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Asymmetric aza-Diels–Alder reactions of indole 2-carboxaldehydes

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Abstract—The aza-Diels–Alder reaction of substituted indole 2-carboxaldehydes with Danishefsky's diene has been investigated. The reaction proceeds with a high degree of diastereoselectivity providing highly functionalized 2-(2-piperidyl)indoles which are further elaborated into novel polycyclic heterocycles.

The aza-Diels–Alder reaction has emerged in recent years as a highly efficient method for the construction of nitrogen heterocycles.[1,2] Most notable successes have been achieved by reaction of aliphatic and aromatic imines with Danishefsky's diene **2** in the presence of a Lewis acid.[1,2] Diastereoselectivities of these reactions have been investigated with imines derived from carbohydrates,[3] amino acids,[2b] and α-alkoxyimines[4]. Enantioselective methods employing chiral Lewis acids have also emerged.[5]

Indoles bearing a substituted piperidine ring at the 2-position of the indole ring comprise of a large and diverse class of naturally occurring and biologically active compounds. The indolo[2,3-*a*]quinolizidine ring system is present in a large number of indole alkaloids of several structural types including the Corynanthean, Eburnan, and Rauwolfia families of alkaloids[6] (Fig. 1). In addition, alkaloids lacking the tryptamine bridge have also been identified.[7] Construction of the polycyclic framework found in many of these complex alkaloids depends on the availability of convenient methods for the preparation of intermediates in the enantiomerically pure form. We have investigated the aza-Diels–Alder reaction of imines derived from substituted indole 2-carboxaldehydes **1** as a means of preparing enantiomerically pure, highly functionallized 2-(2-piperidyl)indoles **3** (Fig. 2). In this letter we disclose our initial observations.

We chose to utilize (*S*)-(−)-α-methylbenzylamine as the chiral auxiliary due to it's low cost and availability in either enantiomeric form. Attempts to form the imine of indole carboxaldehyde **5**[8] in situ in the presence of diene **2** and $ZnCl_2$ or $Zn(OTf)_2$ at 0°C and at rt did not afford the expected cycloadduct **8**.[9] Instead, compounds **6** and **7** were isolated in 45 and 25% yields, respectively.

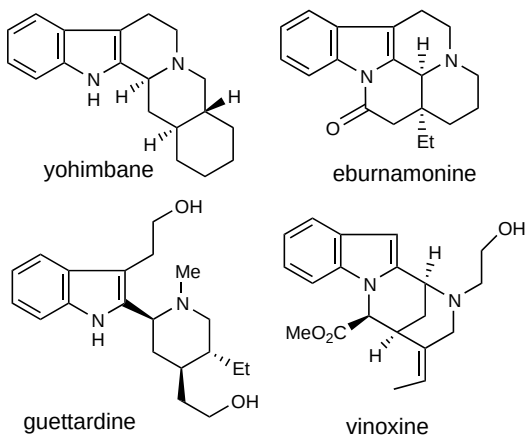

Figure 1.

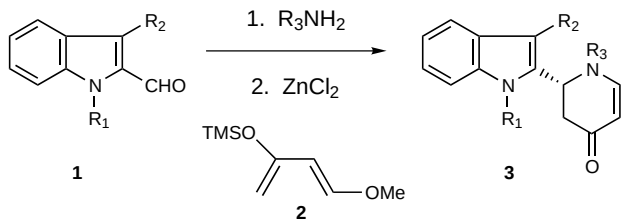

Figure 2.

