Total Synthesis of (+)-Himbacine and (+)-Himbeline

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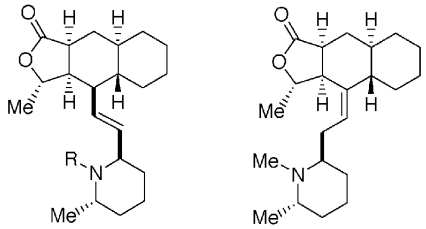
Himbacine (**1**), a complex piperidine alkaloid isolated from the bark of Australian magnolias, is a promising lead in Alzheimer's disease research due to its potent muscarinic receptor antagonist property. We have described here a highly efficient synthetic strategy that resulted in the total synthesis of himbacine (**1**) in about 10% overall yield and isohimbacine (**1a**), an unnatural isomer of himbacine, in 18% overall yield. The total synthesis of himbacine was initially approached using an intramolecular Diels−Alder reaction as the key step to generate intermediate **5** followed by a [3 + 2] cycloaddition with nitrone **4** to produce the isoxazolidine derivative **3**. Methylation followed by catalytic reduction of **3** gave 12′-hydroxyhimbacine (**20**), which, upon dehydration, gave isohimbacine (**1a**) as the sole product. In an alternative approach, an all-encompassing intramolecular Diels−Alder reaction of an appropriately substituted tetraene derivative **31**, which bears the entire latent carbon framework and functional group substitution of himbacine, gave the desired advanced tricyclic intermediate **33,** which was readily converted to (+)-himbeline (**2**) and (+)-himbacine (**1**).

Introduction

Himbacine (**1**) and its congener himbeline (**2**) are complex piperidine alkaloids isolated from the bark of *Galbulimima baccata*, a species that belongs to the magnolia family.[1] Himbacine has attracted considerable attention as a promising lead in Alzheimer's disease research due to its potent muscarinic receptor antagonist property.[2] The senile dementia associated with Alzheimer's disease is directly correlated with diminished levels of synaptic acetylcholine in the cortical and hippocampal areas of brain, and the current form of therapy addresses this issue by inhibiting cholinesterase, which breaks down acetylcholine.[3] Alternatively, biosynthetic enhancement of synaptic acetylcholine levels could be achieved by selectively inhibiting presynaptic muscarinic receptors (M_2), agonist-induced stimulation of which shuts off acetylcholine release.[3] Himbacine is a potent inhibitor of muscarinic receptor of the M_2 subtype (K_i = 4.6 nM) with 20-fold selectivity toward the M_1 receptor.[2c,4] However, to identify a therapeutically useful target, both the selectivity and potency of himbacine need to be optimized through a rigorous structure−activity relationship study in this series. The complex structural features of himbacine forebodes against this task. As part of our efforts to identify potent and selective M_2 receptor antagonists related to himbacine, we needed a practical synthesis of himbacine and closely related analogues. Such a synthesis would proceed through a common advanced intermediate and would be amenable to the construction of close analogues. We wish to report here the successful outcome of this effort as exemplified by the total synthesis of himbacine (**1**) and himbeline (**2**) in about 10% overall yield and isohimbacine (**1a**), an unnatural isomer of himbacine, in 18% overall yield.[5]



1 R = Me Himbacine **1a** Isohimbacine

2 R = H Himbeline

Retrosynthetic Analysis

Our initial approach to himbacine envisioned a diastereoselective intramolecular Diels−Alder reaction to

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(1) (a) Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem*. **1961**, *14*, 106. (b) Brown, R. F. C.; Drummond, R.; Fogerty, A. C.; Hughes, G. K.; Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem*. **1956**, *9*, 283. (c) Ritchie, E.; Taylor, W. C. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, p 529. For X-ray crystallographic studies on himbacine see: Fridrichsons, J.; Mathieson, A. M. *Acta Crystallogr*. **1962**, *15*, 119. (d) Himbacine was isolated from the bark of *Galbulimima baccata* which is a member of the magnolia family, and not a pine tree as stated earlier. See ref 5b, footnote 6.

(2) (a) Darroch, S. A.; Taylor, W. C.; Choo, L. K.; Mitchelson, F. *Eur. J. Pharmacol.* **1990**, *182*, 131. (b) Malaska, M. J.; Fauq, A. H.; Kozikowski, A. P.; Aagaard, P. J.; McKinney, M. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 61 and references therein. (c) Kozikowski, A. P.; Fauq, A. H.; Miller, J. H.; McKinney, M. *Bioorg. Med. Chem. Lett*. **1992**, *2*, 797.

(3) (a) Miller, J. H.; Aagaard, P. J.; Gibson, V. A.; McKinney, M. *J. Pharmacol. Exp. Ther*. **1992**, *263*, 663. (b) Doods, H. N. *Drugs Future* **1995**, *20*, 157.

(4) Five muscarinic receptor subtypes have been reported. See: Levey, A. I. *Life Sci*. **1993**, *52*, 441 and references therein. Himbacine has been reported to bind to M_2 receptor with a K_d value of 10.0 nM and with 15-fold selectivity against M_1 receptor (ref 2b). Our own studies in cloned human muscarinic receptors showed m_2 potency in close agreement with the reported value and an m_1/m_2 ratio of 10.

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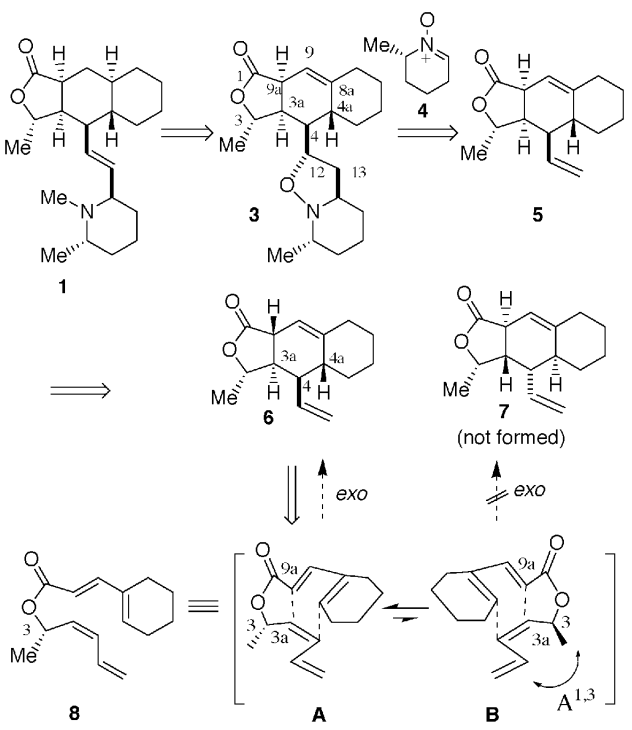
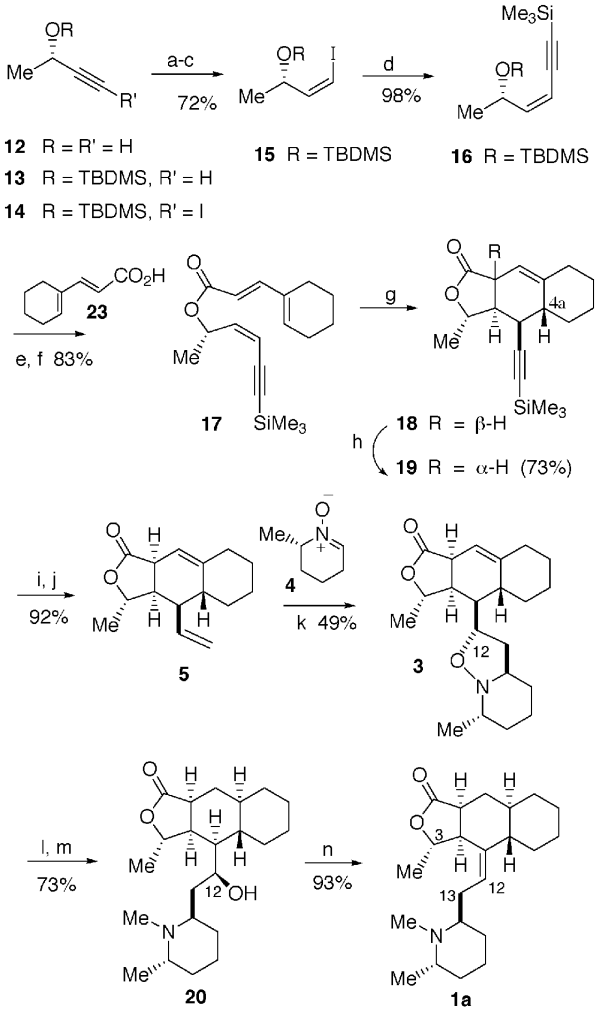
Scheme 1



generate the advanced tricyclic unit **5** in optically pure form followed by a [3 + 2] nitrone cycloaddition reaction with optically pure nitrone **4** to attach the trans-2,6-disubstituted piperidine ring system (Scheme 1). Several points are worth noting regarding this approach. First, with regard to the intramolecular Diels–Alder reaction, we expected that the vinylcyclohexenyl region of tetraene intermediate **8** would act as the diene moiety in preference to the monosubstituted diene, since it is more likely to adopt the required cisoid conformation. The methyl group at C_3 would serve to confer the s-cis orientation to the ester linkage, thereby facilitating cyclization. The face selectivity of C_{3a}–C_{9a} bond formation (Scheme 1) in the intramolecular Diels–Alder reaction[6] would be dictated by the preferred conformation **A** of the intermediate **8**, which averts $A^{1,3}$ strain.[7] During the Diels–Alder process, the absolute chirality at C_3 would be translated to the *R* configuration at C_{3a}, which, in turn, would produce the required absolute configurations at C_4 by virtue of the cis geometry of the dienophile. The exo-selective nature of the intramolecular Diels–Alder reaction, which was expected for a noncatalyzed, high-temperature cyclization of a sterically demanding precursor such as **8**, would produce the trans-fused γ-lactone **6** with the required himbacine absolute configuration at C_{4a}. Epimerization of the *trans*-lactone **6** to the thermodynamically more stable *cis*-lactone **5** was expected to proceed readily to generate the required *S* configuration at C_{9a}. The eventual reduction of the C_{8a}–C_9 double bond of the cis-fused lactone (Scheme 2) would occur stereoselectively from the α-face to produce the trans-decalin ring system with the required absolute configuration at C_{8a}. In short, this synthetic strategy allows for an expedient and highly diastereoselective construction of the tricyclic ring system exploiting the allylic ($A^{1,3}$) strain-induced conformational preference of precursor **8** and the inherent stereoselectivity of the intramolecular Diels–Alder reaction. Starting from enantiomerically pure precursor **8**, this approach

