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Enantioselective Total Synthesis of (–)-Arcutinine

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Supporting Information Placeholder

ABSTRACT: The first total synthesis of an arcutine-type C_{20}-diterpenoid alkaloid arcutinine has been achieved in both racemic and asymmetric forms. Construction of the C4 quaternary center and the pyrrolidine E ring in an early stage proved to be important for achieving the successful synthesis of the target alkaloid. Strategically, an asymmetric conjugate addition/aldol cascade and a decarboxylative allylation reaction allowed the establishment of the vicinal all-carbon quaternary stereocenters at C4 and C5. Furthermore, a sequence consisting of an intramolecular *aza*-Wacker cyclization, an oxidative dearomatization/IMDA cascade, and a ketyl-olefin cyclization enabled the assembly of the core structure and led to the total synthesis of arcutinine.

■ INTRODUCTION

The diterpenoid alkaloids, found within various plants of the genera *Aconitum*, *Delphinium*, and *Spiraea*, represent a large family of natural products that exhibit rich biological activities and fascinating chemical structures.[1] Architecturally, these molecules could be classified into three categories, namely, the C_{20}-, C_{19}-, and C_{18}-diterpenoid alkaloids,[2] possessing 20, 19, and 18 carbon atoms in their scaffolds, respectively. Among them, the C_{20}-subfamily contains the most diverse skeletal types, which have attracted significant attention from synthetic chemists for decades.[2a,3–9]

The arcutine-type C_{20}-diterpenoid alkaloids (Figure 1) are structurally characterized by a congested hexacyclic framework, including a challenging tetracyclo[5.3.3.$0^{4,9}$.$0^{4,12}$]tridecane ring system (BCDF rings, highlighted with blue bonds) and a unique azabicyclo[4.3.0]nonane unit (AE rings), as well as three all-carbon quaternary stereogenic centers (C4, C5, and C8).[2a] Biogenetically, the arcutine alkaloids could be derived from the hetidine core through a C20 (10→5) rearrangement event (Figure 1A).[2a,10] The representative arcutine-type molecules (**1** and **2**, Figure 1B) were first isolated by Saidkhodzhaeva and co-workers from *Aconitum arcuatum*,[11] while arcutinidine (**3**) was obtained as a saponification product through chemical transformation from **1** and **2**.[11b] More recently, aconicarmicharcutinium A (**4**) was reported by Shi *et al* from *Aconitum carmichaelii*.[12] The related diterpene congener of arcutine alkaloids, namely, atropurpuran (**5**), was isolated by the Wang group from *Aconitum hemsleyanum* var. *atropurpureum* in 2009.[13] While syntheses of the members from most C_{20}-diterpenoid alkaloid types and structurally related diterpenes have been accomplished in the synthetic community,[3–9,14] the total synthesis of an arcutine-type alkaloid remains unsolved. As our continuous interest in the synthesis of complex diterpenoids and related alkaloids,[3c,e,4j,14c] here we report the first total synthesis of arcutinine (**2**) in both racemic and asymmetric forms.

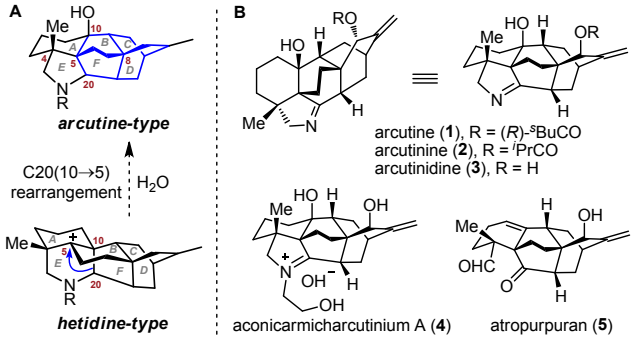


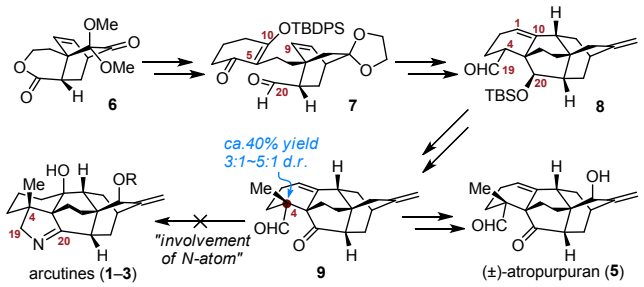
Figure 1. (**A**) Biogenetic relationship between the arcutine and hetidine diterpenoid alkaloids; (**B**) structures of arcutine diterpenoid alkaloids (**1**–**4**) and related diterpene atropurpuran (**5**).

