

Total Synthesis of Tryprostatins A and B**

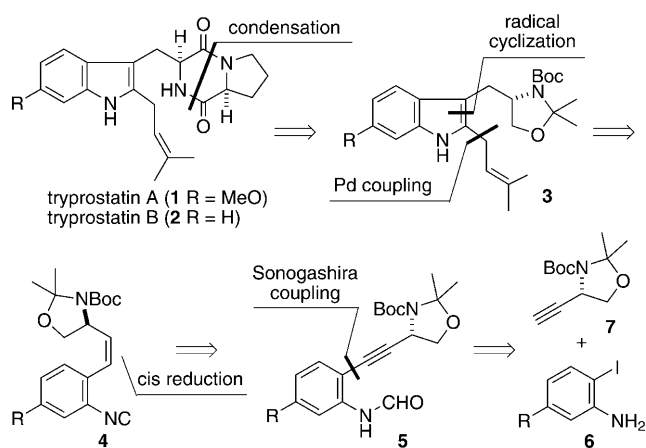
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Multiple-drug resistance toward cell-cycle inhibitors frequently becomes an obstacle in cancer chemotherapy. One strategy for circumventing this problem is to develop antimitotic agents that operate by a new mode of action. Two such compounds, tryprostatins A and B, were isolated in 1995 from the fermentation broth of *Aspergillus fumigatus* BM939 by Osada and co-workers.^[1] Tryprostatin A holds great promise, because it selectively arrests the cell cycle at the mitotic phase in tsFT210 cells.^[2] Interesting biological activity combined with an apparently simple structure has stimulated the synthetic community, and several total syntheses have already been reported.^[3,4]

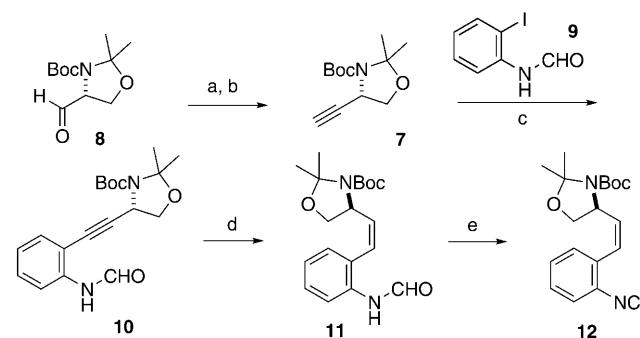
Our research group has long been involved with the radical-mediated construction of a variety of indole cores and the application of these methods to natural product synthesis.^[5,6] We envisioned that our method could also be applied to the synthesis of the 2,3-disubstituted indole moiety of the tryprostatins. The interesting structural features as well as the therapeutic potential of tryprostatin A analogues indicated in a recent structure–activity-relationship study^[4e] prompted us to launch a program toward the synthesis of tryprostatins.

We reasoned that radical-mediated cyclization and subsequent palladium-mediated coupling with a prenyl-group donor would enable facile construction of the 2,3-disubstituted indole core structure **3** (Scheme 1). The requisite *ortho*-alkenyl isocyanide **4** would be prepared from the alkyne **5**, which in turn could be accessed by Sonogashira coupling of the aromatic iodide **6** with the terminal alkyne **7**. To enable synthesis of the target compounds with high enantiomeric purity, the alkyne **7** derived from the Garner aldehyde (**8**)^[7] was employed as a latent amino acid unit to be incorporated into the diketopiperazine.

Initially, we focused our efforts on the synthesis of the isocyanide **12** as a radical-cyclization precursor (Scheme 2). The alkyne **7** was prepared from **8** according to the known protocol^[8] with a slight modification. After the Sonogashira coupling between **7** and 2-iodoformanilide (**9**), partial reduction of the triple bond was examined. Whereas the use of the Lindlar catalyst, Pd/C, nickel boride,^[9] or diimide^[10] resulted in no reaction or overreduction, treatment with Zn/LiCuBr₂



Scheme 1. Retrosynthetic analysis. Boc = *tert*-butoxycarbonyl.



