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Synthesis of the hexacyclic triterpene core of the jujuboside saponins via tandem Wolff rearrangement–intramolecular ketene hetero-Diels–Alder reaction

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ABSTRACT

The jujubosides are saponin natural products reported to have immunoadjuvant, anticancer, antibacterial, antifungal, and antisweet activities. The triterpene component, jujubogenin contains a unique tricyclic ketal motif comprising the DEF ring system. Herein, we describe our efforts toward the total synthesis of jujubogenin, using a sterically-demanding intermolecular Diels–Alder reaction to assemble the C-ring and a tandem Wolff rearrangement–intramolecular ketene hetero-Diels–Alder reaction to form the DF-ring system. Acid-catalyzed cyclization of the resulting bicyclic enol ether then closes the E-ring to provide the hexacyclic core of jujubogenin.

1. Introduction

The jujubosides are glycosylated triterpene natural products isolated mainly from Chinese and Indian herbal plants. They exhibit a wide range of bioactivities including immunoadjuvant, anticancer, antifungal, antibacterial, and antisweet activities.[1–3] In particular, jujuboside A (**2**) has been reported to generate higher antibody titers in mouse vaccinations and lower *in vitro* toxicity compared to QS-21,[2,3] another saponin immunoadjuvant that is a component of the Mosquirix (RTS,S/AS01) malaria vaccine[4] and Shingrix shingles vaccine[5] and has been investigated as the immunoadjuvant of choice in numerous other vaccine clinical trials.[6–12] Based on our laboratory's long-standing interest in saponin immunoadjuvants[13–20] we initiated a research program toward the total synthesis of jujuboside A to enable detailed structure–activity relationships studies. We recently disclosed our synthesis of the complex, doubly-branched pentasaccharide portion of jujuboside A.[21] Herein, we describe our efforts toward the total synthesis of triterpene portion of jujuboside A, called jujubogenin (**1**).[22]

Jujubogenin is a complex triterpene with nine contiguous stereocenters, six of which are quaternary, including four all-carbon quaternary centers (Fig. 1). In addition, the tricyclic DEF ring system bearing a C16 ketal is unique to jujubogenin. Despite these striking structural features and numerous reported biological activities of the jujubosides, a chemical synthesis of the jujubogenin triterpene has not been reported. Developing a synthetic strategy that would address the complexity of these structural features and allow structure–activity relationship studies of this triterpene and related natural products presents a significant challenge.

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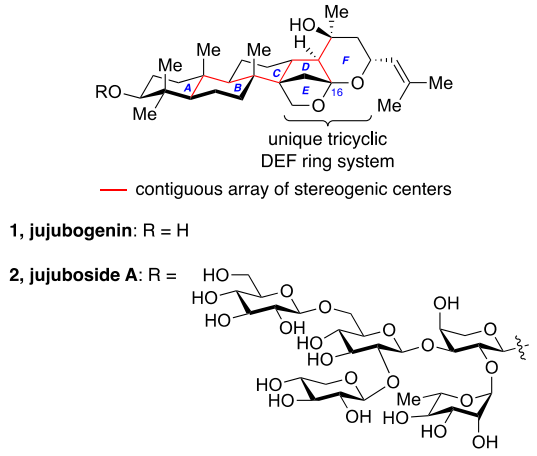


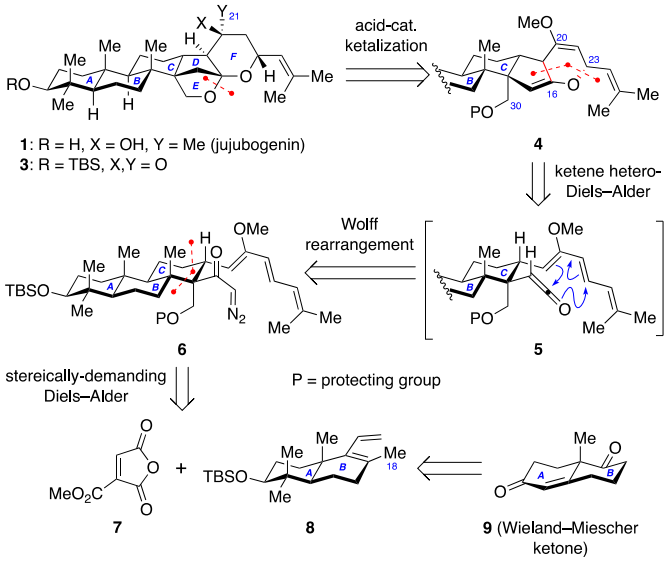
Fig. 1. Structures of jujubogenin (**1**) and jujuboside A (**2**).

