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Asymmetric Total Synthesis of Biphenylquinolizidine Alkaloids 4″-*O*-Demethyllythridine and 14-*epi*-4″-*O*-Demethyllythridine

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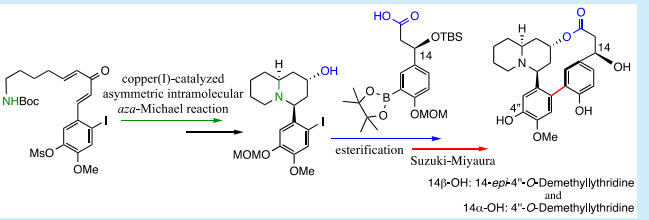
Supporting Information

ABSTRACT: The first asymmetric total synthesis of new biphenylquinolizidine alkaloids 4″-*O*-demethyllythridine and 14-*epi*-4″-*O*-demethyllythridine isolated from *Heimia salicifolia* was accomplished. The key steps in the synthesis were a copper(I)-catalyzed asymmetric intramolecular aza-Michael reaction to build a chiral 4-arylquinolizidine unit and an intramolecular Suzuki−Miyaura cross-coupling reaction to construct a macrolactone ring comprising a biphenyl moiety.



Heimia salicifolia (family Lythraceae) is the main ingredient of the law-evading drug "sinicuichi". When consumed, sinicuichi causes exhilarating feelings and the alteration of awareness accompanied by bradycardia, hypomyotonia, and a pleasant faintness.[1] To date, the active principles and the mechanism of action underlying the neurotropic effects of this drug have not been clarified. In the course of our chemical studies on bioactive alkaloids in medicinal plants,[2] we have isolated a number of biphenylquinolizidine alkaloids,[3] including lythrine (**1**), lythridine (**2**), and new alkaloids 4″-*O*-demethyllythridine (**3**) and 14-*epi*-4″-*O*-demethyllythridine (**4**), from *H. salicifolia*[3b] (Figure 1). To confirm their structures, in particular, the stereochemistry at C14, which was inferred from nuclear Overhauser effect (NOE) correlations and coupling constants in the ^{1}H NMR spectra, we have embarked on the asymmetric total synthesis of these alkaloids. Herein we report the first asymmetric total synthesis of **3** and **4**, which features a copper(I)-catalyzed asymmetric intramolecular aza-Michael reaction to generate an arylquinolizidine unit and an intramolecular Suzuki−Miyaura cross-coupling reaction to construct a macrocyclic lactone ring comprising a biphenyl moiety.

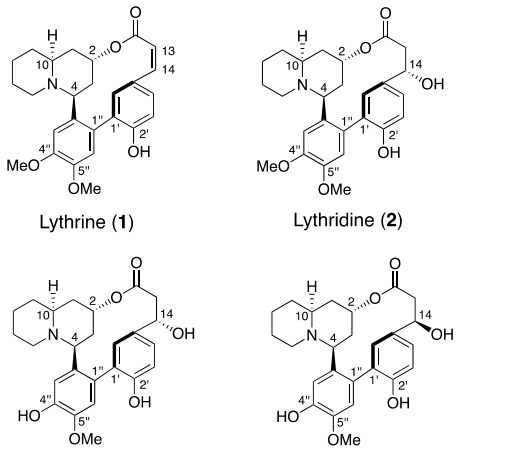


Figure 1. Biphenylquinolizidine alkaloids from *Heimia salicifolia*.

The synthetic targets, 4″-*O*-demethyllythridine (**3**) and 14-*epi*-4″-*O*-demethyllythridine (**4**), consist of a quinolizidine ring with three chiral centers at C2, C4, and C10 and a 12-membered macrolactone ring with a chiral secondary hydroxy group at C14. Our early retrosynthetic analysis of these alkaloids is shown in Scheme 1. In previous synthetic studies, intramolecular esterification[4] (heating under acidic conditions) or ring-closing methathesis[5] was used for the construction of the macrolactone ring. However, these strategies would not be applicable to the synthesis of **3** and **4** having a *β*-hydroxy lactone group. Thus we adopted an intramolecular aldol reaction or the Reformatsky reaction in the final stage of the synthesis using an aldehyde intermediate (**5a** or **5b**). Compound **5** would be prepared from arylquinolizidinone **6** via the installation of arylaldehyde **7** by the Suzuki−Miyaura cross-coupling reaction. Arylquinolizidinone **6** would be constructed from linear dienone **8** via a double intramolecular aza-Michael reaction. In this process, we adopted a copper(I)-catalyzed asymmetric aza-Michael reaction developed by Kanai and coworkers[6] to obtain a chiral quinolizidine moiety. Substrate **8** was prepared by the condensation of three units, that is, aromatic aldehyde **9**, phosphonate **10**, and amine **11**, via the Horner−Wadsworth−Emmons (HWE) reaction and olefin cross-metathesis according to a method previously developed by us.[7]

