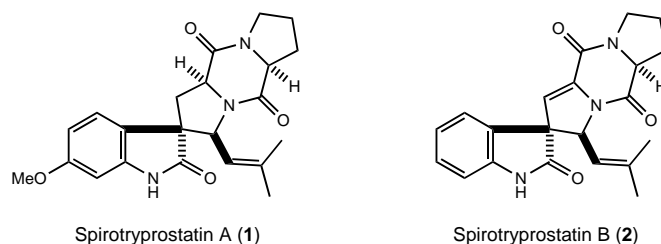


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## Total Synthesis of (–)-Spirotryprostatin B and Three Stereoisomers\*\*

Larry E. Overman\* and Mark D. Rosen

Small-molecule natural products play an important role in contemporary studies to understand and control cellular proliferation.<sup>[1]</sup> From the fermentation broth of the fungus *Aspergillus fumigatus*, Osada and co-workers recently identified a group of novel diketopiperazine alkaloids that inhibit G2/M phase progression of the mammalian cell cycle at micromolar concentrations.<sup>[2, 3]</sup> Spirotryprostatins A (**1**) and B (**2**) are the most complex of these alkaloids,<sup>[2]</sup> all of which appear to arise biosynthetically by prenylation of a diketopiperazine derived from tryptophan and proline.



The novelty of their structures and the potential utility of cell-cycle inhibitors make the spirotryprostatins attractive targets for total synthesis. If such an undertaking were to be stereocontrolled, a central challenge would be to relate the stereochemistry of the quaternary spiro carbon to the adjacent stereocenter bearing the 2-methylpropenyl side chain. In 1998, Danishefsky and co-workers reported the total synthesis of spirotryprostatin A (**1**), which constituted the first total synthesis in this area.<sup>[4]</sup> Earlier this year, the groups of Williams,<sup>[5]</sup> Danishefsky,<sup>[6]</sup> and Ganesan<sup>[7]</sup> disclosed inaugural total syntheses of (–)-spirotryprostatin B (**2**).

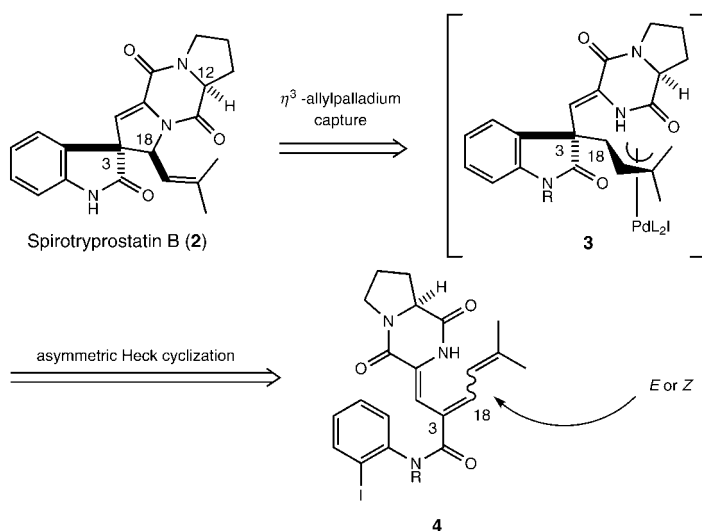
Our approach to spirotryprostatin B (**2**) and congeners is distinctly different from the previous syntheses (Scheme 1). The logic of our strategy is to correlate the relative configurations of C3 and C18 in **2**<sup>[8]</sup> to the geometry of the internal double bond of a triene cyclization substrate **4** by capitalizing on the stereochemical selectivity of two palladium-catalyzed

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Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



Scheme 1. Retrosynthesis of spirotryprostatin B (**2**). L = ligand.

