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# A rapid construction of the ABC tricyclic skeleton of malabanone A†

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**The construction of the ABC tricyclic skeleton of malabanone A with the required 4 stereocenters was accomplished in a concise route starting from *R*-carvone. The synthesis featured an intramolecular [3 + 2] cycloaddition reaction to assemble its A ring and an intramolecular Diels–Alder reaction to construct its C ring.**

Malabanone A (Fig. 1, **1**), a novel octanor-triterpenoid with the [4.3.1.01,6]decane unit in its structure was isolated from *Ailanthus malabarica DC* (Simaroubaceae) of India and Indo-China by Koichi Takeya's group in 2001.[1] Its parent plant has long been used by the local people for treatment of dysentery, dyspepsia, febrifuge and bronchitis and a preliminary bioassay indicated that malabanone A showed weak cytotoxic activity on P-388 murine leukemia cells with an $IC_{50}$ value of 16 μg $mL^{-1}$. To our knowledge, there have been no previous synthetic reports towards malabanone A. Continuing with our long-term research interest in the synthesis of natural polycyclic terpenoids,[2] we recently initiated a program towards the total synthesis of malabanone A.[3] Herein, we reported a concise synthesis of its ABC tricyclic skeleton, a very common structure in many triterpenoids,[4]with the required 4 stereocenters (C5, C7, C8, C10) which featured an intramolecular [3 + 2] cycloaddition reaction to assemble the A ring and an intramolecular Diels–Alder reaction to construct its C ring.

Since the B ring of malabanone A has a similar carbon skeleton to carvone (Scheme 1, red part of **1**), commercially available and inexpensive *R*-carvone was envisioned to be an ideal starting point of our synthesis and our retrosynthetic analysis is outlined in Scheme 1. The cyclopropane subunit (E ring) of malabanone A could be assembled by an intramolecular $S_N2$ substitution cyclization reaction from precursor

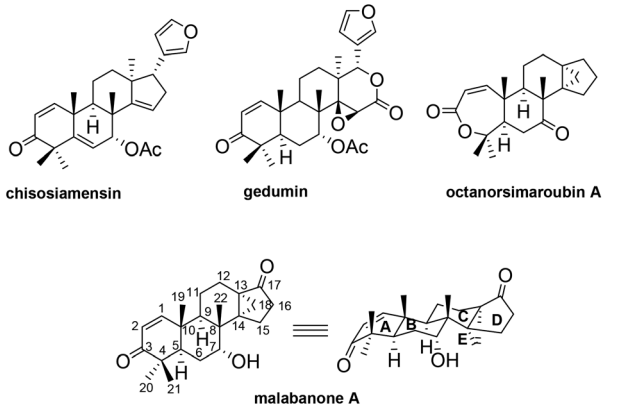
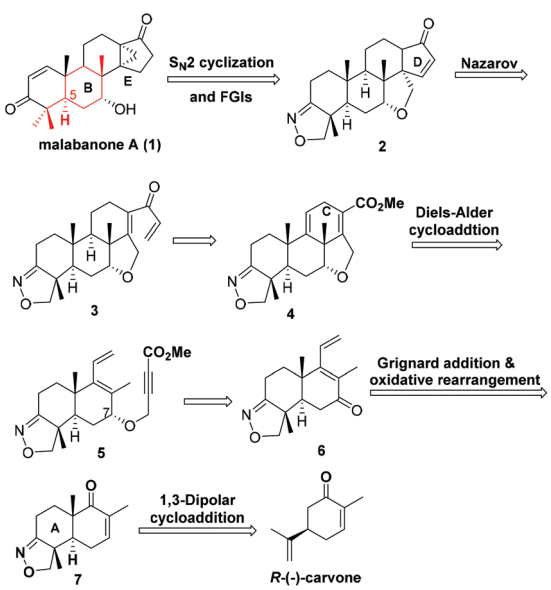



Fig. 1 Structures of chisosiamesin, gedunin, octanorsimaroubin A and malabanone A.




Scheme 1 Retrosynthetic analysis.

