ORGANIC LETTERS

2011
Vol. 13, No. 2
220−223

Tandem Cyclopropane Ring-Opening/Conia-ene Reactions of 2-Alkynyl Indoles: A [3 + 3] Annulative Route to Tetrahydrocarbazoles

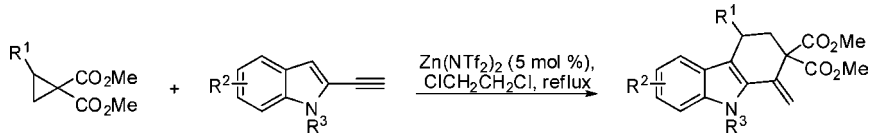
Huck K. Grover, Terry P. Lebold, and Michael A. Kerr*

Department of Chemistry, The University of Western Ontario, London, Ontario, Canada N6A 5B7

makerr@uwo.ca

Received October 29, 2010

ABSTRACT



A $Zn(NTf_2)_2$ catalyzed tandem reaction consisting of a nucelophilic ring opening of 1,1-cyclopropanediesters by 2-alkynyl indoles followed by a Conia-ene ring closure results in the efficient one-step synthesis of tetrahydrocarbazoles. The adducts may be further elaborated to carbazoles.

It is unarguable that indoles rank among the most important heterocyclic compounds. They remain prime scaffolds for pharmaceutical drug discovery, and their prominence in natural products is enormous. As such there continues to be a large degree of activity devoted to the efficient chemical elaboration of the benzopyrrole ring system.[1] A subset of the indoles is the carbazoles and their hydro-derivatives. The preparations of these structures have seen significant interest among the chemical community due in part to the carbazoles and their hydro-derivatives' presence in naturally occurring and bioactive compounds.[2] Figure 1, for example, shows a sampling of carbazole natural products isolated in recent years.[3] Given our recent interest in the synthesis of carbazole natural products,[4] we were compelled to explore new ways to access this ubiquitous ring system. Herein we present a one pot, [3 + 3] annulative route to tetrahydrocarbazoles (and subsequently carbazoles) via a tandem cyclopropane ring-opening/Conia-ene cyclization of 2-alkynyl indoles.[5]

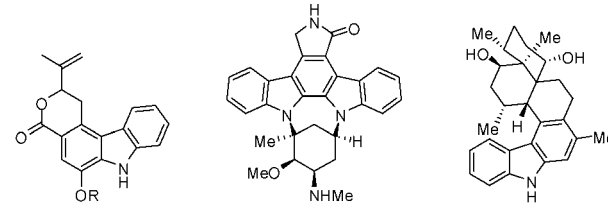


Figure 1. Representative carbazole natural products.

Our idea for the synthesis of tetrahydrocarbazoles in this manner evolved from a general strategy shown in Scheme 1, which was fostered by our longstanding interest in the chemistry of donor−acceptor cyclopropanes[6] and their use

(1) For reviews on the synthesis and functionalization of indoles, see: (a) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Sundberg, R. J. *Indoles*; Academic: New York, 1996.

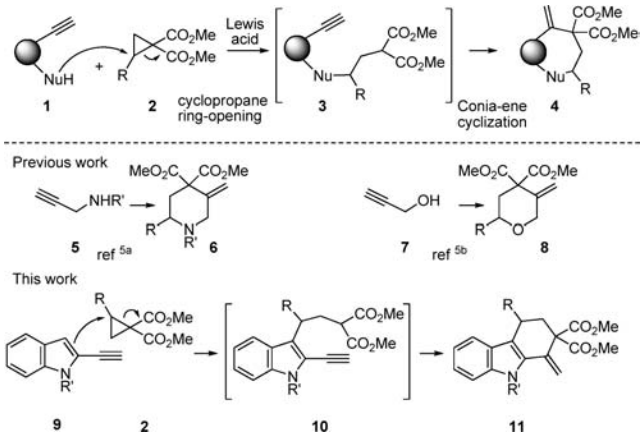
(2) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303.

(3) (a) Clausamines: Ito, C.; Katsuno, S.; Ruangrungsi, N.; Furukawa, H. *Chem. Pharm. Bull.* **1998**, *46*, 344. (b) Staurosporine: Satoshi, O.; Yuzuru, I.; Atushi, H.; Akira, N.; Juichi, A.; Hisae, T.; Yoko, T.; Rokurou, M. *J. Antibiot.* **1977**, *30*, 275. (c) Aflavazole: TePaske, M. R.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Org. Chem.* **1990**, *55*, 5299.

