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Efficient Synthetic Approaches to the Common Scaffold of Indole Alkaloids

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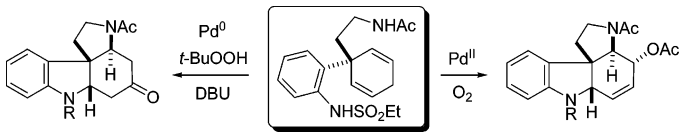
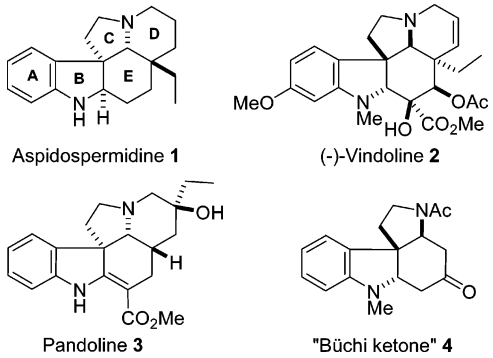
ABSTRACT



Birch reductive alkylation of 2-aminobiphenyls affords access to highly functionalized polyenes that react through a Pd(II)-catalyzed oxidative amination cascade or through a double 1,4-addition process to provide the tetracyclic skeleton of indole alkaloids with up to four stereogenic centers created in a single-pot operation.

Alkaloids of the aspidospermine groups **1** and **2** and pseudoaspidospermidine family including pandoline **3**, isolated from iboga, possess a common pentacyclic framework, with an embedded indole fragment and one or two quaternary carbon centers that have focused the attention of synthetic chemists for more than 40 years (Scheme 1).[1] Among this class of alkaloids, vindoline has attracted the most interest as a synthetic precursor of carcinostatic vinblastine and vincristine.[2] These compounds are biosynthetically related with a common precursor at the origin of the generation of both groups of alkaloids.[3] Although several elegant approaches to alkaloids **1**−**3**[4] and to the Büchi ketone intermediate **4**[5] have been reported, development of flexible and more straightforward approaches to the tetra- and pentacyclic core of these compounds is still required.

Scheme 1. Alkaloids of the Aspidospermine Group



Among the most efficient strategies that may be envisioned for the construction of polycyclic architectures, those relying on cascade processes have attracted a lot of interest, ensuring a rapid increase of the structural complexity and high bond forming efficiency.[6] We report herein two complementary

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(1) Saxton, J. E. In *The Alkaloids, Alkaloids of the Aspidospermine Group*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, p 1.

(2) (a) Saxton, J. E. *Nat. Prod. Rep.* **1995**, *385*. (b) Kuehne, M. E.; Podhorez, D. E.; Mulamba, T.; Bornmann, W. G. *J. Org. Chem.* **1987**, *52*, 347. (c) Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243.

(3) (a) Scott, A. I. *Acc. Chem. Res.* **1970**, *3*, 151. (b) Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98.

(4) (a) Saxton, J. E. In *The Alkaloids, Synthesis of Aspidosperma Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 50, p 343 and refs cited. (b) Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *J. Org. Chem.* **1980**, *45*, 3259.

(5) (a) Ando, M.; Büchi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880. (b) Heureux, N.; Wouters, J.; Marko, I. E. *Org. Lett.* **2005**, *7*, 5245.

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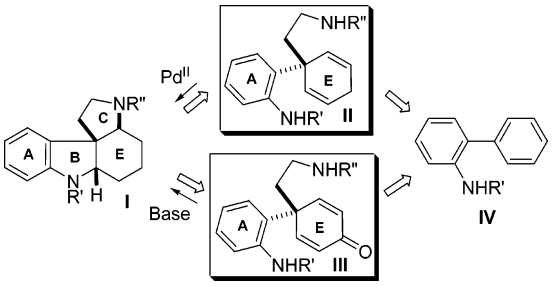
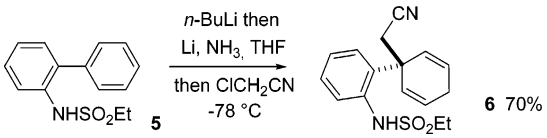


Figure 1. Retrosynthetic analysis.

approaches to the tetracyclic core of alkaloids above (i.e., **I**, Figure 1) based on cascade processes and desymmetrization of cyclohexa-2,5-diene intermediates **II** and **III**, accessible from a simple biaryl **IV** through Birch reductive alkylation. The present BRAD (Birch reductive alkylation−desymmetrization)[7] strategy relies on two distinct processes, i.e., a Pd^{II}-mediated domino oxidative amination of a cyclohexadiene **II** and a double 1,4-nucleophilic addition onto a cyclohexadienone **III**. In both strategies, the stereochemistry of the quaternary stereocenter and that of rings B and C are controlled simultaneously. The symmetrical nature of **II** and **III** also implies that the Pd cascade and the double Michael process may in principle be extended to an enantioselective series.

