The Asymmetric Total Synthesis of (+)- and (−)-Spirotryprostatin B

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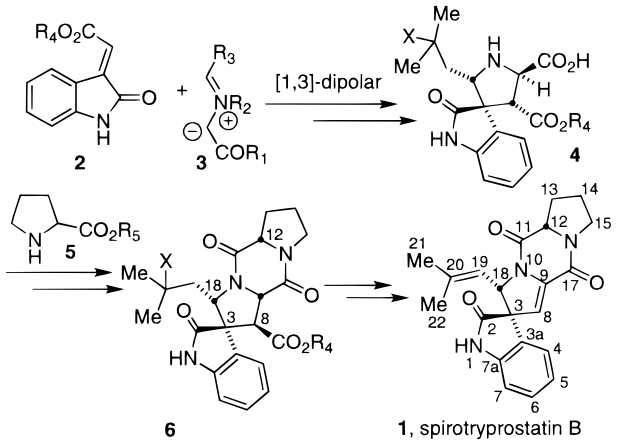
The spirotryprostatins,[1] tryprostatins,[2] and cyclotryprostatins[3] represent a promising class of antimitotic arrest agents. Isolated from the fermentation broth of *Aspergillus fumigatus*, spirotryprostatin B has been shown to completely inhibit the G2/M progression of mammalian tsFT210 cells at concentrations over 12.5 μg/mL. While the cyclotryprostatins and tryprostatins have been shown to act by affecting microtubule assembly,[4] much less is known about the spirotryprostatins due to the limited availability of these compounds. Fermentation of 400 L of culture medium yielded 1 mg of spirotryprostatin A and 11 mg of spirotryprostatin B (**1**), respectively.

Although numerous naturally occurring prenylated alkaloids derived from proline and tryptophan are known,[5] the unique spirooxindole ring system distinguishes the spirotryprostatins. This unique structural array along with the limited quantities and the interesting biological activity render the spirotryprostatins attractive synthetic targets. Recently, the total synthesis of spirotryprostatin A was completed using the classical halohydrin to oxindole spiro-ring-forming contraction sequence.[6] We have directed our research interests toward the total synthesis of the more biologically active congener, spirotryprostatin B, using an entirely new strategy to access this type of amino acid substructure.

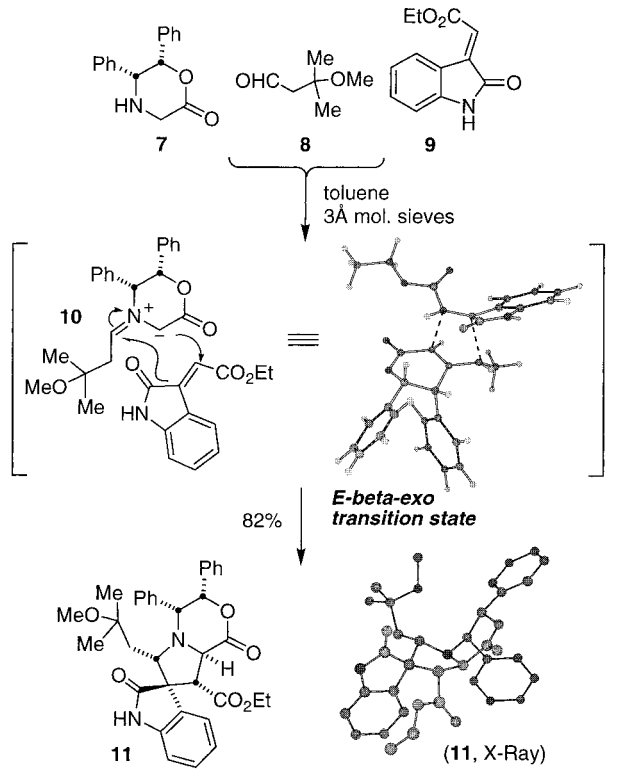
In contemplating the synthesis of spirotryprostatin B, it was envisioned that the core pyrrolidine ring could be formed through an asymmetric [1,3]-dipolar cycloaddition reaction, (Scheme 1).[7] Reaction of a chiral azomethine ylide of the type **3** with an oxindolylideneacetate **2** could set four contiguous stereogenic centers. Of these, the quaternary spirooxindolyl center at C3 and the adjacent C18 center would have to be controlled in a relative and absolute sense culminating in amino acid **4**. Standard peptide coupling protocol with protected proline **5** followed by cyclization would generate the diketopiperazine **6**. Completion of the synthesis mandates unmasking of the prenyl side-chain followed by oxidative decarboxylation. We record here the successful execution of this strategy.

