with the facile access to **16** via *N*-acyliminum Pictet−Spengler reaction,[7] accomplishes a highly efficient synthesis of **18** in only four steps from the methyl ester of L-tryptophan. Dihydrospirotryprostatin B was independently prepared by the Danishefsky group,[11b] by a significantly longer route in which the alkene was introduced by sulfoxide elimination after the oxidative rearrangement. The spectroscopic data for dihydrospirotryprostatin B matches that reported, although our optical rotation was somewhat higher: $[\alpha]^{33}_D = -129$ (*c* 0.785, $CHCl_3$) [lit.[11b] $[\alpha]^{20.1}_D = -79.2$ (*c* 0.171, $CHCl_3$)]. As with the saturated tetrahydro-*β*-carboline **5**, reversing the order of oxidative rearrangement and diketopiperazine formation proved to be unsatisfactory. Although NBS oxidation of the natural product demethoxyfumitremorgin C (**1**) afforded the desired spirooxindole, this occurred in a stereorandom fashion at the newly created chiral center, yielding **18** and its diastereomer **19** in equal proportions. Once again, this highlights the unpredictable effect of the diketopiperazine annulation on the course of the NBS indole oxidation.

Scheme 3[a]



16 17 18 1 19

[a] Reagents and conditions: (a) NBS (1.18 equiv), THF−AcOH−H_2O (1:1:1), 0 °C, 5 min, rt, 12 min, 68%; (b) 20% piperidine in CH_2Cl_2, rt, 12 min, 100%; (c) NBS (1.20 equiv), THF−AcOH−H_2O (3:3:2), rt, 3 h.

At this stage, it was readily apparent that our route would be applicable to a concise total synthesis of spirotryprostatin A, provided we began with chiral 6-methoxytryptophan. However, because of the large deleterious effect of the methoxy group on biological activity, we did not pursue this course and focused instead on spirotryprostatin B. An additional motivation for targeting this alkaloid was the fact that its structure could not be assigned in a completely unambiguous manner. By analogy to the other natural products in this series, it was assumed that the chirality in the diketopiperazine ring was derived from L-proline, although the isolation of this center from the other half of the molecule precludes a definitive assignment based on analysis of long-range NMR couplings. Synthesis also represents the most practical means of obtaining larger amounts of siprotryprostatin B for biological studies, as only 11 mg of the natural product were obtained from a 400 L fermentation.

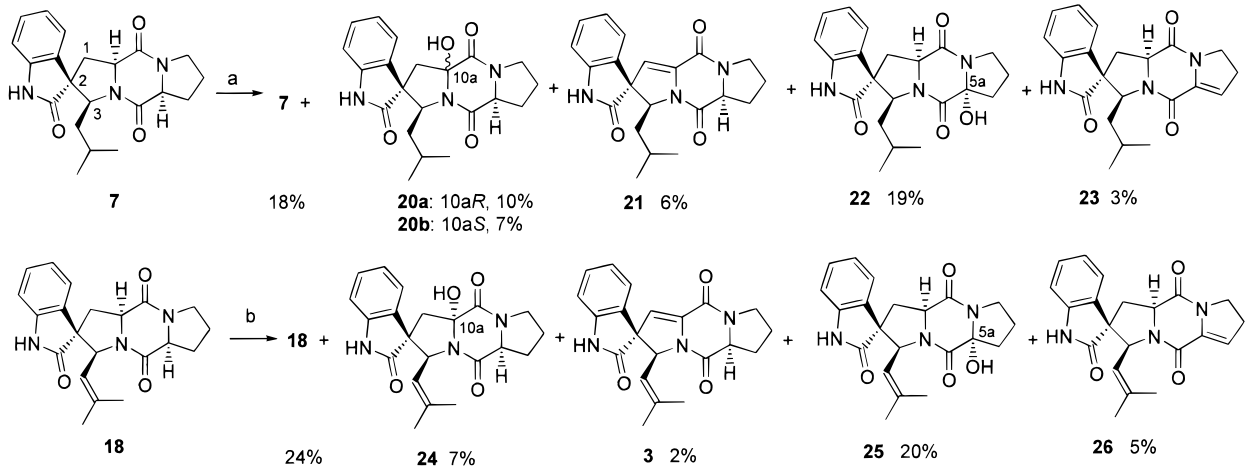
Spirotryprostatin B features the challenge of incorporating the additional unsaturation present in the pyrroline ring. In this respect, starting with a dehydrotryptophan and carrying out the oxidative rearrangement with this alkene already present did not appear feasible, since there are reports[19] of dihydroxylation in such compounds under oxidizing conditions. Thus, we envisioned pyrroline formation after the oxindole rearrangement and diketopiperazine cyclization. Both DDQ[20] and phenylseleninic anhydride[21] have been employed to introduce unsaturation into tetrahydro-*β*-carbolines in the

(18) Sim, M. M.; Ganesan, A. *J. Org. Chem*. **1997**, *62*, 3230−3235.

(19) Hermkens, P. H. H.; Plate, R.; Kruse, C. G.; Scheeren, H. W.; Ottenheijm, H. C. J. *J. Org. Chem*. **1992**, *57*, 3881−3887.

(20) (a) Kodato, S.-I.; Nakagawa, M.; Hongu, M.; Kawate, T.; Hino, T. *Tetrahedron* **1988**, *44*, 359−377. (b) See also ref 12 and 19.

Scheme 4[a]



[a] Reagents and conditions: (a) (i) LDA (2.51 equiv), −75 °C, 30 min; (ii) PhSeBr (2.45 equiv), −75 °C, 1 h; (b) (i) LDA (3.80 equiv), −75 °C, 40 min; (ii) PhSeBr (3.09 equiv), −75 °C, 1 h.

fumitremorgin series. As the DDQ method can result in various products if the indole nitrogen is unsubstituted, we opted for phenylselenenylation/oxidation.[22] Treatment of tetrahydrospirotryprostatin B **7** with excess base, followed by addition of phenylselenenyl bromoride[23] and workup resulted in compounds **20**−**23** besides recovered starting material (Scheme 4). In another trial, **7** was first treated with LDA/TMSCl followed by LDA/PhSeBr, without any improvement. Besides **20**−**23**, we also isolated a small quantity of a doubly unsaturated product in which alkenes were introduced into both the Trp and Pro portions of the diketopiperazine. Unusually, no selenide products were isolated in any of these reactions. Although there are examples[24] of direct selenide elimination under nonoxidative conditions with an excess of phenylselenenyl halides, we believe the formation of alcohol and alkene products with our substrates is more consistent with an addition−elimination mechanism due to the diketopiperazine[25] ring. The initially formed selenide is presumably undergoing elimination assisted by the neighboring amide nitrogen, in an analogous fashion to the mechanism depicted in eq 2. The resulting iminium ion,[26] upon loss of a proton, would give dehydro diketopiperazines **21** and **23**, while protonation of these enamides and capture by water produces alcohols **20** and **22**.

The above experiments also reveal that deprotonation of the diketopiperazine is essentially statistical, occurring at both halves of the molecule. Despite the lack of regiocontrol, this method does provide a rapid means for producing synthetic spirotryprostatin B from the dihydrospirotryprostatin B we already had in hand, both for the purposes of confirming the structure assignment as well as producing material for biological assays. Repeating the phenylselenenylation reaction with dihydrospirotryprostatin B **18** afforded the corresponding products **24**−**26** as well as a small amount of spirotryprostatin B **3**.

To increase the yield of spirotryprostatin B, the dehydration of hydroxy compound **24** was undertaken. The reaction conditions were first tried with the more plentiful isomer **25**, which upon treatment with methanesulfonyl chloride gave products **26**, **27** and **28** (Scheme 5) in a 1:1:1 ratio. The N-mesylation side reaction could be avoided by using a three-step sequence in which the oxindole was first protected with the Boc group. In this manner, **24** was converted to **3** [$[\alpha]^{33}_D = -144$ (*c* 0.035, $CHCl_3$) [lit.[3c] $[\alpha]^{22}_D = -162.1$ (*c* 0.92, $CHCl_3$)]] in 52%. The overall yield of spirotryprostatin B from **18** is then 6%, together with 20% recovered starting material. Because of the paucity of **3** isolated by fermentation, we were unable to obtain a sample of the natural product for comparison. The NMR spectra (^1H, ^{13}C, COSY, HMQC, and HMBC) of our synthetic material is identical with that reported by Osada, thus unambiguously confirming the structure of spirotryprostatin B.