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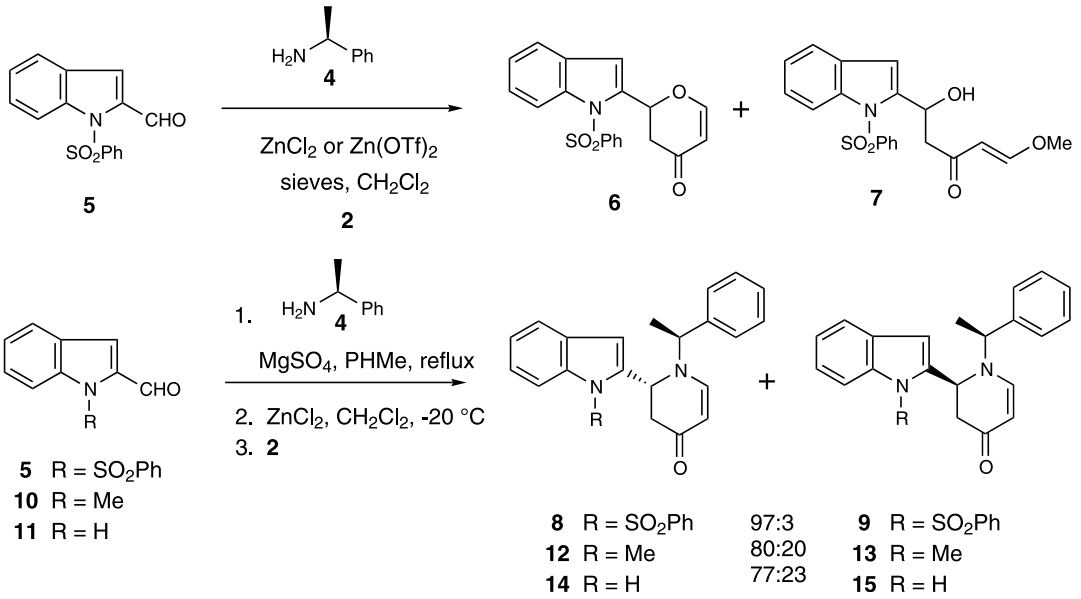


Scheme 1.

The presence of **7** clearly indicates that a tandem Mannich–Michael cyclization pathway is operative.[3,10] On the other hand, treatment of the preformed imine of **5** with $ZnCl_2$ at −20°C followed by addition of diene **2** afforded cycloadduct **8** in 96% yield as a 97:3 mixture of diastereomers (Scheme 1).[11] The absolute configuration of **8** was determined by single crystal X-ray analysis which indicated a preferred pseudoaxial orientation of the indole ring (Fig. 3).[12] We also explored the aza-Diels–Alder reactions of indole 2-carboxaldhydes **10** and **11**.[13] Treatment of the preformed imines of these aldehydes followed by exposure to $ZnCl_2$ and diene **2** gave the desired adducts **12** (76%) and **14** (61%) although with decreased diastereoselectivity. As in the case of cycloadduct **8**, the minor diastereomers could easily be separated by crystallization. We assume the increased diastereoselectivity for **5** is due in large part to steric influences of the sulfonyl group; however, we cannot rule out an electronic influence at this time.

The vast majority of indole alkaloids contain substitution at the 3-position of the indole ring. In order to broaden the synthetic utility of the process, we investigated the reactions of imines derived from readily available indole 2-carboxaldehydes **16**[14] and **18**[15] with diene **2** (Scheme 2). In the case of **16**, the highly functionallized adduct **17** was obtained in 75% isolated yield with the depicted stereochemistry as shown. The diastereomeric ratio was determined to be 85:15 by HPLC analysis of the crude reaction mixture. Exposure of **18** to the identical reaction conditions afforded **19** in 73% yield. The diastereomeric ratio for **19** was 86:14. Both **17** and **19** were stable, crystalline solids which could be obtained in diastereomerically pure form by either chromatography or crystallization.

Having established that the aza-Diels–Alder reaction sequence of substituted indole 2-carboxaldehydes is an efficient method for the construction of the 2-(2-piperidyl)indole framework, we next turned our attention to further elaboration of the piperidone ring. For example, removal of the silyl protecting group of **19** with TBAF followed by bromination (CBr_4, PPh_3) gave bromide **20** (Scheme 3) in 65% overall yield.[16] Interestingly, reduction of **20** with excess $NaBH_4$ in MeOH gave the novel bicyclic aza-octane **22** as a single diastereomer in 92% yield. The unique [2,2,4] aza-octane **22** most likely arises via an intramolecular alkylation of intermediate **21** followed by a stereoselective reduction of the resulting ketone. Intramolecular cyclization also occurred when **20** was treated with lithium hexamethyldisilyazide (LiHMDS) at −20°C giving hexahydro-4*H*-pyrido[2,3-*a*]carbazole **23** in 89% isolated yield.[17]

In conclusion, we have demonstrated that the aza-Diels–Alder reaction of substituted indole 2-carbox-

