ORGANIC LETTERS

2011
Vol. 13, No. 2
196−199

Synthesis of Tylocrebrine and Related Phenanthroindolizidines by VOF_3-Mediated Oxidative Aryl-Alkene Coupling

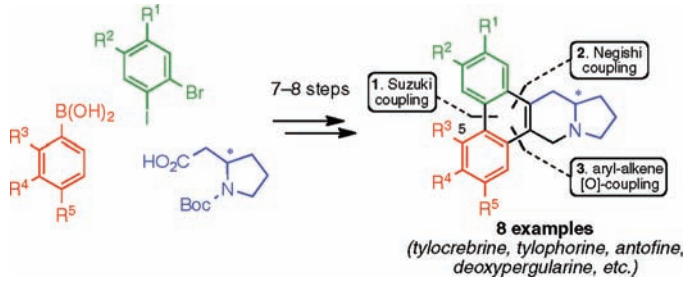
Micah J. Niphakis[†,‡] and Gunda I. Georg[*,‡]

Department of Medicinal Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, United States, and Department of Medicinal Chemistry and The Institute for Therapeutics Discovery & Development, University of Minnesota, 717 Delaware Street SE, Minneapolis, Minnesota 55414, United States

georg@umn.edu

Received October 18, 2010

ABSTRACT



A highly convergent strategy to prepare phenanthroindolizidines is reported involving three consecutive C−C coupling reactions. This sequence features a novel VOF_3-mediated aryl-alkene coupling in the final step, which enables regioselective preparation of C5-substituted phenanthroindolizidines for the first time. This strategy has been applied to the synthesis of eight natural and unnatural members in this class to investigate the scope of this chemistry and to explore structure−activity relationships.

The phenanthroindolizidine and phenanthroquinolizidine alkaloids have received increasing attention over the past decade for their newfound potent anticancer[1] and anti-inflammatory activity.[2] Salient members of this class tylophorine,[3] antofine,[4] and boehmeriasin A,[5] for example inhibit tumor growth with IC_{50} values in the low nanomolar to picomolar range, on par with currently used anticancer drugs. These medicinal properties have inspired numerous total syntheses of the alkaloids and their unnatural analogs. Yet despite a plethora of synthetic strategies,[1,6] several members of this class cannot be prepared efficiently.

The prevailing strategy to construct the phenanthrene system in these natural products whether used early or later

[†] Department of Medicinal Chemistry, University of Kansas.
[‡] Department of Medicinal Chemistry and The Institute for Therapeutics Discovery & Development, University of Minnesota.

(1) Chemler, S. R. *Curr. Bioact. Compd.* **2009**, *5*, 2–19, and references therein.

(2) (a) Gopalakrishnan, C.; Shankaranarayan, D.; Kameswarn, L.; Natarajan, S. *J. Med. Res.* **1979**, *69* (3), 513–520. (b) Gopalakrishnan, C.; Shankaranarayanan, D.; Nazimudeen, S. K.; Kameswaran, L. *Indian J. Med. Res.* **1980**, *71*, 940–948. (c) You, X.; Pan, M.; Gao, W.; Shiah, H. S.; Tao, J.; Zhang, D.; Koumpouras, F.; Wang, S.; Zhao, H.; Madri, J. A.; Baker, D.; Cheng, Y. C.; Yin, Z. *Arthritis Rheum.* **2006**, *54* (3), 877–886. (d) Yang, C. W.; Chen, W. L.; Wu, P. L.; Tseng, H. Y.; Lee, S. J. *Mol. Pharmacol.* **2006**, *69* (3), 749–758.

(3) (a) Ganguly, T.; Khar, A. *Phytomedicine* **2002**, *9*, 288–295. (b) Paull, K. D.; Hamel, E.; Malspeis, L. In *Cancer Chemotherapeutic Agents*; Foye, W. O., Ed.; American Chemical Society: Washington, DC, 1995; pp 9−45. (c) Gao, W.; Lam, W.; Zhong, S.; Kaczmarek, C.; Baker, D. C.; Cheng, Y. C. *Cancer Res.* **2004**, *64*, 678–688.

