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novel macrocyclization strategy

The first total synthesis of the reported structure of ceanothine D, a cyclopeptide alkaloid found in *Ceanothus americanus* (also known as red root or the New Jersey tea plant), was achieved using a novel regio- and stereocontrolled macrocyclization strategy. Although the natural components of *Ceanothus americanus* have not been fully identified, it has a rich history in folk medicine and continues to be used widely among herbal home remedy enthusiasts today.

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Total synthesis of the reported structure of ceanothine D via a novel macrocyclization strategy†

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The first total synthesis of the reported structure of ceanothine D, a cyclopeptide alkaloid found in red root, was achieved using a highly convergent synthetic strategy. Highlights of the synthesis include the first concomitant macrocyclization and formation of the unique chiral tertiary alkyl-aryl ether bond with complete regio- and stereo-control in the presence of a sensitive *Z*-enamide moiety to access the strained *para*-cyclophane present in its structure. This synthetic strategy may be broadly applicable in the generation of other structurally similar cyclopeptide alkaloids, enabling further biological and chemical investigations.

Introduction

Cyclopeptide alkaloids are the most abundant family of natural products isolated from the leaves, stem bark, root bark, and seeds of a wide variety of plant species.¹ Their role in plants has not been fully elucidated due to lack of availability as yields either from isolation or synthesis are very low. Therefore, development of new synthetic approaches has been an important endeavour since their discovery.^{1,2} The structural similarity of cyclopeptide alkaloids is categorized by the size of the macrocycle that can be 13-, 14-, or 15-membered (Fig. 1). The 14-membered group is the most prevalent, yet most challenging to synthesize because of the enhanced rigidity of the molecule, which results in lack of conjugation between the aromatic ring and the double bond of the enamide moiety.¹

Ceanothine D (**1**) was first reported by Servis from the root bark of *Ceanothus americanus* (also known as red root or the New Jersey tea plant) along with at least eighteen other cyclopeptide alkaloids that displayed close structural resemblances (Fig. 1).³ The structure of **1** was proposed based on degradation studies, mass spectrometry, and ¹H NMR using a 60 MHz spectrometer.³ Interestingly, ceanothine D is the only cyclopeptide alkaloid reported to date to contain the unique chiral tertiary alkyl-aryl ether linkage derived from β -hydroxyisoleucine. The stereochemistry was assigned as *L*, since it is the most common stereochemical configuration found in nature, and the alkyl-aryl ether stereochemistry was presumed to be *R*, because most β -hydroxy amino acids in cyclopeptide

alkaloids have this stereochemical assignment.^{1,6,4} To the best of our knowledge, there is no report of the structural elucidation of the naturally occurring form of ceanothine D or total synthesis of the reported molecule to date.

The use of *Ceanothus americanus* to treat a wide variety of ailments including blood coagulation and pressure, spleen pain, and even cancer has been supported by its rich history in folk medicine.^{3,5} In fact, it has been used as a tea substitute during the American Revolutionary and Civil War,⁵ and it can be accessed as an over-the-counter dietary supplement even today. Although the metabolites of *Ceanothus americanus* have been of interest to chemists and biologists for many years,⁶ isolation of individual compounds remains a laborious and difficult challenge since structurally similar cyclopeptide alkaloids are present in varied amounts as complex mixtures.^{3,7} Furthermore,

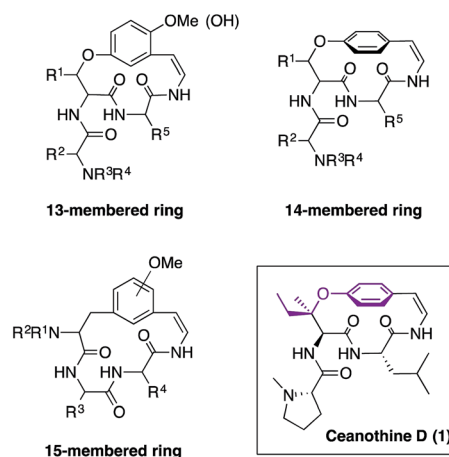


Fig. 1 13-, 14-, and 15-Cyclopeptide alkaloids and reported structure of ceanothine D.

