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# Concise, Asymmetric Total Synthesis of Spirotryprostatin A

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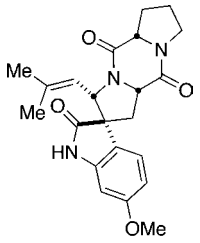
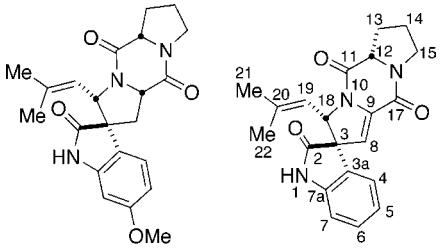
## ABSTRACT



**1**, spirotryprostatin A

**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.**

The spirotryprostatins,[1] tryprostatins,[2] and cyclotryprostatins[3] represent a promising class of antimitotic arrest agents. Isolated in 1996, from *Aspergillus fumigatus*, spirotryprostatin A (**1**, Figure 1) and spirotryprostatin B (**2**) were shown



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

**Figure 1.** Structures of spirotryprostatins A and B.

to completely inhibit the progression of cells at concentrations greater than 253 and 34.4 $\mu$M, respectively.[1] The spirotryprostatins are characterized by a unique *spiro*-oxindole-substituted *cis*-prolyl-tryptophanyl-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. Although total syntheses of spirotryprostatin B (**2**) have been reported by several groups, including us,[4,5] only one total synthesis using the classical halohydrin to oxindole spiro-

(1) (a) Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832. (b) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *51*, 12651. (c) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1997**, *53*, 59.

(2) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1997**, *53*, 59.

(3) (a) Cui, C. B.; Kakeya, H.; Okada, G.; Ubukata, M.; Takahashi, I.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48*, 1382. (b) Cui, C. B.; Kakeya, H.; Okada, G.; Onose, R.; Osada, H. *J. Antibiot.* **1996**, *49*, 527. (c) Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 534.

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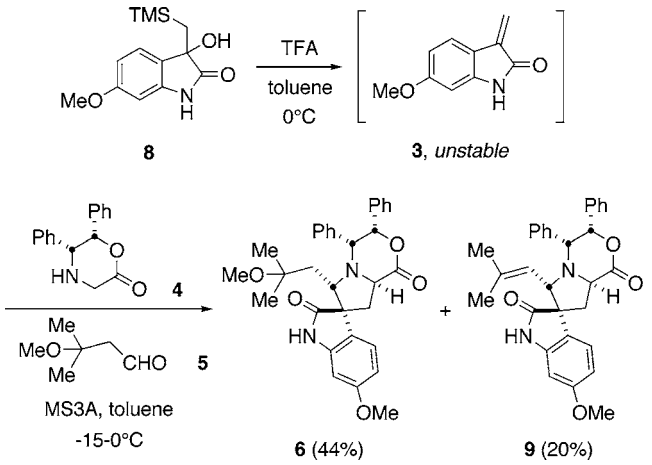
ring-forming contraction sequence has been reported for spirotryprostatin A so far by Danishefsky.[6] We previously described the total synthesis of spirotryprostatin B (**2**) using a stereochemically distinct three-component asymmetric [1,3]-dipolar cycloaddition.[4] Herein, we report a concise asymmetric total synthesis of spirotryprostatin A (**1**).

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 similar to that employed in our spirotryprostatin B synthesis.[4] Spirotryprostatin A (**1**) differs from spirotryprostatin B (**2**) in that it is saturated at C-8 and C-9 and 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. Since it is not necessary to install a carboalkoxy group to address the spirotryprostatin A structure, our strategy revolved around formation of 6-methoxy-3-methylene-1,3-dihydro-indol-2-one (**3**, Scheme 1). If the synthesis of this dipolarophile could be accomplished, [1,3]-dipolar cycloaddition with **4** and **5** would generate a cycloadduct **6** that would have the correct configuration at the adjacent C-3 quaternary and C-18 stereogenic centers. However, on the basis of 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 **7** (Scheme 2). This was anticipated to be a nontrivial operation since, as our spirotryprostatin B synthesis had shown, the thermodynamic instability of *trans*-diketopiperazines in this structural family resulted in the facile epimerization of the prolyl stereogenic center.[4] We report here a successful realization of this strategy.