(4) Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2008**, *10*, 997. (b) Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2007**, *9*, 1883.

10.1021/ol102627e
Published on Web 12/16/2010

Scheme 1. Generalized Tandem Ring-Opening/Conia-ene Process

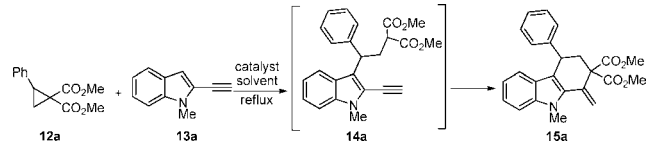


in the synthesis of heterocycles.[7] Any nucleophilic moiety (**1**) with a tethered alkynyl group could, in principle, participate in a two-step sequence involving a nucleophilic cyclopropane ring-opening reaction to yield a pendant malonate and a subsequent Conia-ene[8] reaction of the malonate with the acetylenic group. Recently, we reported successful examples of this process where the nucleophile was an amino or a hydroxyl group resulting in the formation of piperidines[5a] and tetrahydropyrans[5b] (Scheme 1). Given that we have shown that indoles may nucleophilically open cyclopropanediesters,[9] we were curious whether indoles, bearing an acetylene at the 2-position, would undergo the tandem process described above with a net synthesis of tetrahydrocarbazoles in what would be a formal [3 + 3] cycloaddition.

The main challenges for the implementation of the strategy shown in Scheme 1 are twofold: (i) The nucleophiles' reactivity must be orthogonal to that of the acetylenic group (i.e., they must not react with each other), and (ii) a Lewis acid must be found which can activate the cyclopropane toward ring opening and also activate the acetylene in the Conia-ene process. This last issue is somewhat complicated by the fact that it is the harder, oxophilic Lewis acids which are usually required for chelation with the geminal diester moiety on the cyclopropane, while softer metals are usually most successful in the Conia-ene reaction.

Our study began with cyclopropane **12a** (chosen for its well-known reactivity in nucleophilic ring-opening chemistry) and indole **13a**. Knowledge gained from our previous work allowed us to arrive quickly at optimal reaction conditions (Table 1); in fact, $Zn(NTf_2)_2$ at a loading of 5 mol % in refluxing dichloroethane emerged as the reaction conditions of choice, giving tetrahydrocarbazole **15a** in an 84% isolated yield (entry 7).

Table 1. Optimization Studies



entry	indole (equiv)	catalyst	solvent	time (h)	yield (%)
1	1.1	$Sc(OTf)_3$ (10 mol %), then $ZnBr_2$ (3 equiv), NEt_3 (1 equiv)	benzene	1.5	63
2	1.1	$Zn(NTf_2)_2$ (20 mol %)	benzene	2.0	84
3	1.4	$Zn(NTf_2)_2$ (10 mol %)	benzene	2.0	87
4	1.4	$Zn(NTf_2)_2$ (5 mol %)	benzene	4.0	88
5	1.4	$Zn(NTf_2)_2$ (5 mol %)	toluene	24.0	n/a
6	1.4	$Zn(NTf_2)_2$ (5 mol %)	CH_2Cl_2	23.0	84
7	1.4	$Zn(NTf_2)_2$ (5 mol %)	$ClCH_2CH_2Cl$	1.5	84

(5) (a) Lebold, T. P.; Leduc, A. B.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 3770. (b) Leduc, A. B.; Lebold, T. P.; Kerr, M. A. *J. Org. Chem.* **2009**, *74*, 8414.

(6) For reviews on donor−acceptor cyclopropanes, see: (a) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (c) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (d) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (e) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (f) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

(7) For leading references on the synthesis of heterocycles from cyclopropanes, see: (a) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196. (b) Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 8242. (c) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023. (d) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014. (e) Korotkov, V. S.; Larionov, O. V.; Hofmeister, A.; Magull, J.; de Meijere, A. *J. Org. Chem.* **2007**, *72*, 7504. (f) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642. (g) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689. (h) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 1107. (i) Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 4354.