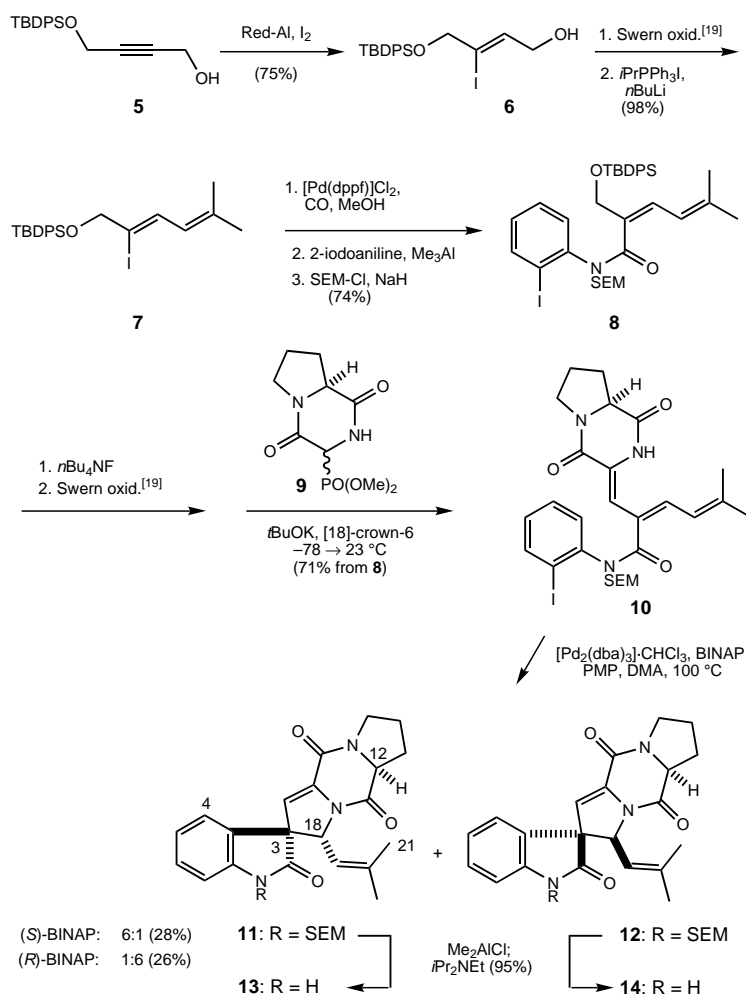
reactions: Heck insertions<sup>[9]</sup> and trapping of  $\eta^3$ -allylpalladium intermediates by nitrogen nucleophiles.<sup>[10]</sup> Under control of an appropriate chiral ligand,<sup>[11]</sup> a suprafacial intramolecular Heck reaction of (*E*)-**4** in a favored 5-exo sense could generate  $\eta^3$ -allylpalladium intermediate **3**, which would not be expected to undergo facile stereomutation.<sup>[12]</sup> If reaction of intermediate **3** with the proximal nitrogen of the tethered diketopiperazine occurred *anti* to the metal, spirotryprostatin B (**2**) would be produced; trapping *syn* to the metal would lead to 18-*epi*-spirotryprostatin B.<sup>[13]</sup> Our strategy would have the flexibility to deal with either stereochemical outcome of the second step by modulation of the stereochemistry of the internal double bond of triene **4**.<sup>[14–16]</sup> Herein we disclose an investigation of the strategy adumbrated in Scheme 1, which culminated in enantioselective total syntheses of (–)-spirotryprostatin B (**2**) and three stereoisomers.

The preparation of triene cyclization substrate **10** began with alcohol **5**,<sup>[17]</sup> which was converted in high yield into dienyl iodide **7** as shown in Scheme 2.<sup>[18, 19]</sup> Palladium-catalyzed carbonylation of **7** in the presence of methanol,<sup>[20]</sup> aminolysis of the resulting ester with 2-iodoaniline,<sup>[21]</sup> and protection of the amide nitrogen with (2-trimethylsilyl)ethoxymethyl chloride (SEM-Cl) gave anilide **8** in 74% yield. Removal of the *tert*-butyldiphenylsilyl (TBDPS) group of **8**, followed by Swern oxidation<sup>[19]</sup> and reaction of the resulting aldehyde with the potassium salt of diketopiperazine phosphonate **9**<sup>[22]</sup> delivered isomerically pure **10** in 71% yield from **8**.

