ORGANIC LETTERS

2013
Vol. 15, No. 17
4426–4429

The Synthesis of Indoline and Benzofuran Scaffolds Using a Suzuki–Miyaura Coupling/Oxidative Cyclization Strategy

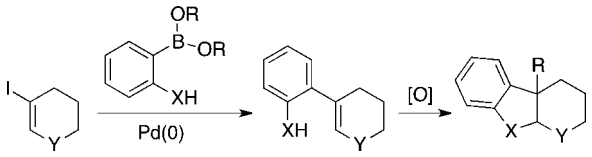
Somnath Jana and Jon D. Rainier*

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, United States

rainier@chem.utah.edu

Received July 12, 2013

ABSTRACT



The generation of indolines and benzofurans from the combination of Suzuki–Miyaura coupling reactions with oxidative cyclizations is described.

Over the past several years we have become intrigued with the synthesis and study of indoline containing natural products including those that have a pyrido[2,3-*b*]indoline (tetrahydro-α-carboline) skeleton as part of their architecture.[1] Tetrahydro-α-carbolines that are of interest to us include cytotoxic metabolites from both marine (kapakahine E) and terrestrial organisms (chaetominine and oxaline) (Figure 1).[2–4]

Previously, all synthetic work to these substrates had relied on the use of indolines or indoles as precursors.[5,6] An example from our laboratory is illustrated in Scheme 1. During our total synthesis of kapakahine E we generated pyrroloindoline **1** from tryptophan and in turn converted **1** into tetrahydro-α-carboline **2** (Scheme 1).[7] While impressive, this latter transformation required a large excess of $AlMe_3$ making it not too surprising that the reaction also

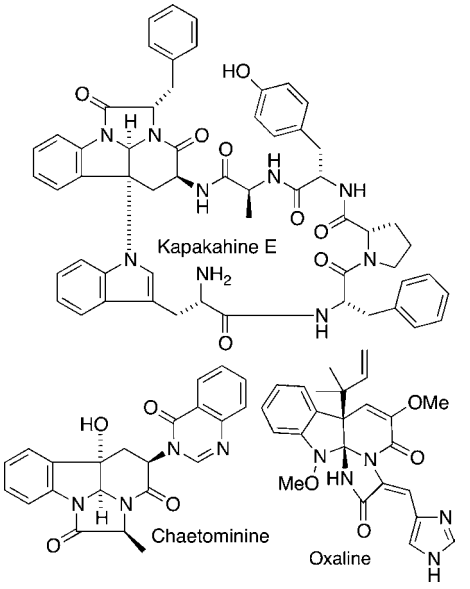


Figure 1. Tetrahydro-α-carboline containing natural products.

(1) (a) Espejo, V. R.; Rainier, J. D. *Org. Lett.* **2010**, *12*, 2154. (b) Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 4317.

(2) (a) Nakao, Y.; Yeung, B. K. S.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. *J. Am. Chem. Soc.* **1995**, *117*, 8271. (b) Yeung, B. K. S.; Nakao, Y.; Kinnel, R. B.; Carney, J. R.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. *J. Org. Chem.* **1996**, *61*, 7168. (c) Nakao, Y.; Kuo, J.; Yoshida, W. Y.; Kelly-Borges, M.; Scheuer, P. J. *Org. Lett.* **2003**, *5*, 1387.

(3) Jiao, R.; Xu, S.; Liu, J.; Ge, H.; Ding, H.; Xu, C.; Zhu, H.; Tan, R. *Org. Lett.* **2006**, *8*, 5709.

