Total Synthesis of the Diterpenoid Alkaloid Arcutinidine Using a Strategy Inspired by Chemical Network Analysis

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ABSTRACT: Arcutinidine and other arcutinidine-type diterpenoid alkaloids feature an intricate polycyclic, bridged framework with unusual connectivity. A chemical network analysis approach to the arcutane skeleton enabled the identification of highly simplifying retrosynthetic disconnections, which indicated that the caged structure could arise from a simpler fused ring system. On this basis, a total synthesis of arcutinidine is reported herein, featuring an unprecedented oxopyrrolium Diels–Alder cycloaddition which furnishes a key tetracyclic intermediate. In addition, the synthesis utilizes a diastereoselective oxidative dearomatization/cycloaddition sequence and a SmI_2-mediated C–C coupling to forge the bridged framework of the natural products. This synthetic plan may also enable future investigations into the biosynthetic relationships between the arcutanes, the related diterpenoid atropurpuran, and other diterpenoid alkaloids.

Natural products that possess a high degree of three-dimensional structural complexity pose significant challenges to identifying strategies for their chemical synthesis. By adopting a retrosynthetic plan that reduces the number of bridged rings in these architecturally intricate structures, the resulting fused ring systems can prompt retrons that guide subsequent disconnections. In 1975, Corey introduced a formalized 'logic' for the retrosynthesis of bridged, polycyclic frameworks that expounded the virtues of identifying a 'maximally bridged ring', which upon disconnection, provides maximal structural simplification.[1] Furthermore, by applying two-bond disconnections (i.e., 'bicyclization transforms'), a rapid decrease in target complexity in the retrosynthetic direction can be realized. In this regard, cycloaddition transforms have proven indispensable.

The diterpenoid alkaloids are a large group of secondary metabolites with highly complex, three-dimensional frameworks that possess wide-ranging activity as modulators of voltage-gated ion channels.[2-4] These structures lend themselves very well to chemical network analysis, which can provide powerfully simplifying bond disconnections as starting points. In 2015, our laboratory reported the application of Corey's chemical network analysis toward syntheses of aconitine-type diterpenoid alkaloids, including liljestrandinine (**1**, Figure 1A).[5] Similar analyses have also guided our preparation of denudatine-type alkaloids such as paniculamine (**2**), and the hetisine-type alkaloid cossonidine (**3**).[6] Building on Corey's graphical analysis, we also introduced a web-based graphing algorithm to facilitate the identification of the maximally bridged ring for any given structure.[7] In this Communication, we describe the application of chemical network analysis to identify a strategy for the synthesis of arcutinidine (**4**), an arcutane-type diterpenoid alkaloid. Natural products in this class include arcutine (**5**), arcutinine (**6**), and aconicarmicharcutinium (**7**),[8-10] the framework of which is presented from three perspectives in Figure 1B (gray box).

Perhaps even more captivating than the ornate framework of these natural products is their postulated biosynthesis.

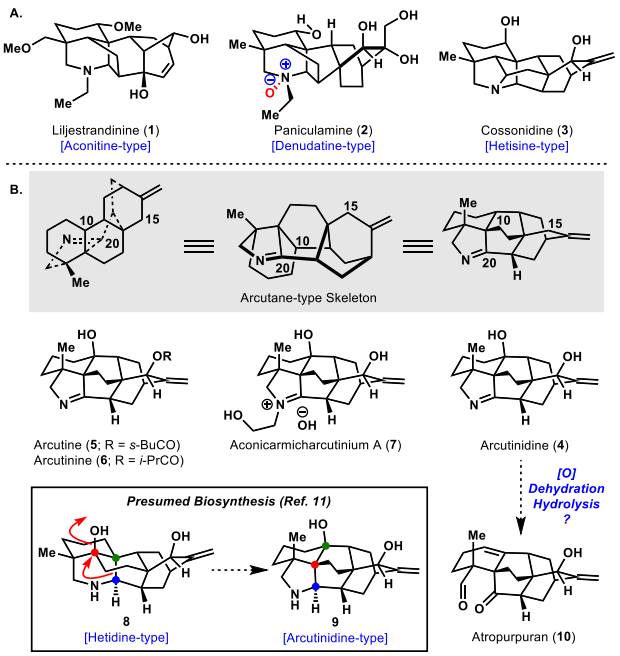
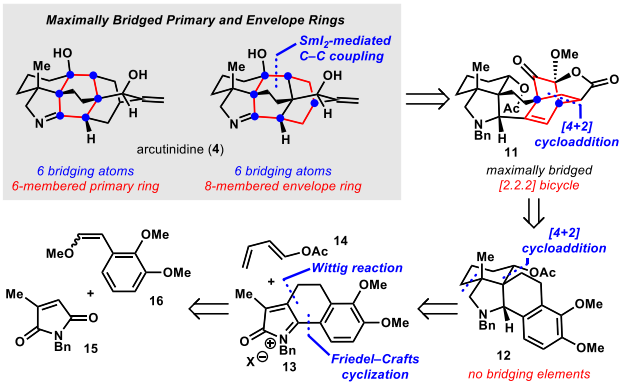


Figure 1. (A) Representative diterpenoid alkaloids. (B) The arcutane-type diterpenoid alkaloids and possible synthetic relationships to related diterpenoids.

