ORGANIC LETTERS

2008
Vol. 10, No. 5
745−748

Catalytic Asymmetric Total Synthesis of (+)-Yohimbine

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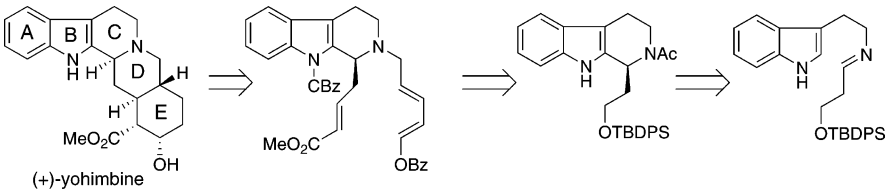
Received November 16, 2007

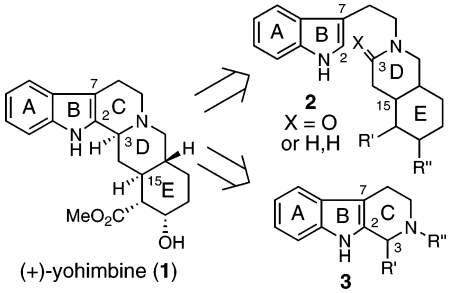
ABSTRACT



The total synthesis of (+)-yohimbine was achieved in 11 steps and 14% overall yield. The absolute configuration was established through a highly enantioselective thiourea-catalyzed acyl-Pictet–Spengler reaction, and the remaining 4 stereocenters were set simultaneously in a substrate-controlled intramolecular Diels–Alder reaction.

Yohimbine (**1**) is an important member of the monoterpenoid indole alkaloids, a large class of natural products that features synthetically challenging structures with diverse biological activity.[1] Total syntheses of **1** and related alkaloids have relied on either of two strategies (Scheme 1).[2−4] One approach relies on the generation of the DE-ring system, followed by cyclization to form the C ring (**2** → **1**). This strategy has been effective; however, control of the C(3) stereogenic center has presented significant difficulties. A second approach involves formation of the tetrahydro-β-carboline ABC-ring system, followed by annulation to set the D and E rings (**3** → **1**). This strategy has been used less frequently, especially in asymmetric syntheses, owing to the

Scheme 1. General Strategies Employed in Previous Syntheses of Yohimbine and Related Alkaloids



(1) For reviews, see: (a) Brown, R. T. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Ed.; John Wiley and Sons: New York, 1983; Vol. 25, Part 4, pp 147−199. (b) Baxter, E. W.; Mariano, P. S. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Springer-Verlag: New York, 1992; Vol. 8, pp 197−319. (c) Szántay, C.; Honty, K. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Ed.; John Wiley and Sons: New York, 1994; Vol. 25, Part 4 Suppl., pp 161−216. (d) Goldberg, M. R.; Robertson, D. *Pharmacol. Rev.* **1983**, *35*, 143−180.

(2) For the first total synthesis of yohimbine, see: (a) van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1958**, *80*, 5006−5007. (b) van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1969**, *91*, 7315−7333.

(3) For other total syntheses of yohimbine, see: (a) Töke, L.; Honty, K.; Szántay, C. *Chem. Ber.* **1969**, *102*, 3248−3259. (b) Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109−5110. (c) Kametani, T.; Kajiwara, M.; Takahashi, T.; Fukumoto, K. *Heterocycles* **1975**, *3*, 179−182. (d) Brown, R. T.; Pratt, S. B. *J. Chem. Soc., Chem. Commun.* **1980**, 165−167. (e) Wenkert, E.; St. Pyrek, J.; Uesato, S.; Vankar, Y. D. *J. Am. Chem. Soc.* **1982**, *104*, 2244−2246. (f) Miyata, O.; Hirata, Y.; Naito, T.; Ninomiya, I. *J. Chem. Soc., Chem. Commun.* **1983**, 1231−1232. (g) Blaskó, G.; Knight, H.; Honty, K.; Szántay, C. *Liebigs Ann. Chem.* **1986**, 655−663. (h) Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124−6134. (i) Hirai, Y.; Terada, T.; Okaji, Y.; Yamazaki, T.; Momose, T. *Tetrahedron Lett.* **1990**, *31*, 4755−4756. (j) Aubé, J.; Ghosh, S.; Tanol, M. *J. Am. Chem. Soc.* **1994**, *116*, 9009−9018.

