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Stereoselective Total Synthesis of Hainanolidol and Harringtonolide via Oxidopyrylium-Based [5 + 2] Cycloaddition

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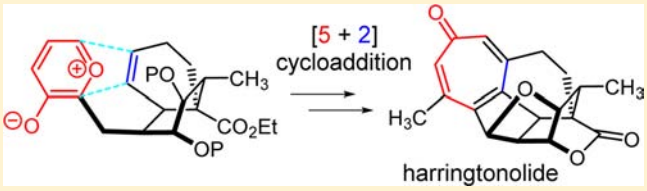
Supporting Information

ABSTRACT: The tetracyclic carbon skeleton of hainanolidol and harringtonolide was efficiently constructed by an intramolecular oxidopyrylium-based [5 + 2] cycloaddition. An anionic ring-opening strategy was developed for the cleavage of the ether bridge in 8-oxabicyclo[3.2.1]octenes derived from the [5 + 2] cycloaddition. Conversion of cycloheptadiene to tropone was realized by a sequential [4 + 2] cycloaddition, Kornblum−DeLaMare rearrangement, and double elimination. The biomimetic synthesis of harringtonolide from hainanolidol was also confirmed.



1. INTRODUCTION

Harringtonolide, hainanolidol, and fortunolides A and B are representative members of *Cephalotaxus* norditerpenes (**1**−**4**, Figure 1). They have complex architectures featuring a fused

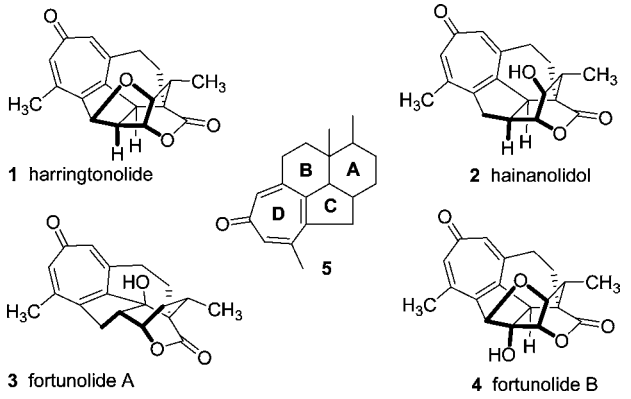


Figure 1. Representative *Cephalotaxus* Norditerpenes.

tetracyclic carbon framework **5**, a cyclohexane ring **A** bearing five or six contiguous stereogenic centers, an unusual tropone ring **D**, and a bridged lactone. The cage-like harringtonolide **1** and fortunolide B **4** have an additional tetrahydrofuran (THF) ring.

Harringtonolide **1** was first isolated in 1978 from *C. harringtonia*, and its structure was assigned unambiguously by X-ray crystallography.[1] In 1979, both **1** (named as hainanolide) and **2** were isolated from *C. hainanensis*.[2] Interestingly, the former was found to possess antineoplastic and antiviral activities, while the latter was inactive.[2,3] This suggests that the THF ring in **1** is important for its bioactivity. Hainanolidol **2** was proposed to be the precursor of harringtonolide **1** as the former could be converted to the latter by transannular oxidation mediated by lead tetraacetate.[4] This biomimetic transformation was validated by identical IR and MS of the semisynthetic and natural **1**. Although the structure of **2** was assigned mainly based on this critical reaction,[4] its yield has never been reported.