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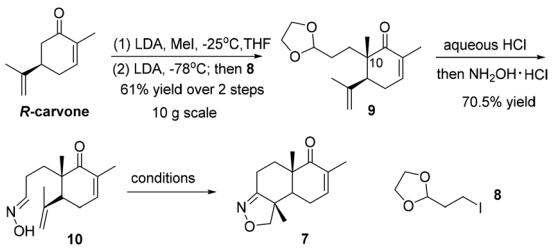
**2** which might be obtained *via* the Nazarov cyclization reaction of divinyl ketone **3**. Compound **3** could be easily derived from diene **4** by vinyl Grignard addition on a weinreb amide derivative. The C ring of compound **4** was envisioned to be constructed through an intramolecular Diels–Alder cycloaddition reaction and the requisite precursor **5** was expected to be obtained from conjugated dienone **6** which could be prepared by a two step process (vinyl Grignard reagent addition/PCC-induced oxidative rearrangement) from the known tricyclic cyclohexenone **7**.[5] And compound **7** could be prepared *via* an intramolecular 1,3-dipolar cycloaddition reaction of the corresponding derivatives of commercially available *R*-carvone.

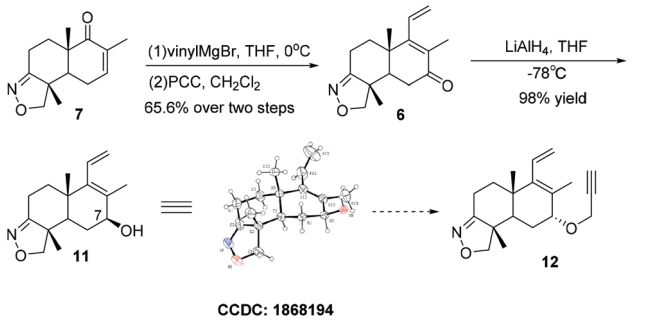
Our synthesis started with dialkylation of C10 of *R*-carvone. As Scheme 2 depicts, the two-step process afforded acetal **9** as a single diastereoisomer with the requisite C10 quaternary carbon stereocenter and could be performed on a 10 g scale in 61% overall yield. The configuration of compound **9** was determined by analogy with the literature.[6a] Subsequent acid hydrolysis and condensation with hydroxyl amine hydrochloride gave the [3 + 2] cycloaddition precursor **10**.

Following literature precedents,[5] only 30% of desired **7** was obtained in our first trial (Table 1, entry 1). The low yield could be attributed to the decomposition of reaction precursor **10** and the formation of other unknown by-products. So the reaction condition optimization was performed and the results are shown in Table 1. Solvents were first screened. While product formation did not occur in $CH_3CN$ or methanol, employing DCM, toluene, or a mixture of toluene and THF gave a comparable yield of 30% (Table 1, entries 2–6). Chloroform proved to be the best choice, as the yield increased to 56% (Table 1, entry 7). Different oxidants were tested, without success (Table 1, entries 8–10). So the optimal conditions at present are performing the reaction in $CHCl_3$ with 14.5% NaClO aqueous solution for 4 h. Under the above reaction conditions, this cycloaddition reaction could be performed on a 1 g scale in 56% yield which expediently fulfilled the requirement of our synthetic program.

With enough tricyclic cyclohexenone **7** in hand, we then turned our attention to its further transformations (Scheme 3). After vinyl Grignard reagent 1,2-addition[7] and a subsequent PCC promoted oxidative rearrangement reaction,[8] conjugated dienone **6** was obtained in 65% yield. LAH reduction of compound **6** gave the corresponding 7β secondary alcohol **11** in 98% yield whose stereo-configuration was confirmed by X-ray single crystal diffraction experiment. However all attempts to invert the configuration of the secondary alcohol under Mitsunobu conditions[9] failed. Nucleophilic substitutions on