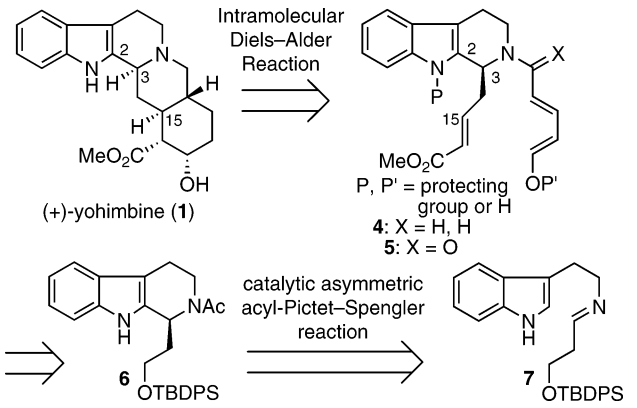
(4) For general reviews of synthetic approaches toward yohimbine alkaloids, see refs 1a−c. See also: Kuehne, M. E.; Muth, R. S. *J. Org. Chem.* **1991**, *56*, 2701−2712.

10.1021/ol702781q CCC: $40.75
Published on Web 02/08/2008

lack of general methods for preparation of enantioenriched tetrahydro-β-carbolines (rings A−C). We have recently reported a thiourea-catalyzed asymmetric acyl-Pictet−Spengler reaction for the enantioselective synthesis of such ring systems.[5−7] A further challenge lies in the diastereoselective formation of the D and E rings. An intramolecular Diels−Alder (IMDA) reaction appears ideally suited to address this challenge, and several indole alkaloids have been prepared through such an approach.[8,9] Herein we report an analysis of the requisite IMDA reaction for the synthesis of yohimbine, and a concise, completely stereocontrolled synthesis of **1** that relies on a successful Pictet−Spengler/IMDA strategy.

Our synthetic plan relied on the generation of a chiral building block such as **4** or **5** via the acyl-Pictet−Spengler reaction, which establishes the absolute configuration at C(3) (Scheme 2). Construction of the DE-ring system, and the

Scheme 2. Retrosynthetic Analysis



remaining four stereocenters present in yohimbine, was then envisioned via an IMDA reaction (**4** or **5** → **1**). IMDA reactions using simple 1,6,8-nonatriene and 1,7,9-decatriene derivatives often display poor trans/cis selectivity across the ring fusion, but activation of the dienophile with electron-withdrawing groups and Lewis acids has been shown to increase selectivity for the trans (i.e., endo) isomer.[10] Despite the extensive body of knowledge about the stereoselectivity of the IMDA reaction,[11,12] the system of interest in our study represents a challenging case: the planar AB ring system and the nitrogen atom at the C−D ring fusion lead to distortions from well-defined chair cyclohexane conformations of the C and D rings. Given that the stereochemical outcome in the cyclization of **4** represented a key and open question in this plan, we turned to computational methods both to better understand the accessible conformations of IMDA substrates and to guide our efforts to develop stereoselective variants.

Computations were performed using model substrates **4a** and **5** (P = H, P′ = Me) for both at the B3LYP/6-311+G-(d,p)//B3LYP/6-31G(d) level of density functional theory.[13,14] Diels−Alder reactions with substrate **4a** are asynchronous, and the transition structures (TSs) have C(15)−C(20) bond lengths of ∼2.0 Å and C(16)−C(17) bond lengths of ∼2.7 Å (Figure 1). TSs in which the incipient D-ring adopts a

