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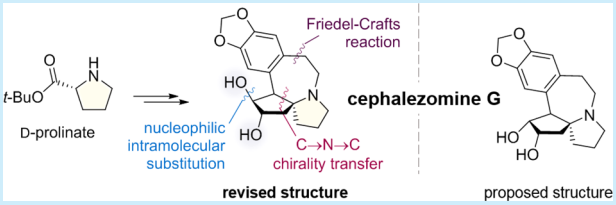
Total Synthesis and Structural Elucidation of (−)-Cephalezomine G

Hongjun Jeon, Hyunkyung Cho, and Sanghee Kim*

College of Pharmacy, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul, 08826, Republic of Korea

Supporting Information

ABSTRACT: The first asymmetric synthesis and configurational elucidation of (−)-cephalezomine G was achieved. The highly functionalized Cα-substituted proline derivative was prepared from D-proline as the only chiral source via a C → N → C chirality transfer method consisting of stereoselective *N*-allylation and [2,3]-Stevens rearrangement. The azaspiranic tetracyclic backbone was constructed using ring-closing metathesis and the Friedel−Crafts reaction. Two contiguous hydroxyl groups were introduced in the later stages.



Cephalotaxus alkaloids have been fascinating synthetic targets for several decades due to their interesting structures and biological activities.[1−3] The principal structural feature of this family of alkaloids is an azaspiranic tetracyclic backbone (Figure 1), which comprises a benzazepine ring system (rings A and B) and a 1-azaspiro[4.4]nonane unit (rings C and D). More than 70 compounds have been isolated to date.[1e] A representative member of this family is (−)-cephalotaxine (**1**), which was isolated from *Cephalotaxus harringtonii* in 1963.[4] One of its naturally occurring ester derivatives, homoharringtonine (**2**), was approved by the FDA in 2012 as a drug for the treatment of chronic myeloid leukemia.[5] The other representative member is drupacine (**3**), which is a C-11 oxygenated analogue of cephalotaxine (**1**).[6] Cephalezomine A (**4**) has a drupacine-type skeleton and the same oxygenated side chain as homoharringtonine.[7] From the same plant from which cephalezomine A was isolated, several other alkaloids were also isolated including cephalezomines G and H.[8] They are unique compared to other *Cephalotaxus* alkaloids in that their C-2 carbons present a lower oxidation state. The structure of cephalezomine H was proposed as the 2*β*,3*α*-*anti*-diol, but it was revised as the *β*,*β*-*syn*-diol **5** by the first total synthesis by Ishibashi.[9] The structure of cephalezomine G was initially proposed as the *α*,*α*-*syn*-diol **6**.[8] It is interesting to note that **6** was synthesized before the isolation of cephalezomine G from a natural source.[10] Later, the structure of cephalezomine G was reproposed by the Ishibashi group as the 2*α*,3*β*-*anti*-diol **7** based on the $^{1}H-^{1}H$ NMR coupling constant.[9] The reproposed structure of cephalezomine G has not yet been validated. Thus, this uncertainty necessitates clarification.

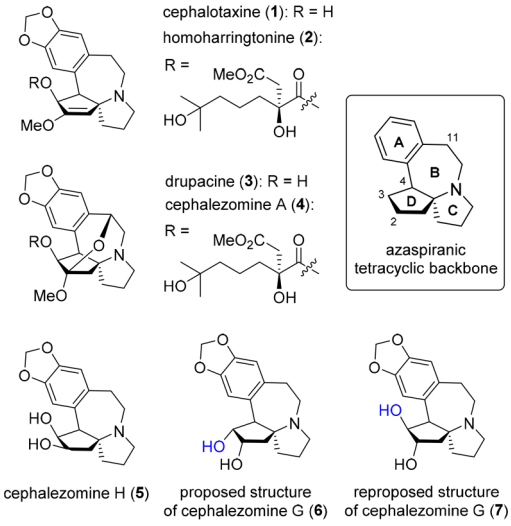


Figure 1. Structures of *Cephalotaxus* alkaloids (**1**−**7**) and their azaspiranic tetracyclic backbone.