Scheme 2[a]



[a] Reagents and conditions: (a) TBDMSCl, imidazole, DMF; (b) (i) *n*-BuLi, THF, (ii) I_2; (c) (i) cyclohexene, BH_3·SMe_2, pentane, (ii) **14**, (iii) AcOH, (iv) $H_2N(CH_2)_2OH$; (d) $HCCSiMe_3$, $PdCl_2(PhCN)_2$, CuI, piperidine, THF; (e) 2% TFA–MeOH; (f) **23**, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, DMAP, CH_2Cl_2; (g) toluene, TEMPO (1 wt equiv), 185 °C, 1.75 h; (h) DBU; (i) K_2CO_3, MeOH; (j) Lindlar catalyst, H_2; (k) **4**, *o*-xylene, 150 °C, 2.5 h; (l) MeI, acetone, 50 °C; (m) RaNi–PtO_2, MeOH, H_2; (n) $SOCl_2$, PhH, 50 °C, 2 h.

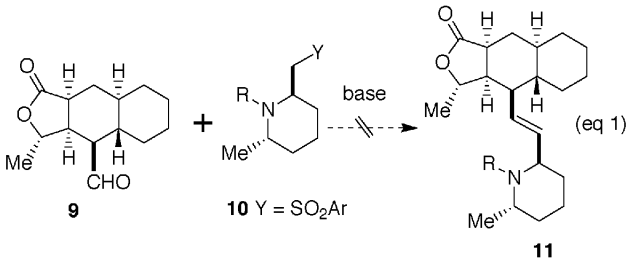
(5) (a) For a preliminary communication of the total synthesis of himbacine, see: Chackalamannil, S.; Davies, R. J.; Asberom, T.; Doller, D.; Leone, D. *J. Am. Chem. Soc.* **1996**, *118*, 9812. (b) For another total synthesis of himbacine, see: Hart, D. J.; Wu, W.-L.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1995**, *117*, 9369. Also see: Hart, D. J.; Li, J.; Wu, W.-L.; Kozikowski, A. P. *J. Org. Chem.* **1997**, *62*, 5023. For studies directed toward the total synthesis of himbacine, see: (c) Baldwin, J. E.; Chesworth, R.; Parker, J. S.; Russell, A. T. *Tetrahedron Lett.* **1995**, *36*, 9551. (d) Hofman, S.; De Baecke, G.; Kenda, B.; De Clercq, P. J. *Synthesis* **1998**, 479.

(6) For reviews on intramolecular Diels–Alder reaction, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 513. (b) Ciganek, E. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1984; Vol. 32, p 1. (c) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 87. (d) Weinreb, S. W. *Acc. Chem Res.* **1985**, *18*, 16. (e) For a discussion of the substituent effect on intramolecular Diels–Alder reactions of enoates see: Jung, M. E. *Synlett* **1990**, *4*, 186.

(7) (a) For a discussion of $A^{1,3}$ strain induced facial selectivity of intermolecular Diels–Alder reactions, see: Adam, W.; Glaser, J.; Peters, K.; Prein, M. *J. Am. Chem. Soc.* **1995**, *117*, 9190 and references therein. (b) Mulzer, J.; Bock, H.; Eck, W.; Buschman, J.; Lugar, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 414. (c) For a review on $A^{1,3}$ strain-induced stereoselectivity see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

would yield the tricyclic unit **5** in a highly enantioselective fashion.

An obvious method of choice for joining the substituted piperidine moiety to the tricyclic region of himbacine is an olefination reaction between the tricyclic aldehyde **9** and the chirally matched, activated precursor **10** (eq 1).



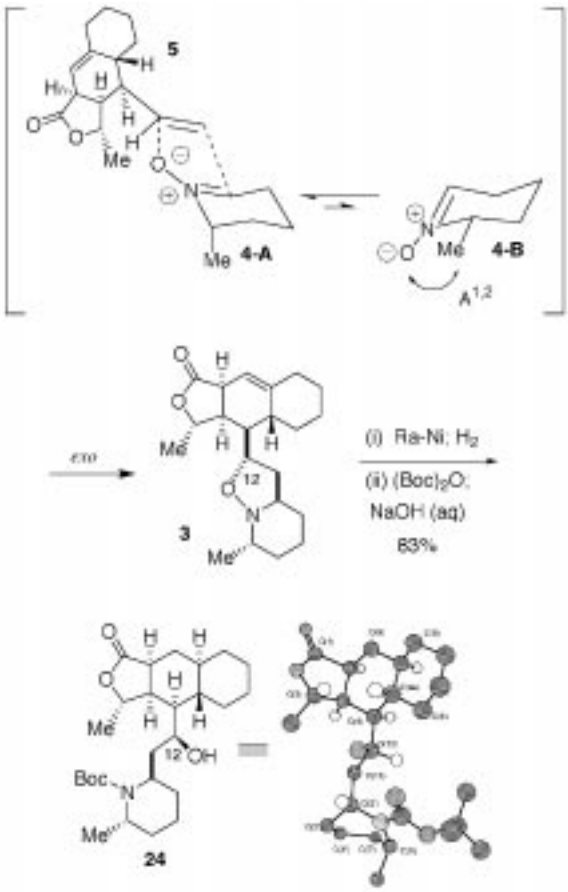
However, Hart et al. have demonstrated that such an approach is not practical, perhaps due to competing proton transfer. This fact has been vindicated by our own experience in this field. Therefore, we chose a [3 + 2] nitrone cycloaddition[8] between optically pure nitrone **4** and the tricyclic unit **5** to incorporate the trans-2,6-disubstituted piperidinyl ring system in a diastereospecific manner (Scheme 1). On the basis of the work of Carruthers and our own previous work in this area, we anticipated that nitrone **4** would undergo 1,3-dipolar cycloaddition to produce the isoxazolidine intermediate **3** in which the incoming dipolarophile would assume a trans-relationship to the preexisting methyl substituent (see Scheme 3).[9,10] This intermediate, upon reductive ring opening, would produce the trans-2,6-disubstituted piperidine ring system.

Results and Discussion

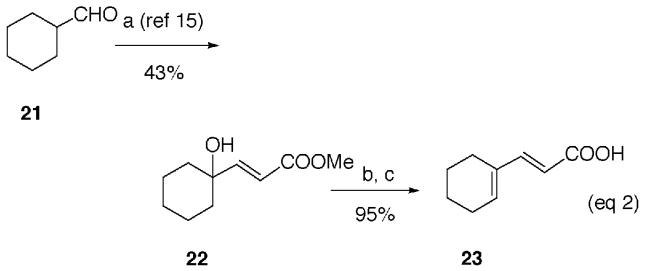
Initial Approach: Synthesis of Isohimbacine. The synthesis of tricyclic precursor **5** is outlined in Scheme 2. Commercially available (*S*)-3-butyn-2-ol (**12**)[11] was converted to the corresponding iodoacetylene **14** using the standard procedure.[12] This compound was reduced to the *cis*-vinyl iodide **15** using dicyclohexylborane.[13] Palladium-mediated coupling of vinyl iodide **15** with (trimethylsilyl)acetylene gave the enyne derivative **16** in 98% yield.[14]

The dienoic acid **23** was readily prepared on a large scale from cyclohexanecarboxaldehyde in an overall yield

Scheme 3



of 41% in three steps via intermediate **22**, which was prepared according to the literature procedure[15] (eq 2).



Reagents and conditions: (a) (4-ClC_6H_4)S(O)CH_2COOMe, CH_3-CN, piperidine, rt; (b) Ac_2O, AcCl, AcOH, heat; (c) (i) NaOH (10%), EtOH, reflux; (ii) H_3O^+.

Deprotection of the hydroxyl group of intermediate **16** followed by esterificaton of the resulting alcohol with dienoic acid **23** yielded the precursor **17** in 83% yield, which was found to undergo intramolecular Diels−Alder reaction readily. Thermal cyclization of a solution of **17** in toluene at 185 °C yielded predominantly the anticipated exo-cycloaddition product[16] **18**, which, under the reaction conditions, underwent partial isomerization to

(8) (a) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; Organic Nitro Chemistry Series; Feuer, H., Ed.; VCH Publishers: New York, 1988. (b) Padwa, A.; Schoffstall, A. M. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press Inc.: Greenwich, CT, 1990; Vol. 3, p 1. (c) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series; Baldwin, J. E., Magnus, P., Eds.; Pergamon Press: Oxford, 1990; Vol. 8, p 269.

(9) Adams, D. R.; Carruthers, W.; Williams, M. J.; Crowley, P. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1507.

(10) Chackalamannil, S.; Wang, Y. *Tetrahedron* **1997**, *53*, 11203.

(11) (*S*)-3-Butyn-2-ol was purchased from Chiroscience Ltd, Cambridge Science Park, Milton Rd, Cambridge CB4 4WE, England. It is also available from DSM Fine Chemicals, 217 Route 46 W, Saddle Brook, NJ 07663-6253.

(12) Sundberg, R. J.; Pearce, B. C. *J. Org. Chem.* **1982**, *47*, 725.

(13) Brown, H. C.; Blue, C. D.; Nelson, D. J. Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6064.