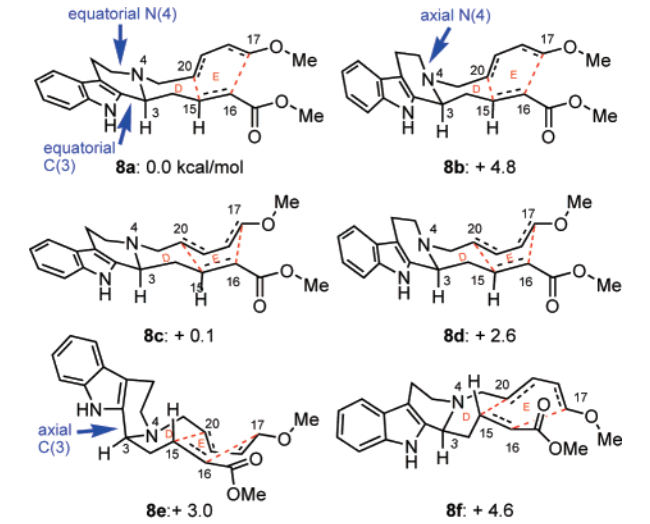


Figure 1. Relative energies of IMDA transition structures **8a−f** calculated for model substrate **4a**. TSs **8c** and **8d** lead to a cycloadduct with the relative configuration of **1**.

chairlike conformation (**8a−8e**) are favored over boatlike TSs (**8f**), and there is a significant preference for an equatorial, rather than an axial, orientation of the substituent at C3 (compare **8a** and **8e**). Thus, the dienophile facial

(5) (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558−10559. (b) Raheem, I. T.; Thiara, P. V.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404−13405. For other approaches to asymmetric catalysis of the Pictet−Spengler reaction, see: (c) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086−1087. (d) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485−7487.

(6) For a total synthesis of (+)-harmicine using a catalytic asymmetric Pictet−Spengler-type cyclization, see ref 5b.

(7) For asymmetric allylations of dihydro- β-carbolines using stoichiometric allylating reagents, see: (a) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646−9746. (b) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489−8490.

(8) (a) Yamaguchi, R.; Otsuji, A.; Utimoto, K. *J. Am. Chem. Soc.* **1988**, *110*, 2186−2187. (b) Meyers, A. I.; Highsmith, T. K.; Buonora, P. T. *J. Org. Chem.* **1991**, *56*, 2960−2964. (c) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161−6171.

(9) For other synthetic approaches to yohimbine, yohimbane, and isoquinoline alkaolids that use IMDA reactions, see: (a) Leonard, J.; Appleton, D.; Fearnley, S. P. *Tetrahedron Lett.* **1994**, *35*, 1071−1074. (b) Sparks, S. M.; Gutierrez, A. J.; Shea, K. J. *J. Org. Chem.* **2003**, *68*, 5274−5285. For a synthetic and theoretical study of IMDA reactions of various azanona- and azadecatrienes, see (c) Tsirk, A.; Gronowitz, S.; Hörnfeldt, A.-B. *Tetrahedron* **1998**, *54*, 9529−9558.

(10) For an example, see: Roush, W. R.; Essenfeld, A. P.; Warmus, J. S. *Tetrahedron Lett.* **1987**, *28*, 2447−2450.

(11) For leading references to theoretical studies on IMDA reactions, see: (a) Pearson, E. L.; Kwan, L. C. H.; Turner, C. I.; Jones, G. A.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *J. Org. Chem.* **2006**, *71*, 6099−6109. (b) Raimondi, L.; Brown, F. K.; Gonzalez, J.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 4796−4804.

(12) For reviews on stereochemical aspects of IMDA reactions, see: (a) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 167−238. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U. K., 1991; Vol.5, pp 513−550. For a review of IMDA reactions in natural products synthesis, see: (c) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779−4807.

selectivity is expected to be high, leading to the C(3)−C(15) cis stereoisomer. The calculations also indicate a preference for an equatorial orientation of the substituent at N(4) with respect to the forming D ring (**8a** and **8c** vs **8b** and **8d**). However, there is negligible endo/exo selectivity predicted for TSs with an equatorial N(4) substituent (**8a** vs **8c**). In contrast, a significant preference for the endo pathway is predicted among TSs with an axial N(4) substituent (compare **8b** and **8d**).

In contrast, computations of the IMDA reaction of model substrate **5** predict a modest preference for boatlike rather than chairlike TSs (Figure 2), leading to cycloadducts with

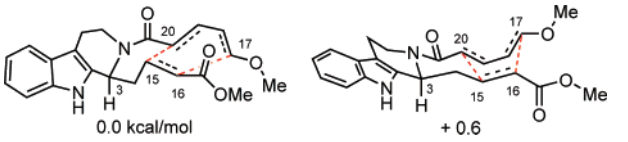


Figure 2. Lowest energy IMDA transition structures using model substrate **5**.

