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A Concise Synthesis of Spirotryprostatin A

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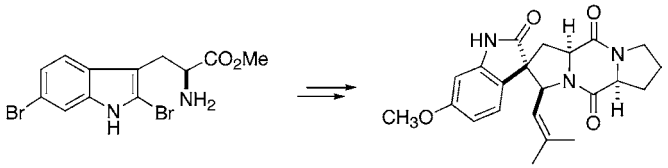
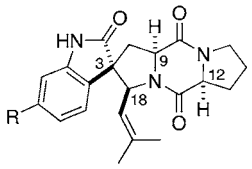
ABSTRACT



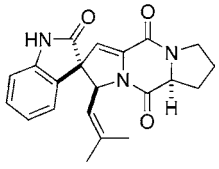
spirotryprostatin A (**1**)

The preparation of two new synthons, 2,5- and 2,6-dibromotryptophan esters, and their use in diastereoselective intramolecular *N*-acyliminium ion spirocyclization methodology for the rapid construction of spirotryprostatin A and analogues are described.

The discovery[1] of mammalian cell cycle inhibitors spirotryprostatin A (**1**) and spirotryprostatin B (**2**) has spawned numerous investigations into their synthesis. These novel prenylated pentacyclic structures are undoubtedly derived from the amino acids L-tryptophan and L-proline, yet their biosynthesis awaits experimental verification.[2]



spirotryprostatin A (**1**) R = OMe
demethoxyspirotryprostatin A (**3**) R = H



spirotryprostatin B (**2**)

To date, there exists seven reported total syntheses[3−9] of **2** and only two of **1**.[10,11] Although both routes to spirotryprostatin A utilize methoxylated indole-based starting materials, they are distinctly different. The approach by Danishefsky and co-workers[10] is fashioned around 6-methoxytryptophan and incorporates a "classical" oxidative β-carboline-spirooxindole rearrangement sequence as a means to construct the quaternary spirooxindole motif. The other approach by Williams[11] begins with commercially available 6-methoxyisatin and incorporates chiral, nonracemic oxazinone template chemistry and the use of a diastereoselective azomethine ylide dipolar cycloaddition. Recently, we reported a short synthesis of spirotryprostatin B (**2**) from 2-chlorotryptophan methyl ester via demethoxyspirotryprostatin A (**3**).[9] The underlying chemistry utilized recently developed iminium ion spirocyclization methodology. In this communication, we describe a rapid synthesis of spirot-

(1) (a) Cui, C.-B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832−835. (b) Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, 12651−12666.

(2) Numerous naturally occurring prenylated alkaloids derived from proline and tryptophan are known. For a review, see: Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. In *Topics in Current Chemistry*; Leeper, F., Vederas, J. C., Eds.; Springer-Verlag: Berlin, Germany, 2000; Vol. 209, Biosynthesis-Terpenes and Alkaloids, pp 97−173.

(3) (a) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666−5667. (b) Sebahar, P. R.; Osada, H.; Usui, T.; Williams, R. M. *Tetrahedron* **2002**, *58*, 6311−6322.

(4) von Nussbaum, F.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2175−2178.

(5) Wang, H.; Ganesan, A., *J. Org. Chem.* **2000**, *65*, 4685−4693.

(6) Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596−4599.

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(8) (a) Meyers, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 694−696. (b) For a review, see: Marti, C.; Carreira, E. M. *Eur. J. Chem.* **2003**, 2209−2219.

(9) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5357−5360.

