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Total Synthesis of Spirotryprostatin B via Asymmetric Nitroolefination

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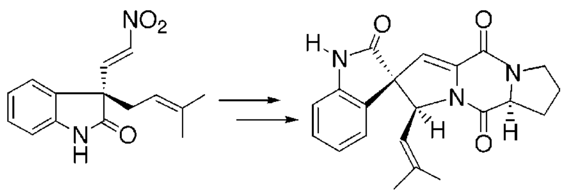
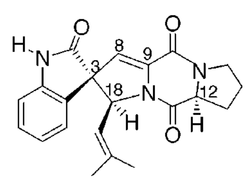
ABSTRACT



A total synthesis of spirotryprostatin B was accomplished via asymmetric nitroolefination as a key step.

The asymmetric construction of molecules with quaternary carbon stereocenters is a challenging and dynamic area,[1] and this is particularly true for the unabated isolation and structural elucidation of various complex natural products with these stereocenters. We have studied this subject[2] and have reported a protocol for creating quaternary asymmetric carbon centers via the asymmetric nitroolefination.[2a,b] This protocol has been applied[2c−h] to the synthesis of various natural products with quaternary stereocenters: for example, (−)-esermethole,[2f] (−)-pseudophrynaminol,[2e,f] (−)-horsifiline,[2g] etc. We report here the total synthesis of spirotryprostatin B (**1**), a potent antimitotic agent that was isolated from the fermentation broth of *Aspergillus fumigatus* and has been shown to inhibit progression of the mammalian cell cycle in the G2/M phase at micromolar concentrations.[3] The synthetically intriguing structural features of **1** are the C-3 quaternary stereocenter of the spirooxindole, the spiro-pyrrolidine with a diketopiperazine ring system and the endocyclic conjugated C(8)−C(9) double bond along with the pendent prenyl moiety. Recently, several successful approaches have been reported for the total synthesis of **1** using the oxidative rearrangement of β-carbolines,[4] 1,3-dipolar cycloaddition of azomethine ylides,[5] and Pd-catalyzed Heck insertion into a conjugated triene followed by an intramolecular nucleophilic attack by amido nitrogen to the resultant η^3-allyl-Pd intermediate.[6]



spirotryprostatin B (**1**)

Our strategy for the synthesis of **1** involves the enantio-selective installation of a C-3 quaternary stereocenter at the

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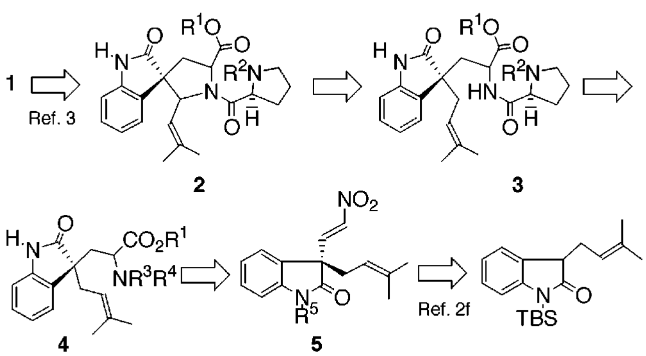
outset, using asymmetric nitroolefination of 3-prenyloxindole (Scheme 1). The nitroolefin **5** should act as a precursor to