C(3)−C(15) trans configuration. Endo TSs, which generate a trans ring fusion, are significantly preferred over exo TSs (see Supporting Information), presumably due to a preference for the amide diene to adopt a C(20)−C(21) s-cis conformation.[15] These calculations are consistent with experimental results reported previously with related substrates.[8,16]

Despite the poor diastereoselectivity predicted for the thermal cyclization of **4a** (Figure 1, TSs **8a** vs **8c**), we decided to investigate substrates akin to **4** for the synthesis of (+)-yohimbine. The C(3) stereogenic center could be set via a catalytic asymmetric acyl-Pictet−Spengler condensation, and this would in turn serve to set the configuration at C(15) via TS **8a** or **8c** in the IMDA reaction. Control over the C(20) stereocenter depends on the endo/exo selectivity in the IMDA reaction, and we reasoned that this might in principle be achieved by a chiral catalyst.[17]

The synthesis began with the preparation of *N*-acetyl tetrahydro-β-carboline **6** via the acyl-Pictet−Spengler reaction.[5a] Condensation of tryptamine (**9**) with aldehyde **10**,[18] and treatment of the resulting imine **7** with acetyl chloride and 2,6-lutidine in the presence of thiourea catalyst **11** (10 mol %) afforded **6** in 81% yield and 94% ee on gram scale. Deacetylation of the amide was then accomplished by treatment of **6** with lithium amidotrihydroborate,[19] providing enantioenriched tetrahydro β-carboline **12** in 74% yield.

The C(17)−C(21) diene side-chain was then installed in one step via a reductive amination. Thus, treatment of **12** with aldehyde **13**,[20] HOBz, and $NaBH_3CN$ in benzene afforded amine **14** in 55% yield. Protection of the indole nitrogen by treatment of **14** with Cbz−Cl and KHMDS afforded the corresponding *N*-Cbz indole in 92% yield. Subsequent removal of the TBDPS group with TBAF gave the corresponding alcohol in 85% yield.[21] Oxidation of this alcohol with SO_3·pyridine[22] and treatment of the resulting aldehyde with $Ph_3P{=}CHCO_2Me$ provided IMDA substrate **4b** in 79% yield over the two steps.

The IMDA reaction of triene **4b** promoted by 4 equiv of $Sc(OTf)_3$ in CH_3CN proceeded with unexpectedly high selectivity, affording the cycloadduct **15** as a single diastereomer in 87% yield. The relative configuration of **15** at C(3), C(15), and C(20) is consistent with reaction through a cis, endo TS analogous to **8c** or **8d** (Figure 1). Removal of both the *N*-Cbz and C(17)−OBz protecting groups was then accomplished by exposure to Cs_2CO_3 in MeOH/THF, giving the corresponding alcohol in 80% yield. Finally, hydrogenation of the C(18)−C(19) olefin yielded (+)-yohimbine (**1**) in quantitative yield. Synthetic (+)-**1** was identified by comparison to a sample of natural (+)-**1** by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, as well as by high-resolution MS and optical rotation.

Although the high C(3)−C(15) cis selectivity of the IMDA reaction could be anticipated, the high endo/exo selectivity was not predicted from our computations. The high dr is not entirely attributable to the presence of a Lewis acid, as thermally induced cyclization of **4b** (70 °C, benzene) provided a 6:1 mixture of endo/exo cyclodducts ($\Delta\Delta G^{\ddagger}$ = 1.2 kcal/mol). Interestingly, *N*-unprotected analogues (i.e., *N*-H indoles) were found to undergo poorly selective thermally induced cyclization (2−3:1 endo/exo selectivity at 23 °C, $\Delta\Delta G^{\ddagger}$ = 0.4−0.6 kcal/mol). To better understand the role of the indole protecting group in enhancing diaste-

(13) B3LYP has been shown to reproduce experimentally observed kinetic isotope effects in Diels−Alder reactions, suggesting that this method yields accurate TS geometries: (a) Beno, B. R.; Houk, K. N.; Singleton, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 9984−9985. Although B3LYP usually yields accurate endo/exo and dienophile facial selectivities, the MP2 method has been suggested to be more accurate for calculating endo/exo selectivities in some cases: (b) Bakalova, S. M.; Santos, A. G. *J. Org. Chem.* **2004**, *69*, 8475−8481. However, MP2 Diels−Alder TS geometries have been shown to be significantly distorted from B3LYP TS geometries. Using substrate **4a**, MP2 predicts dienophile facial selectivities that are inconsistent with experiment, whereas B3LYP predicts a significant preference for the experimentally observed isomer (*vide infra*). A comparison of results using B3LYP and MP2 with various basis sets is provided in the Supporting Information.