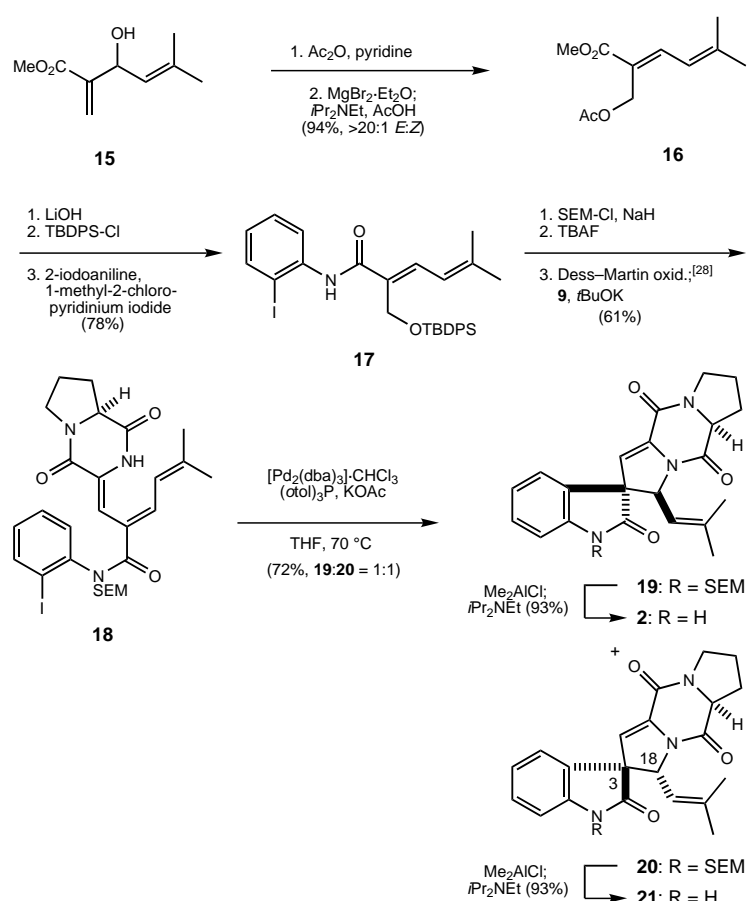
Cyclization of **10** with 20% Pd/(*S*)-BINAP and excess 1,2,2,6,6-pentamethylpiperidine (PMP) in *N,N*-dimethylacetamide (DMA) at 100°C<sup>[11]</sup> produced a 6:1 mixture of pentacycles **11** and **12** in 28% yield, while identical cyclization of **10** using Pd/(*R*)-BINAP proceeded with similar efficiency and selectivity to deliver **12** as

the major pentacyclic product (**12**:**11** = 6:1). After some experimentation, we found that the SEM protecting group could be discharged in high yield from these delicate products by initial exposure to six equivalents of Me<sub>2</sub>AlCl, followed by heating *N*-hydroxymethyl derivatives with diisopropylethylamine in methanol to remove the unit of formaldehyde. Analytically pure samples of 18-*epi*-spirotryprostatin B (**13**) and 3-*epi*-spirotryprostatin B (**14**) could be obtained from these mixtures by preparative HPLC. The *trans* relationship of the phenyl and 2-methylpropenyl groups of **13** and **14** was apparent from the large NOE enhancements observed in each case between H4 and H18, while the stereorelationship of the pyrrolidine and dihydropyrrole rings was established from long-range NOE enhancements observed between H12 and H21 of **13** by DPGFSE NOE experiments.<sup>[23, 24]</sup>

These Pd/BINAP-catalyzed double cyclizations of **10** demonstrate that the  $\eta^3$ -allylpalladium intermediate is generated and captured with high stereochemical fidelity, and that the nitrogen of the tethered diketopiperazine attacks the allylpalladium complex *anti* to the metal center. Consequently, we turned to the synthesis of the stereoisomeric cyclization



Scheme 2. Synthesis of 18-*epi*-spirotryprostatin B (**13**) and 3-*epi*-spirotryprostatin B (**14**). TBDPS = *t*BuPh<sub>2</sub>Si, Red-Al = [(MeOCH<sub>2</sub>CH<sub>2</sub>O)<sub>2</sub>AlH<sub>2</sub>]Na, dppf = 1,1'-bis(diphenylphosphino)ferrocene, SEM = CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>, BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, dba = (*E,E*)-dibenzylideneacetone, PMP = 1,2,2,6,6-tetramethylpiperidine, DMA = *N,N*-dimethylacetamide.



Scheme 3. Synthesis of spirotryprostatin B (**2**) and 3,18-bis-*epi*-spirotryprostatin B (**21**). TBAF = tetrabutylammonium fluoride, *otol* = *ortho*-tolyl, see Scheme 2 for other abbreviations.

substrate **18** that should lead to spirotryprostatin B (**2**; Scheme 3).

