Total Synthesis Hot Paper

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Collective Asymmetric Total Synthesis of C-11 Oxygenated *Cephalotaxus* Alkaloids

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Abstract: *While numerous studies pertaining to the total synthesis of Cephalotaxus alkaloids have been reported, only two strategies have been reported to date for the successful synthesis of the C-11 oxygenated subset, due to the additional synthetic challenge posed by the remote C-11 stereocenter. Herein, we report the collective asymmetric total synthesis of C-11 oxygenated Cephalotaxus alkaloids using a chiral proline both as a starting material and as the only chirality source. A tetracyclic advanced intermediate was synthesized in a highly stereoselective manner from* L*-proline in 8 steps involving sequential chirality transfer steps such as a diastereoselective N-alkylation, stereospecific Stevens rearrangement and intramolecular Friedel–Crafts reaction via an unusual O-acyloxocarbenium intermediate. From a common intermediate, the asymmetric total synthesis of six C-11 oxygenated Cephalotaxus alkaloids was completed by a series of oxidation state adjustments.*

Introduction

For half a century, *Cephalotaxus* alkaloids have been popular synthetic targets due to their intriguing structures and biological activities.[1] The alkaloids of this family have several interesting biological activities, including antileukemic and antitumor activities. The characteristic structural feature of these alkaloids is an azaspiranic tetracyclic scaffold (Figure 1). More than 70 compounds have been isolated from natural sources so far.[1b] The first isolated and most representative member of this family is (−)-cephalotaxine (**1**).[2] One of its naturally occurring ester derivatives, homoharringtonine (**2**), was approved by the FDA in 2012 as an antileukemia drug.[3] The other representative member is drupacine (**3**) which was isolated from *Cephalotaxus harringtonia*.[4] Unlike cephalotaxine (**1**), this alkaloid possesses an oxygen function at C-11. 11-Hydroxycephalotaxine (**4**), which is readily converted to **3** under acidic conditions, was also isolated from the same plant from which **3** was isolated.[4] To

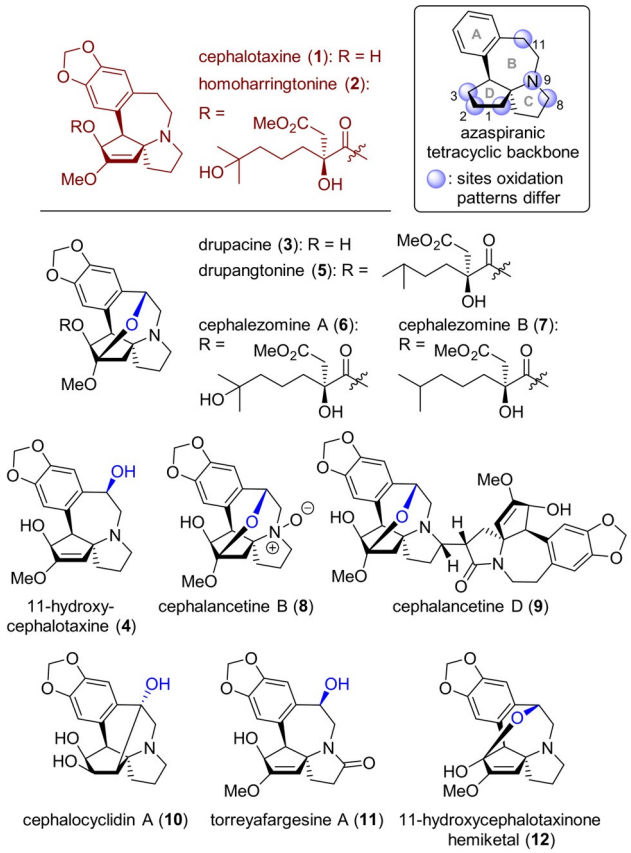

Figure 1. The structures of representative *Cephalotaxus* alkaloids and the C-11 oxygenated subset members.

date, ten C-11 oxygenated *Cephalotaxus* alkaloids have been isolated, including three ester derivatives of **3** (**5**–**7**)[5] and an *N*-oxide derivative cephalancetine B (**8**).[6] A dimeric alkaloid cephalancetine D (**9**)[6] and pentacyclic cephalocyclidin A (**10**)[7] also belong to this subset. Recently, torreyafargesine A (**11**) and 11-hydroxycephalotaxinone hemiketal (**12**) were identified from *Torreya fargesii* Franch as new members of the C-11 oxygenated subset.[8] The major structural differences among these alkaloids are the oxidation patterns on their backbone. The biological activities of this subset of alkaloids have not yet been thoroughly explored presumably because of the limited supply from nature.

