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# Synthesis of the tricyclic core structure of vindoline ☆

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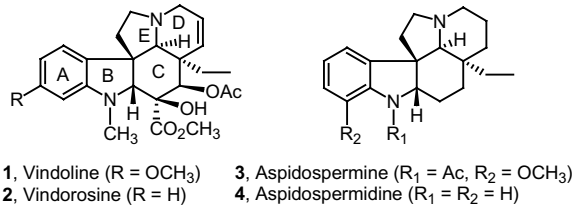
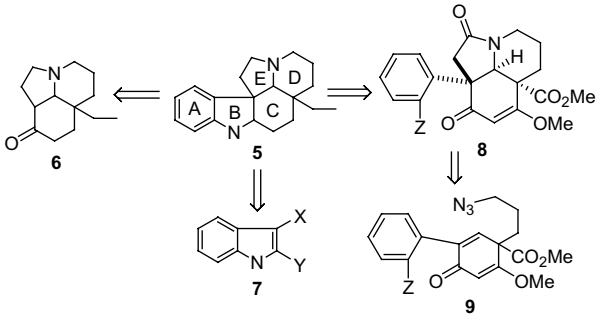
**Abstract**—An efficient synthesis of the core tricyclic structure (**18**) of vindoline has been achieved using the strategy, which features an intramolecular 1,3-dipolar cycloaddition of the azido dienone (**12**) to give aziridine (**13**) with complete region- and stereocontrol.


Vindoline (**1**), the major alkaloid component isolated from the leaves of *Vinca rosea* Linn., is a highly functionalized pentacyclic *Aspidosperma* alkaloid and of important medicinal interest because of its biosynthetic and synthetic role as a precursor of the carcinostateic alkaloid drugs vinblastine and vincristine.[1] *Aspidosperma* alkaloids are a family of over 200 members that share in the molecular structures a common pentacyclic framework with the C ring being of critical importance due to the fact that the entire six stereocenters and most functionalities of the molecule are located on it (**1** in Scheme 1). Individual members differ mainly in functionality and stereochemistry. Over the past 40 years there have been tremendous efforts for developing new methodologies for the synthesis of these highly functionalized alkaloids.[2] Since then, a large number of synthetic strategies for vindoline and other *Aspidosperma* alkaloids have been developed,[3] and most of them fall into one of the two major categories according to the strategies used for the construction of the B ring in the molecule (**5** in Scheme 2). One involves the Fisher indole synthesis, which is widely used in many *Aspidosperma* alkaloid syntheses to construct the B ring, leaving major synthetic efforts to preparation of tricyclic core **6**.[2,4] The other utilizes as building blocks indoles (**7**) that contain suitable functionalities and substituents in the side chains for conversion to the C, D, and/or E rings.[5] A more conceptually new strategy is reported recently where a tandem cyclization–cycloaddition sequence has been used to assemble the C and E rings with four of the stereocenters of vindoline being installed in one step with a high degree of stereocontrol.[6]




**Scheme 1.**




**Scheme 2.**

In this communication, we report an efficient synthesis of the core tricyclic structure of vindoline by utilization of the Birch reduction–alkylation to construct the C ring and an intramolecular 1,3-dipolar cycloaddition to

*Keywords*: Vindoline; Synthesis; 1,3-Dipolar cycloaddition; Birch reduction–alkylation.

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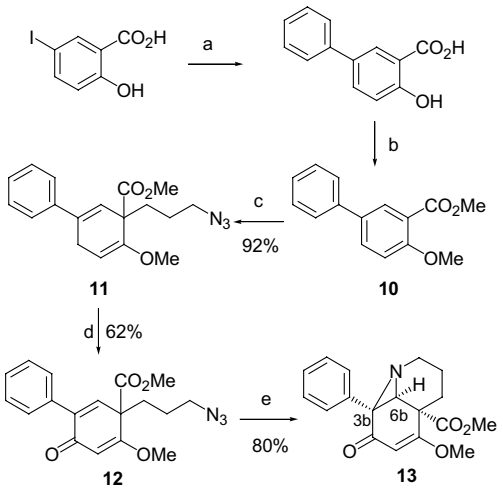


