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Asymmetric Total Syntheses of Euphol and Tirucallol

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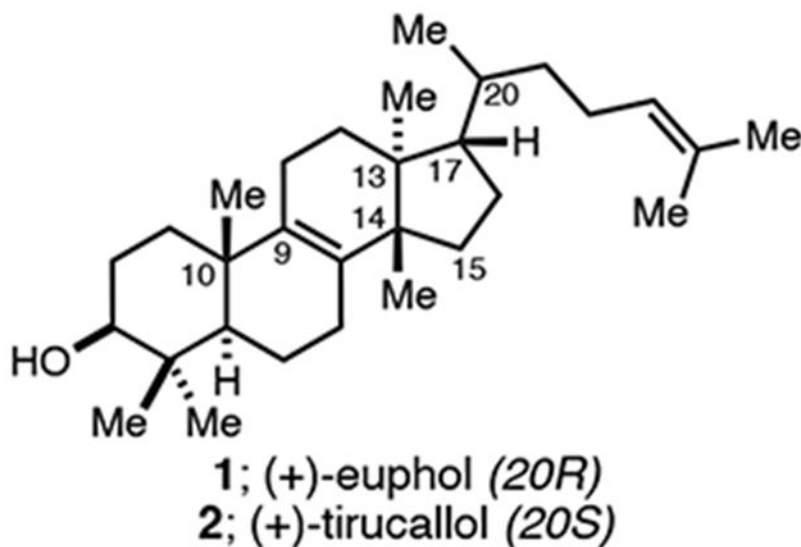
Abstract

Asymmetric *de novo* syntheses of euphol and tirucallol have been accomplished by way of a concise sequence of chemical steps featuring several modern stereoselective transformations. The preparative solution described for these complex problems in natural product synthesis departs significantly from biomimetic polyene cyclization chemistry that has been leveraged to address related tetracyclic triterpenoid targets. In particular, a diastereoselective Friedel–Crafts type cyclization was employed to establish a tetracycle bearing a stereodefined quaternary center at C9 (steroid numbering) that provided access to intermediates of relevance for introducing the C10 and C14 quaternary centers by sequential stereospecific 1,2-alkyl shifts (C9 → C10, and C15 → C14). Finally, the stereodefined C17-side chain was introduced in a single step by late-stage stereoselective conjugate addition to an intermediate possessing a D-ring enone. Notably, these *de novo* asymmetric syntheses are the first of their kind, providing completely synthetic access to enantiodefined euphane and tirucallane systems. Overall, each synthesis has been accomplished in fewer than twenty linear chemical steps from a simple Hajos–Parrish-derived ketone through a sequence that features just fifteen chromatographic operations.

Graphical Abstract

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The authors declare no competing financial interest.



Tetracyclic triterpenoids derived from the cationic cyclization of 2,3-oxidosqualene represent a large family of natural products that have been found to possess a wide array of medically relevant properties.¹ Among these, the fundamental tetracyclic triterpenoids euphol (**1**), tirucallol (**2**) and lanosterol (**3**; Figure 1A), are known not only for their activities as anti-cancer and anti-inflammatory agents, but also appreciated as precursors to scores of bioactive natural products including, in the case of lanosterol, cholesterol and the steroid hormones.² While tetracyclic triterpenoids have played central roles in the development of organic chemistry, first from a structural elucidation perspective, then serving as targets for synthesis, these fundamental examples (**1–3**) remain unsolved problems for asymmetric *de novo* synthesis.³ Structural features that continue to represent obstacles for stereoselective syntheses of these targets include the presence of vicinal quaternary centers at C13 and C14, the central unsaturation at C8–C9, and the stereodefined and unsaturated side chain at C17. In fact, there has not yet been a successful multistep asymmetric synthesis of euphol, tirucallol, or lanosterol reported, the closest being: (1) Woodward's conversion of (–)-cholesterol to (+)-lanosterol, and (2) Johnson's relay synthesis of (+)-euphol and related semisynthesis of (+)-tirucallol.^{4,5} As a result, programs seeking to identify novel synthetic variants of these natural products as leads in medicinal chemistry are constrained to semisynthesis, where only modest structural/skeletal changes are straightforward to accomplish with available reaction technology.⁶ As such, in addition to addressing these enduring problems in *de novo* asymmetric synthesis, we became interested in establishing a concise synthetic entry to these systems that could one day enable medicinal exploration in a manner not feasible currently.⁷ Our efforts, also being guided by using natural product targets as a testing ground for recently developed reaction technology, has resulted in concise asymmetric syntheses of euphol (**1**) and tirucallol (**2**) that feature a stereoselective intramolecular Friedel–Crafts cyclization, tandem oxidative dearomatization/Wagner–Meerwein rearrangement, semi-pinacol rearrangement that forges both the C10 and C14 quaternary centers, and late-stage introduction of stereodefined and unsaturated C17-side chain common to scores of tetracyclic triterpenoid natural products by conjugate

