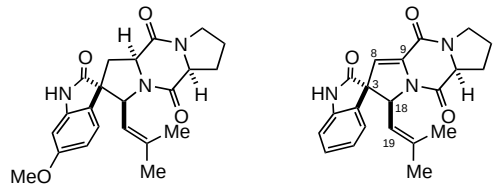
Spiro Alkaloids

Total Synthesis of (−)-Spirotryprostatin B**

*Christiane Meyers and Erick M. Carreira**

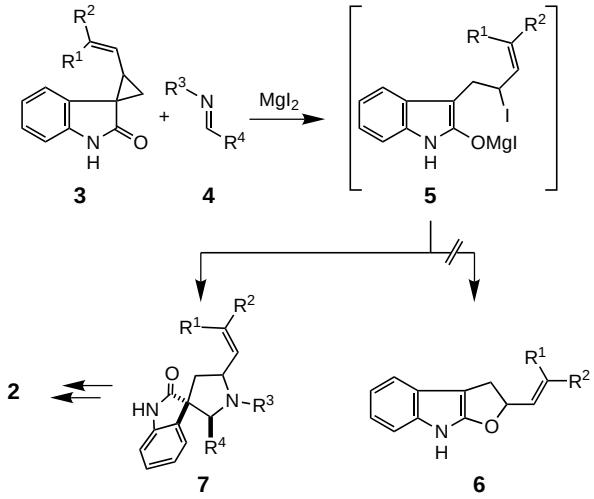
Spirotryprostatin A (**1**) and B (**2**), two powerfully bioactive indole alkaloids, were isolated in 1996 by Osada et al. from the fermentation broth of *Aspergillus fumigatus* BM939.[1] Only miniscule amounts of **1** and **2** (11 and 1 mg, respectively) were isolated from 400 L of fermentation medium. Both



1 spirotryprostatin A **2** spirotryprostatin B

compounds inhibit the cell cycle in the G2/M phase, and **2** shows cytotoxic activity on the growth of human leukemia cell lines. In this communication, we report a novel strategy towards the synthesis of spirotryprostatin B that is characterized by the MgI_2-catalyzed annulation reaction of a spiro[oxindole-3,1′-vinylcyclopropane] and an alkynyl imine. It is notable that in the context of our investigations we have developed the functionalization of an advanced aldehyde intermediate which enables the generation of biologically active congeners. The synthetic chemistry of the spirotryprostatins has recently been the subject of intense investigations by several groups. The various creative, distinct strategies have been devised to provide access to the spiro[oxindole-3,3′- pyrrolidine] core.[2–6]

We have recently developed a novel approach to spiro[oxindole-3,3′-pyrrolidines] by the MgI_2-catalyzed ring-expansion reaction of spiro[cyclopropane-1,3′-oxindoles] and aldimines.[7] The methodological studies we have carried out to date have left unaddressed a pertinent issue, which impacts the general applicability of the method to provide access to a wide range of related alkaloids. In particular, in none of the earlier studies had we or others examined the use of 1,2-disubstituted cyclopropanes, which would give access to 2,5-substituted pyrrolidines.[8] At the outset, there were two key questions we wished to address: the use of vinyl cyclopropane **3** in the ring-expansion reaction to yield **7** and the relative stereochemical outcome of the annulation. With respect to the former, it was not at all clear whether the intermediate allylic iodide/enolate **5** would be stable, as it could collapse by intramolecular cyclization to form a dihydrofuroindole **6** (Scheme 1).[9]