The key challenges associated with the synthesis of *Cephalotaxus* alkaloids are the construction of the azaspiranic tetracyclic core and the stereocontrolled functionalization of the sterically encumbered cyclopentene D ring. Since the first total syntheses of cephalotaxine (**1**) by Weinreb[9a] and Semmelhack[9b] in 1972, a large number of groups have

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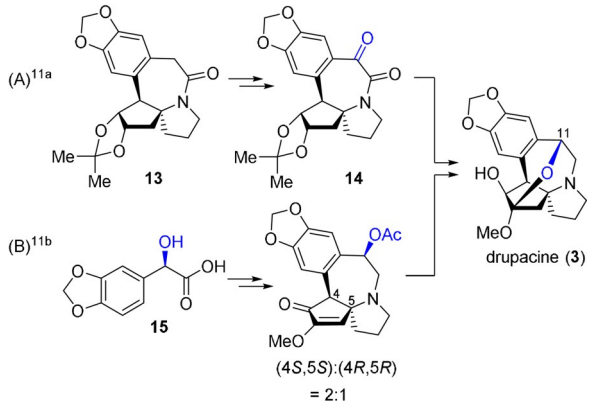
continued to investigate different approaches toward the total synthesis of this family of alkaloids.[9,10] A number of elegant total syntheses of cephalotaxine (**1**) and its relatives have been accomplished. On the other hand, research into the synthesis of the C-11 oxygenated subset of *Cephalotaxus* alkaloids has made little progress, presumably because of the additional synthetic challenge posed by the remote C-11 stereocenter. Only two successful total syntheses of this subset of alkaloids have been reported: the first total synthesis of racemic drupacine (**3**) and 11-hydroxycephalotaxine (**4**) was disclosed by Fuchs in 1990,[11a] and the first asymmetric synthesis of drupacine (**3**) was achieved by Stoltz in 2007, albeit with low stereoselectivity.[11b] Fuchs introduced a C-11 hydroxyl group from tetracyclic lactam **13** through two-step α-oxidation followed by stereoselective reduction of the resulting α-keto lactam **14** (Scheme 1 a). Stoltz employed chiral mandelic acid **15** as the source of the C-11 hydroxyl group (Scheme 1 b).

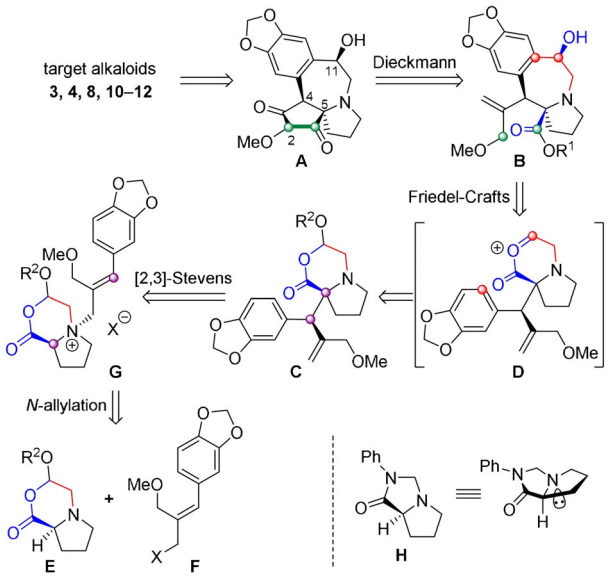


Scheme 1. Previous synthesis of drupacine (**3**).