Initially, we examined the asymmetric intramolecular aza-Michael reaction of dienone **8** using copper(I) alkoxide−chiral

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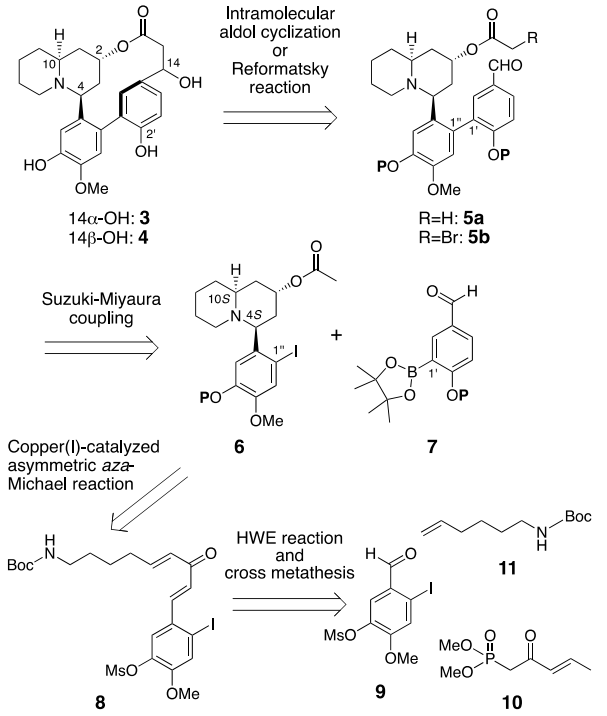
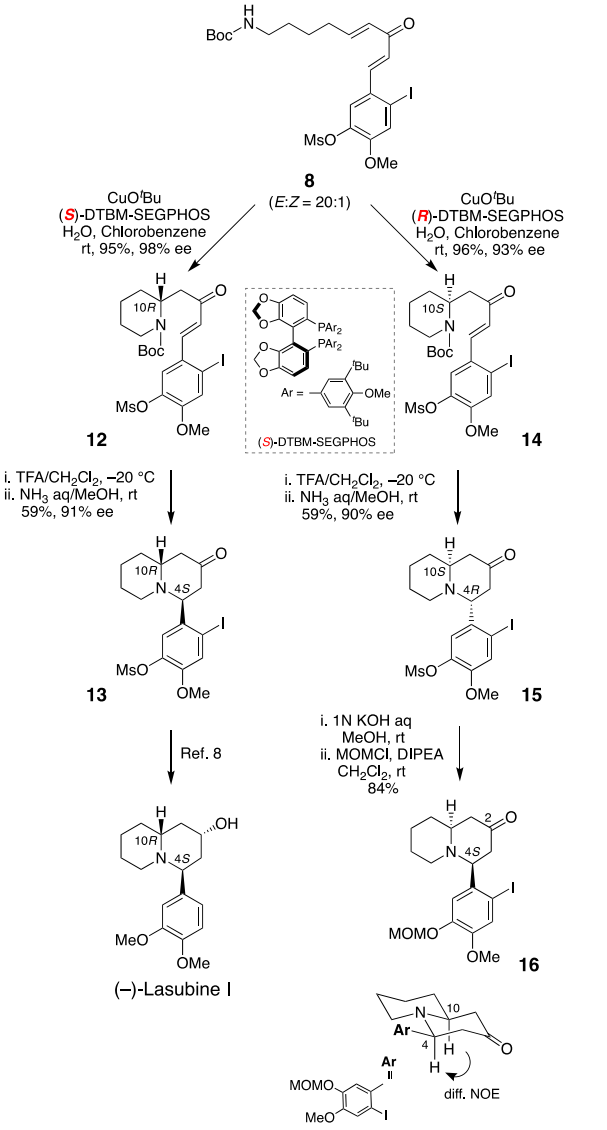
Scheme 1. First Retrosynthetic Analysis



