Alkaloid synthesis

Preparation and Synthetic Applications of 2-Halotryptophan Methyl Esters: Synthesis of Spirotryprostatin B**

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Isolated in small amounts from the fermentation broth of *Aspergillus fumigatus*,[1] spirotryprostatin B (**1**) represents one of the structurally more complex members of a relatively potent class of diketopiperazines that inhibit mammalian G_2/M^{-1} phase cell-cycle progression. Its biological significance and structural novelty has challenged numerous investigators to develop concise total syntheses and analogues with

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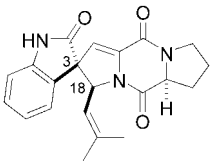
[**] Financial support from Oregon State University and Chugai Pharmaceutical Co. is gratefully acknowledged. We thank Rodger Kohnert for assistance with NMR data acquisition and Jeff Morre of the Mass Spectrometry Facility of the Environmental Health Science Center (NIEHS P30 ES00210) at Oregon State University for recording mass spectral data.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/ange.200460419

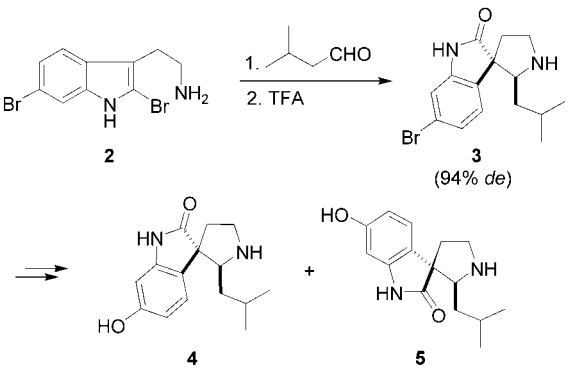
potentially superior biological activity.[2–7] The biosynthesis of this spirooxindole undoubtedly arises from the common amino acid precursors (*S*)-tryptophan and (*S*)-proline, in addition to an isoprene-derived moiety and awaits experimental verification.



spirotryprostatin B (**1**)

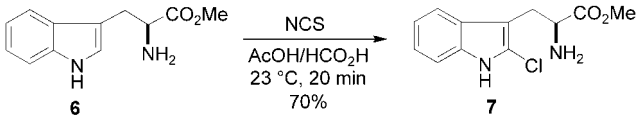
The key synthetic challenge is the asymmetric stereocontrolled construction of the quaternary C3 and adjacent prenyl-substituted C18 centers of the dehydrospiropyrrolidine ring. This has become particularly apparent within the parameters of developing an efficient total synthesis of **1**. Recently, a number of efforts, some successful, have been made to devise solutions to this problem.[8] Of the syntheses that utilize readily available tryptophan esters and prenyl aldehyde starting materials, two "classical" approaches have emerged. The first, by Danishefsky and von Nussbaum,[2] involves a Mannich condensation of a tryptophan-derived oxindole and prenyl aldehyde. The second, by Ganesan and Wang,[3] adopts the well-known Pictet–Spengler/oxidative rearrangement methodology involving a prenyl-substituted tetrahydro-β-carboline. In this communication, we disclose the first direct preparation of 2-chlorotryptophan methyl ester (**7**), its use in stereocontrolled spirooxindole construction, and a concise synthesis of spirotryprostatin B (**1**).

2-Halotryptophan and -tryptamine derivatives are potentially useful synthetic building blocks for a variety of applications in indole-based natural product synthesis. We recently reported a new method for the stereocontrolled construction of spiro[pyrrolidine-3,3′-oxindoles], that is, **3**, in the synthesis of isoelacomine (**4**) and elacomine (**5**) from 2,6-dibromotryptamine (**2**) (Scheme 1).[9] A high degree of stereochemical control at the newly formed quaternary and adjacent alkyl center in **3** was observed, which favored a *cis* relationship between the alkyl group and oxindole benzene ring. Based on this initial work, we felt that the use of 2-halotryptophan esters and the development of new *N*-acyliminium ion spirocyclization methodology would nicely complement existing tryptophan-based methods for constructing the spirotryprostatin architecture exemplified by structure **1**.