■ RESULTS AND DISCUSSION

In 2016, our group realized the total synthesis of the diterpene (±)-atropurpuran (**5**).[14c] As shown in Scheme 1, highlights of the synthesis involved 1) an oxidative dearomatization/intramolecular Diels-Alder cycloaddition (IMDA) cascade to form the bicyclo[2.2.2]octane unit (**6**), 2) a sequential aldol addition and ketyl-olefin cyclization that established the pentacyclic framework (**8**), and 3) careful investigations of late-stage transformations that allowed completion of the synthesis of the target molecule. Considering the structurally relevance between the arcutine-type alkaloids (**1**–**3**) and their diterpenoid counterpart (atropurpuran, **5**),[10] we explored access to the corresponding alkaloid natural products by making use of intermediates possessing the entire carbocyclic core (i.e., **8**), which met without success. First, modifications at the C19 and C20 positions in the presence of the C4 quaternary stereocenter and C1–C10 alkene were challenging probably due to the sterically hindered circumstance and conformational strain of A ring in associated structures. For instance, subjection of aldehyde **9** to reductive amination conditions [e.g., $NaBH_3CN$ with NH_3 (g),

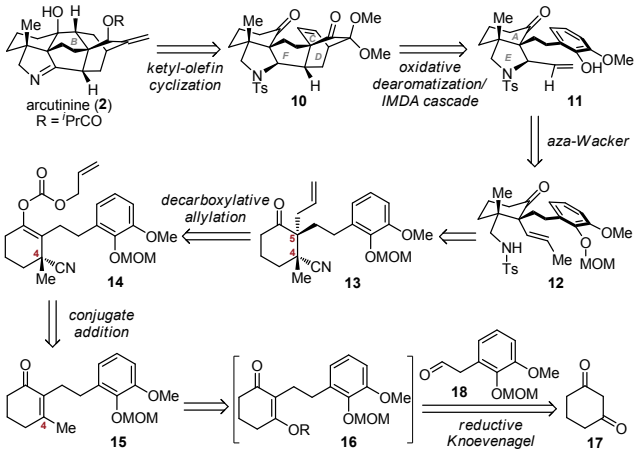
or HCO_2NH_4, or NH_4HCO_3] to introduce the crucial *N*-atom was unfruitful.[15] Second, late-stage installation of the C4 quaternary center (i.e., **9**) via α-methylation of corresponding aldehyde suffered from unsatisfactory efficacy (ca. 40% yield, 3:1~5:1 *d.r.*, a similar result was also observed by Xu et al in their recent synthesis of atropurpuran),[14c,d] which prevented extensive studies because of insufficient materials. Most importantly, preliminary inspections revealed that an asymmetric oxidative dearomatization/IMDA cascade[16] to access enantioenriched **6** would be difficult to achieve, thereby leading us to seek new solutions to an enantioselective total synthesis of the arcutine-type C_{20}-diterpenoid alkaloids.

