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A Short Enantioselective Total Synthesis of the Fundamental Pentacyclic Triterpene Lupeol

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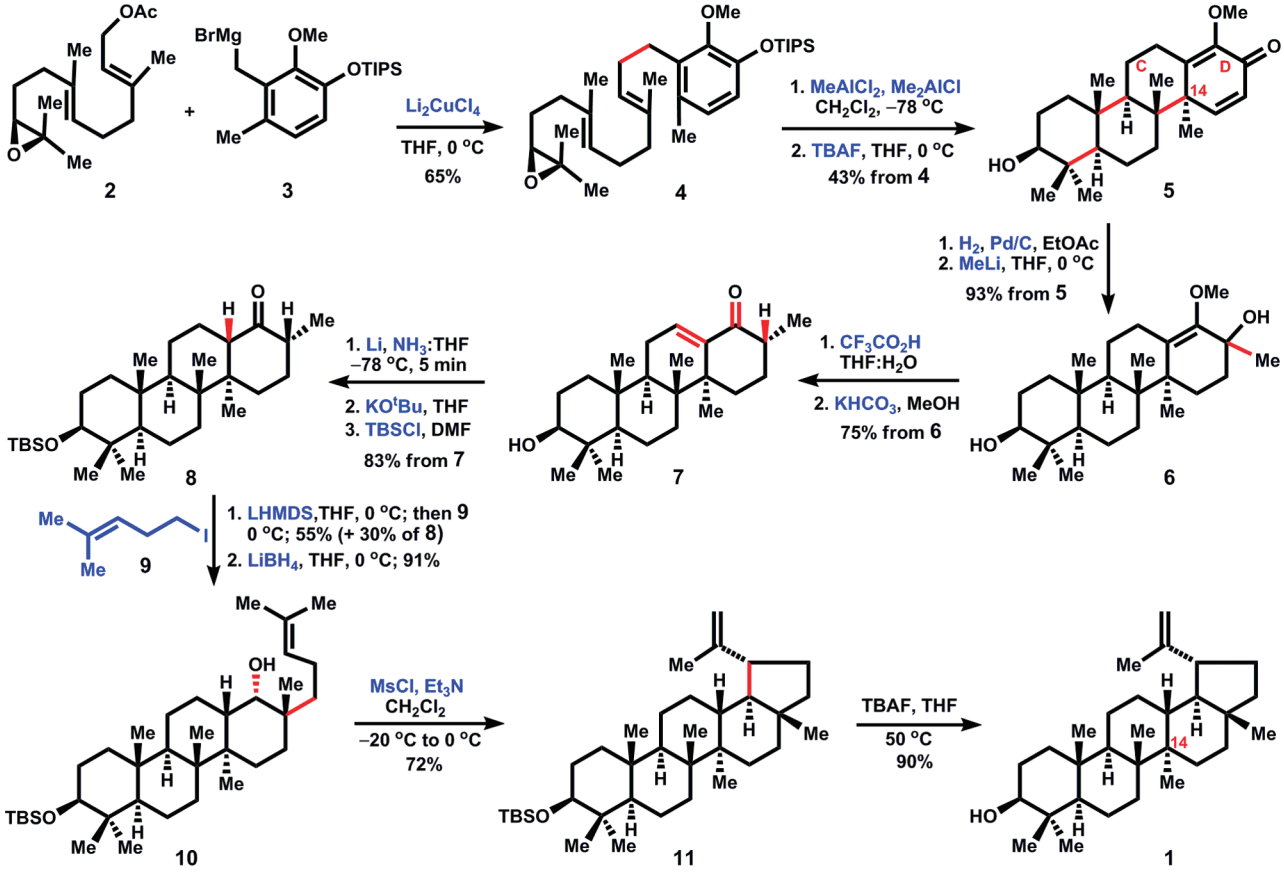
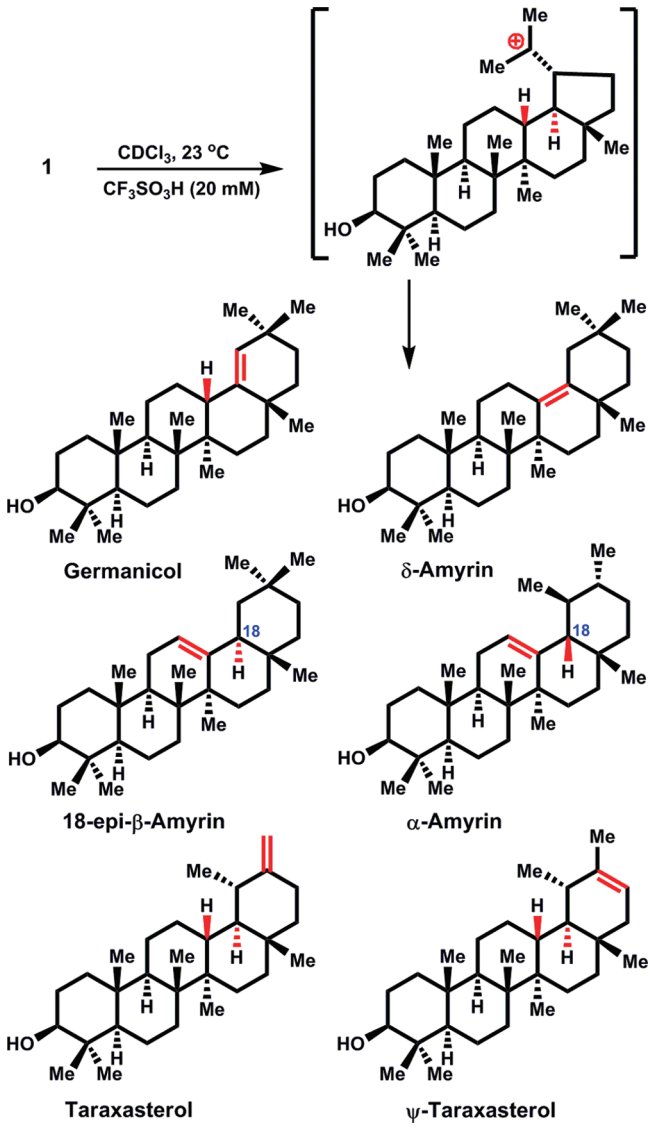
The direct, one-step pentacyclizaion of (*S*)-2,3-oxidosqualene to the pentacyclic triterpene lupeol (**1**, Scheme 1)[1] is a remarkable example of biosynthetic efficiency. The chemical emulation of this elegant biosynthetic conversion remains an elusive challenge in modern synthesis. In fact, there has not even been a successful multistep enantioselective synthesis of lupeol, the closest approximation being a relay synthesis[2] of racemic lupeol via an oxidation product[3] of natural lupeol. Described herein is a simple enantioselective solution to the longstanding challenge posed by the lupeol molecule. Our enantioselective synthesis of lupeol required the careful choice of substrate for stereocontrolled cation olefin polycyclization and was facilitated by recent studies.[4] We also discuss herein a related matter of biosynthetic interest, the further one-step conversion of lupeol to the naturally occurring pentacyclic triterpenes germanicol, δ-amyrin, 18-epi-β-amyrin, taraxasterol, ψ-taraxasterol, and α-amyrin via cationic intermediates.