Fortunolides **3** and **4** together with hainanolidol **2** were also isolated from *C. fortunei* by Chiu's group in 1999.[5] The first synthesis of hainanolidol **2**, and thus a formal synthesis of harringtonolide **1**, was realized by Mander's group in 1998, featuring an elegant arene cyclopropanation followed by ring expansion strategy for the construction of the tropone moiety.[6] Their attempts toward the preparation of harringtonolide **1** by forming the THF ring at earlier stages have not been fruitful.[7] Recently, significantly more synthetic efforts were devoted to harringtonolide **1**,[8] after the discovery of its remarkably potent and selective anticancer activity by Nay's group in 2008 (IC_{50} = 43 nM for KB tumor cells).[9]

2. RESULTS AND DISCUSSION

To evaluate the therapeutic potential of harringtonolide **1** and related natural products as anticancer agents, we embarked on a synthetic program toward their synthesis. We envisioned that the tropone and lactone in natural products **1** and **2** could be derived from intermediate **6** (Scheme 1). We proposed to construct the tetracyclic carbon skeleton of **6** by an intramolecular [5 + 2] cycloaddition of intermediate **7**, where the oxidopyrylium ion could be prepared from oxidative ring expansion of the furan ring in decalin **8**.[10] The six contiguous stereogenic centers and their associated functional groups in decalin **8** would be derived from known compound **9**, available in two steps diastereoselectively.[11]

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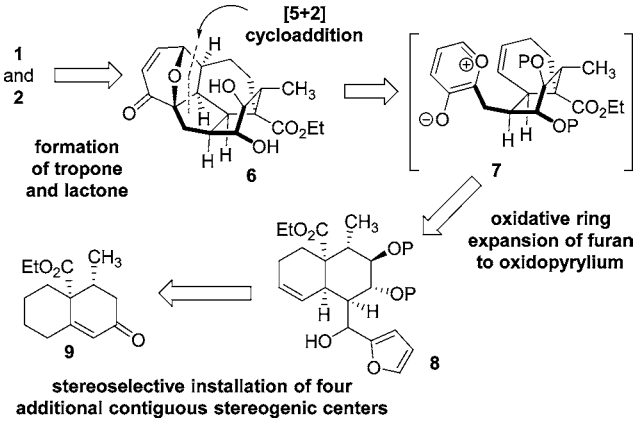
Scheme 1. Retrosynthetic Analysis of 1 and 2



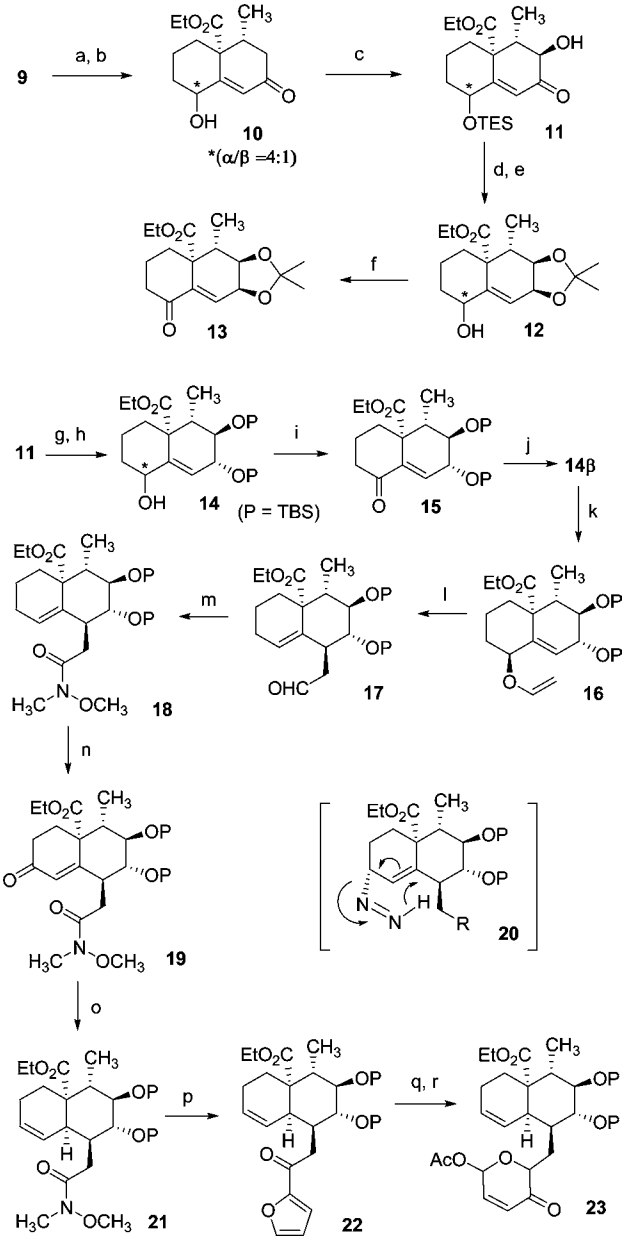
Our synthesis began with oxidation of enone **9** (Scheme 2).[12] A mixture of diastereomeric allylic alcohols in a 4:1 (α/β) ratio was obtained and both of them were converted to ketone **15** eventually. The hydroxyl group in **11** could be installed highly diastereoselectively by dihydroxylation of the corresponding silyl enol ether. Initially, we tried to reduce the ketone in enone **11** to a *trans*-diol by delivering the hydride intramolecularly using $NaBH(OAc)_3$.[13] The fact that the resulting diol could be protected as an acetonide in compounds **12** and **13** suggested that a *cis*-diol was formed.