(14) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Alami, M.; Linstrumele, G. *Tetrahedron Lett.* **1991**, 6109. For reviews on the Sonogashira reaction, see: (d) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proc. Int.* **1995**, *27*(2), 127. (e) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 521.

(15) Tanikaga, R.; Nozaki, Y.; Tamura, T.; Kaji, A. *Synthesis* **1983**, 134.

(16) A tricyclic derivative isomeric to **18** was also isolated in small quantities (<5%). This compound is presumed to be the product of endo-cyclization, which should be epimeric at C_{4a} in comparison to compound **19**.

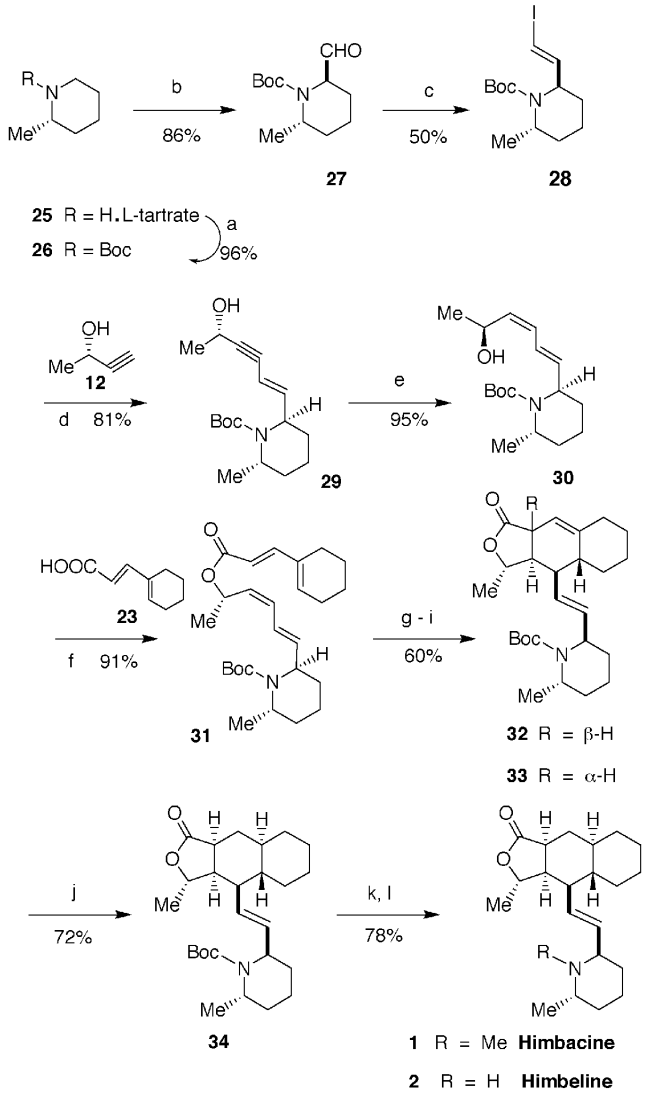
the *cis*-lactone **19**. A brief treatment of the reaction mixture with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) effected complete isomerization to the *cis*-lactone **19** in a combined 73% yield. Desilylation of compound **19** followed by selective reduction of the triple bond gave the tricyclic intermediate **5** in 92% yield.

Optically pure nitrone **4** was readily prepared from *N*-Cbz-L-alanine methyl ester as reported before.[10] Reaction of alkene **5** with nitrone **4** in *o*-xylene (Scheme 2) at 150 °C for 2.5 h gave the isoxazolidine derivative **3** as the sole product in 49% yield (69% based on recovered alkene). The structure of isoxazolidine **3** was initially derived through spectroscopic means and was later corroborated by X-ray crystallographic studies of derivative **24** (Scheme 3). The C_{12} relative stereochemistry of isoxazolidine **3**, irrelevant from the standpoint of the himbacine structure, suggests an exo mode of dipolar cycloaddition,[8] which is not surprising considering the steric bulk of the dipolarophile **5** and the nitrone **4** (Scheme 3). Isoxazolidine **3** is formed with the required trans-2,6-disubstitution pattern on the piperidine ring system. The high level of facial selectivity of the nitrone cycloaddition reaction can be rationalized on the basis of the conformational preference of nitrone **4**. To minimize allylic ($A^{1,2}$) strain, nitrone **4** adopts the favored conformation **4-A** in which the α-methyl group occupies the axial position (Scheme 3). The approach of the dipolarophile **5** occurs from the face opposite to the methyl group, producing a trans-2,6-disubstituted piperidine ring system.

The isoxazolidine intermediate **3** was elaborated to isohimbacine (**1a**) in an initial attempt to synthesize himbacine (Scheme 2). N-Methylation of **3** followed by catalytic hydrogenation over a mixture of Raney nickel and platinum oxide yielded 12(*R*)-hydroxyhimbacine (**20**).[17] Dehydration of the alcohol **20** under a variety of conditions yielded isohimbacine (**1a**) as the only product in excellent yields.[18,19] The geometry of the trisubstituted double bond was deduced from NOE data. The C_{13} methylene protons of isohimbacine (**1a**) showed strong NOE to the C_3 methyl group, whereas the C_{12} vinyl proton displayed no NOE to the C_3 methyl group.

Total Synthesis of Himbacine: An All-Encompassing Intramolecular Diels−Alder Reaction. We next turned our attention to an all-encompassing intramolecular Diels−Alder reaction of an appropriately functionalized tetraene derivative **31**, which bears the entire latent carbon framework including the trans-2,6-disubstituted piperidine ring system of himbacine (Scheme 4). This approach would require, at the penultimate step, a regioselective reduction of the internal double bond of tricyclic intermediate **33** in the presence of the pendent trans-double bond. This feat seemed practical due to the highly hindered nature of the disubstituted double bond, which is flanked by the tricyclic ring system and the *N*-Boc-substituted piperidine. This reduction would occur stereoselectively from the α-face to produce the required *R* configuration at C_{8a} as demonstrated above.

Scheme 4[a]



[a] Reagents and conditions: (a) (i) $(Boc)_2O$ (5 equiv), 10% NaOH, (ii) NH_4OH; (b) (i) *sec*-BuLi, Et_2O, TMEDA, −78 °C, (ii) Me_2NCHO; (c) $CrCl_2$, CHI_3, THF; (d) $PdCl_2(PhCN)_2$, CuI, piperidine, THF, **12**, RT; (e) Lindlar, H_2, quinoline, $MeOH/CH_2Cl_2$ (1:2, v/v); (f) **23**, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, DMAP, TEMPO (1 wt equiv), CH_2Cl_2; (g) toluene, TEMPO (1 wt equiv), 185 °C, 8 h; (h) DBU; (i) $(Boc)_2O$, NaOH (20%); (j) RaNi, H_2, MeOH; (k) TFA/CH_2Cl_2 (1:10, v/v); (l) HCHO (37%), $NaBH_3CN$, CH_3CN.

Scheme 4 outlines the successful total synthesis of (+)-himbacine. Commercially available 2-methylpiperidine was resolved using L-tartaric acid as reported before.[20] The tartrate salt **25** was directly converted to *N*-Boc-protected (*S*)-2-methylpiperidine (**26**) by treatment with excess of Boc anhydride in 96% yield.[21] Treatment of piperidine derivative **26** with *sec*-butyllithium followed by quenching with dimethylformamide according to Beak's procedure[22] yielded the trans-substituted piperidinyl aldehyde **27** in 86% yield. Homologative iodovinylation of aldehyde **27** according to Takai's protocol[23] using

(17) Commercially available (Aldrich) Raney nickel was washed three times with water and three times with methanol prior to use. Reduction using an excess of Raney Nickel in the absence of PtO_2 effected reductive opening of the isoxazolidine ring with sluggish reduction of the $C_{8a}-C_9$ double bond.

(18) Isohimbacine (**1a**) did not undergo isomerization to himbacine (**1**) under several attempted conditions.

(19) The dehydration of 12(*R*)-hydroxyhimbacine (**19**) to isohimbacine (**1a**) might be facilitated by the intramolecular abstraction of the C_4 proton by the piperidine nitrogen.

(20) Doller, D.; Davies, R.; Chackalamannil, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1275.

(21) The workup procedure involved addition of excess of ammonium hydroxide. This step converted the unreacted reagent, which coeluted with the product, to more polar *tert*-butyl urethane.

(22) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.

(23) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

chromous chloride[24] and iodoform yielded the vinyl iodide **28** in 50% yield. Palladium-mediated coupling[14] of vinyl iodide **28** with (*S*)-3-butyn-2-ol (**12**) gave the enyne derivative **29** in 81% yield. Selective reduction of the triple bond of **29** was achieved using catalytic hydrogenation over Lindlar catalyst in the presence of quinoline.

Esterification of alcohol **30** with the acid **23** yielded the Diels−Alder precursor **31** in 91% yield. Intramolecular Diels−Alder reaction was carried out by heating a solution of compound **31** in toluene at 185 °C for 8 h to generate exclusively the exo adduct **32**, which, under reaction conditions, underwent partial isomerization to the *cis*-lactone **33**.[25]

Subsequent treatment of the reaction mixture with excess of DBU effected complete isomerization of **32** to the *cis*-lactone **33** in a 60% combined yield. Regioselective reduction of the internal double bond of **33** occurred stereoselectively from the less hindered α-face under catalytic hydrogenation over Raney nickel[26] to yield the previously reported *N*-Boc-himbeline **34**.[5b,27] N-Deprotection of compound **34** yielded (+)-himbeline (**2**). Direct conversion of *N*-Boc-himbeline (**34**) to (+)-himbacine (**1**) was achieved in a one-pot procedure by deprotection with trifluoroacetic acid followed by reductive methylation[5b] using aqueous formaldehyde and sodium cyanoborohydride. Both synthetic himbeline and himbacine showed spectroscopic properties identical to those reported for the natural products as well as comparable optical rotations.[28,29] An equimolar mixture of synthetic himbacine and natural himbacine showed ^{1}H and ^{13}C NMR spectra that were indistinguishable from those of either individual component.