Tetrahydrospirotryprostatin B **7** and dihydrospirotryprostatin B **18** did not inhibit G_2/M progression of synchronous tsFT210 cells (IC_{50} >500 μM). At 500 μM, they do not disrupt the microtubule network or its assembly.[27] Tetrahydrospirotryprostatin B was also submitted to the National Cancer Institute's 60-cell line in vitro antitumor assay, and the mean panel IC_{50} values was ≥100 μM. In general, it appears that the spirooxindole series is less active compared to tetrahydro-β-carbolines such as demethoxyfumitremorgin C (NCI mean panel IC_{50} = 44 μM) and related analogues.[9]

(21) Boyd, S. A.; Thompson, W. J. *J. Org. Chem.* **1987**, *52*, 1790−1794.

(22) For a review, see: Reich, H. J.; Wollowitz, S. *Org. React. (N.Y.)* **1993**, *44*, 1−296.

(23) We prefer phenylselenenyl bromide to phenylseleninic anhydride, due to the lower solubility and purity of the latter (the commercial product from Aldrich contains 30% $PhSeO_2H$).

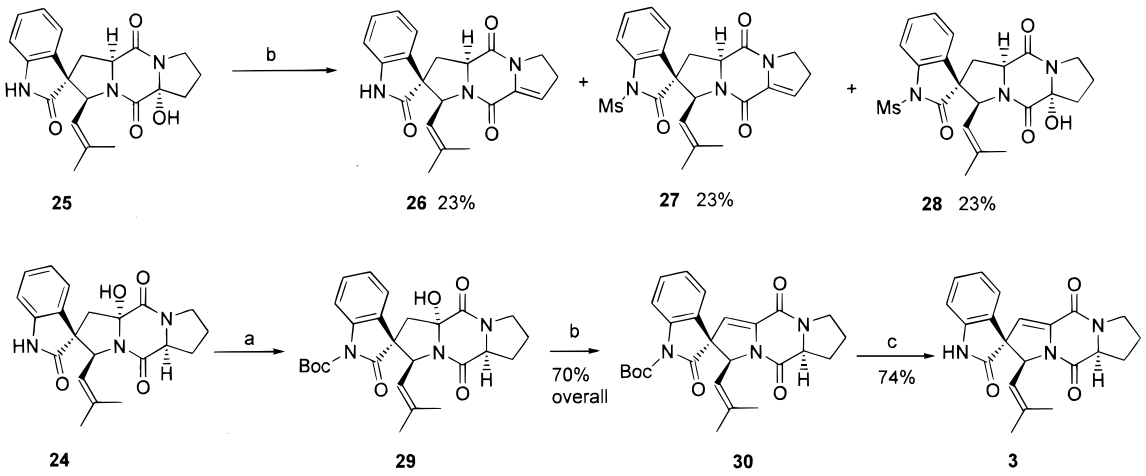
(24) (a) Roberts, M. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 724−725. (b) Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, H. S., III. *J. Org. Chem.* **1981**, *46*, 2920−2923.

(25) For a leading reference on diketopiperazine chemistry, see: Rajappa, S.; Natekar, M. V. *Adv. Heterocycl. Chem.* **1993**, *57*, 187−289.

(26) Similar diketopiperazine iminium ions have been invoked, for example, with thio-subsituted Pro-Pro derivatives, as well as the chemistry of bicyclomycin and related bridgehead compounds: (a) Öhler, E.; Tataruch, F.; Schmidt, U. *Chem. Ber.* **1973**, *106*, 165−176. (b) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1985**, *107*, 3253−3260. (c) Williams, R. M.; Dung, J.-S. *Tetrahedron Lett.* **1985**, *26*, 37−38.

(27) These assays were performed by Professor Osada's group, according to published methods, ref 3, and: (a) Usui, T.; Kondoh, M.; Cui, C.-B.; Mayumi, T.; Osada, H. *Biochem. J.* **1998**, *333*, 543−548. (b) Kondoh, M.; Usui, T.; Mayumi, T.; Osada, H. *J. Antibiot.* **1998**, *5*, 801−804.

Scheme 5[a]



[a] Reagents and conditions: (a) $(Boc)_2O$ (5.2 equiv), DMAP (4.3 equiv), CH_2Cl_2, rt, 5 h; (b) MsCl, Et_3N, CH_2Cl_2, rt; (c) TFA, Et_3SiH, CH_2Cl_2, rt, 15 min.

Summary

The goal of this project was to devise a rapid synthesis of analogues related to the spirotryprostatins, rather than necessarily target the natural products themselves. This was successfully achieved by the tactical combination of *N*-acyliminium Pictet−Spengler reaction and NBS oxidative rearrangement. Both these reactions are compatible with the prenyl side chain present in the natural products, and enabled a 4-step synthesis of dihydrospirotryprostatin B. With this material, we have introduced an additional unsaturation to complete the first total synthesis[28] of spirotryprostatin B. Although the route suffers from a lack of regioselectivity and poor yield in the final step, it has served to unambiguously confirm the original structural elucidation and supply material for biological screening. For an improved second-generation synthesis, the order of steps needs to be modified, such that the double bond is introduced prior to diketopiperazine formation with an intermediate such as **17**, in which the Trp and Pro halves of the molecule are of differing acidity toward deprotonation.

Experimental Section

All chemicals were obtained from commercial suppliers and used without further purification, except for CH_2Cl_2, which was distilled from CaH_2. TLC was carried out on precoated plates: analytical (Merck Kieselgel 60 F_{254}), spots visualized with UV light and iodine vapor; preparative-scale (Aldrich, silica, 1 mm thick). Flash column chromatography was performed with silica (Merck EM9385, 230−400 mesh). ^1H and ^{13}C NMR were recorded at 400 or 300 and at 100 or 75 MHz respectively, in $CDCl_3$ unless otherwise mentioned. Proton and carbon chemical shifts are expressed in ppm relative to internal tetramethylsilane. Protons were assigned according to COSY, HMQC, NOESY or 1D-NOE experiments; coupling constants (*J*) are reported in hertz. Carbons were assigned according to DEPT and/or 2D experiments (HMQC, HMBC) and multiplicity was represented as s = quaternary C, d = CH, t = CH_2 and q = CH_3. Workup means the solution was extracted with CH_2Cl_2 (3×), dried ($MgSO_4$), filtered, and concentrated under reduced pressure.

(2*S*,3*S*,5a*S*,10a*S*)-1,5a,6,7,8,10a-Hexahydro-3-(2-methylpropyl)spiro[5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione (7). Preparation of 4. The mixture of **4** and its trans isomer was prepared by reaction of the imine derived from L-tryptophan methyl ester and isovaleraldehyde with TFA in CH_2Cl_2.[9,12]

Synthesis of 5. To the above crude mixture in CH_2Cl_2 was added 1.3 equiv of Fmoc-L-ProCl[29] and aqueous Na_2CO_3. After being stirred for 2 h at room temperature, the reaction mixture was worked up, and the residue purified by flash chromatography (AcOEt/hexanes = 40:60) to give **5** (55%) and its trans isomer (29%).[9]

NBS Oxidation of 5. Compound **5** (271 mg, 0.447 mmol) was dissolved in THF−AcOH (1:1, 5 mL) followed by water (2.5 mL). The solution was stirred with cooling (ice bath) and NBS (94 mg, 0.526 mmol) added. After 5 min, the flask was stirred at room temperature for 30 min, and the reaction mixture then quenched by addition of solid Na_2SO_3. Following concentration, the residue was neutralized with aqueous Na_2CO_3, worked up, and purified by preparative TLC (AcOEt/$CHCl_3$ = 1:2) to give **6** (235 mg, 85%) as a white solid: mp 195−197 °C dec; IR (film) 1751, 1709 (strong), 1619, 1418 cm^{-1}; due to the presence of at least two rotamers in solution, both ^1H and ^{13}C NMR spectra are very complicated; HRMS (ESI) *m*/*z* calcd for $C_{37}H_{39}N_3O_6Na$ ($[M + Na]^+$) 644.2739, found 644.2750 (+1.7 ppm).

