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Total synthesis of C_{19}-diterpenoid alkaloid: construction of a functionalized ABCDE-ring system†

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A synthetic approach for the ABCDE ring system of methyllycaconitine starting from a BCD tricycle precursor **14** was described. The synthesis features a useful strategy for the full functionalization of ring B, a 1,7-enyne reductive radical cyclization for the construction of ring A, and a straightforward double condensation for installation of the piperidine ring E.

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Norditerpenoid alkaloids (including C_{18}- and C_{19}-diterpenoid alkaloids), isolated from the plants of *Aconitum* and *Delphinium* genera, comprise a large (>800 members) class of structurally complex natural products.[1] Consistent with the fact that the plant species have long been used in traditional medicine for the treatment of pain and cardiovascular diseases, these compounds exhibit a variety of biological activities including anti-inflammatory, analgesic, antiarrhythmic, antipyretic, antiepileptic, hypotensive, and bradycardic.[2] Notably, one of these alkaloids, the hydrobromide salt of lappaconitine, has been approved and commercialized as an analgesic and antiarrhythmic drug in China and Russia.[1b,3] From a chemical structure perspective, most of the norditerpenoid alkaloids share a common hexacyclic ring system, which is composed of a fused 6/7/5/6/5-membered ABCDF-carbocycle and the piperidine E-ring, and heavily substituted by multiple oxygen functional groups. The structural complexity and biological significance of this collection of molecules has attracted significant interest from the synthetic community in the past decades.[4] However, synthesis of these intricate structures is a conspicuous challenge. The groups of Wiesner,[5] Gin,[6] Sarpong[7] and Fukuyama[8] have reported the total synthesis of seven norditerpenoid alkaloids (talatisamine, chasmanine, 13-desoxydelphonine, neofinaconitine, weisaconitine D, liljestrandinine, and most recently, cardiopetaline; Fig. 1, **1**–**7**) to date, representing landmark accomplishments in the field of organic chemistry.

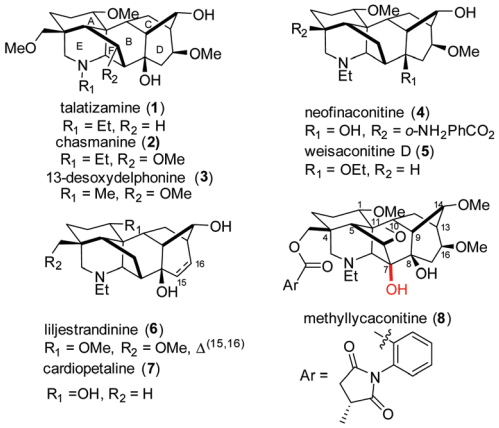

Fig. 1 Structures of selected norditerpenoid alkaloids.

Despite numerous other attempts,[9] these remain the only published total syntheses of norditerpenoid alkaloids.

Given our interest in the total synthesis of methyllycaconitine (**8**), a representative member of the lycoctonine-type C_{19}-diterpenoid alkaloid that has been shown to be a potent nicotinic acetylcholine receptor antagonist related to Alzheimer's disease,[10] we initiated our own synthetic program targeting this complex cage-like ring system. These efforts have led to the construction of some important partial ring systems such as AEF-, ABEF-, ABF- and BCD-rings.[11] Specifically, the unique BCD ring analogue **14**[11c] provides the full potential of functional groups for elaboration into A-, E- and F-rings. In this paper, we report our continuing endeavors for the further installation of ring A and the piperidine ring E resulting in the formation of the pentacyclic ABCDE-ring system **9** as a model target compound for the total synthesis of the lycoctonine-type C_{19}-diterpenoid alkaloid.