In addition to their biological activities, our synthetic interest in the C-11 oxygenated subset of *Cephalotaxus* alkaloids arose from the possibility of using a chiral proline both as a starting material and as the only chirality source to generate all the requisite stereocenters, including the remote C-11 stereocenter. In this report, we present our investigations toward the first and asymmetric total synthesis of cephalancetine B (**8**), cephalocyclidin A (**10**), torreyafargesine A (**11**) and 11-hydroxycephalotaxinone hemiketal (**12**) as well as the stereoselective asymmetric total synthesis of drupacine (**3**) and 11-hydroxycephalotaxine (**4**).[12] One of the keys to the success of this collective asymmetric synthesis was the newly designed bicyclic proline derivative which imparted almost complete stereoselectivity in the sequential chirality-transfer steps and allowed the facile construction of seven-membered B ring.

Results and Discussion

We designed a synthetic scheme starting from the amino acid proline that would permit access to a maximal number of C-11 oxygenated *Cephalotaxus* alkaloids. Retrosynthetic

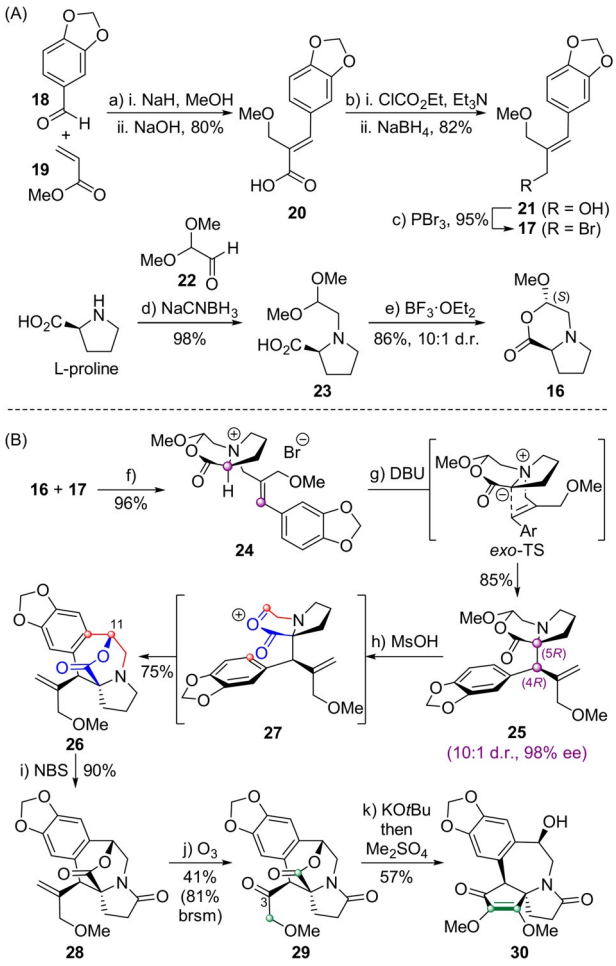


Scheme 2. Retrosynthetic route for the C-11 oxygenated *Cephalotaxus* alkaloids.

modification of the functional groups in a 1-azaspiro-[4.4]nonane unit (C and D rings) of the target alkaloids afforded **A** (Scheme 2). Deconstruction of the 1,3-cyclopentanedione ring (D ring) of **A** by Dieckmann condensation followed by ozonolysis led to **B** as a hypothetical intermediate. The presence of an ester function and a C-11 hydroxyl group on the same face of structure **B** suggested a strategy that would secure the C-11 stereocenter with the concomitant formation of seven-membered B ring. The planned stereocontrolled construction of **B** included the connection of these functional groups and the intramolecular Friedel–Crafts reaction of cyclic *O*-acyl hemiacetal **C**, which would involve an *O*-acyloxocarbenium ion **D** as an intermediate. We envisaged that the bicyclic system of **D** might impart complete diastereoselectivity by permitting the approach of the aromatic nucleophile only from a specific face of the oxocarbenium electrophile.

