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Total Synthesis of (−)-Lepenine

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Supporting Information

ABSTRACT: The first asymmetric total synthesis of lepenine has been accomplished. The synthesis features a tethered intramolecular Diels−Alder reaction, an intramolecular Mannich reaction, and a Diels−Alder reaction between an *ortho*-quinone monoketal and ethylene, resulting in stereoselective construction of the unique hexacyclic system.

Diterpenoid alkaloids feature a range of complex chemical structures that possess many functional groups on a rigid polycyclic system. These compounds have attracted the attention of organic chemists for the past several decades.[1] To date, extensive synthetic efforts have resulted in the successful total syntheses of atisine,[2,3] veatchine,[3−5] garryine,[3,5] delphinine,[6] talatisamine,[7] napelline,[8] chasmanine,[9] nominine,[10] and neofinaconitine.[11] As shown in Figure 1, the denudatine

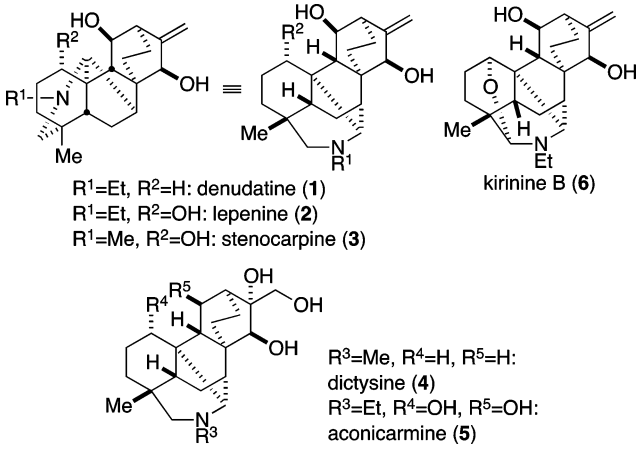
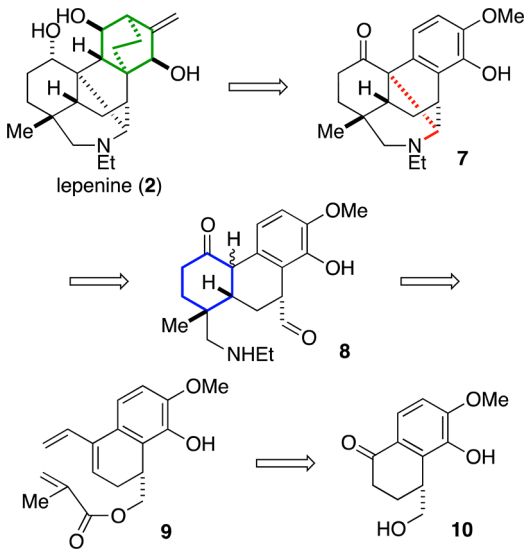


Figure 1. Denudatine-type alkaloids.

family is a group of diterpenoid alkaloids containing more than 30 compounds, such as denudatine (**1**),[12,13] lepenine (**2**),[12,14] stenocarpine (**3**),[15] dictysine (**4**),[16] aconicarmine (**5**),[17] and kirinine B (**6**).[18] These compounds are especially interesting because they are chemical[9] and biosynthetic[19] precursors of aconitine-type alkaloids, which are well-known for their potent bioactivity such as inhibition of the voltage-dependent sodium ion channel.[1a] Moreover, the denudatine framework includes an attractive and challenging hexacyclic system that comprises tetradecahydrophenanthrene, a polycyclic system containing a nitrogen atom, and a bicyclo [2.2.2] skeleton. While a synthetic study of denudatine (**1**) was reported by Wiesner and co-workers,[20] no total synthesis of denudatine-type alkaloids has been accomplished to date. Herein we wish to disclose the first total synthesis of a denudatine-type alkaloid, lepenine (**2**).

Our retrosynthetic analysis of lepenine (**2**) is shown in Scheme 1. We envisioned that construction of the bicyclo

Scheme 1. Retrosynthetic Analysis



[2.2.2] skeleton could be achieved from guaiacol **7** by means of an oxidative dearomatization followed by a Diels−Alder reaction of the corresponding *ortho*-quinone monoketal.[20,21] The polycyclic system containing a nitrogen atom in **7** could be constructed via an intramolecular Mannich reaction[22] of aminoketoaldehyde **8**. The octahydrophenanthrene core could be constructed in a stereoselective manner through a tethered intramolecular Diels−Alder reaction[23] of **9**, which could in turn be prepared from tetralone **10**.