Scheme 1. Our Previous Synthesis of (±)-Atropurpuran (5) and Attempted Access to the Arcutines



Retrosynthetic Analysis. The retrosynthetic analysis of arcutinine (**2**) is illustrated in Scheme 2. Unlike our previous synthesis of atropurpuran that generated the C4 quaternary center at late-stage,[14c] asymmetric construction of the C4 quaternary center followed by assembly of the pyrrolidine E ring in **2** prior to forming its complete carbocyclic core would be feasible for achieving a successful enantioselective synthesis of the target alkaloid. Thus, two late-stage key steps involving a ketyl-olefin cyclization[17] for the assembly of B ring (**10** to **2**) and an oxidative dearomatization/IMDA cascade[3e] to establish C/D/F rings (**11** to **10**) were envisaged to be conducted with the presence of the azabicyclo[4.3.0]nonane moiety (AE rings) and the C4 quaternary center. An intramolecular palladium-catalyzed *aza*-Wacker reaction[18] would secure the formation of the pyrrolidine E ring in compound **11** from the internal alkene **12**, and the latter could be obtained via functional group manipulations of **13**. At this stage, the focus of our retrosynthetic analysis was on how to enantioselectively generate the two vicinal all-carbon quaternary stereogenic centers at C4 and C5 in compound **13**. A palladium-catalyzed decarboxylative allylation[19] reaction would enable the conversion of

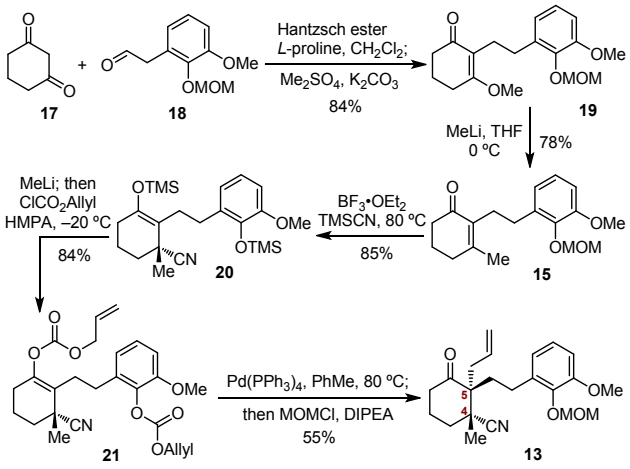
Scheme 2. Retrosynthetic Analysis of Arcutinine (2)



carbonate **14** to **13** and installation of the C5 quaternary carbon center. The enol derivative **14** would be accessible via an asymmetric conjugate addition of cyanide to enone **15** by establishing the initial chiral quaternary stereocenter at C4. In turn, enone **15** could be prepared by a reductive Knoevenagel condensation[20] between 1,3-cyclohexanedione (**17**) and aldehyde **18**[21] followed by addition of a methyl group to the resultant ketone **16** and acidic hydrolysis.

Construction of the C4 and C5 Vicinal All-Carbon Quaternary Stereogenic Centers. According to the synthetic plan, we initiated our study with the preparation of a key intermediate containing C4 and C5 vicinal quaternary stereogenic centers (Scheme 3). A reductive Knoevenagel condensation[20] between 1,3-cyclohexanedione (**17**) and aldehyde **18**[21] was performed in the presence of Hantzsch ester and L-proline in CH_2Cl_2, which was followed by methylation using Me_2SO_4, providing enol ether **19** in 84% yield. Addition of MeLi to the carbonyl group in **19** with acidic aqueous work-up smoothly delivered enone **15** (78% yield). Enone **15** then underwent conjugate addition employing TMSCN and BF_3•OEt_2 at 80 ºC to give silyl enol ether **20** (85% yield) with the desired C4 quaternary stereogenic center. Despite the failure of preliminary investigations on the asymmetric conjugate addition of cyanide to enone **15**,[22] we were eager to examine the subsequent synthetic strategy that sets the vicinal C4 and C5 quaternary centers and thus continued the synthesis with racemic **20**. Ether **20** was then sequentially reacted with MeLi and $ClCO_2Allyl$/HMPA at –20 ºC to furnish dicarbonate **21** (84% yield). The decarboxylative allylic alkylation of **21** with $Pd(PPh_3)_4$ at 80 ºC, followed by masking of the resultant phenol as a MOM ether with MOMCl/DIPEA, afforded the key intermediate **13** with high diastereoselectivity (13:1 *d.r.* at C5, inseparable) and 55% yield.[23] Consequently, the two important vicinal all-carbon quaternary stereogenic centers at C4 and C5 were secured in compound **13**, which was obtained in decagram quantities.