We have previously reported that the addition of an aldehyde to 5,6-diphenylmorpholin-2-one (**7**) generates a mixture of the corresponding *E*- and *Z*-azomethine ylides with a preference for the *E*-ylide in the cases of sterically demanding aldehydes.[8] Dipolar cycloadditions of ylides generated from this system proceed with a high degree of endo selectivity to give substituted pyrrolidines. On the basis of this premise that a bulky isoprene aldehyde progenitor would favor the *E*-ylide geometry, the relative stereochemistry at the isoprene-bearing carbon (C18) of spirotryprostatin seemed attainable. However, it was more difficult to predict the regio- and stereochemical course at the C3 and consequently the C8 positions. Previous reports with azomethine ylides and oxindolylideneacetate dipolarophiles related to **2** suggested that the undesired regiochemistry may result from this type of cycloaddition.[9] The reaction of oxazinone[8] **7** with aldehyde **8**[10] and oxindole **9**[11] in toluene at room temperature in the presence of 3 Å mol sieves, however, afforded cycloadduct **11** in 82% yield.

Scheme 1



Scheme 2



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(7) For a recent review, see: Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909.

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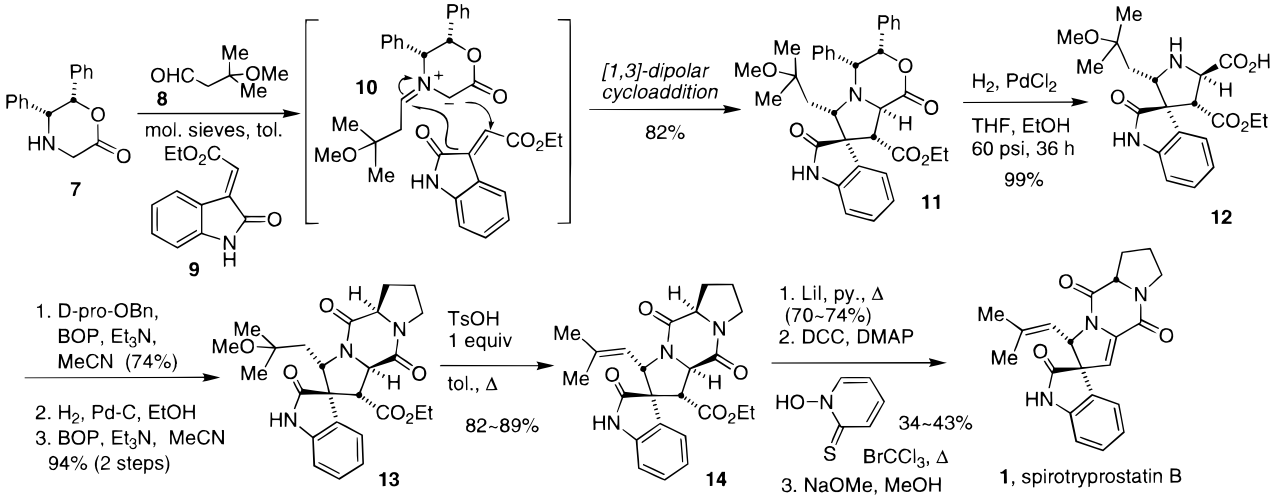
Scheme 3



The relative and absolute stereochemistry of this substance was firmly secured through single-crystal X-ray analysis (see Supporting Information). The dipolar cycloaddition reaction of azomethine ylide **10** therefore must proceed via the *E*-*β*-*exo* transition state (shown in Scheme 2).[12] This reaction, which sets four contiguous stereogenic centers, constructs the entire prenylated tryptophyl moiety of spirotryprostatin B in a single, simple operation.

