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Aza-Diels–Alder/intramolecular Heck cyclization approach to the tetrahydro-β-carboline skeleton of the ajmaline/sarpagine alkaloids

Jeffrey T. Kuethe,* Audrey Wong, Ian W. Davies and Paul J. Reider

Department of Process Research, Merck & Co., PO Box 2000, Rahway, NJ 07065, USA

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Abstract—The aza-Diels–Alder reactions of 2-iodo-3-indoleacetaldehydes in the presence of zinc triflate provides 2-(2-iodoindolylmethyl)-4-pyridones in high yield. Palladium-mediated intramolecular Heck cyclization gives access to the tetracyclic tetrahydro-β-carboline framework of the ajmaline/sarpagine alkaloids.

There have been more than 90 ajmaline/sarpagine-related indole alkaloids isolated from various species of Alstonia and Rauwolfia.[1,2] Due to the diverse biological properties and challenging structural complexities of these alkaloids, they have received a great deal of attention in recent years.[1,2] Common to all of these alkaloids is the tetracyclic tetrahydro-β-carboline framework **5** (Fig. 1). Methods for the preparation of this subunit generally employ the Pictet–Spengler/Dieckmann cyclization protocol outlined by Cook and co-workers.[1,2] A number of alternative routes have also been employed.[1–5]

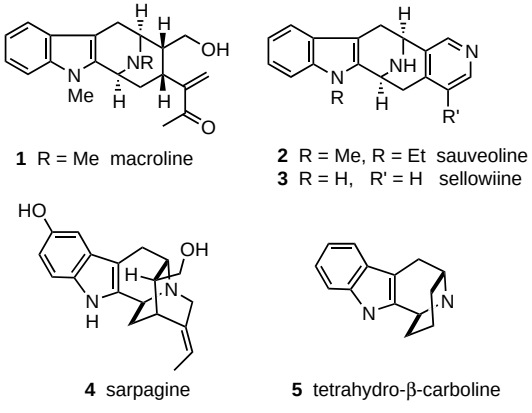

Figure 1.

Our studies on aza-Diels–Alder reactions of substituted indole carboxaldehydes led us to consider readily accessible 2-(2-iodoindolylmethyl)-4-pyridones such as **7** as potential precursors for the rapid entry to the core framework of this unique family of alkaloids (Fig. 2).[6] In this letter we disclose our initial findings in this area.

The pseudoaxial orientation of substituents at the 2-position of 4-pyridones is well established.[7] We reasoned that the indolyl ring of **7** would be in a favorable position for intramolecular 1,4-attack of the 6-position of the pyridone ring.[8] In order to initiate our studies on intramolecular cyclizations of **7**, we utilized an aza-Diels–Alder reaction of 2-iodo-3-indoleacetaldehydes **12** and **13** (Scheme 1). The synthesis of **12** and **13** began with indoles **8**[9] and **9**.[10] Treatment of **8** with *n*-BuLi in refluxing MTBE followed by addition of I_2 at 0°C afforded *N*-methyl-2-iodotryptophol **10**. In similar fashion, treatment of **9** with LDA and then I_2 gave *N*-phenylsulfonyl-2-iodotryptophol **11**. Dess–Martin oxidation[11] provided aldehydes **12** and **13** in 57 and 43% overall yield from **8** and **9**, respectively. The aza-Diels–Alder reaction of each of these aldehydes was conducted at rt by the sequential addition of benzylamine, zinc triflate, and Danishefsky's diene **14**.[12] Following workup and chromatography on silica gel, the desired 2-(2-iodoindolylmethyl)-4-pyridones **15** (70%) and **16** (74%) were obtained as stable crystalline solids.[13–15]

With an efficient method for the preparation of the required 2-(2-iodoindolylmethyl)-4-pyridones in hand, we explored conditions for effecting intramolecular cyclization. Treatment of either **15** or **16** under stan-

