The Total Synthesis of Spirotryprostatin A**

Scott D. Edmondson and Samuel J. Danishefsky*

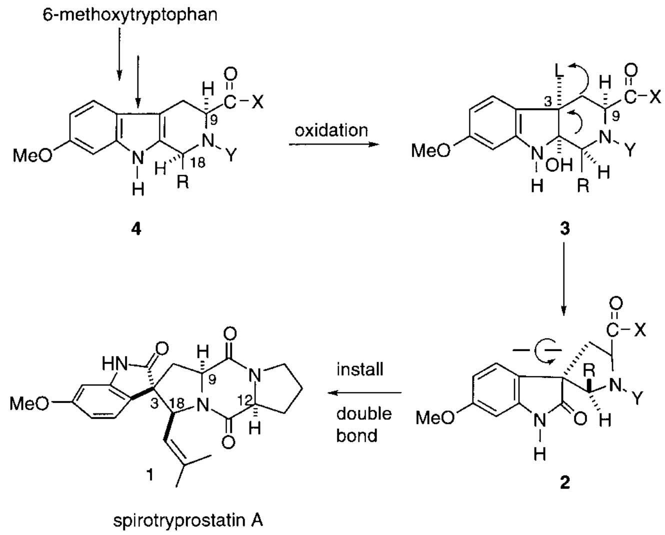
A growing number of alkaloids, formally derivable from L-tryptophan, that bear an additional pyrrole ring in the context of a diketopiperazine system, display a range of biological profiles resulting in cell cycle modulation.[1] Our laboratory has particularly focused on those members of this class that also carry prenyl or "reverse prenyl" substituents. As a prelude to multidisciplinary investigations of structure–activity relationships (SAR) and the mode of action of these compounds, we have concerned ourselves with their total synthesis. To date, we have described the total syntheses of amauramine, the ardeemins, gypsetin, and tryprostatin B.[2]

In this context our attention was drawn to the family of spiroindolinones reported in 1996, which are exemplified by spirotryprostatin A (**1**) (see Scheme 1).[3] This compound and its dehydrocongener spirotryprostatin B[4] are isolated from the fermentation broth *Aspergillus fumigatus* and manifest cell cycle inhibition at the G2/M phase with IC$_{50}$ values in the micromolar range. We began our research into this intriguing subgroup with a program directed toward a total synthesis of **1** and report herein the realization of this goal.

In all the members of the spirotryprostatin family the side chain is a 2-methylprop-1-enyl function, except in tryprostatin B, which bears a 3-methylbut-2-enyl group. Also requiring close attention was the fashioning of the spiro linkage of the pyrrole and indolinone sectors, as well as the correct relative stereochemistry between the spiro carbon, C3, and the side chain at C18, in the context of the L-trpytophan and L-proline related centers C9 and C12, respectively.

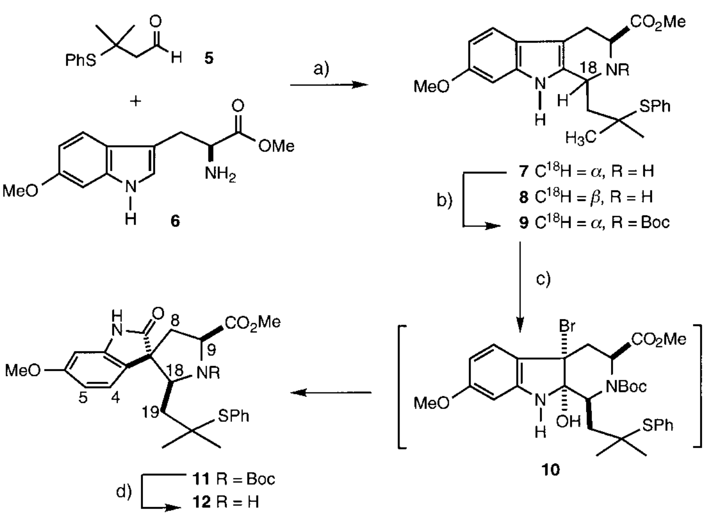
Our strategy relied on the construction of a β-carboline of the type **4** (Scheme 1). The precise timing for presentation of the diketopiperazine ring was not decided at the planning level. At an appropriate stage we would devise means for oxidation of the indole system (→**3**). Given the overall need for oxidative rearrangement, it seemed likely that structures **4**, **3**, and **2** would contain a virtual rather than an actual double bond.