The first step in the synthesis of lupeol (see Scheme 1) was the position-selective, copper-promoted coupling of the readily available (*S*)-epoxy acetate **2**[4,5] with Grignard reagent **3** to form cleanly the primary−primary coupling product **4**. Various other coupling procedures, for example using Pd catalysis, proved to be unsatisfactory because of low position selectivity and yield. Lewis acid activation of the chiral epoxide **4** provided after TBAF treatment the required tetracycle product **5** in acceptable yield (*ca.* 80% per ring formed). This step occurs stereoselectively and also solves the difficult problem of putting in place the angular methyl group at the C/D ring juncture (C(14) position in **1**). Selective catalytic hydrogenation of the disubstituted double bond in **5** and subsequent methylation afforded the tertiary alcohol **6**, which upon sequential exposure to acid and base provided the α,β-enone **7** in good yield. Reduction of the α,β-double bond in **7**, basic stereoequilibration, and silylation gave the desired *trans*−*antitrans*−*antitrans* saturated ketone **8**, alkylation and reduction of which produced the alcohol **10**. Cyclization of **10** to the lupeol ether **11** occurred *spontaneously* under mesylation conditions and led to lupeol itself after desilylation (64%) along with the noncyclized 1,2-elimination product (bacchara-12,21-dien-3β-ol, 16%). Synthetic and natural samples of

Scheme 1. Synthesis of Lupeol (**1**)



Scheme 2



lupeol were identical spectroscopically and by measurements of optical rotation, mp and mixed mp.