Our retrosynthetic plan is outlined in Scheme 1. The simplified methyllycaconitine **9** bearing the key C-7 oxygen func-

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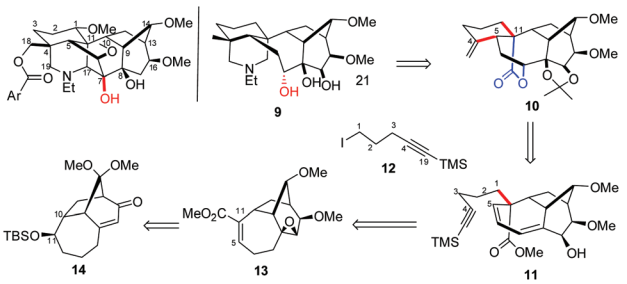
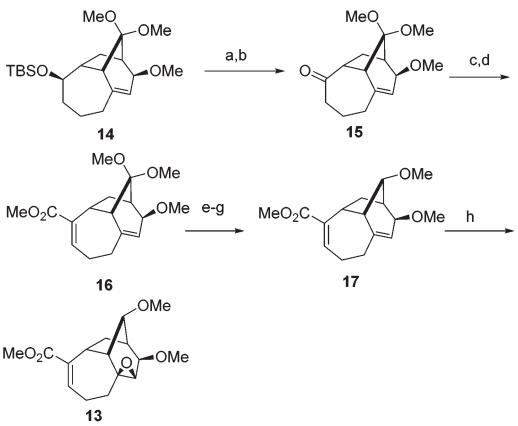


Scheme 1 Retrosynthetic analysis of the model target **9**.

tional group could be assembled by the construction of a quaternary center at C-4 followed by installing the piperidine E-ring[11b] from the tetracyclic carbocycle **10**. The six-membered ring A of **10** could be constructed through a sequence involving the formation of a bridged lactone followed by a 1,7-enyne reductive radical cyclization[12] from the tricyclic diene intermediate **11**, which could arise from the α,β-unsaturated ester **13** by a deconjugative alkylation with **12**. Finally, **13** could be generated by functional group transformation from the known tricycle **14**.

As shown in Scheme 2, we began our synthesis by sequential removal of the TBS protecting group of **14** and the Dess–Martin oxidation of resultant alcohol to provide ketone **15** in 90% yield. **15** was then converted into the α,β-unsaturated methyl ester **16** by vinyl triflate formation followed by palladium catalyzed carboxymethylation in a straightforward manner.[13] Hydrolysis of the ketal moiety of **16** followed by reduction and methylation of the resultant ketone provided the methyl ether **17** as a single diastereomer. The latter was subjected to *m*CPBA epoxidation, which occurred on the more reactive olefin to afford the epoxide **13** in an excellent yield. The stereochemistry of the reduction of the ketone group and the epoxidation of the double bond was established on the basis of the X-ray crystallography analysis of **13x** (Fig. 2),[14] which was prepared through a similar reaction sequence from **14**.[11c]



Scheme 2 Synthesis of the functionalized BCD tricyclic intermediate **13**. Reagents and conditions: (a) TBAF (1.5 equiv.), THF, 25 °C; (b) Dess–Martin periodinane (1.5 equiv.), $NaHCO_3$ (3.0 equiv.), CH_2Cl_2, 0 °C, 90% over 2 steps; (c) NaHMDS (2.0 equiv.), $PhNTf_2$ (1.5 equiv.), THF, −78 °C; (d) $Pd(Ph_3P)_4$ (5.0 mol%), Et_3N (3.0 equiv.), CO, MeOH, DMF, 70 °C, 88% over 2 steps; (e) TsOH (0.5 equiv.), 25 °C, acetone/H_2O (9 : 1); (f) $NaBH_4$ (1.5 equiv.), $CeCl_3{\cdot}7H_2O$ (1.5 equiv.), MeOH, 0 °C; (g) MeI (3.0 equiv.), NaH (2.0 equiv.), THF, 25 °C, 91% over 3 steps; and (h) *m*-CPBA (1.5 equiv.), $NaHCO_3$ (3.0 equiv.), CH_2Cl_2, 0 °C to 25 °C, 91%.

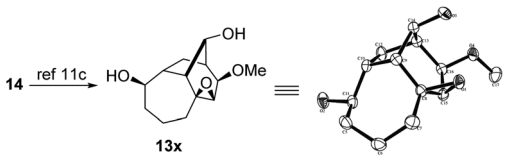


Fig. 2 ORTEP diagram from the X-ray crystal structure of **13x**.