Implementation of the required absolute and relative stereochemistry required for a synthesis of **1** seemed to be feasible under the broad logic of Scheme 1. Thus, maintenance of the L configurations of the proline and tryptophan building blocks would dictate the stereochemistry of the diketopiperazine structure. The eventual stereochemistry of the 2-methyl-1-propenyl function at C18 arises from its relationship to the two "fixed" centers at C9 and C12. The stereochemical connectivity between C18 and C3 would follow from the sense of oxidation of the indole double bond and the anticipated inversion of the configuration at C3 in the rearrangement step.



Scheme 1. Synthetic strategy for spirotryprostatin A (**1**). X, Y = diketopiperazine unit or groups from which one can be generated; L = leaving group; R = group from which the 2-methylprop-1-enyl group can be generated.

Our synthesis commenced with a Pictet–Spengler reaction of aldehyde **5** with the 6-methoxytryptophan derivative **6** (Scheme 2).[5] As would be expected, the desired *cis* product **7** was favored at the kinetic level, albeit in only a 2:1 ratio.[6] In light of the extensive and scholarly research of Cook et al., it was not surprising that under more forcing equilibrating conditions (HCl, MeOH, Δ, 24 h), **8**, the apparent thermodynamic product, prevailed.[7] Amine **7** was readily protected as its *tert*-butylcarbamate derivative (→**9**). Treatment of **9** with



Scheme 2. Synthesis of the spiro framework. a) CH$_2$Cl$_2$, CF$_3$CO$_2$H, molecular sieves (4 Å), 0→20 °C, 88%; b) Boc$_2$O, CH$_3$CN, Et$_3$N, Δ, 84%;[11] c) NBS, THF, H$_2$O, HOAc, 46%;[11] d) CF$_3$CO$_2$H, CH$_2$Cl$_2$, 93%. Boc = *tert*-butoxycarbonyl; NBS = *N*-bromosuccinimide.

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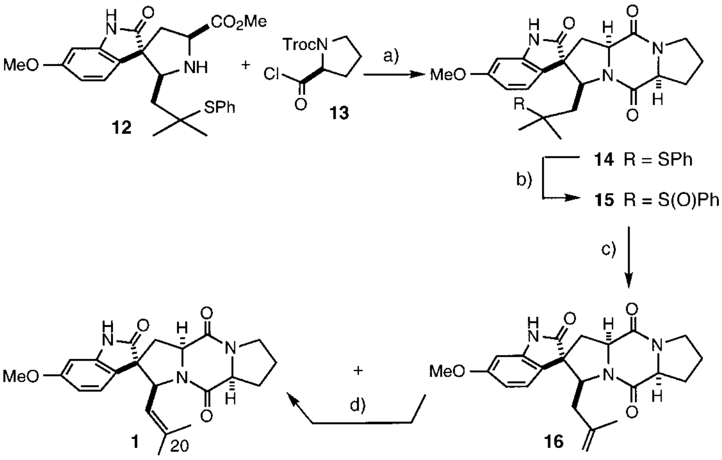
N-bromosuccinimide in THF containing aqueous acetic acid afforded an oxindole, which was tentatively formulated as **11**. We surmised that the oxindole would have arisen from rearrangement of a bromohydrin derivative, which we presumed would have the structure shown in **10**.[8] The stereochemistry of the series could be confirmed by detailed NMR analysis only after cleavage of the Boc function.[9] This transformation was accomplished through the action of trifluoracetic acid on **11** (→**12**).[10]