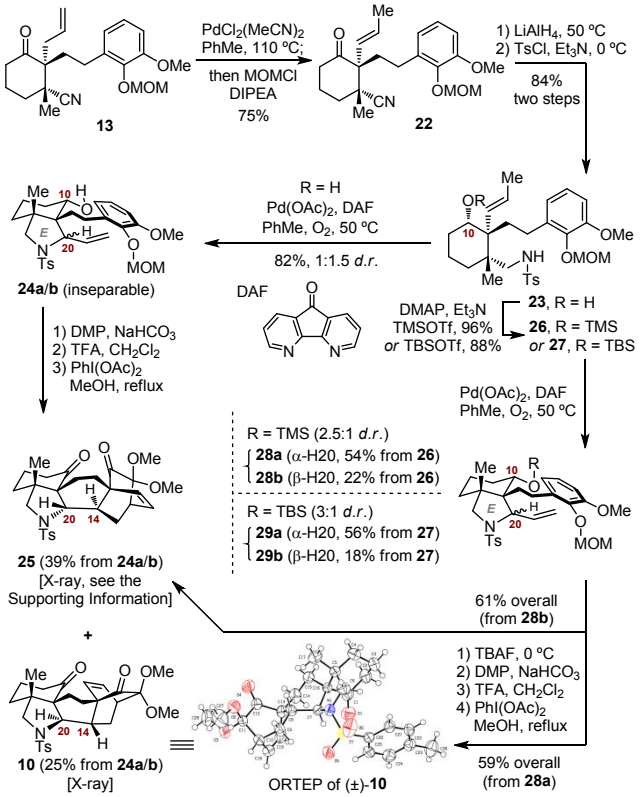
Scheme 3. Preparation of the Key Intermediate 9 with C4 and C5 Vicinal Quaternary Stereogenic Centers



Synthesis of the Hexacyclic Core Structure. Our next task was to explore the assembly of the hexacyclic core structure of the target molecule **2**. As depicted in Scheme 4, isomerization of the terminal olefin in **13** to an internal olefin occurred in the presence of $PdCl_2(MeCN)_2$ in toluene at 110 ºC,[24] under which the MOM group was also cleaved. After filtration of the reaction suspension, the filtrate was re-subjected to MOMCl/DIPEA and produced *E*-alkene **22** in 75% yield. Reduction of the cyano and carbonyl groups in **22** with $LiAlH_4$, followed by selective protection of the resulting primary amine with TsCl in the presence of Et_3N, furnished **23** as a single diastereomer in 84% yield over two steps. The stage was then set for a palladium-catalyzed *aza*-Wacker reaction to form the pyrrolidine E ring. As a result, according to Stahl's protocol,[18b] treatment of sulfonamide **23** with $Pd(OAc)_2$/DAF/PhMe/O_2 at 50 ºC led to the formation of *N*–C20 bond, giving **24a**/**b** as a pair of inseparable diastereomers (1:1.5 *d.r.*at C20) in 82% combined yield. Since the C20 configurations would be eliminated by converting into a sp^2 carbon (an imine moiety) in the target molecule, theoretically both diastereomers could be useful for subsequent synthesis. Thus, subjection of the inseparable mixture (**24a**/**b**) to a three-step sequence, including 1) oxidation of the C10 alcohol to ketone with DMP, 2) removal of the MOM group with TFA, and 3) oxidative dearomatization/IMDA cascade of the resulting phenol, generated separable cycloadducts **10** (25% yield) and **25** (39% yield), respectively. The structures of both pentacyclic products were unambiguously determined by X-ray crystallographic analysis. Of note, the Diels-Alder cycloaddition of both diastereomers proceeded with exclusive *endo* selectivity, and only the isomer bearing an α-H20 yielded the desired cycloadduct (**10**) with the correct C14 configuration.