(14) Calculations were carried out using Gaussian 98: Frisch, M. J.; et. al. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 2002.

(15) For discussions of conformational requirements of carbonyl dienes in IMDA reactions, see: (a) Boeckman, R. K.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789−1792. (b) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170−5180.

(16) For other discussions of boatlike transition structures in IMDA reactions, see: (a) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915−930. (b) Tantillo, D. J.; Houk, K. N.; Jung, M. E. *J. Org. Chem.* **2001**, *66*, 1938−1940.

(17) For previous efforts from this laboratory directed toward natural product synthesis employing catalyst-controlled diastereoselective Diels−Alder reactions, see: (a) Joly, G. D.; Jacobsen, E. N. *Org. Lett.* **2002**, *4*, 1795−1798. (b) Chavez, D. E.; Jacobsen, E. N. *Org. Lett.* **2003**, *5*, 2563−2565. (c) Boezio, A. A.; Jarvo, E. R.; Lawrence, B. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6046−6050. (d) Balskus, E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736−1740.

(18) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102−11113.

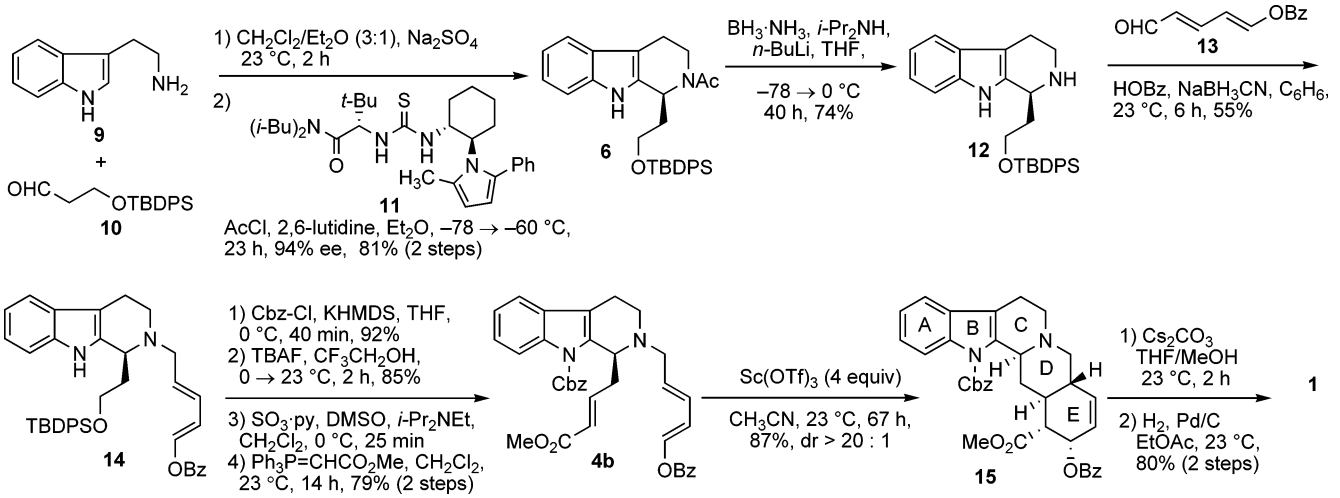
(19) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511. A modified version of the reported procedure was used. See the Supporting Information for details.

(20) Becher, J. *Org. Synth.* **1980**, *59*, 79−83.

(21) Trifluoroethanol was used as solvent for this transformation to suppress transfer of the *N*-carbobenzyloxy group to the liberated alcohol.

