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Concise Synthesis and Transannular Inverse Electron Demand Diels–Alder Reaction of [3](3,6)Pyridazino[3](1,3)indolophane. Rapid Access to a Pentacyclic Indoloid System

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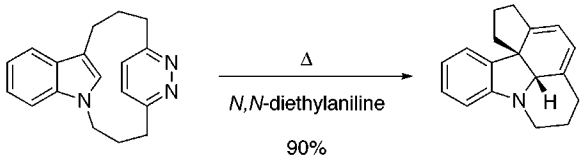
ABSTRACT



The title compound was synthesized concisely from indole. A 2-fold sequential hydroboration/Suzuki–Miyaura cross-coupling was employed to generate the cyclophane. When heated in *N,N*-diethylaniline, it underwent a transannular inverse electron demand Diels–Alder (IEDDA) reaction to form a pentacyclic product, which appears to be well suited as a precursor to a variety of indole alkaloids such as strychnine.

Small cyclophanes have been the subjects of broad interest for several decades,[1] and they continue to provide the chemical community with interesting and fruitful avenues of investigation.[2] The overwhelming majority of work in this area can be loosely classified as fundamental research, the focus being on such themes as synthetic challenge, stereochemistry, aromaticity, and the effect of strain on structure, conformational behavior, and reactivity. In contrast, there are very few examples of small cyclophane natural products. As a result, small cyclophanes do not have a high profile in the synthesis of natural products, either as targets[3] or as key intermediates.[4] Barring the discovery of new naturally occurring small cyclophanes, future applications of cyclophanes in synthetic studies will have to be directed toward their use as key intermediates.

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(2) For some recent examples of novel small cyclophanes, see: (a) Bodwell, G. J.; Miller, D. O.; Vermeij, R. J. *Org. Lett.* **2001**, *3*, 2093−2096. (b) Boydston, A. J.; Bondarenko, L.; Dix, I.; Weakley, T. J. R.; Hopf, H.; Haley, M. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2986−2989. (c) Bodwell, G. J. In *Organic Synthesis Highlights IV*; Schmalz, H.-G., Ed.; Wiley-VCH: Weinheim, Germany, 2000.

(3) (a) Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925−5937. (b) Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984−4985. (c) Smith, A. B., III; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423−7424. (d) Hoye, T. R.; Humpal, P. E.; Moon, B. *J. Am. Chem. Soc.* **2000**, *122*, 4982−4983.

(4) Pyrrolophanes have served as key intermediates in the synthesis of roseophylin: (a) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509−8514. (b) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8509−8514. A furanophane was constructed as a key intermediate in the synthesis of eleutherobin: (c) Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563−6579. Furanophanes and their transannular Diels−Alder reactions have been reported in synthetic approaches to chanticin: (d) Toró, A.; Wang, Y.; Deslongchamps, P. *Tetrahedron Lett.* **1999**, *40*, 2765−2768. (e) Toró, A.; Wang, Y.; Drouin, M.; Deslongchamps, P. *Tetrahedron Lett.* **1999**, *40*, 2769−2772. See also: (f) Toró, A.; L'Heureux, A.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 2737−2740.

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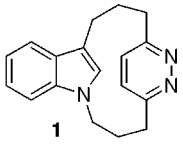
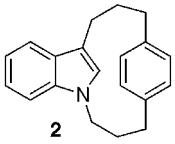
An important structural feature of many small cyclophanes that has not yet been exploited synthetically is that two aromatic systems can be held closely in a specific orientation with respect to one another. This being the case, reaction between the arenes would be expected to occur with complete regiochemical control and with the entropic advantages of intramolecular reaction. Thus, the initial challenge is to design and synthesize cyclophanes that are not only capable of intramolecular reaction between the two decks but also afford products that are both structurally related to important classes of natural products and lend themselves to further elaboration. We now report the initial results of a project aimed at using cyclophanes as precursors to natural products.

The inverse electron demand Diels−Alder (IEDDA) reaction was selected as the key intramolecular reaction because there are many examples of such reactions in which both reaction partners are aromatic species.[5] Indole has often served as an IEDDA dienophile,[5a] and its prevalence in nature cemented its choice as the dienophile. Although 1,2,4,5-tetrazines and 1,2,4-triazines are the most common aromatic IEDDA dienes (especially in reactions with indoles), it was decided that the less reactive pyridazine (1,2-diazine) system would receive the initial attention. As pointed out by Snyder,[5a] the indole-pyridazine pairing is particularly attractive because it should provide direct access to the carbazole skeleton (or reduced versions), which is present in a wide array of indole alkaloids.