Conclusion

In conclusion, we have achieved a highly convergent and efficient synthesis of himbacine (**1**) in about 10% overall yield and established a practical route to himbacine analogues as exemplified by the synthesis of (+)-isohimbacine (**1a**) 18% overall yield. We hope that the practical and convergent nature of this synthesis will stimulate further interest in the exploration of the promising biological properties of this important class of compounds. It should be mentioned in this context that the methodology outlined in this synthesis, such as the intramolecular Diels−Alder reaction for the efficient construction of the tricyclic ring system and the [3 + 2] nitrone cycloaddition reaction for the incorporation of the heterocyclic unit, has been further applied in our laboratories in the exploration of the structure−activity relationship of this series of compounds. The results of these studies will be published in the future.

Experimental Section

General Procedures. Flash chromatography was carried on Selecto Scientific flash grade silica gel (particle size 32−63 μm). Ether and tetrahydrofuran (THF) were distilled over sodium−benzophenone prior to use. *N*,*N*′-Diisopropylamine and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) were distilled over calcium hydride. Anhydrous benzene, toluene, *o*-xylene, and methanol were purchased from Aldrich (Sure Seal). 2,2,6,6-Tetramethyl-1-piperidinyloxy free radical (TEMPO) was purchased from Aldrich. (*S*)-3-Butyn-2-ol was purchased from Chiroscience Ltd.[11] Halogenated solvents were used as purchased. Anionic reactions were conducted under a static argon atmosphere. Atmospheric pressure hydrogenation reactions were conducted under a balloon filled with hydrogen attached directly to the flask via a three-way stopcock. All reactions were conducted at room temperature unless otherwise mentioned. All reactions, except those involving oxidation and hydrolysis, were conducted under argon. Commercial organic and inorganic reagents were used as purchased.

(1,1-Dimethylethyl)[(3-iodo-1-methyl-2-propynyl)oxy]-dimethylsilane (14). To a solution of *tert*-butyldimethylsilyl-protected alcohol[30] **13** (4.532 g, 24.6 mmol) in tetrahydrofuran (15 mL), cooled to 0 °C under argon, was added a solution of *n*-BuLi (1.6 M in cyclohexane, 17 mL, 27 mmol). After the mixture was stirred at 0 °C for 40 min, a solution of iodine (6.24 g, 24.6 mmol) in tetrahydrofuran (10 mL) was added, and the reaction mixture was stirred for an additional 15 min. The reaction was quenched by addition of water and diluted with hexane. The aqueous phase was extracted with hexane. The combined organic phase was washed with 5% sodium thiosulfate solution, dried over magnesium sulfate, and evaporated in vacuo to give the acetylenic iodide **14** as an orange oil (7.281 g, 95%): $[\alpha]^{23}_D$ −48.8 (*c* 1.23, $CHCl_3$); IR (CH_2Cl_2) 2200 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 3 H), 0.12 (s, 3 H), 0.90 (s, 9 H, $C(CH_3)_3$), 1.40 (d, J = 6.5 Hz, 3 H, CH_3), 4.63 (q, J = 6.4 Hz, 1 H, CH(OTBS)); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.65, −0.31, 18.21, 25.35, 25.76 (3 carbons), 60.50, 96.98 (one acetylenic carbon not seen).

(1,1-Dimethylethyl)[(2*Z*)-[3-iodo-1-methyl-2-propenyl]-oxy]dimethylsilane (15). To a solution of cyclohexene (6.8 mL, 67 mmol) in anhydrous pentane (50 mL), stirred at 0 °C under argon, was added borane−methyl sulfide complex (2 M in tetrahydrofuran, 16.7 mL, 33.4 mmol). The solution was warmed to room temperature and stirred for 1 h to give a cloudy suspension to which was added the acetylenic iodide **14** (8.446 g, 27.2 mmol). The resulting clear solution was stirred at room temperature for 80 min, and glacial acetic acid (5 mL, 87.3 mmol) was added. After the reaction mixture was stirred for 20 min, ethanolamine (5.2 mL, 86.2 mmol) was added, and stirring was continued for an additional 15 min. The mixture was diluted with ethyl acetate and washed with water, followed by brine. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo to yield the crude product as a yellow oil. Purification by column chromatography on silica gel (hexane) gave *cis*-vinyl iodide **15** as a colorless oil (7.167 g, 84%): $[\alpha]^{23}_D$ +68.1 (*c* 0.79, $CHCl_3$); IR (KBr pellet) 1610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 3 H), 0.16 (s, 3 H), 0.95 (s, 9 H, $C(CH_3)_3$), 1.27 (d, J = 6.4 Hz, 3 H, CH_3), 4.56 (dq, J = 6.4, 6.2 Hz, 1 H, OCH), 6.18 (d, J = 7.6 Hz, 1 H, HC=C*H*I), 6.28 (dd, J = 7.6, 7.6 Hz, 1 H,

(24) The technical grade chromous chloride (95%) available from Aldrich was used. Chromous chloride of high purity (99.9%), purchased from Strem Chemicals, gave inferior yields.

(25) Prolonged reaction time resulted in the formation of substantial amounts of N-deprotected free amine corresponding to **33**, which could be readily converted to **33** by treatment of the crude reaction mixture with Boc anhydride in the presence of 20% aqueous sodium hydroxide. Thermolytic deprotection of the *tert*-butoxycarbonyl protecting group on indoles and pyrroles has been reported: Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141.

(26) A large excess (8−12 wt equiv) of Raney nickel was necessary. Commercially available (Aldrich) Raney nickel was washed as mentioned before (ref 17) prior to use.

(27) *N*-Boc-himbeline showed ^{1}H NMR and ^{13}C NMR data identical to those reported.[5b] Specific rotation: $[\alpha]^{20}_D$ +66.7 (*c* 0.19, $CHCl_3$) (lit.[5b] $[\alpha]^{20}_D$ +60.6 (*c* 0.55, $CHCl_3$)].

(28) The ^{13}C NMR and ^{1}H NMR spectra of himbeline were identical to those reported.[5b] The melting point of synthetic himbeline hydrochloride was 261−263 °C dec (lit.[1b] mp 265−266 °C) and specific rotation $[\alpha]^{20}_D$ +22.4 (*c* 0.33, $CHCl_3$) [lit.[5b] $[\alpha]^{20}_D$ +17.1 (*c* 0.56, $CHCl_3$), lit.[1b] $[\alpha]^{20}_D$ +19 (2.4% in $CHCl_3$)].

(29) Synthetic himbacine was identical to the natural product by ^{1}H NMR, ^{13}C NMR, and TLC. Synthetic himbacine melted at 129−130 °C (lit.[5b] mp 129−130 °C). A 1:1 mixture of synthetic himbacine and authentic natural himbacine melted undepressed. Specific rotation: $[\alpha]^{20}_D$ +59.4 (*c* 0.35, $CHCl_3$) [lit.[5b] $[\alpha]^{20}_D$ +51.4 (*c* 1.01, $CHCl_3$), lit.[1b] $[\alpha]^{20}_D$ +63 (1.04% in $CHCl_3$)].

(30) (a) Cotterill A. S.; Gill, M. *Tetrahedron Lett.* **1993**, *34*, 3155. (b) Ku, Y.-Y.; Patel; Elisseou, E. M.; Sawick, D. P. *Tetrahedron Lett.* **1995**, *36*, 2733.

C*H*=CHI); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.15, −4.95, 17.80, 22.37, 25.29 (three carbons), 71.63, 78.25, 145.09.

(1,1-Dimethylethyl)dimethyl[(1*S*,2*Z*)[(1-methyl-5-trimethylsilyl)-2-penten-4-ynyl]oxy]silane (16). To a solution of $PdCl_2(PhCN)_2$ (58.1 mg, 0.15 mmol) and CuI (58.8 mg, 0.31 mmol) in piperidine (3 mL) was added a solution of the *cis*-vinyl iodide **15** (303 mg, 0.97 mmol) in anhydrous tetrahydrofuran (3 mL). This was followed by addition of (trimethylsilyl)-acetylene (0.35 mL, 2.48 mmol), which was accompanied by a color change from dark green to pale green and then to black over 5 min. The solution was stirred at room temperature under argon for 18 h. The solvents were removed in vacuo, and the mixture was purified by flash chromatography on silica gel (hexane, followed by 5% ethyl acetate in hexane) to give the product as a yellow oil (267 mg, 98%): $[\alpha]^{25}_D$ +128.7 (*c* 0.745, $CHCl_3$); IR (CH_2Cl_2) 2151, 1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.15 (s, 3 H), 0.25 (s, 9 H, Si-$(CH_3)_3$), 0.95 (s, 9 H, C$(CH_3)_3$), 1.29 (d, J = 6.2 Hz, 3 H, CH_3), 4.89 (dq, J = 8.5, 6.3 Hz, 1 H, OCH), 5.46 (d, J = 11.0 Hz, 1 H, CH=C), 5.97 (dd, J = 8.5, 11.0 Hz, 1 H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.34, −5.07, −0.60 (3 carbons), 17.72, 23.13, 25.38 (3 carbons), 66.54, 99.04, 100.64, 106.91, 148.37; MS (CI/CH_4) 283 (M + H)$^+$, 267, 225.

(1*S*,2*Z*)-[(1-Methyl-5-(trimethylsilyl)-2-penten-4-ynyl]-3-[(2*E*)-1-cyclohexen-1-yl)]-2-propenoate (17). To a solution of the protected enyne **16** (2.927 g, 10.38 mmol) in methanol (30 mL) was added trifluoroacetic acid (0.6 mL). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo, and the residue was diluted with ether (40 mL) and water (40 mL). The aqueous phase was extracted with ether, and the combined organic phase was washed with brine, dried over magnesium sulfate, and concentrated. The final trace of solvent was removed under high vacuum.