Deprotection and Cyclization of 6. Compound **6** (218 mg, 0.360 mmol) was stirred with piperidine (1 mL) in CH_2Cl_2 (4 mL) at room temperature for 12 min. The solution was then concentrated, and the residue was purified by flash chromatography (AcOEt/hexanes = 50%, then AcOEt, followed by 10% MeOH in CH_2Cl_2) to give tetrahydrospirotryprostatin B **7** (133 mg, 100%) as a white solid: mp 150−152 °C; $[\alpha]^{33}_D = -93$ (*c* 1.18, $CHCl_3$); IR ν_{max} ($CHCl_3$) 1709, 1669, 1620, 1420 cm^{-1}; ^1H NMR δ 9.00 (br s, 1H, 1′-H), 7.28 (t, 1H, *J* = 6.8), 7.26 (d, 1H, *J* = 7.7, 4′−H), 7.04 (t, 1H, *J* = 7.6), 6.93 (d, 1H, *J* = 8.2, 7′-H), 4.94 (dd, 1H, *J* = 10.4, 7.0, 10a−H), 4.30 (t, 1H, *J* = 8.0, 5a−H), 4.17 (dd, 1H, *J* = 9.1, 3.0, 3-H), 3.65−3.55 (m, 2H), 2.70 (dd, 1H, *J* = 13.4, 10.8, 1-Hβ), 2.39 (dd, 1H, *J* = 13.4, 7.0, 1-Hα), 2.41−2.36 (m, 1H), 2.24 (m, 1H), 2.10−1.95 (m, 3H), 1.70 and 1.63 (each of m and 1H, Me_2CHCH_2), 0.83 (d, 3H, *J* = 5.2), 0.84−0.75 (m, 1H), 0.65 (d, 3H, *J* = 6.0); ^{13}C NMR δ 181.5, 167.7, 167.0, 141.1 (s), 129.1 (d), 127.1 (s), 125.2 (d), 122.4 (d), 110.2 (d), 61.4 (C-5a), 60.7 (C-3), 58.4 (C-10a), 54.9 (spiro C-2), 45.1 (C-8), 40.3 (Me_2CHCH_2), 33.8 (C-1), 27.8 (t), 25.1 (d), 23.7 (t), 22.7 (q), 21.1 (q); NOE data: 1-Hα (1-Hβ,

(28) **Note Added in Proof.** After submission of this paper, we have learned of independent syntheses of **3** by the groups of Danishefsky, Overman, and Williams.

(29) Carpino, L. A.; Cohen, B. J.; Stephens, K. E., Jr.; Sadat-Aalaee, S. Y.; Tien, J.-H.; Langridge, D. C. *J. Org. Chem.* **1986**, *51*, 3732−3734.

3-H, 10a-H), 1-Hβ (1-Hα, 10a-H, 4′-H), 5a-H (1-Hα, 10a-H), 10a-H (1-Hα, 3-H, 5a-H), 7′-H (1′-H), 4′-H (δ 1.63, 1-Hβ); HRMS (APCI) *m*/*z* calcd for $C_{21}H_{26}N_3O_3$ ([M + H]$^+$) 368.1974, found 368.1971 (−0.8 ppm).

NBS Oxidation of Diketopiperazine 8. Compound **8**[12] was prepared by deprotection and cyclization of **5** with piperidine in CH_2Cl_2. The diketopiperazine (21.9 mg, 0.062 mmol) was dissolved in THF−AcOH (1:1, 3 mL) followed by water (1.5 mL). NBS (12.9 mg, 0.0725 mmol) was added at room temperature and the reaction mixture stirred at room temperature for 1.5 h. After being quenched with solid Na_2SO_3 and evaporation to dryness, the resulting residue was diluted with CH_2Cl_2 and aqueous Na_2CO_3. After usual workup, the residue was purified by preparative TLC (ethyl acetate/chloroform = 6:4) to give products **10** (0.9 mg, 3%), **9** (15.7 mg, 69%), **11** (2.9 mg, 13%), and **7** (0.7 mg, 3%).

(3*S*,8a*S*)-3-[2-(3-Methylbutyryl)-1*H*-indol-3-ylmethyl]-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (9): white solid; its ^{1}H NMR spectrum was identical to that reported;[12] ^{13}C NMR δ 194.8, 169.9, 165.6, 136.3, 133.1, 127.7 (d), 126.7, 121.1 (d), 121.1 (d), 117.9, 112.4 (d), 59.2 (d), 56.6 (d), 49.1 (t), 45.5 (t), 28.2 (t), 25.3 (t), 25.0 (d), 22.69 (q), 22.68 (t), 22.65 (q); MS (ESI) *m*/*z* 368.20 ([M + H]$^+$).

(3*S*,8a*S*)-3-[5-Bromo-2-(3-methylbutyryl)-1*H*-indol-3-ylmethyl]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (10): white solid; IR (film) 1673, 1647, 1528 cm^{-1}; ^{1}H NMR δ 8.86 (br s, 1H, 1′-H), 7.93 (d, 1H, *J* = 1.2, 4′-H), 7.46 (dd, 1H, *J* = 8.8, 1.7, 6′-H), 7.31 (d, 1H, *J* = 8.8, 7′-H), 6.62 (br s, 1H, 2-H), 4.38 (dd, 1H, *J* = 8.8, 3.4, 3-H), 4.04 (t, 1H, *J* = 7.4, 8a-H), 3.90 (dd, 1H, *J* = 14.7, 3.9, Trp-CH_2), 3.69−3.55 (m, 2H, 6-H × 2), 3.44 (dd, 1H, *J* = 14.7, 9.2, Trp-CH_2), 2.82 (dd, 1H, *J* = 15.9, 7.0, Me_2CHCH_2), 2.75 (dd, 1H, *J* = 16.0, 6.8, Me_2CHCH_2), 2.37−2.27 (m, 2H, Me_2CH− and one of 8-H), 2.00−1.85 (m, 3H, 7-H ×2 and one of 8-H), 1.020 (d, 3H, *J* = 6.6, Me), 1.017 (d, 3H, *J* = 6.6, Me); ^{13}C NMR δ 193.7 (ketone, identified by HMBC), 169.6 (C-1), 165.3 (C-4), 134.5, 133.7, 129.9 (C-6′), 129.4, 123.7(C-4′), 117.3, 114.5 (C-5′), 113.7 (C-7′), 59.2 (C-8a), 56.3 (C-3), 49.2 (Me_2CHCH_2), 45.5 (C-6), 28.2 (C-8), 25.3 (Trp-CH_2), 24.8 (Me_2CH−), 22.7 (2 × Me), 22.5 (C-7); NOE data: 1′-H (7′-H, Me_2CHCH_2), 4′-H (3-H, δ 3.90, δ 3.44), 6′-H (7′-H), 7′-H (1′-H, 6′-H), δ 3.90 (4′-H, 3-H, δ 3.44), δ 3.44 (4′-H, 2-H, δ 3.90); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{25}{}^{79}BrN_3O_3$ ([M + H]$^+$) 446.1079, found 446.1090 (+2.5 ppm); $C_{21}H_{25}{}^{81}BrN_3O_3$ ([M + H]$^+$) 448.1059, found 448.1077 (+4.0 ppm).

(2*R*,3*S*,5a*S*,10a*S*)-1,5a,6,7,8,10a-Hexahydro-3-(2-methylpropyl)spiro[5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione (11): IR (film) 1717, 1662, 1620, 1472, 1418 cm^{-1}; ^{1}H NMR δ 7.86 (br s, 1H, 1′-H), 7.27 (td, 1H, *J* = 7.6, 1.4, 6′-H), 7.10 (d, 1H, *J* = 6.7, 4′-H), 7.05 (td, 1H, *J* = 7.5, 0.9, 5′-H), 6.92 (d, 1H, *J* = 7.7, 7′-H), 4.57 (dd, 1H, *J* = 10.0, 7.4, 10a-H), 4.29 (t, 1H, *J* = 8.0, 5a-H), 4.09 (dd, 1H, *J* = 9.3, 2.7, 3-H), 3.65−3.56 (m, 2H, 8-H × 2), 2.97 (dd, 1H, *J* = 13.2, 10.3, 1-Hβ), 2.36 (m, 1H, 6-Ha), 2.26 (m, 1H, 6-Hb), 2.25 (dd, 1H, *J* = 13.1, 7.3, 1-Hα), 2.06−1.98 (m, 3H, 7-H × 2 and one of Me_2CHCH_2), 1.63−1.56 (m, 1H, one of Me_2CHCH_2), 1.34 (m, 1H, Me_2CH−), 0.86 (d, 3H, *J* = 6.5), 0.82 (d, 3H, *J* = 6.6); ^{13}C NMR δ 176.2 (C-2′), 167.1 (C-5), 166.0 (C-10), 139.1 (C-7′a), 133.4 (C-3′a), 128.8 (C-6′), 123.0 (C-5′), 122.6 (C-4′), 110.0 (C-7′), 64.8 (C-3), 61.3 (C-5a), 59.0 (C-10a), 53.5 (spiro C-2), 45.2 (C-8), 37.8 (Me_2CHCH_2), 35.5 (C-1), 27.7 (Me_2CH−), 26.2 (C-6), 23.7 (C-7), 23.0 (Me), 21.4 (Me); NOE data: δ 1-Hα (1-Hβ, 3-H, 10a-H), 1-Hβ (1-Hα), 3-H (Me, Me_2CH−, 10a-H, 4′-H), 5a-H (6-Ha, 10a-H), 10a-H (1-Hα, 5a-H, 4′-H), 7′-H (6′-H, 1′-H), 4′-H (3-H, 10a-H); HRMS (APCI) *m*/*z* calcd for $C_{21}H_{26}N_3O_3$ ([M + H]$^+$) 368.1974, found 368.1962 (−3.3 ppm).