The preparation of **18** began with allylic alcohol **15**.<sup>[25]</sup> The acetate derivative of **15** reacted cleanly with  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$  to give the primary allylic bromide,<sup>[26]</sup> which was displaced with acetate to provide (*E*)-dienoate **16**. Conversion of **16** into the siloxycarboxylic acid and coupling<sup>[27]</sup> of this intermediate with 2-iodoaniline provided **17** in excellent overall yield. Following a sequence similar to that employed in the stereoisomeric series (**8** → **10**), **17** was elaborated to form isomerically pure **18** in 61 % overall yield.<sup>[28, 29]</sup>

Cyclization of **18** with  $\text{Pd}(\text{S})$ -BINAP under conditions identical to those employed with stereoisomer **10** unexpectedly led to the formation of pentacycle **11**. Control experiments conducted in the absence of  $\text{Pd}(\text{S})$ -BINAP indicated that **18** underwent rapid isomerization of the internal double bond of the triene to give **10** when heated above 80 °C in DMA with excess PMP. As a result, a wide variety of reaction conditions, including many with scavengers of HI less basic than PMP, were surveyed in an attempt to accomplish the asymmetric double cyclization under conditions that did not isomerize the triene unit of **18**. While these attempts met with failure, we did discover that cyclization of **18** with 10%  $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ , 40 mol % tri-*o*-tolylphosphane, and excess KOAc in THF at 70 °C cleanly led to the formation of a 1:1 mixture of pentacycles **19** and **20**. Removal of the SEM

group from these products and chromatographic purification provided pure (–)-spirotryprostatin B (**2**;  $[\alpha]_{\text{D}}^{23} = -159$  ( $c = 0.40$ ,  $\text{CHCl}_3$ )) in 21 % overall yield from **18**, as well as 3,18-bis-*epi*-spirotryprostatin B (**21**).<sup>[30]</sup>

In summary, (–)-spirotryprostatin B (**2**) was synthesized in 9 % yield from methyl acrylate and 3-methyl-2-butenal (the commercially available precursors of **15**) by way of ten isolated intermediates. This synthesis and the related syntheses of stereoisomers **13**, **14**, and **21**, introduce a new strategy for stereocontrolled construction of quaternary spiro and adjacent stereocenters. Moreover, this investigation shows for the first time that a) intramolecular Heck insertions of conjugated trienes can proceed with high regioselectivity, b)  $\eta^3$ -allylpalladium intermediates can be trapped by the nitrogen of a tethered diketopiperazines, and c) the latter reactions proceed with *anti* stereochemistry. These methodological advances further expand the potential applications of organopalladium chemistry in the construction of complex heterocyclic ring systems.

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## Reconstitution of Channel Proteins in (Polymerized) ABA Triblock Copolymer Membranes\*\*

Wolfgang Meier,\* Corinne Nardin, and Mathias Winterhalter

Lipid bilayers are the basic constituent of biological membranes. The lipids serve as a fluid matrix for membrane or membrane-associated proteins, which are responsible for various key functions such as signaling or transport. Many of these membrane proteins are pharmacologically important or have biotechnological potential. For such applications one has to immobilize them in an artificial membrane system. This creates a biosensor which can be used, for example, for rapid drug screening. The great advantage of planar freestanding films is the direct access to both sides of the membrane. Thus, these can be applied to carry out, for example, conductance measurements to monitor transport processes across membranes or to detect minor changes on reconstituted channel-forming membrane proteins. An early model system for freestanding films was the so-called “black lipid membranes”, named as such because during the thinning out of the membrane the intensity of the reflected light vanishes and the membrane appears black in the reflected light. In addition to their biological functions, lipid membranes have unique material properties; for instance, they are extremely flexible but at the same time mechanically very stable. In contrast, artificial, freestanding membranes were always fragile and thus of little technological interest. Above a certain size, supported lipid membranes contain defects, which rules out conductance measurements as a recording technique. Herein we present a new type of matrix for membrane proteins. This material is stable and defect-free and allows the formation of giant dense planar membranes.

Similar to conventional lipids, amphiphilic block copolymers may also form membrane-like superstructures in aqueous solution.<sup>[1–6]</sup> Hence they can be regarded as higher molecular weight analogues of lipids. Moreover, the high diversity of block copolymer chemistry may lead to a plethora of new artificial membrane structures inaccessible with conventional lipids. For example, it is possible to vary the molecular weight, the block–length ratio, the chemical constitution, or even the molecular architecture of these molecules. Owing to their larger size and their slower dynamics, amphiphilic block copolymers may lead to signifi-

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