Scheme 1. Retrosynthetic Strategy

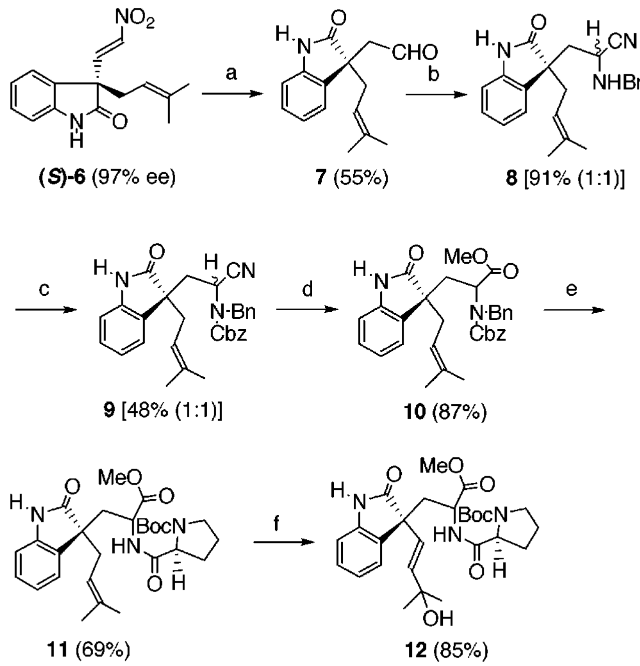


amino acid surrogate **4**, which on coupling with L-proline would lead to dipeptide **3** with all of the requisite functionality. Oxidation of the prenyl unit would provide a route to spiropyrrolidine ring closure to **2**. Incorporation of a conjugated double bond in the spiropyrrolidine unit according to methods described in the literature[4c] followed by removal of R_2 and cyclization should furnish the target molecule **1**.

Our synthesis began with the preparation of chiral oxindole with a quaternary carbon center, (*S*)-**6** (97% ee), according to our protocol for asymmetric nitroolefination (Scheme 2).[2e,f] Reduction of **6** with 20% aqueous titanium(III) chloride in the presence of excess ammonium acetate followed by in situ hydrolysis[7] afforded the aldehyde (*S*)-**7** in 55% yield. Strecker reaction of aldehyde **7** was performed[8] by treatment with benzylamine followed by trimethylsilyl cyanide to afford the cyano benzylamine **8** (91%) as a 1:1 diastereomeric mixture. Attempted hydrolysis of the cyano group of **8** without protecting the secondary amine resulted in a complicated reaction mixture. Hence, the cyano amine **8** was subjected to Cbz protection to yield **9** in 48% yield with 50% recovery of **8** (96% yield based on recovered **8**). Forcing the reaction to completion resulted in the introduction of a Cbz group at the oxindole nitrogen. Treatment of a methanolic solution of **9** with K_2CO_3 followed by acidification with dilute HCl resulted in the formation of methyl ester **10** in 87% yield (Scheme 2).[9]

Having incorporated the amino ester functionality, our next task was to introduce proline as a peptidic linkage. Thus, it was essential to remove the benzyl and Cbz groups in the presence of ester and a trisubstituted double bond. We found that palladium black (80 wt % of **10**) under hydrogen transfer conditions was suitable for this purpose. A short reaction time (20−30 min) is essential for the chemoselectivity of this reaction, since a longer reaction time results in reduction

Scheme 2[a]



[a] (a) $TiCl_3$ (20% aqueous, 5.0 equiv), NH_4OAc (5.0 equiv), MeOH:H_2O (4:1), rt, 3 h; (b) i. $BnNH_2$ (1.0 equiv), DCM, rt, 3 h; ii. TMSCN (1.05 equiv), rt, 3 h; (c) CbzCl (1.2 equiv), Et_3N (2.4 equiv), DCM, rt, 12 h; (d) i. K_2CO_3, MeOH, rt, 6 h; ii. aqueous 1 M HCl, rt, 0.5 h; (e) i. Pd black (80 wt %), 5% HCO_2H in MeOH, 20 min; ii. *N*-Boc-L-prolide (1.1 equiv), WSC (1.2 equiv), DMC, 12 h; (f) i. *m*-CPBA (1.1 equiv), DCM, 0 °C, 6 h; ii. PhSeSePh (0.6 equiv), $NaBH_4$ (1.2 equiv), MeOH, reflux, 10 h; iii. 30% H_2O_2 (20 equiv), THF, 0 °C, 6 h.

of the double bond. The crude free α-aminoester was subjected to peptide coupling with *N*-Boc-L-proline using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (WSC) to give dipeptide **11** in 69% overall yield. For the spiropyrrolidine ring closure, it was essential to activate or functionalize the allylic methylene moiety. It has been reported[10] that allylic alcohols with tethered nitrogenous nucleophiles undergo ring closure upon treatment with a catalytic amount of acid via an intramolecular nucleophilic attack of nitrogen at an allylic carbocation. Hence, the prenyl moiety in **11** was transformed to an allylic alcohol as in **12** in 85% yield, according to a protocol reported by Sharpless and Lauer.[11]

Treatment of **12** with 10 mol % of *p*-toluenesulfonic acid in acetonitrile under reflux for 15 min gave the key spirocyclic intermediates as a 1:1 mixture of two diastereomers **13** and **14** in 47% yield with 50% recovery of **12** (94% yield based on recovered **12**) (Scheme 3). A longer reaction time to achieve complete transformation resulted in significant