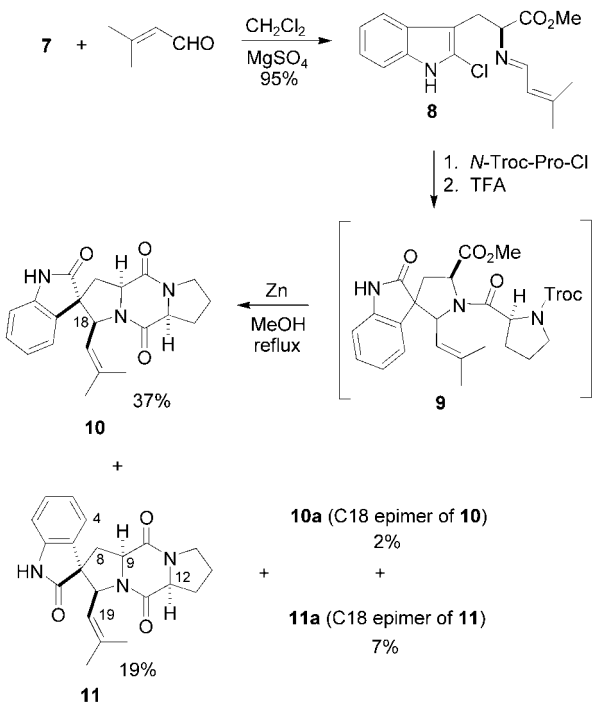
Scheme 1. Synthesis of isoelacomine (**4**) and elacomine (**5**) by stereocontrolled spirocyclization. TFA = trifluoroacetic acid.

To date, only a few 2-halo-substituted tryptophan derivatives have been prepared.[10–12] Their preparation utilizes multistep protocols that involve nitrogen group protection, chiral auxiliary introduction, and/or enzymatic transformations. Clearly, a procedure that could readily deliver 2-halotryptophan esters directly from readily available tryptophan esters would be highly desirable. In recent work, we demonstrated the direct and regioselective introduction of bromine and chlorine at the 2-position of tryptamine with NBS and NCS to afford 2-bromo- or 2-chlorotryptamine, respectively.[9] This methodology has now been successfully extended to tryptophan esters wherein treatment of the hydrochloride salt of tryptophan methyl ester (**6**) (AcOH/HCO_2H, 4:1, 23 °C, 20 min with NCS regioselectively produced 2-chlorotryptophan methyl ester (**7**) ($[\alpha]_D^{23} = +27.8$, $c = 0.3$, MeOH, as the HCl salt) in good yields (Scheme 2).[13] Multigram quantities of **7** can be prepared easily by using this protocol.



Scheme 2. Preparation of 2-chlorotryptophan methyl ester (**7**). NCS = *N*-chlorosuccinimide.

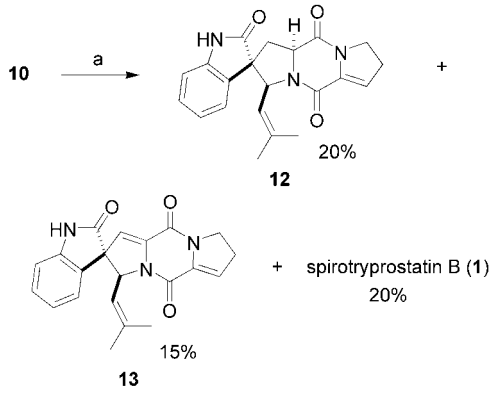
With **7** in hand, we turned our attention to the spirocyclization reaction with prenyl aldehyde (Scheme 3). As anticipated, condensation of amine **7** with prenyl aldehyde produced imine **8** as a stable entity. Activation of imine **8** as