(5*S*,11a*S*)-5-(2-Methylpropyl)-2-phenyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (12) and (5*R*,11a*S*)-5-(2-Methylpropyl)-2-phenyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (13). The above crude mixture of **4** and its trans isomer (0.558 g, from 1.81 mmol of L-tryptophan methyl ester) was dissolved in CH_2Cl_2 (5 mL). Phenyl isocyanate (0.25 mL, 2.30 mmol) was added, and after the mixture was stirred at room temperature for 15 h, Et_3N (0.50 mL, 3.59 mmol) was added followed by stirring for an additional 8.5 h. The reaction mixture was worked up and the residue purified by flash chromatography (20−33% AcOEt/hexanes) to give **13** (less polar fractions, 0.251 g, 37%) and **12** (more polar, 0.156 g, 23%).

For **12**: pale yellow solid; mp 202−204 °C; $[\alpha]^{22}_D$ = −0.8 (*c* 0.46, MeOH); IR (film) 1771, 1713 (very strong), 1418 cm^{-1}; ^{1}H NMR δ 7.97 (br s, 1H, H6), 7.57 (d, 1H, *J* = 7.7, H10), 7.51−7.44 (m, 4H), 7.42−7.36 (m, 1H), 7.38 (d, 1H, *J* = 7.7, 7-H), 7.24 (td, 1H, *J* = 7.8, 1.3, 8-H), 7.19 (td, 1H, *J* = 7.4, 1.1, 9-H), 5.12 (br s like, 1H, 5-H), 4.38 (dd, 1H, *J* = 11.4, 4.3, 11a−H), 3.51 (ddd, 1H, *J* = 14.8, 4.3, 1.0, 11-Hα), 2.98 (ddd, 1H, *J* = 14.8, 11.4, 1.9, 11-Hβ), 2.62 (dt, 1H, *J* = 14.4, 5.7, Me_2CHCH_2), 2.14 (ddd, 1H, *J* = 14.4, 7.4, 3.3, Me_2CHCH_2), 1.69 (m, 1H, Me_2CH), 0.95 (d, 3H, *J* = 6.6), 0.77 (d, 3H, *J* = 6.6); ^{13}C NMR δ 170.5, 154.2, 136.2, 133.6, 131.5 (s), 129.1 (d), 128.2 (d), 126.29 (s), 126.26 (d), 122.6 (C-8), 120.3 (C-9), 118.3 (C-10), 111.1 (C-7), 107.6 (s), 58.3 (C-11a), 52.1 (C-5), 41.1 (t), 24.6 (d), 23.5 (q), 22.9 (q), 22.4 (C-11); NOE data: 6-H (7-H, 5-H), 10-H (11-Hα), 7-H (6-H), 5-H (6-H, 11-Hα, δ 2.62, δ 2.14), 11a−H (5-H, 11-Hα), 11-Hα (10-H, 11a−H, 11-Hβ), 11-Hβ (11a−H), δ 2.62 (5-H, δ 2.14); HRMS (APCI) *m*/*z* calcd for $C_{23}H_{24}N_3O_2$ ([M + H]$^+$) 374.1869, found 374.1878 (+2.4 ppm).

For **13**: white solid; mp 216−218 °C; $[\alpha]^{22}_D$ = −9.9 (*c* 0.50, MeOH); IR (film) 1771, 1713 (very strong), 1423 cm^{-1}; ^{1}H NMR δ 7.97 (br s, 1H), 7.51 (d, 1H, *J* = 7.7, H10), 7.50−7.45 (m, 4H), 7.40−7.37 (m, 1H), 7.35 (d, 1H, *J* = 8.0, 7-H), 7.22 (td, 1H, *J* = 7.5, 1.1, 8-H), 7.16 (ddd 1H, *J* = 8.1, 6.8, 1.0, 9-H), 5.40 (dd, 1H, *J* = 10.0, 3.1, 5-H), 4.47 (dd, 1H, *J* = 10.8, 5.8, 11a−H), 3.48 (dd, 1H, *J* = 15.4, 5.9, 11-Hα), 2.96 (ddd, 1H, *J* = 15.4, 10.8, 1.4, 11-Hβ), 1.93−1.86 (m, 1H, Me_2CH−), 1.81 (ddd, 1H, *J* = 14.2, 10.0, 4.3, Me_2CHCH_2), 1.70 (ddd, 1H, *J* = 14.0, 9.5, 3.9, Me_2CHCH_2), 1.16 (d, 3H, *J* = 6.4), 0.99 (d, 3H, *J* = 6.6); ^{13}C NMR δ 172.0, 154.4, 136.2, 133.1, 131.5 (s), 129.1 (d), 128.2, 126.3 (s), 126.1 (d), 122.7 (C-8), 120.2 (C-9), 118.3 (C-10), 111.0 (C-7), 105.6, 52.8 (C-11a), 47.1 (C-5), 45.7 (t), 25.1 (d), 23.9 (C-11), 23.5 (q), 22.1(q); NOE data 6-H (7-H, 5-H, δ 1.81, δ 2.87), 10-H (11-Hα), 7-H (6-H), 5-H (6-H, 11a−H), 11a−H (5-H, 11-Hα), 11-Hα (10-H, 11a−H, 11-Hβ), 11-Hβ (11a-H); HRMS (APCI) *m*/*z* calcd for $C_{23}H_{24}N_3O_2$ ([M + H]$^+$) 374.1869, found 374.1870 (+0.3 ppm).

Spirohydantoin (14). Compound **12** (46.0 mg, 0.123 mmol) was dissolved in THF−AcOH (1:1, 2 mL) and water (1 mL), followed by addition of NBS (24.9 mg, 0.140 mmol) at room temperature. After the mixture was stirred at room temperature for 75 min, solid Na_2SO_3 was added, the reaction worked up, and the residue was purified by preparative TLC (eluant: 3% MeOH/CH_2Cl_2) to give **14** (26.1 mg, 54%) as a pale yellow solid: mp 195−197 °C; IR (film) 1776, 1716 (very strong), 1620 cm^{-1}; ^{1}H NMR δ 8.51 (br s, 1H), 7.54−7.46 (m, 4H, PhH), 7.42 (tt, 1H, *J* = 7.2, 1.5, PhH), 7.24 (td, 1H, *J* = 7.8, 1.1), 7.03 (dt, 1H, *J* = 7.6, 0.8), 6.91 (d, 1H, *J* = 7.7, oxindole 7-H), 6.86 (d, 1H, *J* = 7.5, oxindole 4-H), 4.67 (dd, 1H, *J* = 11.2, 5.4, Trp-C*H*N), 4.04 (dd, 1H, *J* = 10.6, 4.0, Me_2CHCH_2CHN), 2.99 (dd, 1H, *J* = 14.2, 11.2, Trp-CH_2), 2.46 (dd, 1H, *J* = 14.2, 5.4, Trp-CH_2), 2.03 (m, 1H, Me_2CHCH_2), 1.95 (m, 1H, Me_2CH), 0.87 (d, 3H, *J* = 6.2), 0.85 (d, 3H, *J* = 6.3); 0.78 (m, 1H, Me_2CHCH_2); ^{13}C NMR δ 178.6, 172.1, 156.1, 140.2, 131.6, 130.5 (s), 129.4 (d), 128.8 (d), 128.5, 126.2, 123.6, 123.5, 110.6, 67.9 (d), 61.3 (d), 59.5 (s), 38.2 (t), 34.8 (t), 25.7 (d), 23.1 (q), 21.8 (q); NOE data δ 2.46 (δ 2.99, 4.67, 6.86), δ 2.99 (2.46, 4.04, 4.67 (strong)), δ 4.04 (2.99, 4.67), δ 4.67 (2.99, 4.04), δ 6.86 (2.46); HRMS (APCI) *m*/*z* calcd for $C_{23}H_{24}N_3O_3$ ([M + H]$^+$) 390.1818, found 390.1804 (−3.6 ppm).

