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# A Concise, Enantioselective Approach for the Synthesis of Yohimbine Alkaloids

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**ABSTRACT:** We report a concise, enantioselective synthesis of the yohimbine alkaloids (-)-rauwolscine and (-)-alloyohimbane. The key transformation involves a highly enantio- and diastereoselective NHC-catalyzed dimerization and an amidation/*N*-acyliminium ion cyclization sequence to furnish four of the five requisite rings and three of the five stereocenters in two operations. This route also provides efficient access to all four diastereomeric arrangements of the core stereotriad of the yohimbine alkaloids from a common intermediate. This platform approach in combination with the ability to access both enantiomers from the carbene-catalyzed reaction is a powerful strategy that can produce a wide range of complex alkaloids and related structures for future biomedical investigations.

A lkaloids are secondary metabolites containing a basic nitrogen atom that are ubiquitous in nature and medicine.<sup>1</sup> The prevalence of these molecules in pharmaceuticals and the increased desire to investigate sp<sup>3</sup>-carbon-rich molecules in drug discovery campaigns necessitates the efficient construction of complex nitrogen-containing heterocycles with high levels of enantiocontrol.<sup>2,3</sup> Moreover, the design of adaptable syntheses that enable rapid access to a diverse array of structurally related molecules is of comparable importance. Over the past 15 years, the field of *N*-heterocyclic carbene (NHC) catalysis has distinctively enabled the construction of enantioenriched heterocycles,<sup>4-6</sup> and the power of cascade and one-pot processes has led to an everincreasing level of synthetic efficiency in the assembly of complex architectures.<sup>7-9</sup> Herein we report the union of these strategies for the synthesis of yohimbine alkaloids.

The yohimbine natural products are a family of pentacyclic indole alkaloids derived from the amino acid tryptophan and the secoiridoid monoterpene secologanin (Scheme 1).<sup>10</sup> Following the isolation of yohimbine (1) by Spiegel in 1900 and its structural determination by Witkop in 1943,<sup>11</sup> a wide variety of yohimbine stereoisomers have been identified. These alkaloids can be divided into four different subfamilies, normal, allo, pseudo, or epiallo, which differ in their stereochemical arrangement around the D-ring; yohimbine (1), rauwolscine (2), pseudoyohimbine (3), and reserpine (4) are representative members, respectively (Scheme 1). These alkaloids show a wide range of activity within the central nervous system (CNS), and although the structural variations between diastereomeric subfamilies are modest, they lead to an impressive degree of divergence in their pharmacology.<sup>12-15</sup> It is therefore of great interest to be able to access these alkaloids in a concise, modular, and stereoselective fashion to enable thorough investigation of structural analogues.

The traditional approach to the yohimbines follows precedent set by Woodward and co-workers in their landmark synthesis of 4 in 1958, which involves construction of a fully functionalized E-ring precursor followed by tethering of the tryptamine subunit and ring closure.<sup>16,17</sup> This general strategy has been utilized in a myriad of total and formal syntheses, and continues to be the predominant approach to these natural products today.  $^{18-21}$  While this conventional approach has been successful in accessing specific natural products, the key  $\beta$ -carboline pharmacophore is not introduced until the latter stages of the synthesis.<sup>22</sup> Consequently, efficient access to related analogues with biomedical potential is thereby limited and would require reworking of the early stages of the synthesis in order to introduce structural variation in the terpene portion of the molecule. Syntheses that introduce the E-ring last are comparatively less explored, 18,23-25 but have increased potential for access to a large array of related alkaloids.<sup>26,27</sup> In the context of this broad synthetic landscape, we sought to develop a general approach for the synthesis of vohimbine alkaloids that would (a) be fewer than 10 steps for maximum efficiency to drive future biomedical exploration, and (b) be derived from a key intermediate that could be easily converted into the different subtype structures (see Scheme 1).