Cephalezomine G characteristically contains four contiguous stereogenic centers in the cyclopentane D ring, one of which is a tetrasubstituted carbon atom bearing a nitrogen substituent. The selective installation of these stereogenic centers would be a major synthetic challenge, especially considering the sterically encumbered nature of the D ring. In addition, the efficient construction of the embedded azaspirocycle system is also demanding. We herein describe the configurational elucidation of (−)-cephalezomine G and its first total synthesis relying on our recently reported chirality transfer method for the asymmetric synthesis of *α*-substituted proline derivatives.[11]

We planned to synthesize both the originally proposed and reproposed structures of cephalezomine G, **6** and **7**, for unambiguous structural validation. After disconnection of the B ring via intramolecular Friedel−Crafts cyclization, we identified olefinic compound **I** as a possible platform to obtain stereochemicial diversity of two hydroxyl groups (Scheme 1). We envisioned accessing **I** from Cα-substituted proline derivative **II** through construction of a cyclopentene ring by way of a ring-closing metathesis (RCM) reaction. The proline derivative **II** was expected to be asymmetrically prepared from

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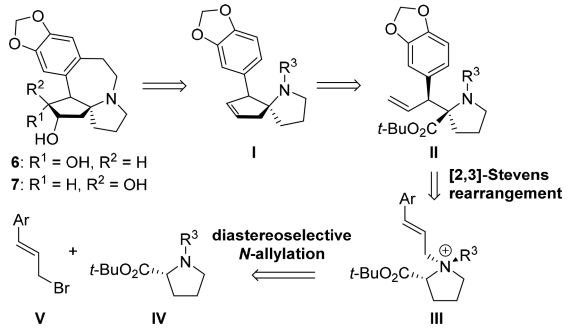
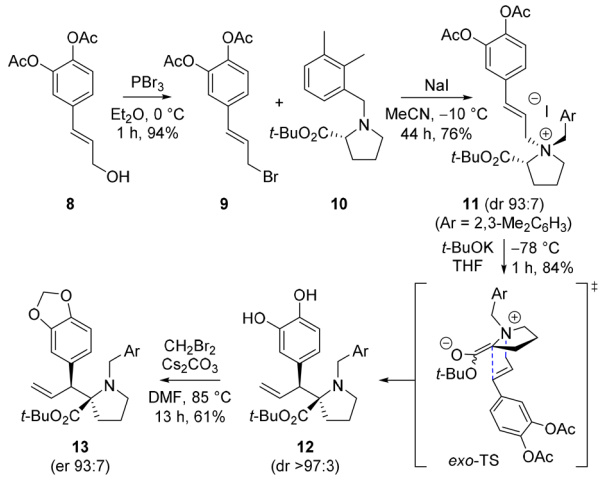
Scheme 1. Retrosynthetic Route for the Originally Proposed and Reproposed Structure of Cephalezomine G (6 and 7)



D-proline ester **IV** without the aid of external chiral sources by the method that we developed recently.[11] In this transformation, the diastereoselective *N*-allylation with cinnamyl bromide **V** was required to generate the quaternary ammonium salt **III** exhibiting *N*-chirality. We previously found that high diastereoselectivity was obtained when a 2,3-disubstituted benzyl group was used as an *N*-substituent (R^3). The subsequent *exo*-selective [2,3]-Stevens rearrangement of **III** would deliver the enantiomerically enriched proline derivative **II**, having a relative stereochemistry required for an azaspiranic tetracyclic backbone, by transferring the generated *N*-chirality back to the α-carbon chirality.

Although cephalezomine G contains a methylenedioxy group on the aromatic ring, we started our synthesis with the known (*E*)-cinnamyl alcohol **8**, containing a 3,4-diacetoxy group (Scheme 2). This is because our previous study

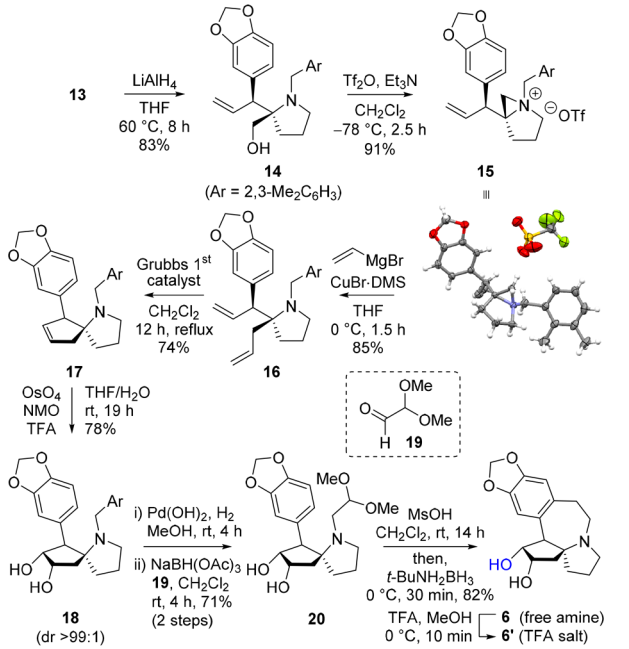
Scheme 2. Construction of Cα-Substituted Prolinate via *N*-Allylation and [2,3]-Stevens Rearrangement