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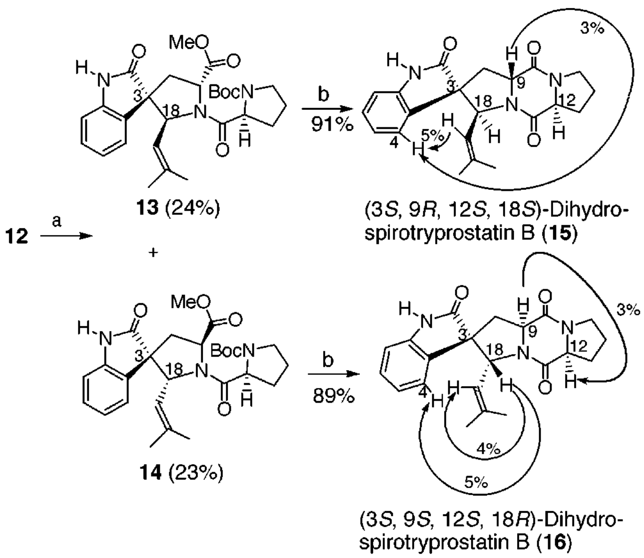
Scheme 3[a]

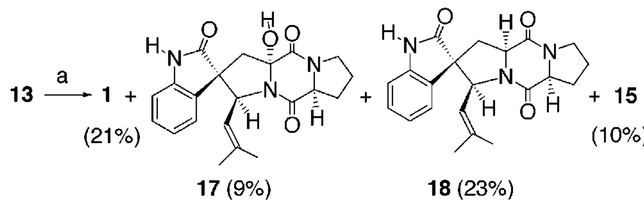


[a] (a) p-TSA (10 mol %), CH_3CN, reflux, 25 min; (b) i. 4 M HCl in dioxan, 0 °C, 30 min; ii. Et_3N, DCM, rt, 4−6 h. Arrows in **15** and **16** denote the observed NOEs.

deprotection of the Boc moiety, and hence the reaction was stopped at 50% conversion. Stereochemical assignment of **13** and **14** was unsuccessful because of the broadening of NMR peaks due to amide *E*/*Z* isomerization. Thus, the stereochemistry of **13** and **14** was determined through their transformation to diketopiperazine derivatives **15** (91%) and **16** (89%), respectively. The configurations at C(9) and C(18) were assigned using $^1H-^1H$ NOESY, and NOE experiments based on the known (*S*)-configuration at both the C(3) and C(12) stereocenters. Thus, diastereomer **13** was found to have the desired *S* configuration at C(18) in its transformation to **1**.

The final transformations required for the synthesis of **1** are the introduction of a double bond in conjugation to the ester in **13** and cyclization of the diketopiperazine ring. During our progress toward the synthesis of **1**, Nussbaum and Danishefsky reported[4c] a total synthesis of **1** via a mixture of four diastereomers at the C(3) and C(18) stereocenters of **14**. Thus, the synthesis of diastereomerically pure **13** with the desired configuration at C(18) and C(3) itself represents a formal total synthesis of **1**. To make sure that this particular diastereomer leads to **1**, it was subjected to the reported protocol for the introduction of a double bond. This procedure led to an inseparable mixture of multiple products and hence the crude mixture was subjected to diketopiperazine ring formation by deprotection of the Boc group with 4 M HCl solution in dioxan followed by cyclization with triethylamine. Isolation and purification revealed the presence of the desired natural product **1** (21%) along with two diastereomeric dihydrospirotryprostatin B analogues, **15** (10%) and **18** (23%),[4b,d] and the unexpected hemiaminal **17** (9%), which has also been shown to be a key precursor to **1** by Ganesan and Wang.[4d] The spectral characteristics of **1**, **17**, and **18** are identical to those reported in the literature (Scheme 4).[4−6]

Scheme 4[a]



[a] (a) i. LiHMDS, THF, 0 °C, 30 min; ii. PhSeCl, THF, 0 °C, 2 h; iii. DMDO, THF, 0 °C, 4 h; iv. 4 M HCl in dioxan, 0 °C, 30 min; v. Et_3N, DCM, 4 h. DMDO = dimethyldioxirane. LiHMDS = lithium hexamethyldisilazide.

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Supporting Information Available: Experimental procedures and characterization data for compounds **7**−**17**. This material is available free of charge via Internet at http://pubs.acs.org.

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