Our retrosynthetic plan is depicted in Scheme 1. We envisioned accessing (–)-rauwolscine (2) from the known  $\beta$ -ketoester  $5^{26}$  via diastereoselective reduction.  $\beta$ -Ketoester 5 would be obtained by reduction and homologation of diester 6 followed by ring closure. This key intermediate would arise from an amidation/*N*-acyliminium ion cyclization sequence with enol lactone  $7,^{28-31}$  which could be accessed via NHC-catalyzed dimerization of commercially available aldehyde  $8.^{32}$  Additionally, we envisioned *allo*-configured tetracycle 6 as a potential precursor to access the diastereomeric *normal, pseudo,* 

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Scheme 1. Representative Yohimbine Alkaloids and Retrosynthetic Approach



and *epiallo* yohimbine cores by selective stereochemical inversions at the C/D and D/E ring junctions.

Our synthesis commenced with the construction of enantioenriched enol lactone 7 from aldehyde 8 (Scheme 2). After evaluating various conditions (see the Supporting Information for details), it was found that the use of 1 mol % of NHC precatalyst 9 delivered 7 in 83% yield with excellent control of the enantio- and diastereoselectivity; notably, this transformation could be conducted on 30-g scale without loss of efficiency. With ample quantities of 7, we began to explore the key amidation/N-acyliminium ion cyclization sequence with tryptamine to access 6. Initial experiments revealed that the acylation of tryptamine by 7 was rapid, but intramolecular N-acyliminium ion formation was inhibited by intermolecular imine formation with an additional equivalent of tryptamine. This side reaction proved to be minimally reversible even in the presence of water, as only 55% conversion of 7 was seen after 3 days when using equimolar quantities of 7 and tryptamine (see Figure S1). However, we were pleased to find that acidification of the reaction mixture triggered facile imine hydrolysis, and N-acyliminium ion formation and cyclization occurred readily upon addition of TFA. Additional optimization revealed that treatment of 7 with 2 equiv of 10 in a biphasic solvent system of CH<sub>2</sub>Cl<sub>2</sub> and aqueous Na<sub>2</sub>CO<sub>3</sub> followed by acidification and TFA-promoted cyclization

delivered **6** as a separable 80:20 mixture of diastereomers in 74% yield on decagram scale.<sup>30</sup> Selective reduction of the lactam with  $BH_3$ ·DMS then provided tertiary amine **11** in 94% yield, whose structure was confirmed by X-ray crystallography of its TFA salt.

With the ABCD ring system assembled, we turned our attention to construction of the E-ring, which required the homologation of both ester side chains by one carbon, followed then by ring closure. Unfortunately, attempts to directly homologate 11 using Arndt-Eistert<sup>33</sup> or Kowalksi<sup>34</sup> conditions returned starting material or decomposition products, respectively, and LAH reduction to the diol followed by various logical conditions for  $S_N^2$  with cyanide anion resulted only in quaternization of the tertiary amine.<sup>35</sup> We then turned our attention to Wittig-Horner-type homologation conditions. Since an ester oxidation state was desired for the ring closure step, known phosphonate 12 reported by Mikołajczykand co-workers was selected because the resulting ketene dithioacetal can be easily converted to an ester.<sup>36</sup> We also elected to employ conditions disclosed by Takacs in our experimental design, wherein the partial reduction is performed in the presence of the metalated phosphonate to mitigate overreduction and ensure high efficiency in this transformation.<sup>37</sup> A temperature and reducing reagent screen revealed that using lithium diisobutyl-*tert*-butoxyaluminum hydride (LDBBA)<sup>38</sup> at 0 °C in the presence of excess 12 afforded 13 in 70% yield on multigram scale. Although 13 could be converted to the bis(methyl ester) under forcing acidic conditions [p-TsOH (10 equiv), MeOH, 80 °C], its cyclization under the Dieckmann conditions reported previously led to a mixture of 14a, 14b.<sup>26</sup> Even more confounding was that these compounds and their enol isomers proved inseparable under multiple conditions and derivatizations. These roadblocks necessitated an alternative tactic for cyclization. We soon discovered that using a milder set of conditions [p-TsOH (2 equiv), DCM/MeOH, 0-45 °C] delivered an easily separable 60:40 mixture of  $\alpha$ -oxo ketene dithioacetal 15 (major) and its regioisomer (not shown) in 80% combined yield. This transformation not only provided the ring closed product, but also showed the desired regioselectivity along with much needed separability. The unmasking of the resultant  $\alpha$ -oxo-ketene dithioacetal of 15 with HgCl<sub>2</sub> and BF<sub>3</sub>·OEt<sub>2</sub> in methanol then provided the desired methyl ester 5 in 62% yield on >100 mg scale. Temperature proved to be critical to the success of this transformation; reactions conducted below 40 °C were exceedingly sluggish, while those in excess of 50 °C produced significant amounts the ring-opened bis(methyl ester).