We planned asymmetrically accessing **C** from the bicyclic L-proline derivative **E** based on the concept of C-N-C chirality transfer[13] which comprises of diastereoselective *N*-quaternization (**E**/**F** to **G**) and the subsequent stereospecific [2,3]-Stevens rearrangement (**G** to **C**). According to this retrosynthetic scheme, all of the stereochemistry in the target alkaloids would be derived exclusively from a single stereocenter of proline. Prior to this study, as an approach for the conservation of chirality during α-substitution of proline, we have developed a couple of C-N-C chirality transfer methods.[13c–e] For the high diastereoselectivity during the *N*-quaternization with allylic electrophiles, one method employed a rigid nitrogen-fused bicyclic derivative **H** in which the nitrogen lone-pair electrons were forced to be located on the convex face.[13c] Unlike [5,5]-bicyclic compound **H**, the designed [5,6]-bicyclic system **E** would be conformationally flexible. Thus, unclear was the stereoselectivity in the *N*-quaternization of **E** which was critical to conserve the chirality of proline.

Assuming success in our synthetic plan especially the chirality transferring transformations, synthetic efforts commenced with the preparation of the newly designed bicyclic proline derivative **16** and its *N*-alkylation partner cinnamyl halide **17** (Scheme 3a). The synthesis of cinnamyl halide **17** started from the condensation between piperonal (**18**) and an anion formed by the Michael addition of methoxide to acrylate **19**.[14] Subsequent one-pot hydrolysis afforded cinnamic acid **20**, in which a C-2 methoxy group (natural product numbering) was installed. Acid **20** was reduced to the corresponding alcohol **21**, which was brominated to afford **17** in good overall yield. The bicyclic proline derivative **16** was prepared from L-proline in two steps. Reductive amination of L-proline with 2,2-dimethoxyacetaldehyde (**22**) afforded **23** in an almost quantitative yield. Various acid catalysts and solvents were explored to generate bicyclic product **16** in high diastereoselectivity and yield (see the Supporting Information for details). The optimal result was obtained when **23** was treated with $BF_3{\cdot}OEt_2$ in MeCN. The major isomer was obtained in a diastereomeric ratio of 10:1 and was assigned as **16** with (*S*)-stereochemistry at the anomeric center.[15] Our computational and experimental studies suggested that this reaction is under thermodynamic control (see the Supporting Information for details).



Scheme 3. Stereoselective synthesis of advanced intermediate **30**. Reagents and conditions: a) i. **18** (1.0 equiv), NaH (1.8 equiv), MeOH (1.8 equiv), **19** (1.5 equiv), THF, 0 °C to rt, 16 h; ii. NaOH(aq), reflux, 30 min, 80%; b) i. $ClCO_2Et$ (1.0 equiv), Et_3N (1.0 equiv), THF, 0 °C, 30 min; ii. $NaBH_4$ (4.0 equiv), MeOH, 0 °C, 1 h, 82%; c) PBr_3 (1.5 equiv), Et_2O, 0 °C, 1 h, 95%; d) **22** (1.0 equiv), $NaBH(OAc)_3$ (1.0 equiv), CH_2Cl_2, 0 °C to rt, 16 h, 98%; e) $BF_3{\cdot}OEt_2$ (8.0 equiv), MeCN, 0 °C to rt, 20 h, 86% (10:1 d.r.); f) **16** (1.0 equiv), **17** (1.05 equiv), MeCN, rt, 24 h, 96%; g) DBU (1.5 equiv), CH_2Cl_2, −78 °C, 1 h, 85% (10:1 d.r., 98% *ee*); h) MsOH (10 equiv), CH_2Cl_2, 0 °C to reflux, 5 h, 75%; i) NBS (2.5 equiv), 1,4-dioxane/H_2O (9:1), rt, 1.5 h, 90%; j) O_3, CH_2Cl_2, −78 °C, 1 h, then Me_2S (10 equiv), rt, 16 h, 41% (81% brsm); k) KO*t*Bu (1.0 equiv), THF, 0 °C, 1 h, then Me_2SO_4 (5.0 equiv), rt, 16 h, 57%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. MsOH = methanesulfonic acid; NBS = *N*-bromosuccinimide.