Arcutinidine (**4**) is believed to arise from oxidation and rearrangement of the hetidine skeleton (see inset in Figure 1B). This presumed cation-initiated rearrangement is supported by computations that we reported in 2015.[11-12] These calculations also indicate that the reverse of the proposed biosynthesis (i.e., **9**→**8**) may also be possible under laboratory conditions; a transformation which could provide synthetic access to the hetidine alkaloids from the arcutinidine skeleton. Furthermore, oxidation and

Scheme 1. Network-analysis-guided retrosynthesis of arcutinidine.



hydrolysis of the arcutinidine 1-pyrroline moiety could yield the related diterpenoid atropurpuran (**10**).[13-15] Therefore, a synthesis of arcutinidine could set the stage for investigation of the possible biogenesis of atropurpuran and provide access to other diterpenoid alkaloids. During the preparation of this manuscript, Qin and coworkers published their synthesis of **4** and **6**.[16]

In contemplating a synthetic approach to **4**, we sought disconnections that would rapidly reduce structural complexity by applying multiple cycloaddition transforms. We identified two comparable maximally-bridged rings, one of which is a 'primary' ring whereas the other is an 'envelope' ring[17] (see Scheme 1, gray box). A strategic bond disconnection of a key *ex-endo* bond,[18] as shown for **4**, led back to **11** as a precursor. Application of a [4+2] bicyclization transform to **11** unveiled tetracycle **12** as a precursor. In turn, **12** could arise in the forward sense through another [4+2] cycloaddition of diene **14**[19] and oxopyrrolium dienophile **13**, a reaction that would forge two contiguous, all-carbon quaternary stereocenters. To our knowledge, no precedent exists for cycloadditions involving oxopyrrolium dienophiles, thus our work would serve to probe the unprecedented reactivity of these heterocyclic cations. In the forward sense, our desired oxopyrrolium **13** was envisioned to arise through a Wittig reaction between known citraconimide **15**[20] and methyl enol ether **16**[21] and subsequent Friedel–Crafts cyclization.

We commenced our studies by investigating a more conventional cycloaddition between diene **17** and maleimide **18** (Figure 2). On the basis of HOMO–LUMO considerations (compare HOMO of –5.6 eV for **17** versus LUMO of –2.4 eV for **18**),[22] it was anticipated that poor reactivity and selectivity would be observed due to the lack of electronic differentiation at the reacting carbon atoms. Conversely, the LUMO of oxopyrrolium **13** (–4.3 eV) is energetically matched and possesses complementary polarization relative to the HOMO of diene **14** (–6.5 eV).[23] These factors were expected to contribute to a more facile and selective cycloaddition.

Maleimide derivative **18** and the oxopyrrolium precursor **19**

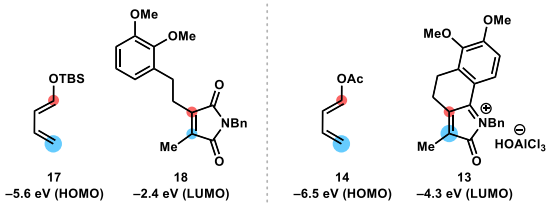
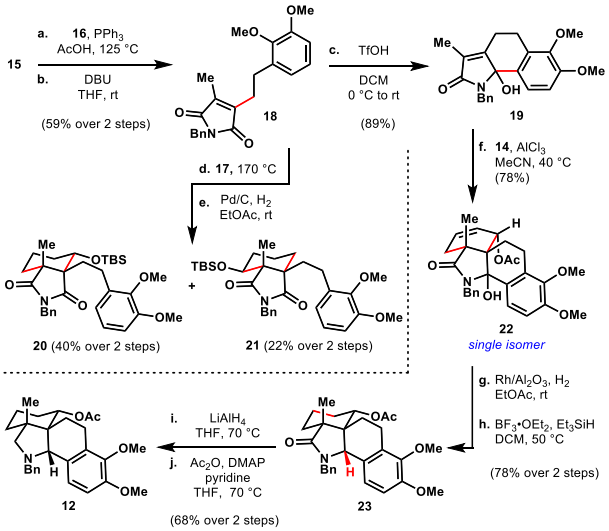


Figure 2. HOMO–LUMO considerations calculated using DFT basis set 6-31G**++ with a B3LYP functional and empirical dispersion.