Scheme 2. Synthesis of the *ortho*-alkenyl isocyanide **12**: a) CBr₄, PPh₃, Et₃N, CH₂Cl₂, –60–0°C, 88%; b) EtMgBr, THF, 0°C, 98%; c) **9**, CuI, [PdCl₂(PPh₃)₂], Et₃N, room temperature, 97%; d) Zn, BrCH₂CH₂Br, CuBr, LiBr, THF, CF₃CH₂OH, 70°C, 99%; e) triphosgene, pyridine, CH₂Cl₂, 0°C, 87%.

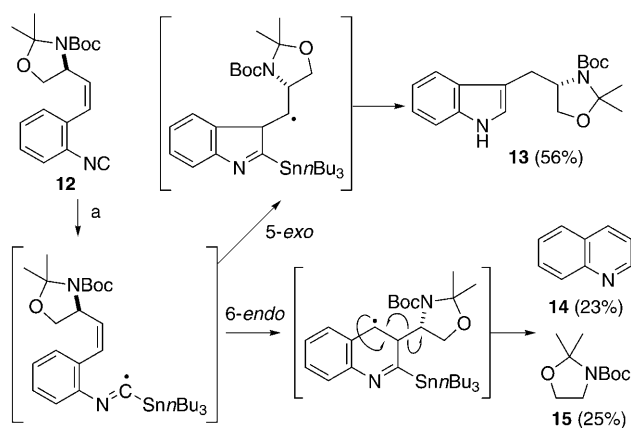
in ethanol^[11] gave the desired product **11** along with the corresponding amine. The use of 2,2,2-trifluoroethanol^[12] as the solvent suppressed the undesired solvolysis and improved the yield of **11** to 99%. Subsequent dehydration with bis(trichloromethyl) carbonate (triphosgene) gave the *ortho*-alkenyl isocyanide **12** and thus set the stage for a radical-mediated cyclization.

When isocyanide **12** thus obtained was subjected to our previously established radical-cyclization conditions,^[5a] the desired 5-*exo* adduct **13** was obtained in moderate yield after acidic treatment with silica gel along with a considerable amount of products **14** and **15** of a 6-*endo* cyclization–cleavage process (Scheme 3). We were aware of the tendency of this imidoyl-radical cyclization to give a mixture of the 5-*exo* and 6-*endo* products if the intermediate radical of the

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Scheme 3. Troublesome radical-mediated cyclization: a) $n\text{Bu}_3\text{SnH}$ (2.0 equiv), AIBN (15 mol%), MeCN, 100 °C; silica gel, room temperature. AIBN = azobisisobutyronitrile.

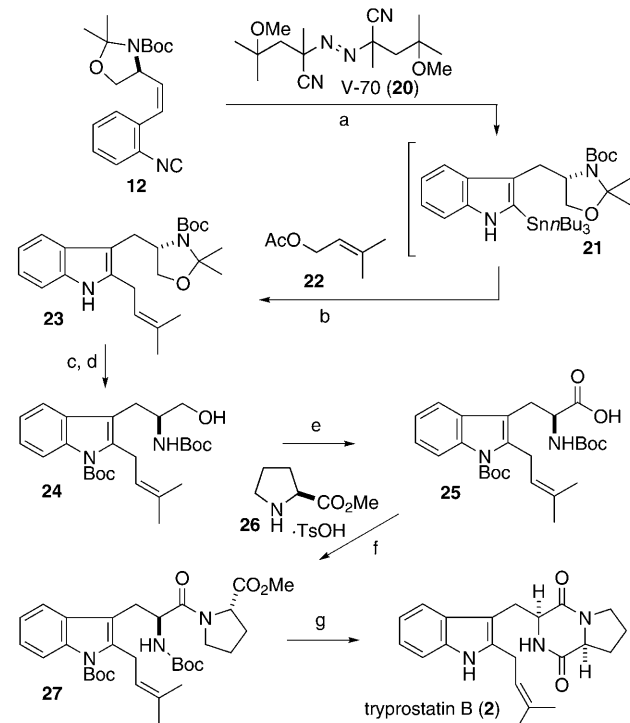
5-*exo* cyclization is not stabilized by the neighboring substituent.^[5] Although we showed in our previous studies that the 5-*exo* cyclization is dominant under conditions of kinetic control,^[5d] generally applicable conditions for the formation of 2-stannylindoles had yet to be determined. In an attempt to reduce the reaction temperature, we employed 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70, **20**) as a radical initiator with a lower decomposition temperature.^[13] To assess the potential of V-70, we chose substrates without radical-stabilizing substituents. When subjected to the reported conditions (AIBN, 100 °C), substrates **16** and **17** afforded a mixture of the 5-*exo* adduct **18** and the 6-*endo* adduct **19**, and cyclization of the *trans* isomer **17** proved to be more difficult than that of the *cis* isomer **16** (Table 1, entries 1 and 4).^[14] However, the use of V-70 at 30 °C virtually suppressed the formation of the 6-*endo* adduct: after acidic treatment, indole **18** was obtained in good yield as the dominant product, regardless of the configuration of the substrate (Table 1, entries 3 and 6). Thus, we established reliable conditions for imidoyl-radical-mediated indole synthesis.