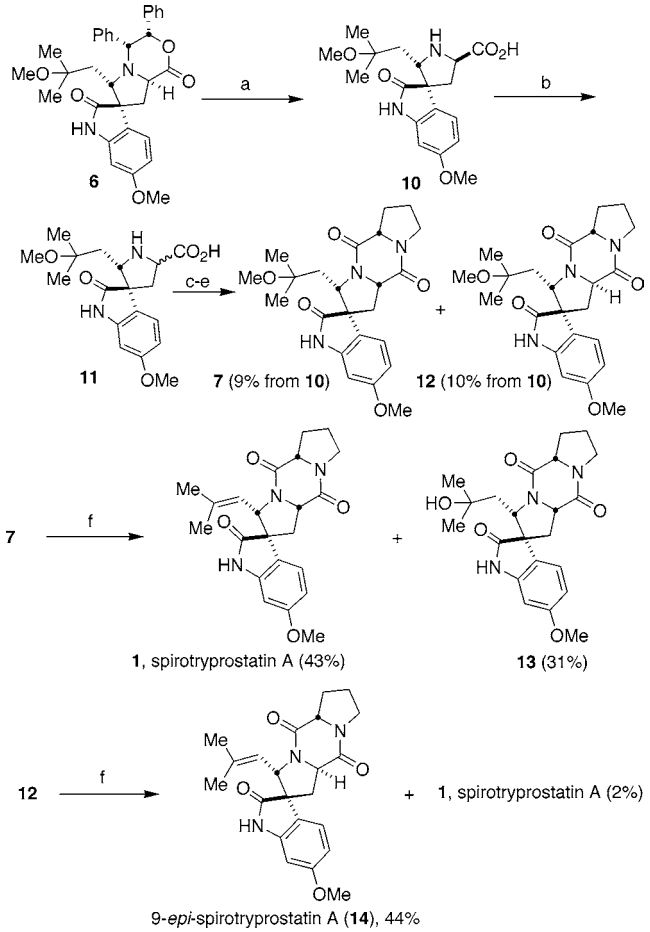
**Scheme 1.** Azomethine Ylide Dipolar Cycloaddition




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.[7] However, the dipolarophile was generated by flash vacuum pyrolysis and did not seem compatible with the synthesis of the methoxy-substituted derivative we required. After extensive exploration, we found that the Peterson olefination,[8] which has proven to be an efficient method for the generation of terminal olefins, afforded a suitable method for the formation of **3**.

As shown in Scheme 1, addition of trimethylsilyl methyllithium to 6-methoxy-isatin[9] afforded tertiary alcohol **8** in 80% yield. The olefin **3** could be prepared *in situ* by the treatment of **8** with trifluoroacetic acid at 0 °C. Compound **3** proved to be an unstable species that was not isolable due to polymer formation upon concentration. Thus, after neu-

**Scheme 2.** Synthesis of Spirotryprostatin A[a]




[a] Reaction conditions: (a) $H_2$, $Pd(OH)_2$, THF−MeOH (quant.); (b) $^n$PrCHO, AcOH, 65 °C; (c) L-Pro-OBn HCl, BOP, $Et_3N$, MeCN; (d) $H_2$, Pd/C, EtOH−MeOH; (e) WSC, $Et_3N$, MeCN; (f) *p*-TsOH $H_2O$, 3 Å sieves, toluene, 110 °C. Abbreviations: BOP = benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate; WSC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (also known as EDCI).

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

(7) Bell, S. E. V.; Brown, R. F. C.; Eastwood, F. W.; Horvath, J. M. *Aust. J. Chem.* **2000**, *53*, 183.

(8) (a) Chan, T.-H.; Chang, E.; Vinokur, E. *Tetrahedron Lett.* **1970**, *11*, 1137. (b) Hudrlik, P. F.; Peterson, D. *Tetrahedron Lett.* **1972**, *13*, 1785.

(9) Giovannini, E.; Portmann, P. *Helv. Chim. Acta* **1948**, *31*, 1381.

tralization with triethylamine, the reaction mixture was washed with water by phase separation and crude **3** was directly used for the cycloaddition. In the event, addition of **4** and **5** to the resultant crude mixture of **3** resulted in rapid [1,3]-dipolar cycloaddition yielding a mixture of cycloadducts (**6** and **9**). We were unable to detect the generation of alternate regio- or diastereoisomers. In initial attempts performed at room temperature, the ratio of products unfortunately heavily favored the methanol elimination product **9**. Although a strategy utilizing **9** as a potential intermediate was explored, the olefin and oxindole functionalities were incompatible with the conditions required to remove the chiral auxiliary.

