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Asymmetric Synthesis of the Oxygenated Polycyclic System of (+)-Harringtonolide

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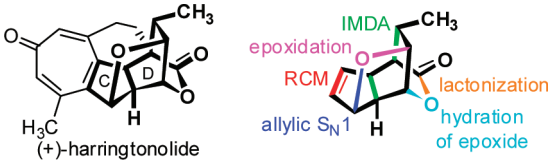
ABSTRACT



A straightforward asymmetric synthesis of the cage oxygenated structure of (+)-harringtonolide has been accomplished for the first time. The key steps involved (i) a templated stereoselective IMDA reaction to build a highly functionalized cyclohexene ring D, (ii) functionalization of the cycloadduct, (iii) ring-closing metathesis providing the five-membered ring C, and finally (iv) a challenging one-step cascade cyclization of an epoxy-alcohol toward the target structure, whose mechanism was investigated.

(+)-Harringtonolide (**1**, Figure 1) is a norditerpene isolated in 1978 from the Asian plum yew *Cephalotaxus harringtonia*,[1] a tree which first attracted attention because it contains antitumor alkaloids (i.e., homoharringtonine).[2] It was described as a phytotoxic compound, leading to plant growth inhibition on tobacco and beans. Later, analogous compounds in this terpenoid series were isolated from other *Cephalotaxus* species.[3] During our work aiming at discovering new terpenic and alkaloidic compounds from *Cephalotaxus*, harringtonolide was retrieved from the plant extract. The compound was found strongly cytotoxic at IC_{50} = 43 nM on KB tumor cells, while X-ray crystallography of a brominated derivative allowed for determining the absolute stereochemistry (as shown).[4]

Yet neither the pharmacophoric moiety of **1** nor its mechanism of action have been determined. Only recently,

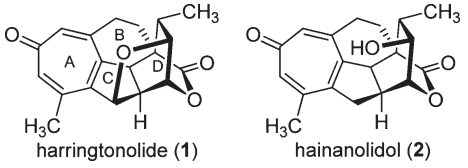


Figure 1. Structure of *Cephalotaxus* norditerpenes **1** and **2**.

simplified analogues were reported, featuring the tricarbocyclic portion corresponding to the ABC ring system of **1**.[5] Hereafter, we describe the first asymmetric synthesis of the

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oxygen-bridged CD ring system, as part of our ongoing work toward the total synthesis of **1**.[6]

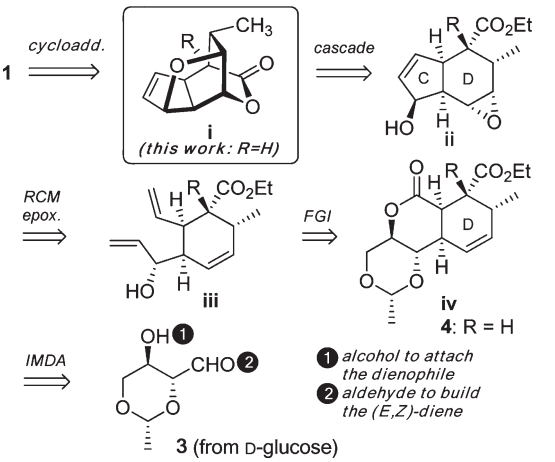
The racemic total synthesis of **1** was first reported by Mander and co-workers in the 1990s,[7] and an elegant complementary strategy was later designed by the same group.[8] In fact during their work, Mander and co-workers synthesized hainanolidol (**2**, Figure 1) and thus accomplished a formal synthesis of **1**[7b] since pseudobenzylic oxidation of **2** (from natural origin) was known to promote ether bridge formation, as previously demonstrated by others.[3a] Their most recent report described the construction of the CD bicyclic system by the Diels–Alder reaction between an indenone dienophile (also incorporating the future A-ring) and a α-pyrone diene, thus introducing the lactone bridge at the same time.[8b]

Our synthetic approach ensues from the following analysis of **1** (Scheme 1). The A-ring may be constructed via intramolecular cycloaddition involving the advanced intermediate **i** bearing an appropriate R group. The ether and lactone bridges of this compound (**i**), which will be described below with R = H, would be derived from cascade cyclization of the epoxide intermediate **ii**. This is expected to be formed from the densely functionalized cyclohexene **iii** through ring closing metathesis (RCM) and regioselective epoxidation. This intermediate (**iii**) would be derived by functional group interconversion (FGI) of cycloadduct **iv** constructed by asymmetric intramolecular Diels–Alder reaction (IMDA). In order to make the correct enantiomer of the natural product, we designed a stereodirected IMDA reaction based on the chiral dioxane template **3** available from D-glucose.[6b,c] This allowed for installing the chirality of **1**, which is indeed carried by central ring D.