addition. Figure 1B illustrates the basic features of our retrosynthetic analysis that ultimately concludes with our plan of employing hydrindane **6** and tosylate **7** as readily available starting materials.

Prior to presenting the asymmetric *de novo* synthesis of **1** and **2** central to this work, we offer a summary of prior studies by Johnson that ultimately resulted in a relay synthesis of (+)-**1** and a semisynthesis of (+)-**2**.⁵ As illustrated in Figure 2A, cationic cyclization of (+/-)-**8** was employed to generate the polycyclic product (+/-)-**9**; a structure containing a C8–C9 alkene and vicinal quaternary stereocenters at C13 and C14. While confirming the feasibility of the planned cationic cyclization, the process proceeded in only ~16% yield. Moving along, seven additional steps were used to convert this intermediate to (+/-)-**10** in 9% yield. Instead of advancing racemic **10** to the targeted natural products, degradation of euphol acetate was used to secure sufficient quantities of (-)-**10** to complete a relay-based synthesis of (+)-euphol (**1**) and a semisynthesis of (+)-tirucallol (**2**) (Figure 2B).

Our efforts to accomplish the asymmetric *de novo* synthesis of these tetracyclic triterpenoid targets began with base-mediated alkylation of enone **6** (derived from the Hajos–Parrish ketone) and the homobenzylic tosylate **7** (Figure 3).⁸ In short, α -alkylation of the conjugated enolate of **6** is followed by base-mediated equilibration to generate enone **11**.⁹ With our next goal of accomplishing a stereoselective intramolecular Friedel–Crafts cyclization, we applied a two-step sequence that first introduces a C9 methyl group by 1,2-addition of MeMgBr to the ketone of **11**. As we have previously shown, treatment of the tertiary alcohol product of this reaction with BF₃•OEt₂ results in a highly stereoselective cyclization that establishes the C9 stereocenter of **12** with 20:1 ds.¹⁰ Desilylation followed by oxidation to the enone provided access to **14** via the intermediacy of ketone **13**. Notably, dienone **14** was thought to be an ideal intermediate for conversion to a tetracycle that possesses key structural features of euphane natural products.

First, the differential substitution of dienone **14** was leveraged to accomplish site-selective conjugate addition (MeMgBr, CuI), resulting in a product that possesses a C15 α -methyl substituent (**5**). Moving forward, anisole demethylation with DIBAL also stereoselectively reduced the C17 ketone of **5**, delivering a phenolic product that was smoothly converted to **15** by PIDA-mediated oxidative dearomatization followed by group-selective Wagner–Meerwein rearrangement as depicted in **A**. Through this two-step sequence, the methyl group previously located at C9 is shifted to C10, and a diene is generated that spans C9,C8,C14 and C15. This latter functionality was appreciated to be of great potential future value in setting the critical vicinal quaternary centers characteristic of euphane and tirucallane natural products.

With **15** in hand, chemoselective reduction of the C1–C2 alkene (Wilkinson's catalyst, H₂) was followed by dissolving metal reduction of the enone, and alkylation of the resulting enolate with MeI. The combined features present in the resulting product, a 17 α -hydroxy group that was generated from the reductive demethylation of **5** and the aforementioned conjugated diene spanning the C and D rings that was generated naturally from the oxidative dearomatization process, were then exploited to accomplish initial chemo- and stereoselective hydroxy-directed epoxidation [VO(O*i*-Pr)₃, TBHP] and BF₃•OEt₂-mediated

semi-Pinacol rearrangement.¹¹ Notably, the intermediate generated from the stereoselective epoxidation positions the C15-methyl group on the β -face and sets the stage for precise installation of the C14 quaternary center in **17** by way of the allylic cation **B**. Finally, β -hydroxy ketone **17** was converted to the targeted enone **4** by the action of MsCl and DBU.