Scheme 3. Synthesis of dihydrospirotryprostatin B (**10**). Troc = 2,2,2-trichloroethoxycarbonyl.

its *N*-acyliminium species with *N*-Troc proline acid chloride[14] induced spirocyclization. Subsequent TFA-assisted hydrolysis of the putative chloroindolenine intermediate produced oxindole **9** as a mixture of single diastereomers. Rather than attempt a chromatographic separation at this stage, we transformed **9** in one-pot to the requisite diketopiperazine by removal of the Troc group and cyclization. Flash chromatography of the reaction products afforded desired dihydrospirotryprostatin B (**10**), $[\alpha]_D^{23}-123$ ($c=2.1$, $CHCl_3$), as the major diastereomer, and, to a lesser extent, C3 epimer **11**, $[\alpha]_D^{23}-193$ ($c=1.8$, $CHCl_3$). Diastereomers **10a**, $[\alpha]_D^{23}+32$ ($c=1.4$, $CHCl_3$) and **11a**, $[\alpha]_D^{23}-42$ ($c=1.2$, $CHCl_3$), were also obtained but only in minor quantities. The ^1H and ^{13}C NMR spectra of **10**, **10a**, and **11** were identical to those previously reported for these compounds.[3,6,15] The relative configuration of previously unknown **11a** was determined from NOE data; significant NOEs were observed between H19, H9, H8α ($\delta=2.65$ ppm), and H4, as well as between H12 ($\delta=4.44$ ppm) and H9, in CD_3OD.

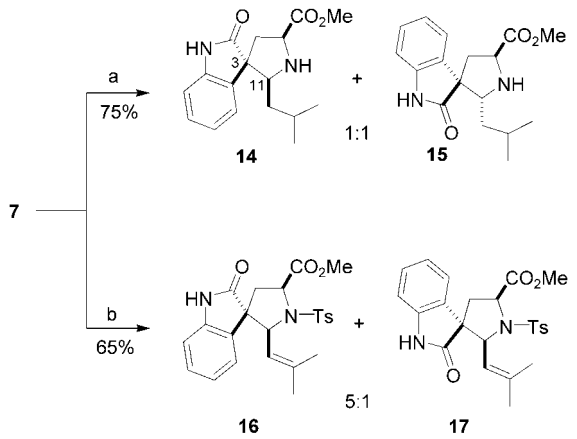
Ganesan et al. reported the conversion of dihydrospirotryprostatin B (**10**) to spirotryprostatin B (**1**) in low yield as a mixture of several products.[3] In an attempt to improve this route, a "nonoxidative" protocol[16] was pursued to install the dehydroproline unit (Scheme 4). This proceeded with modest



Scheme 4. Synthesis of spirotryprostatin B (**1**). a) LiHMDS (3 equiv), THF, 0 °C, 30 min; then PhSeCl (3 equiv), 3 h, 0 °C; then PhSeCl (3 equiv), 23 °C, 16 h.

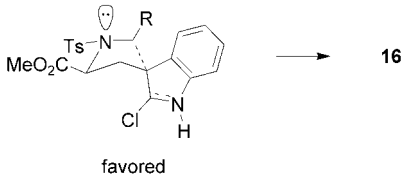
success in which spirotryprostatin B (**1**), $[\alpha]_D^{23}-149.0$ ($c=0.3$, $CHCl_3$) [ref: $[\alpha]_D^{23}-162.1$ ($c=0.92$, $CHCl_3$)[1]], was obtained in 20% yield along with known analogues **12**[3] and **13**.[4]