Reduction of ketone **11** by $NaBH_4$, on the other hand, afforded a diol that could not be protected as an acetonide. This diol was assigned as a *trans*-1,2-diol.[14] Protection of the resulting diol with TBSOTf followed by selective removal of the TES group by TFA afforded allylic alcohol **14**. The desired β-stereochemistry in alcohol **14** could be realized by a sequence of oxidation and diastereoselective reduction,[14] through enone **15**.

A highly stereoselective Claisen rearrangement of vinyl ether **16** yielded bicyclic compound **17** with five contiguous stereogenic centers. An olefin isomerization was required for the conversion of this intermediate to desired compound **8** in addition to the appendage of a furan. We envisaged that a stereoselective [3,3]-sigmatropic rearrangement of intermediate **20** might afford a *cis*-fused decalin derivative with an olefin in the desired position.[15] To this end, aldehyde **17** was converted to enone **19** through allylic oxidation of amide **18**.[16] Treatment of this enone with tosylhydrazine followed by diastereoselective reduction[15c] of the corresponding hydrazone gave us intermediate **20** (R = Weinreb amide), which underwent stereoselective rearrangement to form *cis*-decalin **21**.[15a,b] Ketone **22** was then obtained after the addition of furanyl Grignard reagent to amide **21**. In the absence of $MgBr_2$ salt, the furanyl lithium reagent also reacted with the angular ester group. Reduction of ketone **22** by $NaBH_4$ then afforded a mixture of diastereomeric alcohols **8**. The synthesis of alcohol **8** from aldehyde **17** would be much more efficient if the olefin isomerization could be performed on intermediate **20** where R is a furanyl alcohol. The furan moiety, however, could not be tolerated under the allylic oxidation conditions.

Substrate **23** was then obtained as a mixture of four diastereomers after $VO(acac)_2$-catalyzed oxidative ring expansion[17] of furanyl alcohol **8** followed by esterification. The stereochemistry on the dihydropyran ring of **23** is inconsequential as an achiral oxidopyrylium moiety is formed in the subsequent [5 + 2] cycloaddition. After screening different

Scheme 2. Preparation of a Decalin Derivative with Six Contiguous Stereogenic Centers for [5 + 2] Cycloaddition[a]