While compound **4** possesses the majority of structural features seen in euphane and tirucallane natural products, it lacks the stereodefined eight carbon side chain at C17. Noting that many triterpenoid natural products possess related side chains at this position, it was appreciated that approaches to the installation of this unit typically rely on several sequential chemical steps.¹² Here, we sought a means to introduce the entire side chain in a single step by stereoselective conjugate addition of an appropriately functionalized cuprate to the D-ring enone of **4**. Previous studies targeting an unrelated natural product have revealed that such a strategy might well be quite complex, owing to the fact that this type of conjugate addition establishes two stereocenters (one at C17 and one at C20).¹³ Preliminary studies with a simple cuprate derived from *i*-PrMgBr revealed that the stereochemical course of 1,4-addition to **4** was highly selective, delivering a product whereby C–C bond formation preferentially occurs on the undesired β -face at C17 (not depicted; see Supporting Information for details). To address this stereochemical issue, conjugate addition of the cuprate derived from **18** was conducted in the presence of TMSCl, resulting in an intermediated enolsilane that was subsequently oxidized to the corresponding enone by Saegusa–Ito oxidation.¹⁴ The result of this sequence was a 2:1 mixture of enones **19** and **20** that were separated by HPLC and subsequently converted to (+)-euphol (**1**) and (+)-tirucallol (**2**) by stereoselective reduction of the D-ring enone and C3 ketone (Li^0 , NH_3 followed by NaBH_4), followed by deoxygenation of the C15 ketone by Wolff–Kishner reduction.

Overall, these studies have resulted in the first *de novo* asymmetric total synthesis of any euphane or tirucallane natural product, doing so by completing the syntheses of the foundational tetracyclic triterpenoids (+)-euphol (**1**) and (+)-tirucallol (**2**). Key aspects of our synthetic design include: (1) stereoselective Friedel–Crafts cyclization that converts **11** to the tetracyclic intermediate **12** that possesses the critically important C9 quaternary stereocenter, (2) capitalizing on the differential substitution of the conjugated dienone **14** to introduce a methyl group that later winds up at the C14 quaternary center of the natural product targets, (3) PIDA-mediated oxidative dearomatization and group-selective Wagner–Meerwein rearrangement that establishes the C10 quaternary centers of the natural products and a conjugated diene spanning the C and D rings, (4) chemo- and stereoselective epoxidation of diene **16** that sets up subsequent semi-Pinacol rearrangement to install the C14 quaternary center, and (5) late-stage introduction of the stereodefined and unsaturated side chain at C17. We expect that aspects of this synthesis pathway will enable access to unique unnatural variants of euphanes and tirucallanes that would not be straightforward to access through established semisynthesis or relay synthesis-based approaches. Future efforts aiming to exploit such features in the design and synthesis of medically relevant natural product-inspired agents will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT:

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Data Availability Statement:

The data underlying this study are available in the published article and its Supporting Information.

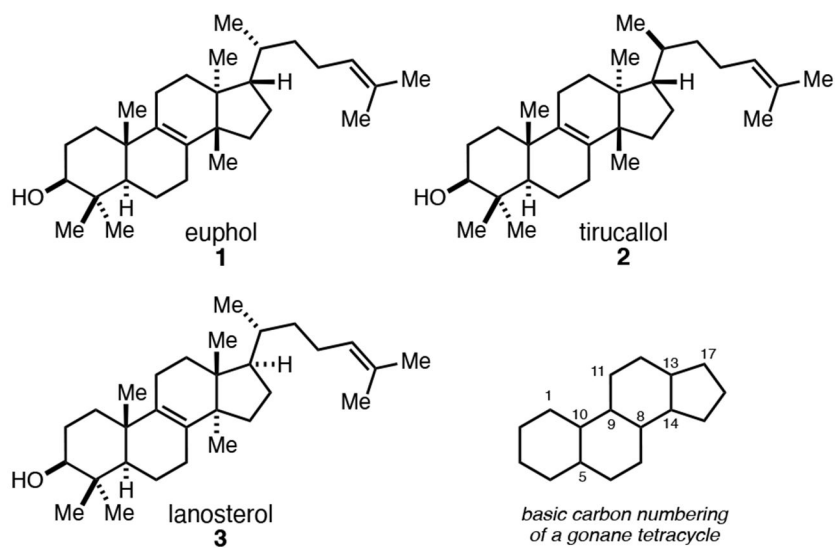
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A. Introduction to the fundamental tetracyclic triterpenoids euphol and tirucallol.