Table 1: Low-temperature radical cyclization.

Entry	Substrate	Initiator	Solvent	T [°C]	Yield [%] ^[d]	
					18	19
1 ^[a]	16	AIBN	MeCN	100	72	18
2 ^[b]	16	AIBN	toluene	100	64	23
3 ^[c]	16	V-70	toluene	30	84	2
4 ^[a]	17	AIBN	MeCN	100	51	33
5 ^[b]	17	AIBN	toluene	100	48	34
6 ^[c]	17	V-70	toluene	30	77	6

[a] See reference [5a] for the reaction conditions. [b] Reaction conditions: $n\text{Bu}_3\text{SnH}$ (2.0 equiv), AIBN (15 mol%), toluene (0.2 M), 1 h, 100 °C; 1 M aqueous HCl, room temperature. [c] Reaction conditions: $n\text{Bu}_3\text{SnH}$ (2.0 equiv), V-70 (**20**, 15 mol%), toluene (0.2 M), 3 h, 30 °C; 1 M aqueous HCl, room temperature. [d] Yield of the isolated product.

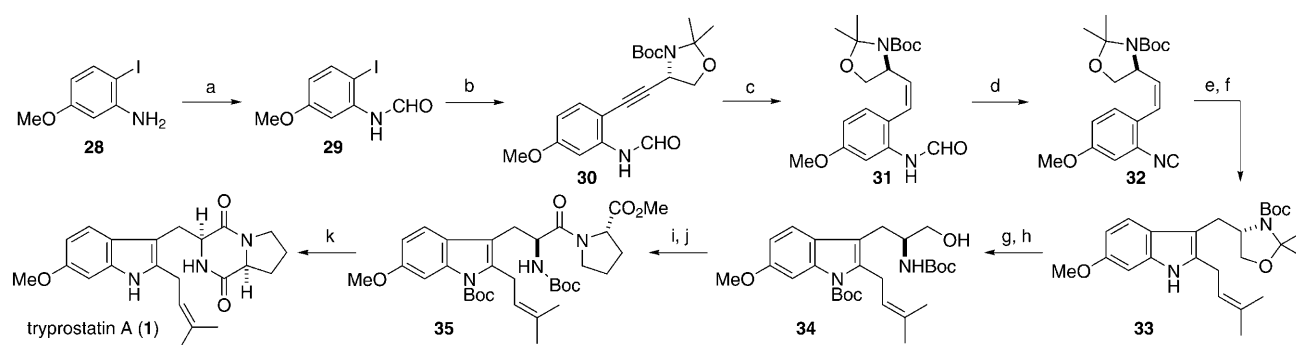
When this method was applied to the radical cyclization of the isocyanide **12**, complete selectivity was observed for the cyclization of the imidoyl radical to give the 2-stannylindole **21** (Scheme 4). Although we previously reported a one-pot Stille-type coupling reaction between aromatic or vinylic halides and 2-stannylindoles generated in situ for the



Scheme 4. Total synthesis of tryprostatin B: a) $n\text{Bu}_3\text{SnH}$ (3.0 equiv), V-70 (**20**, 20 mol%), toluene, 30 °C; b) **22**, LiCl (3.0 equiv), $[\text{Pd}_2(\text{dba})_3]$ (10 mol%), AsPh_3 (40 mol%), DMF, 80 °C, 73%; c) Boc_2O , DMAP, MeCN, room temperature, 99%; d) TFA/THF/ H_2O (4:2:1), 0 °C, 88%; e) TEMPO, $\text{PhI}(\text{OAc})_2$, MeCN, phosphate buffer (pH 6.8), room temperature, 91%; f) **26**, HATU, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , room temperature, 88%; g) NMP, reflux, 89%. dba = dibenzylideneacetone, DMAP = 4-dimethylaminopyridine, DMF = *N,N*-dimethylformamide, HATU = *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl, TFA = trifluoroacetic acid.

