ORGANIC LETTERS

2007
Vol. 9, No. 15
2763−2766

# Total Synthesis of Spirotryprostatin B via Diastereoselective Prenylation

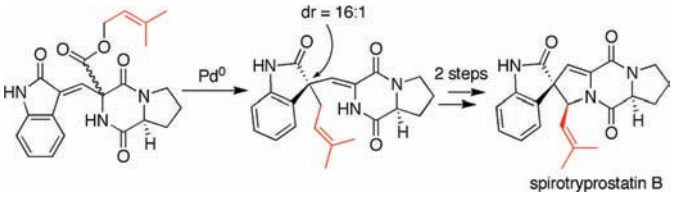
**Barry M. Trost* and Dylan T. Stiles**

*Department of Chemistry, Stanford University, Stanford, California 94305-0508*

*bmtrost@stanford.edu*

**Received April 25, 2007**

## ABSTRACT




**Spirotryprostatin B was synthesized in eight steps, utilizing an efficient palladium-catalyzed prenylation reaction to construct the quaternary C3 stereocenter. The decarboxylation–alkylation of a series of substituted β-keto esters is described, demonstrating the broad scope of this class of pronucleophiles and allylating agents.**

In an endeavor to identify natural products capable of regulating specific stages of the cell cycle, Osada et al. isolated spirotryprostatins A (**1**) and B (**2**) from the fermentation broth of *Aspergillus fumigatus* in 1996.[1] These compounds inhibit the G2/M phase of the mammalian cell cycle at micromolar concentrations. Biosynthetically, **1** and **2** likely derive from the diketopiperazine of tryptophan and proline, a motif also found in the tryprostatin[2] and fumitremorgin[3] families of natural products. A number of syntheses of **2** have been reported,[4] motivated in part by its scarce natural abundance (11 mg from a 400 L fermentation) and its unique structure. The scaffold of spirotryprostatin B has recently served as the blueprint for a library of cellular probes.[5]

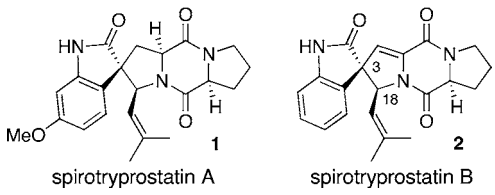



**Figure 1.** Spirotryprostatin A (**1**) and spirotryprostatin B (**2**).

The most synthetically challenging structural features in **2** are the spirocyclic ring juncture at C3 and the adjacent prenyl-substituted C18. Our approach to spirotryprostatin B involves the construction of the C3 quaternary stereocenter in a highly controlled manner—a feat that has proven difficult in prior syntheses. Approaches toward **2** that generate the spirocyclic stereocenter by using substrate control, e.g., using Mannich-type processes,[4c,i] typically result in a mixture of

(1) (a) Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832−835. (b) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651−12666.

(2) Cui, C. B.; Kakeya, H.; Okada, G.; Onose, R.; Ubukata, M.; Takahashi, I.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48*, 1382−1384.

(3) (a) Yamazaki, M.; Fujimoto, H.; Kawasaki, T. *Chem. Pharm. Bull.* **1980**, *28*, 245−254. (b) Hino, T.; Nakagawa, M. *Heterocycles* **1997**, *46*, 673−704.

(4) (a) Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596−4599. (b) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666−5667. (c) von Nussbaum, F.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2175−2178. (d) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 4685−4693. (e) Sebahar, P. R.; Osada, H.; Usui, T.; Williams, R. M. *Tetrahedron* **2002**, *58*, 6311−6322. (f) Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249−251. (g) Meyers, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 694−696. (h) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209−2219. (i) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5357−5360. (j) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505−11515.

(5) Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077−16086.

10.1021/ol070971k CCC: $37.00 
**Published on Web 06/26/2007**

diasteromeric products, resulting in a low overall yield for this relatively simple natural product. While this problem has been addressed with the use of stoichiometric chiral auxiliaries, there has been only one report of a strategy that invokes asymmetric catalysis to forge the C3 spirocenter, although the route ultimately proved to be rather long.[4a] The shortest route exercises no stereocontrol at any step.[4c]

Retrosynthetically, we envision that **2** can derive from the functionalization of **3** (Figure 2), which raises the question