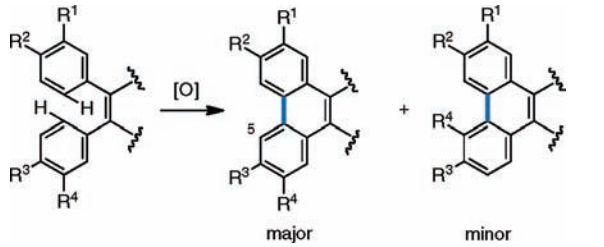
(4) (a) Lee, S. K.; Nam, K. A.; Heo, Y. H. *Planta Med.* **2003**, *69* (1), 21–25. (b) Stærk, D.; Lykkeberg, A. K.; Christensen, J.; Budnik, B. A.; Abe, F.; Jaroszewski, J. W. *J. Nat. Prod.* **2002**, *65*, 1299–1302. (c) Fu, Y.; Lee, S. K.; Min, H. Y.; Lee, T.; Lee, J.; Cheng, M.; Kim, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 97–100.

(5) (a) Luo, Y.; Liu, Y.; Luo, D.; Gao, X.; Li, B.; Zhang, G. *Planta Med.* **2003**, *69*, 842–845. (b) Yan, J.; Luo, D.; Luo, Y.; Gao, X.; Zhang, G. *Int. J. Gynecol. Cancer* **2006**, *16*, 165–170.

10.1021/ol1023954
Published on Web 12/14/2010

in the reaction sequence is through dehydrogenative biaryl coupling (Scheme 1). Although this approach is flexible with

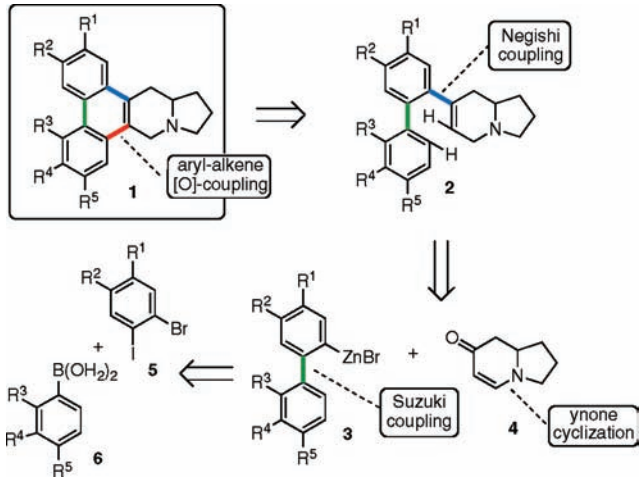
Scheme 1. Typical Strategy for Synthesis of Phenanthrene Moiety



respect to the aryl substituents being installed, it poses a noteworthy limitation on the accessibility of particular phenanthrene substitution patterns. Specifically, these reactions cannot accommodate sterically disfavored substituents, such as the obtrusive C5-methoxy group seen in tylocrebrine (**1a**), with any practical degree of selectivity.

To avoid the problem of regioselectivity, we designed a new approach for the phenanthrene construction that involved three sequential C−C bond forming steps (Scheme 2). The

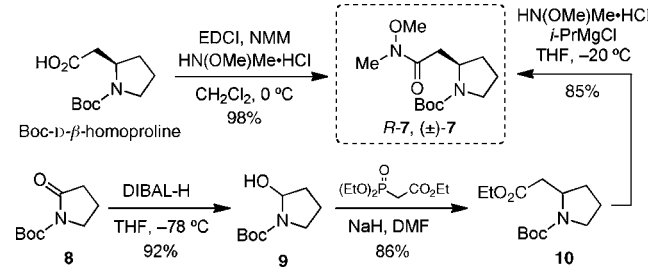
Scheme 2. Phenanthroindolizidine Retrosynthetic Analysis