To a solution of the deprotected enyne from above in anhydrous dichloromethane (30 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.412 g, 23.01 mmol), (dimethylamino)pyridine (DMAP) (2.836 g, 23.2 mmol), TEMPO (2 mg), and dienoic acid **23** (2.414 g, 15.9 mmol). The reaction mixture was stirred at room temperature under argon for 18 h. The solvents were removed, and the mixture was diluted with ethyl acetate. The organic phase was washed with water, 0.5 N HCl solution, and brine and dried over anhydrous magnesium sulfate. Evaporation under reduced pressure yielded the ester **17** as a brown oil (2.601 g, 83%) that was sufficiently pure to be used in the next step directly. An analytical sample was prepared by chromatography on silica gel (5% ethyl acetate in hexane): $[\alpha]^{25}_D$ +190.7 (*c* 1.04, $CHCl_3$); IR (CH_2Cl_2) 2151, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 9 H, C$(CH_3)_3$), 1.40 (d, J = 6.4 Hz, 3 H, CH_3), 1.58−1.66 (m, 2 H), 1.66−1.73 (m, 2 H), 2.10−2.18 (m, 2 H), 2.23−2.30 (m, 2 H), 5.57 (dd, J = 11.0, 1.1 Hz, 1 H, C=CH), 5.76 (d, J = 15.6 Hz, 1 H, CH=C), 5.86 (dq, J = 6.4, 7.5 Hz, 1 H, CHOCO-), 5.97 (dd, J = 7.8, 11.0 Hz, 1 H, CH=C), 6.22 (t (broad), J = 4.0 Hz, 1 H, CH=C), 7.31 (d, J = 15.6 Hz, 1 H, CH=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.203 (3 carbons), 19.81, 21.98, 22.01, 24.07, 26.40, 69.02, 100.20, 101.51, 110.35, 114.55, 134.85, 138.77, 143.55, 148.21, 166.65; HRMS (FAB) calcd for $C_{18}H_{27}O_2Si$ (M$^+$) *m*/*e* 302.1702, found *m*/*e* 302.1695.

(3*S*,3a*R*,4*R*,4a*R*,9a*S*)-3a,4,4a,5,6,7,8,8a-Octahydro-3-methyl-4-[2-(trimethylsilyl)ethynyl]naphtho[2,3-*c*]furan-1(3*H*)-one (19). To a solution of intermediate **17** (2.125 g, 7.03 mmol) in anhydrous, degassed toluene (25 mL) was added TEMPO (2 mg). The solution was heated in a sealed tube at 185 °C for 2.5 h. The reaction mixture was cooled to room temperature, DBU (1 mL) was added, and the resulting mixture was stirred for 30 min. The mixture was diluted with ethyl acetate and washed with water, 0.5 N HCl solution, and brine. The organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to give the crude product as a yellow oil (2.290 g). Purification by chromatography on silica gel (8% ethyl acetate in hexane) gave the tricyclic derivative **19** as a pale yellow oil (1.541 g, 73%): $[\alpha]^{21}_D$ +115.6 (*c* 1.01, $CHCl_3$); IR (CH_2Cl_2) 2170, 1768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21 (s, 9 H, Si$(CH_3)_3$), 0.98 (dddd, J = 12.0, 10.5, 10.5, 3.5 Hz, 1 H, C_5H_{ax}), 1.22−1.38 (m, 1 H), 1.40−1.54 (m, 1 H), 1.66 (d, J = 6.1 Hz, 3 H, CH_3), 1.78−1.94 (m, 2 H), 1.96−2.15 (m, 2 H), 2.31−2.44 (m, 2 H), 2.54−2.68 (m, 2 H), 3.23−3.29 (m, 1 H, C(O)CH), 4.52−4.62 (m, 1 H, OC*H*(CH_3), 5.35 (d, J = 2.2 Hz, 1 H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.10 (three carbons), 21.29, 25.80, 26.79, 32.94, 33.18, 34.87, 38.16, 43.49, 44.73, 77.67, 88.22, 107.05, 113.12, 142.13, 168.70, 175.75; HRMS (FAB) calcd for $C_{18}H_{27}O_2Si$ (M + H)$^+$ *m*/*e* 303.1780, found *m*/*e* 303.1775.

(*E*)-3-(1-Cyclohexenyl)acrylic Acid (23). To a solution of methyl 4-chlorophenylsulfinyl acetate[15] (316 g, 1.35 mol) in dry acetonitrile (2.4 L) was added piperidine (140 g). To this was added cyclohexanecarboxaldehyde (183 g, 1.63 mol) over 5 min. The suspension was refluxed for 2.5 h under mechanical stirring. The homogeneous solution was cooled, and solvents were removed in vacuo. The residue was dissolved in dichloromethane (3 L) and washed with water (1 L). The organic phase was washed with HCl (10%, 1 L) followed by water (1 L), dried over magnesium sulfate, and concentrated. The residue was chromatographed on silica gel (5−20% ethyl acetate in hexane) to give the hydroxy intermediate **22**[15] (107.6 g, 43%).

To a solution of the above product in glacial acetic acid (650 mL) was added acetic anhydride (215 mL) followed by acetyl chloride (215 mL). The reaction mixture was refluxed for 1.5 h and cooled to room temperature, and solvents were removed under reduced pressure. The residue was poured into ice, basified with aqueous sodium hydroxide (25%), and extracted with dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate, and filtered. The solvents were removed under reduced pressure to give the methyl ester corresponding to **23**.

To a solution of the above crude product in ethanol (250 mL) was added sodium hydroxide (1.5 L, 2.5 N), and the mixture was refluxed under nitrogen for 2.5 h. The reaction mixture was cooled and poured into ice (1 kg) and was acidified to pH 2 using concentrated HCl. The precipitate was collected by suction filtration and air-dried. The product was dried at 40 °C in a vacuum oven at 20 mm Hg. This was followed by drying over phosphorus pentoxide under high vacuum to a constant weight to give 84 g (95%) of product **23** as a white solid. An analytical sample was prepared by sublimation at 15 mm Hg at about 125 °C: mp 114−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65−1.95 (m, 4 H), 2.21 (br s, 2 H), 2.28 (br s, 2 H), 5.82 (d, J = 15.6 Hz, 1 H), 6.28 (br s, 1 H), 7.42 (d, J = 15.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (2 carbons), 23.6, 26.1, 113.2, 134.5, 139.8, 148.0, 172.7. Anal. Calcd for $C_{19}H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.01: H, 7.97.

(3*S*,3a*R*,4*R*,4a*R*,9a*S*)-4-Ethenyl-3a,4,4a,5,6,7,8,8a-octahydro-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one (5). To a solution of TMS-acetylene derivative **19** (971 mg, 3.22 mmol) in anhydrous methanol (50 mL) was added potassium carbonate (973 mg, 7.04 mmol). The reaction mixture was stirred at room temperature for 3 h, diluted with dichloromethane, and washed with water. The aqueous phase was extracted with dichloromethane, and the combined organic phase was dried over magnesium sulfate. Evaporation of the solvents gave the deprotected acetylene derivative corresponding to **19** (680 mg, 92%): $[\alpha]^{25}_D$ +135.6 (*c* 1.026, $CHCl_3$); IR (KBr pellet) 1776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (dddd, J = 12.0, 11.5, 11.5, 3.4 Hz, 1 H), 1.23−1.38 (m, 1 H), 1.39−1.54 (m, 1 H), 1.67 (d, J = 6.1 Hz, 3 H, CH_3), 1.79−1.95 (m, 2 H), 1.98−2.18 (m, 2 H), 2.26 (d, J = 2.6 Hz, 1 H), 2.32−2.47 (m, 2 H), 2.55−2.69 (m, 2 H), 3.25−3.32 (m, 1 H, C(O)CH), 4.53−4.63 (m, 1 H, C(O)OCH), 5.36 (d, J = 2.2 Hz, 1 H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.34, 25.69, 26.74, 31.77, 33.07, 34.79, 38.10, 43.39, 44.46, 71.91, 77.51, 84.55, 113.07, 142.01, 175.58; HRMS (FAB) calcd for $C_{15}H_{18}O_2Na$ (M + Na)$^+$ *m*/*e* 253.1204, found *m*/*e* 253.1207.

To a solution of the above acetylene (643 mg, 2.79 mmol) in CH_2Cl_2/MeOH (82 mL, 9:1, v/v) was added Lindlar catalyst (319 mg). The solution was hydrogenated at atmospheric pressure for 1.75 h. The suspension was filtered and the filtrate evaporated to give the tricyclic diene **5** as a yellow oil

(647 mg, 100%) that did not require further purification: $[\alpha]^{22}_D$ +130.8 (*c* 0.59, $CHCl_3$); IR (KBr pellet) 1768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (ddd, J = 3.3, 6.0, 11.8 Hz, 1 H), 1.23−1.44 (m, 2 H), 1.47 (d, J = 6.1 Hz, 3 H, CH_3), 1.78−1.89 (m, 2 H), 1.90−2.11 (m, 3 H), 2.24−2.32 (m, 1 H), 2.32−2.41 (m, 1 H), 2.41−2.49 (m, 1 H), 3.27−3.35 (m, 1 H), 4.50−4.59 (m, 1 H, −C(O)OCH), 5.18 (d, J = 5.2 Hz, 1 H, CH═C), 5.21 (pseudo singlet, 1 H, CH═C), 5.35 (d, J = 2.0 Hz, 1 H, C═CH), 5.70 (ddd, J = 17.9, 9.2, 5.2 Hz, 1 H, C═CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.82, 25.95, 27.05, 32.96, 35.12, 36.88, 44.15, 44.39, 47.13, 77.09, 112.98, 117.10, 139.53, 142.77, 176.51; HRMS (FAB) calcd for $C_{15}H_{21}O_2$ (M + H)$^+$ *m/e* 233.1542, found *m/e* 233.1545.