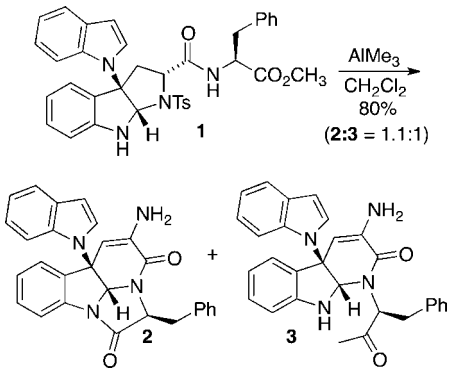
(4) (a) Konda, Y.; Onda, M.; Hirano, A.; Õmura, S. *Chem. Pharm. Bull.* **1980**, *28*, 2987. (b) Koizumi, Y.; Arai, M.; Tomoda, H.; Õmura, S. *Biochim. Biophys. Acta* **2004**, *1693*, 47.

(5) (a) Kennedy, A. R.; Taday, M. H.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2407. (b) Boyarskikh, V.; Nyong, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5374. (c) Espejo, V. R.; Rainier, J. D. *J. Am. Chem. Soc.* **2008**, *130*, 12894. (d) Espejo, V. R.; Li, X.-B.; Rainier, J. D. *J. Am. Chem. Soc.* **2010**, *132*, 8282.

10.1021/ol401974v
Published on Web 08/16/2013

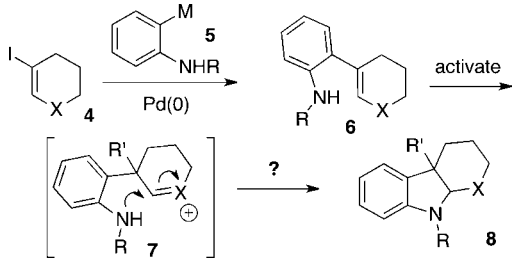
resulted in the generation of significant quantities of methyl ketone **3**.

Scheme 1. α-Carbolines from Pyrroloindolines



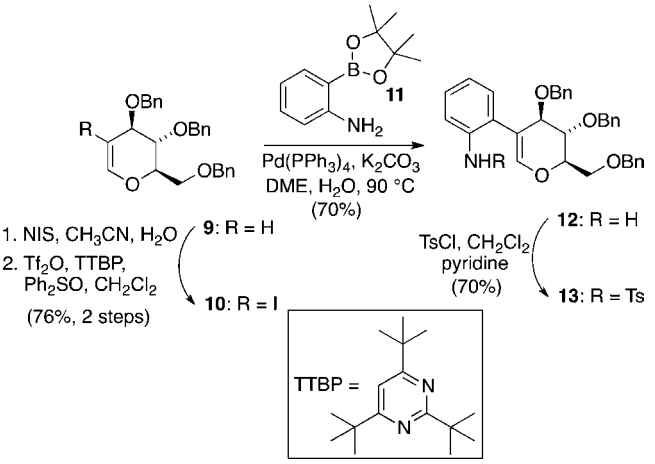
Our struggles with the generation of **3** from **1** along with the lack of a general synthetic approach to tetrahydro-α-carbolines led us to consider whether a route that started with the piperidine subunit intact might be feasible. This idea ultimately led us to explore the coupling, oxidative cyclization route that is the focus of this letter (Scheme 2).[8−10] In addition to leading to the synthesis of tetrahydro-α-carbolines, a bonus to our approach is that it has enabled us to extend the targets that are accessible to us to include aminals and benzofurans.

Scheme 2. Proposed Coupling−Oxidative Cyclization Strategy to Tetrahydro-α-carbolines



Although, as mentioned above, our inspiration for these studies was the tetrahydro-α-carboline skeleton, we chose to initially examine the proposed sequence using D-glucal **9** (Scheme 3). This was largely a consequence of reports from Boutrueira, Davis and co-workers that described the generation and conversion of 3-iododihydropyrans into 3-arylglycosides using Suzuki−Miyaura coupling reactions.[11,12] Pleasingly, we were able to follow the Boutrueira protocol and both convert glucal **9** into 2-iodoglucal **10** and generate 2-arylglycal **12** by subjecting **10** to 2-aminophenylpinacolborane **11** and Pd(0). Sulfonamide formation gave cyclization precursor **13**. It was interesting to us that the sulfonamide analog of **11** underwent exclusive protodeborylation when exposed to the Suzuki−Miyaura reaction conditions.[13]