At this stage, we were poised to investigate the final disconnection from our retrosynthetic analysis, the diastereoselective reduction of  $\beta$ -ketoester 5. Using NaBH<sub>4</sub>, 17-*epi*rauwolscine 16 was furnished in good yield, with no detectable amount of 2 produced.<sup>26</sup> To circumvent this, we sought out reagents that would provide some semblance of the presumed thermodynamic control. A survey of the literature suggested that SmI<sub>2</sub> would be well suited for this application.<sup>39</sup> Initial experiments using alcoholic additives such as MeOH, <sup>i</sup>PrOH, or <sup>t</sup>BuOH returned the starting material unchanged. However, when H<sub>2</sub>O was used as the protic additive, SmI<sub>2</sub> rapidly delivered (–)-rauwolscine 2 as a single diastereomer in 65% yield. Additionally,  $\beta$ -ketoester 5 could be decarboxylated using LiOH followed by a modified Wolff–Kishner deoxygenation to provide the unsubstituted E-ring product (–)-al-

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Scheme 2. Synthesis of (-)-Rauwolscine (2) and (-)-Alloyohimbane (17)



loyohimbane 17 in 36% yield over 3 steps. Notably, the step economy of our syntheses of 2, 16, and 17 compare favorably to previously reported asymmetric syntheses.<sup>40–43</sup>

With an efficient and general route to allo configured yohimbines secured, we began investigating methods to access other diastereomeric yohimbine frameworks. We began by exploring conditions to control the diastereoselectivity of the key N-acyliminium ion cyclization step. To fully examine activating agents for this transformation, we elected to conduct the N-acyliminium ion cyclization under anhydrous conditions. Hence, the intermediate hydroxylactam 18 (~85:15 d.r.) was isolated by extraction following the imine hydrolysis step in the initially optimized conditions (Table 1). In this new two-step process, employing acetyl chloride at cryogenic temperatures further improved selectivity for 6 over the previous one-pot conditions (entry 1). At higher temperatures (entry 2) or with the use of alternative acetate activating agents (entry 3), the reaction efficiency and selectivity decreased markedly. Lewis and Brønsted acids could also be employed successfully (entries 4-6), with high levels of selectivity and efficiency for **6** being observed with TMSCl at cryogenic temperatures (95:5

d.r. and 78% yield). However, performing the reaction at 40  $^{\circ}$ C rather than -78  $^{\circ}$ C lead to *reversal* of diastereoselectivity, providing **19**, a potential precursor for *epiallo* yohimbines, in 69% yield and 73:27 d.r. (entry 7).

To gain further understanding of the diastereoselectivity, pure 6 was subjected to the reaction conditions employed in entry 7, and the same diastereomeric ratio (6:19 = 27:73) was obtained after 4 days at 40 °C (entry 8); extended reaction times or the use of chiral additives (thioureas or phosphoric acids)<sup>31,44</sup> did not alter this ratio. Additionally, treatment of 18 with anhydrous HCl instead of TMSCl at 40 °C did not provide the same product distribution (entry 9), indicating that acid catalysis is not responsible for equilibration. Our current working model based on this data is that the high diastereoselectivity observed at cryogenic temperatures is the result of a kinetically controlled ring closure,<sup>27</sup> whereas at elevated temperatures, an equilibrating mechanism is operative,<sup>45</sup> delivering the more thermodynamically stable tetracycle **19** as the major diastereomer.

