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Synthetic approach to the functionalized tricyclic core of atropurpuran

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ABSTRACT

A strategy for synthesizing the tricyclic fragment **5** of atropurpuran **1** is reported. Rings A and C of atropurpuran were assembled stereoselectively via two intramolecular Michael additions. The advanced tricyclic skeleton **5** shows the correct functionality and stereochemistry for atropurpuran **1**, so the skeleton may serve as a key intermediate in its total synthesis.

1. Introduction

The genus *Aconitum*, an important source of traditional medicines, is widely used in China to treat various diseases, including rheumatic and neurological disorders as well as pain symptoms.[1] Most compounds isolated from *Aconitum* species are structurally classified as C_{18}-, C_{19}- and C_{20}-diterpenoid alkaloids.[2] In 2009, Wang et al. reported the isolation of a novel non-alkaloidal diterpene, atropurpuran **1**, from the roots of *A. hemsleyanum* var. *atropurpureum*.[3]

Atropurpuran **1** features an unprecedented cage-like skeleton containing an unusual tetracyclo[5.3.3.$0^{4,9}$.$0^{4,12}$]-tridecane unit (rings B–E) fused to a highly functionalized cyclohexene fragment (ring A) with two adjacent chiral quaternary centers (Fig. 1). Because of its intriguing structure, atropurpuran has been an attractive target for synthetic chemists around the world. The groups of Kobayashi[4] and Hsung[5] reported elegant approaches, respectively, to the pentacyclic core (fragment A) and to rings B–D (fragment B) of atropurpuran **1**. Work from our group led to the preparation of ring A (fragment C) via an organocatalytic asymmetric intramolecular Michael addition.[6] Despite these advances and continuing efforts, the total synthesis of atropurpuran **1** has not yet been reported. This reflects the difficulty in constructing its rigid pentacyclic structure and in installing its three quaternary stereocenters. Here we describe a substantial advance toward the total synthesis of atropurpuran **1** by constructing the tricyclic framework (fragment D) via intramolecular Michael addition. This fragment may serve as a key intermediate in a future synthetic approach.

2. Results and discussion

We devised a retrosynthetic analysis of atropurpuran **1** (Scheme 1) based on the biosynthetic pathway proposed by Wang and co-workers.[3,7] We envisioned that **1** could be accessed via functional group transformations from the advanced intermediate **2**. The critical ring D of atropurpuran could be forged through an

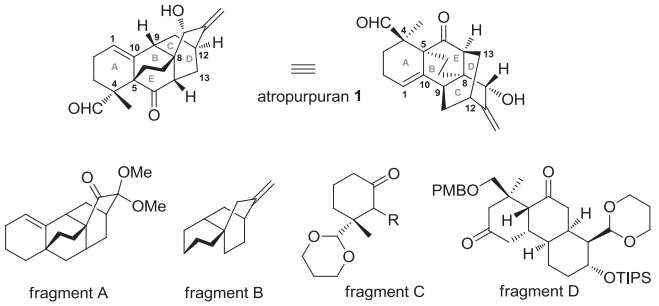

Fig. 1. Structure of atropurpuran **1** and synthesized intermediates.

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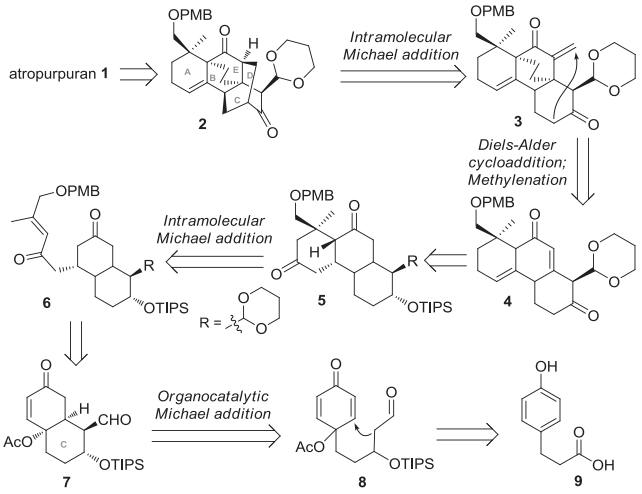
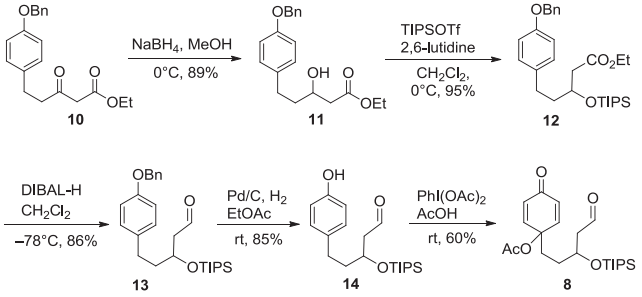
intramolecular Michael addition of enone **3**, while rings B and E could be constructed via a Diels–Alder cycloaddition and methylenation from compound **4**. Several functional group manipulations of **4** would simplify it to the tricycle **5**. Transformation of the bicyclic intermediate **6** into **5** could be achieved via an intramolecular Michael addition. Compound **6** could be generated from the decalin **7**, containing four contiguous stereogenic centers, which could be derived stereoselectively from aldehyde **8** via an intramolecular organocatalytic Michael addition.[8]



Scheme 1. Retrosynthetic analysis of atropurpuran **1**.