Examples of intermolecular IEDDA reactions involving an indole−pyridazine pairing are scarce, and these all required the use of a strongly activated pyridazine.[5a,6] Attempts to perform intramolecular indole−pyridazine IEDDA reactions in which a less activated pyridazine moiety was tethered to an indole system were reported to be unsuccessful.[7] For the present investigation, it was envisaged that the "doubly tethered", i.e., transannular,[8] arrangement of diene and dienophile in cyclophane **1** would facilitate their reaction.



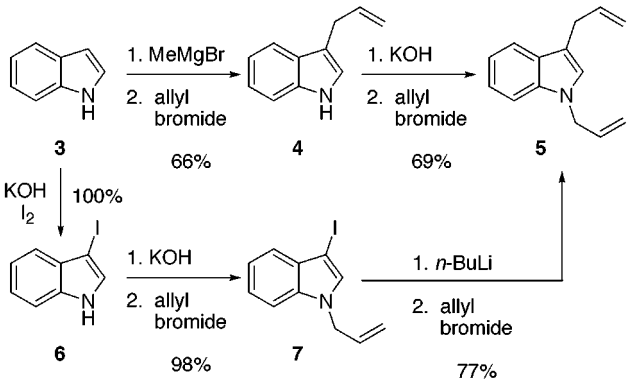
1



2

Surprisingly, very few indolophanes have been reported.[9] With indolophane **2** recently prepared by a seven-step sequence,[9b] it was hoped that a similar synthetic approach would lead to cyclophane **1**. However, this approach proved to be unsuitable,[10] and an alternative strategy had to be devised.

Scheme 1



The successful approach was based on the sequential hydroboration/Suzuki−Miyaura cross-coupling reaction, which has been reported to be an effective method for the formation of medium- to large-sized rings.[11] To apply this methodology to the synthesis of **1**, 1,3-diallylindole **5** was required. This was first synthesized in two steps from indole **3** by successive allylations at the 3 position[12] to give **4**[13] (66%) and at the 1 position[14] to afford **5** (69%) (Scheme 1). A three-step sequence was subsequently found to be higher yielding. Iodination of indole gave 3-iodoindole **6**[15] quantitatively, and this could be *N*-allylated to afford **7** (98%). Treatment of this compound with *n*-BuLi followed by allyl bromide then furnished **5** (77%).

With ready access to **5**, the synthesis of **1** was then attempted (Scheme 2). Treatment of **5** with 6 equiv of 9-BBN presumably gave the doubly hydroborated species **8**, which was not isolated but rather reacted immediately with 3,6-

(5) (a) Lee, L.; Snyder, J. K. *Adv. in Cycloaddit.* **1999**, *6*, 119−171. (b) Chen, C.-H.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2049−2052. (c) Wan, Z.-K.; Woo, G. H. C.; Snyder, J. K. *Tetrahedron* **2001**, *57*, 5497−5507. (d) González, J. C.; Dedola, T.; Santana, L.; Uriarte, E.; Begala, M.; Copez, D.; Podda, G. *J. Heterocycl. Chem.* **2000**, *37*, 907−910. (e) Li, J.-H.; Snyder, J. K. *J. Org. Chem.* **1993**, *58*, 526−519. (f) Wan, Z.; Snyder, J. K. *Tetrahedron Lett.* **1997**, *38*, 7495−7498. (g) Dang, Q.; Brown, B. S.; Erion, M. D. *J. Org. Chem.* **1996**, *61*, 5204−5205. (h) Dang, Q.; Liu, Y.; Erion, M. D. *J. Am. Chem. Soc.* **1999**, *121*, 5833−5834. (i) Yu, Z.-X.; Dang, Q.; Wu, Y.-D. *J. Org. Chem.* **2001**, *66*, 6029−6036.

(6) For example, see: (a) Nesi, R.; Giomi, D.; Turchi, S.; Falai, A. *J. Chem. Soc., Chem. Commun.* **1995**, 2201−2202. (b) Haider, N.; Mereitner, K.; Wanko, R. *Heterocycles* **1995**, *41*, 1445−1459.

(7) Benson, S. C.; Lee, L.; Yang, L.; Snyder, J. K. *Tetrahedron* **2000**, *56*, 1165−1180.

(8) Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243−4260. For a transannular Diels−Alder reaction of a [3.3]cyclophane see: (b) Longone, D. T.; Gladysz, J. A. *Tetrahedron Lett.* **1976**, *17*, 4559−4562.

(9) (a) Ortner, B.; Waibel, R.; Gmeiner, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1283−1285. (b) Bodwell, G. J.; Li, J.; Miller, D. O. *Tetrahedron* **1999**, *55*, 12939−12956. (c) Bergman, J.; Bäckvall, J.-E. *Tetrahedron Lett.* **1973**, 2899−2902. (d) Bergman, J.; Carlsson, R.; Sjöberg, B. *J. Heterocycl. Chem.* **1977**, *14*, 1123−1134. (e) Oliver, J. E.; Waters, R. M.; Lusby, W. R.; Flippen-Anderson, J. L. *J. Heterocycl. Chem.* **1991**, *28*, 1569−1572.