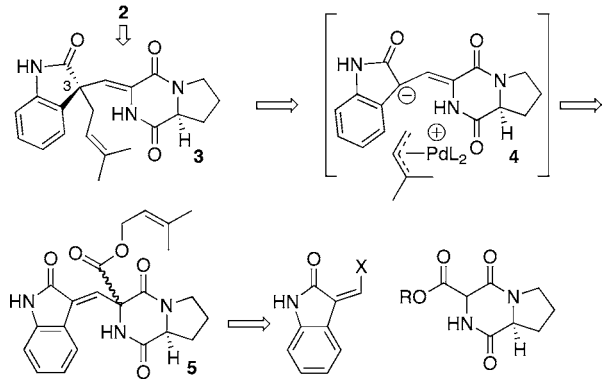


**Figure 2.** Retrosynthetic analysis.

of whether a prenyl chain can be introduced via palladium-catalyzed allylic alkylation. The required nucleophile **4** is a stabilized carbanion that can be thought of as a vinylogous 1,3-dicarbonyl species. As the location of the double bond in **4** is presumably labile, a number of compounds could potentially serve to generate the same reactive intermediate. We ultimately targeted the use of ester **5** as a nucleophile precursor. Upon exposure to palladium catalysis, **5** would potentially ionize and decarboxylate, triggering the prenylation reaction.

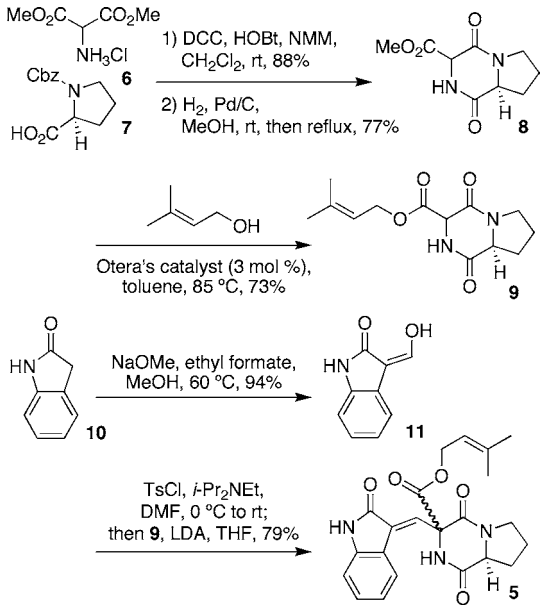
The decarboxylation−alkylation of **5** is related to the Carroll reaction[6,7] of allyl-$\beta$-ketoesters. While this reaction was originally conducted by thermolysis, Saegusa[8] and Tsuji[9] demonstrated that it could be catalyzed by palladium at much lower temperatures. More recently, enantioselective variants have been developed by our group[10] and others.[11,12]

Reports of palladium-catalyzed decarboxylation−alkylation using phosphinooxazoline (PHOX) ligands pioneered by Williams[13] and Pfaltz and Helmchen[14] have been limited to allyl or 2-substituted allyl groups. Going beyond such limited substrates would be an important step in enhancing the utility of this methodology. Therefore we have undertaken an examination of systems with trisubstituted olefins such as prenyl, presented here in the context of a natural product synthesis.

The type of anion depicted in **4** also poses the challenge of control of regioselectivity. Compound **4** features two nucleophilic sites (the oxindole and diketopiperazine carbons), making eight potential isomeric products. We desire the product arising from decarboxylative allylation with double bond transposition, which has not previously been reported.

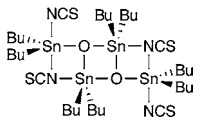
A rapid synthesis of **5** was accomplished starting with Cbz-proline and dimethyl aminomalonate hydrochloride (Scheme 1). Known diketopiperazine **8**[15] was transesterified to prenyl

**Scheme 1.** Synthesis of Prenylation Substrate



ester **9** with use of Otera's catalyst.[16] In a one-pot reaction, oxindole **11**[17] was activated as its vinyl tosylate, then treated with the lithium salt of **9**. The coupled product **5** was obtained in good yield as a 1:1.7 mixture of diastereomers,[18] a stereogenic center that is later destroyed and subsequently reconstituted.