key step is the final ring closure, involving an aryl-alkene dehydrogenative coupling. Unlike the standard biaryl-coupling strategy to phenanthrenes, this disconnection imposes regioselective control by exploiting the problematic C5-substituent (R^3) to block coupling at C5, thereby, preventing regioisomer formation. The requisite precursor **2**, in turn, could be derived from a Negishi reaction of biphenylzinc reagent **3** and a triflate derived from indolizidine **4**. Having recently developed a concise route to six-membered cyclic enaminones involving the cyclization of amino acid derived ynones,[7] we thought these versatile synthons would be apt precursors to enantiomerically pure phenanthropiperidines. The third C−C bond could be realized through a Suzuki−Miyaura biaryl coupling reaction from iodobromobenzene (**5**) and boronic acid (**6**) precursors.

First looking to the indolizidine fragment, we began our synthesis with commercially available Boc-D-β-homoproline (Scheme 3). Weinreb amide *R*-**7** could be formed directly

Scheme 3. Synthesis of Weinreb Amide



using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI). In order to facilitate library development, a scalable approach was developed for the synthesis of the racemic Weinreb amide (±)-**7**. Boc-pyrrolidinone was reduced to hemiaminal **9** and then subjected to HWE conditions. The resultant ring-opened ester spontaneously cyclized to provide the racemic β-proline derivative **10**. Amide (±)-**7** was then obtained from ester **10** using conditions reported by Williams et al.[8] Although this sequence is more lengthy than that of amide *R*-**7**, the payoff is the ease and economy of scale-up.

Constructing the indolizidine fragment was our next goal. We have conducted extensive studies into the formation of cyclic enaminones from β-amino ynones.[7] Grignard addition of ethynylmagnesium bromide to Weinreb amide *R*-**7** provided the desired ynone **11** in excellent yield (Scheme 4).

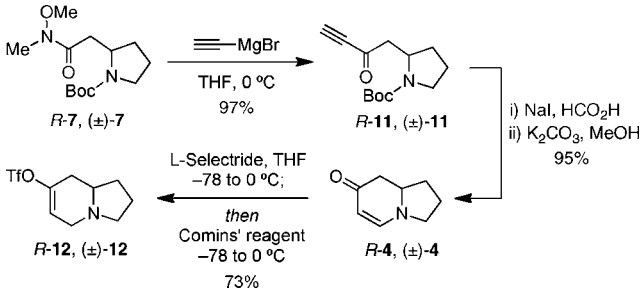
Indolizidine formation could be achieved using our one-pot deprotection/cyclization strategy. Either 4 N HCl in dioxane or NaI in HCO_2H can be used for Boc-deprotection.[7b] Although the yields of the latter conditions (i.e., NaI/HCO_2H) were generally higher, workup following the cyclization was easier using the HCl method. It should be noted that the use of HCl promotes *retro*-Michael/Michael-type racemization of the β-stereocenter and, therefore, was not used for constructing indolizidine *R*-**4**. With

(6) For selected recent examples, see: (a) Yang, X.; Shi, Q.; Bastow, K. F.; Lee, K. H. *Org. Lett.* **2010**, *12*, 1416–1419. (b) Wang, K. L.; Su, B.; Wang, Z. W.; Wu, M.; Li, Z.; Hu, Y. N.; Fan, Z. J.; Mi, N.; Wang, Q. M. *J. Agric. Food. Chem.* **2010**, *58*, 2703–2709. (c) Stoye, A.; Opatz, T. *Org. Lett.* **2010**, *12*, 2140–2141. (d) Dumoulin, D.; Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **2010**, 1943–1950. (e) Yamashita, S.; Kurono, N.; Senboku, H.; Tokuda, M.; Orito, K. *Eur. J. Org. Chem.* **2009**, 1173–1180. (f) Wang, K.; Su, B.; Wang, Z.; Wu, M.; Li, Z.; Hu, Y.; Fan, Z.; Mi, N.; Wang, Q. *J. Agric. Food Chem.* **2009**, *58*, 2703–2709. (g) Li, S. T.; Han, L.; Sun, L.; Zheng, D.; Liu, J.; Fu, Y. B.; Huang, X. S.; Wang, Z. Y. *Molecules* **2009**, *14*, 5042–5053. (h) Cui, M. B.; Wang, Q. M. *Eur. J. Org. Chem.* **2009**, 5445–5451.