Scheme 3. Suzuki−Miyaura Coupling to Aryl Glycal **13**



With **13** in hand, we explored its conversion into the desired indolines (Schemes 4 and 5). To this end we were pleased to find that **13** was transformed into hydroxyindoline **14** after being exposed to *m*-CPBA. This transformation could also be carried out with dimethyldioxirane but only if the oxidation was followed by the treatment of the presumed epoxide intermediate with SiO_2.[14] That **14** was *cis*-fused was verified by the ^3J value between H-4 and H-5 (9.5 Hz), by the NOE that was observed between H-2 and H-6, and by comparison of the spectral data for **14** with those for *trans*-fused **16** (*vide infra*).

As alluded to above, the stereochemistry at the new ring junction was dependent on the reagent used to activate the dihydropyran. In contrast to the epoxide initiated cyclization, the use of NBS as the oxidant resulted in the generation of *trans*-fused indoline **16** in 62% yield (Scheme 5). As with

(6) For other syntheses of α-carbolines, see: (a) Newhouse, T.; Lewis, C. A.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 6360. (b) Snider, B. B.; Wu, X. *Org. Lett.* **2007**, *9*, 4913. (c) Toumi, M.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 5027. (d) Malgesini, B.; Forte, B.; Borghi, D.; Quartieri, F.; Gennari, C.; Papeo, G. *Chem.—Eur. J.* **2009**, *15*, 7922. (e) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Synthesis* **2009**, 2927. (f) Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119.

(7) See ref 1a and Espejo, V. R.; Rainier, J. D. *Isr. J. Chem.* **2011**, *51*, 473.

(8) For a recent review, see: de Vries, J. G. *Top. Organomet. Chem.* **2012**, *42*, 1.

(9) For a related NBS induced oxidative cyclization, see: Chang, M.-Y.; Tai, H.-Y.; Chen, Y.-L. *Tetrahedron* **2011**, *67*, 7673.

(10) For examples of related oxidative spirocyclizations, see: (a) Liu, G.; Wurst, J. M.; Tan, D. S. *Org. Lett.* **2009**, *11*, 3670. (b) Robertson, J.; Chovatia, P. T.; Fowler, T. G.; Withey, J. M.; Woollaston, D. J. *Org. Biomol. Chem.* **2010**, *8*, 226. (c) Potuzak, J. S.; Moilanen, S. B.; Tan, D. S. *J. Am. Chem. Soc.* **2005**, *127*, 13796.

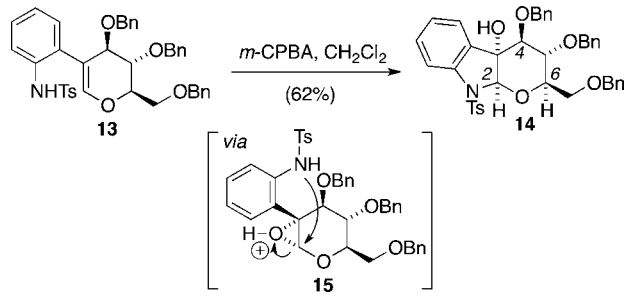
(11) Rodríguez, M.; Boutureira, O.; Matheu, M.; Díaz, Y.; Castillón, S.; Seeberger, P. *J. Org. Chem.* **2007**, *72*, 8998.

(12) Cobo, I.; Matheu, M.; Castillón, S.; Boutureira, O.; Davis, B. *Org. Lett.* **2012**, *14*, 1728.

(13) Fier, P. S.; Luo, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2552.