Our synthesis commenced with preparation of tetralone **16** with careful control of the stereochemistry at the benzylic position (Scheme 2). The Mitsunobu reaction[24] between L-lactic acid methyl ester (**11**) and guaiacol afforded **12** with complete inversion of configuration. Sequential treatment of ester **12** with diisobutylaluminum hydride and then with vinylmagnesium chloride gave a 1:1.6 mixture of diastereomers of **13**.[25] By heating **13** at reflux in triethyl orthoacetate in the presence of 4-nitrophenol, a combination of the Johnson−

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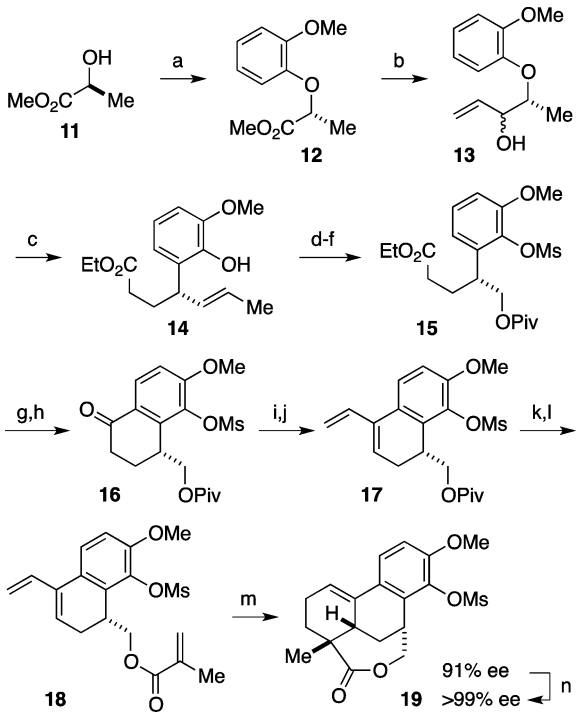
Scheme 2. Construction of the Phenanthrene Skeleton[a]



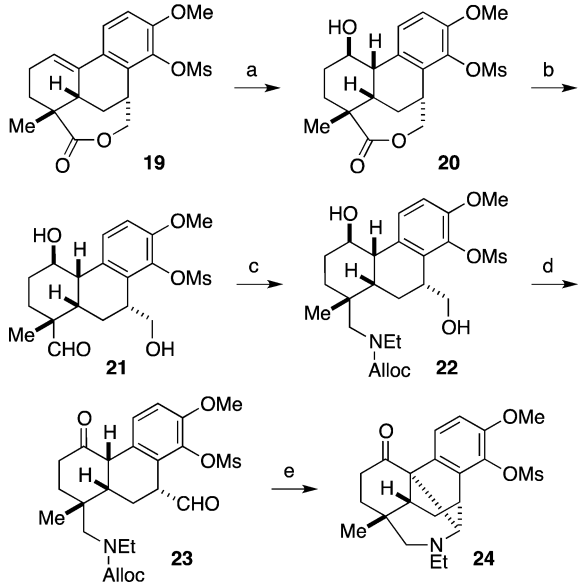
[a]Reagents and conditions: (a) guaiacol, Ph_3P, DEAD, toluene, 0 °C, 87%, >99% ee; (b) *i*-Bu_2AlH, Et_2O, hexane, −78 to −40 °C; vinylmagnesium chloride, THF, −40 to 0 °C, 94% (1:1.6 mixture); (c) 4-$O_2NC_6H_4OH$ (5 mol %), $(EtO)_3CMe$, reflux, 9 d, 85%; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 85%; (e) O_3, CH_2Cl_2, MeOH, −78 °C; $NaBH_4$, −78 to 0 °C, 86%; (f) PivCl, pyridine, DMAP, CH_2Cl_2, rt, 80%, 91% ee; (g) aq LiOH, THF, MeOH, 0 °C; (h) TFAA, TFA, CH_2Cl_2, rt, 82% (two steps); (i) vinylmagnesium chloride, THF, −40 °C, 85%; (j) AgOTf (5 mol %), toluene (20 mM), reflux, 1 h, 63%; (k) *i*-Bu_2AlH, hexane, CH_2Cl_2, 0 °C, 89%; (l) methacrylic acid, DCC, DMAP, CH_2Cl_2, rt, 85%; (m) BHT, PhCN (20 mM), 160 °C, 6 h, 90%; (n) crystallization from $CHCl_3$/hexane (1:2), 84%.