(7) (a) Turunen, B. J.; Georg, G. I. *J. Am. Chem. Soc.* **2006**, *128*, 8702–8703. (b) Niphakis, M. J.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6793–6805.

(8) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.

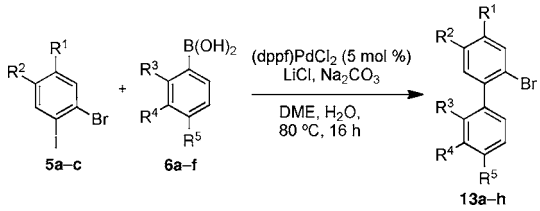
Scheme 4. Synthesis of Indolizidine Fragment



the indolizidine core assembled, triflate **12** was prepared using a 1,4-reduction and enolate trapping with Comins' reagent.

We then turned to the synthesis of the biaryl fragment via Suzuki−Miyaura cross-coupling. Fürstner and Kennedy have reported a straightforward route to biarylbromides that was used for the synthesis of several phenanthropiperidine alkaloids.[9] This method was well-suited for our purposes (Table 1). Although biarenes with *ortho* substituents had not

Table 1. Synthesis of Biaryl Fragment



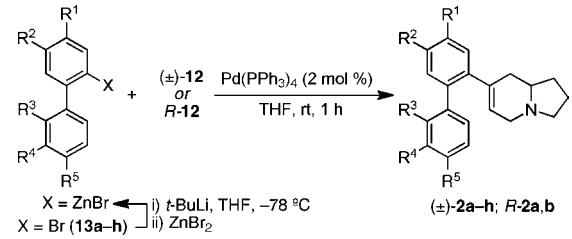
entry	R^1	R^2	R^3	R^4	R^5	yield (%)[a]
1	OMe	OMe	OMe	OMe	H	72 (**13a**)
2	OMe	OMe	H	OMe	OMe	67 (**13b**)
3	OMe	OMe	OMe	H	H	77 (**13c**)
4	OMe	OMe	H	OMe	H	68 (**13d**)
5	OMe	OMe	H	H	OMe	70 (**13e**)
6	H	OMe	H	OMe	OMe	70 (**13f**)
7	H	H	H	OMe	OMe	75 (**13g**)
8	OMe	OMe	H	H	H	40[b] (**13h**)

[a] Isolated yield. [b] Isolated along with 4′,5′-dimethoxy-1,1′:2′,1″-terphenyl as an inseparable mixture.

been previously synthesized by this method, the reported conditions worked well with these hindered boronic acids (entries 1 and 3, Table 1). Coupling phenyl boronic acid to 1-bromo-2-iodo-4,5-dimethoxybenzene (entry 8), however, was problematic due to the formation of an inseparable impurity.[10] Nevertheless, the mixture could still be used in subsequent reactions without detrimental effects.

We next employed a Negishi cross-coupling reaction between either triflate (±)-**12** or (*R*)-**12** and the appropriate biarylzinc coupling partner. Only two biarenes, **13a** and **13b**, were appended to the enantiopure indolizidine core as a proof of concept and to complete the synthesis of (*R*)-tylocrebrine for the first time. We were pleased to find that these cross-couplings proceeded in under an hour at room temperature providing near quantitative yields of indolizidines **2a**−**h** without significant variation (Table 2).