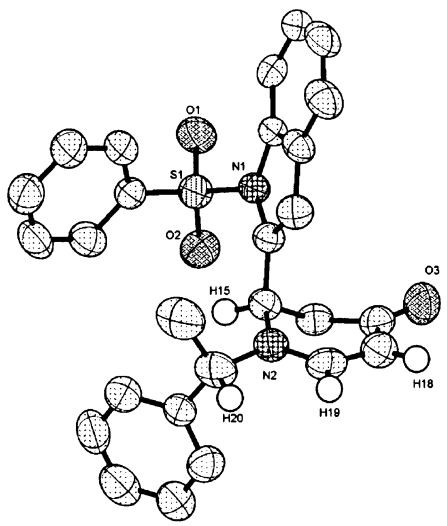
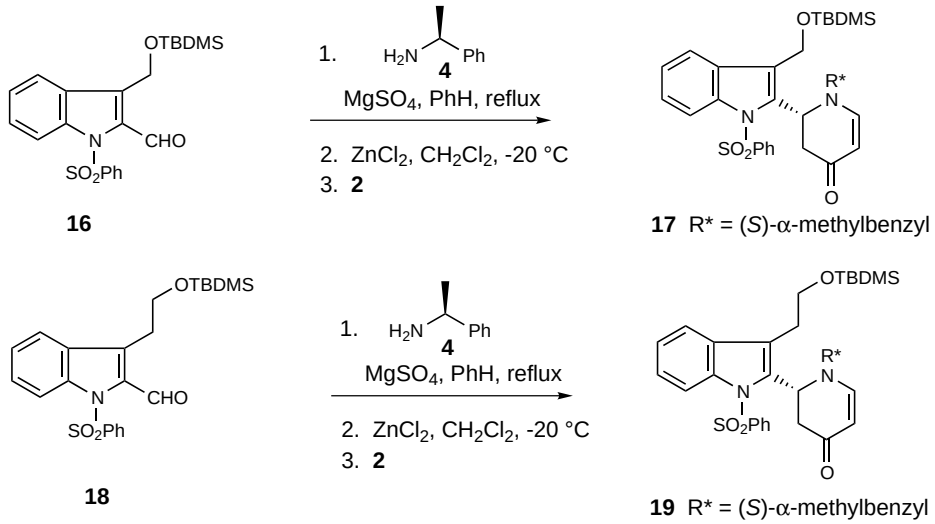
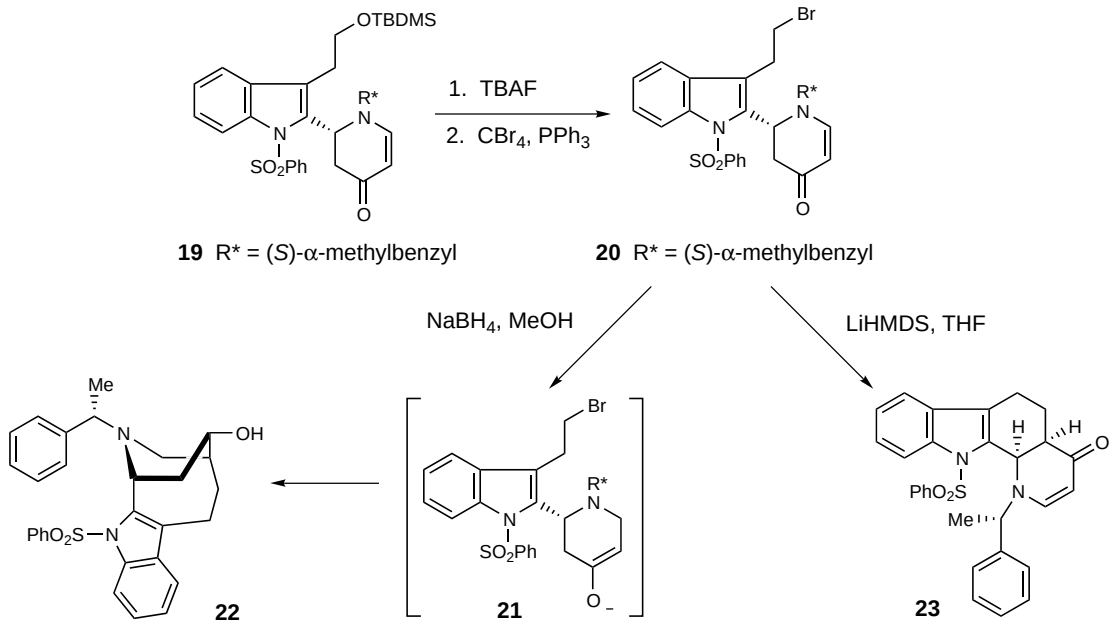


Figure 3. X-Ray structure of **8**.



Scheme 2.



Scheme 3.

aldehydes proceeds with good to excellent diastereoselectivity and high yield. Subsequent transformations allow for the construction of novel heterocyclic ring systems possessing multiple stereogenic centers. We are currently examining the use of chiral Lewis acids and alternative nitrogen protecting groups in order to gain access to advanced alkaloid ring systems. The results of our findings will be reported in due course.