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(11) Williams, R. M.; Onishi, T.; Sebahar, P. R. *Org. Lett.* **2003**, *5*, 3135−3137

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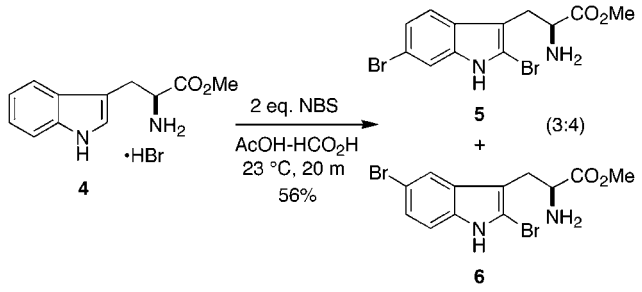
ryprostatin A (**1**) and related pentacyclic analogues **8**−**12** from newly synthesized 2,6- and 2,5-dibromotryptophan methyl esters (**5**) and (**6**) as convenient synthons for the construction of 6- and 5-methoxytryptophan-based spiro-[pyrrolidine-3,3′-oxindoles], respectively.

In previous work from our labs, we have shown that tryptamine and/or tryptophan derivatives substituted with halogen at the 2-position undergo stereocontrolled spiro-annulation reactions to afford spiro[pyrrolidine-3,3′-oxindole] ring systems.[9,12] A key feature of this chemistry is the direct incorporation of halogen at the 2-position of unprotected tryptophan ester (or tryptamine). This allowed for intramolecular iminium ion cyclizations to occur at the 3-position of the indole ring. In the present case, implementation of this methodology for the synthesis of spirotryprostatin A (**1**) begins with the dibromination of tryptophan methyl ester (**4**). Exposure of **4**·HBr with 2 equiv of NBS produced isomeric indole dibromides 2,6- and 2,5-dibromotryptophan methyl esters (**5**) and (**6**) in 56% yield as a 3:4 mixture of regioisomers, respectively (Scheme 1). NOE data obtained

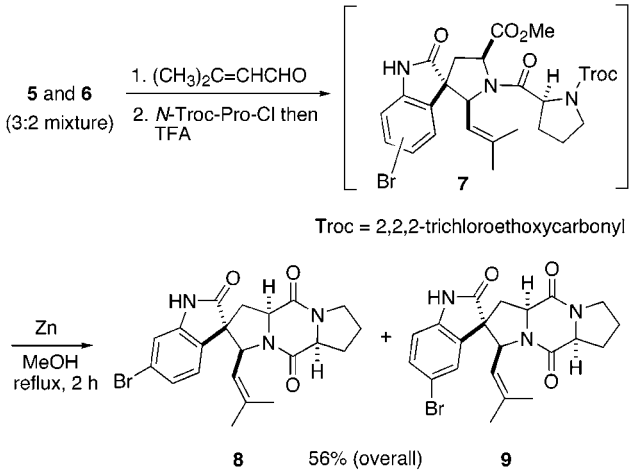
Scheme 1



with pure materials established the positions of the bromine incorporation. Because bulk separation of **5** and **6** proved to be difficult by flash chromatography, a mixture of **5** and **6** was used in the next step. Thus, condensation of a 3:2 mixture **5** and **6**, respectively, with prenyl aldehyde afforded the corresponding imines, which were not isolated. Activation of the imine functionality to the *N*-acyliminium species with *N*-Troc prolinyl chloride[13] facilitated spirocyclization. Hydrolysis of the resulting chloroindolenine intermediate yielded oxindole **7** mainly as a mixture of bromo-substituted regioisomers, which also were not isolated (Scheme 2). Zn-facilitated removal of the Troc group induced diketopiperazine formation to give 6-bromodemethoxyspirotryptrostatin A (**8**) (26%) and 5-bromodemethoxyspirotryprostatin A (**9**) (30%) after purification by flash chromatography.[14] The relative stereochemistries of **8** and **9** were determined from NOE experiments and by comparison of their ^{1}H and ^{13}C NMR spectra with related compounds.