Using the new conditions outlined in Table 1, the *allo* configured product **6** could be readily secured with high levels

 Table 1. Effect of Additives and Temperature on Cyclization

 Diastereoselectivity



<sup>a</sup>Isolated yield over 2 steps starting from 7. <sup>b</sup>No reaction. <sup>c</sup>Reaction time of 2 days. <sup>d</sup>Starting material was pure 6. <sup>e</sup>Reaction time of 4 days. n.d. = not determined.

of diastereoselectivity (Scheme 3). The subjection of 6 to NaOEt in THF-EtOH (1:1) at -20 °C led to selective epimerization of the C-15 (yohimbine numbering) stereocenter, producing the *pseudo* configured product 20 in 52% yield. Alternatively, the oxidation of 20 to the enamide using copper(II) acetate in an atmosphere of molecular oxygen followed by reduction with NaBH<sub>4</sub> in AcOH provided the *normal* configured tetracycle 21 in 72% yield (2 steps) as a single diastereomer.<sup>46</sup> Finally, as shown in Table 1 above, simple modulation of the conditions for cyclization delivered the *epiallo* configured product 19 in 69% yield with modest control of the diastereoselectivity (73:27 d.r.). Combined, these connected approaches provide concise entry into multiple yohimbine stereoisomer subfamilies.

In conclusion, we have developed a concise synthesis of (-)-rauwolscine 2 and (-)-alloyohimbane 17 from commercially available ethyl 4-oxobutenoate 8. The key NHC catalyzed annulation product 7 is readily accessible in enantiopure form and can be converted to the complex tetracyclic lactam 6 in a single operation on multigram scale, which allows facile access to *allo*-configured yohimbines. Selective manipulation of this intermediate also facilitates entry into the *normal, pseudo,* and *epiallo* classes of this important natural product family. Additionally, by employing either enantiomeric NHC catalyst (+ or -), it is feasible that all eight possible stereoisomeric cores of these alkaloids are accessible, enabling production of a wide range of molecules to drive the discovery of new biologically active molecules.



# ASSOCIATED CONTENT

### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b12319.

Experimental procedures and spectroscopic data for compounds (PDF) X-ray data (11) (CIF) X-ray data (2) (CIF)

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#### Notes

The authors declare no competing financial interest.

Scheme 3. Access to All Yohimbine Stereoisomeric Cores

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#### REFERENCES

(1) Roberts, M. F.; Wink, M. Alkaloids: Biochemistry, Ecology, and Medicinal Applications; Plenum, 1998.

(2) Lovering, F.; Bikker, J.; Humblet, C. Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **2009**, *52*, 6752–6756.

(3) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274.

(4) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An overview of N-heterocyclic carbenes. *Nature* **2014**, *510*, 485–496.

(5) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115* (17), 9307–87.

(6) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. A Continuum of Progress: Applications of N-Hetereocyclic Carbene Catalysis in Total Synthesis. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686–11698.

(7) Nicolaou, K. C.; Chen, J. S. The art of total synthesis through cascade reactions. *Chem. Soc. Rev.* **2009**, *38*, 2993–3009.

(8) Grondal, C.; Jeanty, M.; Enders, D. Organocatalytic cascade reactions as a new tool in total synthesis. *Nat. Chem.* **2010**, *2*, 167.

(9) Coulthard, G.; Erb, W.; Aggarwal, V. K. Stereocontrolled organocatalytic synthesis of prostaglandin PGF2 $\alpha$  in seven steps. *Nature* **2012**, 489, 278.

(10) O'Connor, S. E.; Maresh, J. J. Chemistry and biology of monoterpene indole alkaloid biosynthesis. *Nat. Prod. Rep.* **2006**, 23, 532–547.

(11) Witkop, B. Zur konstitution des yohimbins und seiner abbauprodukte. *Liebigs Ann.* **1943**, 554, 83–126.

(12) Saxton, J. E. The Indole Alkaloids. In *The Alkaloids: Chemistry* and *Physiology*; Manske, R. H. F., Ed.; Academic Press, 1960; Vol. 7, Chapter 10, pp 1–199.

(13) Szántay, C.; Blaskó, G.; Honty, K.; Dörnyei, G. Corynantheine, Yohimbine, and Related Alkaloids. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press, 1986; Vol. 27, Chapter 2, pp 131–268.

(14) Shore, P. A.; Giachetti, A. Reserpine: Basic and Clinical Pharmacology. In *Handbook of Psychopharmacology*; Iversen, L. L., Iversen, S. D., Snyder, S. H., Eds.; Springer US: Boston, MA, 1978; Vol. 10: Neuroleptics and Schizophrenia, pp 197–219.

