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Synthetic study of marine diterpenoid aberrarone: stereocontrolled construction of tetracyclic framework

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ABSTRACT

Highly stereocontrolled synthesis of the tetracyclic framework of the marine diterpenoid aberrarone, which possesses antimalarial activity against a chloroquine-resistant strain of *Plasmodium*, has been accomplished. A key feature of the synthesis is the complete stereocontrolled construction of C- and D-ring using stereoselective 1,4-addition followed by intramolecular aldol reaction protocol.

1. Introduction

Aberrarone (**1**), a new class of tetracyclic diterpenoid, was isolated from the Caribbean sea whip *Pseudopterogorgia elisabethae* by Rodríguez and co-workers in 2009.[1] Aberrarone (**1**) exhibits inhibitory activity against the chloroquine resistant strain of the protozoan parasite *Plasmodium falciparum*. The molecular structure and relative configuration of the stereogenic centers of **1** were determined by spectral analysis and X-ray crystallographic analysis. Aberrarone (**1**) has a unique tetracyclic framework, called aberrarane skeleton **2**, and contains the seven stereocenters including two all-carbon quaternary centers. This tetracyclic carbon framework, a cyclohexane angularly fused with a linear triquinane, has also been found in idiogenanes diterpenoids, represented by conidiogenol (**4**) and conidiogenone B (**5**), which differ from aberrarane skeleton **2** in the location of two of the methyl groups on the C- and D-rings.[2] Aberrarone (**1**) possesses intriguing structural features and biological activities of are interest to organic chemists. Although few synthetic studies of the such kind of tetracyclic framework were reported,[3] no total synthesis or synthetic study of the ABCD ring system of aberrarone (**1**) has been reported. As the synthetic study of **1**, there is only one report, which is the asymmetric synthesis of ABC and ABD ring systems.[4] Therefore, developing a practical route for the synthesis of the tetracyclic framework is needed before the total synthesis of aberrarone (**1**) can be accomplished. To develop a practical route, a synthetic study of model compound **3** with an ABCD ring system that lacks the two methyl groups at 3 and 7 positions on the C- and D-rings was done. Herein, we describe the complete stereocontrolled synthesis of tetracyclic compound **3** using stereoselective 1,4-addition followed by intramolecular aldol reaction protocol for construction of the C- and D-rings (Fig. 1).

2. Results and discussion

The synthetic strategy for the tetracyclic framework **3** is outlined in Scheme 1. Construction of the C- and D-rings would be achieved using stereoselective 1,4-addition followed by an intramolecular aldol reaction. Thus, the tetracyclic compound **3** could be constructed by the intramolecular aldol reaction of aldehyde **6** followed by the oxidation of the resulting secondary alcohol. Aldehyde **6** would be obtained from tricyclic compound **7** via stereoselective 1,4-addition. Furthermore, the stereoselective 1,4-addition of bicyclic compound **9** followed by intramolecular aldol condensation would be provided the compound **7**. The bicyclic

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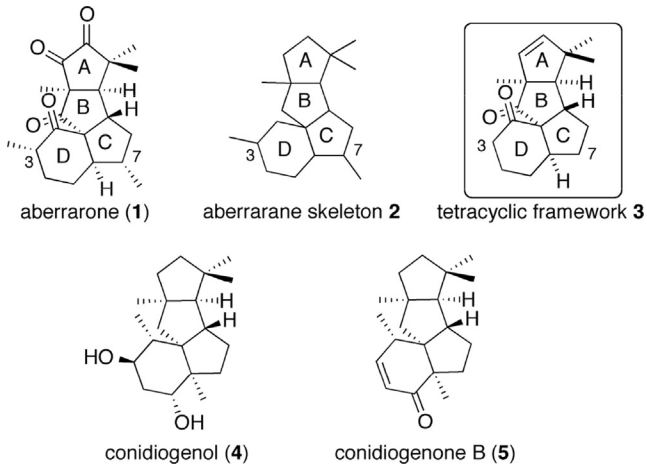
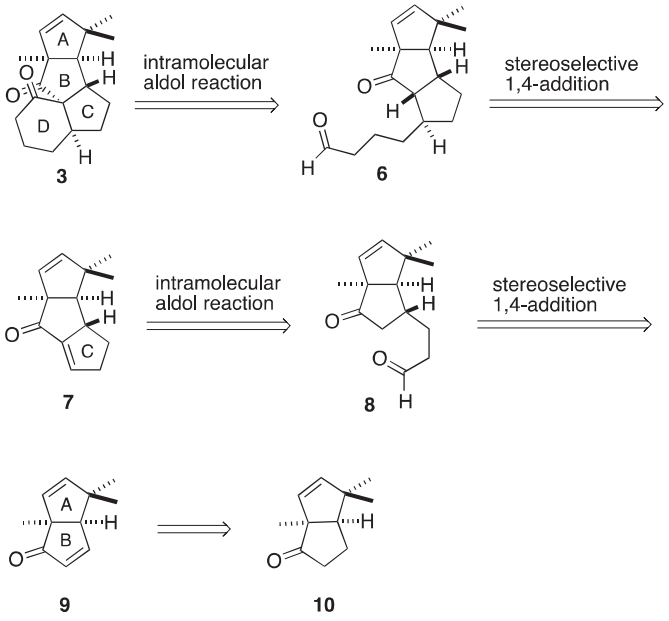


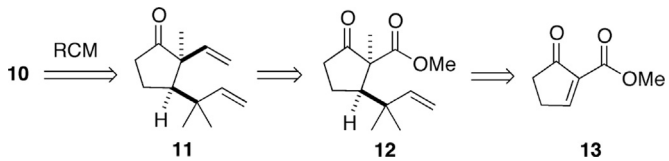
Fig. 1. Structures of abberarone (**1**) and related compounds.

unsaturated ketone **9** would be derived from compound **10** through Ito-Saegusa oxidation.