[a](a) TMSCl, NaI, Ac_2O, 0 °C to rt, 85%; (b) oxone, $NaHCO_3$, 70%; (c) LDA, TESCl; then OsO_4, NMO, THF/H_2O (10:1), 72% over 2 steps, dr >20:1; (d) $NaBH(OAc)_3$, AcOH, MeCN, 72%, dr >20:1; (e) acetone, TsOH, 74%; (f) Dess–Martin periodinane, 76%; (g) $NaBH_4$; then TBSOTf, 2, 6-lutidine, 84% over two steps, dr >20:1; (h) TFA, 76%; (i) Dess–Martin periodinane, 84%; (j) $NaBH_4$, 93%, dr >20:1; (k) $Hg(TFA)_2$, vinylbutyl ether, Et_3N, 86%; (l) toluene, reflux, 85%, dr >20:1; (m) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; then MeONHMe·HCl, PyBOP, Et_3N, 76% over two steps; (n) $Mn(OAc)_3$, TBHP, 76%; (o) $TsNHNH_2$; then catecholborane and NaOAc, 75% over two steps, dr >20:1; (p) furan, BuLi, $MgBr_2$, 92%; (q) $NaBH_4$; then $VO(acac)_2$, TBHP, DCM, 87% over two steps; (r) Ac_2O, DMAP, pyridine, 91%; (P = TBS).

solvents and bases, we found that the intramolecular Hendrickson [5 + 2] cycloaddition[18] occurred smoothly in refluxing chloroform in the presence of DBU (Scheme 3).[10] Only one stereoisomer was observed for the cycloaddition product **24**. Its structure and relative stereochemistry are

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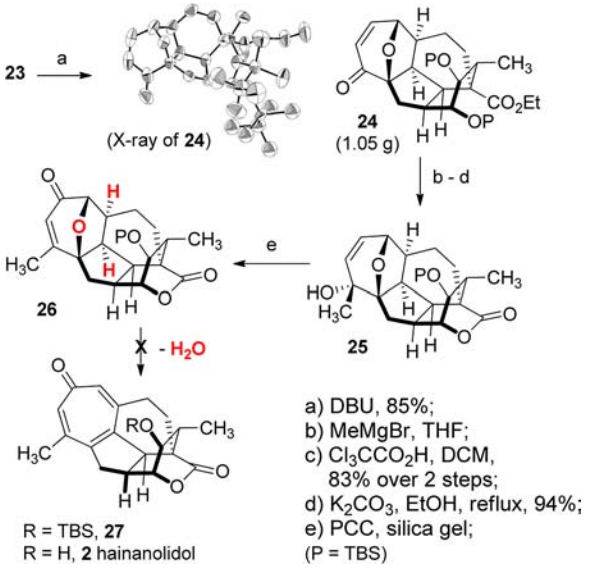
Scheme 3. [5 + 2] Cycloaddition and Attempts for the Synthesis of Tropone by Dehydration



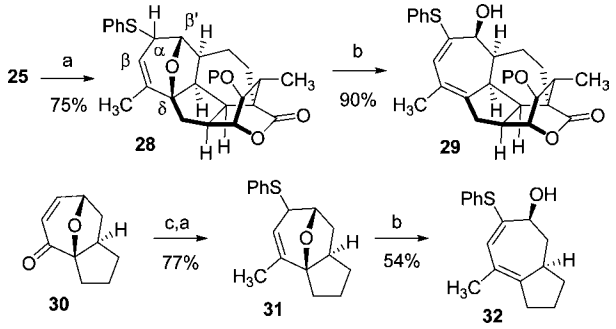
confirmed by X-ray analysis as shown in the Supporting Information. It is worth to mention that the synthesis of product **24** via the key [5 + 2] cycloaddition could be carried out on gram scale.

Addition of methyl Grignard reagent, selective removal of one of the two silyl protecting groups under acidic conditions, and lactonization in the presence of potassium carbonate afforded hexacyclic compound **25**. Although the steric environments of the two silyl ethers in **24** are quite different, strong acids or fluoride salts removed both of them nonselectively. High chemoselectivity was achieved by using trichloroacetic acid. The tertiary allylic alcohol in **25** could undergo a PCC-mediated tandem 1,3-transposition/oxidation sequence to afford enone **26**. The yield of this reaction, however, varied from 10% to 40%.