In this context, we turned back to investigate the *aza*-Wacker cyclization in hoping of improving the diastereoselectivity of this key transformation. It was supposed that a bulky substitution group rather than a hydroxyl group at C10 in **23** would provide a steric hindrance environment to force the resultant vinyl group far away from the C10 substituent and

Scheme 4. Synthesis of the Key Intermediate 10

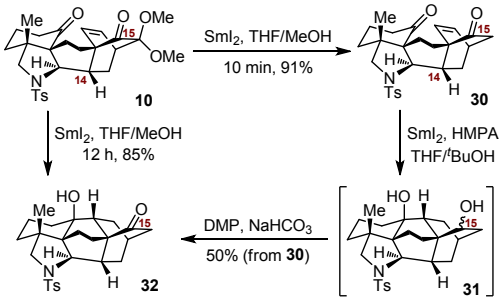


yield the desired product with α-H at C20. Various silyl protecting groups were investigated for this purpose. As expected, after installing a TMS group at the C10 hydroxyl group in **23** with TMSOTf/DMAP/Et_3N, the resultant **26** was subjected to the same *aza*-Wacker conditions and generated allylic sulfonamides **28a** and **28b** as a pair of separable diastereomers (2.5:1 *d.r.*) in 76% combined yield. Use of a TBS protecting group for this cyclization reaction was trivial to further improve the diastereoselectivity (**27** to **29a** and **29b**, 3:1 *d.r.*). However, deprotection of TBS group in the next step failed under various attempted conditions (e.g., TBAF, HF•Pyr., TASF) presumably due to steric factors. Installation of other bulky substituents (e.g., TES, TIPS, TBDPS) at the C10 hydroxyl group in compound **23** was unsuccessful, which once again demonstrated the sterically hindered circumstance of this position. Meanwhile, we determined the configurations at the newly generated C20 stereocenter in **28a** and **28b** by converting them to the corresponding Diels-Alder cycloadducts (**10** and **25**) via a four-step transformation, respectively. The major diastereomer **28a** of the *aza*-Wacker reaction with α-H20 was confirmed to deliver the desired pentacyclic intermediate **10** and was ready for accessing the core of the target molecule. Similarly, the minor isomer **28b** with β-H20 yielded the undesired pentacyclic compound **25** bearing the incorrect C14 configuration.

Next, compound **10** was treated with SmI_2 in THF/MeOH for 10 min to firstly remove the two methoxy groups and produce diketone **30** (91% yield, Scheme 5). According to our previous study,[14c] the crucial ketyl-olefin cyclization of **30** occurred in the presence of SmI_2 and HMPA in THF/^{t}BuOH to give diol **31**, under which the C15 carbonyl group was also reduced. The intermediate **31** was inseparable from HMPA and was thus directly subjected to oxidation employing DMP, affording ketone **32** in 50% yield over two steps. Pleasingly, we later found that exposure of diketone **10** to

SmI_2/THF/MeOH in the absence of HMPA with prolonged reaction time (12 h) was able to remove the two methoxy groups and trigger the expected ketyl-olefin cyclization in one pot, leaving the C15 ketone unreduced, thereby forming the complete skeleton of arcutinine and delivering **32** in 85% yield.

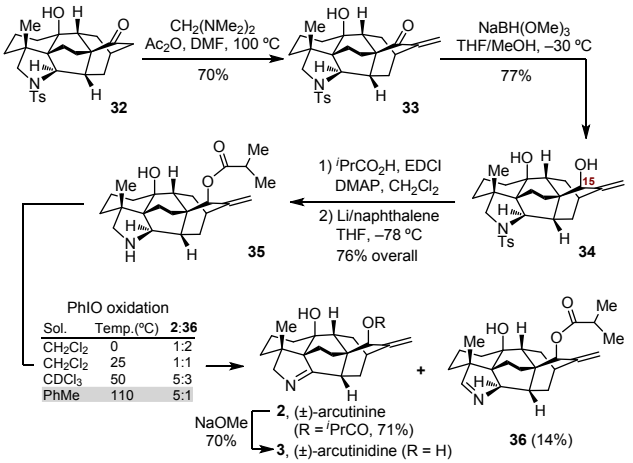
Scheme 5. Construction of the Hexacyclic Core



