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Communication

Norditerpenes

One-Pot, Enantioselective Synthesis of 2,3-Dihydroazulen-6(1*H*)-one: A Concise Access to the Core Structure of *Cephalotaxus* Norditerpenes

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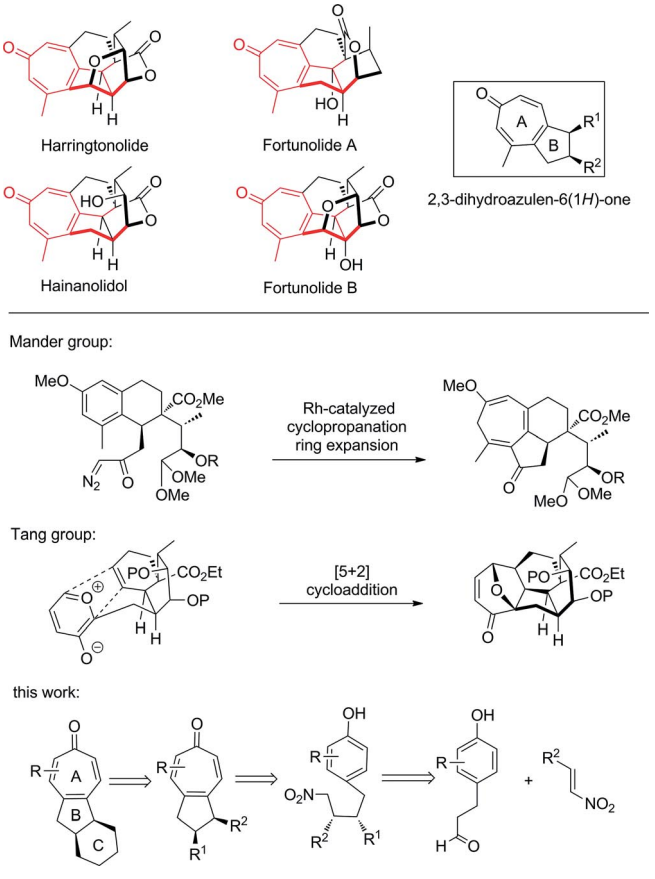
Abstract: A one-pot enantioselective synthesis of *cis*-substituted 2,3-dihydroazulen-6(1*H*)-one is described. In this cascade reaction, an organocatalyzed asymmetric Michael reaction furnishes a highly optically pure nitrobutylphenol intermediate, which is converted into an annulated tropone species by sequential oxidative dearomatization, conjugate addition, electrocyclic ring opening and nitrous acid elimination in the same reaction vessel. Both aliphatic and aromatic nitroalkenes are good substrates for the one-pot reaction, and this protocol appears to be general for various phenylpropionaldehydes as well. In the case of asymmetrically substituted phenylpropionaldehydes, the regioselectivity is likely determined by both the steric and electronic properties of the substituents. This methodology is successfully applied to the synthesis of the tricyclic core structure of *Cephalotaxus* norditerpenes.

Introduction

Harringtonolide was first isolated from *Cephalotaxus harringtonia*, and X-ray crystallography analysis of the natural product revealed that it possesses a complex, polysubstituted 2,3-dihydroazulen-6(1*H*)-one moiety fused with a heavily decorated cyclohexane motif (Scheme 1).[1] After the initial account, harringtonolide and related *Cephalotaxus* norditerpenes including hainanolidol, fortunolide A and B were also extracted from other *Cephalotaxus* species.[2] Harringtonolide was reported to have interesting antineoplastic and antiviral properties,[3] and a more recent study from Nay's group found that harringtonolide exhibits potent cytotoxicity to KB cells with an IC_{50} of 43 nM.[4] The intriguing structural features, in conjunction with its anticancer activity, have enticed significant synthetic efforts towards these norditerpenes.[5] To date, two elegant racemic total syntheses of the norditerpenes have been achieved by Mander's group and Tang's group. Both teams employed reliable chemistry to create the polysubstituted precursor at an early stage and used novel methodologies to construct the tropone motif at the late stage of the synthesis. Mander and co-workers utilized a rhodium-catalyzed arene cyclopropanation followed by a ring expansion reaction to create the fused tricyclic system;[6] and Tang's group disclosed a [5+2] cycloaddition reaction as the key step to form the core structure of harringtonolide.[7]

One promising strategy for accomplishing an enantioselective total synthesis of harringtonolide is to create the 2,3-dihydroazulen-6(1*H*)-one skeleton, an annulated tropone with two *cis* substituents, in optically pure form, and subsequently



Scheme 1. *Cephalotaxus* norditerpenes and strategies to the core structure.