On the basis of some recent work from our laboratory,[8] it was envisaged that dienes such as **II** could be prepared via a regioselective Birch reductive alkylation of a biaryl **IV**. While these studies demonstrated that such a process is efficient when at least one electron-rich arene is present on the biaryl, there was no precedent on simple *ortho*-amino biphenyls such as **IV**. The Birch reduction was thus tested on commercially available 2-aminobiphenyl, protected with various electron-withdrawing groups (Piv, Boc, and SO_2Et). While modest results were obtained with Piv- and Boc-protective groups, excellent yields were observed starting from sulfonamide **5** (Scheme 2). Deprotonation of **5** with

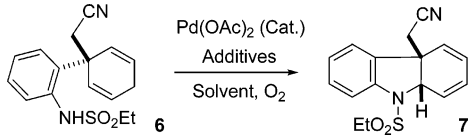
Scheme 2. Birch Reductive Alkylation of Biaryl **5**



n-BuLi prior to the addition of Li/NH_3 was found to be essential, "protecting" the *o*-aminophenyl ring from reduction and directing the reductive alkylation onto the unsubstituted ring. Cyclohexadiene **6**, thus obtained in reproducible yield, possesses the suitable nitrogen functional groups and constitutes a valuable precursor for testing the Pd(II)-mediated oxidative amination on 1,4-dienes.

Pd^{II}-catalyzed oxidative amination of olefins and 1,3-dienes has recently received a great deal of attention as an atom-economical process, allowing the elaboration of highly functionalized heterocycles.[9] On the basis of these premises, we investigated the possible extension of the process to our 1,4-dienes, by treating precursor **6** with $Pd(OAc)_2$ and O_2 in DMSO as a solvent.[10] Without additives, oxidative amination of **6** effectively provided the cyclized product **7** but in moderate yield (Table 1, entry 1). A significantly better result was obtained when using NaOAc as a base (entry 2).

Table 1. Pd^{II}-Catalyzed Oxidative Amination of Diene **6**



entry	solvent	additives (equiv)	temp [°C]	time (h)	yield[a]
1	DMSO	—[b]	55	24	50%
2	DMSO	NaOAc (2)[b]	55	24	75%
3	DMSO	CuOAc (2)[b]	55	30	49%
4	toluene	pyridine[b]	80	30	52%
5	DMSO	NaOAc (2)/C[b]	55	24	91%
6	DMSO	NaOAc (2)/C[c]	55	24	84%

[a] Isolated yield of **7**. [b] 10 mol % of $Pd(OAc)_2$ was used. [c] 5 mol % of $Pd(OAc)_2$ was used.

Other additives such as pyridine[10b] and CuOAc led to no improvement (entries 3 and 4). It was observed that oxygen concentration was a critical factor, indicating that Pd^0 reoxidation is the turnover limiting step of the process.[11] Inefficient reoxidation of Pd^0 into Pd^{II} leads to aggregation of Pd^0 and precipitation of Pd metal.[12] Charcoal (noted as C in Table 1) was thus added to the mixture to prevent the Pd^0 aggregation.[13] To our delight, this resulted in a significant improvement of the yield and also allowed a reduction of Pd loading (entries 5 and 6).

(6) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Poli, G.; Giambastani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959.

(7) (a) Abd Rahman, N.; Landais, Y. *Curr. Org. Chem.* **2002**, *6*, 1369. (b) Studer, A.; Schleth, F. *Synlett* **2005**, 3033. (c) Lebeuf, R.; Robert, F.; Landais, Y. *Org. Lett.* **2006**, *8*, 4755.

(8) Lebeuf, R.; Robert, F.; Landais, Y. *Org. Lett.* **2005**, *7*, 4557.

(9) (a) Rogers, M. M.; Wendlandt, J. E.; Guzei, I. A.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 2257. (b) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164. (c) Bäckvall, J.-E.; Andersson, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 3683. (d) Verboom, R. C.; Persson, B. A.; Bäckvall, J.-E. *J. Org. Chem.* **2004**, *69*, 3102. (e) Hosokawa, T.; Miyagi, S.; Murahashi, S.-I.; Sonoda, A. *J. Org. Chem.* **1978**, *43*, 2752. (f) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444.

(10) (a) van Benthem, R. A. T. M.; Hiemstra, H.; Longarela, G. R.; Speckamp, W. N. *Tetrahedron Lett.* **1994**, *35*, 9281. (b) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749. (c) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584.