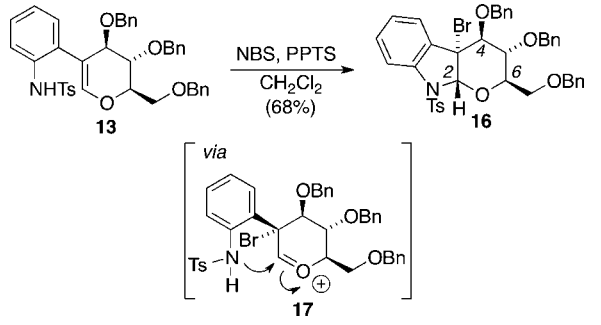
(14) For seminal work on glycal epoxides and their reactivity, see: Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

Scheme 4. Glycal Epoxide Cyclization to Indoline **14**



14, the relative stereochemistry of **16** was determined using a series of ^{1}H NMR experiments (lack of NOE between H-2 and H-6, the H-4, H-5 ^{3}J value (3.3 Hz), and a comparison with the spectral data for **14**).[15] We speculate that **16** comes from axial attack of the sulfonamide onto oxocarbenium ion intermediate **17** while the *cis*-fused ring in **14** results from the direct addition of the sulfonamide onto the activated epoxide intermediate **15**.[16]

Scheme 5. NBS Initiated Cyclization to Indoline **15**



Having generated pyrano[2,3-*b*]indolines **14** and **16**, we targeted tetrahydro-α-carbolines next and used glutarimide (**18**) as the starting material (Scheme 6). The conversion of **18** into enamide **19** was relatively straightforward.[17] The generation of iodide **20** did not require a separate dehydration as was required for **10** but instead occurred directly from **19** by treating it with NIS.[18] The Suzuki–Miyaura coupling of **20** with aniline **11** was equally uneventful providing cyclization precursor **22** after sulfonamide formation.

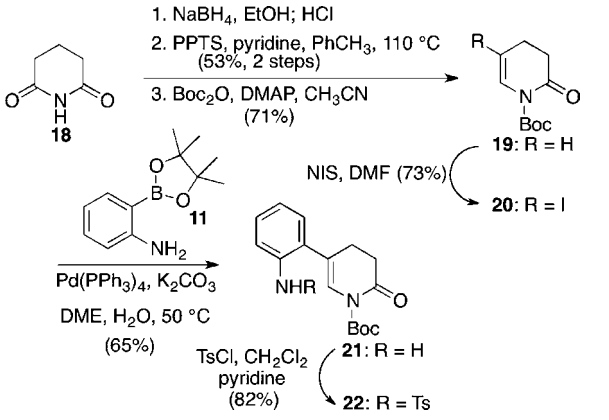
(15) The ^{3}J coupling constants in **16** are consistent with the pyran ring adopting a boat conformation.

(16) For a related argument in the stereoselective generation of *C*-glycosides, see: (a) Rainier, J. D.; Cox, J. M. *Org. Lett.* **2000**, *2*, 2707. (b) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997. (c) Roberts, S. W.; Rainier, J. D. *Org. Lett.* **2005**, *7*, 1141.

(17) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

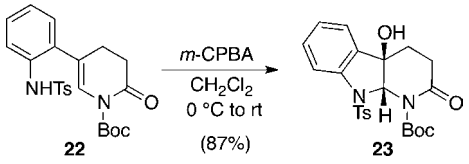
(18) Related reactions are known. See: van den Broek, S. A. M. W.; Rensen, P. G. W.; van Delft, F. L.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2010**, 5906.

Scheme 6. Suzuki–Miyaura Coupling to Piperidine **21**



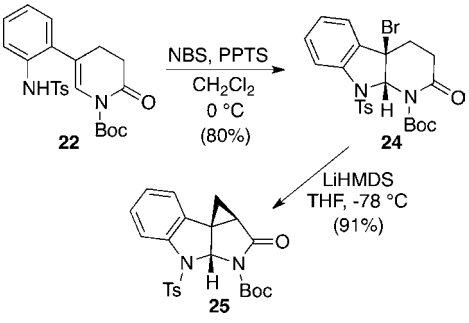
In a related fashion to the reaction of **13**, **22** underwent a smooth oxidative cyclization reaction when treated with *m*-CPBA to give *cis*-fused indoline **23** (Scheme 7).[19]