Claisen and the ensuing Claisen rearrangements proceeded smoothly to provide phenol **14**.[26] After protection of the phenol with a mesyl group, oxidative cleavage of the double bond, followed by reduction with sodium borohydride, afforded a primary alcohol that was protected as its pivalate to furnish **15**. The optical purity of **15** was determined and found to be 91% ee,[27] indicating that the chirality of L-lactic acid was effectively transferred during the course of the Claisen rearrangement. After hydrolysis of the ethyl ester moiety in **15** with lithium hydroxide, the resultant carboxylic acid was subjected to an intramolecular Friedel–Crafts reaction[28] by treatment with trifluoroacetic anhydride to afford tetralone **16**.

With the requisite tetralone in hand, we next focused on the intramolecular Diels–Alder reaction. Ketone **16** was converted into diene **17** in a two-step procedure involving addition of vinylmagnesium chloride followed by silver triflate mediated dehydration of the resulting tertiary alcohol. The pivaloyl group of **17** was then removed and replaced with a methacryloyl group to furnish triene **18**. Upon heating **18** at 160 °C in benzonitrile in the presence of a radical scavenger, the crucial intramolecular Diels–Alder reaction proceeded smoothly to give tetracyclic lactone **19** in 90% yield. At this stage, crystallization of lactone **19** from chloroform/hexane gave enantiomerically pure material in good yield.

The next challenge was to construct the polycyclic system containing a nitrogen atom (Scheme 3). Hydroboration of **19** occurred exclusively from the convex face to give secondary alcohol **20**. Subsequent reduction of the seven-membered lactone with diisobutylaluminum hydride afforded aldehyde **21**. The aldehyde was subjected to reductive amination with ethylamine to give a secondary amine, which was protected with an Alloc group. Oxidation of the resultant diol **22** with Dess–Martin periodinane[29] afforded ketoaldehyde **23**. Gratifyingly, upon treatment with a palladium catalyst and acetic acid, **23** underwent smooth deprotection of the Alloc group and the intramolecular Mannich reaction to provide **24**, a polycyclic system containing a nitrogen atom.

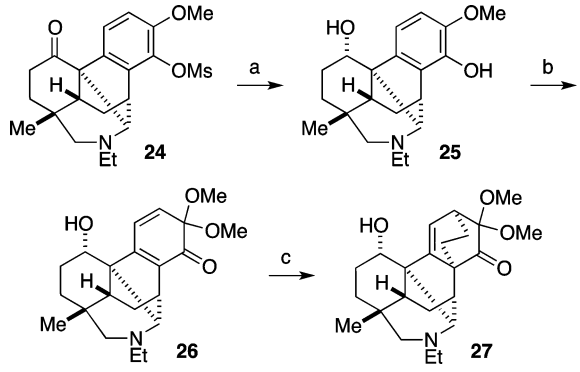
Scheme 3. Intramolecular Mannich Reaction[a]



[a]Reagents and conditions: (a) BH_3·THF, THF, rt; MeOH, 0 °C; aq NaOH, aq H_2O_2, 97%; (b) *i*-Bu_2AlH, hexane, CH_2Cl_2, −40 °C, 97%; (c) $EtNH_2$·HCl, Et_3N, AcOH, MeCN, rt; $NaBH(OAc)_3$; aq NaOH, 0 °C; AllocCl, 93%; (d) Dess–Martin periodinane, CH_2Cl_2, rt, 79%; (e) $Pd(PPh_3)_4$, AcOH, CH_2Cl_2, reflux, 75%.

As shown in Scheme 4, our next task was to establish the bicyclo [2.2.2] skeleton. Removal of the mesyl group in **24** with

Scheme 4. Construction of the Bicyclo [2.2.2] Skeleton[a]



[a]Reagents and conditions: (a) KOH, MeOH, 60 °C, 3 h; $NaBH_4$, 0 °C, 95%; (b) methyl red, AcCl, MeOH, rt; $PhI(OAc)_2$, 0 °C, 88%; (c) ethylene (70 bar), CH_2Cl_2, 70 °C, 5 d, 84%.