With two fragments **16** and **17** in hand, their ligation through *N*-alkylation was investigated (Scheme 3b). The reaction in MeCN without any additive at room temperature was smooth and completely stereoselective, providing the quaternary ammonium salt **24** as the only detectable diastereomer in an excellent yield. The NOESY spectrum indicated that **24** was formed as the *cis*-fused isomer as shown. To understand the excellent stereoselectivity in the *N*-quaternization, we carried out a Density Functional Theory (DFT) computational investigation (Figure 2). The computational results revealed that the nitrogen-fused bicycle **16** slightly favors the *trans*-fused conformer, while the energy barrier of *N*-inversion in the *trans*-fused form was predicted to only be 5.1 kcal mol^{-1} (Figure 2a). These results suggested that bicycle **16** is conformationally rather flexible, as we had initially expected (see the Supporting Information for details). On the other hand, the obtained product *cis*-**24** is thermodynamically more favored than its *trans* isomer (Figure 2b). The computed transition state energy for *cis*-**24** (TS 1) is lower than that for *trans*-**24** (TS 2). This energy profile suggested that the kinetics

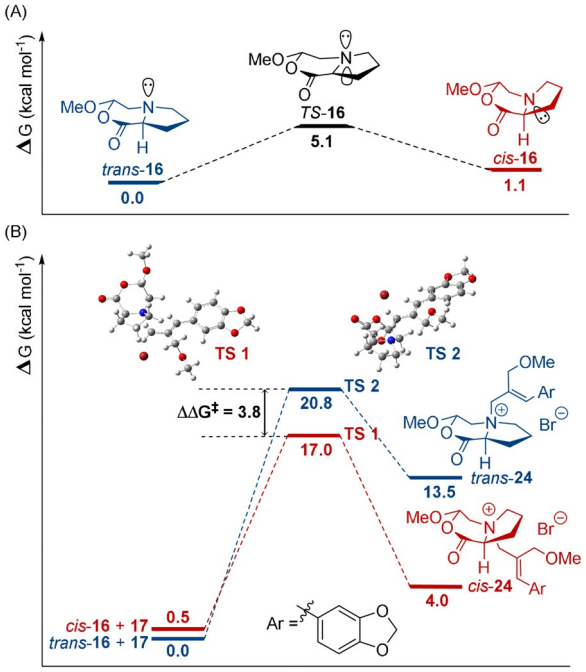


Figure 2. DFT computational investigations calculated at the B3LYP/6–31 + G(d) level of theory. A) Energy profiles of **16** in MeCN. B) Energy profiles for the diastereoselective *N*-quarternization of **16** with **17**.

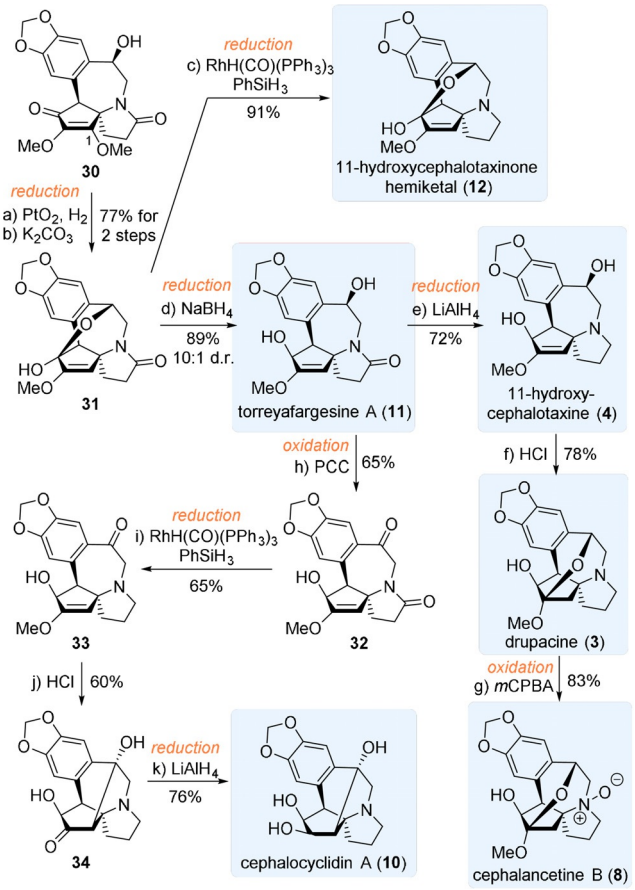
of the *N*-quaternization of **16** are most likely controlled by the Curtin–Hammett principle (see the Supporting Information for details).[16]