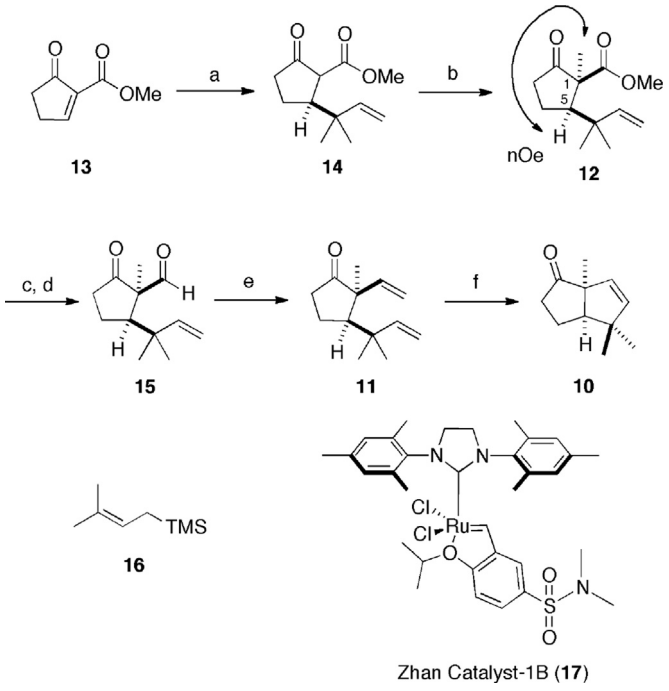
Scheme 1. Synthetic strategy for C- and D-ring construction.

The bicyclic compound **10** has been reported by Yamamoto and co-workers.[5] However, their synthetic route was inefficient (7 steps, overall yield 6% from *m*-methylanisole) for application to the synthesis of compound **2**. Therefore, we attempted to develop a new route for synthesis of compound **10**. The synthetic plan for compound **10** is shown in Scheme 2. Compound **10** would be derived by the ring-closing metathesis (RCM) of compound **11**, which was prepared from compound **12** through a three-step operation. Compound **12** would be obtained from the unsaturated β-ketoester **13**[6] by 1,4-addition using trimethylprenylsilane and stereoselective methylation to an activated methine moiety.



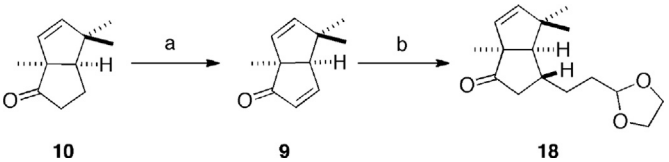
Scheme 2. Synthetic plan of bicyclic compound **10**.

The synthetic study started with introduction of the isoprenyl group into unsaturated β-ketoester **13** using Hosomi-Sakurai reaction as shown in Scheme 3. Treatment of **13** with trimethylprenylsilane **16**[7] in the presence of a titanium tetrachloride afforded the compound **14** in 91% yield. Stereoselective methylation of compound **14** furnished the compound **12** in 83% yield as a single diastereomer. Stereochemistry of compound **12** was determined by the NOE correlation between the methyl group at C1 and H5. The Compound **12** then was transformed to compound **11** via a three-step operation, including reduction of **12** with lithium aluminum hydride, Swern oxidation of the resulting diol, and Wittig reaction of aldehyde **15**. Subsequently, the RCM of diene **11** was attempted. After screening a ruthenium catalyst for RCM, the Zhan catalyst-1B (**17**)[8] was found to be suitable for this reaction.[9] Thus, the RCM of diene **11** with Zhan catalyst-1B (**17**) in toluene at 80 °C for 2 h gave the bicyclic compound **10** in 90% yield. Obviously, this synthetic route to bicyclic compound **10** is more efficient compared with the method of Yamamoto[5] (6 steps, 47% vs 7 steps, 6%).



Scheme 3. Reagents and conditions: (a) **16**, $TiCl_4$, CH_2Cl_2, −78 °C, 91%; (b) CH_3I, *t*-BuOK, *t*-BuOH, rt, 48 h, 82%, dr=> 95:5; (c) $LiAlH_4$, THF, 0 °C, 6 h, 91%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 30 min then −40 °C, 1 h, 88%; (e) $[Ph_3PCH_3]Br$, KHMDS, THF, −78 °C, 30 min then rt, 3 h, 87%; (f) Zhan catalyst-1B (**17**), toluene, 80 °C, 48 h, 90%.

With the successful synthesis of bicyclic compound **10**, focus was on the construction of C- and D-rings using stereoselective 1,4-addition followed by intramolecular aldol reaction protocol. Ito-Saegusa oxidation[10] of **10** provided the compound **9** in 70% yield for 2 steps (Scheme 4). Treatment of **9** with Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane in the presence of copper bromide dimethyl sulfide complex afforded the compound **18** in 83% yield as a single diastereomer. The high stereoselectivity



Scheme 4. Reagents and conditions: (a) (i) TMSOTf, Et_3N, CH_2Cl_2, 0 °C, 1 h; (ii) $Pd(OAc)_2$, O_2, DMSO, rt, 24 h, 70% for 2 steps; (b) 2-(2-bromoethyl)-1,3-dioxolane, Mg, $CuBr{\cdot}SMe_2$, THF, −78 °C, 83%, dr=>95:5.