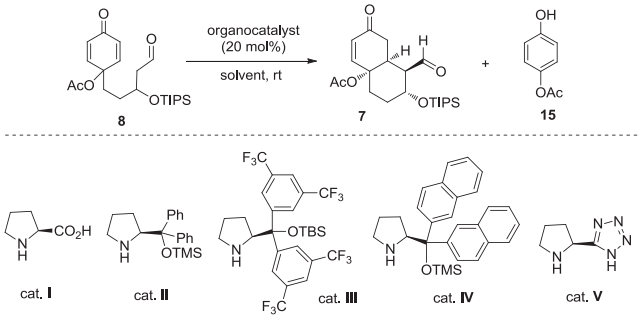
Our synthetic endeavors began with the preparation of cyclohexadienone **8** from the known compound **10** (Scheme 2), which was accessed in three steps from the commercially available acid **9**.[9] Reduction of the ketone carbonyl group in **10** using $NaBH_4$, followed by silyl protection of the resulting alcohol afforded ester **12** in high yield. This ester was then converted into aldehyde **13** in the presence of DIBAL-H. After removal of the benzyl group via hydrogenation, phenol **14** was mixed with $PhI(OAc)_2$/AcOH, generating dearomatization product **8** in 60% yield.[10]



Scheme 2. Synthesis of the Michael addition precursor **8**.

The organocatalytic Michael addition has proven to be a versatile approach for stereocontrolled synthesis of complex molecules with multiple stereocenters.[8] With precursor **8** in hand, we investigated its organocatalytic Michael addition using several proline-type catalysts (Table 1, entries 1–5). Only catalyst **II** afforded the desired addition product **7** as a major stereoisomer, while the other screened catalysts gave low conversion (<5%, cat. **III** and **IV**), required long reaction time (>5 days), or generated complex mixtures (cat. **I** and **V**). Screening various additives, such as phthalimide, picric acid, and *p*-toluenesulfonic acid, failed to improve yield (not shown in Table 1).[11] Screening various solvents showed that CH_2Cl_2 gave the best results (Table 1, entries 2, 6–10), affording the highest stereoselectivity (ee%>99%, dr>19:1) and moderate yield (40%) (entry 2). We speculated that the racemic starting aldehyde **8** might undergo a kinetic resolution during the reaction. Except for generation of the desired product **7**, the other enantiomer of **8** was surprisingly converted to phenol **15** as a main byproduct in most cases. Since its formation involves a reductive C–C bond cleavage, future studies are needed to explain how it forms under these reaction conditions.

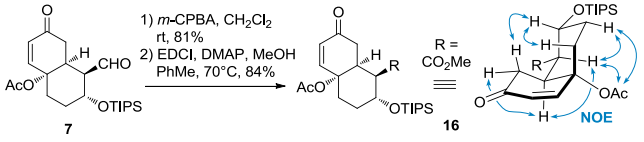
Table 1
The organocatalytic Michael addition reaction of **8**[a]



Entry	Solvent	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]	dr[c]
1	CH_2Cl_2	cat. **I**	10	20[d]	—[e]	—[e]
2	CH_2Cl_2	cat. **II**	12	40	**>99%**	**>19:1**
3	CH_2Cl_2	cat. **III**	>5 days	<5	—[e]	—[e]
4	CH_2Cl_2	cat. **IV**	>5 days	<5	—[e]	—[e]
5	CH_2Cl_2	cat. **V**	1	—[d]	—[e]	—[e]
6	MeOH	cat. **II**	10	20	94.5	>19:1
7	DME	cat. **II**	10	40	>99%	5:1
8	Et_2O	cat. **II**	72	26	96.6%	7.5:1
9	CH_3CN	cat. **II**	24	35	95.8%	4.7:1
10	DMF	cat. **II**	48	30	85.4%	1.3:1

[a] Unless otherwise noted, reactions were performed with 1 equiv of **8** and 20 mol % of catalyst at 25 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralpak AD-H).
[d] Complex mixtures.
[e] The ee and dr values were not determined.

The stereochemistry of aldehyde **7** was established by analyzing its methyl ester derivative **16** (Scheme 3). This derivative was obtained efficiently by oxidizing the aldehyde to carboxylic acid, followed by treatment with EDCI/DMAP/MeOH. Extensive NOE experiments (Scheme 3) clearly indicated a *cis*-fused decalin system, as well as *trans* relationships between aldehyde and OTIPS substituents on the newly formed ring.



Scheme 3. Structural determination of **7**.

Having successfully assembled ring C of atropurpuran, we continued the synthesis as planned, but encountered several challenges while attempting to forge ring A (Scheme 4). The aldehyde functionality in compound **7** was selectively protected via treatment with 1,3-propanediol and $BF_3{\cdot}Et_2O$ in CH_2Cl_2. Efforts to get enone **17** to undergo Diels–Alder cycloaddition with diene **18** were unsuccessful.[12] Attempts to achieve double Michael addition between **17** and enone **20** also failed,[13] possibly due to steric hindrance of the methyl groups and the protected alcohol.