Spirohydantoin (15). Compound **13** (103 mg, 0.275 mmol) was dissolved in THF−AcOH−H_2O (1:1:1, 6 mL), followed by addition of NBS (50.9 mg, 0.286 mmol) at room temperature. The reaction mixture was stirred at room temperature for 24 h, quenched, and worked up, and the residue was purified by preparative TLC (ethyl acetate/hexanes = 1:2) to yield recovered **13** (19.3 mg, 19%) and product **15** (59.6 mg, 56%). For **15**: pale yellow solid; mp 220 °C dec; IR (film) 1778, 1717 (very strong), 1618, 1404 cm^{-1}; ^{1}H NMR δ 9.15 (s, 1H), 7.54 (d like, 2H, *J* = 7.4), 7.46 (t, 2H, *J* = 7.6), 7.38 (t, 1H, *J* = 7.2), 7.21 (d, 1H, *J* = 7.4, oxindole 4-H), 7.11 (t, 1H, *J* = 7.7), 7.02 (t,

1H, J = 7.5), 6.45 (d, 1H, J = 7.7), 4.65 (dd, 1H, J = 8.4, 6.1, Trp-C*H*N), 4.41 (dd, 1H, J = 12.4, 3.5, Me_2CHCH_2CHN), 2.67 and 2.64 (each 1H, strong coupled AB system, Trp-CH_2), 1.88 (m, 1H, Me_2CH), 1.64 (td, 1H, J = 12.9, 3.6, Me_2CHCH_2), 1.24 (ddd, 1H, J = 13.4, 10.0, 3.5, Me_2CHCH_2), 0.98 (d, 3H, J = 6.7), 0.94 (d, 1H, J = 6.5); ^{13}C NMR δ 182.5, 173.9, 160.7, 141.5, 132.5 (s), 129.1 (d), 128.2 (d), 126.8 (s), 126.5 (d), 125.3, 122.3, 110.8, 63.0 (d), 60.6 (d, Trp-*C*HN), 57.1 (s), 40.2 (t), 35.2 (t), 25.0 (d), 23.8 (q), 20.7 (q); NOE data δ 1.24 (1.64, 4.44, 7.21), δ 1.64 (1.24, 1.88, 2.64, 4.65, 7.21), δ 7.21 (1.24, 1.64, 2.67/2.64, 4.65); HRMS (APCI) m/z calcd for $C_{23}H_{24}N_3O_3$ ([M + H]$^+$) 390.1818, found 390.1831 (+3.3 ppm).

(2*S*,3*S*,5a*S*,10a*S*)-1,5a,6,7,8,10a-Hexahydro-3-(2-methyl-1-propenyl)spiro[5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione (18). Preparation of 16. Compound **16** was prepared in 32% overall yield from L-tryptophan methyl ester by our previously reported *N*-acyliminium Pictet−Spengler condensation[7] with a slight modification (1.5 equiv of Fmoc-L-ProCl and 3.0 equiv of pyridine were used).

NBS Oxidation of 16. Compound **16** (247 mg, 0.409 mmol) was dissolved in THF−AcOH (1:1, 5 mL), followed by water (2.5 mL). The solution was stirred in an ice bath and NBS (86 mg, 0.483 mmol) added. After 5 min, the flask was stirred at room temperature for 12 min. Solid Na_2SO_3 was then added and the reaction mixture neutralized with aqueous Na_2CO_3. After workup, the residue was purified by preparative TLC (AcOEt/hexanes = 50:50) to give recovered **16** (16 mg, 7%) and product **17** (171 mg, 68%). For **17**: white foam; mp 203−205 °C dec; IR (film) 1747, 1713 (strong), 1622, 1421 cm^{-1}; due to the presence of at least two rotamers in $CDCl_3$ solution, both ^{1}H and ^{13}C NMR spectra were very complicated, the two major rotamers being in a ratio of 2.1:1. For **17**: HRMS (ESI) m/z calcd for $C_{37}H_{37}N_3O_6Na$ ([M + Na]$^+$) 642.2580, found 642.2602 (+3.4 ppm).

Deprotection and Cyclization of 17. Compound **17** (151 mg, 0.243 mmol) was stirred with piperidine (0.8 mL) in CH_2Cl_2 (3.2 mL) at room temperature for 12 min. The solution was evaporated and purified by preparative TLC (AcOEt/MeOH/CH_2Cl_2 = 50:5:45) to give dihydrospirotryprostatin B **18** (89 mg, 100%) as a white solid: mp 172−174 °C; $[\alpha]^{33}_D$ = −129 (*c* 0.785, $CHCl_3$) [lit.[11b] $[\alpha]^{20.1}_D$ = −79.2 (*c* 0.171 $CHCl_3$)]; IR ν_{max} ($CHCl_3$) 1709, 1666, 1621, 1472, 1423 cm^{-1}; ^{1}H NMR δ 8.90 (br s, 1H, NH), 7.21 (td, 1H, J = 7.6, 1.1), 7.03 (d, 1H, J = 7.2, 4′−H), 6.97 (t, 1H, J = 7.5), 6.87 (d, 1H, J = 7.8), 5.07 (dm, 1H, J = 9.1, Me_2C═CH), 5.05 (overlapped 1H, 10a−H), 4.84 (d, 1H, J = 9.1, 3-H), 4.32 (t, 1H, J = 8.0, 5a−H), 3.67−3.55 (m, 2H), 2.66 (dd, 1H, J = 13.4, 10.8, 1-Hβ), 2.43 (dd, 1H, J = 13.4, 6.9, 1-Hα), 2.31 (m, 1H), 2.27 (m, 1H), 2.07−1.97 (m, 2H), 1.63 (s, 3H), 1.11 (s, 3H); ^{13}C NMR δ 181.0, 167.09, 167.06, 141.2, 138.4, 128.6, 127.0, 126.5, 121.9, 121.4, 109.6, 61.1, 60.3, 58.6, 56.0 (spiro C-2), 45.2, 34.2, 27.5, 25.4, 23.7, 17.9; NOE data: 1-Hα (1-Hβ, 10a-H), 1-Hβ (1-Hα, δ 5.07, 4′-H), 5a-H (10a-H), δ 5.07/10a-H (4′-H, 3-H, 5a-H, 1-Hα); HRMS (APCI) m/z calcd for $C_{21}H_{24}N_3O_3$ ([M+H]$^+$) 366.1818, found 366.1802 (−4.4 ppm).

(2*R*,3*S*,5a*S*,10a*S*)-1,5a,6,7,8,10a-Hexahydro-3-(2-methyl-1-propenyl)spiro[5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione (19). Demethoxyfumitremorgin C **1**[7] (28.2 mg, 0.081 mmol) was dissolved in THF−AcOH (1:1, 3 mL), followed by addition of water (1 mL) and NBS (17.2 mg, 0.097 mmol) at room temperature. After the mixture was stirred at room temperature for 3 h, solid Na_2SO_3, was added, followed by neutralization with aqueous Na_2CO_3 and workup. The residue was purified by preparative TLC ($MeOH/CH_2Cl_2$/AcOEt = 5:45:50) and gave three major fractions: recovered **1** (9.1 mg, 32%), **18** (5.8 mg, 20%), and **19** (6.1 mg, 21%). For **19**: $[\alpha]^{33}_D$ = −270 (*c* 0.115, $CHCl_3$); IR (film) 1717, 1662 (strong), 1620, 1472, 1421 cm^{-1}; ^{1}H NMR δ 7.88 (br s, 1H, NH), 7.25 (t, 1H, J = 7.7), 7.16 (d, 1H, J = 7.3, 4′-H), 7.04 (t, 1H, J = 7.5), 6.87 (d, 1H, J = 7.7), 5.25 (d, 1H, J = 9.8, Me_2C═C*H*), 4.78 (d, 1H, J = 9.8, 3-H), 4.57 (t, 1H, J = 8.1, 10a-H), 4.24 (t, 1H, J = 8.1, 5a-H), 3.65−3.55 (m, 2H), 3.06 (dd, 1H, J = 13.5, 8.0, 1-Hβ), 2.35 (dd, 1H, J = 13.4, 8.1, 1-Hα), 2.34−2.23 (m, 2H), 1.65 (s, 3H), 1.41 (s, 3H); ^{13}C NMR δ 176.5, 167.0, 166.0, 140.2, 136.4, 131.7, 128.9, 122.8, 122.7, 119.1, 109.9, 64.1 (d), 61.1 (d), 59.3 (d), 56.0 (spiro C-2), 45.3 (t), 34.5 (t), 27.7 (t), 25.9, 23.6 (t), 18.1; NOE data: 5a-H (10a-H), 10a-H (4′-H, 5a-H, 1-Hα), 3-H (4′-H), δ 5.25 (1-Hβ); HRMS (APCI) m/z calcd for $C_{21}H_{24}N_3O_3$ ([M + H]$^+$) 366.1818, found 366.1803 (−4.1 ppm).