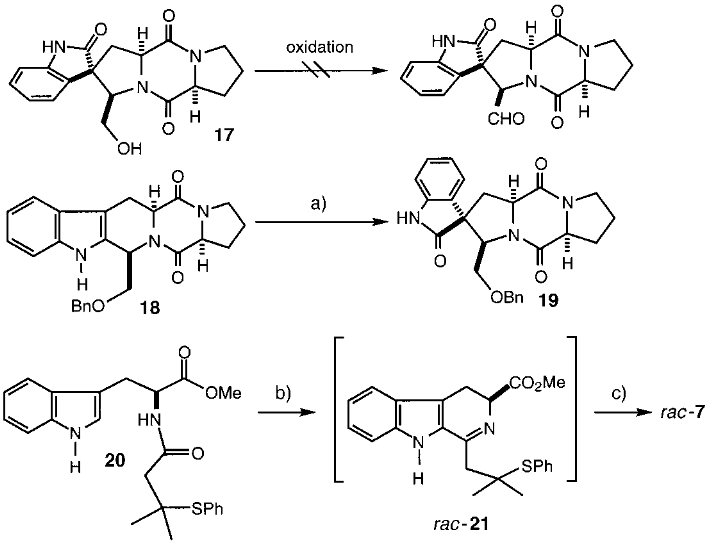
In the next stage the diketopiperazine linkage was introduced. Toward this end, we prepared the N-protected prolinyl acid chloride **13** (Scheme 3).[12] Coupling of **12** and **13** was accomplished with triethylamine in methylene chloride. Zinc-mediated cleavage of the 2,2,2-trichloroethoxycarbonyl (Troc) group also induced diketopiperazine formation, leading to compound **14** in 68% yield.[13] Thus, under these carefully defined conditions the thiophenyl group on the tertiary carbon in the side chain had been sustained through a remarkably diverse series of steps. The time was now at hand to effect its elimination. Clearly, the whole undertaking was at considerable risk since elimination could produce directly either of two olefinic products (Δ^{19} or Δ^{20}). Another concern was that of rapid isomerization of the double bond en route to a Δ^{18} "enamide" type of structure. In the event, sulfide **14** was oxidized with sodium metaperiodate to give the sulfoxide **15**, which was pyrolyzed in toluene under reflux to afford a separable mixture of spirotryprostatin A (**1**) and **16** (2.6:1) in 80% yield. Remarkably, isomerization of **16** with rhodium trichloride afforded **1** in 40% yield without further isomerization to the enamide.



Scheme 3. Synthesis of spirotryprostatin A (**1**). a) CH_2Cl_2, Et_3N; Zn, NH_4Cl, H_2O, THF, MeOH, 68%; b) $NaIO_4$, H_2O, MeOH; c) $PhCH_3$, △; 80% over two steps; d) $RhCl_3 \cdot 3H_2O$, EtOH, △, 41%. Troc = 2,2,2-trichloroethoxycarbonyl.

The synthetically derived spirotryprostatin A (**1**) was identical to the naturally occurring material by comparison of its high-field ^{1}H NMR and ^{13}C NMR with corresponding spectra of the natural product. Moreover, the high-resolution mass spectrum of the synthetic product independently confirmed its molecular formula. We note that the optical rotation of synthetic **1** ($[\alpha]^{\mathrm{D}}_{20} = -116.2^\circ$) differs substantially from that reported by Osada et al.[3] ($[\alpha]^{\mathrm{D}}_{26} = -34.0^\circ$). Since, in principle, every chiral center of **1** is susceptible to epimerization, it is conceivable that during its isolation naturally occurring **1** had undergone substantial racemization. Alternatively, the discrepancy may also reflect the fact that only small, inhomogeneous samples of **1** were isolated from natural sources.