Total Synthesis of (±)-Arcutinine. Having the core structure **32** secured, the total synthesis of (±)-arcutinine (**2**) was completed in a few steps (Scheme 6). Performing an α-methylenation of ketone **32** using $CH_2(NMe)_2$ and Ac_2O in DMF at 100 ºC yielded enone **33** (70%).[25] Reduction of the carbonyl group in **33** took place efficiently with $NaBH(OMe)_3$,[14c] giving diol **34** as the major product in 77% yield (see reference 26 for discussion).[26] Subsequent installation of the isobutyryl group at C15 secondary alcohol in **34** with isobutyric acid and removal of the *N*-Ts protecting group with Li/naphthalene provided **35** (76% overall yield). The only remaining step to arcutinine (**2**) was to generate an imine functionality at the C20 position. To this end, PhIO was found to be an appropriate oxidant and the oxidation took place in CH_2Cl_2 at 0 ºC to give the desired imine **2** and its regioisomer **36** with 1:2 ratio in an initial experiment. Further investigations revealed that the reaction temperature played an important role in determining the ratio of the two regioisomers. Ultimately, oxidation of the secondary amine in **35** employing PhIO/PhMe at 110 ºC furnished (±)-arcutinine (**2**) in 71% yield, along with the regioisomer **36** (14% yield).

Spectroscopic data of the synthetic arcutinine (**2**) were identical to those reported for the natural product, expect for the carbon chemical shift of the carbonyl group in the isobutyryl moiety (synthetic: δ_C176.98 *vs* reported: δ_C 175.80).[11b] In the isolation paper, the natural products arcutine (**1**) and arcutinine (**2**) were isolated as an inseparable mixture in 2:1 ratio.[11] However, the carbon chemical shift of both the carbonyl groups in **1** and **2** were assigned to be the same (δ_C 175.80). We suspected that the reported data might belong to the major component (**1**) and the one from the minor (**2**) was neglected. After saponification of the synthetic arcutinine (**2**) to arcutinidine (**3**) using NaOMe/MeOH (70% yield), the NMR data of the obtained **3** completely matched those reported in the literature,[11b] which thus further confirmed the structure of our synthetic arcutinine (**2**) (see the Supporting Information for more details).

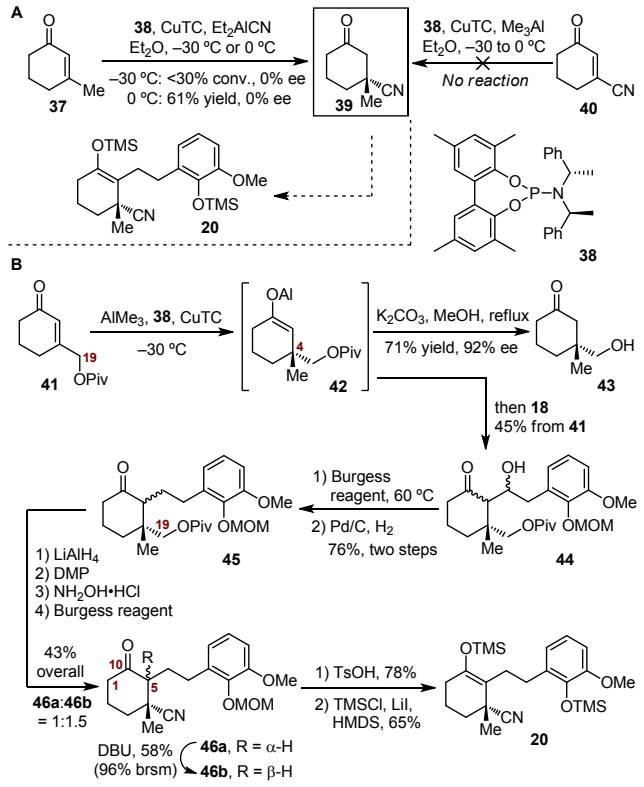
Scheme 6. Completion of the Total Synthesis of (±)-Arcutinine (2)