LDA/PhSeBr Reaction of 7. To a 10 mL flask were added anhydrous THF (1.0 mL) and (i-Pr)$_2$NH (0.036 mL, 0.257 mmol) under N_2. *n*-BuLi (1.5 M in hexane, 0.20 mL, 0.30 mmol) was added to the flask cooled in a −75 °C dry ice/EtOH bath. The flask was kept at ca −30 °C for 30 min and then recooled to −75 °C. Compound **7** (37.6 mg, 0.102 mmol) in THF (1.1 mL) was added to the flask. After the mixture was stirred at the same temperature for 30 min, a solution of PhSeBr (59.3 mg, 0.251 mmol) in THF (0.6 mL) was added. After 1 h, the reaction mixture was poured into a mixture of Et_2O−hexanes (1:1, 10 mL)/5% aqueous HCl (10 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (×3). The organic layers were combined, dried ($MgSO_4$ + $NaHCO_3$), filtered, and evaporated. The yellow residue was purified by preparative TLC (AcOEt) to give five bands: yellow PhSeSePh (34.1 mg, 87%), **20a** (3.8 mg, 9.7%), two overlapping bands, and **20b** (2.6 mg, 6.6%). The overlapping bands were further purified by preparative TLC (5% MeOH/CH_2Cl_2) to afford **23** (1.1 mg, 2.9%), **22** (7.5 mg, 19%), recovered **7** (6.8 mg, 18%) and **21** (2.2 mg, 5.9%).

20a: ^{1}H NMR δ 8.16 (br s, 1H, NH), 7.31 (t, 1H, J = 7.7), 7.29 (d, 1H, J = 7.6), 7.14 (s, 1H, 10a-OH), 7.11 (t, 1H, J = 7.7), 6.95 (d, 1H, J = 7.7), 4.61 (t, 1H, J = 8.3), 4.36 (dd, 1H, J = 8.6, 3.8), 3.60 (dd, 1H, J = 8.4, 4.7), 3.07 (d, 1H, J = 14.8), 2.46 (d, 1H, J = 14.8), 2.40 (m, 1H), 2.11−1.54 (m, 3H), 1.61−1.54 (m, 2H), 0.81 (d, 3H, J = 6.4), 0.56 (d, 3H, J = 6.4), 0.45 (m, 1H); MS (ESI) m/z 406.6 ([M + Na]$^+$), 366.0[M + H − H_2O]. The 10a-hydroxy-carbon was assigned as 10a*R* by comparing the similarity of its ^{1}H NMR spectrum with that of **24**.

(2*S*,3*S*,5a*S*,10a*S*)-1,5a,6,7,8,10a-Hexahydro-10a-hydroxy-3-(2-methyl-1-propenyl)spiro[5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione (20b): IR (film) 1699, 1651, 1621 cm^{-1}; ^{1}H NMR δ 7.70 (d, 1H, J = 7.6, 4′-H), 752 (br s, 1H, NH), 7.26 (t, 1H, J = 7.1, 6′-H), 7.09 (t, 1H, J = 7.6, 5′-H), 6.88 (d, 1H, J = 7.7, 7′-H), 4.80 (t, 1H, J = 7.7, 3-H), 4.27 (dd, 1H, J = 11.2, 6.0, 5a−H), 4.17 (br s, 1H, 10a-OH), 3.97 (dt, 1H, J = 12.3, 8.1, one 8-H), 3.44 (ddd, 1H, J = 12.5, 9.4, 3.5, one 8-H), 2.76 (d, 1H, J = 13.4, 1-Hα), 2.50 (d, 1H, J = 13.5, 1-Hβ), 2.52−2.48 (m, 1H, one 6-H), 2.12 (m, 1H), 2.00−1.92 (m, 2H), 1.91 (m, 1H, Me_2CHCH_2), 1.41 (m, 1H, Me_2CHCH_2), 1.07 (m, 1H, Me_2CH), 0.83 (d, 3H, J = 6.6), 0.68 (d, 3H, J = 6.5); ^{13}C NMR δ 181.7 (C-2′), 165.0 (C-10), 164.9 (C-5), 140.6 (C-7′a), 129.7 (C-3′a), 128.6, 127.7, 122.7, 109.7, 89.3 (C-10a), 65.5 (C-3), 61.1 (C-5a), 54.8 (spiro C-2), 49.9 (C-1), 45.0 (C-8), 42.2 (Me_2CHCH_2), 29.9, 25.0, 22.4, 22.3, 22.0; NOE data: 4′-H (5′-H, 1-Hβ, δ 1.41), 1′-H (7′-H), 7′-H (1′-H), 3-H (1-Hα, δ 1.07), 10a-OH (4′-H, 1-Hβ), 1-Hα (3-H, 1-Hβ), 1-Hβ (4′-H), δ 1.91 (4′-H), δ 1.41 (4′-H, 3-H); MS (ESI) m/z calcd for $C_{21}H_{25}N_3O_4Na$ ([M + Na]$^+$) 406.17, found 406.18.

(2*S*,3*S*,5a*S*)-5a,6,7,8-Tetrahydro-3-(2-methylpropyl)spiro[5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione (21): IR (film) 1719, 1678, 1645, 1471, 1417 cm^{-1}; ^{1}H NMR δ 7.86 (br s, 1H, NH), 7.29 (td, 1H, J = 7.7, 1.1), 7.23 (d, 1H, J = 7.4), 7.06 (t, 1H, J = 7.6), 6.92 (d, 1H, J = 7.8), 5.71 (s, 1H, 1-H), 4.82 (dd, 1H, J = 10.5, 3.9), 4.29 (dd, 1H, J = 10.5, 5.9), 3.83 (dt, 1H, J = 12.6, 8.3), 3.56 (ddd, 1H, J = 12.5, 9.3, 3.0), 2.50 (m, 1H), 2.17−2.07 (m, 2H), 2.01−1.95 (m, 2H), 1.70 (m, 1H), 0.85 (d, 3H, J = 6.4), 0.73 (m, 1H), 0.56 (d, 3H, J = 6.5); ^{13}C NMR δ 178.4, 163.7, 155.1, 140.3, 138.2, 129.5 (d), 127.5 (s), 126.8 (d), 122.8 (d), 116.4 (d, C-1), 110.3 (d), 65.0, 61.6, 60.8 (spiro C-2), 44.7, 38.7, 29.5, 24.8 (d), 22.9, 22.1, 21.2; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3O_3$ ([M + H]$^+$) 366.1818, found 366.1808 (−2.7 ppm).