were prepared as detailed in Scheme 2. The synthesis began with the treatment of citraconimide **15** with PPh_3 and methyl enol ether **16** in a modified Wittig reaction[24] to give the non-conjugated alkene adduct, which was isomerized to the desired maleimide (**18**) upon treatment with DBU. As expected, our initial attempts to employ **18** in a cycloaddition with dienes such as **17**[25] resulted in poor regioselectivity. The resulting cycloadducts were separable upon hydrogenation of the double bond and the desired constitutional isomer **20** was advanced through several steps. Ultimately, this synthetic plan proved untenable, in part, because of the inefficiency of the cycloaddition step. Our attention was therefore turned to investigating oxopyrrolium dienophile **13**. Upon exposing imide **18** to TfOH, a Friedel–Crafts cyclization ensued to afford key tricyclic intermediate **19**. This tricycle serves as a masked oxopyrrolium dienophile that can be unveiled under

Scheme 2. Synthesis of key tetracycle **12**.

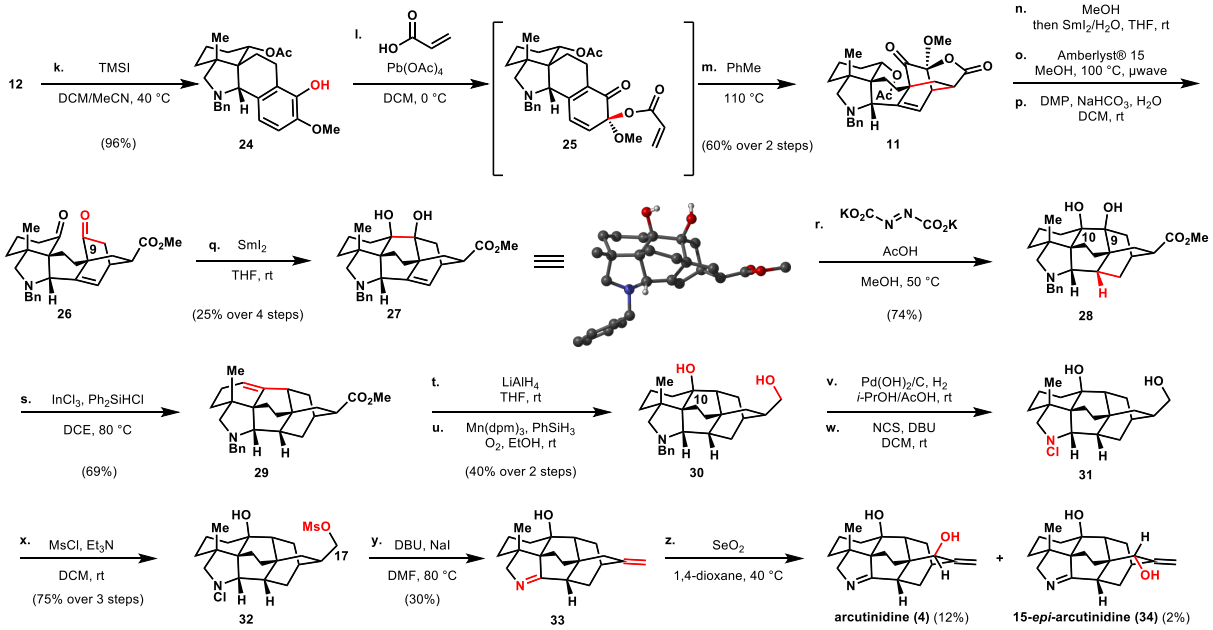


acidic conditions. When **19** was treated with $AlCl_3$ and diene **14**, a Diels–Alder cycloaddition, presumably through the intermediacy of oxopyrrolium **13**, occurred to furnish **22** bearing two new vicinal quaternary carbon centers. Tetracycle **22** possesses nearly all of the carbon atoms found in arcutinidine and can be readily synthesized on multigram scale.

Reduction of the cyclohexenyl double bond in **22**, using Rh/Al_2O_3 and hydrogen, followed by ionic reduction of the hemiaminal functional group using BF_3•OEt_2 and Et_3SiH, gave amide **23** as a single diastereomer. The amide group was then reduced to the corresponding amine using $LiAlH_4$. Concomitant reduction of the acetate unveiled a secondary hydroxy group, which was subsequently re-acetylated to give amine **12**.