With the enoate **13** in hand, the installation of a C-11 quaternary center by deconjugative alkylation and the construction of ring A was next addressed (Scheme 2). As anticipated, treatment of **13** with LDA/HMPA and then with iodide derivative **12** at −78 °C effected the stereospecific alkylation[15] at C-11 from the relatively less hindered *exo*-side of the molecule to give the enyne **18** in 70% yield. Further desilylation of the alkyne side chain of **18** furnished the terminal alkyne **19a**, which could be smoothly converted to the enyne ester **19b** by acylation. Interestingly, it was found that the epoxy group of **18** is fragile under acidic conditions. Subjection of **18** to Ti$(OiPr)_2Cl_2$ could afford the epoxy-opening dienyne **20** in a high yield of 90%. With these differential enyne and dienyne substrates (**18**, **19ab** and **20**) in hand, a strategy of the 1,7-enyne cycloisomerization reaction[16] to close the six-membered ring A was initially attempted. However, extensive screening of a variety of catalysts including $[CpRu(CH_3CN)_3]PF_6$,[17] Pd_2dba_3,[18] $PtCl_2$ [19] and $Hg(OTf)_2$ [20] showed that all failed to give any cyclization product. In light of our previous model study for successfully constructing the ABF ring system of franchetine-type norditerpenoid alkaloids using a radical addition as the key ring closure step for ring A,[11d] a 1,7-enyne reductive radical cyclization strategy based on the formation of a bridged lactone moiety on the seven-membered ring was further attempted. Thus, oxidation of diene **20a** with *m*CPBA gave the epoxide **21** as a single regio- and stereoisomer. Next, the Lewis acid promoted transannular lactonization of **21** was achieved in a straightforward manner by treatment with catalytic $Ti(OiPr)_2Cl_2$,[15c] exclusively affording the bridged lactone **22** in 78% yield. Protection of the vicinal diol of **22** followed by its desilyation under basic conditions gave the enyne **23**, ready for the next pivotal radical cyclization. To our delight, upon treatment of **23** with tri-*n*-butyltinhydride (4 equiv.) and AIBN (40 mol%), the desired reductive radical cyclization occurred efficiently.[12] We obtained the cyclization product **10** exclusively in 87% yield after *in situ* destannylation with silica gel. The structure assignment of **10** was unambiguously confirmed by X-ray diffraction.[14] The highly *trans* stereoselectivity of this cyclization reaction is perhaps a reflection of the fact that the upside of olefin in a seven-membered ring is more congested than the downside due to the conformation restriction caused by the bridged lactone moiety (Scheme 3).

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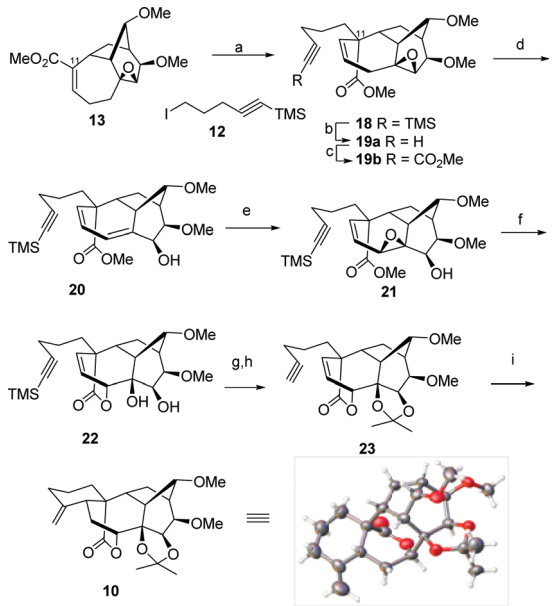
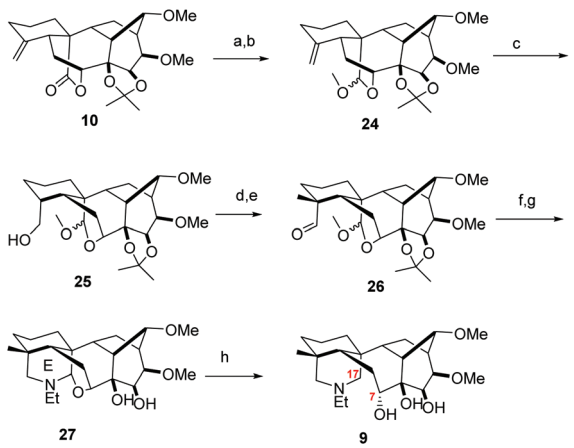