(2*S*,3*S*,5a*R*,10a*S*)-1,5a,6,7,8,10a-Hexahydro-5a-hydroxy-3-(2-methylpropyl)spiro[5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]-pyrazine-2(3*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione (22): IR (film) 1700, 1661, 1620, 1472, 1423 cm^{-1}; ^{1}H NMR δ 8.66 (br s, 1H, H1′), 7.26 (t, 1H, J = 7.0, 6′−H), 7.24 (d, 1H, J = 7.1, 4′−H), 7.03 (t, 1H, J = 7.6, 5′−H), 6.90 (d, 1H, J = 7.7, 7′−H),

5.55 (br s, 1H, 5a-OH), 5.29 (dd, 1H, J = 11.2, 6.9, 10a−H), 4.10 (d, 1H, J = 7.7, 3-H), 3.75 (m, 1H), 3.53 (m, 1H), 2.61 (dd, 1H, J = 13.3, 11.3, 1-Hβ), 2.41 (dd, 1H, J = 13.3, 6.9, 1-Hα), 2.31 (m, 1H), 2.28−2.21 (m, 2H), 2.01 (m, 1H), 1.76 (m, 1H, Me_2CHCH_2), 1.60 (m, 1H, Me_2CHCH_2), 0.79 (d, 3H, J = 6.0), 0.65 (m, 1H, Me_2CH−), 0.60 (d, 3H, J = 5.5); ^{13}C NMR δ 181.5, 168.0, 166.5, 140.8, 129.3 (d), 127.0 (s), 125.1 (d), 122.6 (d), 110.3 (d), 90.3 (s), 61.0, 57.6, 54.6 (s), 45.0 (t), 39.5 (t), 36.8 (t), 33.9 (t), 25.2 (d), 22.7 (q), 21.0 (t), 20.8 (q); NOE data: 4′-H (1-Hβ, δ 1.60), 5a-OH (10a-H, 3-H), 10a-H (3-H, 1-Hα), 1-Hβ (4′-H, 1-Hα, δ 1.60), 1-Hα (10a-H, 1-Hβ); HRMS (ESI) m/z calcd for $C_{21}H_{25}N_3O_4Na$ ([M + Na]$^+$) 406.1743, found 406.1753 (+2.5 ppm).

(2*S*,3*S*,10a*S*)-1,7,8,10a-Tetrahydro-3-(2-methylpropyl)-spiro[5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione (23): IR (film) 1718, 1674, 1638 cm^{-1}; ^{1}H NMR δ 7.66 (br s, 1H), 7.28 (t, 1H, J = 7.7), 7.23 (d, 1H, J = 7.5), 7.06 (t, 1H, J = 7.6), 6.90 (d, 1H, J = 7.8), 6.22 (t, 1H, J = 3.0, 6-H), 5.07 (dd, 1H, J = 10.3, 7.4), 4.23 (dd, 1H, J = 9.5, 2.7), 4.14 (td, 1H, J = 11.4, 5.4), 3.92 (td, 1H, J = 11.7, 8.9), 2.83 (m, 1H), 2.55 (dd, 1H, J = 13.2, 4.0), 2.52 (dd, 1H, J = 13.1, 7.1), 1.97 (dd, 1H, J = 12.5, 10.9, 2.8), 1.52 (m, 1H), 0.85 (d, 3H, J = 6.2), 0.80 (m, 1H), 0.60 (d, 3H, J = 6.4); ^{13}C NMR δ 180.7, 163.3, 156.8, 140.5, 136.3, 129.9, 127.9, 125.2, 122.7, 119.1, 110.0, 62.1, 59.0, 54.0, 45.1, 38.6, 35.9, 28.8, 25.2, 22.7, 21.0; MS (ESI) m/z calcd for $C_{21}H_{23}N_3O_3Na$ ([M + Na]$^+$) 388.16, found 388.18.

LDA/PhSeBr Reaction of 18. Compound **18** (39.0 mg, 0.107 mmol) was treated in a similar manner as **7**, except for the reagent quantities [(*i*-Pr)$_2$NH (3.81 equiv), *n*-BuLi (3.80 equiv), and PhSeBr (3.09 equiv)]. The reaction gave PhSeSePh (80%), **24** (7.0%), **26** (5.0%), recovered **18** (24%), **3** (2.0%), and **25** (20%).

(2*S*,3*S*,5a*S*,10a*R*)-1,5a,6,7,8,10a-Hexahydro-10a-hydroxy-3-(2-methyl-1-propenyl)spiro[5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione (24): ^{1}H NMR δ 8.03 (br s, 1H, 1′-H), 7.27−7.23 (overlapped, 1H), 7.18 (br s, 1H, 10a-OH), 7.04−7.00 (m, 2H, including 4′-H), 6.88 (d, 1H, J = 7.8, 7′-H), 5.04 (d, 1H, J = 8.9, 3-H), 4.93 (dt, 1H, J = 8.9, 1.3, Me_2C=CH), 4.65 (dd, 1H, J = 8.9, 7.6, 5a−H), 3.62 (m, 2H, 8-H ×2), 3.05 (d, 1H, J = 14.8, 1-Hβ), 2.51 (d, 1H, J = 14.8, 1-Hα), 2.36 (m, 1H, 6-H), 2.14−2.98 (m, 3H), 1.59 (s, 3H), 1.04 (d, 3H, J = 0.9); ^{13}C NMR δ 183.2 (C-2′), 169.0 (C-5), 165.3 (C-10), 140.3, 139.1, 129.0, 127.1, 127.0, 122.6, 121.5, 109.8, 89.9 (C-10a), 61.2 (C-3), 60.9 (C-5a), 56.3 (spiro C-2), 45.3, 40.9, 27.7, 25.3, 23.4, 17.9; NOESY data 1-Hα (10a-OH), 1-Hβ (δ 4.93), δ 4.93 (7.04−7.00, including 4′-H), 7′-H (1′-H).

(2*S*,3*S*,5a*R*,10a*S*)-1,5a,6,7,8,10a-Hexahydro-5a-hydroxy-3-(2-methyl-1-propenyl)spiro[5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione (25): pale yellow solid; mp 169−171 °C; IR (film) 1701, 1660, 1621, 1472, 1425 cm^{-1}; ^{1}H NMR δ 8.81 (br s, 1H, NH), 7.20 (td, 1H, J = 7.6, 1.1, 6′-H), 7.00 (d, 1H, J = 6.9, 4′-H), 6.95 (t, 1H, J = 7.5, 5-H′), 6.85 (d, 1H, J = 7.7, 7′-H), 5.77 (br s, 1H, 5a-OH), 5.38 (dd, 1H, J = 11.1, 7.0, 10a-H), 5.04 (dd, 1H, J = 9.1, 1.2, Me_2C=CH), 4.80 (d, 1H, J = 9.1, 3-H), 3.77 (m, 1H, one 8-H), 3.54 (m, 1H, one 8-H), 2.57 (t, 1H, J = 12.3, 1-Hβ), 2.45 (dd, 1H, J = 12.3, 6.9, 1-Hα), 2.31−2.19 (m, 3H), 2.00 (m, 1H), 1.61 (s, 3H), 1.05 (s, 3H); ^{13}C NMR δ 181.3 (C-2′), 168.3 (C-5), 166.2 (C-10), 141.1, 138.7, 128.8, 127.0, 126.4, 122.0, 121.0, 110.0, 90.2 (C-5a), 60.6 (d), 57.9 (d), 55.8 (spiro C-2), 45.2 (t), 36.5 (t), 34.5 (t), 25.5 (q), 21.1 (t), 17.9 (q); NOE data 4′-H (δ 5.04, 1-Hβ), 7′-H (6′-H), 5a-OH (10a-H, 3-H (weak)), 10a-H (5a-OH (negative), 1-Hα), δ 5.04 (4′-H, 1-Hβ), 1-Hβ (4′-H, 10a-H (weak), 3-H), 1-Hα (10a-H); MS (ESI) m/z calcd for $C_{21}H_{23}N_3O_4Na$ ([M + Na]$^+$) 404.16, found 404.16.

(2*S*,3*S*,10a*S*)-1,7,8,10a-Tetrahydro-3-(2-methyl-1-propenyl)spiro[5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione (26): IR (film) 1701, 1675 cm^{-1}; ^{1}H NMR δ 7.78 (br s, 1H, 1′-H), 7.23 (td, 1H, J = 7.5, 1.6), 7.04−6.97 (m, 2H, including 4′-H), 6.85 (d, 1H, J = 7.8, 7′-H), 6.20 (t, 1H, J = 3.0, 6-H), 5.24 (dd, 1H, J = 11.2, 6.4, 10a−H), 5.10 (dd, 1H, J = 9.0, 1.3, Me_2C=CH), 4.94 (d, 1H, J = 9.0, 3-H), 4.15 (td, 1H, J = 11.4, 5.3), 3.92 (td, 1H, J = 11.6, 9.1), 2.90−2.78 (m, 2H), 2.57 (dd, 1H, J = 13.1, 6.4, 1-Hα), 2.50 (dd, 1H, J = 13.0, 11.4, 1-Hβ), 1.62 (s, 3H), 1.19 (s, 3H); ^{13}C NMR δ 180.4 (C-2′), 163.3 (C-10), 156.1 (C-5), 140.5, 138.2, 136.1 (s), 128.7 (d), 127.6 (s), 126.6 (d), 122.1, 121.1, 119.0, 109.5, 61.2, 59.0 (C-3a), 55.1 (spiro C-2), 45.2 (t), 36.2 (C-1), 28.7 (t), 25.4 (q), 18.1 (q); NOESY data 1-Hβ (δ 5.10, 7.04−6.97), 1-Hα (10a-H); HRMS (ESI) m/z calcd for $C_{21}H_{22}N_3O_3$ ([M + H]$^+$) 364.1661, found 364.1677 (+4.4 ppm).