demonstrated that the cinnamyl aromatic ring having an electron-withdrawing substituent shows better diastereoselectivity in *N*-allylation compared to that with an electron-donating substituent. Cinnamyl alcohol **8** was prepared in a two-step process from caffeic acid, according to the literature.[12] Bromination of cinnamyl alcohol **8** afforded cinnamyl bromide **9**. *N*-Quaternization of 2,3-dimethylbenzyl D-proline *tert*-butyl ester (**10**) was performed with the obtained cinnamyl bromide **9** in the presence of sodium iodide[13] at −10 °C to afford ammonium salt **11** in 76% yield with a good diastereomeric ratio of 93:7.[14] When ammonium salt **11** was treated with *t*-BuOK in THF for the [2,3]-Stevens rearrangement,[15] the desired *exo* product **12** was obtained as the major diastereomer (dr >97:3).[14] The reaction conditions led to partial deacetylation of the product. Complete deacetylation was achieved upon basic workup affording catechol **12** in 84% yield. Treatment of rearrangement product **12** with dibromomethane produced methylenedioxy compound **13**. The enantiomeric ratio of **13** (93:7)[16] was essentially the same as the diastereomeric ratio of **11**, which indicates that the diastereopurity of the *N*-quaternization product was completely transmitted to the enantiopurity of the [2,3]-Stevens rearrangement product.

Having achieved the diastereo- and enantioselective synthesis of substituted proline **13**, we next focused on the construction of the azaspirocycle system using an ester group and olefin moiety. To this end, the sterically hindered *tert*-butyl ester group of **13** was first reduced with $LiAlH_4$ to the corresponding primary alcohol (Scheme 3). We successfully

Scheme 3. Synthesis of the Originally Proposed Structure of Cephalezomine G (6)



converted the hydroxymethyl group of **14** to the allyl group in **16** via aziridinium intermediate[17] **15**, the identity of which was confirmed by X-ray crystallography. The RCM of diene **16** was successfully performed with the Grubbs first generation catalyst, furnishing the azaspirocycle **17**.

The obtained RCM product **17** was subjected to dihydroxylation conditions with OsO_4 to generate *cis*-diol **18** as the only observable diastereomer. Without trifluoroacetic acid, diol **18** was obtained only in very low yield (16%). For the formation of the benzazepine ring system by intramolecular Friedel–Crafts cyclization, a two-carbon unit was introduced in two steps by removing the benzyl-type *N*-substituent followed by reductive amination with 2,2-dimethoxyacetaldehyde (**19**) to afford acetal **20**. Carbon–carbon bond formation by Friedel–Crafts reaction was accomplished with an excess of methanesulfonic acid to produce the corresponding enamine intermediate, which was directly reduced in a one-

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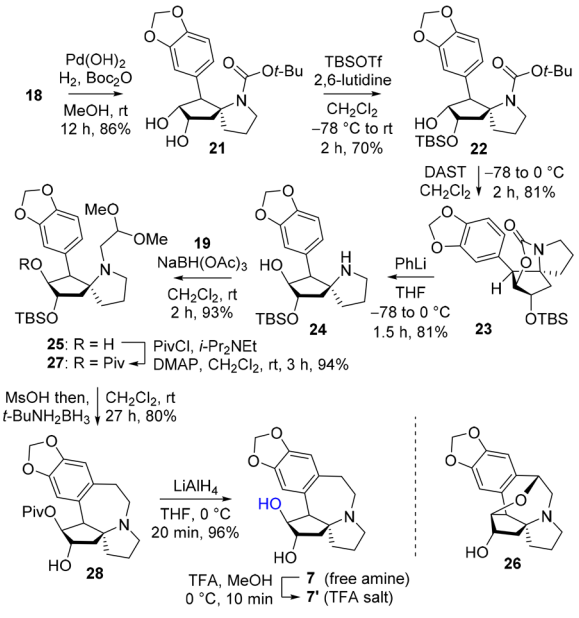
pot process with a borane *tert*-butylamine complex to the originally proposed cephalezomine G (**6**) in high yield.[18]

The ^{1}H NMR spectrum of our synthetic compound **6** in CD_3OD did not match that of the natural product. Because trifluoroacetic acid (TFA) was used as an HPLC eluent additive during the isolation of natural products,[8] the reported data of natural cephalezomine G might represent those of the TFA salt. Comparison of our ^{1}H NMR spectrum of TFA salt **6′** to that reported in CD_3OD revealed very little agreement. However, the ^{1}H and ^{13}C NMR spectra of **6** in $CDCl_3$ were in good agreement with those previously reported for the *α,α-syn*-diol **6**.[10]