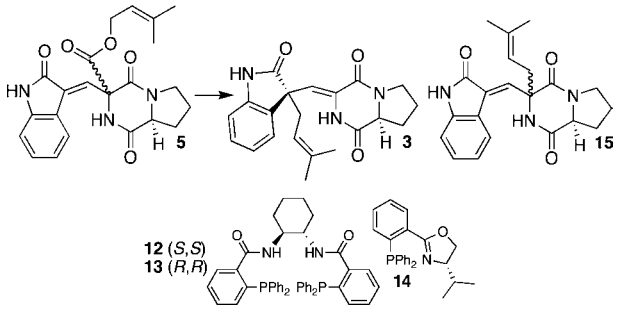
(6) Carroll, M. F. *J. Chem. Soc.* **1940**, 1266−1268.
(7) Kimel, W.; Cope, A. C. *J. Am. Chem. Soc.* **1943**, *65*, 1992−1998.
(8) Tsuda, T.; Chujo, Y.; Nishi, S.-I.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381−6384.
(9) (a) Tsuji, J. *Pure Appl. Chem.* **1982**, *54*, 197−206. (b) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988−2995.
(10) (a) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846−2847. (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180−17181.
(11) (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044−15045. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924−6927.
(12) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113−4115.
(13) Williams, J. M. *Synlett* **1996**, 705−710.
(14) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336−345.
(15) (a) Kametani, T.; Kanaya, N.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 959−963. (b) Kardassis, G.; Brungs, P.; Steckhan, E. *Tetrahedron* **1998**, *54*, 3471−3478.
(16) (a) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307−5311. (b) Otera, J. *Chem. Rev.* **1993**, *93*, 1449−1470. The isothiocyanate catalyst pictured below was used:



(17) Wenkert, E.; Bhattacharyya, N. K.; Reid, T. L.; Stevens, T. E. *J. Am. Chem. Soc.* **1956**, *78*, 797−801.
(18) The *E*/*Z* configuration of oxindole-bound olefin in **5** and its derivatives is not known, but presumed to be as depicted based on known trends of $\alpha,\beta$-unsaturated amides.

With the key substrate in hand, **5** was subjected to palladium catalysis. We were pleased to find that prenylation indeed occurred, giving the desired isomer **3** as the major product. A screening of reaction conditions (Table 1)

**Table 1.** Selected Optimization Studies[a]




| entry | ligand | solvent | mol % Pd | dr of **3** | **3**:**15** | yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | $PPh_3$ | dioxane | 10 | 1:1 | 1.2:1 | 89 |
| 2 | **12** | dioxane | 10 | 2.4:1 | 4.5:1 | 83 |
| 3 | **12** | DCE | 10 | 2.6:1 | 1.4:1 | 69 |
| 4 | **12** | toluene | 10 | 8.8:1 | 10:1 | 75 |
| 5[c] | **12** | toluene | 10 | *16:1* | *14:1* | *89*[d] |
| 6 | **12** | toluene | 2 | 9:1 | 1.3:1 | 71 |
| 7 | **13** | toluene | 10 | 1:1.7 | 11:1 | 71 |
| 8[e] | **14** | THF | 10 | | | 0 |

[a] Unless otherwise indicated, all reactions were conducted at 60 °C on a 24 $\mu$mol scale at 24 $\mu$M with $Pd_2(dba)_3$·$CHCl_3$ as a catalyst precursor. [b] Based on NMR relative to *N*-methylformanilide as an internal standard. [c] Reaction conducted on a 300 mg scale. [d] Isolated yield. [e] Reaction conducted at 50 °C.

determined that the best results were obtained with ligand **12** in toluene at 60 °C (entries 4 and 5).

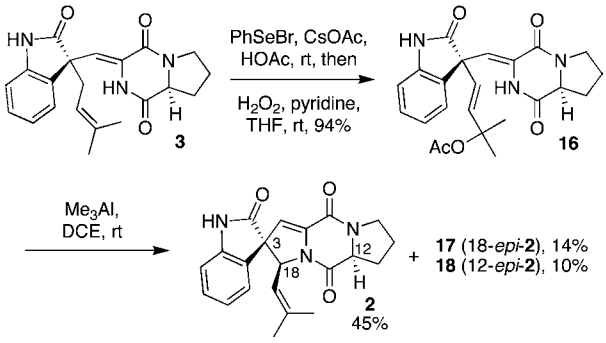
The use of triphenylphosphine gave essentially a statistical mixture of product isomers, highlighting the need for asymmetric catalysis. The catalyst loading could be lowered to 2 mol % palladium (entry 6), but the regioselectivity was diminished. Entry 7 shows that the use of (*R*,*R*)-**13** is stereochemically mismatched. When the two diastereomers of **5** were separated and reacted individually, a similar product mixture was obtained in each case. These results support the notion that the reaction proceeds through common intermediate **4**. Therefore, it was more convenient to carry **5** through the synthesis as a mixture of isomers. We were pleased to find that the prenylation reaction gave even better results (dr = 16:1, regioselectivity = 14:1) on a larger scale (300 mg), affording **3** in 89% isolated yield.

To functionalize the prenyl chain and complete the synthesis (Scheme 2), we turned to selenium chemistry originally developed by Sharpless.[19] In one operation, **3** was first treated with PhSeOAc (prepared in situ), and then the selenide was oxidized and eliminated with hydrogen peroxide, giving the allylic acetate **16** in excellent yield.