Enantioselective Total Synthesis of (–)-Arcutinine. Having established a successful synthetic approach to the arcutine-type C_{20}-diterpenoid alkaloid (±)-arcutinine (**2**) in racemic form in 18 steps, we sought to further complete its asymmetric total synthesis. Installing the initial C4 stereogenic center in compound **20** (Scheme 3) enantioselectively would allow us to achieve the asymmetric synthesis of (–)-arcutinine in a substrate-controlled fashion. As direct asymmetric conjugate addition of cyanide to enone **15** to access enantioenriched **20** was unfruitful (Scheme 3), we envisioned to prepare a simpler chiral intermediate **39** (i.e., a precursor of **20**, Scheme 7A) that possessed the desired C4 quaternary center by conjugate addition of a cyano group to 3-methylcyclohex-2-enone (**37**) or of a methyl group to 3-oxocyclohex-1-enecarbonitrile (**40**). A known catalytic asymmetric conjugate addition of cyanide to enone **37** was described by Shibasaki et al harnessing a chiral Gd-complex,[22] producing **39** in 70% yield and 25% ee.[27] Because of the low ee value, the Shibasaki's protocol for asymmetric installation of the C4 quaternary center was abandoned. In this context, we then examined the asymmetric conjugate addition of enones **37** and **40** employing Alexakis's approach that has proved to be useful for installing quaternary stereocenters.[28] However, when **37** was subjected to cyanide addition with Et_2AlCN and the phosphoramidite ligand **38**, the adduct **39** was only obtained in racemic form either at –30 ºC (<30% conv.) or at 0 ºC (61% yield). In addition, an attempted methyl group addition to **40** in the presence of Me_3Al and **38** resulted in no reaction.

A cyano group at C4 proved to be important for ensuring the desired relative stereochemistry of the vicinal C4 and C5 stereocenters in the palladium-catalyzed decarboxylative allylation step (**21** to **13**, Scheme 3). The failure of direct enantioselective installation of the C4 quaternary center with a cyano group (e.g., **39**) promoted us to design a substrate containing an *O*-functionalized group for the asymmetric conjugate addition, which could be converted to a cyano group later. Thus, enone **41**[29] with a pivalate at C19 was examined for the asymmetric conjugate addition according to Alexakis's method.[28] Specifically, as shown in Scheme 7B, treatment of enone **41** with $AlMe_3$ and copper(I) thiophene-2-carboxylate (CuTC) in the presence of the chiral ligand **38** at –30 ºC afforded the aluminum enolate intermediate **42**. Gratifyingly, such a protocol succeeded in generating the C4 quaternary stereocenter in enantioselective manner. The enantioselectivity

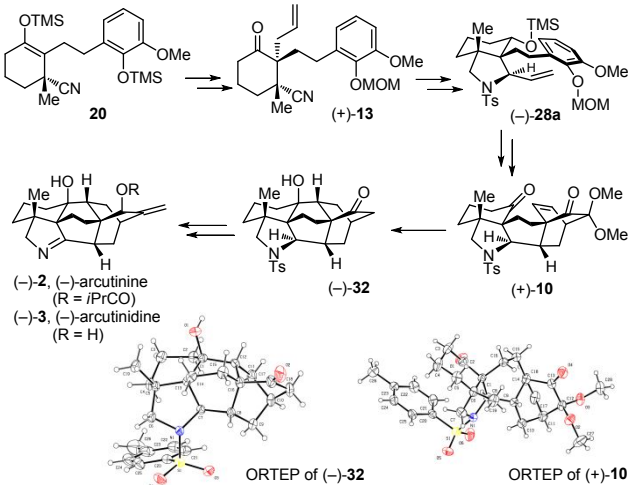
Scheme 7. (A) Unsuccessful Asymmetric Conjugate Additions and (B) Preparation of the Enantioenriched Intermediate 20