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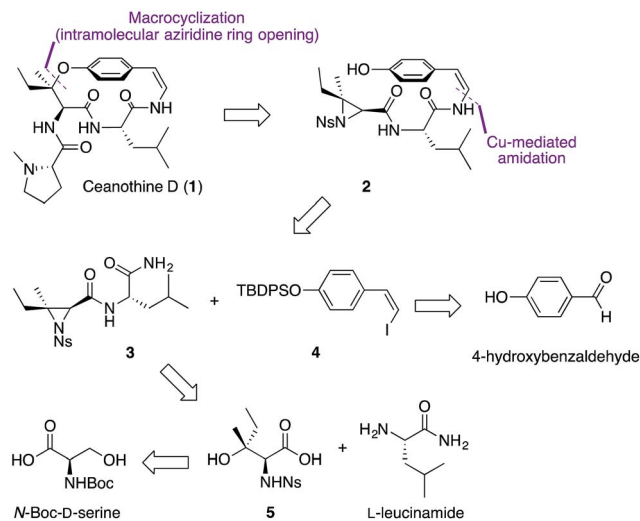
† Electronic supplementary information (ESI) available: Experimental details and spectral data are provided. CCDC 1588828. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8sc00234g

extraction yields vary from 0.0002 to 1% depending on the plant species, season, maturity of the plant, geographical location, and isolation method.^{1,8} Due to these limitations, surprisingly few cyclopeptide alkaloids have been pharmacologically investigated, and biological activities of this class of compounds remain under investigation.^{1,9} Efficient synthetic strategies to generate these compounds will not only facilitate structural elucidation, but also allow rapid biological profiling of the metabolites and related non-natural analogues.

To this end, research in our group¹⁰ along with that in other synthetic groups (*e.g.*, Rapoport,¹¹ Schmidt,¹² Lipshutz,¹³ Han,¹⁴ Zhu,¹⁵ Evano^{8,16}) focused on the development of new synthetic strategies to access cyclopeptide alkaloids. Synthetic challenges include stereocontrolled construction of the alkyl-aryl ether bond under mild reaction conditions and formation of the sensitive *Z*-enamide moiety. In particular, diverse bond disconnections have been examined for the non-trivial macrocyclization step. For the 13- and 15-membered cyclopeptides, the most widely employed approach is *via* intramolecular copper(I)-mediated amidation,^{8,16} while as macrolactamization,¹⁷ followed by late-stage elaboration of the *Z*-enamide^{10–12,14} is the most common strategy for the 14-membered compounds. Despite the steady progress in this area, synthesis of 14-membered cyclopeptides still remains a relevant synthetic task^{14,10–15,18,19} especially in comparison to 13- or 15-membered counterparts because of the intrinsic ring strain^{12e,20} associated with the 14-membered macrocycle.²¹ Synthesis of ceanothine D poses an additional unique challenge due to the presence of a chiral tertiary alkyl-aryl ether vicinal to a stereogenic centre in the molecule. Previous research efforts in our group led to the development of a new methodology to generate such motifs *via* stereocontrolled regioselective ring opening of a trisubstituted aziridine by a variety of phenol nucleophiles.²² This intermolecular reaction was successfully implemented on the syntheses of natural products and analogues containing chiral tertiary alkyl-aryl ethers.²³ Ceanothine D presented an excellent opportunity to further highlight the utility and versatility of this robust methodology, utilizing an intramolecular variant of the reaction, which addresses two major synthetic challenges associated with the molecule: the formation of the chiral tertiary alkyl-aryl ether fragment and macrocyclization in a single transformation.