Noteworthy is the fact that the entire pentacyclic core of spirotryprostatins has been assembled in a stereocontrolled

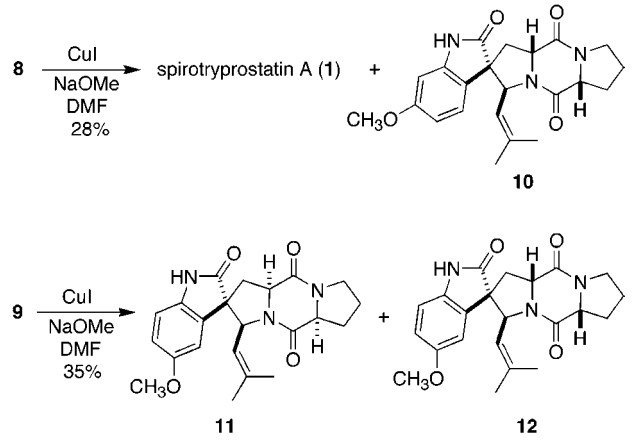
Scheme 2



fashion in a single pot from 2-bromotryptophan esters. Of the four possible stereoisomeric configurations that could have arisen from the spirocyclization of 2,6- and 2,5-dibromotryptophan methyl esters (**5**) and (**6**), only one major diastereomeric configuration predominates corresponding to desired regioisomers **8** and **9**. High levels of stereocontrol at C3 and C18 favor a *cis* orientation of the prenyl side chain and benzene ring using these bromotryptophan derivatives. The level of stereocontrol is appreciably higher than what was previously observed with 2-chlorotryptophan esters.[9]

All that remained for completion of the synthesis was introduction of the 6-methoxy substituent (Scheme 3). This

Scheme 3



was accomplished under Cu-catalyzed methoxylation conditions in which treatment of bromide **8** with NaOMe, CuI, and DMF[12,15] produced spirotryprostatin A (**1**) (11%), $[\alpha]^{23}_{D}$ −94.3 (lit.[1] $[\alpha]^{26}_{D}$ −34.0 and lit.[10] $[\alpha]^{21.4}_{D}$ −116.2) and, predictably, 9,12-bis-epispirotryprostatin A (**10**) (17%) under

(12) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2004**, *6*, 711−713.

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(14) A small amount (<4%) of the C3 epimer (**8a**) of **8** was also obtained.

(15) Miyake, Y.; Kikugawa, Y. *J. Heterocycl. Chem.* **1983**, *20*, 349−352.

these basic conditions. Similarly, the 5-bromo analogue, **9**, produced 5-methoxydemethoxyspirotryprostatin A (**11**) (14%) and 9,12-bis-epi-5-methoxydemethoxyspirotryprostatin A (**12**) (21%). Epimerization of **10** to **1** and **12** to **11** could be accomplished by heating (MeOH/DMF, 120 °C, 6 h) in the presence of NaOMe, which afforded a 2:3 ratio of the corresponding diastereomeric pairs in good yields. Comparison of ^{1}H and ^{13}C NMR spectra of synthetic **1** with data reported by Osada for the natural product produced a satisfactory match.[16] Despite the shortcomings of the methoxylation step,[17] the utility of 2-bromotryptophans is demonstrated in what amounts to be the shortest route to spirotryprostatin A and its pentacyclic derivatives to date.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for compounds **1**, **5**, **6**, and **8**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Despite previous reports on the synthesis of **1**, we note a difference in NMR chemical shift assignments for H22 and C3 of synthetic **1** compared to natural **1** as originally reported by Osada.[1] We found that in $CDCl_3$ H22 resonates at δ 1.17 ppm (s, 3H) (reported as δ 1.26 ppm) and C3 resonates at δ 55.9 ppm (reported as δ 59.99 ppm). The C3 signal overlaps with the OMe signal (δ 55.9 ppm), which became apparent in comparing spectra in $CDCl_3$ and acetone-d_6.

(17) 6-Methoxy-2-bromotryptophan ethyl ester is available by the method of Cook and may serve as an important intermediate for the synthesis of spirotryprostatin A using the present *N*-acyliminium ion spirocyclization methodology. Gan, T.; Liu, R.; Yu, P.; Cook, J. M. *J. Org. Chem.* **1997**, *62*, 9298−9304.