phosphine complexes as the chiral catalyst[6] (Scheme 2). When (*S*)-DTBM-SEGPHOS was used as the ligand, piperidine derivative **12** ($[\alpha]_D$ −26.9) was obtained in 95% yield with 98% ee, which was stereoselectively converted into quinolizidinone derivative **13** ($[\alpha]_D$ −54.3) by the removal of the Boc group under acidic conditions and successive treatment with aqueous ammonia. Its structure including relative and absolute stereochemistries was confirmed by the comparison of physicochemical data with those of authentic **13**,[7] which was previously prepared in our laboratory by a different procedure using an organocatalyzed asymmetric reaction. For the synthesis of target natural products, the enantiomer of **13** was required. Then, (*R*)-DTBM-SEGPHOS was used as the ligand to give enantiomeric piperidine derivative **14** ($[\alpha]_D$ +23.2) in 96% yield with 93% ee, which was converted into quinolizidinone derivative **15** ($[\alpha]_D$ +55.3) under the same reaction conditions as above. Epimerization at C4 in **15** under basic conditions (aq. KOH in MeOH),[5] followed by the protection of the resultant phenol with an MOM group gave compound **16**. The relative configuration at C4 and C10 in **16** was determined from the NOE correlation between H-10 and H-4.

Then, the ketone in **16** was diastereoselectively reduced with K-Selectride to yield alcohol **17** (91% ee) (Scheme 3). After acetylation of the secondary alcohol in **17**, aryl iodide **18** was coupled to arylboronate **19**[5] under Suzuki−Miyaura conditions (cat. $Pd(PPh_3)_4$, CsF in dimethoxyethane (DME), 100 °C) to generate biphenyl derivative **20** in 82% yield. Next, we examined an intramolecular aldol reaction of **20** under various conditions (lithium diisopropylamide (LDA), potassium bis(trimethylsilyl)amide (KHMDS), NaH, etc.) but were unable to obtain the desired product (**21** or **22**). Then, we attempted to carry out an intramolecular Reformatsky reaction to obtain a *β*-hydroxy lactone ring. *α*-Bromoacetoxy derivative **23** was prepared from **20** through hydrolysis and acylation reactions. However, we were unable to realize the transformation of **23**

Scheme 2. Synthesis of Both Enantiomers of Quinolizidine Derivatives



into the cyclized compound (**21** or **22**) under various conditions that used SmI_2,[9] Rieke Zn,[10] or Rh catalyst.[11]

Given the above results, we reformulated our synthetic plan (Scheme 4), which featured the incorporation of fragment **24** or **25** possessing a secondary hydroxy group at C14 with defined absolute stereochemistry and the intramolecular Suzuki−Miyaura cross-coupling reaction for the construction of the macrolactone ring in the final step of the total synthesis.[12]

Boronates **24** and **25** with a *β*-hydroxy propionate group were prepared as follows (Scheme 5). Racemic **30** obtained by the aldol condensation of aldehyde **31** and ethyl acetate was converted into *β*-ketoester **32** by oxidation with Dess−Martin periodinane. The thus-obtained **32** was subjected to Noyori transfer hydrogenation.[15] When RuCl[(*R*,*R*)-Tsdpen](*p*-cymene) was used as the catalyst, alcohol **33** having *R* configuration was obtained in 83% yield with 95% ee. The absolute configuration was determined by the modified Mosher method.[16] (See the SI.) On the contrary, when RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) was used as the catalyst, alcohol **34** having *S* configuration was obtained in 94% yield

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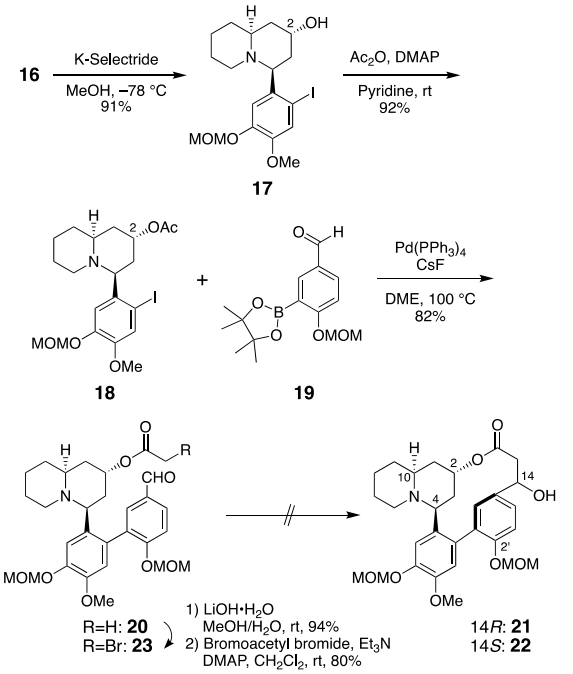
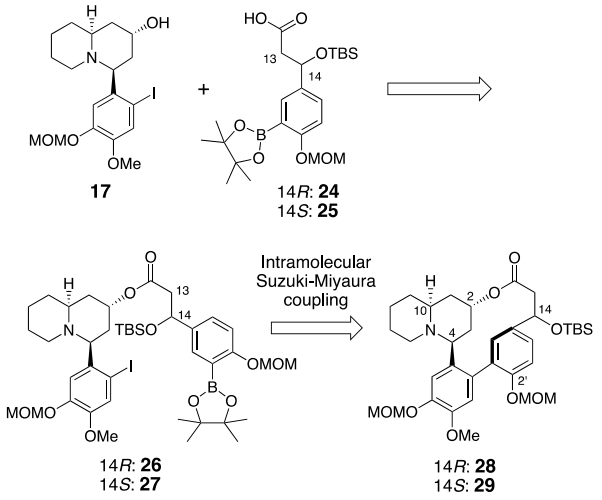
Scheme 3. First Attempts at Macrocyclization