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introduce other essential functional groups on the core structure. There are many chemical methods to prepare tropones, and they have been thoroughly reviewed in the literature.[5h,8] However, employing the known chemistry to synthesize chiral dihydroazulenones will require multiple operations to assemble the stereocenters and the tropone motif. In this regard, a direct enantioselective cascade protocol[9] that allows access to chiral dihydroazulenone in a one-pot operation is highly desirable.

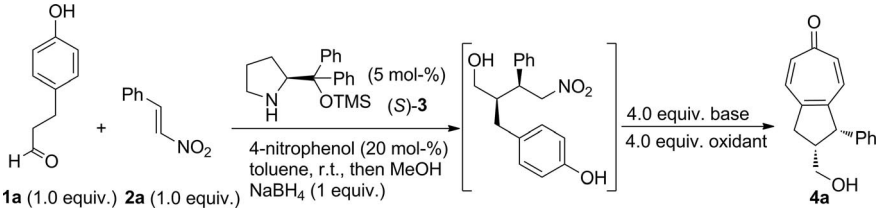
Inspired by the methodology developed by Kende[10] and its application to natural product total synthesis,[11] we envision that a polysubstituted, enantiomerically pure nitroalkane with a pendant *para*-hydroxyphenyl group can be converted into the corresponding dihydroazulenone, the core structure of harringtonolide, by sequential oxidative cyclization and ring expansion. One advantage of this approach is that optically pure nitroalkanes are easily prepared by enantioselective Michael reactions, for instance, organocatalyzed conjugate additions.[12] To maximize the overall efficiency, it is appealing to carry out the conjugate addition and the subsequent oxidative dearomatization in the same reaction vessel; thus we chose to convert the aldehyde group to the corresponding alcohol and to explore the feasibility of accessing the enantiomerically pure dihydroazulenone in a one-pot process.

Results and Discussion

The Michael reaction between aldehyde **1a** and nitrostyrene **2a** was effected by Jørgensen's catalyst[13] (*S*)-**3** in the presence of 4-nitrophenol in toluene.[14] Upon completion, the toluene solution was diluted by an equal volume of MeOH followed by the addition of 1.0 equiv. of $NaBH_4$, which led to the clean formation of an alcohol intermediate. Without any purification, the reaction mixture was subjected to the oxidative conditions to generate the optically pure dihydroazulenone, and the results are summarized in Table 1. First, inorganic metal salt based single electron transfer (SET) reagents were evaluated for their effectiveness to enable the oxidative dearomatization using KOH as a base. Mild reagents such as $Mn(OAc)_3$[15] and $CuCl_2$[16] only gave a negligible amount of anticipated product or turned out to be completely ineffective; in contrast, strong SET reagents such as $Ce(NH_4)_2(NO_3)_6$ and Ag_2O caused extensive decomposition of the alcohol intermediate. To our delight, $K_3[Fe(CN)_6]$, which was used in Kende's initial report,[10] was very effective in promoting the one-pot transformation and gave the *cis*-disubstituted dihydroazulenone in 85 % yield. A stabilized organic radical like TEMPO was also tested for the one-pot reaction, but the desired dihydroazulenone was not detected. KOH was the optimal base in our current investigation, and the attempts to replace it with organic bases, for example iPr_2NEt or DBU, were unsuccessful. In this one-pot process, the stereoselectivity was determined by the organocatalyzed Michael reaction, and we were pleased to find out that dihydroazulenone **4a** was enantiomerically and diastereomerically highly pure (*ee* > 99 %, *dr* = 14:1). This protocol is very reliable and can be extended to a gram-scale reaction, and dihydroazulenone **4a** was obtained in comparable yield and excellent stereoselectivity.