In previous reports, the cycloadduct **4** was synthesized in 8 steps and 20% overall yield starting from D-erythrose ethylidene acetal.[6c,9] The asymmetric 1,3-dioxane ring was used as a rigid template to promote stereocontrol in the IMDA reaction leading to **4**. The key stereogenic centers were introduced by taking advantage of anticipated stereoelectronic interactions within a 1,3,9-decatriene system holding a (*Z*,*E*,*E*) geometry. Several tens of grams of the expected product **4** were thus successfully prepared in a diastereomerically pure form.[6c]

A straightforward route was used to functionalize the cycloadduct **4** toward the metathesis substrates **9a**–**c** (Scheme 2). Unraveling under acidic conditions (TFA, H_2O, 80 °C) led to diol **5** in 76% yield through acetal hydrolysis and concomitant lactone ring contraction. The rearranged acetal **6** was also isolated (15%) but was recycled by acid hydrolysis into **5**.[6c] The diol **5** holds all appropriate functional groups to construct our metathesis substrate. Indeed, the one-step conversion of **5** into alkene **7** was

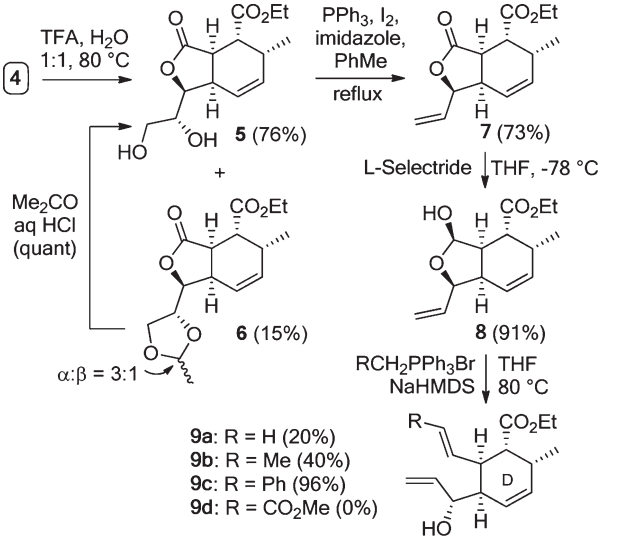
Scheme 1. Retrosynthetic Analysis of **1**



performed in 73% yield using Garegg and Samuelsson conditions (PPh_3, I_2, imidazole, toluene, reflux).[10] Subsequent regioselective reduction of the lactone ring in the presence of L-selectride allowed the formation of lactol **8** in 91% yield. Finally, this intermediate was engaged in Wittig reactions.

The traceless R groups in **9a**–**d** opened the way to several alternatives. Four ylides were tested, with R = H, Me, Ph, or CO_2Me. We found that only the semistabilized ylide $Ph_3P{=}CHPh$ gave satisfying results, with 96% yield of diene **9c** (R = Ph). Poor yields of compounds **9a** (R = H) and **9b** (R = Me) were attributed to instability of products upon purification, while the reaction with R = CO_2Me was unsuccessful.[11] The intermediate **9c** was submitted to RCM in the presence of the Grubbs catalyst (either first or second generation, at reflux or room temperature in dichloromethane, 84 and 93%, respectively), providing the chiral CD bicyclic system **10** (Scheme 3). Efforts were then engaged to reach the retrosynthetic intermediate **ii**.