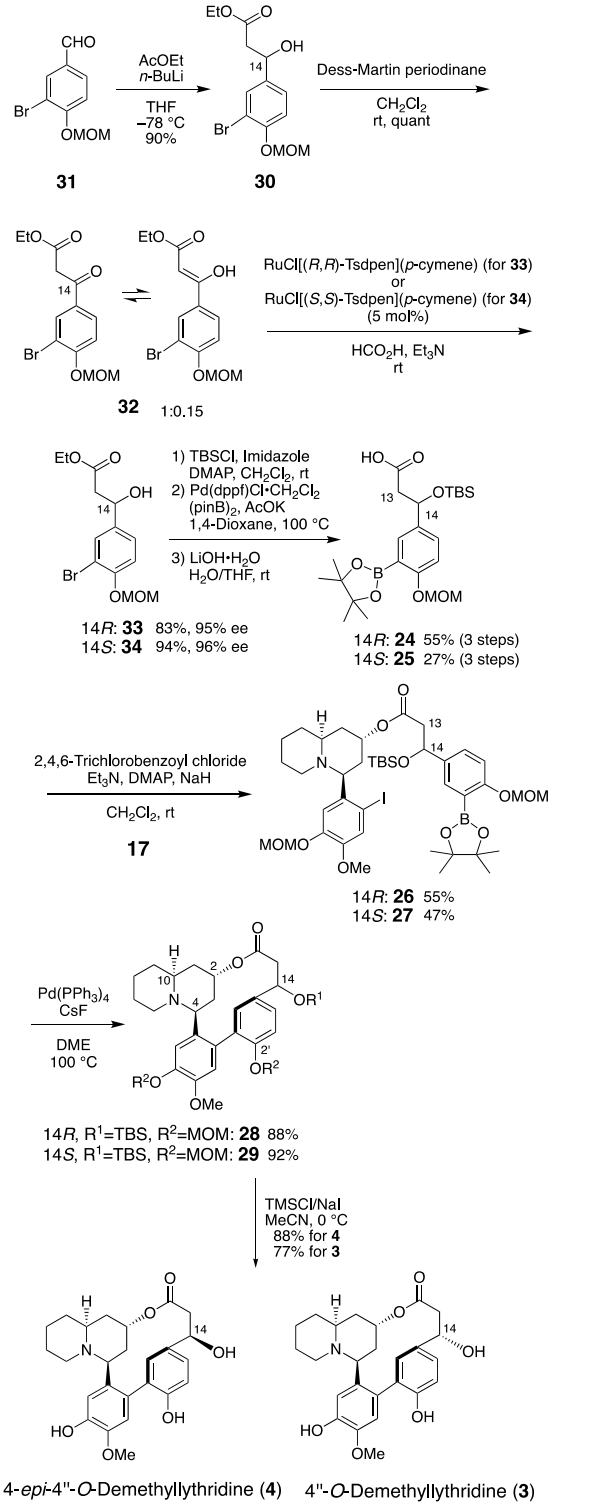


Scheme 4. New Synthetic Plan



with 96% ee. Compounds **33** and **34** were, respectively, converted into boronates **24** and **25** by a three-step operation: (i) protection of the alcohol with a *tert*-butyldimethylsilyl (TBS) group; (ii) installation of boronate using bis-(pinacolato)diboron, Pd(dppf)Cl_2·CH_2Cl_2, and AcOK in 1,4-dioxane; and (iii) hydrolysis of the ester function with aq. LiOH. The thus-obtained carboxylic acid was, respectively, condensed with alcohol **17** using the Yamaguchi esterification method with a slight modification (see the SI) to give **26** and **27**. Intramolecular Suzuki−Miyaura cross-coupling reactions[17] of **26** and **27** proceeded smoothly to give cyclic products **28** and **29** in good yield. Finally, the simultaneous deprotection of TBS and MOM groups with TMSCl/NaI afforded 14-*epi*-4″-*O*-demethyllythridine (**4**) and 4″-*O*-demethyllythridine (**3**). Synthetic **4** and **3** were identical in all respects to the natural product, including the optical properties. Therefore, the structures of 14-*epi*-4″-*O*-demethyllythridine (**4**) and 4″-*O*-demethyllythridine (**3**) including the absolute stereochemistry

Scheme 5. Completion of the Total Synthesis



of the secondary hydroxy group at C14 were unambiguously established.

Next, we examined the dehydration of the 14-hydroxy group in lythridine (**2**). Most of the natural phenylpropanoids having an *α,β*-unsaturated carboxylic acid (or ester), such as coumaric acid, caffeic acid, and so on, take the *E* configuration, whereas all of the biphenylquinolizidine alkaloids having an *α,β*-unsaturated lactone possess the *Z* configuration, like lythrine (**1**). For this reason, we hypothesized that in the enzymatic or

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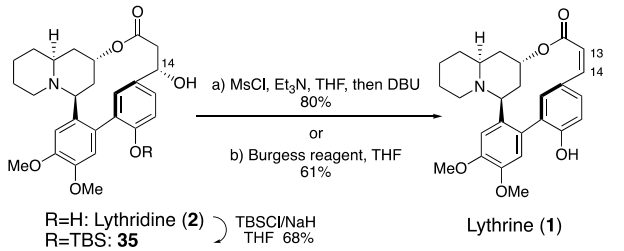
nonenzymatic process, dehydration at the β-hydroxy lactone moiety would proceed stereoselectively to yield the *cis* form. To prove this hypothesis, the following experiments were conducted. As shown in Scheme 6, 2′-*O*-TBS lythridine (**35**)

Scheme 6. Transformation of Lythridine (2) into Lythrine (1)