(8) Thermal: (a) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1. Au mediated: (b) Pan, J.-H.; Yang, M.; Gao, Q.; Zhu, N.-Y.; Yang, D. *Synthesis* **2007**, 2539. (c) Ochida, A.; Ito, H.; Sawamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16486. (d) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350. (e) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. Pd mediated: (f) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764. (g) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168. In mediated: . (h) Hatakeyama, S. *Pure Appl. Chem.* **2009**, *81*, 217. (i) Itoh, Y.; Tsuji, H.; Yamagata, K.-i.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 17161. (j) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6244. (k) Tsuji, H.; Yamagata, K.-i.; Itoh, Y.; Endo, K.; Nakamura, M.; Nakamura, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8060. Cu/Ag cocatalyzed: (l) Deng, C.-L.; Zou, T.; Wang, Z.-Q.; Song, R.-J.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 412. (m) Deng, C.-L.; Song, R.-J.; Guo, S.-M.; Wang, Z.-Q.; Li, J.-H. *Org. Lett.* **2007**, *9*, 5111. Ni mediated: (n) Gao, Q.; Zheng, B.-F.; Li, J.-H.; Yang, D. *Org. Lett.* **2005**, *7*, 2185. Ti mediated: (o) Kitigawa, O.; Suzuki, T.; Inoue, T.; Watanabe, Y.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 9470. Co mediated: (p) Renaud, J.-L.; Aubert, C.; Malacria, M. *Tetrahedron* **1999**, *55*, 5113. (q) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699. (r) Cruciani, P.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1994**, *35*, 6677. Zn mediated: . (s) Morikawa, S.; Yamazaki, S.; Tsukada, M.; Izuhara, S.; Morimoto, T.; Kakiuchi, K. *J. Org. Chem.* **2007**, *72*, 6459. (t) Morikawa, S.; Yamazaki, S.; Furusaki, Y.; Amano, N.; Zenke, K.; Kakiuchi, K. *J. Org. Chem.* **2006**, *71*, 3540. (u) Nakamura, M.; Liang, C.; Nakamura, E. *Org. Lett.* **2004**, *6*, 2015. (v) Cavicchioli, M.; Marat, X.; Monteiro, N.; Hartmann, B.; Balme, G. *Tetrahedron Lett.* **2002**, *43*, 2609. (w) Marat, X.; Monteiro, N.; Balme, G. *Synlett* **1997**, 845. Cu mediated: . (x) Montel, S.; Bouyssi, D.; Balme, G. *Adv. Synth. Catal.* **2010**, *352*, 2315.

(9) (a) Harrington, P. E.; Kerr, M. A. *Tetrahedron Lett.* **1997**, *38*, 5949. (b) Kerr, M. A.; Keddy, R. G. *Tetraheron Lett.* **1999**, 5671. (c) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704.

It should be noted that benzene and dichloromethane were also effective media for the reaction; however, dichloromethane required extended reaction times. As expected, the harder Lewis acid $Sc(OTf)_3$ was effective in the ring-opening step but required the addition of NEt_3 and excess $ZnBr_2$ to effect the Conia-ene ring closure (entry 1).

With optimal conditions in hand, we set out to investigate the substrate scope. Gratifyingly, a variety of cyclopropanes underwent the desired cyclization in excellent yield. Figure 2 shows the results of several indoles (varying in the N-substitution) with a variety of 1,1-cyclopropanediesters. As seen from the table, there was a wide tolerance for the substituents on the cyclopropanediester. Both electron-rich and electron-poor aryl substituents performed with equal aplomb. Heterocycles were also well tolerated, although the furan substituted adduct (**15g**) decomposed somewhat under the reaction conditions. Both styrenyl and vinyl cyclopropanediesters gave good yields of products. As expected, the parent cyclopropane (no substituent) produced **15l** in greatly diminished yield; this is due the absence of a π-donor group vicinal to the geminal diester moiety. Typically harder Lewis acids, not compatible with Conia-ene chemistry, are required to activate this cyclopropane successfully. If the cyclopropane was used optically enriched, this was transferred with stereochemical fidelity to the adducts (**15a** and **15k**).