We assumed that the correct structure of cephalezomine G is 2*α*,3*β*-*anti*-diol **7**, as proposed by the Ishibashi group.[9] For installation of the *anti*-stereochemistry of the C-2 and C-3 stereocenters, a number of *trans*-dihydroxylation reactions were first attempted on azaspiranic substrate **17**. The Prévost type reactions were unsuccessful, and no product was observed. Attempts for the epoxidation and opening of the epoxide proved unsuccessful. The attempts to effect inversion of configuration of the C-3 hydroxyl groups in **18** and **6**, through a reaction sequence of C-2 hydroxyl group protection followed by S_N2 type displacement at C-3 with nucleophiles, were met with failure. We attributed these failures to the steric congestion around the cyclopentene ring which prevents the facile access of external nucleophiles from the *β*-face.

To overcome this steric hindrance problem, we utilized the nitrogen atom on the *β*-face to deliver an oxygen nucleophile to the C-3 position in an intramolecular fashion. We chose the *N*-Boc group as an internal nucleophile. Replacement of the benzyl-type *N*-substituent in **18** with a Boc group was achieved by hydrogenolysis in the presence of Boc_2O to provide **21** (Scheme 4). Monoprotection of a less hindered C-2 hydroxyl group in diol **21** was achieved with TBSOTf at low temperature to give **22** as a major product with an isomeric ratio of 5:1. The intramolecular nucleophilic substitution of the C-3 hydroxyl group was successfully accomplished by treatment of **22** with diethylaminosulfur trifluoride (DAST) to yield the seven-membered cyclic carbamate **23**.[19]

Scheme 4. Completion of the Total Synthesis of Cephalezomine G (7)



The cyclic carbamate group of **23** was cleaved by the action of phenyl lithium to give amino alcohol **24**. Under several standard conditions including KOH/EtOH and HCl, no desired product was obtained.[20] As in the synthesis of the originally proposed structure of cephalezomine G (**6**), an external two carbon source was introduced by reductive amination with **19** to afford compound **25**. Unlike the previous case, acid-catalyzed Friedel−Crafts reaction of **25** yielded benzyl ether **26** with concomitant deprotection of the TBS group. The formation of **26** might result from the capture of the oxonium intermediate by the C-3 hydroxyl group. Reduction at the benzylic position of **26** was difficult probably due to the incomplete orbital overlap between the C−O *σ*-bond and the *π*-system of benzene.[21] Thus, the C-3 hydroxyl group was protected as a pivalate **27** to prevent its involvement in the Friedel−Crafts reaction. Subsequent one-pot Friedel−Crafts reaction and reduction gave benzazepine **28**. Deprotection of the pivaloyl group of **28** with $LiAlH_4$ finally led to compound **7**.

^{1}H NMR spectra of our synthetic compound **7** did not match those of the natural product. However, spectroscopic data for its TFA salt **7′** were identical to those reported for the natural product. The optical rotation sign and value obtained for **7′** {$[\alpha]_D^{20}$ = −46.9 (*c* 1.8, MeOH), lit.[8] $[\alpha]_D$ = −48 (*c* 1.8, MeOH)} were also in good agreement, which confirmed that the absolute configuration of natural (−)-cephalezomine G is 2*S*,3*S*,4*S*,5*S*.

In conclusion, we have achieved the first total synthesis and structural elucidation of (−)-cephalezomine G by using our recently developed chirality transfer method. D-Proline was the only chiral source for this asymmetric synthesis. [2,3]-Stevens rearrangement delivered the C*α*-substituted proline with the relative stereochemistry required for an azaspiranic tetracyclic backbone. Two contiguous stereogenic centers bearing hydroxyl groups were installed in the late stages. For the introduction of a hydroxyl group in the sterically hindered face, an internal *N*-Boc group was utilized. With this achievement as a stepping stone, we are currently investigating asymmetric synthesis of other *Cephalotaxus* alkaloids and their analogues, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00036.

Experimental procedures, analytical data, and copies of the ^{1}H and ^{13}C NMR spectra for all new products (PDF)

Accession Codes

CCDC 1864102 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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AUTHOR INFORMATION

Corresponding Author

*E-mail: pennkim@snu.ac.kr.

ORCID

Sanghee Kim: 0000-0001-9125-9541

Notes

The authors declare no competing financial interest.

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(13) Sodium iodide was used for acceleration of the reaction.

(14) The diastereomeric ratio was determined by ^{1}H NMR analysis.

(15) For a review of Stevens rearrangement of ammonium ylides, see: *Tetrahedron* **2006**, *62*, 1046 and references therein.

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