A highly selective mono-demethylation of the veratrole unit using TMSI afforded guiacol **24**, which was primed to undergo oxidative dearomatization (Scheme 3). Following the addition of in situ generated lead (IV) acrylate, **24** underwent a diastereoselective Wessely-type oxidation[26] to generate a masked diketone intermediate, appended with an acrylate dienophile (**25**). Upon heating, an intramolecular [4+2] cycloaddition proceeded to afford the [2.2.2] bicycle that is present in **11** and is characteristic of the arcutanes, as well as a large subset of other diterpenoid alkaloids. With all the carbon atoms found in arcutinidine now in place, we pursued the installation of the last C–C bond to complete the arcutinidine skeleton. We sought to utilize a reductive C–C bond formation by employing a pinacol coupling inspired by the Qin synthesis of atropurpuran.[14] Upon dissolution in methanol, lactone **11** underwent solvolysis to afford the ring opened

Scheme 3. Completion of arcutinidine (**4**).



product featuring a diketone on the [2.2.2] bicycle and a methyl ester on the bridge of the bicycle. In the same pot, introduction of SmI_2 effected reductive removal of one of the carbonyl groups to give a hydroxy group at C9 as a single, inconsequential, diastereomer. At this stage, solvolysis of the acetate under microwave irradiation and subsequent global oxidation with DMP yielded diketone **26**. Pinacol coupling using SmI_2 gave the desired hexacyclic diol (**27**), which possesses the full arcutinidine skeleton. The structure of **27** was unambiguously confirmed through X-ray crystallographic analysis.

Reduction of the highly strained double bond in the [2.2.2] bicycle of **27** using diimide gave the fully saturated arcutinidine core (**28**). Upon treatment of vicinal diol **28** with $InCl_3$ and Ph_2SiHCl,[27] elimination of the C10 hydroxy group and a subsequent deoxygenation of the other—now allylic—C9 hydroxy group ensued to give alkene **29**. At this stage, $LiAlH_4$ reduction of the methyl ester, followed by Mukaiyama hydration to reinstall the tertiary hydroxy group at C10, gave diol **30**. Hydrogenolysis of the benzyl group in diol **30** with Pearlman's catalyst in the presence of acetic acid, followed by *N*-chlorination of the resulting secondary amine gave **31**. The *N*-Cl moiety acted as a protecting group for the amine and allowed for mesylation of the primary hydroxy group to give mesylate **32**. With leaving groups installed on the nitrogen and at C17 of the [2.2.2] bicycle, a double elimination was effected by heating mesylate **32** in the presence of DBU and NaI to afford imine **33** bearing an exocyclic alkene. This penultimate imine was advanced to arcutinidine (**4**) and its C15 epimer (**34**) through an allylic oxidation with SeO_2.

In summary, we report the synthesis of the arcutane-type diterpenoid alkaloid arcutinidine.[28] Our synthetic approach was inspired by chemical network analysis, which enabled rapid simplification of the three-dimensional architecture of the target compound through [4+2] cycloaddition transforms. Ultimately, these disconnections led us to identify an oxopyrrolium intermediate as a viable dienophile in an unprecedented [4+2] cycloaddition reaction. The synthesis reported herein sets the stage for the preparation of the related congeners arcutine (**5**) and arcutinidine (**6**) and may provide a starting point for the preparation of atropurpuran (**10**). These studies, as well as the development of an enantioselective cycloaddition of the oxopyrrolium dienophile and the potential conversion of the arcutane skeleton to the hetidine skeleton, are the subject of ongoing investigations in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and spectroscopic data (PDF)
X-ray crystallographic data for (±)-**27** (CIF)

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Notes

The authors declare no competing financial interest.

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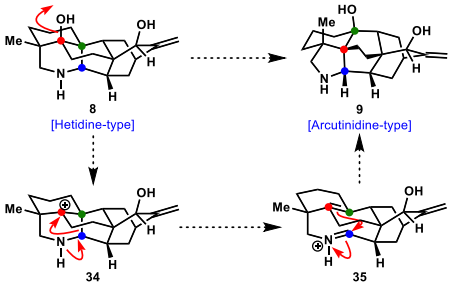

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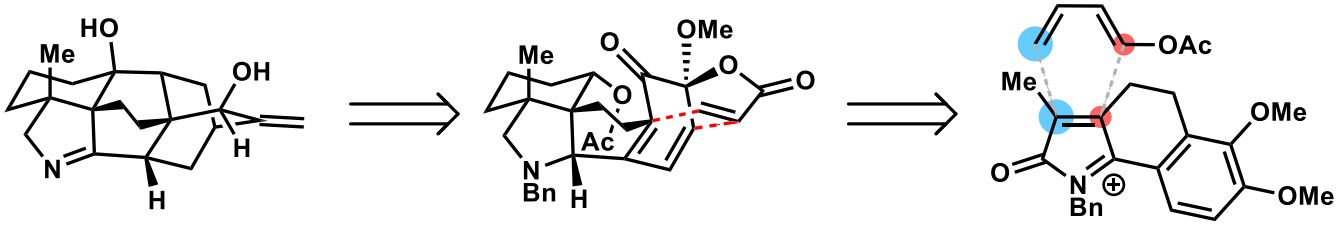

arcutinidine

intramolecular
Diels–Alder cycloaddition

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