$^1$H NMR studies were then conducted to decipher at what stage 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-butenal. 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 reaction was then performed at 0 °C. Under these conditions, the desired cycloadduct (**6**) was obtained in 44% yield as a major product along with 20% of **9**.

The regiochemistry of **6** 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.[10] As anticipated, these data indicated that the cycloadduct possesses the correct relative configuration at C-3 and C-18 but possesses the incorrect relative stereochemistry at position C-9 (spirotryprostatin numbering).

Amino acid **10** was cleanly produced from catalytic hydrogenation of **6** using $Pd(OH)_2$ as a catalyst in quantitative yield (Scheme 2). At this juncture, we investigated the epimerization of the α-proton of **10** in the presence of an aldehyde and acid.[11] Butyraldehyde (0.5 equiv) and **10** were dissolved in $CD_3COOD$, and the mixture was heated to 65 °C. 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.[12] When acetic acid was substituted for $CD_3COOD$, **10** was epimerized to give an inseparable diastereomeric mixture of amino acids (**11**). Separation by PTLC was possible only after conversion to the pentacyclic substances **12** and **7** by the following three-step sequence.[4] First, **10** was directly coupled with L-proline benzyl ester in the presence of BOP to give a diastereomeric mixture of dipeptides that was used for the next reaction without additional purification. Reduction of the benzyl ester followed by WSC-mediated cyclization afforded the *cis*-fused product **7** (9% from **10**), which has the natural relative and absolute configuration for the synthesis of spirotryprostatin A, plus the *trans*-fused substance (**12**, 10% from **10**), which was converted into 9-*epi*-spirotryprostatin A. Finally, **7** was subjected to treatment with TsOH in refluxing toluene to give spirotryprostatin A (**1**) in 43% yield along with tertiary alcohol **13** (31%). The spectroscopic data for the synthetic material were in excellent agreement with that of the natural product kindly provided to us by Dr. Hiroyuki Osada. 9-*epi*-Spirotryprostatin A (**14**) was also prepared by subjecting **12** to the same conditions. The relative configuration of **14** was confirmed by NOESY to be a *trans*-fused diketopiperazine.[13] Curiously, only a trace amount (2%) of the cis-fused substance (spirotryprostatin A, **1**) was generated from **12**. It is well-known that *cis*-diketopiperazines are thermodynamically more stable than the corresponding *trans* isomers for cyclic anhydrides of proline.[14]

In summary, a concise asymmetric total synthesis of spirotryprostatin A utilizing the asymmetric [1,3]-dipolar cycloaddition reaction of methylene indolinone **3** has been achieved. The synthesis recorded herein requires only 12 steps (7 steps in the longest linear sequence) from commercially available reagents.[4,9] Future efforts in this area, directed at the preparation and biological evaluation of synthetic analogues of the spirotryprostatins, are currently underway and will be reported in due course.

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**Supporting Information Available:** Spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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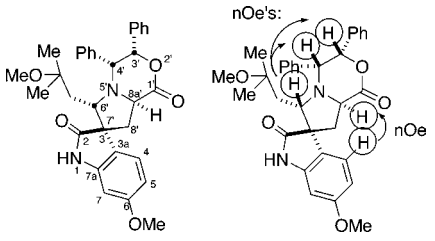
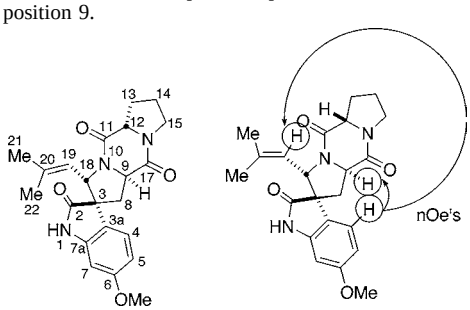
(10) NOEs were observed between the proton at position 4 of the oxindole and the proton at 8′a, between the proton at 6′ and the proton at 3′, and between the proton at 6′ and the proton at 4′.




(11) Yamada, S.; Hongo, C.; Chibata, I. *Agric. Biol. Chem.* **1977**, *41*, 2413.

(12) After conversion into the corresponding methyl ester by the treatment with $TMSCHN_2$, these diastereomers could be isolated by PTLC.

(13) A NOE was observed between the proton at position 4 of the oxindole and the olefinic proton of the 2-methyl-1-propenyl group. A NOE was also observed between the proton at position 4 of the oxindole and the proton at position 9.

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