A dehydration process involving the removal of two Hs and one O highlighted in red in **26** would furnish product **27**, which is just one step away from hainanolidol **2**. We were not able to prepare the tropone moiety directly, however, under various dehydration conditions, regardless the thermodynamic preference for the formation of a nonbenzenoid aromatic tropone ring. We then turned our attention to the reductive cleavage of the ether bridge in **26** using SmI_2. This reductive process would produce an enone, which may be converted to tropone by elimination of water and dehydrogenation. However, treatment of enone **26** with SmI_2 or other reducing agents led to either no reaction or a complex mixture.[19]

After many trials, we developed a two-step protocol to open the ether bridge (Scheme 4). A phenylthio group was first introduced to **28** through a Lewis acid-mediated S_N1' substitution of **25**.[20] Only one diastereomer was observed for thio ether **28**. The thiophenol likely approached intermediate **25** from the less sterically hindered β-face based on the X-ray structure of compound **24**. The α-proton of the phenyl sulfide was then removed by LDA in the presence of HMPA, and the oxygen bridge was cleaved under this condition. Two potential isomeric dienes can be generated in this anionic ring-opening reaction by cleaving either C(β')−O or C(δ)−O bonds. HSQC spectra indicated that diene **29** was formed by the cleavage of the C(δ)−O bond.

Scheme 4. Opening of Ether Bridge[a]

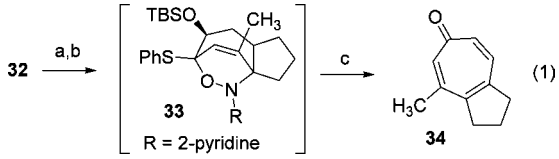


[a](a) PhSH, $BF_3{\cdot}OEt_2$; (b) LDA, HMPA, THF; (c) MeMgBr; (P = TBS).

The introduction of the phenylthio group not only solved the reproducibility issue of the 1,3-transposition but also provided a handle for the opening of the oxygen bridge. To test the generality of this strategy, we prepared allylic thio ether **31** from known compound **30**[21] using the same sequence of addition of methyl Grignard reagent and S_N1' displacement by thiophenol. The anionic opening worked smoothly to yield bicyclic product **32**. In related anionic ring-opening reactions reported by Lautens and his co-workers,[22] oxabicyclo[3.2.1]-octene was opened by a S_N2' process[22a,b] or a base-mediated β-elimination.[22c]

Diene **32** was then used as a model system for the synthesis of tropone. We envisioned that a sequence of hetero-Diels−Alder cycloaddition of a cycloheptadiene with a nitrosoarene,[23] reductive cleavage of the N−O bond to an amino alcohol, and double elimination of amine and water might provide the tropone moiety. After protecting the free alcohol in **32**, the resulting diene was treated with 2-nitrosopyridine (Scheme 5).

Scheme 5. Synthesis of Model Tropone 34[a]



[a](a) TBSOTf, 2,6-lutidine, DCM; (b) 2-nitrosopyridine, DCM, 90% over two steps; (c) $SnCl_2$, EtOAc, 50%.

The hetero-Diels−Alder cycloaddition occurred and afforded adduct **33**, which was directly converted to tropone **34** by the treatment of $SnCl_2$. Elimination of both 2-aminopyridine and water indeed occurred after the reductive cleavage of the N−O bond. The structure of intermediate **33** was assigned based on the regioselectivity observed in a similar hetero-Diels−Alder reaction involving nitroso compounds.[24] With this method in hand, we then treated diene **29** or its derivatives with 2-nitrosopyridine in the absence or presence of different Lewis acids.[25] Unfortunately, no desired cycloaddition product was observed.