Although the synthesis of lupeol described above is very different from the process used in biosynthesis, it shares the use of cationic cyclization to simplify and shorten the synthesis. It is important to note, however, that in a chemical setting careful choice of the substrates for cyclization is absolutely crucial for success. A previous study provided essential guidance.[4]

We have also examined the transformation of lupeol *via* cationic intermediates to other pentacyclic triterpenes.[6] This research was motivated in part by recent work in our laboratory on the conformational energetics of backbone rearrangement of pentacyclic triterpenes,[7] and specifically by the finding that the conformational energetics for the conversion of the lupanyl cation to the germanicyl and oleanyl (β-amyrin) cations favor rearrangement. Consequently, we performed some simple experiments with lupeol to clarify the tendency of the lupanyl cation to rearrange under minimal acidic conditions.

Thus, lupeol was treated with a 20 mM solution of triflic acid in $CDCl_3$ at 23 °C, and the appearance of the resulting rearrangement products was monitored by ^{1}H NMR at 500 MHz by comparison with reference ^{1}H NMR data for lupeol, germanicol, β-amyrin, δ-amyrin (13,18-double bond isomer of β-amyrin), 18-epi-β-amyrin, α-amyrin, ψ-taraxasterol, and taraxasterol.[8] After 60 min only 18% of lupeol remained, the rest having been converted to germanicol (12%), δ-amyrin (16%), 18-epi-β-amyrin (12%), α-amyrin (6%), ψ-taraxasterol (38%), and taraxasterol (5%). The relative amounts of these compounds after 2 h were (respectively): 0%, 12%, 18%, 12%, 8%, 42%, and 5%. After 12 h, they were (respectively): 0%, 15%, 12%, 17%, 10%, 29% and 10%. At near equilibrium (24 h), 0% lupeol 15% germanicol, 12% δ-amyrin, 17% 18-epi-β-amyrin, 10% α-amyrin, 29% ψ-taraxasterol, and 10% taraxasterol were present. As anticipated from the recent results,[7] further backbone rearrangement in the direction of friedelin, which is sharply higher in terms of conformational energetics, does not happen under the conditions of our experiments. The amazing ability of a pentacyclic triterpene synthase to channel the cyclization of (*S*)-2,3-oxidosqualene to a particular pentacyclic triterpene product is a consequence of (1) the precise positioning on the protein of a single proton accepting group and (2) driving force for backbone rearrangement that results from a *favorable total energy for the combination* of enzyme *and* bound cationic substrate. The results summarized above on the facile conversion of lupeol to other pentacyclic triterpenes carry synthetic meaning since they imply that any projected chemical route to lupeol that relies on protic acid catalyzed formation of this target is problematic.

The enantioselective synthetic pathway described herein is noteworthy not only for its brevity and stereocontrol but also for its inclusion of two unusually interesting ring-forming steps. First, the conversion of **4** to tetracycle **5** depends on the careful choice of the substituents on the aromatic ring to (1) activate that ring for a sterically difficult cyclization, (2) channel the cyclization to a single tetracyclic product, (3) establish functionality in **5** that allows rapid execution of the final steps of the synthesis, and (4) minimize the possibility of Lewis acid coordination to the electron supplying groups (which would deactivate the aromatic ring). Second, the *unusually facile* cationic conversion of **10** to **11** under essentially nonacidic conditions is highly instructive.

Supporting Information Available: Experimental procedures and characterization data for all reactions and products, including copies of ^{1}H NMR and ^{13}C NMR spectra. Time course studies of the triflic acid catalyzed rearrangement of lupeol to other naturally occurring pentacyclic triterpenes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For the details of the ^{1}H NMR data and time course studies of the acid-catalyzed rearrangement of lupeol, see: Supporting Information.

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