4-[(2*S*,3a*R*,7*S*)-Hexahydro-7-methyl-2*H*-isoxazolo[2,3-a]pyridin-2-yl]-[(3*S*,3a*R*,4*R*,4a*S*,9a*S*)-3a,4,4a,5,6,7,8,8a-octahydro-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one (3). Nitrone **4** was prepared as reported before.[10] A solution of nitrone **4** (189 mg, 1.67 mmol) in *o*-xylene (3 mL) was added to a solution of tricyclic alkene **5** (315 mg, 1.36 mmol) in *o*-xylene (3 mL), under argon, in three equal portions at approximately 50 min intervals. Between the additions, the reaction mixture was heated under argon at 158 °C in a Diels−Alder reaction vessel with threaded Teflon stopper. After completion of addition, the reaction mixture was heated for an additional 1 h (total reaction time = 2.5 h). The solvents were removed, and the residue was purified by column chromatography (dichloromethane, followed by 5% methanol in dichloromethane) to give the isoxazolidine **3** as a yellow oil (230 mg, 49% or 69% based on recovered alkene) and 91 mg of recovered alkene **5**: $[\alpha]^{20}_D$ +129.6 (*c* 1.75, $CHCl_3$); IR (CH_2Cl_2) 1769, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96−1.12 (m, 1 H), 1.18 (d, J = 6.0 Hz, 3 H, CH_3), 1.20−1.50 (m, 4 H), 1.55 (d, J = 6.1 Hz, 3 H, CH_3), 1.62−1.75 (m, 1 H), 1.75−2.20 (m, 10 H), 2.30−2.47 (m, 2 H), 2.60−2.74 (m, 1 H, NCH), 2.86−2.95 (m, 1 H), 3.19−3.28 (m, 1 H), 3.53−3.62 (m, 1 H, NCH), 4.22−4.32 (m, 1 H), 4.52−4.63 (m, 1 H), 5.35 (s, 1 H, C═CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.57, 20.63, 21.18, 25.47, 26.06, 26.76, 32.48, 33.47, 35.44, 37.23, 37.34, 41.78, 44.07, 45.25, 52.99, 60.50, 76.47, 77.45, 113.87, 143.35, 176.51; HRMS (FAB) calcd for $C_{21}H_{32}NO_3$ (M + H)$^+$ *m/e* 346.2382, found *m/e* 346.2379.

4-[(1*R*)-1-Hydroxy-2-[(2*R*,6*S*)-1,6-dimethyl-2-piperidinyl)ethyl][(3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-octahydro-3-methylnaphtho[2,3-*c*]furan-1(3*H*)one (20). To a solution of isoxazolidine **3** (160 mg, 0.464 mmol) in acetone (4 mL) was added excess of freshly distilled iodomethane (2 mL). The mixture was heated at 50 °C in a sealed tube for 5 h. The solvent was evaporated to give an orange solid that was recrystallized from 70% acetone in hexane to give the quaternary ammonium salt corresponding to **3** as orange crystals (210 mg, 93%): $[\alpha]^{24}_D$ +66.1 (*c* 1.00, $CHCl_3$); IR (KBr pellet) 3425, 1743, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10−1.23 (m, 1 H), 1.23−1.37 (m, 1 H), 1.42−1.52 (m, 1 H), 1.50 (d, J = 4.4 Hz, 3 H, CH_3), 1.52 (d, J = 4.3 Hz, 3 H, CH_3), 1.72−2.21 (m, 2 H), 2.23−2.45 (m, 4 H), 2.52−2.61 (m, 3 H), 2.72−2.82 (m, 3 H), 2.94−3.20 (m, 3 H), 3.36−3.80 (m, 2 H), 3.78 (s, 3 H, NCH_3), 4.50−4.69 (m, 2 H), 4.84−4.94 (m, 1 H), 5.07−5.16 (m, 1 H, COOCH), 5.29 (s, 1 H, C═CH); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 14.08, 16.48, 20.36, 22.79, 25.49, 26.32, 32.89, 34.81, 36.13, 36.86, 41.61, 43.22, 44.29, 44.57, 65.15, 74.34, 75.83, 82.14, 113.71, 142.45, 205.09 (one carbon not observed); HRMS (FAB) calcd for $C_{22}H_{35}NO_3$ (M + H)$^+$ *m/e* 360.2539, found *m/e* 360.2544.

To a solution of the above quaternary ammonium salt (39 mg, 0.081 mmol) in methanol (2.5 mL) was added Raney nickel (450 mg, wet weight; washed three times with water followed by three times with methanol) and platinum oxide (PtO_2) (90 mg). The reaction mixture was subjected to hydrogenation at atmospheric pressure for 2.5 h. The mixture was diluted with methanol (15 mL) and filtered through a 0.45 μm PTFE filter and the filtrate evaporated. The residue was redissolved in chloroform and filtered. Evaporation of the filtrate gave the alcohol **20** as a colorless oil (23 mg, 78%): $[\alpha]^{20}_D$ = +30.46 (*c* 0.765, $CHCl_3$); IR (CH_2Cl_2) 3053, 1765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83−0.97 (m, 1 H), 1.02−1.20 (m, 1 H), 1.10 (d, J = 6.6 Hz, 3 H, CH_3), 1.22−1.82 (m, 15 H), 1.71 (d, J = 5.9 Hz, 3 H, CH_3), 1.83−1.97 (m, 3 H), 2.04−2.13 (m, 1 H), 2.39 (s, 3 H, NCH_3), 2.51−2.66 (m, 2 H), 2.86−2.98 (m, 2 H), 3.15−3.50 (broad s, 1 H, OH), 4.28−4.36 (m, 1 H), 4.79−4.89 (m, 1 H, OCH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.38, 19.39, 21.52, 25.78, 26.43, 26.73, 29.13, 29.52, 32.32, 32.72, 33.96, 38.05, 38.42, 41.36, 43.54, 43.77, 46.39, 52.75, 55.71, 66.23, 78.73, 178.47; HRMS (FAB) calcd for $C_{22}H_{38}NO_3$ (M + H)$^+$ *m/e* 364.2852, found *m/e* 364.2845.

(4*E*)-4-[(2*R*,6*S*)-2-[(1,6-Dimethyl-2-piperidinyl)ethylidine]][(3*S*,3a*S*,4a*S*,8a*R*,9a*S*)-octahydro-3-methylnaphtho[2,3-*c*]furan-(3*H*)-one (Isohimbacine) (1a). To a solution of 12′-hydroxyhimbacine (**20**) (60 mg, 0.165 mmol) in benzene (5 mL) was added thionyl chloride (500 μL, 6.85 mmol). The reaction mixture was heated in a sealed tube at 50 °C for 2 h, cooled to room temperature, diluted with ethyl acetate (15 mL), and quenched with water (5 mL). The reaction mixture was basified to pH 12 using 20% aqueous sodium hydroxide. Layers were separated, and the aqueous phase was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by chromatography on silica gel (10% methanol in dichloromethane) to give isohimbacine **1a** as an oil (53 mg, 93%): $[\alpha]^{20}_D$ + 27.0 (*c* 0.625, $CHCl_3$); IR (CH_2Cl_2) 1762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 6.5 Hz, 3 H, CH_3), 1.44 (d, J = 6.1 Hz, 3 H, CH_3), 1.04−1.53 (m, 8 H), 1.53−1.64 (m, 2 H), 1.65−1.83 (m, 5 H), 1.87−1.95 (m, 2 H), 1.95−2.03 (m, 1 H), 2.08−2.19 (m, 1 H), 2.40 (s, 3 H, NCH_3), 2.44−2.56 (m, 1 H), 2.63−2.75 (m, 2 H), 2.76−2.86 (m, 1 H), 3.26 (dd, J = 7.3, 10.4 Hz, 1 H), 4.62 (m, 1 H, COOCH), 5.36 (dt, J = 7.0, 1.8 Hz, 1 H, C═CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.13, 19.19, 19.26, 25.88, 26.26, 29.06, 29.42, 32.14, 33.03, 34.38, 40.08, 41.33, 43.01, 43.10, 45.67, 53.30, 59.29, 78.08, 123.98, 135.91, 178.53 (one carbon not observed); HRMS (FAB) calcd for $C_{22}H_{36}NO_2$ (M + H)$^+$ *m/e* 346.2746, found *m/e* 346.2745.

1,1-Dimethylethyl[(2*R*,6*S*)-2-formyl-6-methyl-1-piperidine]carboxylate (27). To a solution of (*S*)-*N*-(*tert*-butoxycarbonyl)-2-methylpiperidine[20] (**26**) (4.438 g, 22.3 mmol) and TMEDA (3.4 mL, 22.5 mmol) in anhydrous ether (40 mL), cooled to −72 °C (internal temperature), was added, dropwise, *s*-BuLi (1.3 M in cyclohexane, 20.6 mL, 26.8 mmol). The reaction mixture was stirred for 15 min, gradually warmed to −20 °C, stirred at this temperature for 30 min, and then cooled to −72 °C. Anhydrous dimethylformamide (DMF) (2.45 mL, 31.6 mmol) was added to the reaction mixture, which was subsequently stirred for 20 min and then quenched by addition of saturated aqueous ammonium chloride. The mixture was allowed to warm to room temperature and diluted with ether and water. The aqueous phase was extracted with ether. The combined organic phase was dried over magnesium sulfate and concentrated in vacuo to yield the crude product as a pale yellow oil (5.01 g, trans/cis ratio 22:1 by ^1H NMR). Purification by silica gel chromatography (10% ethyl acetate in hexane) yielded the *trans*-aldehyde **27** as a colorless oil (4.35 g, 86%): $[\alpha]^{20}_D$ +139.9 (*c* 0.96, $CHCl_3$) [lit.[5b] $[\alpha]^{20}_D$ +121.7 (*c* 0.96, $CHCl_3$)]; IR (neat) 1733, 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, J = 6.8 Hz, 3 H, CH_3), 1.29−1.48 (m, 1 H), 1.45 (s, 9 H, $C(CH_3)_3$), 1.52−1.76 (m, 5 H), 3.61 (dt, J = 3.8, 11.5 Hz, 1 H, NCH), 4.25 (br s, 1 H, NCH), 9.27 (d, J = 3.8 Hz, 1 H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.96, 16.11, 25.17, 27.86, 28.98, 47.02, 58.84, 80.83, 195.90; HRMS (FAB) calcd for $C_{12}H_{22}NO_3$ (M + H)$^+$ *m/e* 228.1598, found *m/e* 228.1600.