It is well to point out features of several alternative modalities which had to be set aside but are nevertheless of possible future interest. Thus, chemistry very similar to that described here was used to synthesize compound **17** (Scheme 4). However, all attempts to obtain the corresponding aldehyde (which appeared suitable for introduction of the 2-methylprop-1-enyl group) were unsuccessful. Also of note is the dependence of the stereochemistry of oxidation of the indole system on the presence of the diketopiperazine ring. For instance, with compound **18**, which contains this unit, oxidative rearrangement gave rise to **19**, a C3 epimer of the desired series. Additionally, we have attempted to attain a fully satisfying solution for control over the required *cis* relationship between C9 C18 by controlling the stereochemistry in the rearrangement substrates **7** and **9**. To this end, compound **20** was synthesized from tryptophan methyl ester. Bischler–Napieralski cyclization of **20** afforded **21**, which upon reduction with sodium borohydride provided **7**. Unfortunately, however, this compound was obtained in racemic form.[14] Thus, while the required *cis* relationship between C9 and C18 can now be fashioned stereospecifically, the solution involves unacceptable forfeiture of enantiocontrol.



Scheme 4. Further investigations. a) NBS, THF, H_2O, HOAc; b) $POCl_3$, C_6H_6, △; c) $NaBH_4$, MeOH, 0 °C. Bn = benzyl.

We would hope to improve upon the synthesis of **1** by productive incorporation of these or related refinements. Nonetheless, the total synthesis presented herein already delivers spirotryprostatin A in 12% overall yield. Now that the problem of the availability of this drug has been solved, studies directed toward its chemistry and its biology can be instituted in earnest.

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[9] Relevant NOE enhancements in ^{1}H NMR spectra of **12**: irradiated signal (enhancements), H4 (H8β, H19), H8α (H8β, H9, H18), H8β (H4, H8α, H19), H9 (H8α, H8β, H18), H18 (H8α, H9), H19 (H4, H5, H18).

[10] **12**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.54$ (s, 1H), 7.40 (d, $J = 2.3$ Hz, 1H), 7.31–7.16 (m, 5H), 6.54 (dd, $J = 8.3$, 2.3 Hz, 1H), 6.47 (d, $J = 2.3$ Hz, 1H), 4.18 (dd, $J = 10.6$, 5.6 Hz, 1H), 3.78 (s, 3H), 3.78 (s, 3H), 3.64 (d, $J = 9.5$ Hz, 1H), 2.83 (dd, $J = 13.7$, 10.6 Hz, 1H), 2.68 (br s, 1H), 2.11 (dd, $J = 13.7$, 5.6 Hz, 1H), 1.27–1.09 (m, 2H), 1.21 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 180.8$, 174.4, 159.9, 141.2, 137.6 (2C), 131.7, 128.7, 128.3 (2C), 125.1, 124.2, 107.4, 97.2, 66.2, 59.1, 58.6, 55.5, 52.3, 48.0, 43.3, 41.3, 29.2, 29.1.

[11] Yields based on recovered starting material. Actual yields are 57% for **9** and 31% for **11**.

[12] S. A. Boyd, W. J. Thompson *J. Org. Chem.* **1987**, *52*, 1790.

[13] **14**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.02$ (s, 1H), 7.41–7.30 (m, 5H), 6.53 (d, $J = 8.4$ Hz, 1H), 6.36 (d, $J = 2.3$ Hz, 1H), 6.08 (dd, $J = 8.4$, 2.3 Hz, 1H), 4.84 (dd, $J = 10.7$, 5.7 Hz, 1H), 4.25 (dd, $J = 8.0$, 8.0 Hz, 1H), 4.09 (dd, $J = 6.7$, 6.3 Hz, 1H), 3.72 (s, 3H), 3.55 (m, 1H), 2.49 (dd, $J = 13.4$, 11.1 Hz, 1H), 2.36–1.92 (m, 8H), 1.31 (s, 3H), 0.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 181.7$, 167.5, 166.8, 160.4, 142.4, 138.1 (2C), 131.7, 128.7, 128.5 (2C), 126.5, 119.2, 106.6, 97.6, 61.3, 58.7, 58.0, 55.4, 55.1, 48.3, 45.0, 42.8, 34.5, 27.9, 27.7, 26.5, 23.6.