B. Retrosynthetic analysis.

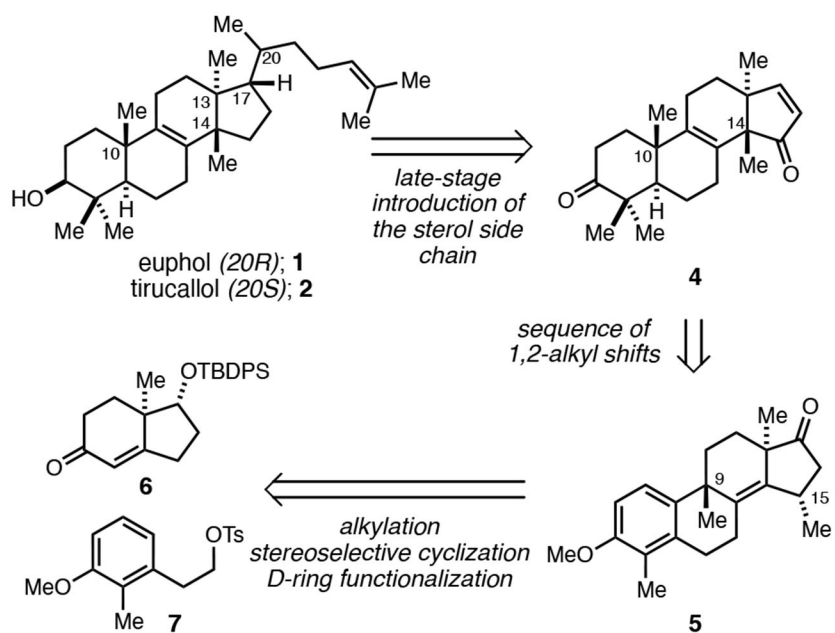
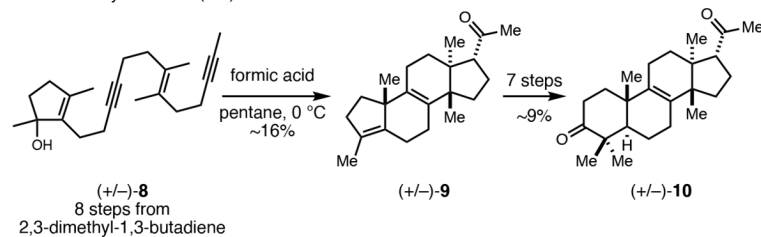
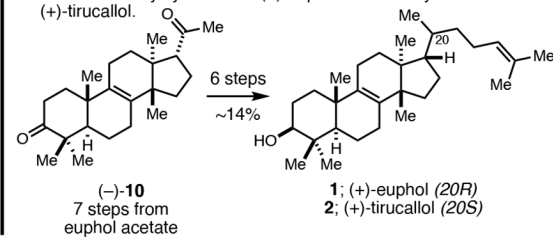


Figure 1.
Introduction.

A. Johnson's synthesis of (+/-)-10.



B. Johnson's relay synthesis of (+)-euphol and semisynthesis of (+)-tirucalol.

**Figure 2.**

Summary of Johnson's relay synthesis of euphol that exploits an acid-mediated cyclization of a dienediynol (**8**).