For the final cyclization, a survey of conditions using catalytic palladium or copper failed. However, the use of an

(19) Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, *39*, 429−430.

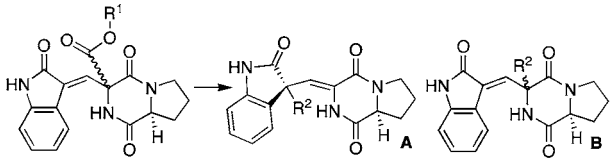
**Scheme 2.** Synthesis of Spirotryprostatin B




aluminum amide, generated in situ by the treatment of **16** with trimethylaluminum, does succeed in promoting the cyclization to give spirotryprostatin B in 45% isolated yield along with minor amounts of isomers **17** and **18**.[20] The effectiveness of this reagent can be attributed to its dual role as both a Brønsted base and a Lewis acid.

Having completed the synthesis of the natural product, we decided to explore the key allylic alkylation in more detail (Table 2). Compounds **19**−**21**, bearing a variety of allylic

**Table 2.** Allylic Alkylation with Various Substrates[a]




| entry | $R^1$ | $R^2$ | dr of **A**[b] | **A**:**B** | yield[c] (%) |
|---|---|---|---|---|---|
| 1 | **5** | **3** | 16:1 | 14:1 | 89 |
| 2 | **19** | **3** | 12:1 | 3.9:1 | 83 |
| 3[d] | **20** | **22** | 3.3:1 | >20:1 | 55 |
| 4[d] | **21** | **23** | 2.3:1 | >20:1 | 79 |

[a] All reactions were conducted at 60 °C on a 24 $\mu$mol scale at 24 $\mu$M at 60 °C with $Pd_2(dba)_3$·$CHCl_3$ as a catalyst precursor. [b] Absolute stereochemistry assigned by analogy to **3**. [c] Isolated yields. [d] Reaction run at 40 °C.

substituents, were synthesized in a manner analogous to **5**. As a means to obviate the selenium step, we imagined introducing the side chain at a higher oxidation state. Thus, vinyl chloride **21** was prepared.

With all substrates, the reaction proceeded with alkylation primarily at the oxindole carbon. Nucleophilic attack occurred at the more sterically accessible terminus of the Pd-allyl intermediate, giving linear products in all cases.

(20) The formation of **18** (12-*epi*-**2**) can be attributed to the basicity of the reaction conditions. This stereocenter has been shown to be labile, e.g., ref 4e.

Therefore, vinyl chloride **23** was not useful for further elaboration to **2**. The "reversed ester" **19** also functioned. Although the dr was somewhat reduced compared to **5**, good regioselectivity was observed.

We propose a model for this reaction depicted in Figure 3.[21] In our standard "wall and flap" depiction of the ligand/

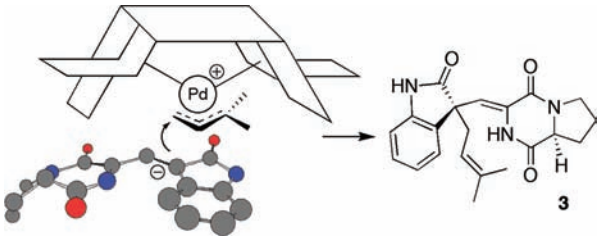



**Figure 3.** Model for observed selectivity.

catalyst environment,[22] the ionization event occurs preferentially under the flap. For prenyl ester **5**, this initially places the prenyl group such that the primary carbon is under the flap. In that conformation, nucleophilic addition also occurs under the flap, leading to the results observed. The unfavorable steric clash between the wall and the geminal dimethyl substituents of the prenyl group may force rapid collapse of the ion pair, giving the kinetic product **3**. A slower reaction may allow the Pd-bound prenyl to equilibrate its position on the catalyst, giving reduced selectivity. This notion is supported by the diminished regioselectivity observed in a reaction with 2 mol % palladium catalyst (Table 1, entry 6).

In conclusion, we have developed a rapid synthesis of spirotryprostatin B that delivers the natural product in 8 steps and 13% overall yield. The decarboxylation−prenylation of **5**, with transposition of the double bond, is an unprecedented transformation. The exquisite control in the formation of the quaternary C3 stereocenter presents a major improvement in the synthesis of this family of alkaloids.

**Acknowledgment.** We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences Institute (GM33049), for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Facility of the University of California−San Francisco, supported by NIH Division of Research Resources. We thank Johnson Matthey for their generous donation of palladium salts.

**Supporting Information Available:** Experimental details for the synthesis of all intermediates, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070971K

(21) The structure of the nucleophile generated by energy-minimized Chem3D calculations.

(22) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545−4554.