* Corresponding author. E-mail: jeffrey_kuethe@merck.com

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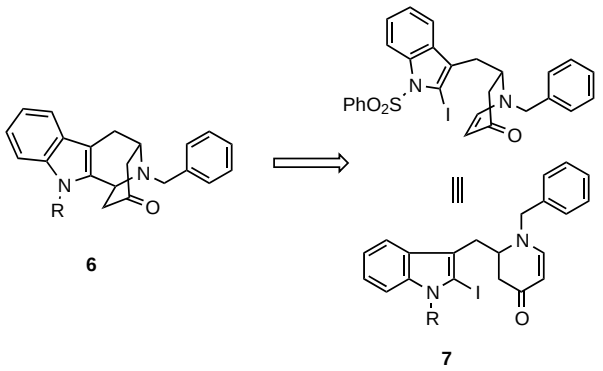
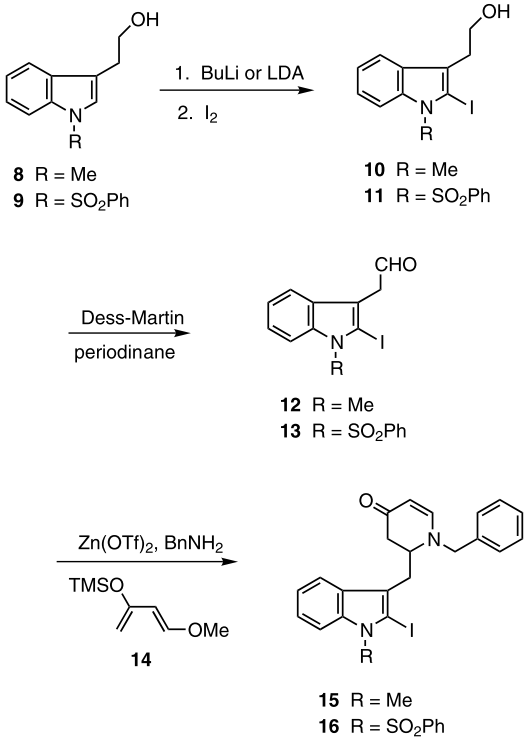


Figure 2.



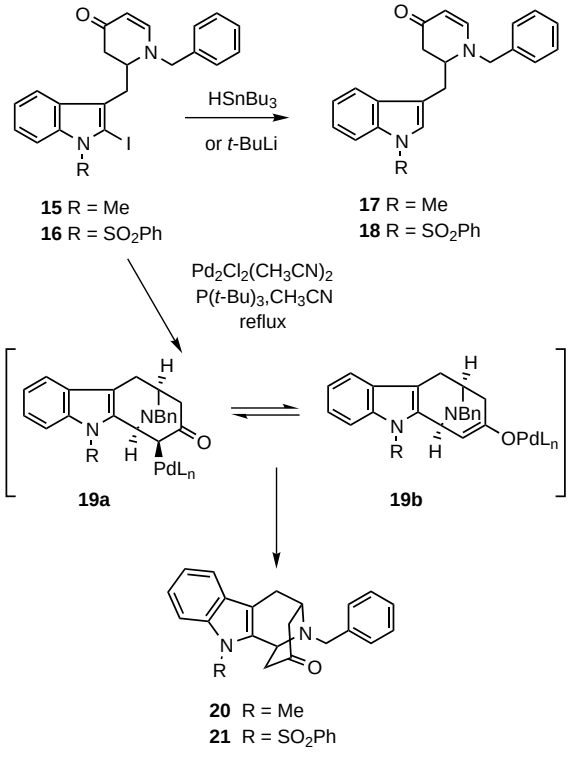
Scheme 1.

dard radical initiation conditions (Bu_3SnH, cat. AIBN, toluene, reflux) failed to bring about 1,4-addition to the C-6 position of the pyridone ring. In each case, only the reduced indoles **17** and **18** were obtained as the only identifiable products (Scheme 2). In addition, treatment of either **15** or **16** under anionic cyclization conditions with *t*-BuLi (–78°C, THF) gave reduced indoles **17** and **18** as the only isolated products.