was converted into its mesyl derivative, which was then subjected to E2 elimination conditions using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give lythrine (**1**) in 80% yield. No *trans* derivative was generated. Furthermore, lythridine (**2**) was treated with Burgess reagent, which is known to promote dehydration with *syn* elimination, to furnish exclusively lythrine (**1**) in 61% yield. Newman projection analysis suggested that the formation of both isomers from **2** would be mechanistically possible via either an E2 or a *syn* elimination process. However, the above experimental results imply that a 12-membered lactone comprising a biphenyl moiety prefers the formation of the *Z* configuration, as anticipated.

In conclusion, the first asymmetric total synthesis of new biphenylquinolizidine alkaloids 4″-*O*-demethyllythridine (**3**) and 14-*epi*-4″-*O*-demethyllythridine (**4**) isolated from *Heimia salicifolia* was accomplished (nine steps in the linear route from known compound **8**, 14.4 and 17.2% overall yields for **3** and **4**, respectively), and this resulted in the confirmation of their structures including their absolute configurations. The key steps in the synthesis were a copper(I)-catalyzed asymmetric intramolecular aza-Michael reaction to build a chiral 4-arylquinolizidine unit and an intramolecular Suzuki−Miyaura cross-coupling reaction to construct a macrolactone ring comprising a biphenyl moiety.

The present study including the development of new strategies for the intended preparation of both enantiomers at C10 in the quinolizidine unit, for the stereoselective synthesis of a β-hydroxy lactone moiety, and for the selective formation of a *Z*-configured α,β-unsaturated lactone would be of benefit to the facile asymmetric total syntheses of ∼30 biphenylquinolizidine lactone alkaloids that show structural diversity at C10, different substituents on the biphenyl ring, and different groups at the α and β positions of the lactone group, that is, unsaturated, saturated, or β-hydroxylated type.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02962.

Experimental procedures and copies of ^{1}H and ^{13}C NMR spectral data for **12**−**18**, **20**, **S1**, **23**, **30**, **32**−**34**, **S2**−**S7**, **24**−**29**, **35**, synthetic and natural **4** and **3**, and semisynthetic and natural **1** (PDF)

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Notes

The authors declare no competing financial interest.

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