Several conditions have been reported for the hydrolysis of vinyl phenylthio ethers to ketones.[26] Under these conditions, however, the thio ethers in **29**, **32**, or their derivatives could not be hydrolyzed to the corresponding enone. We then decided to remove the phenylthio group in **29** and examine conditions for the conversion of the resulting diene **35** (Scheme 6) to a

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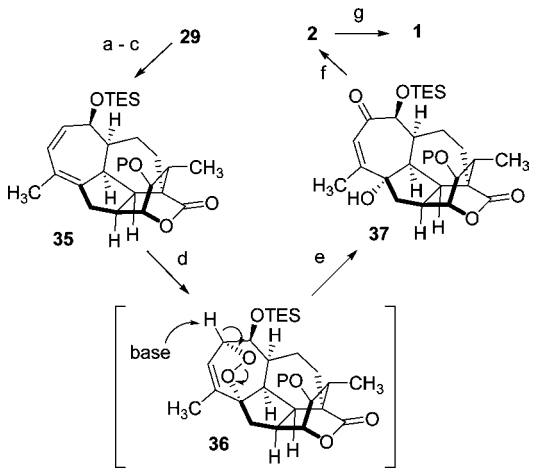
Scheme 6. Formation of Tropone and Completion of the Synthesis of 1 and 2[a]



[a](a) TESCl, DMAP, TEA, DCM; (b) MMPP on silica gel, DCM; (c) SmI_2, DMPU, MeOH, THF, 70% over three steps; (d) O_2, TPP, light, CH_3CN, 40%; (e) DBU, DCM; (f) TsOH, $CDCl_3$, 85% over two steps; (g) $Pb(OAc)_4$, benzene, 90 °C, 52%. (P = TBS).

tropone. We could not obtain diene **35** by treating **29** with Raney-Ni directly. Although reductive cleavage of a carbon−sulfone bond by SmI_2 has been reported,[27] we were not able to prepare the corresponding sulfone from **29** in a good yield. Interestingly, the corresponding sulfoxide can be synthesized efficiently, and the reductive cleavage of a carbon−sulfoxide bond worked well. After silyl protection, the phenylthio group in **29** was removed by a two-step sequence: oxidation by magnesium monoperoxyphthalate (MMPP) to its sulfoxide[28] and reduction with SmI_2.

Inspired by the strategy of [4 + 2] cycloaddition, N−O bond cleavage, and double elimination to access tropone **34** in Scheme 5, we envisioned a sequence of [4 + 2] cycloaddition of diene **35** with singlet oxygen to afford peroxide **36**, Kornblum−DeLaMare rearrangement of **36** to ketone **37**,[29] and double elimination to prepare tropones in natural products **1** and **2**. Indeed, peroxide **36** was formed by the cycloaddition between diene **35** and singlet oxygen together with a byproduct derived from an ene reaction, using tetraphenylporphyrin (TPP) as the photosensitizer. DBU-promoted Kornblum−DeLaMare rearrangement provided ketone **37**. In the presence of acid, removal of silyl groups and elimination of two water molecules occurred to yield hainanolidol **2**. The ^1H and ^{13}C NMR spectra of our synthetic hainanolidol are in accordance with natural product as shown in the Supporting Information. 2D NMR data (COSY, HMBC, HSQC, and NOE) further confirmed the structure and stereochemistry of hainanolidol.

Treatment of hainanolidol **2** with lead tetraacetate in refluxing benzene finally provided harringtonolide **1** in a 52% isolated yield.[4] The ^1H and ^{13}C NMR spectra of our synthetic harringtonolide are in agreement with those reported for natural harringtonolide.[1,2,9] The key biomimetic transformation of biologically inactive hainanolidol **2** to bioactive harringtonolide **1** is thus confirmed for the first time by total synthesis.

3. CONCLUSION

In summary, the total synthesis of natural products hainanolidol and harringtonolide was realized featuring two stereoselective [3,3]-sigmatropic rearrangements, an oxidopyrylium-based [5 + 2] cycloaddition to construct the tetracyclic carbon skeleton, an anionic ring opening of the ether bridge derived from [5 + 2] cycloaddition, and the formation of a tropone through a sequence of [4 + 2] cycloaddition, Kornblum−DeLaMare rearrangement, and double elimination. This new synthetic route for hainanolidol and harringtonolide offers the flexibility to access other members of *Cephalotaxus* norditerpenes and various simplified analogues. Evaluation of the anticancer activity of harringtonolide and its analogues will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, and spectra (IR, ^1H, ^{13}C NMR, and HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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