Results and discussion

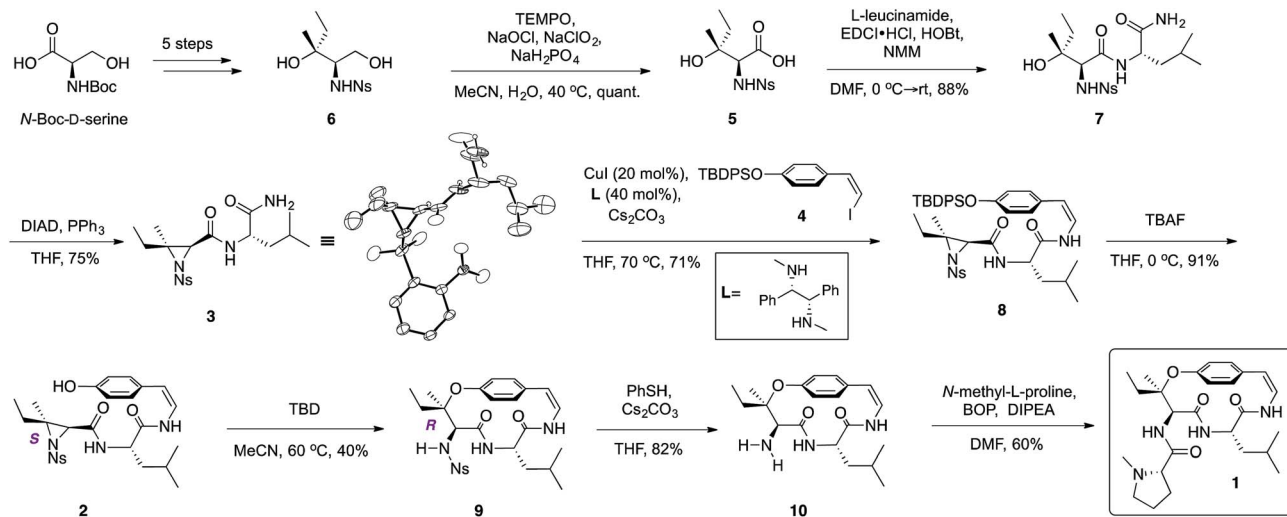
From the retrosynthetic perspective, access to ceanothine D (**1**) was envisioned through macrocyclization *via* intramolecular stereocontrolled regioselective aziridine ring opening by the phenol group of **2** (Scheme 1). Peptide coupling of acid **5** and free amine of *L*-leucineamide followed by subsequent intramolecular Mitsunobu reaction of the resultant amino alcohol would afford **3**. Acid **5** could be easily derived from commercially available *N*-Boc-*D*-serine. The *Z*-vinyl iodide moiety of **4** would be constructed by stereoselective olefination of the silyl protected 4-hydroxybenzaldehyde using the Stork–Zhao reagent.²⁴



Scheme 1 Retrosynthetic analysis.

Starting from commercially available *N*-Boc-*D*-serine, known precursor **6** was prepared in five steps (Scheme 2).^{22b,25} Pinnick oxidation^{22,23d} to the corresponding acid **5**, followed by EDCI-mediated coupling with free amine of *L*-leucineamide afforded the amino alcohol **7** in good yield. Mitsunobu cyclization^{22,23a,b,d} furnished the desired trisubstituted aziridine (**3**), and its structure was secured by X-ray crystallographic analysis. Treatment of the TBDPS protected commercially available 4-hydroxybenzaldehyde with the Stork–Zhao reagent^{16,24} gave the corresponding *Z*-vinyl iodide **4** as the major product (see ESI†). With requisite **3** and **4** in hand, the copper-mediated amidation was examined next. Surveying of current literature revealed the possibility of using catalytic Cu(I)-systems for the formation of *Z*-enamides especially in the presence of sensitive functional groups.^{8,16,26} In particular, utilization of diamine ligands with copper(I) iodide was the most prevalent approach in synthesis of enamide containing complex molecules.^{26d–f} Indeed, initial synthetic efforts employing CuI with various diamine ligands in our system led to synthetically significant yields. Size of the diamine ligand²⁷ was crucial in optimizing the yield of the reaction. Switching from sterically less bulky *N,N'*-dimethylethylenediamine to *N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine^{27a,b} resulted in significantly increased yields,[‡] presumably due to suppression of intermolecular aziridine ring opening side reaction(s) of **3** and/or **8** by the diamine ligand.²⁸ The optimized procedure afforded desired *Z*-enamide **8** in good yield without any observable epimerization at stereocenters or isomerization of the *Z*-vinyl iodide (**4**). Next, rapid removal of the silyl protecting group furnished linear precursor **2**, which was suitably positioned for the key macrocyclization step. Gratifyingly, our methodology²² in regio- and stereoselective ring opening of a trisubstituted aziridine translated well into the present intramolecular system despite concerns of creating a strained *para*-cyclophane (Scheme 2). To the best of our knowledge, this is the first effective macrocyclization of a 14-membered cyclopeptide precursor with the chemically sensitive *Z*-enamide intact. This successful outcome could be attributed





Scheme 2 Total synthesis of the reported structure of ceanothine D.