With the optimized one-pot conditions in hand, we evaluated the generality of this dihydroazulenone synthesis with different nitroalkenes as illustrated in Figure 1. Generally speaking, substituted nitrostyrenes with either electron-donating or electron-withdrawing groups were well tolerated for this one-pot protocol, and *cis*-dihydroazulenone **4b**–**4k** were isolated in good yields with excellent enantio- and diasteresoselectivity. The mildly basic conditions can be adapted to more complex aromatic groups with different electronic properties. For example, nitro olefins derived from 1-naphthaldehyde, carbazole-3-carbaldehyde and indole-3-carbaldehyde were successfully converted into the optically highly pure dihydroazulenones in modest to good yields. The modest yields of **4m** and **4n** were partially attributed to the low solubility of the corresponding nitronates in the mixed solvent. Aliphatic nitroalkenes also pro-

Table 1. Optimization for the one-pot reaction.[a]



Entry	Oxidant	Base	Yield [%][b]
1	$Mn(OAc)_3$	KOH	< 2
2	$CuCl_2$	KOH	0
3	$Ce(NH_4)_2(NO_3)_6$	KOH	decomposition
4	Ag_2O	KOH	decomposition
5	$K_3[Fe(CN)_6]$	KOH	85
6	TEMPO	KOH	0
7	$K_3[Fe(CN)_6]$	DBU	0
8	$K_3[Fe(CN)_6]$	iPr_2NEt	0
9	$K_3[Fe(CN)_6]$	KOH	83[c]

[a] All reactions were performed on a 0.4 mmol scale with 5 mol-% of (*S*)-**3**, 20 mol-% of 4-nitrophenol in toluene at room temp. [b] Isolated yield. [c] The reaction was performed on a 1 g scale.

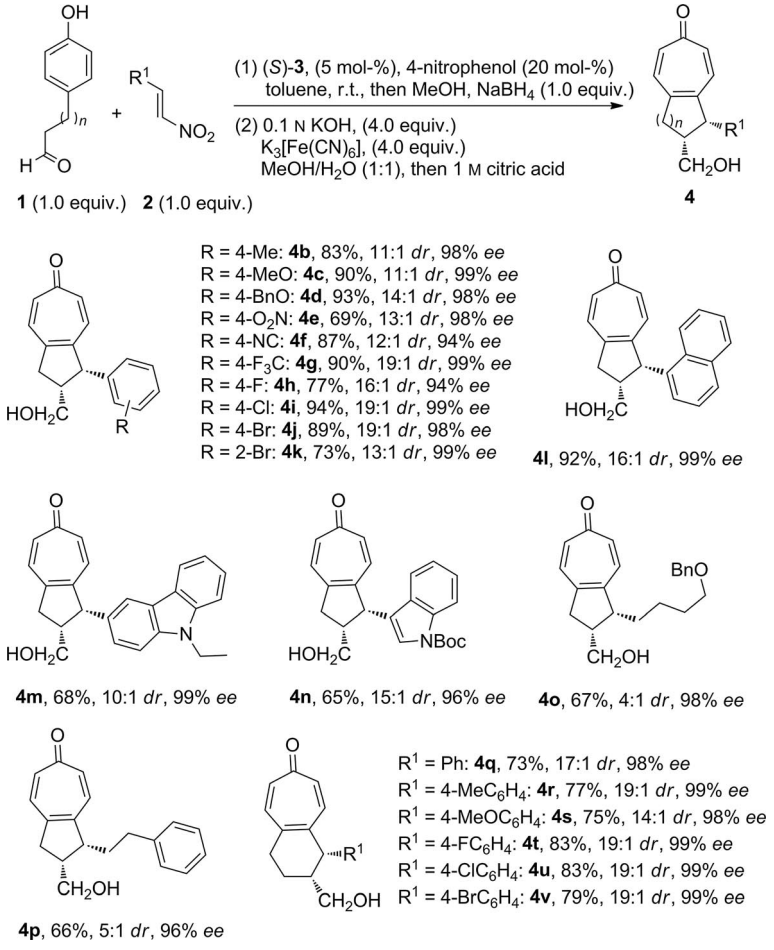


Figure 1. Substrate scope for nitroalkenes.

ceeded smoothly under the optimized conditions and afforded the desired dihydroazulenones **4o** and **4p** in enantiomerically highly pure form. However, the Michael reactions with such aliphatic substrates had to be carefully monitored in order to avoid prolonged reaction time, which would lead to very poor *dr* values in the final products. Finally, we tested whether the one-pot transformation was applicable to the preparation of cyclohexane-fused tropones in an enantioselective manner. Under the optimized conditions, when (hydroxyphenyl)butyraldehyde **1b** was mixed with various nitrostyrenes, cyclohexane fused tropones **4q**–**4v** were conveniently prepared in similar yields and selectivity to that of cyclopentane-fused counterparts.