1,1-Dimethylethyl[(2*R*,6*S*)-2-[(1*E*)-2-iodoethenyl]-6-methyl-1-piperidine]carboxylate (28). To a stirring suspension of chromous chloride ($CrCl_2$) (Aldrich, 95%) (14.77 g, 120 mmol) in tetrahydrofuran (300 mL) at 0 °C, under argon, was added a solution of iodoform (15.91 g, 40 mmol) and aldehyde **27** (4.80 g, 21 mmol) in tetrahydrofuran (100 mL). The suspension, which changed from dark green to red over 5 min, was stirred at room temperature for 16 h. The mixture was filtered through a bed of Florisil (100−200 mesh), which was rinsed with ether four times. Evaporation of the solvent yielded a dark green oil which was purified by flash chromatography on silica gel, eluting initially with hexane followed by 5% and 10% ethyl acetate in hexane to give the *trans*-vinyl iodide **28** as a colorless oil (3.74 g, 50%): $[\alpha]^{20}_D$ +110.7 (*c* 0.40,

$CHCl_3$); IR (neat) 2971, 1688, 1388, 1364 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.6 Hz, 3 H, CH_3), 1.43 (s, 9 H, $C(CH_3)_3$), 1.46−1.95 (m, 6 H), 4.02 (br s, 1 H, NCH), 4.33 (m, 1 H, NCH), 6.11 (dd, J = 1.4, 14.4 Hz, 1 H, CH=C), 6.56 (dd, J = 5.76, 14.4 Hz, 1 H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.41, 20.16, 25.11, 26.21, 28.23 (three carbons), 46.90, 54.83, 75.21, 79.27, 147.47, 154.45; HRMS (FAB) calcd for $C_{13}H_{23}INO_2$ $(M + H)^+$ *m/e* 352.0774, found *m/e* 352.0775.

1,1-Dimethylethyl-[(2*R*,6*S*)-2-[(1*E*,5*S*)-5-hydroxy-1-hexen-3-ynyl]-6-methyl-1-piperidine]-carboxylate (29). To a solution of $PdCl_2(PhCN)_2$ (190 mg, 0.50 mmol) and copper iodide (CuI) (190 mg, 1.00 mmol) in piperidine (9 mL) was added a solution of vinyl iodide **28** (1.12 g, 3.19 mmol) in tetrahydrofuran (18 mL). (*S*)-(−)-3-Butyn-2-ol (**12**)[11] (0.7 mL, 8.93 mmol) was added, and a color change from dark green to pale green and then to black was observed over 3−4 min. The reaction mixture was stirred at room temperature under argon for 18 h. The solvents were removed in vacuo, and the mixture was purified by flash chromatography on silica gel (20% ethyl acetate in hexane) to give the product as a brown oil (0.758 g, 81%). An analytical sample was prepared by further chromatography on silica gel (20% ethyl acetate in hexane): $[\alpha]^{20}_D$ +80.3 (*c* 0.61, $CHCl_3$); IR (neat) 3435 (broad), 2975, 1688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.6 Hz, 3 H, CH_3), 1.42 (s, 9 H, $C(CH_3)_3$), 1.44 (d, J = 6.6 Hz, 3 H, CH_3), 1.45−1.98 (m, 6 H), 2.34 (br s, 1 H, OH), 4.01 (m, 1 H, NCH), 4.38 (m, 1 H, NCH), 4.61 (m, 1 H, C*H*OH), 5.49 (d, J = 16.0 Hz, 1 H, CH=C), 6.14 (dd, J = 5.4, 16.0 Hz, 1 H, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.50, 20.04, 24.08, 25.59, 26.21, 28.20 (three carbons), 46.92, 52.23, 58.42, 79.22, 81.91, 90.98, 107.86, 145.83, 154.91; HRMS (FAB) calcd for $C_{17}H_{27}NO_3$ $(M + H)^+$ *m/e* 294.2069, found *m/e* 294.2069.

1,1-Dimethylethyl[(2*R*,6*S*)-2-[(1*E*,3*Z*,5*S*)-5-hydroxy-1,3-hexadienyl]-6-methyl-1-piperidine]carboxylate (30). To a solution of enyne **29** (236 mg, 0.8 mmol) in 20 mL of MeOH/CH_2Cl_2 (1:2, v/v) was added quinoline (142 mg) followed by Lindlar catalyst (120 mg). The solution was hydrogenated at atmospheric pressure for 40 min. The suspension was filtered and the filtrate evaporated. The residue was dissolved in ethyl acetate and washed sequentially with 0.5 M HCl solution, saturated sodium bicarbonate solution, and brine. The organic phase was dried over sodium sulfate and evaporated to give the product as a yellow oil (226 mg, 95% recovery), which was used directly in the subsequent step: $[\alpha]^{20}_D$ +59.8 (*c* 0.52, $CHCl_3$); IR (neat) 3422 (broad), 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 6.6 Hz, 3 H, CH_3), 1.25 (d, J = 6.3 Hz, 3 H, CH_3), 1.43 (s, 9 H, $C(CH_3)_3$), 1.72−2.20 (m, 6 H), 4.05 (m, 1 H, NCH), 4.44 (m, 1 H, NCH), 4.76 (m, 1 H), 5.38 (t, J = 11.0 Hz, 1 H), 5.76 (dd, J = 15.2, 5.7 Hz, 1 H), 5.98 (t J = 11.2 Hz, 1 H), 6.33 (dd, J = 15.2, 11.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.66, 20.19, 23.27, 25.81, 26.27, 28.23 (three carbons), 46.98, 52.16, 63.78, 78.96, 123.31,128.54, 133.46, 137.95, 154.45; HRMS (FAB) calcd for $C_{17}H_{29}NO_3Na$ $(M + Na)^+$ *m/e* 318.2045, found *m/e* 318.2040.

1,1-Dimethylethyl[(2*R*,6*S*)-2-[(1*E*,3*Z*,5*S*)-5-[(2*E*)-[3-(1-cyclohexen-1-yl)-1-oxo-2-propenyl]oxy]-5-methyl-1,3-pentadienyl]-6-methyl-1-piperidine]carboxylate (31). To a solution of diene **30** (1.439 g, 4.87 mmol) in dichloromethane (30 mL) were added (dimethylamino)pyridine (1.310 g, 10.72 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.070 g, 10.80 mmol), dienoic acid **23** (1.160 g, 7.63 mmol), and TEMPO (15 mg). The mixture was stirred at room temperature under argon for 3.5 h. Solvents were removed in vacuo, and the residue was dissolved in ethyl acetate and washed with 0.2 M HCl solution, saturated sodium bicarbonate solution, and brine. The organic phase was dried over magnesium sulfate, filtered, and evaporated to give the crude product as a brown oil (2.35 g). Purification by flash chromatography on silica gel (25% ethyl acetate in hexane) gave the product as a colorless oil (1.902 g, 91%): $[\alpha]^{20}_D$ +151.8 (*c* 0.4, $CHCl_3$); IR (CH_2Cl_2) 1695, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 6.7 Hz, 3 H, CH_3), 1.32 (d, J = 6.4 Hz, 3 H, CH_3), 1.44 (s, 9 H, $C(CH_3)_3$), 1.55−1.72 (m, 7 H), 1.72−2.00 (m, 3 H), 2.11 (br s, 2 H), 2.18 (br s, 2 H), 4.07 (m, 1 H), 4.45 (m, 1 H), 5.35 (t, J = 11.0 Hz, 1 H), 5.70 (m, 1 H, CHO-), 5.72 (d, J = 15.7 Hz, 1 H), 5.80 (dd, J = 15.2, 5.4 Hz, 1 H), 6.04 (t, J = 11.2 Hz, 1 H), 6.14 (br s, 1 H), 6.37 (dd, J = 15.2, 11.2 Hz, 1 H), 7.25 (d, J = 15.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.82, 20.12, 20.77, 21.76, 23.82, 25.65, 26.16, 26.20, 26.36, 28.22 (3 carbons), 47.05, 52.10, 66.57, 78.99, 114.52, 123.09, 128.91, 129.92, 134.63, 138.44, 138.75, 147.80, 150.52, 160.63; HRMS (FAB) calcd for $C_{26}H_{39}NO_4Na$ ($(M + Na)^+$ *m/e* 452.2777, found *m/e* 452.2770.