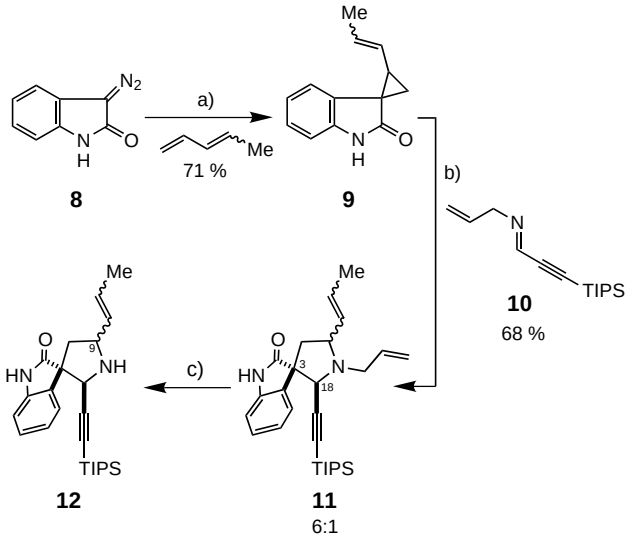


3 **4** **5** **2** **7** **6**

Scheme 1. MgI_2-catalyzed ring-expansion reaction of spiro[cyclopropane-1,3′-oxindole], and a potential side reaction.

An additional problem we wished to explore was whether an aldehyde at C18 (spirotryprostatin B numbering) would serve as a useful precursor to the requisite prenyl side chain through an olefination reaction. Because earlier work in this area had concluded that olefination of a related aldehyde was unfeasible, revisting this strategic challenge was not without risk.

Our synthesis commenced with known diazoketone **8**, accessible in two steps and 79% yield from isatin (Scheme 2).[10] Rhodium-catalyzed cyclopropanation of



8 **9** **10** 68 % **12** **11** 6:1

Scheme 2. a) Piperylene, [{Rh(OAc)$_2$}$_2$] (1 mol%), benzene, reflux, slow addition of **8** in CH_2Cl_2; b) **10**, MgI_2 (1 equiv), THF, sealed tube, 75°C; c) [Pd(PPh$_3$)$_4$] (6 mol%), NDMBA, CH_2Cl_2, 30°C. TIPS = triisopropylsilyl, NDMBA = 1,3-dimethylbarbituric acid.

[*] Prof. Dr. E. M. Carreira, C. Meyers
Laboratorium für Organische Chemie
ETH Hönggerberg, HCI H335
8093 Zürich (Schweiz)
Fax: (+41) 1-632-1328
E-mail: carreira@org.chem.ethz.ch

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piperylene with diazoketone **8** afforded spiro[cyclopropane-1,3′-oxindole] **9** in 71 % yield as an inconsequential mixture of diastereomers.[11] The stage was set for investigation of the critical key step. When a solution of cyclopropane **9** and imine **10**[12] was heated in THF at 75 °C in a sealed tube in the presence of 1.0 equiv of MgI_2, **11** was isolated in combined 68 % yield, as a mixture of diastereomers favoring the desired relative stereochemistry at C3 and C18 found in the natural product in a ratio of 6:1. Deprotection of the secondary amine (cat. $[Pd(PPh_3)_4]$ and 1,3-dimethylbarbituric acid)[13] afforded **12**.[14]

Coupling of amine **13** with *N*-Boc-L-proline chloride[15] proceeded in 90 % yield and allowed the resolution of product **14** into two enantiomers which permitted its stereochemistry to be unambiguously determined by X-ray crystallographic analysis (Scheme 3; Figure 1). Oxidative cleavage of the olefin under standard conditions (see legend to Scheme 3) furnished aldehyde **15** (97 % yield over two steps),[16] which was oxidized to the corresponding acid by using the Lindgren protocol ($NaClO_2$, 2-methyl-2-butene, *t*BuOH, pH 3.6 buffer)[17] and converted to ester **16** (89 % yield over two steps).[18] Subsequent cleavage of the acetylenic C–Si bond was effected in 99 % yield to afford terminal alkyne **17**. The reaction sequence from **14** to **17** could be achieved with no significant decrease in the yield of **17** without purification of any intermediate (80 % overall yield over five steps). Semihydrogenation of alkyne **17** proceeded smoothly ($Pd/BaSO_4$, quinoline; 90 % yield)[19] to afford **18,** which in turn was oxidized to the corresponding aldehyde **19** in 77 % yield.