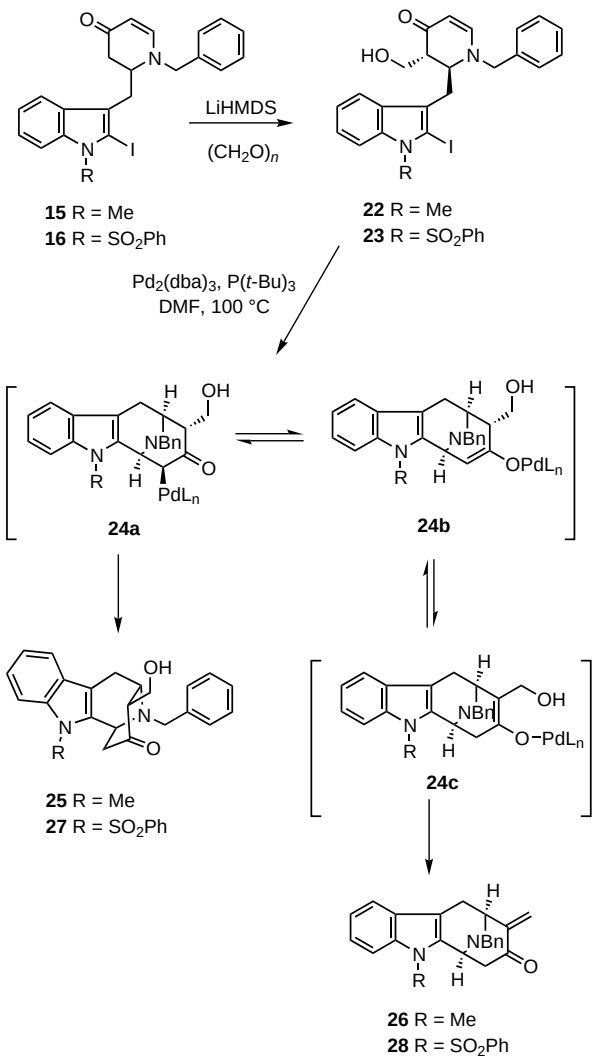
We next chose to investigate a transition-metal approach. Since there is no β-hydrogen available in intermediates **19a** or **19b**[8d,16] for completion of the Heck[17] catalytic cycle, we chose to investigate a number of reductive Heck[18] conditions; however, in all attempts reduced indoles **17** or **18** were formed as the sole products with no detectable amounts of the desired products in the crude NMR. Evidently the reduction of the intermediate 2-indolyl-palladium species is significantly faster than intramolecular cyclization onto the double bond of the pyridone ring. On the other hand, when **15** was subjected to standard Heck conditions employing a stoichiometric amount of palladium ($PdCl_2(CH_3CN)_2$, 2 equiv. P(*t*-Bu)$_3$, CH_3CN, reflux), the desired product **20** was obtained in 85% isolated yield. During the course of the reaction, palladium black is quickly deposited indicating a rapid decomposition of intermediates **19a** and **19b**. Under identical reaction conditions, tetracyclic indole **21** was formed in 83% yield from **18**.[19] While the use of stoichiometric palladium clearly has limitations, it did provide access to these complex alkaloid ring systems in a stereocontrolled manner and in a limited number of steps.

The majority of ajmaline/sarpagine alkaloids contain a hydroxymethyl group at the C-16 position of the tetrahydoro-β-carboline skeleton. In order to gain access to this functionality, we also investigated the intramolecular Heck reactions of iodoindoles **22** and **23** (Scheme 3). Deprotonation of either **15** or **16** (LiHMDS, THF, –20°C) followed by the addition of paraformaldehyde gave **22** (67%) and **23** (73%). This alkylation was extremely diastereoselective (>90% d.e.) with only trace amounts of the corresponding *cis*-diastereomers in the crude NMR.[7] Minor diastereomers of **22** and **23** were effectively removed by chromatography.

Interestingly, reaction of **22** under Heck cyclization conditions ($Pd_2(dba)_3$, P(*t*-Bu)$_3$, DMF, 100°C) gave a mixture of the desired product **25** (33%) and exocyclic methylene compound **26** (29%). We assume that compound **26** arises from intermediate **24c**[8d] and compound



Scheme 2.

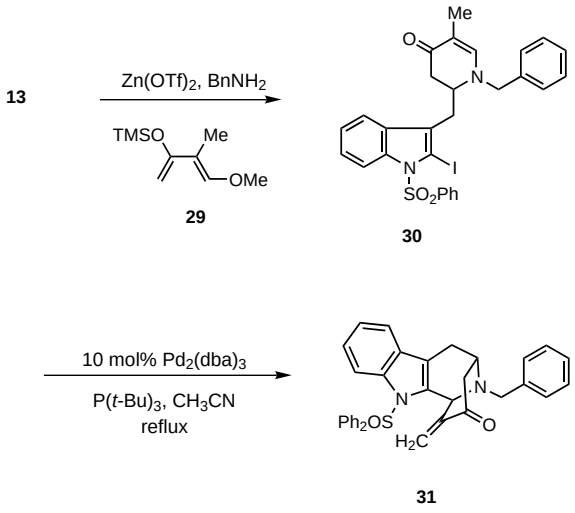


Scheme 3.