With this key intermediate in hand, the synthesis of spirotryprostatin B required coupling of the spriooxindole amino acid with proline, and installation of the two olefinic units (Scheme 3). Thus, reductive cleavage of bibenzyl from oxazinone **11** proceeded in essentially quantitative yield affording the amino acid **12**. Coupling with D-proline benzyl ester (BOP reagent, MeCN, triethylamine, 74%) furnished the requisite dipeptide.[13] It is interesting to note that the steric bulk of the environment around the amino group of **12** obviated the need for a protecting group during the peptide coupling procedure and the free amino acid **12** was directly and effectively used in the reaction. Deprotection of the benzyl ester under standard conditions followed by BOP-mediated cyclization generated the diketopiperazine **13** in 94% yield over 2 steps.

Several strategies were examined for the installation of the two olefinic units that had to be judiciously sequenced with the planned oxidative decarboxylation. Ultimately, it was found that installation of the isoprenyl unsaturation could be accomplished by subjecting **13** to dehydrating conditions in the presence of TsOH in refluxing toluene yielding **14** in 82−89% yield *without* the production of double bond isomers. It should be noted that hydrolysis of the ethyl ester of **14** under standard conditions (LiOH in THF/MeOH/H_2O) failed to give any of the desired product. We found that the use of LiI in refluxing pyridine produced the desired carboxylic acid in 74% yield.[14] The final oxidative decarboxylation proved problematic under a range of Kochi-type conditions ($Pb(OAc)_4$[15] or iodosobenzene diacetate[16]). After extensive experimentation, we found that a modified Hunsdiecker reaction using conditions developed by Barton et al.[17] gave 12-*epi*-spirotryprostatin B in 34−43% yield. This substance was then epimerized with NaOMe in MeOH to give a 2:1 ratio of **1** to 12-*epi*-spirotryprostatin B that were easily separable by silica gel chromatography. The synthetic (−)-spirotryprostatin B (**1**) spectra were identical with the ^{1}H NMR,^{13}C NMR, IR, and HR-EI-MS spectra of the natural product kindly provided by Dr. Hiroyuki Osada.[1] With use of the antipode of **7**, (+)-*ent*-spirotryprostatin B was prepared in like manner (see data in Supporting Information).

In summary, the application of a stereochemically distinct asymmetric 1,3 dipolar cycloaddition provides access to both antipodes of spirotryprostatin B in an efficient nine-step sequence. This approach appears well-suited to preparing the simpler congener spirotryprostatin A, and several analogues that may prove useful in defining the antimitotic properties of this class of unique spirooxindole alkaloids and studies toward those objectives are in progress in these laboratories.[18]

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Supporting Information Available: Complete spectroscopic data for all new compounds including details of the X-ray structure determination for compound **11** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Aldehyde **8** is obtained from inexpensive, commercially available 3-methoxy-3-methyl-1-butanol (Aldrich Chemical Co.) by Swern oxidation in 89% yield.

(11) The unsaturated oxindole **10** is readily prepared from isatin (Aldrich Chemical Co.) by condensation with $(Ph)_3PCHCO_2Et$ in refluxing diglyme in 84% yield.

(12) "*β*" refers to the approach of the dipolarophile from the top face as drawn in Scheme 2.

(13) The yield for the conversion of **12** to the L-proline isomer corresponding to **13** was 52% and this diminished yield appears to reflect the thermodynamic instability of forming the corresponding *trans*-diketopiperazine.

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(18) Since submission of our paper, we have learned that Profs. Overman and Danishefsky have also independently achieved the synthesis of spirotryprostatin B; we thank both Profs. Danishefsky and Overman for making us aware of their work prior to publication.