The precise factors controlling the stereochemistry of the *N*-acyliminium ion spirocyclization derived from (*S*)-2-chlorotryptophan methyl ester (**7**) are unclear at this time. It is evident, however, that the cyclization favors an *S* absolute configuration at C18 and a relative *cis* orientation of the prenyl side chain and oxindole benzene ring. With the hope of gaining further insight into the stereochemistry of this cyclization reaction, additional experiments were performed (Scheme 5). Condensation of **7** with isovaleraldehyde followed by proton-facilitated iminium ion cyclization produced spirooxindoles **14** and **15** in ≈1:1 ratio.[17,18] The relative C3 and C11 configuration of **14** and **15** is such that the isovaleryl side chain and oxindole benzene ring are oriented *cis* for both



Scheme 5. Stereocontrolled spirocyclization of 2-chlorotryptophan (**7**) and aldehydes. a) $(CH_3)_2CHCH_2CHO$, CH_2Cl_2, 23 °C, 2 h; then TFA (6 equiv), 23 °C, 1 h; b) $(CH_3)_2C{=}CHCHO$, CH_2Cl_2, 23 °C, 2 h; then TsCl (2.5 equiv), Et_3N (3 equiv), 23 °C, 36 h; then TFA (6 equiv), 23 °C, 2 h. TsCl = *p*-toluenesulfonyl chloride.

diastereomers. This is consistent with the achiral tryptamine model recently published.[9] In the present case, it appears that the methoxycarbonyl chiral center has no effect in controlling the relative configuration at C11 under proton activation. On the other hand, when TsCl was used in the spirocyclization of **7** and prenyl aldehyde, oxindoles **16** and **17** were obtained in a 5:1 ratio.[19] Relatively good stereocontrol at C3 and C11 can be achieved in this case compared to *N*-Troc-proline acid chloride. These results suggest that the structure of the activating substituent plays a significant role in governing the formation of the C3 and C11 (or C18 in **10**) centers. The issues governing stereocontrol in the spirocyclization reaction are undoubtedly complex. In the case of TsCl activation, a late transition state may be operable with the Ts group oriented *trans* to the methoxycarbonyl and R groups, which leads predominantly to the formation of diastereomer **16** (Scheme 6).



Scheme 6. Possible stereochemical rationale.

In conclusion, we have described a short synthesis of spirotryprostatin B featuring new intramolecular *N*-acyliminium ion spirocyclization methodology based on 2-halotryptophan esters. The methodology provides direct and rapid access to versatile tryptophan building blocks. Notably, the cyclization products are the result of a kinetically controlled process that complements thermodynamic outcomes often associated with classical Mannich oxindole conditions. Stereocontrolled spirocyclizations to form non-racemic spirochloroindolenine intermediates should afford new opportunities not only in spirooxindole construction but also in the

synthesis of other indole-based natural product ring systems of biological and structural significance.

Received: April 22, 2004

Keywords: Alkaloids · Halogenations · Natural products · Spiro compounds · Synthetic methods

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[17] NOEs observed for compound **14**: between H-11, H-9, and H_α-8; between H-4 and H_β-8. NOEs observed for compound **15**: between H-9, H_α-8, and H-4; between H_β-8 and H-11.
[18] It is well-known that spirooxindoles whose structures are related to compounds **3**–**5** (ref. [9]) having an amino, not amido, nitrogen atom in the spiropyrrolidine ring can undergo facile equilibration and epimerization at C3 and C11 (or C18 in **10**) through a retro-Mannich process. Oxindoles **14** and **15**, however, are configurationally stable in CD_3OD at 23 °C over a period of 7 d. a) C. Pellegrin, M. Weber, H.-J. Borshberg, *Helv. Chim. Acta* **1996**, *79*, 151 – 168; b) M. Ito, C. W. Clark, M. Mortimore, J. B. Goh, S. F. Martin, *J. Am. Chem. Soc.* **2001**, *123*, 8003 – 8010, and references therein.
[19] NOEs observed for compound **16**: between H-11, H-9, and H_α-8; between H-4 and H_β-8. NOEs observed for compound **17**: between H-11, H-9, H_α-8, and H-4.