[14] For an example of racemization of phenylalanine derivatives under these conditions, see: R. D. Larsen, R. A. Reamer, E. G. Corely, P. Davis, E. J. J. Grabowski, P. J. Reider, I. Shinkai *J. Org. Chem.* **1991**, *56*, 6034.

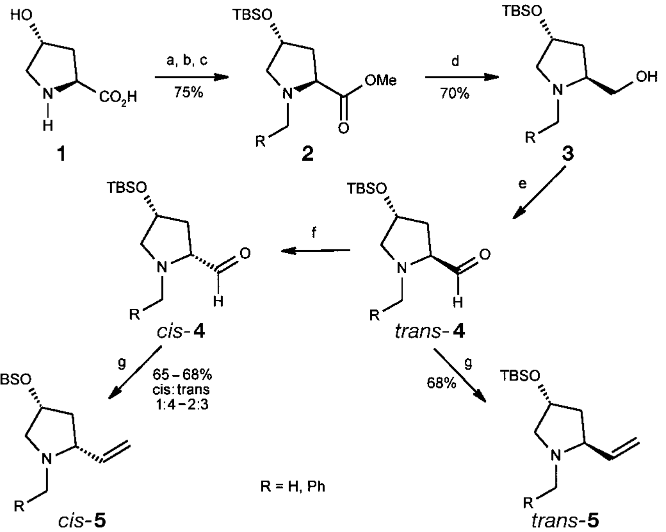
Unusual Diastereoselection in the Synthesis of Nine-Membered Ring Lactams and Conformation-Controlled Transannular Reactions to Generate Optically Active Indolizidinones[**]

Alexander Sudau and Udo Nubbemeyer*

Nine-membered ring lactams ("azoninones") of defined constitutions and configurations had been synthesized from vinylpyrrolidines by a zwitterionic aza-Claisen rearrangement.[1, 2] The highly ordered chairlike transition state[3] of the [3,3] sigmatopic rearrangement always induced the complete 1,3-chirality transfer from an (E)-allylamine to the corresponding γ,δ-unsaturated lactam.[1, 3] Furthermore an almost complete simple diastereoselection was operative[2, 3] resulting from a defined (Z)-enolate geometry in the hypothetical zwitterionic intermediate. A diastereoselective transannular reaction then converted the azoninones into indolizidinones.[2]

Here we report on the 1,4-chirality[3] transfer of the zwitterionic rearrangement induced by the defined enolate geometry, which had been sparsely investigated up to now. Terminally unsubstituted allylamines served as reactants, and the azoninones so formed were used as the key intermediates in the synthesis of chiral indolizidinones.

As starting compounds we chose the optically active *N*-benzyl- and *N*-methylvinylpyrrolidines *trans*-**5** and *cis*-**5**, which were generated from 4-*trans*-hydroxy-L-proline (**1**) in six steps (Scheme 1).



Scheme 1. Synthesis of the vinylpyrrolidines. a) $SOCl_2$, MeOH, reflux, 6 h; b) 98% HCO_2H, 37% CH_2O, reflux, 7h or PhCHO, $NaBH_3CN$, MeOH, 60°C, 2 d; c) TBSCl, imidazole, CH_2Cl_2, 20°C, 12 h; d) DIBAH, Et_2O, 0°C, 5 h; e) $C_2O_2Cl_2$, DMSO, Et_3N, CH_2Cl_2, −60°C, 2 h; f) cat. base, CH_2Cl_2, 20°C, 1 d;[12] g) $[Ph_3PCH_3]^+I^-$, n-BuLi, THF, −78°C to 20°C, 16 h.

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