(92% ee) of this transformation was determined after converting **42** into the ketone **43** with K_2CO_3/MeOH at reflux. Directly adding a solution of aldehyde **18**[21] in Et_2O to the reaction mixture of **42** provided the hydroxyl ketone **44** (45% yield) through an asymmetric conjugate addition/aldol cascade reaction. The inseparable diastereomeric mixtures of **44** were then subjected to dehydration with Burgess reagent and hydrogenation of the resultant alkene to give ketone **45** as a pair of inseparable diastereomers in 76% combined yield. Next, the C19 pivalate in **45** was switched to a cyano functionality by a four-step sequence including $LiAlH_4$ reduction of both the pivaloyl and C10 carbonyl groups to diol, oxidation of the diol to the keto-aldehyde with Dess-Martin periodinane (DMP), conversion of the aldehyde to oxime with hydroxylamine hydrochloride, and dehydration of the resulting oxime to a nitrile with Burgess reagent, providing **46** as a pair of separable diastereomers with 43% overall yield and 1:1.5 *d.r.* value.[30] Unfortunately, subjecting both **46a** and **46b** to various conditions for enol silane formation led to the undesired regioselectivity at C1 rather than C5. After much experimentation, we were delighted to observe that the intermediate with a free phenol group resulted from **46b** by deprotection of the MOM group (with TsOH) was able to generate the desired enol silane **20** predominately by treating with TMSCl/LiI/HMDS in 65% yield. By contrast, treating the free phenol compound obtained from the minor isomer **46a** under the similar conditions led to the undesired C1 enol silane. Fortunately, epimerization of **46a** to **46b** proceeded using DBU with 58% yield (96% brsm) and allowed recycling of the material.

Although not as straightforward as the racemic synthesis, the established synthetic route to the enantioenriched intermediate **20** was able to be performed on multigram scales, providing us sufficient materials for the enantioselective total synthesis of (–)-arcutinine (**2**). As a result, using enantioenriched **20** as the starting material, we went through the remaining synthetic route as that described for the synthesis of racemic **2** and completed the total synthesis of (–)-arcutinine and (–)-arcutinidine (see the Supporting Information for details). Key intermediates are shown in Scheme 8, and the structures of (+)-**10** and (–)-**32** were again verified through X-ray crystallographic methods.

Scheme 8. Enantioselective Total Synthesis of (–)-Arcutinine and (–)-Arcutinidine



■ CONCLUSION

In summary, we have achieved the first total synthesis of the arcutine-type C_{20}-diterpenoid alkaloid arcutinine (**2**) in both racemic and asymmetric formats. Several key features of the synthesis deserve to be highlighted. Initial installation of the vicinal chiral all-carbon quaternary stereocenters at C4 and C5 was secured through an asymmetric conjugate addition reaction and a palladium-catalyzed decarboxylative allylation reaction, respectively. Early stage construction of the pyrrolidine E ring by taking advantage of an intramolecular *aza*-Wacker cyclization proved to be critical for realizing the successful synthesis. In addition, an oxidative dearomatization/IMDA cascade and a ketyl-olefin cyclization allowed access to the remaining tetracyclo[5.3.3.$0^{4,9}$.$0^{4,12}$]tridecane ring system (BCDF rings) and assembly of the complete arcutine skeleton. We anticipate the synthetic approach disclosed here will be helpful to probe the biological profiles of related alkaloids.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, characterization data, and NMR spectra (PDF)
X-ray crystallographic data for (±)-**10** (CIF)
X-ray crystallographic data for (±)-**25** (CIF)
X-ray crystallographic data for (+)-**10** (CIF)

X-ray crystallographic data for (−)-**32** (CIF)

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†W.N. and J.G. contributed equally.

Notes

The authors declare no competing financial interests.

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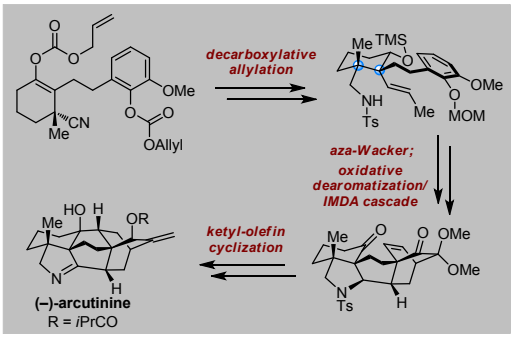
decarboxylative allylation
aza-Wacker; oxidative dearomatization/ IMDA cascade
ketyl-olefin cyclization
(–)-arcutinine
R = iPrCO