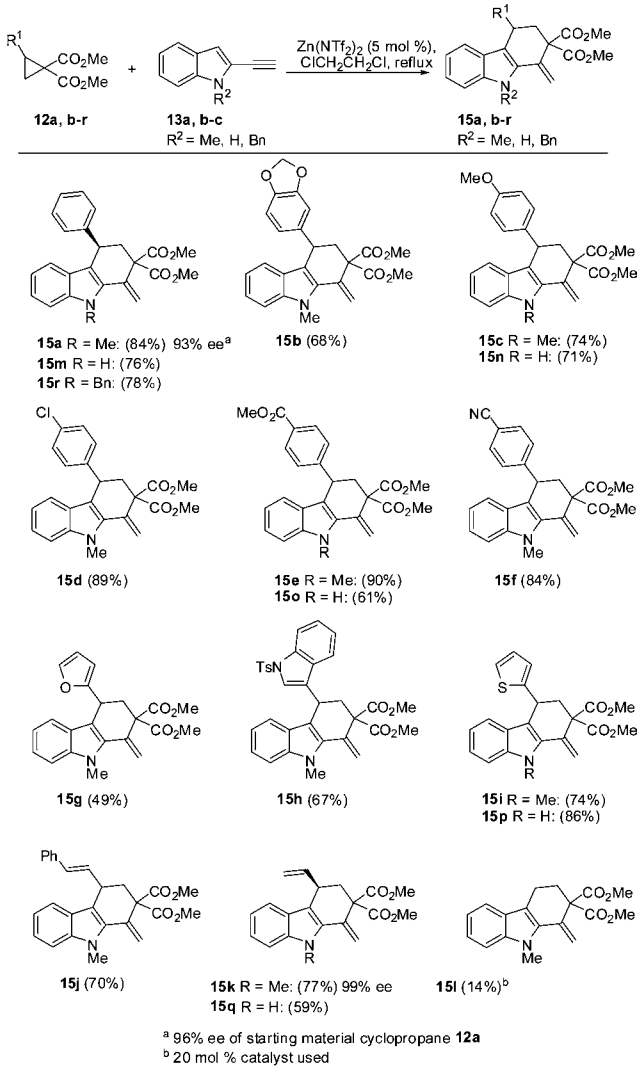


Figure 2. Substrate scope.

Figure 3 shows a short array of products using benzenoid-substituted indoles. The purpose of this study was to see whether electron-withdrawing groups on the benzenoid ring would attenuate the indoles' nucleophilicity. We were happy to observe that the presence of a trifluoromethyl or carbomethoxy moiety not only was tolerated but also produced the adducts in superb yields.

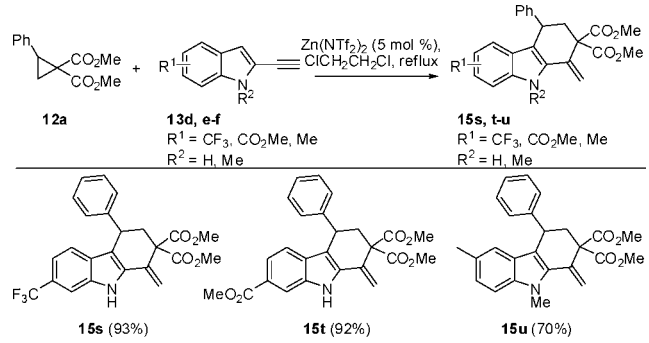


Figure 3. Use of substituted indoles.

We next investigated the effects of substitution on the 2-alkynyl moiety in the hopes of furthering functional group inclusion for application to the synthesis of complex target molecules. To our disappointment, we found that internal alkynes (Figure 4) produced solely the acyclic products (**14b**, **14c**, **14d**), despite an exhaustive study of reaction conditions. In addition to the formation of **14d**, an additional 25% of

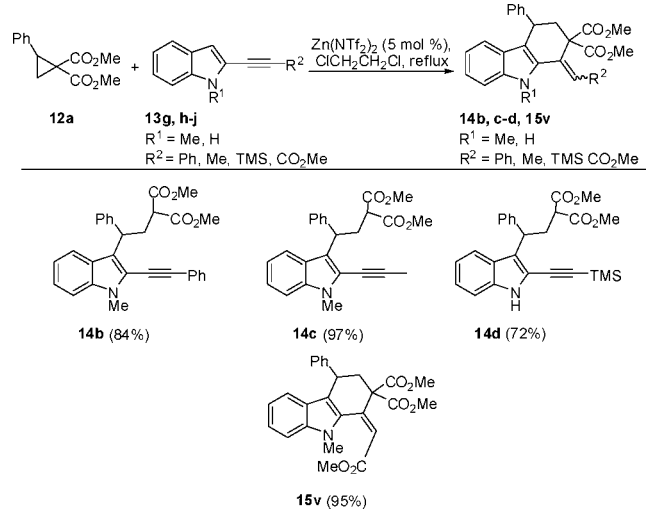
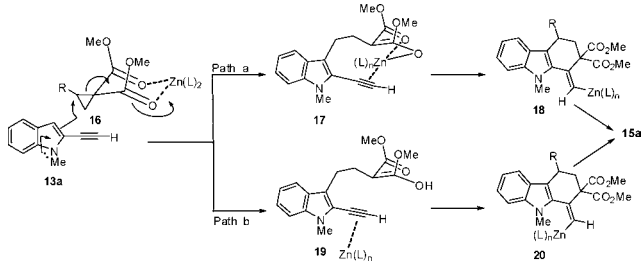


Figure 4. Cyclization attempts using internal alkyne.