Table 2. Coupling of Indolizidine and Biaryl Fragments



entry	R^1	R^2	R^3	R^4	R^5	yield (%)[a]
1	OMe	OMe	OMe	OMe	H	95 (**2a**)
2	OMe	OMe	H	OMe	OMe	98 (**2b**)
3	OMe	OMe	OMe	H	H	97 (**2c**)
4	OMe	OMe	H	OMe	H	95 (**2d**)
5	OMe	OMe	H	H	OMe	98 (**2e**)
6	H	OMe	H	OMe	OMe	98 (**2f**)
7	H	H	H	OMe	OMe	95 (**2g**)
8	OMe	OMe	H	H	H	92 (**2h**)

[a] Isolated yield.

Having all the desired carbons in place, we explored the oxidative aryl-alkene coupling. To our knowledge there has only been only one report of such a reaction.[11] Concerned by this lack of precedent, we undertook a systematic investigation using reagents that have found use in the related biaryl coupling reaction.[12] Using indolizidine **2a** as a model system, we identified VOF_3, which gave the desired product in 70% yield by NMR, as a suitable reagent for this transformation.

With this initial success, we applied this reaction to our small collection of biarylindolizidines **2a**−**h** to prepare the corresponding phenanthroindolizidines **1a**−**1h** (Table 3). Notably, we did not observe the formation of regioisomers in substrates lacking the C5-methoxy group. However, there were noticeable differences between the reactivity of substrates **2a** and **2c**, where R^3 = OMe, compared with the rest, and as such, two variations of the oxidative coupling method were employed. Substrates **2a** and **2c** required warming the reaction mixture from −78 to −10 °C and addition of up to 4.5 equiv of VOF_3 to drive the reaction to completion (Method A). For all other substrates, where the C5-methoxy group was absent, the reactions were kept at −78 °C and only 2.2−2.5 equiv of VOF_3 were required for complete

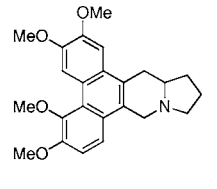
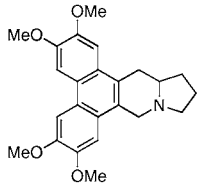
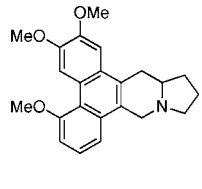
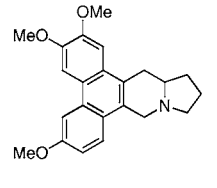
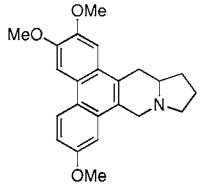
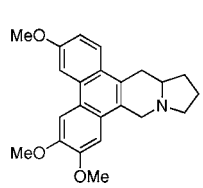
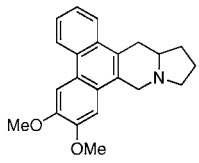
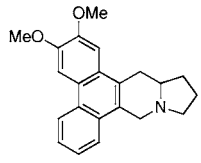
(9) Fürstner, A.; Kennedy, J. W. J. *Chem.—Eur. J.* **2006**, *12*, 7398–7410.

(10) The impurity is presumably 4′,5′-dimethoxy-1,1′:2′,1″-terphenyl resulting from a bis-phenylation of 1-bromo-2-iodo-4,5-dimethoxybenzene.

(11) Lapouyade, R.; Villeneuve, P.; Nourmamode, A.; Morand, J. P. *J. Chem. Soc., Chem. Commun.* **1987**, 776–778.

(12) See Supporting Information.

Table 3. Aryl-Alkene Biaryl Couplings

phenanthroindolizidine products (% yield,[a] method[b])
 (±)- and (*R*)-tylocrebrine (**1a**) (62%, A)
 (±)- and (*R*)-tylophorine (**1b**) (89%, B)
 (±)-**1c** (28%, A)
 (±)-antofine (**1d**) (85%, A)
 (±)-**1e** (70%, A)
 (±)-**1f** (68%, A)
 (±)-**1g** (85%, A)
 (±)-**1h** (65%, A)