preparation of 2,3-disubstituted indoles,^[5a] no such coupling reactions with allylic systems have been reported. When $[\text{Pd}(\text{PPh}_3)_4]$ was used as the catalyst, the desired product was obtained in only 29% yield with prenyl acetate (**22**) as the coupling partner. Extensive investigations revealed that a combination of $[\text{Pd}_2(\text{dba})_3]$, triphenylarsine, and lithium chloride gave the best results and afforded the desired product **23** in 82% yield in a one-pot process from the isocyanide **12**.

Once construction of the indole moiety was complete, **23** was converted into the corresponding amino acid **25** in a three-step sequence consisting of protection of the indole with a Boc group, hydrolysis of the acetonide, and oxidation of the resulting alcohol **24** to the carboxylic acid **25** with TEMPO. After condensation with L-proline methyl ester



Scheme 5. Total synthesis of tryprostatin A: a) HCO_2H , Ac_2O , CH_2Cl_2 , 0°C , 98%; b) **7**, CuI , $[\text{PdCl}_2(\text{PPh}_3)_2]$, $\text{Et}_3\text{N}/\text{THF}$, room temperature, 98%; c) Zn , $\text{BrCH}_2\text{CH}_2\text{Br}$, CuBr , LiBr , THF , $\text{CF}_3\text{CH}_2\text{OH}$, 70°C , 94%; d) triphosgene, pyridine, CH_2Cl_2 , 0°C , 85%; e) $n\text{Bu}_3\text{SnH}$ (3.0 equiv), V-70 (20 mol %), toluene, 30°C ; f) **22**, LiCl (3.0 equiv), $[\text{Pd}_2(\text{dba})_3]$ (10 mol %), AsPh_3 (40 mol %), DMF , 80°C , 80%; g) Boc_2O , DMAP , MeCN , room temperature, 92%; h) $\text{TFA}/\text{THF}/\text{H}_2\text{O}$ (4:2:1), 0°C , 96%; i) TEMPO , $\text{PhI}(\text{OAc})_2$, phosphate buffer (pH 6.8), MeCN , 0°C , 91%; j) **26**, HATU , $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , room temperature, 77%; k) NMP , reflux, 78%.

(**26**), the remaining transformations involved the removal of the two Boc groups in **27** and cyclization to construct a diketopiperazine core structure. However, the conventional method for removing Boc groups under acidic conditions caused substantial decomposition of the substrate. Thus, we attempted thermal removal of the Boc groups.^[15] After extensive optimization, this transformation was carried out by heating the substrate under reflux in *N*-methylpyrrolidinone (NMP). Under these conditions, spontaneous cyclization occurred to give tryprostatin B (**2**) in 89% yield. Thus, tryprostatin B was synthesized in 11 steps from **8** in 33% overall yield on a half-gram scale.

Having established a generally applicable protocol for the preparation of 2-stannylindoles with V-70, we undertook the total synthesis of tryprostatin A (**1**) to showcase the synthetic utility of this approach (Scheme 5). The synthesis commenced with the preparation of **28** from 4-methoxy-2-nitroaniline in a two-step, slightly modified sequence, including the Sandmeyer reaction and iron-mediated reduction.^[4c,16] By following the route established for tryprostatin B, we synthesized tryprostatin A in 30% overall yield from **28** on a half-gram scale.

In summary, optimization of the radical-mediated indole synthesis by the use of V-70 made it possible to access 2-stannyl 3-substituted indoles with substituents at C3 that cannot effectively stabilize the radical intermediate. In combination with a subsequent palladium-mediated coupling reaction at C2, the radical cyclization enables the preparation of a variety of 2,3-disubstituted indoles, such as tryprostatins A and B. Further investigations into the synthesis and biological activity of tryprostatin analogues are under way.

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- [16] See the Supporting Information for a detailed description of the preparation of **28**.