(10) Details of this unsuccessful route will be described in a forthcoming publication.

(11) (a) Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695−2698. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314−321. (c) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201−2208.

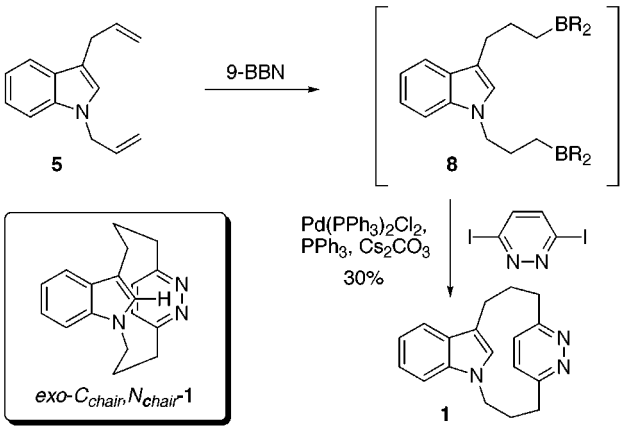
(12) (a) Holzapfel, C. W.; Bischohberger, K.; Olivier, J. *Synth. Commun.* **1994**, *24*, 3197−3212. (b) Sainsbury, M.; Weerasinghe, D.; Dolman, D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 587−590. (c) Fishwick, C. W. G.; Jones, A. D.; Mitchell, M. B. *Heterocycles* **1991**, *32*, 685−692.

(13) Brown, J. B.; Henbest, H. B.; Jones, E. R. N. *J. Chem. Soc.* **1952**, 3172−3176.

(14) (a) Kikugawa, Y.; Miyake, Y. *Synthesis* **1981**, 461−462. (b) Barry, J.; Bram, G.; Decodts, G.; Loupy, A.; Pigeon, P.; Sansoulet, J. *Tetrahedron* **1983**, *39*, 2669−2672.

(15) Witulski, B.; Buschmann, N.; Bergsträsser, U. *Tetrahedron* **2000**, *56*, 8473−8480.

Scheme 2

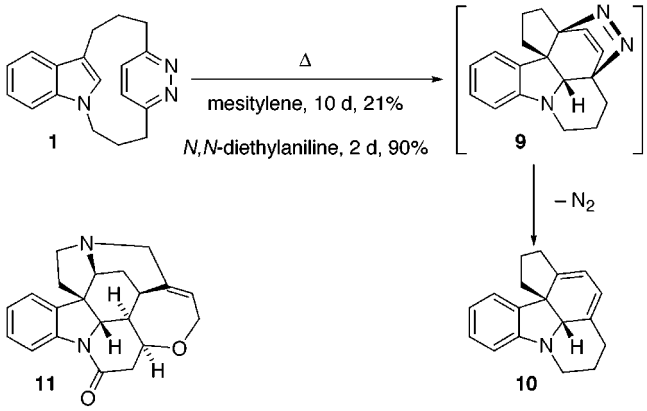


diiodopyridazine[16] under Suzuki−Miyaura conditions.[17] The desired cyclophane **1** was obtained in 30% yield. No other cyclic oligomers were isolated. Unfortunately, **1** was isolated as an oil, which ruled out an X-ray crystallographic determination of its solid-state structure.

Analysis of a molecular model of **1** revealed that this cyclophane has a considerably more complicated set of conformational processes available to it than does indolophane **2**.[9b] AM1 calculations were performed on the eight possible conformers arising from all permutations of an endo or exo[18] orientation of the two arenes and chair or boat conformations of the two unique bridges. The lowest-energy conformer was found to be the *exo*-C_{chair},N_{chair} conformer shown in Scheme 2. A full discussion of the conformation behavior of **2** will form the basis of a subsequent publication.

The 500 MHz ^{1}H NMR spectrum of **1** exhibits a singlet at δ 5.78 due to the internal proton of the indole deck. This is slightly less shielded than the analogous proton of **2** (δ 5.59),[9b] but still much more strongly shielded than the corresponding proton of the direct cyclophane precursor **5** (δ 6.87). The protons on the pyridazine ring appear as an AX system at δ 6.13 and 6.33. These chemical shifts are 1.07 and 0.87 ppm, respectively, upfield from the aromatic proton of the model compound 3,6-dimethylpyridazine (δ 7.20).[19] In the low-temperature spectrum of **2**, the endo protons of the benzene deck (the protons situated underneath the indole deck) were observed at δ 6.00 and δ 6.21,[9b] high-field shifted by 1.06 and 0.85 ppm, respectively, from the aromatic signal for the model compound *p*-xylene (δ 7.06). The exo protons of the benzene deck (δ 6.94 and δ 7.04) have chemical shifts very similar to that of the model compound. What these NMR data strongly suggest is that the ring conformation of **1** is predominantly exo in solution.