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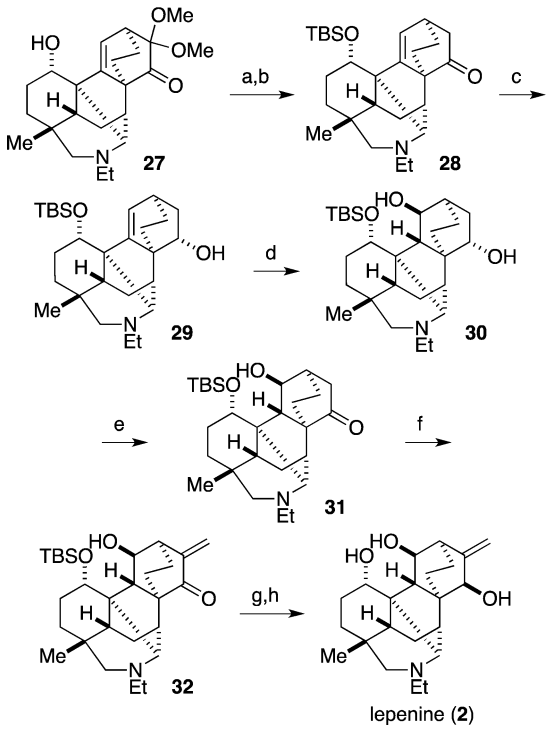
potassium hydroxide and reduction of the ketone moiety with sodium borohydride were carried out in one pot in methanol to give phenol **25**. Initial attempts at oxidative dearomatization of **25** using iodobenzene diacetate in methanol, however, resulted in decomposition of the substrate. Since the tertiary amine moiety appeared to react with the oxidant under these conditions, we decided to protect it as an ammonium salt. Treatment of **25** with methanolic hydrogen chloride followed by oxidation with iodobenzene diacetate gave the desired *ortho*-quinone monoketal **26**. Upon heating **26** under an ethylene atmosphere, the desired Diels–Alder reaction proceeded smoothly to give **27** with complete control of stereochemistry.

Finally, manipulations of the functional groups on the bicyclo [2.2.2] system were performed (Scheme 5). Protection of the hydroxy group of **27** with a TBS group, followed by reductive removal of the two methoxy groups at the α-position of the ketone using samarium(II) iodide,[30] furnished **28**. The ketone in **28** was stereoselectively reduced with Red-Al to give **29**, which was subjected to a hydroboration/oxidation sequence to afford diol **30**.[31] The two hydroxy groups in **30** were effectively differentiated through oxidation with Dess–Martin periodinane in the presence of trifluoroacetic acid to give hydroxyketone **31**. Since direct α-methylenation of the ketone met with only limited success, a formyl group was introduced at the α-position of the ketone. Thus, treatment with KHMDS and ethyl formate, and subsequent addition of formalin, gave **32** in 70% yield. Luche reduction[32] of enone **32** and removal of the TBS group gave lepenine (**2**), which was identical in all respects to natural lepenine.[12b]

Scheme 5. Total Synthesis of Lepenine[a]



[a]Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 91%; (b) SmI_2, MeOH, THF, 0 °C, 96%; (c) Red-Al, toluene, 0 °C, 88%; (d) BH_3·THF, THF, rt; H_2O, 0 °C; $NaBO_3$·H_2O, 0 °C to rt, 54%; (e) Dess–Martin periodinane, TFA, CH_2Cl_2, rt, 72%; (f) HCO_2Et, KHMDS, toluene, 70 °C; aq HCHO, THF, 50 °C, 70%; (g) $NaBH_4$, $CeCl_3$·$7H_2O$, MeOH, 0 °C, 83%; (h) TBAF, THF, 65 °C, 93%.

In summary, we have achieved the straightforward asymmetric synthesis of lepenine, the first member of the denudatine-type alkaloids that succumbed to total synthesis. Our synthesis features an effective construction of the complex hexacyclic system via a tethered intramolecular Diels–Alder reaction, an intramolecular Mannich reaction, and a Diels–Alder reaction between an *ortho*-quinone monoketal and ethylene. Another key feature of the synthesis is a chirality transfer from L-lactic acid methyl ester via a Claisen rearrangement.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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