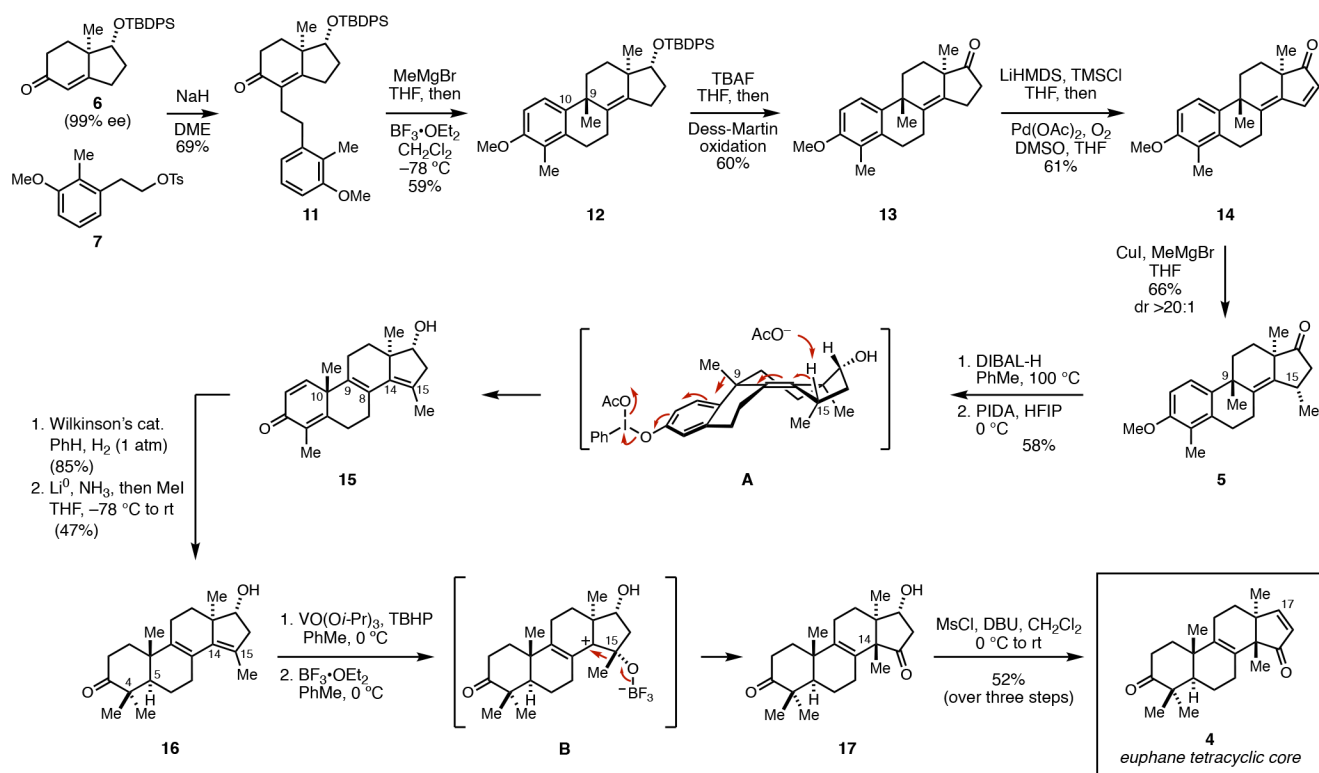


Figure 3. Synthesis of a tetracyclic enone (**4**) comprising the stereodefined euphol core from the Hajos-Parrish ketone-derived hydrindane **6**.

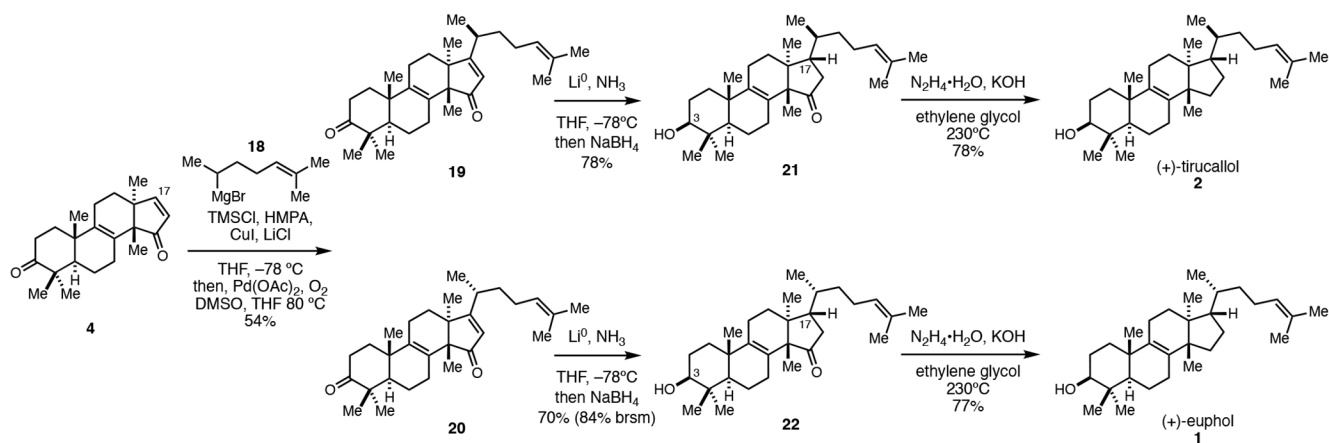


Figure 4. Introduction of the C17 side chain by conjugate addition and completion of the total syntheses of (+)-euphol and (+)-tirucalol.