Dehydration of 5a-Hydroxyl Compound (25) to 5a-Alkene. To **25** (5.2 mg) in CH_2Cl_2 (2 mL) were added $MeSO_2$-Cl (0.10 mL) and Et$_3$N (0.15 mL). The reaction mixture was stirred at room temperature for 7 h. After addition of aqueous Na_2CO_3 and workup, the residue was purified by preparative TLC (5% MeOH/CH_2Cl_2) to give **27** (1.4 mg, 23%) and a mixture (1:1, by ^{1}H NMR) of **26** and **28** (2.6 mg, 46%). For **27**: IR (film) 1743, 1674, 1645, 1606 cm^{-1}; ^{1}H NMR δ 7.75 (d, 1H, J = 8.2), 7.34 (td, 1H, J = 7.9, 1.3), 7.17 (dt, 1H, J = 7.6, 0.9), 7.06 (dd, 1H, J = 7.7, 1.1), 6.23 (t, 1H, J = 3.0), 5.11 (dd, 1H, J = 11.0, 6.7), 5.02 (dt, 1H, J = 9.0, 1.3), 4.96 (d, 1H, J = 9.1), 4.16 (td, 1H, J = 11.4, 5.3), 3.93 (td, 1H, J = 11.5, 9.0), 3.42 (s, 3H), 2.92−2.80 (m, 2H), 2.66 (dd, 1H, J = 13.3, 6.6), 2.53 (dd, 1H, J = 13.3, 11.1), 1.58 (s, 3H), 1.20 (d, 3H, J = 1.0); MS (ESI) m/z 442.2 ([M + H]$^+$).

(2*S*,3*S*,5a*S*)-5a,6,7,8-Tetrahydro-3-(2-methyl-1-propenyl)-spiro[5*H*,10*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-2(3*H*),3′-[3*H*]indole]-2′,5,10(1′*H*)-trione (Spirotryprostatin B, 3). Protection of 24 with (Boc)$_2$O. Compound **24** (5.5 mg, 0.014 mmol) in CH_2Cl_2 (1 mL) was reacted with (Boc)$_2$O (16.4 mg, 0.075 mmol) and DMAP (7.6 mg, 0.062 mmol). The solution was stirred at room temperature for 5 h, followed by addition of 5% MeOH/CH_2Cl_2 (ca. 20 mL) and evaporation to dryness. The residue was purified by preparative TLC (MeOH/CH_2Cl_2/AcOEt/hexanes = 2.5:47.5:25:25) to give a much less polar major fraction and a minor fraction. The ^{1}H NMR showed the two fractions to be the same, and analytical TLC also showed they had the same R_f value. It is assumed that the major product was the unstable *O*,*N*-bis-Boc-derivative of **24**, which decomposes to **29** on exposure to silica: ^{1}H NMR δ 7.79 (d, 1H, J = 8.2), 7.33 (td, 1H, J = 7.9, 1.3), 7.14 (td, 1H, J = 7.6, 0.9), 7.03 (dd, 1H, J = 7.6, 0.8, 4′−H), 6.65 (br s, 1H, 10a-OH), 5.05 (d, 1H, J = 8.9, 3-H), 4.84 (dt, 1H, J = 8.9, 1.3, Me_2C=CH), 4.65 (dd, 1H, J = 9.2, 7.5, 5a−H), 3.63−3.59 (m, 2H), 3.09 (d, 1H, J = 15.0, 1-Hβ), 2.53 (d, 1H, J = 15.0, 1-Hα), 2.35−2.33 (m, 1H), 2.13−1.95 (m, 3H), 1.67 (s, 9H), 1.56 (s, 3H), 1.02 (d, 3H, J = 0.8); NOE data 10a-OH (3-H, 5a-H, 1-Hα), δ 4.84 (4′-H, δ 1.56), 5a-H (10a-OH, δ 2.35−2.33); MS (ESI) m/z calcd for $C_{26}H_{31}N_3O_6Na$ ([M + Na]$^+$) 504.21, found 504.22.

Elimination of 10a-Hydroxyl Group of 29. The above **29** in CH_2Cl_2 (2 mL) was reacted with Et$_3$N (0.202 g, 1.99 mmol) and $MeSO_2Cl$ (0.064 g, 0.56 mmol). The solution was stirred at room temperature for 15 h, diluted with 5% MeOH/CH_2Cl_2, and concentrated. The residue was purified by preparative TLC (MeOH/CH_2Cl_2/AcOEt/hexanes = 2.5:47.5:25:25) to afford **30** (4.7 mg, 70% overall): ^{1}H NMR δ 7.85 (d, 1H, J = 8.2), 7.33 (dt, 1H, J = 7.6, 1.9), 7.14−7.08 (m, 2H), 5.77 (s, 1H), 5.41 (d, 1H, J = 9.0), 5.18 (dt, 1H, J = 9.0, 1.3), 4.34 (dd, 1H, J = 10.5, 6.0), 3.83 (m, 1H), 3.58 (m, 1H), 2.48 (m, 1H), 2.11 (m, 1H), 2.01−1.94 (m, 2H), 1.64 (s, 9H), 1.56 (s, 3H), 1.24 (s, 3H); HMQC data for nonquaternary carbons: δ 129.5, 127.7, 123.9, 120.4 (Me_2C=CH), 116.3 (Trp-CH=), 115.0, 65.5, 61.8, 44.9, 29.0, 28.2 (($CH_3)_3CO$), 25.6 (Me), 22.6, 18.4 (Me); MS (ESI) m/z 486.0 ([M + Na]$^+$), 464.3 ([M + H]$^+$), 364.1 [M + H − Boc].

Synthesis of 3. To compound **30** (4.5 mg, 0.0097 mmol) in CH_2Cl_2 (0.2 mL) was added Et$_3$SiH (0.05 mL), followed by TFA (0.3 mL). After being stirred at room temperature for 15 min, the solution was diluted with CH_2Cl_2 and evaporated to dryness. The residue was purified by preparative TLC (5% MeOH/CH_2Cl_2) to give **3** (2.6 mg, 74%) as a pale yellow solid: $[\alpha]^{33}_D$ = −144 (*c* 0.035, $CHCl_3$) [lit.[3c] $[\alpha]^{22}_D$ = −162.1 (*c* 0.92, $CHCl_3$)]; IR (film) 3274, 1717, 1684, 1675, 1636 cm^{-1}; ^{1}H NMR δ 7.54 (br s, 1H), 7.24 (dt, 1H, J = 7.6, 1.3), 7.07 (d, 1H, J = 6.9), 7.00 (t, 1H, J = 7.1), 6.85 (d, 1H, J = 7.8), 5.78 (s, 1H), 5.43 (d, 1H, J = 8.9), 5.21 (dt like, 1H, J = 8.9, 1.3), 4.34 (dd, 1H, J = 10.4, 6.1), 3.85 (dt, 1H, J = 12.2, 8.1), 3.57 (ddd, 1H,

J = 12.4, 9.4, 2.9), 2.48 (m, 1H), 2.12 (m, 1H), 2.05−1.94 (m, 2H), 1.57 (s, 3H), 1.28 (d, 3H, J = 1.1); ^{13}C NMR δ 177.8, 162.6, 155.1, 140.3, 138.33, 138.29, 129.1, 127.9, 127.3, 122.3, 120.5, 116.2, 109.7, 64.2, 61.7 (s), 61.6, 44.8, 29.3, 25.3, 22.1, 18.3; the NMR spectra (^{1}H, ^{13}C, DEPT, COSY, HMQC, and HMBC) of synthetic **3** is identical to that both reported and provided by Osada; HRMS (ESI) m/z calcd for $C_{21}H_{22}N_3O_3$ ($[M + H]^+$) 364.1661, found 364.1653 (−2.2 ppm).

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Supporting Information Available: ^{1}H NMR spectra for **6**, **10**−**11**, **17**, **20a**,**b**, **21**−**27**, and **29** and ^{13}C NMR spectra for **6**, **7**, **12**−**15**, **17**−**19**, **21**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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