(15) Hatch, R. C.; Kitzman, J. V.; Zahner, J. M.; Clark, J. D. Antagonism of xylazine sedation with yohimbine, 4-aminopyridine, and doxapram in dogs. *Am. J. Vet. Res.* **1985**, *46*, 371–375.

(16) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. The total synthesis of reserpine. *Tetrahedron* **1958**, *2*, 1–57.

(17) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. The Total Synthesis of Reserpine. *J. Am. Chem. Soc.* **1956**, *78*, 2023–2025.

(18) Baxter, E. W.; Mariano, P. S. Recent Advances in the Synthesis of Yohimbine Alkaloids. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Springer: New York, NY, 1992; pp 197–319.

(19) Stork, G.; Tang, P. C.; Casey, M.; Goodman, B.; Toyota, M. Regiospecific and stereoselective syntheses of  $(\pm)$ -reserpine and (-)-reserpine. J. Am. Chem. Soc. **2005**, 127, 16255–16262.

(20) Chen, F.-E.; Huang, J. Reserpine: a challenge for total synthesis of natural products. *Chem. Rev.* 2005, 105, 4671–4706.

(21) Lebold, T. P.; Wood, J. L.; Deitch, J.; Lodewyk, M. W.; Tantillo, D. J.; Sarpong, R. A divergent approach to the synthesis of the yohimbinoid alkaloids venenatine and alstovenine. *Nat. Chem.* **2013**, 5, 126–31.

(22) Maity, P.; Adhikari, D.; Jana, A. K. An overview on synthetic entries to tetrahydro-β-carbolines. *Tetrahedron* **2019**, *75*, 965–1028.

(23) Herlé, B.; Wanner, M. J.; van Maarseveen, J. H.; Hiemstra, H. Total Synthesis of (+)-Yohimbine via an Enantioselective Organocatalytic Pictet-Spengler Reaction. *J. Org. Chem.* **2011**, *76*, 8907–8912.

(24) Barcan, G. A.; Patel, A.; Houk, K. N.; Kwon, O. A torquoselective  $6\pi$  electrocyclization approach to reserpine alkaloids. *Org. Lett.* **2012**, *14*, 5388–5391.

(25) Rajapaksa, N. S.; McGowan, M. A.; Rienzo, M.; Jacobsen, E. N. Enantioselective total synthesis of (+)-reserpine. *Org. Lett.* **2013**, *15*, 706–709.

(26) Toke, L.; Gombos, Z.; Blasko, G.; Hont, K.; Szabo, L.; Tamas, J.; Szantay, C. Synthesis of yohimbines. II. Alternative route to alloyohimbine alkaloids. *J. Org. Chem.* **1973**, *38*, 2501–2509.

(27) Zhang, W.; Bah, J.; Wohlfarth, A.; Franzén, J. A stereodivergent strategy for the preparation of corynantheine and ipecac alkaloids, their epimers, and analogues: efficient total synthesis of (–)-dihy-drocorynantheol, (–)-corynantheol, (–)-protoemetinol, (–)-corynantheal, (–)-protoemetine, and related natural and nonnatural compounds. *Chem. - Eur. J.* **2011**, *17*, 13814–13824.

(28) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. Cyclizations of N-Acyliminium Ions. *Chem. Rev.* **2004**, *104*, 1431–1628.

(29) Wu, P.; Nielsen, T. E. Scaffold Diversity from N-Acyliminium Ions. Chem. Rev. 2017, 117, 7811-7856.

(30) Franzén, J.; Fisher, A. Asymmetric alkaloid synthesis: a one-pot organocatalytic reaction to quinolizidine derivatives. *Angew. Chem., Int. Ed.* **2009**, *48*, 787–791.

(31) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. Enantioselective Brønsted Acid-Catalyzed N-Acyliminium Cyclization Cascades. *J. Am. Chem. Soc.* **2009**, *131*, 10796–10797.

(32) Latendorf, K.; Mechler, M.; Schamne, I.; Mack, D.; Frey, W.; Peters, R. Titanium Salen Complexes with Appended Silver NHC Groups as Nucleophilic Carbene Reservoir for Cooperative Asymmetric Lewis Acid/NHC Catalysis. *Eur. J. Org. Chem.* **2017**, 2017, 4140–4167.