25 is derived from either intermediates **24a** or **24b**[8d,e]. Reaction of **23** gave similar results where **27** was isolated in 29% yield and **28** was isolated in 25% yield.

We also prepared iodoindole **30** which was expected to undergo a catalytic intramolecular Heck cyclization followed by β-hydride elimination to provide enone **31** (Scheme 4). Iodoindole **30** was synthesized from **13** by an aza-Diels–Alder reaction with diene **29**[20] providing **30** in 52% yield. When subjected to catalytic Heck cyclization conditions (10 mol% $Pd_2(dba)_3$, 20 mol% P(*t*-Bu)$_3$, DMF, 100°C, 24 h), the desired product **31** was obtained as the only product in 85% yield based on recovered starting material.

In conclusion, we have demonstrated that the aza-Diels–Alder/intramolecular Heck cyclization reactions of 2-(2-iodoindolylmethyl)-4-pyridones provides rapid entry into the tetracyclic tetrahydro-β-carboline skeleton of the ajmaline/sarpagine alkaloids. Work is currently in progress to identify a catalytic procedure for the conversion of these readily accessible starting materials into complex natural products. In addition, we are examining the use of chiral auxiliaries which will allow for the asymmetric synthesis of these targets.[15] The results of our findings will be reported in due course.

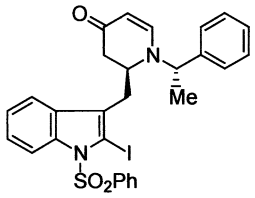


Scheme 4.

References

1. (a) Lounasmaa, M.; Hanhinen, P.; Westersund, M. In *The Alkaloids*; Cordell, G. A., Ed. The sarpagine group of indole alkaloids; Academic Press: San Diego, 1999; Vol. 52; (b) Bi, Y.; Hamaker, L. K.; Cook, J. M. In *Studies in Natural Products Chemistry*, *Bioactive Natural Products*, *Part A*; Basha, F. Z.; Rahman, A., Eds. The synthesis of macroline related alkaloids; Elsevier Science: Amsterdam, 1993; Vol. 13, p. 383; (c) Hamaker, L. K.; Cook, J. M. In *Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed. The synthesis of macrolin related sarpagine alkaloids; Elsevier Science: New York, 1995; Vol. 9, p. 23.
2. (a) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998 and references cited therein; (b) Zhao, S.; Liao, X.; Cook, J. M. *Org. Lett.* **2002**, *4*, 687.
3. (a) Bailey, P. D.; Hollinshead, S. P.; Moore, M. H.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *Tetrahedron Lett.* **1994**, *35*, 3585; (b) Bailey, P. D.; Collier, I. D.; Hollinshead, S. P.; Moore, M. H.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1209.
4. Craig, D.; McCague, R.; Potter, G. A.; Williams, M. R. V. *Synlett* **1998**, 58.
5. (a) van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1958**, *80*, 5006; (b) Masamune, S.; Ang, S. K.; Egli, C.; Nakatsuka, N.; Sakhar, S. K.; Yasunari, Y. *J. Am. Chem. Soc.* **1967**, *89*, 2506; (c) Kutney, J. P.; Eigendorf, G. K.; Matsue, H.; Murai, A.; Tanaka, K.; Sung, W. L.; Wada, K.; Worth, B. R. *J. Am. Chem. Soc.* **1978**, *100*, 938.