Scheme 2. Unraveling and Functionalization of Cycloadduct **4**



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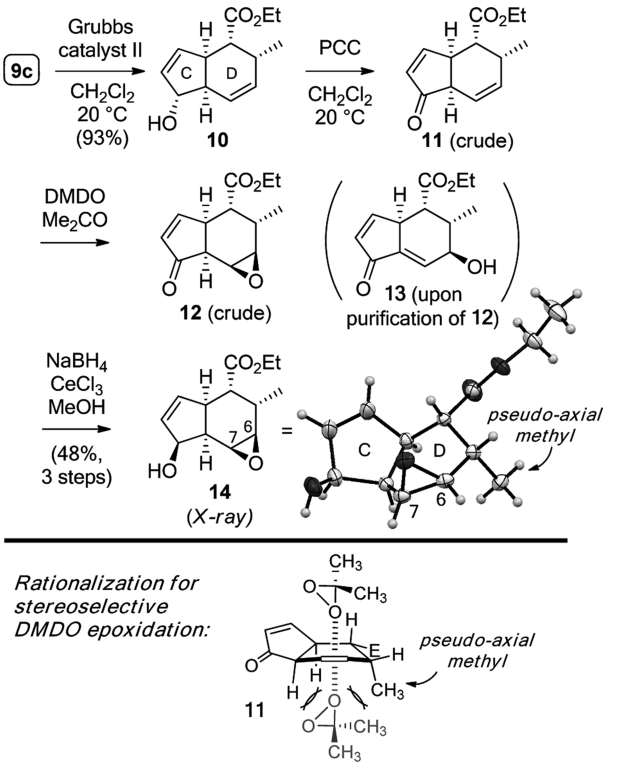
To prevent epoxidation at the C-ring, the allylic alcohol was oxidized into the electron-deficient enone **11**. The cyclohexene double bond was then regio- and stereoselectively epoxidized in the presence of DMDO in acetone at 0 °C, leading to the epoxide **12** (complete stereoselectivity). At this stage, it was not possible to determine the stereochemical outcome of the reaction by classical spectroscopic methods. Moreover, neither **11** nor **12** were stable upon purification on silica gel, occasionally leading to epoxide opening, giving **13** from **12**. Purification was thus undertaken after the final reduction of the ketone in the presence of $NaBH_4$ and $CeCl_3$ in MeOH,[12] performed with a stereoselectivity of 6:1 in favor of the β-alcohol **14**, as expected. Overall, compound **14** was obtained in 48% yield from **10** (three steps). Fortunately, **14** (β-OH) gave crystals allowing the relative stereochemistry to be determined by X-ray crystallography (Scheme 3).[13] In fact, we were not expecting such a complete β-stereoselectivity for the epoxidation. It was explained by possible steric interactions of DMDO with the likely pseudoaxial methyl group, as it was observed for **14** (see X-ray structure), of compound **11** (Scheme 3).

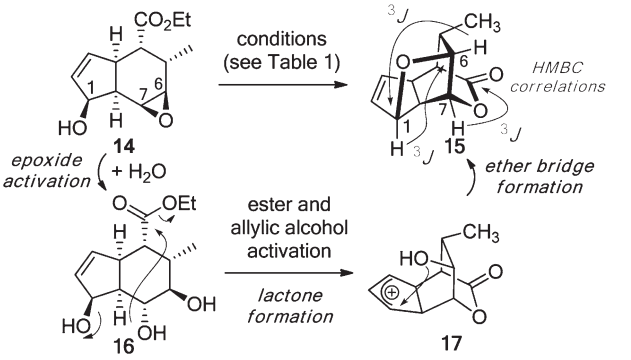
For the final stage of this work, a challenging one-step cyclization of intermediate **14** (1:6 mixture of α- and β-OH epimers) was envisaged to get the oxygenated cage structure of the natural product (Scheme 4). Although the epoxide stereochemistry was inverted compared to our initial retrosynthetic intermediate **ii**, it was reasoned that since the methyl group was likely to have a shielding effect on the α-face during epoxidation, it may also congest the nearest carbon C-6 on the epoxide. Therefore, we believed that hydrating the epoxide **14** would take place on the alternative carbon C-7. In fact, the all cascade process could be acid-activated, first leading to triol **16** and then to lactone closure and ether bridge formation, necessarily through the allylic cation **17**, to form the targeted product **15**.

A profusion of conditions were attempted for acid-catalyzed epoxide opening by water before finding that treating the epoxy-alcohol **14** with a 1 M solution of $KHSO_4$ in water and in the presence of $Yb(OTf)_3$ in THF at 50 °C (condition 1) provided 39% yield of the polycyclic system **15** (Table 1). The Lewis acid was used to accelerate the reaction (still uncompleted after three days with the sole presence of $KHSO_4$). Increasing the temperature (80 °C) resulted in degradation, while changing the Lewis acid occasionally gave the unexpected indene by-product **18** (70% yield with CuF_2 in condition 3), probably resulting from successive dehydrations. This product was also observed when **14** was heated (80 °C) with catalytic amounts of *p*TSA (0.1 equiv) in toluene. Eventually, the

Scheme 3. Construction of the Bicyclic CD Ring System (**10**) and Setting-up of Oxygenated Functionalities (Top), Rationalization of the Stereochemical Outcome of Epoxidation (Bottom)



Scheme 4. Final Step and Mechanism of the Cascade Cyclization Towards the Cage Structure **15** from **14**



aqueous conditions developed by Hudlicky and co-workers, using silica gel alone or associated to Lewis acids,[14] were applied to **14** (condition 4(i): $Yb(OTf)_3$ over SiO_2 in water at 120 °C). Although no trace of the aim product **15** could be detected, only the triol **16** with the desired stereochemistry was selectively formed in 56% yield after three days. It showed that hydration of the epoxide was

(11) In the case of **9a**, the crude extract could be engaged in the next metathesis step, leading to the expected product **10** in 35% yield (over two steps from **8**) after purification.