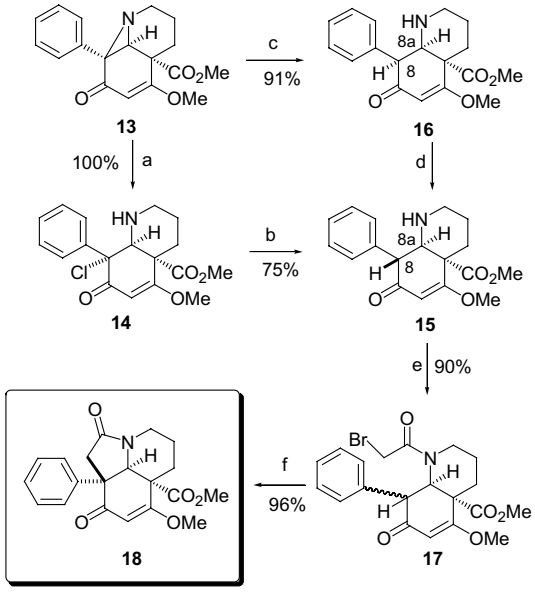

**Scheme 3.** Reagents and conditions: (a) $PhB(OH)_2$, $(Ph_3P)_4Pd$, $K_2CO_3$, $H_2O$, Tol., MeOH, reflux; (b) $Me_3SO_4/K_2CO_3$, acetone, reflux; (c) $Li/NH_3/THF/t$-BuOH, −78 °C, piperylene, $I(CH_2)_3N_3$; (d) $PDC/t$-$BuO_2H$, PhH, Celite; (e) PhH, reflux, 2 days.

install the D ring of the alkaloid. Our disconnection of vindoline is based upon the following considerations: First, the B ring could result from an intramolecular ring closure in **8** to avoid the low yielding and poor regioselectivity of the Fisher indolization. Secondly, the D ring is formed through an intramolecular azide–enone 1,3-dipolar cycloaddition of **9** with region- and stereocontrol; Lastly, the most important C ring (the tetrasubstituted cyclohexadienone ring in **9**) is derived from Birch reductive alkylation of the corresponding biaryl substrate, followed by bis-allylic oxidation. An important strategic element of the approach is an early incorporation of the aromatic ring (ring A) in **8** as the 5-phenyl substituent in **10** (Scheme 3). The early incorporation methodology has received attention from several groups.[7]

Our synthesis of the core tricycle of vindoline (equivalent to the structure **8**) starts with intramolecular 1,3-dipolar cycloaddition of azido dienone **12**, which is prepared using a procedure that we described recently (Scheme 3).[8] Previous studies show that under photochemical conditions (366 nm) **12** rearranges to a bicyclic ketone product, while irradiation at 300 nm a tetrasubstituted phenol is formed.[8] In refluxing benzene, however, **12** was converted to an aziridine product **13** in 80% yield with complete region- and stereocontrol. The isolation of aziridine **13** rather than a triazoline product should be due to the triazoline instability in refluxing benzene, which accelerates the extrusion of nitrogen in the corresponding triazoline intermediate.[9] The aziridine structure of **13** was determined based upon its $^1H$ and $^{13}C$ NMR spectra along with a chemical ionization mass spectrum. The molecular ion peak of 314 ($M^+$+1, 100%) for **13** was observed, ruling out the possible structure of a triazoline product. Furthermore, a 2D NOESY experiment showed interactions among the protons of phenyl, C(6b), and carboxylic methyl ester, indicating that the phenyl at C(3b), proton at C(6b), and methoxycarbonyl at C(6a) are in a *syn* position as shown in Scheme 3.

With the C and D rings constructed, our attention was turned to cleavage of the aziridine ring and installation of a two-carbon chain to form the E ring as the next step. Treatment of **13** with a methanolic HCl solution at room temperature gave the chloride **14** as a single diastereoisomer in quantitative yield, the stereochemistry of which is as shown in **14** (Scheme 4). The high stereoselectivity might be a result of protonation of the nitrogen, followed by an $S_N2$ attack of a chloride anion, resulting in ring opening of the aziridine ring. Reduction of chloride **14** with zinc in acetic acid at room temperature for 48 h afforded amine **15** in 75% isolated yield. It was found that the direct reductive cleavage of the aziridine ring in **13** with Zn/HOAc to **15** required long reaction time and afforded low yields. Finally a one-step reduction of **13** was achieved using Birch reduction conditions to give **16**, a diastereoisomer of **15**. Treated with acetic acid, **16** was isomerized to **15** exclusively. Calculations using the MM2 force field were made to predict the relative stereochemistry about the two protons at C(8) and C(8a). The stereochemistry of **15** and **16** was deduced with a comparison between the experimentally observed $^1H$–$^1H$ coupling constants, 11.0 and 2.7 Hz, and the calculated ones, 11.7 and 5.6 Hz, respectively. This provided us with relatively high confidence in the stereochemical assignment (Scheme 4).