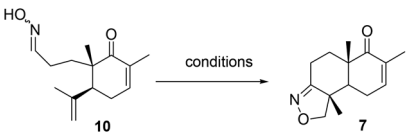



**Scheme 2** Preparation of tricyclic cyclohexenone **7**.




**Scheme 3** Failed route towards compound **12**.

**Table 1** Optimization of the [3 + 2] dipolar cycloaddition reaction of **10** [a]




| Entry | Solvent | Time (h) | *T* (°C) | Oxidant[b] | Yield[c] (%) |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 4 | 25 | NaClO | 30 |
| 2 | $CH_2Cl_2$ : THF = 2 : 1 | 4 | 25 | NaClO | 31 |
| 3 | $CH_3CN$ | 4 | 25 | NaClO | N.R |
| 4 | Toluene | 4 | 25 | NaClO | 30 |
| 5 | $CH_3OH$ | 4 | 25 | NaClO | N.R |
| 6 | $CH_2Cl_2$ | Overnight | 75 | NaClO | 33 |
| 7 | **$CHCl_3$** | **4** | **25** | **NaClO** | **56** |
| 8 | EtOH | 4 | 25 | Tolamine | Complex |
| 9 | $CHCl_3$ : THF = 2 : 1 | 4 | 25 | $NaClO{\cdot}5H_2O$ | 38 |
| 10 | $CHCl_3$ | 4 | 0 | $PhI(OAc)_2$ | Trace |

[a] All the reactions were performed on a 0.2 mmol scale at 0.04 M concentration. [b] In entries 1–7, 14.5% NaClO aqueous solution was used as the oxidant. [c] Isolated yield.

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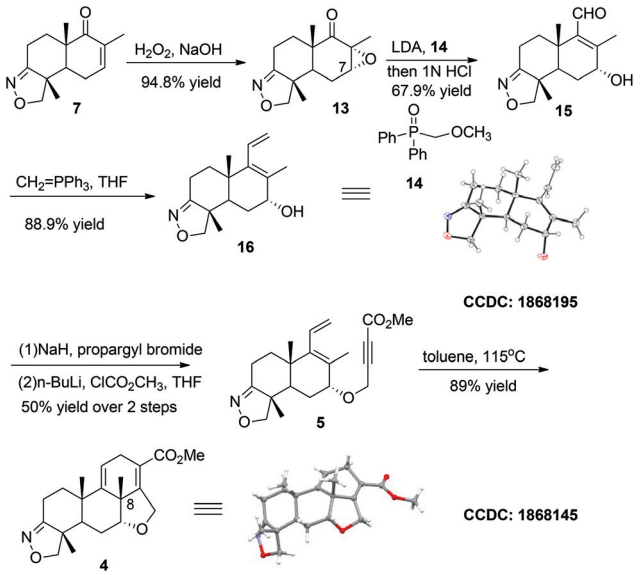


**Scheme 4** Synthesis of **4**.

the mesylate[10] or tosylate derivatives of **11** did not afford propargyl ether **12**. The poor reactivity of alcohol **11** may be attributed to the steric hindrance preventing the required approach of a nucleophile from the α face.

Inspired by Antonio Abad's and Craig M. Williams's excellent work,[11,12] tricyclic hexenone was firstly transformed to α-epoxide **13** as a single diastereoisomer with basic $H_2O_2$.[11,13] The configuration of compound **13** was determined by analogy with the literature.[11] Then it was treated with the lithium derivative of **14** followed by 1 N hydrochloric acid quenching to obtain the secondary alcohol **16** with the requisite C-7 stereocenter in 57% overall yield.[11] The configuration of **16** was also confirmed by X-ray single crystal diffraction experiment. At this time, the corresponding propargyl ether was obtained smoothly and the requisite Diels–Alder precursor **5** was obtained *via* a subsequent common propargyl ester assembly.[11] The Diels–Alder reaction[11,14] proceeded smoothly in toluene at 115 °C to give the desired adduct **4** in 89% yield and its stereo configuration was also confirmed by X-ray single crystal diffraction experiment analysis (Scheme 4).

## Conclusions

In summary, the construction of the ABC tricyclic skeleton of malabanone A with the requisite 4 stereocenters (C5, C7, C8 and C10) was accomplished in a concise route starting from *R*-carvone. Our synthesis featured two highly effective intramolecular cycloaddition reactions to assemble the required cyclic system and the essential stereocenters: (1) a [3 + 2] cycloaddition reaction to assemble the A ring; (2) a Diels–Alder cycloaddition reaction to construct its C ring. Further synthetic work towards malabanone A is being undertaken in this laboratory now and it will be reported in due course.

## Conflicts of interest

The authors declare no competing financial interest.

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