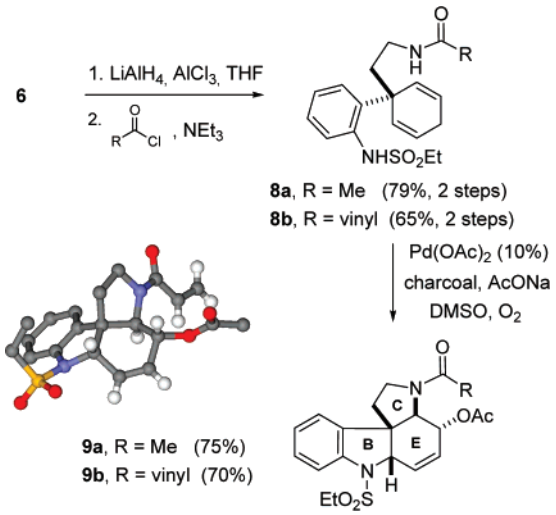
(11) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612.

(12) Deposition of black Pd metal was effectively observed in some cases.

(13) (a) Mahaim, C.; Carrupt, P.-A.; Hagenbuch, J-P.; Florey, A.; Vogel, P. *Helv. Chim. Acta* **1980**, *63*, 1149. (b) Steunenberg, P.; Jeanneret, V.; Zhu, Y.-H.; Vogel, P. *Tetrahedron: Asymmetry* **2005**, *16*, 337.

With these conditions in hand, we then turned our attention to the consecutive formation of rings B and C. Precursors **8a**,**b**, having orthogonal protecting groups, were first prepared through reduction of the nitrile and conversion of the resulting amine into the desired amides (Scheme 3). When

Scheme 3. Oxidative Amination Cascade on Dienes **8a**,**b** and X-Ray Crystal Structure of **9b**



subjected to the conditions above, **8a**, led after double oxidative amination, in a one-pot operation, to *tetracyclic compound* ***9a*** *having four new stereogenic centers, as a single regio- and stereoisomer*. **9a** was obtained in only four steps and 41% overall yield from biaryl **5**.

Oxidative amination of precursor **8b** having an acrylamide moiety was also tested and led as above to tetracyclic allylic acetate **9b** whose structure was secured through X-ray crystallography, thus supporting the relative configuration of **9a** (^{1}H NMR) and the regiochemistry of the acetate incorporation. The formation and the stereochemistry of the tetracyclic skeleton of **9a**,**b** may be tentatively explained as follows. Formation of ring B probably occurs prior to ring C due to higher acidity of the $NHSO_2Et$ group.[14] Ring B is thus formed with subsequent β-elimination of an hydrido−Pd species to generate a 1,3-cyclohexadiene such as **7**.[15] Pd^0 is then reoxidized by oxygen into Pd^{II} which can catalyze the second oxidative amination with the amido group approaching anti relative to ring B to form a π-allyl-Pd acetate such as **V** (Figure 2). Assuming an *anti*-amino palladation step during the formation of ring C, **V** is then

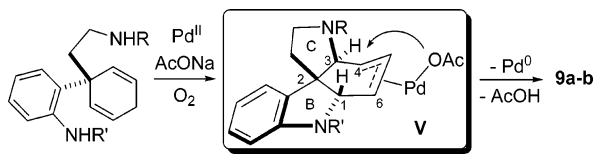
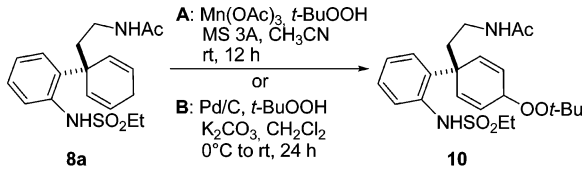


Figure 2. Tentative rationale for the acetate insertion.

generated with the stereochemistry as shown and thus delivers, during reductive elimination, the acetate group bound to palladium on the bottom face and at the less-hindered C4 site to give **9a**,**b** as single regio- and stereoisomers.[16,17] The consecutive formation of rings B and C is further supported by the access to **9a**,**b** from **7** through a three-step sequence, including a reduction of the nitrile function of **7** and acylation of the resulting amino group, followed by oxidative amination, which led to **9a**,**b**, respectively, in 53 and 52% overall yield (see Supporting Information).

Encouraged by these results, we then turned our attention to the second approach that was anticipated to provide a similar tetracyclic skeleton but with different functionalization on ring E.[18] The alternative approach using a double 1,4-addition[19] was thus investigated starting from diene **8a**, which was tentatively oxidized into the desired dienone using various conditions.[20] Allylic oxidation of **8a** with $Mn(OAc)_3$ (Scheme 4, conditions A) interestingly led to the correspond-

Scheme 4. Allylic Oxidation of Diene **8a**



Conditions **A**: 60% isolated yield
Conditions **B**: 56% isolated yield

ing peroxide **10** instead of the expected dienone. It is worth noticing that the same oxidation performed on an analogue of **8a**, lacking the $NHSO_2Et$ group, directly provided the cyclohexadienone. We observed that dihydrate $Mn(OAc)_3$ in the presence of molecular sieves afforded the best yields. When the hexahydrate was used, various amounts of a mono-1,4-addition product (involving the sulfonamide group) were detected which could not be separated from minor byproducts. More reproducible results were obtained following Corey's method using Pd/C-*t*-BuOOH (Scheme 4, conditions

(14) We noticed that quenching the reaction between **8a**,**b** and $Pd(OAc)_2$ before complete consumption of the starting material led to the formation in a small amount of a monocyclized product analogous to **7**.