When **24** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 at −78 °C for the [2,3]-Stevens rearrangement, **25** was obtained as the major diastereomer (dr = 10:1).[17] The configuration of **25** was determined to be (4*R*,5*R*) by X-ray crystallographic analysis of **26** (see the Supporting Information for details) after the Friedel–Crafts reaction (vide infra) and confirmed later by total synthesis. The [2,3]-Stevens rearrangement proceeded via an *exo* transition state as shown and this can be rationalized by the repulsion between the anomeric methoxy group and the CH_2OMe substituent in the *endo* transition state. The *ee* value of **25** was 98%, which indicated that the Cα-chirality of the proline derivative **16** was successfully conserved via the C-N-C chirality transfer process.

With the key intermediate **25** in hand, we proceeded to perform the intramolecular Friedel–Crafts reaction to construct the seven-membered B ring and install the C-11 stereocenter. This transformation would involve an *O*-acyloxocarbenium ion (AOI), which is a very reactive subfamily of the oxocarbenium ion class, as an intermediate. AOIs have been less explored in organic synthesis than other oxocarbenium ions, probably due to the lack of an efficient method for AOI formation.[18] We expected that AOI intermediate **27** would be formed from **25** under acidic conditions, analogous to the widely applied method for the formation of the *N*-acyliminium ion from *N*-acyl hemiaminal ether. After some trials, we found that the treatment of *O*-acyl hemiacetal **25** with MsOH as an acid catalyst in CH_2Cl_2 led to the formation of **26** as the only regio- and stereoisomer, the identity of which was confirmed by X-ray crystallography. This efficient seven-membered ring formation reaction installed the oxygen function at C-11 with the desired stereochemistry, presumably through geometric constraints where only the *Re* face of oxocarbenium moiety is accessible for nucleophilic attack as shown in intermediate **27**. The postulated AOI intermediate **27** was not observed during the reaction process apparently because of the high reactivity and instability. However, the lactone functionality in the product strongly suggested that the reaction proceeded through the cyclic AOI intermediate **27**.

With a route to **26** secured, we proceeded to construct the D ring with two substituents at C-4 and C-5. Toward this end, we employed Dieckmann condensation. Prior to the oxidative cleavage of the methylene moiety of **26** to afford the bis-carbonyl substrate for the Dieckmann ring closure, the tertiary amine of **26** was oxidized to amide using NBS to obtain **28** with almost perfect regioselectivity.[19] This step was necessary in this stage to synthesize torreyafargesine A (vide infra) and also to prevent the susceptible skeletal cleavage via retro-Mannich type fragmentation; the cephalotaxine skeleton is susceptible to cleavage via retro-Mannich type fragmentation when a carbonyl group was present at the C-3 position.[9g,i,10a,11b,20] Ozonolysis of **28** in CH_2Cl_2 solvent at −78 °C successfully afforded the desired ketone **29** along with the recovered starting material (81% brsm). The KO*t*Bu-mediated Dieckmann ring closure of **29** yielded the tetracyclic system, and in situ etherification of enolate intermediate with dimethyl sulfate afforded **30** as the only regioisomer.

Having constructed the carbon framework of *Cephalotaxus* alkaloids, we sought to streamline our total synthesis (Scheme 4). The target subset of C-11 oxygenated alkaloids differ in their oxidation patterns. Thus, chemo- and regioselective oxidation state adjustments were investigated to convert the advanced intermediate **30** to the target alkaloids. First, the oxidation state of the C-1 atom of **30** was reduced to give **31** via a two-step sequence involving hydrogenation using Adam's catalyst and base-promoted β-elimination. According to NMR analysis, the obtained product **31** predominantly existed in a hemiketal form. The reduction of the lactam moiety of **31** using $RhH(CO)(PPh_3)_3$ and phenylsilane[21] afforded 11-hydroxycephalotaxinone hemiketal (**12**). Detailed NMR analysis revealed that **12** existed as an 8:1 mixture of hemiketal and ketone forms in $CDCl_3$.[22] Torreya-