6. Kuethe, J. T.; Davies, I. W.; Dormer, P. G.; Reamer, R. A.; Mathre, D. J.; Reider, P. J. *Tetrahedron Lett*. **2002**, *43*, 29.
7. Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 2, pp. 251–294 and references cited therein.
8. For leading references, see: (a) Comins, D. L.; Joseph, S. P.; Zhang, Y. *Tetrahedron Lett*. **1996**, *37*, 793; (b) Comins, D. L.; Zhang, Y. *J. Am. Chem. Soc*. **1996**, *118*, 12248; (c) Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett*. **1995**, *36*, 7047; (d) Kirschbaum, S.; Waldmann, H. *J. Org. Chem*. **1998**, *63*, 4936. (e) Pays, C.; Mangeney, P. *Tetrahedron Lett*. **2001**, *42*, 589 and references cited therein.
9. Rahman, A.; Sultana, M.; Hassan, I. *Tetrahedron Lett*. **1983**, *24*, 1845.
10. Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Slvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith, A. B., III; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. R.; Strder, C. D. *J. Am. Chem. Soc*. **1993**, *115*, 12550.
11. Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155.
12. Lin, Y. M.; Oh, T. *Tetrahedron Lett*. **1997**, *38*, 727.
13. The structure assigned to each new compound is in full accord with its ^{1}H and ^{13}C NMR and elemental analysis.
14. General procedure for the aza-Diels–Alder reaction of **13** with diene **14**: To a solution of **13** (600 mg, 1.41 mmol) in 25 mL of CH_2Cl_2 was added benzylamine (166 mg, 1.55 mmol), $Zn(OTf)_2$ (564 mg, 1.55 mmol), and diene **14** (316 mg, 1.83 mmol). The resulting mixture was stirred at rt for 3 h and poured into 15 mL of 0.5 M HCl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue chromatographed on silica gel to give 608 mg (74%) of **16** as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07 (d, 1H, $J=16.2$ Hz), 2.57 (dd, 1H, $J=16.2$ and 6.6 Hz), 2.86 (dd, 1H, $J=13.9$ and 7.2 Hz), 3.30 (dd, 1H, $J=13.9$ and 7.9 Hz), 3.75 (m, 2H), 4.01 (d, 2H, $J=14.9$ Hz), 5.07 (d, 1H, $J=7.1$ Hz), 7.00 (m, 3H), 7.31 (m, 8H), 7.48 (t, 1H, $J=7.5$ Hz), 7.85 (m, 2H), 8.33 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.0, 39.9, 55.1, 58.6, 80.5, 97.7, 16.1, 118.7, 124.3, 125.6, 126.8, 127.2, 127.6, 128.4, 128.7, 129.0, 129.2, 130.8, 134.2, 136.4, 138.1, 139.2, 152.3, 190.1. Anal. calcd for $C_{27}H_{23}N_2IO_3S$: C, 55.68; H, 3.98; N, 4.81. Found: C, 55.30; H, 3.84; N, 4.63.
15. Preliminary investigations reveal that the asymmetric aza-Diels–Alder reaction of **13** with (*S*)-α-methylbenzylamine gave compound **32** as a 92:8 mixture of diastereomers (63%).



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16. Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett*. **1995**, *36*, 7047.
17. (a) Heck, R. F. *Org. React*. **1982**, *27*, 345–390; (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985; (c) Hegedus, L. S. *Angew. Chem*. **1988**, *100*, 1147; (d) Hegedus, L. S. In *Organometallics in Synthesis—A manual*; Schlosser, M., Ed. Palladium in organic synthesis; Wiley: New York, 1994; pp. 383–459.
18. (a) Schmidt, B.; Hoffmann, H. M. R. *Tetrahedron* **1991**, *47*, 9357; (b) Clayton, S. C.; Regan, A. C. *Tetrahedron Lett*. **1993**, *34*, 7493.
19. General procedure for the preparation of tetracyclic tetrahydro-β-carboline **21**: To a solution of **16** (500 mg, 0.858 mmol) in 35 mL of CH_3CN was added 223 mg (0.858 mmol) of $PdCl_2(CH_3CN)_2$ followed by tri-*t*-butylphosphine (347 mg, 1.72 mmol). The resulting mixture was heated to reflux for 1.5 h, cooled to rt, and filtered over a pad of Celite. The mixture was concentrated under reduced pressure and chromatographed on silica gel to give 325 mg (83%) of **21** as a colorless solid: mp: 166–167°C (MTBE); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (d, 1H, $J=15.4$ Hz), 2.54 (d, 1H, $J=17.1$ Hz), 2.91 (m, 1H), 2.95 (m, 1H), 3.09 (m, 2H), 3.72 (d, 1H, $J=14$ Hz), 3.75 (d, 1H, $J=14$ Hz), 4.85 (m, 1H), 7.27 (m, 1H), 7.37 (m, 9H), 7.52 (m, 1H), 7.58 (d, 2H, $J=8.2$ Hz), 8.12 (d, 1H, $J=8.2$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.3, 46.0, 48.3, 52.1, 54.0, 57.0, 114.6, 118.8, 123.8, 125.2, 126.3, 127.6, 128.2, 128.7, 129.4, 129.5, 133.8, 134.9, 138.4, 138.8, 208.5. Anal. calcd for $C_{27}H_{24}N_2O_3S$: C, 71.03; H, 5.30; N, 6.14. Found: C, 70.67; H, 5.12; N, 5.90.
20. Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem*. **1991**, *56*, 4976.