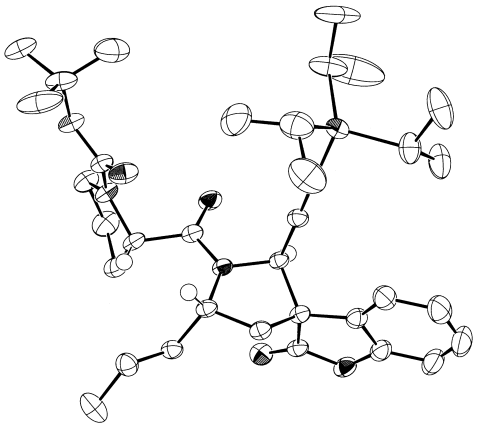
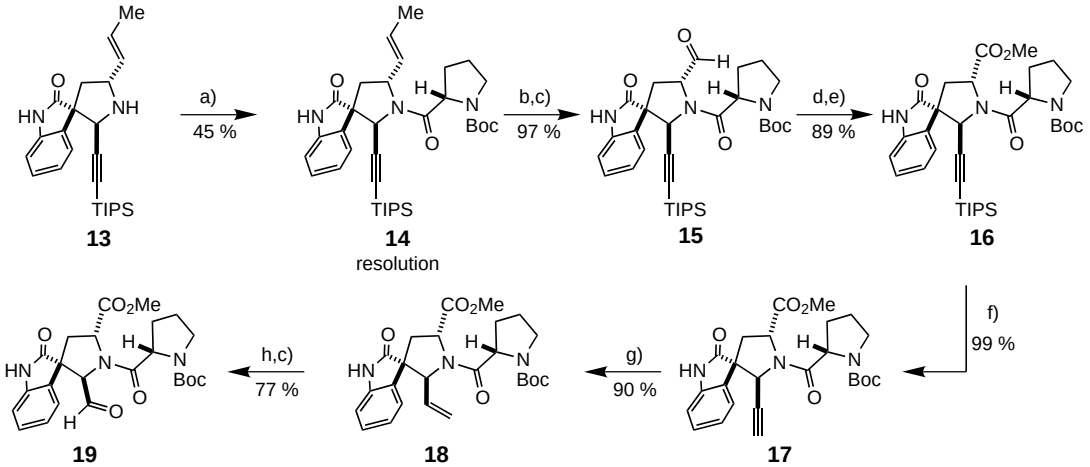


Figure 1. ORTEP drawing of **14**.[23]

In pioneering studies, Danishefsky et al. had noted the importance of intermediates bearing an aldehyde functionality at C18, as these would allow facile preparation of side chain analogues at a late stage in the synthesis of the spirotryprostatins. However, in an elegant study en route to spirotryprostatin A, a compound closely related to **19** was recalcitrant to a variety of olefination procedures.[20]

In a similar manner, severe difficulties were also encountered upon attempted olefination of **19**. However, a lead result was realized through the application of the Julia–Lythgoe olefination,[21] in which the desired trisubstituted olefin could be obtained, albeit in poor yield (11 % over three steps) and with extensive epimerization at C18. Further investigation revealed that the use of the Kociensky modification afforded the desired product **21** without scrambling at C18 in 78 % yield (Scheme 4).[22] The structure of compound **21** was confirmed by X-ray crystallographic analysis (Figure 2). From **21**, the synthesis of spirotryprostatin B was completed in four steps following the Danishefsky route. Thus, selenylation of **21** followed by elimination with DMDO afforded **22** (74 %) with introduction of the C8–C9 olefin. Deprotection of the proline and subsequent closure of the diketopiperazine ring led to spirotryprostatin B (**2**) in 74 % yield with analytical characteristics (^1H and ^{13}C NMR spectra, MS, IR, optical rotation) identical to those reported in the literature.[3]

In summary, we have described the total synthesis of spirotryprostatin B (16 steps from **8**). Our approach is highlighted by the rapid assembly of the spirotryprostatin core by employing the MgI_2-catalyzed ring-expansion reaction of