(22) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

Scheme 3. Total Synthesis of (+)-Yohimbine



reoselectivity, we applied DFT methods to model substrate **4c** (P = CO_2Me, P′ = Me) to help characterize IMDA TSs.

Comparison of computed TSs **16a**−**16d** with **8a**−**8d** reveals a plausible explanation for moderately enhanced endo/exo selectivities with protected indole substrates (Figure 3). TSs with equatorial N(4) substituents with respect to the

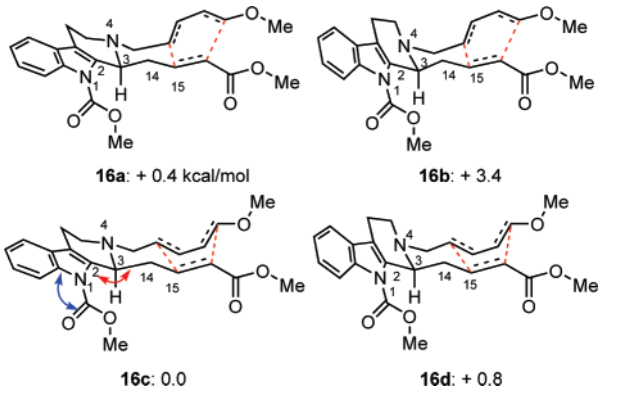


Figure 3. Relative energies of IMDA transition structures **16a**−**d** calculated for model substrate **4c**. TSs **16c** and **16d** lead to a cycloadduct with the relative configuration of **1**.

incipient D ring display a small preference for endo TS **16c** compared with exo TS **16a**. In addition, TSs with axial N(4) substituents are accessible, and N(4)-axial, endo TS **16d** is substantially more stable than N(4)-axial, exo TS **16b**. The carbamate C═O of the protecting group displays a strong preference to be coplanar with the aromatic ring of the indole (blue arrow, Figure 3),[23] leading to repulsive nonbonding interactions between the protecting group and the C(3)−C(15) side chain (red arrow, Figure 3). Although it is likely that the relative distribution of TSs **16a**−**d** will be further influenced by the structure of the indole and C(17) protecting groups and by solvent and Lewis acid,[24] the data in Figures 1 and 3 suggest a basis for the observed high diastereoselectivity in the IMDA reaction.

We have developed a concise and stereoselective synthesis of (+)-yohimbine (**1**) that features an enantioselective acyl-Pictet−Spengler reaction, a reductive amination to install the diene side chain, and an exceptionally diastereoselective IMDA reaction (see Scheme 3). The brevity and efficiency of this synthesis (11 steps, 14% overall yield) highlights the utility of enantioenriched tetrahydro-β-carboline building blocks now readily accessible via asymmetric catalysis. Alternative stereochemical outcomes to IMDA reactions of aza-decatrienes related to **4** and **5** could lead to efficient routes to both natural and unnatural congeners of the yohimbane alkaloid family.[25]

Acknowledgment. This work was supported by the NIH (GM-59316) and by fellowship support to SJZ from the ACS and Roche.

Supporting Information Available: Complete experimental procedures, characterization data, ^{1}H NMR spectra for all isolated products, geometries and energies of calculated TSs, and complete ref 14. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) The energetic cost of rotating the carbamate C═O out of the indole aromatic plane is ca. 10 kcal/mol. See the Supporting Information for details.

(24) Quantitative understanding of the role of the Lewis acid represents a particularly complex problem. The requirement for a large excess of $Sc(OTf)_3$ raises the possibility that multiple equivalents bind to the substrate, and indeed **4b** contains four Lewis basic sites. The most Lewis basic site is the tertiary amine; whereas binding to this site should not substantially affect the IMDA activation energy, it will likely lead to a reduced preference for TS **16a** compared with **16b**−**d**, because the pseudo-axial conformation of C(19) blocks binding of large Lewis acids. The relative energies of TSs **16a**−**d** with BH_3 bound to the tertiary amine are: **16a·BH$_3$**: 10.0 kcal/mol; **16b·BH$_3$**: 3.8; **16c·BH$_3$**: 3.6; **16d·BH$_3$**: 0.0.

(25) Reserpine, for example, shares the same pentacyclic core as yohimbine but is epimeric at the 3, 16, and 20 positions.