Scheme 3 Synthesis of the functionalized ABCD tetracyclic intermediate **10**. Reagents and conditions: (a) LDA (1.7 equiv.), HMPA (2.0 equiv.), **12** (1.7 equiv.), THF, –78 °C, 70%; (b) K_2CO_3 (1.2 equiv.), MeOH, rt, 95%; (c) *n*-BuLi (1.2 equiv.), $ClCO_2Me$ (1.3 equiv.), THF, 78 °C, 82%; (d) $Ti(OiPr)_2Cl_2$ (1.5 equiv.), CH_2Cl_2, 0 °C, 90%; (e) *m*-CPBA (4.0 equiv.), CH_2Cl_2, 25 °C, 85%; (f) $Ti(OiPr)_2Cl_2$ (1.5 equiv.), CH_2Cl_2, –20 °C, 78%; (g) 2,2-dimethoxy-propane (10.0 equiv.), PPTS (3.0 equiv.), acetone, 65 °C, 81%; (h) TBAF (2.0 equiv.), CH_2Cl_2, 25 °C, 95%; (i) AIBN (0.4 equiv.), *n*-Bu_3SnH (4.0 equiv.), benzene, 90 °C, then silica gel (10.0 equiv. wt), CH_2Cl_2, 25 °C, 87%.



Scheme 4 Synthesis of the ABCDE pentacyclic ring system **9**. Reagents and conditions: (a) DIBAL-H (2.0 equiv.), CH_2Cl_2, –78 °C; (b) Ag_2O (4.0 equiv.), MeI/MeCN (1 : 1, v/v), 50 °C, 85% over 2 steps; (c) BH_3·THF (4.0 equiv.), THF, 0 °C; then NaOH (10.0 equiv.), H_2O_2 (30%, 10.0 equiv.), 80%; (d) Dess–Martin periodinane (2.0 equiv.), $NaHCO_3$ (4.0 equiv.), CH_2Cl_2, 25 °C; (e) *t*-BuOK (2.0 equiv.), MeI (4.0 equiv.), THF, –25 °C; (f) $EtNH_2$ in MeOH (10%), 50 °C, then $NaBH_4$ (2.0 equiv.), MeOH, 25 °C; (g) HOAc : THF : H_2O (2 : 2 : 1), 80 °C, 39% over 4 steps; (h) $NaBH_4$, MeOH, 0 °C, 71%.

With the ABCD tetracyclic precursor **10** in hand, the installation of the piperidine ring E was next addressed by using a similar strategy,[11b] developed in our modeling construction of the ABEF ring system (Scheme 4). Thus, reduction of the lactone group with DIBAL-H and methylation of the resultant lactol with methyl iodide in the presence of Ag_2O afforded the methyl ether **24** as an inconsequential mixture of two diastereomers. After the hydroboration–oxidation of **24** to provide the primary alcohol **25** (80% yield), the following Dess–Martin oxidation and α-methylation of aldehyde proceeded efficiently to give the methylaldehyde intermediate **26** coupling with a quaternary center at C-4. Without careful purification, the mixture **26** was quickly subjected to reductive amination with ethylamine followed by a thermotical condensation in a mixed solvent (AcOH/MeOH/H_2O) to form the piperidine E, furnishing the hexacycle **27** bearing an extra *N*,*O*-acetal moiety in 39% overall yield over four steps. Further reduction of the *N*,*O*-acetal moiety with $NaBH_4$ in methanol[15c] ultimately provided the ABCDE pentacyclic analogue **9** of methyllycaconitine in 71% yield.

Conclusions

In summary, the ABCDE-ring skeletal analogue **9** of methyllycaconitine was successfully constructed from the BCD ring precursor **14**. In the course of our synthetic studies, we have disclosed an efficient deconjugative alkylation/Lewis acid promoted epoxy ring-opening and elimination strategy to realize the full functionalization of the seven-membered ring B. Moreover, an unprecedented 1,7-enyne reductive radical cyclization was applied to construct a *trans*-fused 6,7-bicyclic unit based on the formation of a bridged lactone moiety on ring B. A double condensation with ethylamine smoothly achieved the piperidine ring E. Our future efforts will be directed toward application of these effective key protocols for the total syntheses of methyllycaconitine and other diverse lycoctonine-type C_{19}-diterpenoid alkaloids.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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