(in part) to comparably large release of ring strain associated with ring-opening of the aziridine that compensates for the formation of the strained macrocycle. Furthermore, previous work by Pais²⁹ suggests that the selection of suitable reagents (*i.e.* 1,5,7-triazabicyclo[4.4.0]dec-5-ene, TBD) is critical, since a macrocyclization event using a similar, albeit less strained, dihydro version of the linear precursor failed in the presence of Lewis acid promoters. As hypothesized from our past studies, the use of TBD as a bifunctional hydrogen-bonding guanidine base that activates the aziridine ring towards nucleophilic attack by the phenol,^{22b,c} dictated success in the current system. Taken together, the synthetic utility and versatility of our methodology was successfully showcased, resulting in a synthetically significant yield of the desired macrocycle (**9**) (Scheme 2). Extensive NMR studies further confirmed the structure of **9** (see ESI†). Finally, removal of the nosyl protecting group with thiophenol afforded the free amine **10**, which was subsequently coupled to *N*-methyl-*L*-proline completing the synthesis of the reported structure of ceanothine D (**1**) in good yields (Scheme 2). The full structure of **1** was elucidated on the basis of quantum-chemical calculations³⁰ and experimental NMR analysis (see ESI†).

Since the first report of ceanothine D (**1**) by Servis in 1969,³ the structural elucidation of **1** has been incomplete. This occurrence is not unusual, since the relative or absolute configuration of cyclopeptide alkaloids that were originally reported before 2006 are only recently being investigated.¹⁴ Other than the low-resolution ¹H NMR spectrum^{3b} of ceanothine D provided by Servis, the only other comparable piece of information was optical rotation. Interestingly, the optical rotation of the synthetic version of **1** did not match that of the reported value of the natural product,[§] suggesting the revision of the reported structure of ceanothine D. At this stage, the absolute structure of ceanothine D remains unknown due to the inaccessibility of natural samples for further analysis and full structural elucidation. Isolation and extraction from *Ceanothus americanus* is non-trivial, since extraction methods suffer from

low yields of complex mixtures.^{1,8} Despite this limitation, usage of *Ceanothus americanus* is prevalent and widely supported by herbal home remedy enthusiasts.^{1,3,5} Further chemical and biological investigations enabled by an efficient macrocyclization strategy will expand the knowledge and highlight the relevance of this interesting class of natural products. In particular, the presence of the unique chiral tertiary alkyl-aryl ether linkage in **1** might induce structural changes and result in distinct biological activities relative to other 14-membered cyclopeptide alkaloids.

Conclusions

In conclusion, the first total synthesis of the reported structure of ceanothine D has been achieved with a novel macrocyclization method in eight steps from a known intermediate **6** (ref. 22b and 25) in overall 8.4% yield. Highlights of the synthesis include the first concomitant, sterecontrolled macrocyclization and formation of the chiral tertiary alkyl-aryl ether bond, particularly in the presence of a chemically sensitive *Z*-enamide moiety to afford the notoriously strained^{1,19} 14-membered cyclopeptide alkaloid. The developed strategy may be useful in related research fields as a contribution to the synthetic methods available for the generation of a variety of macrocycles, and will be the goal of future investigations.

Conflicts of interest

The authors declare no conflict of interest.

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Notes and references

‡ No preference for either (*S,S*)- or (*R,R*)-*N,N'*-dimethyl-1,2-diphenyl-1,2-ethylenediamine enantiomer was observed in the reaction.

§ The observed optical rotation of synthetic **1** ($[\alpha]_D^{25} = +128.6$) was found to be different from the reported value^{3a} ($[\alpha]_D = -347$). The reason for this discrepancy is unclear at the present as it could be attributed to a variety of factors.

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