Scheme 3



Heating **1** in mesitylene (bp = 162−164 °C) led to the formation of pentacyclic product **10** (21%), presumably via a transannular IEDDA reaction to give adduct **9**,[20] followed by expulsion of N_2 in a retro Diels−Alder fashion. The sluggishness of this reaction and the apparently low solubility of **1** in mesitylene, even at reflux, prompted the use of *N*,*N*-diethylaniline[21] (bp = 217 °C), in which **1** dissolved readily. This reaction led to the formation of **10** in 90% yield in a much shorter time. The overall yield of **10** from indole was 12% by the four-step route and 20% by the five-step sequence. Not only does **10** contain a reduced carbazole moiety, but the former bridges of the cyclophane progenitor also manifest themselves as fused five- and six-membered rings that render the skeleton of **10** structurally very similar to five of the seven rings of strychnine **11**.[22]

With regard to the relative stereochemistry, AM1 calculations (MOPAC, Chem3D) predict that the expected cis isomer **10** is approximately 35 kcal/mol lower in energy than the corresponding trans isomer. Nevertheless, a NOE experiment was performed to support the stereochemical assignment. Irradiation of the methine proton at δ 4.16 resulted in a 0.9% enhancement of the multiplet centered at δ 1.93 and a 1.9% enhancement of the multiplet centered at δ 1.81. Each of these two proton multiplets was shown using ^{1}H−^{1}H COSY, HMQC, and HMBC experiments to be due to overlapping signals of one homoallylic and one bishomoallylic proton of the five-membered ring. Although the

(16) Shin, M.-S.; Kang, Y.-J.; Chung, H.-A.; Park, J.-W.; Kweon, D.-H.; Lee, W. S.; Yoon, Y.-J. *J. Heterocycl. Chem.* **1999**, *36*, 1135−1142.

(17) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419−422. (c) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749−1758. (d) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178−184.

(18) For this cyclophane, the term endo is used to describe conformers in which the nitrogen atoms of the pyridazine ring are situated underneath the indole system. The term exo is used to describe conformers in which the nitrogen atoms of the pyridazine ring are situated away from the indole system, as shown in Scheme 2.

(19) Ohsawa, A.; Abe, Y.; Igeta, H. *Chem. Pharm. Bull.* **1978**, *26*, 2550−2554.

(20) Intermediate **9** is the result of an intramolecular IEDDA reaction from an exo conformation. Reaction from an endo conformation would afford a different diastereoisomer, but this would also produce (±)-**10** upon expulsion of nitrogen.

(21) Boger, D. L.; Wolkenberg, S. E. *J. Org. Chem.* **2000**, *65*, 9120−9124.

(22) (a) For a review of strychnine syntheses, see: Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455−3482. For subsequent strychnine syntheses, see: (b) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003−8010. (c) Eichberg, M. J.; Dorta, R. L.; Lamottke, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *2*, 2479−2481. (d) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **2001**, *123*, 9324−9337.

specific interactions could not be identified unambiguously, the enhancements of signals in the five-membered ring would not be expected for the trans isomer. Expected enhancements (1,3-diaxial relationships to the irradiated methine proton) of one of NCH_2 protons (δ 3.22, 1.2%) and one of the allylic CH_2 protons (δ 2.19, 1.2%) in the piperidine ring were also observed.

Despite the low yields of **1**, the concise preparation of pentacycle **10** is very encouraging. It has been demonstrated that indole and an unactivated pyridazine can participate in the transannular IEDDA. More importantly, the main objective of using an intramolecular reaction of a cyclophane to rapidly construct (four or five synthetic operations from indole) a polycyclic system that is structurally related to an important class of natural products has been achieved. Furthermore, modification of the length and constitution of the cyclophane bridges should provide access to functionalized versions of **10** that are more closely related to strychnine **11** and its known precursors[22a] as well as other reduced carbazole-based pentacyclic systems.

Work aimed at the improvement of the yields of the cyclophane-forming step is underway, as are attempts to apply the "cyclophane approach" to the synthesis of complex indole alkaloids such as strychnine **11**. Additionally, the synthesis of **1** is the first example of the use of the Suzuki−Miyaura cross-coupling for the preparation of a [3.3]-cyclophane. The generality of this approach for the synthesis of [3.3]cyclophanes is also under investigation.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**, **5**, **7**, and **10** and ^{1}H NMR spectra for compounds **1** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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