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7. For leading references for the molecules depicted in Fig. 1 see: (a) Diez, A.; Merce, T.; Rugiralta, M. *Tetrahedron* **1990**, *46*, 4393; (b) Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 1156.
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11. General procedure for the aza-Diels–Alder reaction of **5** with diene **2**: To a solution of of **5** (379 mg, 1.32 mmol) in 5 mL of toluene was added amine **4** (177 mg, 1.46 mmol) and 150 mg of $MgSO_4$. The mixture was heated at reflux for 12 h, cooled, and filtered over a pad of solka flok (filter aid). The toluene was removed under reduced pressure and the crude imine redissolved in 10 mL of CH_2Cl_2 and the mixture cooled to −20°C. To the solution was added 2.0 mL of a 1.0 M solution of $ZnCl_2$ and the mixture stirred for 10 min. Diene **2** (273 mg, 1.58 mmol, Aldrich) was then added dropwise and the mixture maintained at −20°C for 2 h. The reaction mixture was quenched with 5 mL of 1.0 M HCl and allowed to reach rt. The layers were separated and the aqueous layer was extracted with an additional 10 mL of CH_2Cl_2. The combined organic extracts were dried, and chromatographed on silica gel to give 510 mg (96%) of **8** as a colorless solid: $[\alpha]_D^{23}$ −32.8 (*c* 0.04, $CDCl_3$); mp 146–147°C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) d 1.45 (d, 3H, $J=6.9$ Hz), 2.71 (dd, 1H, $J=16.6$ and 3.0 Hz), 2.96 (dd, 1H, $J=16.6$ and 7.7 Hz), 4.47 (q, 1H, $J=6.9$ Hz), 4.98 (d, 1H, $J=7.7$ Hz), 5.58 (dd, 1H, $J=7.7$ and 3.0 Hz), 6.74 (s, 1H), 7.10 (d, 1H, $J=7.7$ Hz), 7.18–7.56 (m, 11H), 7.63 (d, 2H, $J=8.2$ Hz), 8.17 (d, 1H, $J=8.4$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.0, 42.0, 52.9, 61.9, 98.4, 112.2, 115.4, 121.2, 124.3, 125.3, 126.1, 127.2, 128.4, 129.0, 129.3, 129.5, 134.3, 138.0, 138.8, 139.7, 150.9, 189.5. Anal calcd. for $C_{22}H_{24}N_2O_3S$: C, 71.03; H, 5.30; N, 6.14. Found: C, 69.92; H, 5.29; N, 6.12.
12. The authors have deposited crystallographic data under the number CCDC–170495. Copies of the data can be obtained, free of charge, on application to CCDC, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.ul].
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15. Prepared by directed lithiation of the known 1-(*O*-*tert*-butyldimethylsilyl)-2-[3-(1-*N*-phenylsulfonyl)indolyl]-ethanol, see: Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith, III, A. B.; 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. To a solution of LDA, prepared by from diisopropylamine (3.10 g, 30.60 mmol) and *n*-butyllithium (2.5 M in hexane, 12.0 mL, 30.00 mmol), in 50 mL of THF at −78°C was added dropwise 1-(*O*-*tert*-butyldimethylsilyl)-2-[3-(1-*N*-phenylsulfonyl)indolyl]-ethanol (8.34 g, 20.01 mmol) in 15 mL of THF. The mixture was allowed to stir at −78°C for 30 min and then allowed to warm to rt and stirred for 1 h. The mixture was cooled to −78°C and DMF (7.30 g, 100 mmol) was added in one portion. The reaction mixture was allowed to warm to rt and quenched with sat. NH_4Cl. The mixture was extracted with EtOAc, dried, and chromatographed on silica gel to give 5.34 g (63%) of **18** as a colorless solid: mp 67–68°C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ −0.20 (s, 6H), 0.72 (s, 9H), 3.19 (t, 2H, $J=6.3$ Hz), 3.80 (t, 2H, $J=6.3$ Hz), 7.34 (m, 3H), 7.52 (m, 2H), 7.71 (m, 3H), 8.23 (d, 1H, $J=8.7$ Hz), 10.6 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.6, 18.2, 28.7, 63.1, 115.6, 122.8, 124.6, 126.7, 129.1, 129.2, 130.8, 134.1, 134.4, 137.2, 184.7.
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