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Concise Synthesis of the Tetracyclic Framework of Azadiradione: Tandem Radical Cyclization Route

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Azadiradione, a limonoid isolated from the neem plant, possesses a unique stereostructure distinct from that of the steroids. We describe a concise synthesis of the tetracyclic framework of azadiradione by a tandem radical cyclization process.

Limonoids, highly oxygenated triterpenes, are abundant secondary metabolites of citrus fruit, and more than 300 congeners have been isolated.[1] While the prototypical limonoid framework is characterized by a 4,4,8-trimethyl-17-furylandrostane, this family encompasses a diverse array of structural architectures as a result of oxidation and skeletal rearrangements, and features a unique C13α-methyl group. Limonoids exhibit a wide spectrum of biological properties such as antifeedent and growth regulating activities on insects, as well as antibacterial, antifungal, anticancer, antiviral, and a number of pharmacological activities in humans.[2] Owing to their significant biological activities and complex architectures, the limonoids have attracted keen interest from synthetic chemists. Only two groups have succeeded in the total synthesis of limonoids to date,[3,4] though many synthetic efforts have been conducted.[5] We describe here a concise synthesis of the framework of azadiradione (**1**) (Chart 1),[6] a representative member of the limonoids, through a tandem radical cyclization reaction.

Our synthesis commenced with farnesol (**2**), which was converted to allylic alcohol **3** (Scheme 1).[15] Subsequent chlorination of **3**, addition of ethyl 2-chloroacetoacetate dianion,[7] and removal of the TMS group furnished acyclic β-ketoester **4**. Manganese-mediated tandem radical cyclization of **4** according to Snider's method[8] gave rise to the tetracyclic framework **5** along with its C13-epimer **6** (23% combined yield, **5**:**6** = 2:1). The structures of **5** and **6** were unambiguously confirmed by X-ray crystallographic analyses of **5** and **7**, the latter of which was derived from dechlorination of **6**, respectively[9] (Figures 1 and 2).[15] Note that **5** possesses the *cis*-fused CD-ring, which is a characteristic of limonoids, while a well-established cation–π cyclization gave only the *trans*-fused isomer.[10–12]

Oxidative cleavage of the exo methylene of **5** with a catalytic amount of $RuCl_3$ in the presence of $NaIO_4$ afforded **8** (Scheme 2).[15] Simultaneous removal of the ethyl ester and chlorine of **8** was accomplished by the Krapcho reaction to give enone **9** in 61% yield.[13,14] Finally, chemo- and regioselective dimethylation at the C4 position of **9** furnished the azadiradione framework **10** in 41% yield.

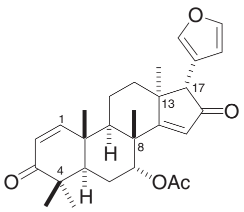
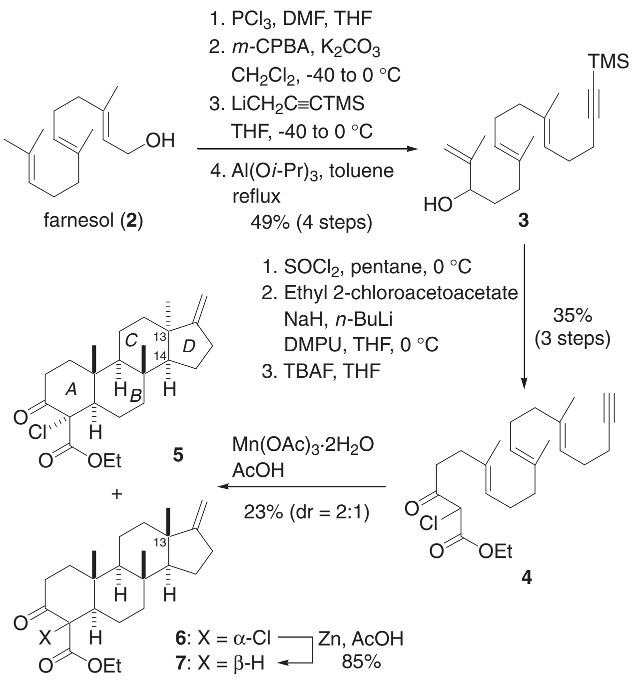


Chart 1.

In summary, we have developed a concise radical route to the framework of **1**, in which the four carbon–carbon bonds and seven stereocenters featuring the C13,14-*cis* configuration were



Scheme 1. Tandem radical cyclization.

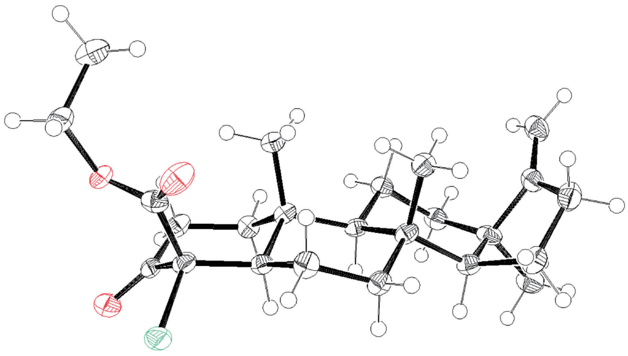


Figure 1. ORTEP drawing of **5**.

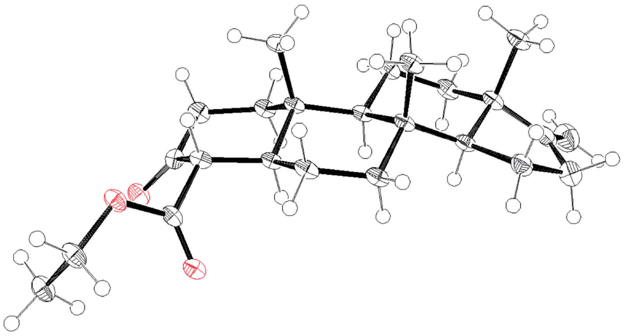
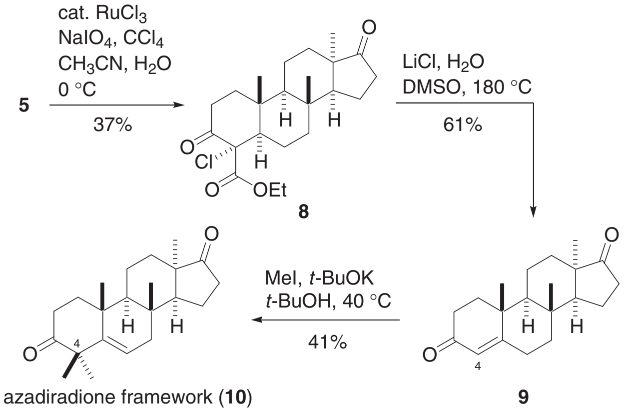


Figure 2. ORTEP drawing of **7**.



Scheme 2. Synthesis of azadiradione framework.

constructed in one step (**4** → **5**). The application of this radical strategy to the total syntheses of **1** and other limonoids is being actively investigated in our laboratory.

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