Scheme 3. a) NEt_3, Boc-L-ProCl, CH_2Cl_2, RT; b) $NMO{\cdot}H_2O$, OsO_4 (4 mol %), THF/*t*BuOH/H_2O 4:4:1, RT; c) $Pb(OAc)_4$, EtOAc, RT; d) $NaClO_2$, 2-methyl-2-butene, *t*BuOH, pH 3.6 buffer, RT; e) CH_2N_2, Et_2O, RT; f) TBAF, THF, RT; g) H_2, $Pd/BaSO_4$ (33 wt %), quinoline, EtOH, RT; h) $NMO{\cdot}H_2O$, OsO_4 (1 equiv), THF/*t*BuOH/H_2O 4:4:1, RT. Boc = *tert*-butoxycarbonyl, NMO = *N*-methylmorpholine-*N*-oxide, TBAF = tetrabutylammonium fluoride.

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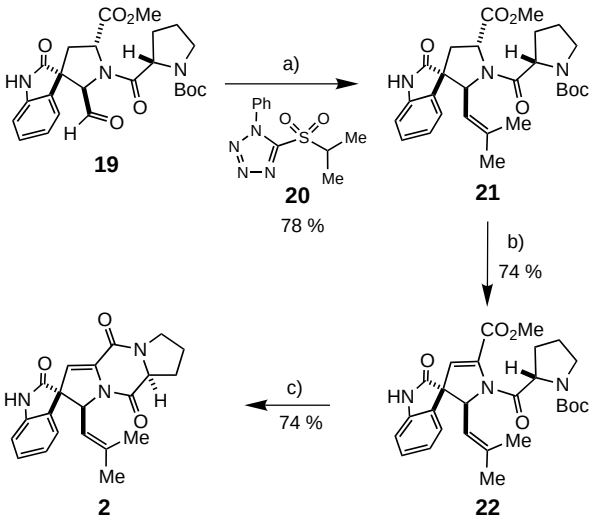

Scheme 4. a) **20**, LHMDS, THF, −78 °C; b) 1. PhSeCl, LHMDS, THF, 0 °C; 2. DMDO, THF, 0 °C; c) 1. TFA, CH_2Cl_2, RT; 2. NEt_3, CH_2Cl_2, RT. LHMDS = lithium hexamethyldisilazide, DMDO = dimethyl dioxirane, TFA = trifluoroacetic acid.

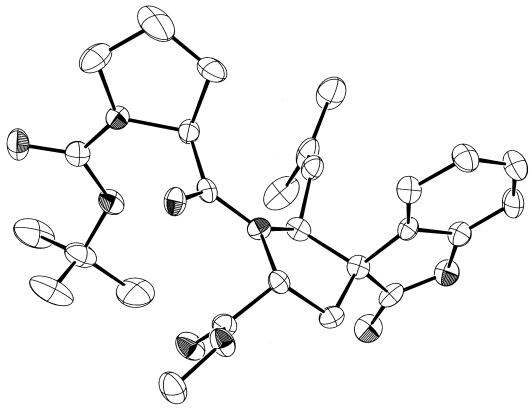

Figure 2. ORTEP drawing of **21**.[23]

spiro[oxindole-3,1′-vinylcyclopropane] **9** and an alkynyl imine **10** for the synthesis of substituted spiro[oxindole-3,3′- pyrrolidine] alkaloids. The study documents for the first time the use of substituted spiro[cyclopropane-1,3′-oxindoles] in the annulation reaction and thus considerably expands the scope of the method and its potential for additional applications in complex molecule synthesis. A key difficulty with the olefination of aldehyde **19** was overcome by using the Kociensky–Julia reaction. In principle, it is now possible to generate the related C18 aldehyde from the natural product which provides a handle for olefination. This opens up new avenues for the facile synthesis of analogues that should enable the elucidation of structure–activity relationships of this important class of natural products.

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[23] CCDC 196803 (**14**) and CCDC 196804 (**21**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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