Scheme 4. Completion of the total synthesis of C-11 oxygenated *Cephalotaxus* alkaloids. Reagents and conditions: a) PtO_2, H_2, EtOH, rt, 16 h; b) K_2CO_3 (5.0 equiv), MeOH, reflux, 5 h, 77% for 2 steps; c) $RhH(CO)(PPh_3)_3$ (0.15 equiv), $PhSiH_3$ (5.0 equiv), THF, rt, 1 h, 91%; d) $NaBH_4$ (30 equiv), MeOH, 0 °C to rt, 1 h, 89% (10:1 d.r.); e) $LiAlH_4$ (12 equiv), THF, 0 °C to rt, 16 h, 72%; f) 1 N HCl(aq)/THF (1:1), rt, 48 h, 78%; g) *m*CPBA (1.0 equiv), CH_2Cl_2, 0 °C, 30 min, 83%; h) PCC (1.2 equiv), CH_2Cl_2, rt, 3 h, 65%; i) $RhH(CO)(PPh_3)_3$ (0.15 equiv), $PhSiH_3$ (5 equiv), THF, rt, 2 h, 65%; j) 1 N HCl in 1,4-dioxane, rt, 30 min, 60%; k) $LiAlH_4$ (4.3 equiv), THF, 0 °C, 30 min, 76%. *m*CPBA = 3-chloroperoxybenzoic acid; PCC = pyridinium chlorochromate.

fargesine A (**11**) could also be obtained from **31** by the reduction of the hemiketal moiety using an excess amount of $NaBH_4$. From **11**, a series of natural products were readily accessible. The reduction of the lactam moiety of **11** afforded 11-hydroxycephalotaxine (**4**), which was converted to drupacine (**3**) under acidic conditions. Treatment of *m*CPBA to **3** provided cephalancetine B (**8**).

The pentacyclic alkaloid cephalocyclidin A (**10**) was also accessible from **11**, similar to the proposed biosynthetic pathway.[7] The oxidation of the 11-hydroxy group of **11** using PCC afforded **32** in a moderate yield (65%) along with a small amount of compound **31** (11%). The reduction of the lactam moiety of **32**, using the identical reaction conditions employed for the chemoselective reduction of **31**, provided **33**.[23] The acidic hydrolysis of the methyl enol ether of **33** was accompanied by the desired intramolecular aldol reaction and led to the formation of the pentacycle **34**. Finally, cephalocyclidin A (**10**) was obtained by the reduction of **34** using $LiAlH_4$. The spectral data and optical rotations of all obtained compounds were in good agreement with those of natural products. Overall, six C-11 oxygenated *Cephalotaxus* alkaloids were synthesized from the common intermediate **31**.

Conclusion

In conclusion, we have achieved stereoselective asymmetric total synthesis of six C-11 oxygenated *Cephalotaxus* alkaloids in 11–15 steps from L-proline (12–16 steps from piperonal). The total number of steps from commercially available materials are comparable to those reported for asymmetric synthesis of *Cephalotaxus* alkaloids without an oxygen at C-11. Our synthesis minimized the need for protecting-group manipulations. L-Proline was utilized both as a starting material and as the only chirality source to generate all the requisite stereocenters. Key to the success of this concise synthesis was a three-step sequential transformation of the proline derived nitrogen-fused bicycle **16** into the far more complex ring structure **26** with chirality propagation. This complexity-generating sequence involved an *N*-allylation, [2,3]-Stevens rearrangement, and intramolecular Friedel–Crafts reaction via an unusual AOI intermediate. The azaspiranic tetracyclic scaffold of *Cephalotaxus* alkaloids was readily constructed from **26**. Using **30** as an advanced intermediate, the total synthesis of six target alkaloids was completed without problem of skeletal cleavage by a series of selective oxidation state adjustments. This synthesis presents a good example of divergent total syntheses of complex natural products and an attractive strategy in terms of chiral economy. The concise synthetic route to C-11 *Cephalotaxus* alkaloids would enable investigations into their biological activities, which have been relatively less explored. Further applications of the proline-derived nitrogen-fused bicycle **16** and its related acyclic amino acid derivatives to the synthesis of complex molecules are underway in our group.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · asymmetric synthesis · chirality transfer · collective synthesis · total synthesis

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[23] Like **12**, compounds **32** and **33** exist as mixtures of hemiketal and ketone forms in $CDCl_3$. See the Supporting Information for details.

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