Acylation of either **15** or **16** with bromoacetyl chloride in THF in the presence of $NaHCO_3$ for 30 min at 0 °C furnished bromoamide **17** as a diastereomeric mixture in 90% yield after chromatography on silica gel. Finally, **17** was treated with *t*-BuOK in warm benzene for 48 h to give the core tricyclic product **18** in 96% yield. The assignment of the structure of tricyclic product **18** was




**Scheme 4.** Reagents and conditions: (a) HCl/MeOH (6 N, 1:1); (b) Zn, HOAc, 72 h; (c) $Li/NH_3/THF$, −78 °C; (d) acetic acid; (e) $BrCH_2COCl/NaHCO_3/THF$; (f) *t*-BuOK/PhH, reflux, 48 h.

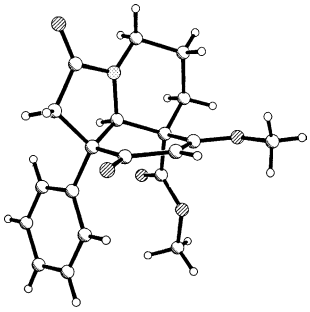


**Figure 1.** X-ray structure of the core tricycle **18**.

made based upon the $^{1}H$ and $^{13}C$ NMR, IR, and mass spectra and was further confirmed by X-ray crystallographic studies (Fig. 1).

The supplementary data is available online with the paper in ScienceDirect. Experimental procedures and analytical data for compounds **13**, **14**, **15**, **17**, and **18**.

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## References and notes

1. For reviews, see: (a) Verpoorte, R.; van der Heijden, R.; Moreno, P. R. H. Biosynthesis of Terpenoid Indole Alkaloids in *Cantharaus roseus* Cells. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: San Diego, 1997; Vol. 49, pp 221–299; (b) Kutchan, T. M. Molecular Genetics of Plant Alkaloid Biosynthesis. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: San Diego, 1998; Vol. 50, pp 257–316.
2. For the first syntheses of aspidospermine and vindoline, see: Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872, and Ando, M.; Buchi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880, respectively.
3. Saxon, J. E. Synthesis of the Aspidosperma Alkaloids. In *The Alkaloids*; Cordell, J. A., Ed.; Academic: San Diego, 1998; Vol. 50, pp 343–376.
4. For examples, see: (a) Ban, Y.; Sato, Y.; Inoue, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, *1*, 2261; (b) Kuehne, M. E.; Bayha, C. *Tetrahedron Lett.* **1968**, 2639; (c) Stevens, R. V.; Fizpatrick, J. M.; Kaplan, M.; Zimmerman, R. L. *Chem. Commun.* **1971**, 857; (d) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673.
5. For examples, see: (a) Kutney, J. P.; Chan, K. K.; Failli, A.; Fromson, J. M.; Gletsos, C.; Velson, V. R. *J. Am. Chem. Soc.* **1968**, *90*, 3891; (b) Barton, J. E. D.; Harley-Mason, J. *Chem. Commun.* **1965**, 298; (c) Harley-Mason, J.; Kaplan, M. *Chem. Commun.* **1967**, 915; (d) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901; (e) Schultz, A. G.; Pettus, L. *J. Org. Chem.* **1997**, *62*, 6855; (f) Kuehne, M. E.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3702; (g) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750; (h) Buchi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299; (i) Ando, M.; Buchi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880. For the synthesis of vindorosine, see Ref. (h).
6. (a) Padwa, A.; Price, A. T. *J. Org. Chem.* **1998**, *63*, 556; (b) Padwa, A.; Price, A. T. *J. Am. Chem. Soc.* **1995**, *60*, 6258; (c) However, relative little effort has been directed at an asymmetric synthesis. See: Kuehne, M. E.; Podhorez, D. E.; Mulamaba, T.; Bornmann, W. G. *J. Org. Chem.* **1987**, *52*, 347; (d) Feldman, P. L.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 1603.
7. Recently three examples of this early incorporation in the synthesis of the aspidosperma alkaloids have appeared. See: (a) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966; (b) Bonjoch, J.; Sole, D.; Bosch, J. *J. Am. Chem. Soc.* **1995**, *117*, 11017; (c) Toczko, M. A.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 2642.
8. Guo, Z.; Schultz, A. G.; Antoulinkis, E. G. *Org. Lett.* **2001**, *3*, 1177.
9. Schultz, A. G.; Dittami, J. P.; Myong, S. O.; Sha, C. K. *J. Am. Chem. Soc.* **1983**, *105*, 1255; For a review, see: Schultz, A. G. In *Advances in Cycloaddition Chemistry*; Curran, D. P., Ed.; JAI: 1988.