(33) Arndt, F.; Eistert, B. Ein Verfahren zur Überführung von Carbonsäuren in ihre höheren Homologen bzw. deren Derivate. *Ber. Dtsch. Chem. Ges. B* 1935, 68, 200–208.

(34) Kowalski, C. J.; Haque, M. S.; Fields, K. W. Ester homologation via  $\alpha$ -bromo  $\alpha$ -keto dianion rearrangement. *J. Am. Chem. Soc.* **1985**, 107, 1429–1430.

(35) Kalaus, G.; Malkieh, N.; Katona, I.; Kajtar-Peredy, M.; Koritsanszky, T.; Kalman, A.; Szabo, L.; Szantay, C. Synthesis of Vinca alkaloids and related compounds. 21. Preparation of  $(\pm)$ -eburnamonine,  $(\pm)$ -3-epieburnamonine, and  $(\pm)$ -C-norquebrachamine from a common intermediate. *J. Org. Chem.* **1985**, *50*, 3760–3767.

(36) Mikołajczyk, M.; Grzejszczak, S.; Zatorski, A.; Mlotkowska, B.; Gross, H.; Costisella, B. Organosulphur compounds—XVIII: a new and general synthesis of ketene S, S- and O, S-thioacetals based on the Horner-Wittig reaction. *Tetrahedron* **1978**, *34*, 3081–3088.

(37) Takacs, J. M.; Helle, M. A.; Seely, F. L. An improved procedure for the two carbon homologation of esters to  $\alpha,\beta$ -unsaturated esters. *Tetrahedron Lett.* **1986**, *27*, 1257–1260.

(38) Kim, M. S.; Choi, Y. M.; An, D. K. Lithium diisobutyl-tbutoxyaluminum hydride, a new and efficient reducing agent for the conversion of esters to aldehydes. *Tetrahedron Lett.* **200**7, *48*, 5061– 5064.

(39) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. Total synthesis of the macrolide antibiotic cytovaricin. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031.

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(40) Feng, W.; Jiang, D.; Kee, C.-W.; Liu, H.; Tan, C.-H. Bicyclic guanidine catalyzed asymmetric tandem isomerization intramolecular-Diels-Alder reaction: the first catalytic enantioselective total synthesis of (+)-alpha-yohimbine. *Chem. - Asian J.* **2016**, *11*, 390–394.

(41) Aube, J.; Ghosh, S.; Tanol, M. Symmetry-driven synthesis of indole alkaloids: asymmetric total syntheses of (+)-yohimbine, (-)-yohimbone, (-)-yohimbane, and (+)-alloyohimbane. J. Am. Chem. Soc. **1994**, 116, 9009–9018.

(42) Wang, X.; Xia, D.; Qin, W.; Zhou, R.; Zhou, X.; Zhou, Q.; Liu, W.; Dai, X.; Wang, H.; Wang, S.; Tan, L.; Zhang, D.; Song, H.; Liu, X.-Y.; Qin, Y. A Radical Cascade Enabling Collective Syntheses of Natural Products. *Chem.* **2017**, *2*, 803–816.

(43) Miyafuji, A.; Ito, K.; Katsuki, T. Application of Oxidative Desymmetrization of meso-Tetrahydrofurans: Syntheses of Functionalized Chiral Building Blocks and of (–)-Alloyohimbane. *Heterocycles* **2000**, *52*, 261–272.

(44) Taylor, M. S.; Jacobsen, E. N. Highly Enantioselective Catalytic Acyl-Pictet-Spengler Reactions. J. Am. Chem. Soc. **2004**, 126, 10558–10559.

(45) Lounasmaa, M.; Berner, M.; Brunner, M.; Suomalainen, H.; Tolvanen, A. Acid-catalysed epimerization of indolo[2,3-a]quinolizidine derivatives: role of the nitrogen lone pairs in the mechanism. *Tetrahedron* **1998**, *54*, 10205–10216.

(46) Bohlmann, C.; Bohlmann, R.; Rivera, E. G.; Vogel, C.; Manandhar, M. D.; Winterfeldt, E. Reaktionen an Indolderivaten, LIII. Enantioselektive Totalsynthese von (+)-Geissoschizin und (-)-Geissoschizol. *Liebigs Ann.* **1985**, 1985, 1752–1763.