The tropone motif in *Cephalotaxus* norditerpene has an additional methyl group besides the fused cyclopentane, and this asymmetric substitution pattern warrants a systematic study of regioselectivity in the second conjugate addition step. As illustrated in Figure 2, if the phenyl ring is asymmetrically substituted, the intramolecular conjugate addition can potentially generate a distal isomer (red-arrow pathway) and a proximal isomer (black-arrow pathway). To better understand the regioselectivity, we prepared an aldehyde that possesses a methyl group to increase the steric hindrance at the β-position in one of the conjugated enones in the spirocyclic intermediate, and only distal isomer **4w** was obtained according to the one-pot protocol. In contrast, when a carboxylate group activated one of the enone systems in the spirocyclic intermediate, only proximal isomer **4x** was detected in the crude reaction mixture. These results suggested that the regioselectivity was likely controlled by the steric and electronic properties of the spirocyclic Michael acceptor, but not the substituents or the stereochemistry on the cyclopentane. When the carboxylate group was replaced by a mildly electron-donating methyl group, proximal isomer **4y** was also formed exclusively with excellent stereoselectivity. However, when aldehyde **1c** was used in the dihydroazulenone synthesis, a 1:1 mixture of the two regioisomers was generated, albeit both **4z** and **4z′** retained good optical purity. Finally, we assessed whether the one-pot reaction was applicable to hindered substrates. Thus, a dimethyl-substituted aldehyde was treated with nitrostyrene **2a** in the presence of the organocatalyst, and the resulting product was subjected to $NaBH_4$ reduction and oxidative dearomatization; the desired dihydroazulenone **5** was isolated in 54 % yield.

To illustrate the practical utility of the dihydroazulenones, some of the one-pot products were used as substrates for different derivatizations (Scheme 2). Amination of the tropone **4w** was achieved by the treatment of hydrazine in EtOH,[17] and aminodihydroazulenone **6** was obtained as a single isomer. Aromatization of **4w** to polysubstituted azulene **7**, a family of compounds that have found broad applications in materials science

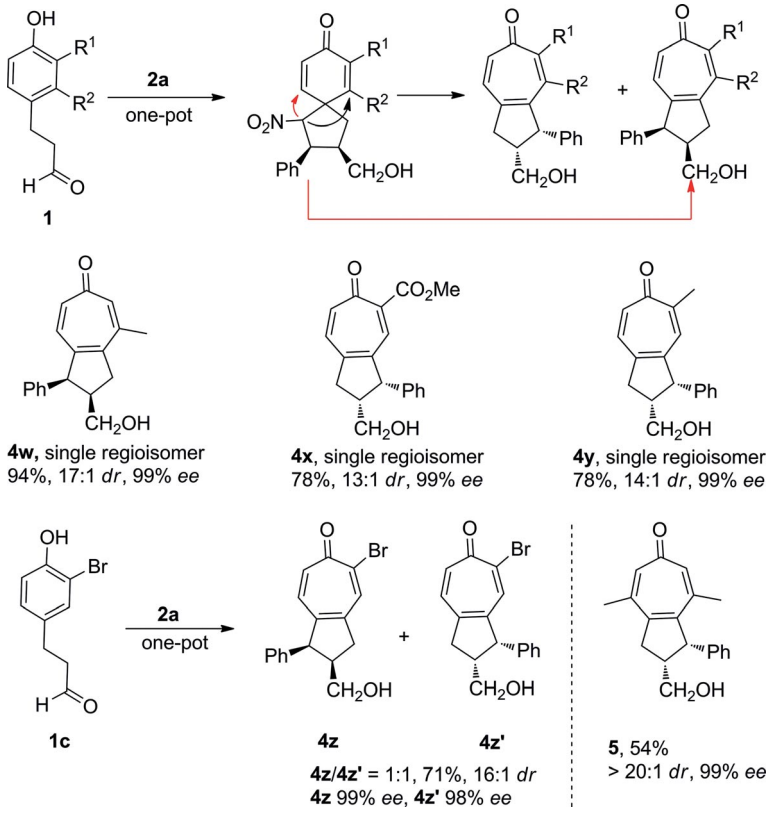
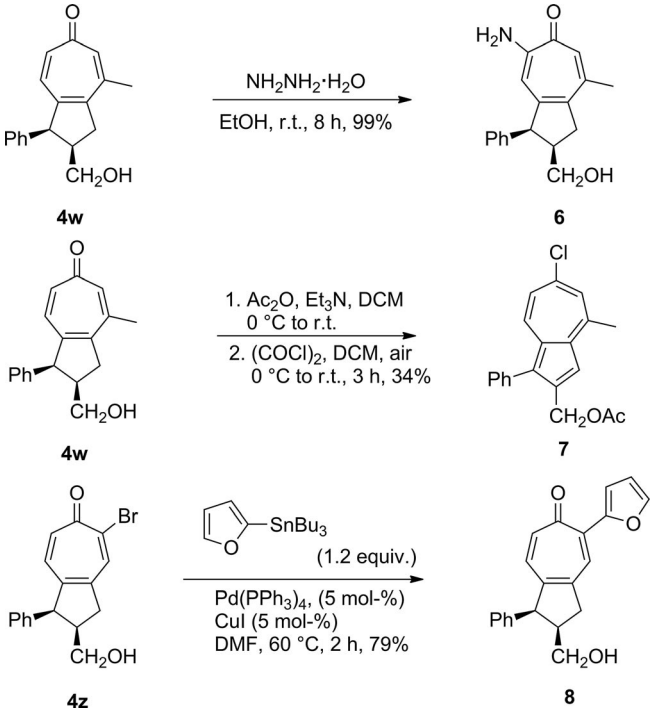