(15) With 1,4-dienes, allylic C−H activation followed by amination of the resulting π-allyl-Pd(II) intermediate might also be considered. For recent studies, see: Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274.

(16) Stahl recently proposed that oxidative amination of olefins with tosylamine occurred through a syn pathway. See: Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328. This cannot be ruled out in our case.[10]

(17) Trapping of π-allyl-Pd(II) intermediates such as **V** with various nucleophiles in an intramolecular fashion has led so far to low yield of the desired pentacyclic systems. Investigations on this approach are still in progress.

(18) This feature is important in the context of the functionalization of this ring for the synthesis of Aspidosperma and Iboga alkaloids.

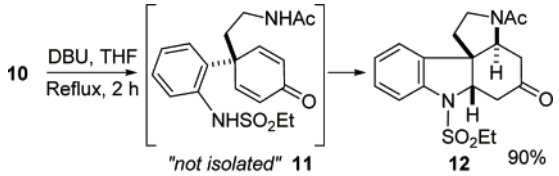
(19) (a) Martin, S. F.; Campbell, C. L. *J. Org. Chem.* **1988**, *53*, 3184. (b) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (c) Bland, D.; Chambournier, G.; Dragan, V.; Hart, D. J. *Tetrahedron* **1999**, *55*, 8953. (d) Bru, C.; Guillou, C. *Tetrahedron* **2006**, *62*, 9043.

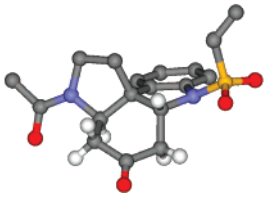
(20) (a) Page, P. C. B.; McCarthy, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol. 7, p 83. (b) Müller, P. M.; Pfister, R. *Helv. Chim. Acta* **1983**, *66*, 771. (c) Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149.

B).[21] Again, despite the different conditions employed,[22b] only the particularly stable peroxide **10** was formed.

Various attempts at converting peroxide **10** into the desired dienone were then carried out. After extensive experimentations, it was finally found that when heating **10** in the presence of DBU (2 equiv)[22] cyclohexadienone **11** was formed but reacted spontaneously to provide the double 1,4-addition product **12**, an analogue of Büchi ketone **4**, whose structure was unambiguously assigned through X-ray crystallography (Scheme 5).

Scheme 5. Synthesis of Protected Büchi Ketone **12** from Peroxide **10** and X-Ray Crystal Structure of **12**





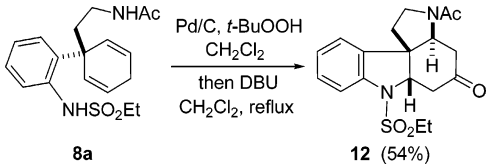
Interestingly, the use of a catalytic amount of a stronger base such as *t*-BuOK at room temperature led to a mixture of products in which the monocyclized product was again present. The role of the base is critical as heating **10** at 65 °C in the absence of a base left the peroxide unchanged. The isolation of the stable peroxide **10** is noteworthy as it allows a control of the double 1,4-addition, which is not possible with dienone **11**, which reacts spontaneously. Such a feature should be helpful in the perspective of an extension of the approach into an enantioselective series.

(21) (a) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727. (b) The use of $Pd(OAc)_2$-*t*-BuOOH led to a similar result.

(22) **10** was found to react similarly with benzyl amine and Hünig's base (*i*-Pr_2NEt).

The diene oxidation−double 1,4-addition sequence may finally be carried out in a single-pot operation, providing **12** directly from **8a** in a reasonable yield (Scheme 6). This

Scheme 6. One-Pot Preparation of Protected Büchi Ketone **12** from Diene **8a**



sequential cascade process thus provides a useful intermediate, i.e., **12**, in the synthesis of the titled alkaloids in only five steps and 22% overall yield from commercially available 2-aminobiphenyl.

In summary, we have described two efficient approaches to the tetracyclic core of aspidosperma alkaloids based on a one-pot double oxidative amination reaction and a double 1,4-addition process. The starting diene is easily at hand from commercially available 2-aminobiphenyl using a regioselective Birch reductive alkylation. This strategy to polycyclic indole alkaloids with significant savings in effort is actively pursued in our laboratory, with a particular emphasis on the asymmetric version of the above processes.

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Supporting Information Available: Representative experimental procedures including product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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