2. Results and discussion

2.1. Retrosynthetic analysis of jujubogenin (*1*)

Retrosynthetically, we envisioned late-stage installation of the C21 methyl group of jujubogenin (**1**) by addition of methyl lithium to the convex α-face of ketone **3** (Scheme 1). Ketone **3** could be assembled from bis(enol ether) **4** through a series of functional group interconversions including an acid-catalyzed tandem C30 alcohol deprotection, ketalization, and methyl enol ether hydrolysis.

The structural complexity of bis(enol ether) **4** could be dramatically reduced by a tandem Wolff rearrangement–intramolecular ketene hetero-Diels–Alder reaction starting from diazoketone **6** via ketene intermediate **5**. The highly functionalized C-ring of the jujubogenin would be furnished using a sterically-demanding intermolecular Diels–Alder reaction between diene **8** and dienophile **7**. Diene **8** would be prepared in enantioenriched form from the Wieland–Miescher ketone (**9**).[23]



Scheme 1. Retrosynthetic analysis of jujubogenin (**1**).

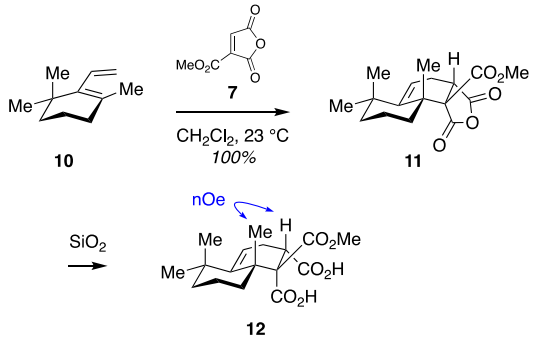
2.2. Model study of sterically demanding Diels–Alder reaction

One of the key transformations in our synthetic plan for the synthesis of jujubogenin involved a sterically-demanding Diels–Alder reaction between diene **8** and dienophile **7**. Such sterically-demanding cycloadditions are challenging despite many advances in Diels–Alder reaction methodology due to several reasons: 1) the diene **8** bears a C18 methyl group that hinders the adoption of s-*cis* conformation of the diene required for the Diels-Alder reaction; 2) the dienophile **7** is trisubstituted, thus the desired reaction pathway involves a highly congested transition state with two adjacent all-carbon quaternary centers; 3) the diene **8** lacks a strong electron-donating substituent to control the regioselectivity of the reaction.

In support of the challenges highlighted above, it has been shown that dienes that are structurally similar to our proposed diene **8** react only with highly activated and sterically accessible dienophiles, such as tetracyanoethylene and acetylene dienes with an electron-withdrawing group, or under forcing condition such as high pressure.[24,25] Diactivated dienophiles such as dimethyl fumarate/maleate and maleic anhydride do not react with this type of diene. On the other hand, (carbomethoxy)maleic anhydride **7** is a highly activated dienophile.[26] Kinetic studies by Hall and co-workers revealed that it is more reactive than tetracyanoethylene. Interestingly, dienophile **7** reacts even with styrene as a diene to give the corresponding Wagner–Jauregg type[27] adduct. Despite this high reactivity, there has been limited use of this dienophile to deliver substituted cyclohexanes.[26,28–33] In fact, only one application to natural product synthesis has appeared in the literature.[33]

We anticipated that the high reactivity of dienophile **7** would compensate for the poor reactivity of diene **8** in our proposed sterically-demanding Diels–Alder reaction. To test this hypothesis, we first conducted a model study with readily accessible diene **10**.[34] We were delighted to find that the reaction between diene **10** and dienophile **7** proceeded smoothly at ambient temperature to give tricycle **11** as a single regio- and stereoisomer (Scheme 2). Structural assignment was based on extensive 2D-NMR and nOe studies of the dicarboxylic acid derivative **12**, which was recovered after silica gel purification of anhydride **11**. Mechanistically, the cycloadduct **11** arises from an *endo* transition state relative to the anhydride portion of the dienophile.

Although this achiral model system **10** does not address the facial selectivity of dienophile approach, it validated the feasibility of this approach with respect to reactivity, setting the stage for its evaluation in the context of the more complex jujubogenin system below.



Scheme 2. Model study of sterically-demanding Diels–Alder reaction.