15m was isolated, presumably via in situ desilylation and subsequent ring closure. To overcome this drawback in reaction scope, a methyl ester was used as the alkyne substituent. With the ester present we obtained product **15v** in a 95% yield. Tetrahydrocarbazole **15v** is most likely the product of a conjugate addition reaction rather than a Conia-ene cyclization. The ability to form **15v**, however, allows a strategy for further structural elaboration. We believe the geometry of the alkene in **15v** to be as shown based on the absence of an NOE correlation, which is always apparent between the indole N-methyl group and a proximal vinyl hydrogen.

A plausible mechanistic description is shown in Scheme 2 where initial coordination of diesters allows nucleophilic

Scheme 2. Plausible Mechanism

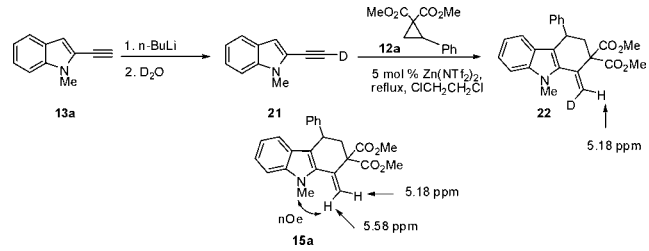


ring opening of the cyclopropanediester. Following the ring opening, it is postulated that the Conia-ene ring closure could occur through one of two mechanistic paths. Pathway *a* occurs by having the Zn species coordinate to not only the alkyne but also the oxygen of the ester (**17**) as well. This arrangement sets the alkynyl hydrogen of the starting material *cis* to the *N*-methyl group of the indole in the intermediate product (**18**). Alternatively, pathway *b* has the Zn species coordinate specifically to the alkyne (**19**) and has the malonic nucleophile perform an attack on the activated alkyne *anti* to the zinc. The end result would see the alkenylzinc moiety *cis* to the *N*-methyl group of the indole in the penultimate intermediate (**20**).

It should be noted that the nature of the Conia-ene ring closure (specifically the role of the metal) is somewhat ambiguous. Our depiction in Scheme 2 is reminiscent of that shown by Toste in 2004 in which the role of the gold catalyst in a Conia-ene ring closure was probed.[8e] In Toste's case, the two options put forth are gold activation similar to pathway *b* in Scheme 2 and a carbometalation very much similar to pathway *a*.

We were able to shed some light on the mechanistic situation in a manner similar to that of Toste (see Scheme 3). The hydrogen on the alkyne compound **13a** was replaced with a deuterium (**21**) by deprotonation and quenching with D_2O. A standard reaction with compound **12a** was per-

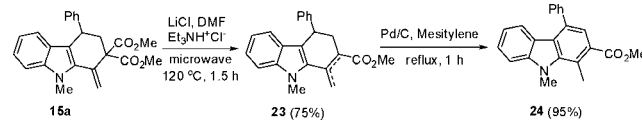
Scheme 3. Labeling Study To Elucidate Mechanism



formed, leading to product **22**, the identity of which was determined by comparison to the NOE spectra of the fully protonated species. In **22**, the relevant NOE observed in the protio species **15a** was absent, leading us to assign the olefin geometry as shown. Since the deuterium was determined to be *cis* to the *N*-methyl group on the indole, pathway *a* must be operational for this process.

To show that the adducts could be elaborated, **15a** was subjected to Krapcho dealkoxycarbonylation to yield the monoester **23**. Unsurprisingly, conjugation of the alkenyl moiety occurred under these conditions, leading to a mixture of products. Treatment of this mixture (**23**) with catalytic palladium on charcoal in refluxing mesitylene resulted in dehydrogenation to the carbazole (**24**) (Scheme 4); this

Scheme 4. Elaboration to Carbazoles



should be useful, given the ubiquity of carbazole natural products.

In summary, we have successfully developed an efficient method for producing substituted tetrahydrocarbazoles using a tandem nucleophilic ring-opening Conia-ene reaction.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for funding. We are grateful to Mr. Doug Hairsine of the University of Western Ontario Mass spectrometry facility for performing MS analyses. T.P.L. is a CGS-D awardee.

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

OL102627E