[a] Isolated yield. [b] Method A: VOF_3 (2.5 equiv), CH_2Cl_2, EtOAc, TFA, TFAA, −78 °C; *then* VOF_3 (1.5−2.0 equiv), −10 °C. Method B: VOF_3 (2.5 equiv), CH_2Cl_2, EtOAc, TFA, TFAA, −78 °C.

conversion (Method B). We suggest that these observations can be explained by the rates of intramolecular versus intermolecular coupling. The C5-substituent evidently slows the progression of this reaction resulting in the starting material, product or both being shunted into competing intermolecular coupling pathways. The end result is nonproductive consumption of VOF_3, hence the requirement for excess amounts of this reagent to prepare tylocrebrine (**1a**) and its unnatural analogue **1c**. In spite of the consequential loss in yield, all of the desired products could be obtained in sufficient quantities to assess their antiproliferative properties.

As seen in Table 4, these alkaloids are very potent antiproliferative agents in COLO-205, MCF-7, and drug-resistant NCI/ADR-RES cell lines. Most of these analogs have comparable activity with paclitaxel for COLO-205 and MCF-7 cells and retain their antiproliferative effects in the paclitaxel-resistant NCI/ADR-RES cell line. It has been previously shown that (*S*)-tylophorine is more active than its *R*-enantiomer.[13] Although this is not clear from the present data in the COLO-205 and MCF-7 cells, tylophorine's racemate shows greater activity in the NCI/ADR-RES cell line than pure (*R*)-tylophorine. On the other hand, (*R*)-tylocrebrine exhibits greater activity than its racemate, which suggests that the (*R*)-enantiomer is more active. With the exception of analog **1f**, the removal or relocation of each of the methoxy groups has surprisingly little effect on the alkaloids' activity. The NCI/ADR-RES cell line, however, appears to be more sensitive to these structural modifications, particularly in analogs **1e**, **1f**, **1g**, and **1h**. The retention of activity across this series is an indication that the phenanthroindolizidines are well suited for further lead development in order to improve their potential for use in the clinic.

(13) Gao, W.; Chen, A. P. C.; Leung, C. H.; Gullen, E. A.; Fürstner, A.; Shi, Q.; Wei, L.; Lee, K. H.; Cheng, Y. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 704–709.

Table 4. Antiproliferative Activity of Phenanthroindolizidines[a]

	IC_{50} (nM)		
product	COLO-205	MCF-7	NCI/ADR-RES
paclitaxel	5.3	2.3	>6400
(*R*)-tylocrebrine (**1a**)	1.3	15	26
(±)-tylocrebrine (**1a**)	12	39	46
(*R*)-tylophorine (**1b**)	17	32	160
(±)-tylophorine (**1b**)	10	42	50
(±)-**1c**	9.5	22	16
(±)-antofine (**1d**)	2.8	21	23
(±)-**1e**	270	530	1300
(±)-**1f**	8.5	5.8	200
(±)-**1g**	48	25	180
(±)-**1h**	29	21	180

[a] COLO-205 = human colorectal adenocarcinoma; MCF-7 = human breast carcinoma; NCI-ADR-RES = drug-resistant human ovarian adenocarcinoma.

In summary, we have developed a highly convergent route to phenanthroindolizidine alkaloids by aid of a novel aryl-alkene oxidative coupling reaction. Most notably, this method gives access to C5-substituted analogues, such as tylocrebrine (**1a**), with complete regioselectivity for the first time. The modularity of this approach allows for late stage diversification and has enabled the synthesis and biological evaluation of eight alkaloids with varying phenanthrene substitution patterns.

Acknowledgment. The authors are grateful to Defang Tian (University of Minnesota) for carrying out the antiproliferative assays and to Matthew W. Leighty (University of Minnesota) for useful discussions about aryl-alkene coupling conditions. This work was supported by the University of Minnesota through the Vince and McKnight Endowed Chairs. M.J.N. gratefully acknowledges the ACS-Division of Medicinal Chemistry for a predoctoral fellowship.

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

OL1023954