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(13) Crystallographic data for structures of **14** and **15** were deposited with the Cambridge Crystallographic Data Center as numbers CCDC 863114 and 863115, respectively. Copies of data can be obtained free of charge at www.ccdc.cam.ac.uk/products/csd/request, or on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, U. K. (Fax: + 44 1233 336033 or E-mail: deposit@ccdc.cam.ac.uk). ORTEP drawings in Scheme 3 and Figure 2 were generated using Mercury software.

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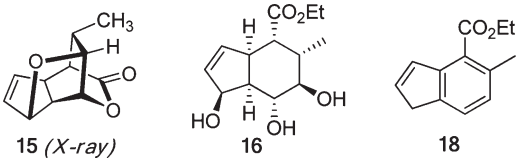
Table 1. Reaction Conditions toward **15**, **16**, and **18** from **14**



conditions	isolated yield (%)		
	15	**16**	**18**
(1) $Yb(OTf)_3$ (0.2 equiv), 1 M aq $KHSO_4$/ THF (v/v 1:4), 50 °C, 24 h	39	[a]	[a]
(2) $Yb(OTf)_3$ (0.2 equiv), 1 M aq $KHSO_4$/ THF (v/v 1:4), 80 °C, 24 h	[b]	[b]	[b]
(3) $CuF_2 \cdot 2H_2O$ (0.2 equiv), 1 M aq $KHSO_4$/ THF (v/v 1:4), 50 °C, 24 h	12	0	70
(4) (i) $Yb(OTf)_3$ (0.2 equiv) on activated silica gel, water, 120 °C, 72 h then:	0	56	0
(ii) $BF_3 \cdot OEt_2$ (10 equiv), CH_2Cl_2, −78 °C → rt, 6 h	27	0	0
or: (ii) $Yb(OTf)_3$ (1 equiv), THF, 80 °C	57	0	[a]

[a] Traces observed on TLC. [b] Degradation.

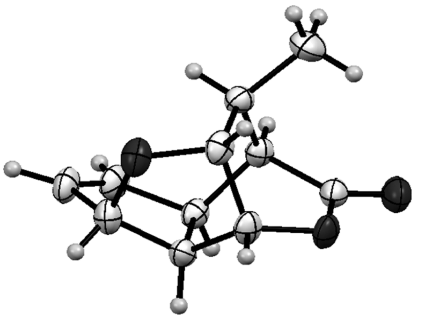


Figure 2. X-ray structure of compound **15**.

completely regioselective upon C-7, confirming hindrance of the α-face at C-6. Last treatment of **16** in the presence of boron trifluoride etherate even lead to product **15** in 27% yield. This transformation was greatly improved by the use of $Yb(OTf)_3$ in refluxing THF (57% yield).

The structure of **15** was first confirmed by 2D NMR, especially HMBC experiments, which clearly showed correlations across the ether and lactone bridges (Scheme 4). Remarkably, both proton and carbon spectra were closely related to those of the natural product (**1**), especially in the δ 3.5−5.5 and δ 80−90 ranges for atoms at positions 1, 6, and 7 (see the Supporting Information). Finally, a crystal of compound **15** was analyzed by X-ray crystallography, which revealed the beautiful structure of this caged compound (Figure 2).[13]

In conclusion, we have designed and accomplished the first asymmetric synthesis of the cage oxygenated structure (**15**) found in the cytotoxic natural product (+)-harringtonolide (**1**). Showing no cytotoxicity against KB cells, this structure alone does not account for the cytotoxic activity of the natural product, for which the tropone ring may be necessary. Cycles D and C were successively constructed with minimum use of protecting groups, respectively by IMDA and RCM reactions, while the oxygen bridges in **15** were formed in one step during a regioselective tandem process performed on the epoxy-alcohol **14** under acid catalysis. Our work is still in progress toward the total synthesis of **1**.

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Note Added after ASAP Publication. The Supporting Information was replaced on February 21, 2012 to correct the information over the arrow in the Scheme on p S3.

Supporting Information Available. Experimental procedures, CIF files, full spectroscopic data, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.