1,1,-Dimethylethyl[(2*R*,6*S*)-2-[(1*E*)-[2-(3*S*,3a*R*,4*R*,4a*R*,-9a*S*)-(1,3,3a,4,4a,5,6,7,8,9a-decahydro-3-methyl-1-oxonaphtho[2,3-*c*]furan-4-yl)ethenyl]-6-methyl-1-piperidine]carboxylate (33). A solution of ester **31** (101 mg, 0.23 mmol) and TEMPO (1 mg) in toluene (3 mL) was heated in a sealed tube at 185 °C under argon for 8 h. The reaction mixture was cooled to room temperature, DBU (77 mg) was added, and the resulting mixture was stirred for 30 min. The solvents were evaporated, the residue was dissolved in tetrahydrofuran (3 mL) and cooled in an ice bath, and 20% aqueous sodium hydroxide (3 mL) and an excess of Boc anhydride (0.410 g, 1.88 mmol) were added. Cooling was discontinued after 10 min, and the reaction mixture was stirred at room temperature for 16 h. Tetrahydrofuran was removed under reduced pressure, and ethyl acetate was added. The organic phase was washed with water, 0.5 N HCl solution, and saturated aqueous sodium bicarbonate. The basic aqueous phase was extracted with ethyl acetate, the organic extracts were combined, dried over sodium sulfate, filtered, and evaporated to give a yellow oil (96 mg). Purification by chromatography on silica gel (25% methyl *tert*-butyl ether in hexane) gave the cycloadduct **33** as a white solid (60.3 mg, 60%): $[\alpha]^{20}_D$ +86.1 (*c* 0.10, $CHCl_3$); IR (KBr pellet) 2833, 1775, 1688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76−0.92 (m, 1 H), 1.23 (d, J = 6.7 Hz, 3 H, CH_3), 1.41 (d, J = 6.1 Hz, 3 H, CH_3), 1.44 (s, 9 H, $C(CH_3)_3$), 1.18−2.03 (m, 13 H), 2.17−2.43 (m, 3 H), 3.24 (m, 1 H), 4.02 (br s, 1 H), 4.41 (br s, 1 H), 4.48 (m, 1 H), 5.31 (br s, 1 H), 5.29 (dd, J = 15.2, 9.5 Hz, 1 H), 5.59 (dd, J = 15.2, 5.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.57, 20.93, 22.02, 25.66, 26.13, 26.43, 27.22, 28.61 (3 carbons), 33.22, 35.27, 37.70, 43.50, 44.31, 47.23, 47.37, 52.26, 77.23, 79.21, 113.21, 130.72, 135.06, 143.03, 155.17, 176.67; HRMS (FAB) calcd for $C_{26}H_{39}NO_4Na$ $(M + Na)^+$ *m/e* 452.2777, found *m/e* 452.2770.

1,1,-Dimethylethyl[(2*R*,6*S*)-2-[2-(1*E*)-[2-(3*S*,3a*R*,4*R*,4a*S*,-8a*R*,9a*S*)-dodecahydro-3-methyl-1-oxonaphtho[2,3-*c*]furan-4-yl]-ethenyl]-6-methyl-1-piperidine]-carboxylate (*N*-Boc-himbeline) (34). To a solution of compound **33** (81 mg, 0.19 mmol) in methanol (12 mL) was added Raney nickel (1.26 g, wet weight; washed three times with water followed by three times with methanol). The reaction mixture was subjected to hydrogenation for 2.5 h at atmospheric pressure. The solvent was decanted and the catalyst washed with ethyl acetate. The combined organic phase was concentrated to a volume of 2 mL under reduced pressure, diluted with ethyl acetate (15 mL), and filtered through a 0.45 μm PTFE filter. The solvent was evaporated to give the crude product (81 mg), which was purified by chromatography on silica gel (25% methyl *tert*-butyl ether in hexane) to give the product as a colorless oil (59 mg, 72%): $[\alpha]^{20}_D$ +66.7 (*c* 0.19, $CHCl_3$) [lit.[5b] $[\alpha]^{20}_D$ +60.6 (*c* 0.55, $CHCl_3$)]; IR (neat) 3055, 1768, 1678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.69 (m, 1 H), 0.97 (m, 3 H), 1.08−1.36 (m, 3 H), 1.22 (d, J = 8.3 Hz, 3 H, CH_3), 1.40 (d, J = 6.0 Hz, 3 H, CH_3), 1.43 (s, 9 H, $C(CH_3)_3$), 1.44−2.13 (m, 12 H), 2.23 (m, 1 H), 2.61 (dt, J = 6.7, 12.8 Hz, 1 H), 3.99 (m, 1 H, NCH), 4.41 (br s, 1 H, NCH), 4.63 (m, 1 H), 5.21 (ddd, J = 1.2, 10.0, 15.2 Hz, 1 H), 5.52 (dd, J = 6.1, 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.05, 20.66, 21.92, 25.25, 25.86, 25.95, 26.10, 28.22 (three carbons), 30.96, 31.74, 33.38, 39.75, 41.29, 42.05, 45.41, 46.75, 48.47, 51.92, 78.84, 131.05, 133.86, 154.75, 178.21 (one carbon was not observed); HRMS (FAB) calcd for $C_{26}H_{41}NO_4Na$ $(M + Na)^+$ *m/e* 454.2933, found *m/e* 454.2932.

(3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[(*E*)-2-[(2*R*,6*S*)-6-methyl-2-piperidinyl]ethenyl]-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one (Himbeline) (2). To a solution of *N*-Boc-himbeline (**34**) (28 mg, 0.06 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (0.4 mL). The reaction mixture was stirred at room temperature for 1 h. The volatiles

were removed in vacuo, and the resulting oil was redissolved in dichloromethane. The organic phase was washed with 10% sodium hydroxide solution. The aqueous phase was extracted with dichloromethane. The combined organic phase was dried over anhydrous potassium carbonate. Evaporation of the solvent gave himbeline (21.3 mg, 99%) as an oil that required no further purification: $[\alpha]^{20}_D$ +22.4 (*c* 0.33, $CHCl_3$) [lit.[5b] $[\alpha]^{20}_D$ +17.1 (*c* 0.56, $CHCl_3$), lit.[1b] $[\alpha]^{20}_D$ +19 (2.4% in $CHCl_3$)]; IR (CH_2Cl_2) 3055, 1769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.72 (m, 1 H), 1.00 (m, 3 H), 1.08 (d, J = 6.4 Hz, 3 H, CH_3), 1.10−1.29 (m, 4 H), 1.40 (d, J = 5.9 Hz, 3 H, CH_3), 1.38−1.45 (m, 1 H), 1.47−1.80 (m, 10 H), 2.09 (m, 1 H), 2.23 (dt, J = 6.4, 10.0 Hz, 1 H, −CHCOO), 2.62 (dt, J = 6.6, 13.0 Hz, 1 H), 3.09 (m, 1 H, NCH), 3.53 (q, J = 5.0 Hz, 1 H), 4.64 (m, 1 H), 5.24 (dd, J = 10.4, 15.4 Hz, 1 H), 5.70 (dd, J = 6.7, 15.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.62, 21.31, 22.22, 26.07, 26.37, 30.96, 31.27, 31.93, 32.51, 33.58, 39.88, 41.42, 42.22, 45.50, 46.28, 48.96, 53.01, 76.80, 131.46, 135.00, 178.32; HRMS (FAB) calcd for $C_{21}H_{34}NO_2$ $(M + H)^+$ *m/e* 332.2590, found *m/e* 332.2598. The hydrochloride was recrystallized from absolute ethanol as fine, white needles: mp (hydrochloride) 261−263 °C dec (lit.[1b] mp 265−266 °C).

(3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-4-[(*E*)-2-[(2*R*,6*S*)-(1,6-Dimethyl-2-piperidinyl)ethenyl]decahydro-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one, (+)-Himbacine (1). *N*-Boc-himbeline (**34**), (45.3 mg, 0.10 mmol) was dissolved in anhydrous dichloromethane (6.5 mL), and trifluoroacetic acid (0.65 mL) was added. The reaction mixture was stirred at room temperature for 1 h, and solvents were removed in vacuo. Traces of solvents that remained were removed under high vacuum. The residue was dissolved in acetonitrile, and sodium cyanoborohydride (38 mg, 0.61 mmol) and aqueous formaldehyde solution (37%, 140 mg, 0.171 mmol) were added. The reaction mixture was stirred at room temperature for 1 h, neutralized (pH 7) by dropwise addition of glacial acetic acid, and allowed to stir at room temperature for an additional 2 h. The solvents were removed under reduced pressure, the residue was dissolved in dichloromethane, and 10% aqueous sodium hydroxide (10 mL) was added. The aqueous phase was extracted with dichloromethane (4 × 5 mL). The combined organic phase was dried over anhydrous potassium carbonate, filtered, and evaporated. The crude product was purified by chromatography on activity grade II alumina eluting with 20% ethyl acetate in hexane to give himbacine (28.3 mg, 78%), which crystallized as fine needles from hexane: $[\alpha]^{20}_D$ +59.4 (*c* 0.35, $CHCl_3$) [lit.[5b] $[\alpha]^{20}_D$ +51.4 (*c* 1.01, $CHCl_3$), lit.[1b] $[\alpha]^{20}_D$ +63 (1.04% in $CHCl_3$)]; IR (CH_2Cl_2) 3055, 2931, 1770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (m, 1 H), 1.00 (d, J = 6.4 Hz, 3 H, CH_3), 0.91−1.08 (m, 3 H), 1.10−1.30 (m, 3 H), 1.40 (d, J = 5.8 Hz, 3 H, CH_3), 1.37−1.48 (m, 2 H), 1.50−1.58 (m, 2 H), 1.63−1.80 (m, 6 H), 1.87 (m, 1 H), 2.10 (m, 1 H), 2.20−2.27 (m, 1 H), 2.22 (s, 3 H, NCH_3), 2.62 (dt, J = 6.7, 12.8 Hz, 1 H, −CHCOO), 2.84 (m, 1 H), 3.02 (m, 1 H), 4.63 (m, 1H), 5.26 (dd, J = 9.8, 15.2 Hz, 1 H), 5.57 (dd, J = 9.2, 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.95, 18.91, 22.19, 26.06, 26.43, 31.41, 31.98, 32.57, 33.21, 33.54, 39.83, 41.15, 41.49, 42.18, 45.67, 49.09, 53.35, 61.29, 76.77, 133.30, 133.48, 178.32; HRMS (FAB) calcd for $C_{22}H_{36}NO_2$ $(M + H)^+$ *m/e* 346.2746, found *m/e* 346.2752; mp 129−130 °C, mixed MP (synthetic + natural himbacine; 1:1, w/w) 129−130 °C, natural himbacine 130−131 °C (lit.[5b] mp 129−130 °C, lit.[1b] mp 132 °C).

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **1**, **1a**, **2**, **3**, **5**, **14**−**17**, **19**, **28**, **29**, **33**, and **34**. Tables of crystal data, fractional coordinates and thermal parameters, and interatomic distances with standard deviations for compound **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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