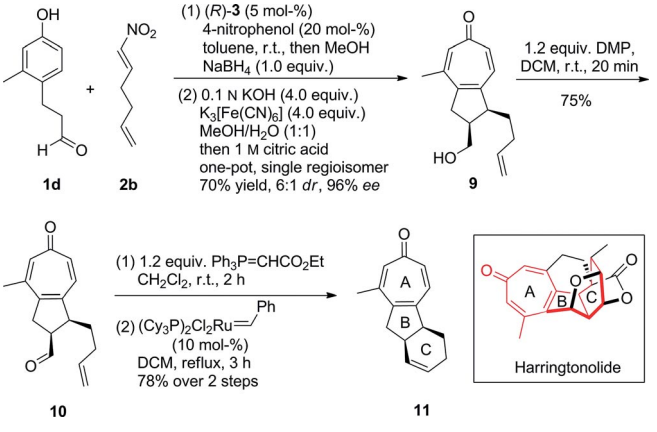
Figure 2. Regioselectivity of asymmetrically substituted aldehydes.

and optics,[18] was accomplished in two steps: first, the free alcohol was protected as the corresponding acetate, and then the carbonyl group was converted into the geminal dichloride[19] followed by elimination and aerobic oxidation. In the third transformation, vinyl bromide **4z** was proven to be a valid substrate for the transition-metal-catalyzed cross-coupling reaction. Under the effect of catalytic amounts of $Pd(PPh_3)_4$ and CuI,[20] furylstannane was treated with **4z** to smoothly afford furyltropone **8** in 79 % yield.

Finally, we turned our attention to demonstrating the power of the one-pot protocol by preparing the ABC ring skeleton of *Cephalotaxus* norditerpenes. The synthesis commenced from the union of aldehyde **1d** and nitroalkene **2b** (Scheme 3). Under the optimized conditions, the readily available starting materials underwent sequential Michael addition, $NaBH_4$ reduction,



Scheme 2. Derivatization of dihydroazulenones.



Scheme 3. Synthesis of the tricyclic ring skeleton of harringtonolide.

and oxidative dearomatization to afford dihydroazulenone **9** as a single regioisomer in 70 % yield with 6:1 *dr* and 96 % *ee*. The pedant alcohol group was oxidized by Dess–Martin periodinane to give aldehyde **10** in 75 % yield, and the diastereomers were separated at this stage. Conversion of the C=O bond into a C=C bond was achieved by standard Wittig reaction using a stabilized phosphorane, and the resulting enone was subjected to ring-closing metathesis under the effect of Grubbs' first-generation catalyst to furnish compound **11** with the desired tricyclic framework in 78 % yield.

Conclusions

We have developed a highly efficient, one-pot procedure to prepare enantiomerically pure 2,3-dihydroazulen-6(1*H*)-ones by organocatalyzed Michael reaction and selective oxidative dearomatization. This protocol has been extended to a diverse range of nitroalkenes to give the desired tropone derivatives with remarkable efficiency. When the methodology is applied to various aldehydes bearing asymmetrically substituted aromatic rings, the distinctive regioselectivity pattern is likely an outcome of both steric and electronic influences of the substituent. Finally, we demonstrate the power of this methodology by preparing the tricyclic framework of *Cephalotaxus* norditerpenes, and we will continue our investigation on the enantioselective total synthesis of harringtonolide by this one-pot protocol with more complex precursors.

Acknowledgments

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Keywords: One-pot · Enantioselective · Organocatalysis · Dihydroazulenone · Norditerpene

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