Scheme 7. Oxidative Cyclization to α-Carboline **22**



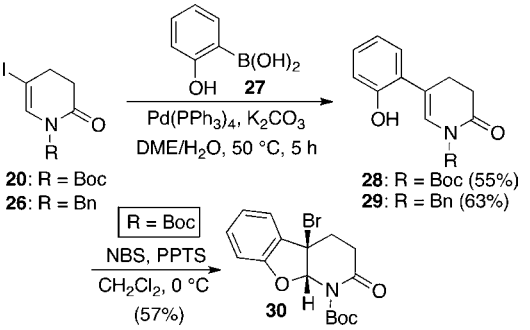
In contrast to the reaction of dihydropyran **13**, the reaction of **22** with NBS gave *cis*-fused bromide **24** (Scheme 8). The ring junction stereochemistry in **24** was determined by subjecting **24** to LiHMDS to generate cyclopropane **25** whose relative stereochemistry was confirmed through NOE correlations.[20] While additional experiments are required to fully explain these results, we speculate that the active intermediate from enamide **22** reacts as a bromonium ion rather than as an iminium ion.

Scheme 8. Oxidative Cyclization to α-Carboline **24** and Its Conversion into Cyclopropane **25**



Having demonstrated the synthesis of tetrahydro-α-carbolines, we decided to determine whether the oxidative

Scheme 9. Oxidative Cyclizations to Benzofurans



cyclization strategy could be employed in the synthesis of benzofurans. To this goal, we examined both Boc protected enamide **20** and Bn protected substrate **26**.[21] Both reacted with *ortho*-substituted boronic acid **27** in the presence of Pd(0) to give **28** and **29** in 55% and 63% yields, respectively (Scheme 9). As with the corresponding aniline, the treatment of **28** with NBS and PPTS resulted in the generation of benzofuran **30**.

Interestingly, the epoxidation and cyclization of **28** resulted in an intractable mixture of products. In contrast, *N*-benzyl analog **29** successfully underwent cyclization to

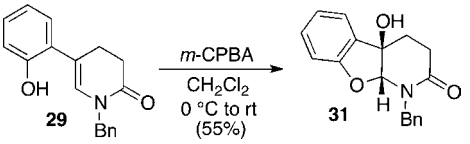
(19) The ring junction stereochemistry for **23** has been assigned based on an assessment of NOE correlations in the corresponding *N*-benzyl isopropyl ester. See Supporting Information.

(20) We believe that **25** comes from an intramolecular S_N2 displacement. See ref 5d.

(21) de Villar, I. S.; Gradillas, A.; Pérez-Castells, J. *Eur. J. Org. Chem.* **2010**, 5850 and the Supporting Information for the synthesis of **26**.

(22) We speculate that competitive quinone methide generation leads to the observed decomposition of the epoxide from **28**.

Scheme 10. Oxidative Cyclization to Benzofuran **29**



31 when exposed to *m*-CPBA (Scheme 10). Presumably, the difference in reactivity between **28** and **29** is due to the enhanced ability of the benzyl amide to donate electron density to the epoxide intermediate when compared to the corresponding Boc amide.[22]

In conclusion, we have uncovered a simple and general means of synthesizing pyrido[2,3-*b*]indolines (tetrahydro-α-carbolines), pyrano[2,3-*b*]indolines, and corresponding benzofurans that is centered around Suzuki–Miyaura coupling reactions of electron-rich olefins with a subsequent oxidative cyclization.

Acknowledgment. We are grateful to the National Science Foundation (CHE 0650405) and to Cephalon for support of this work. We would like to thank the support staff at the University of Utah and especially Dr. Peter Flynn (NMR) and Dr. Jim Muller (mass spectrometry) for help in obtaining data.

Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.