

Sesquiterpenes

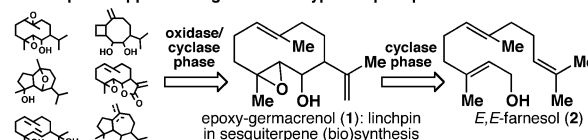
Scalable, Enantioselective Synthesis of Germacrenes and Related Sesquiterpenes Inspired by Terpene Cyclase Phase Logic**

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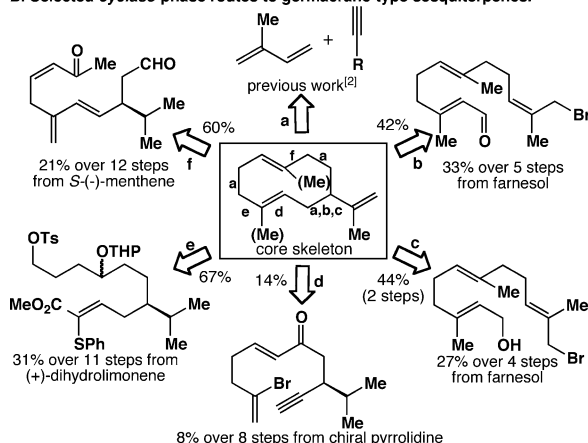
Our research group has a longstanding interest in harvesting new chemical knowledge by learning from terpene biosynthesis. The straightforward construction of carbocyclic terpene backbones, such as epoxy-germacrenol (**1**, Scheme 1 A), in a low oxidation state (*cyclase* phase) followed by regio-, chemo-, and stereoselective oxidative modifications (*oxidase* phase) allow Nature to access a wide variety of related family members in a divergent manner.^[1] Earlier this year, we reported our initial forays into the redox-economic synthesis of terpenes that resemble **1** by oligomerization of unfunctionalized isoprene (Scheme 1 B, path a).^[2] These studies ultimately led us to a new approach that utilizes the more advanced, yet readily available, C₁₅ building block farnesol (**2**, Scheme 1 A) as a starting point. In this Communication, a short, efficient, scalable, and enantioselective synthesis of **1** is described. Furthermore, we demonstrate how the key intermediate **1** can be processed not only to germacrene-type natural products by chemo- and stereoselective oxidations, but also to a variety of polycyclic sesquiterpene frameworks (like selinanes, guaianes, or elemenes) by acid-mediated transannular cyclization reactions.

For the goal of establishing a scalable, divergent, and broadly applicable entry to a variety of related sesquiterpene families, the germacrenes were identified as strategic key intermediates due to the following reasons: 1) germacrenes constitute a large class of cyclic terpenes, many of which have been shown to exhibit promising bioactivities and, in addition, are of growing importance in the perfumery industry; 2) germacrenes are known to be a biosynthetic linchpin en route to various related terpene congeners; and 3) most importantly, many studies have demonstrated that germacrenes can be transformed into mono-, di-, and tricyclic sesquiterpene subclasses (e.g., the elemenes, cadinanes, eudesmanes, guaianes, and bourbonanes) with the “Achilles heel” of these approaches being the accessibility of germacrene precursors in quantity.^[3]

A. Two-phase approach to germacrene-type sesquiterpenes.



B. Selected *cyclase*-phase routes to germacrene-type sesquiterpenes.



Scheme 1. A) Retrosynthetic outline. B) Known *cyclase*-phase routes (letters indicate retrosynthetic disconnections) yielding the germacrene skeleton.^[5] Cyclization conditions: a) cat. [Ni(cod)₂], PPh₃; b) CrCl₃·LiAlH₄, DMF, RT, 42%; c) 1. NaH, dicyclohexano-[18]crown-6, PhH, 80 °C, 2 h; 2. *t*BuLi, Et₂O, −78 °C, 10 h, 44% over 2 steps; d) Bu₃SnH, AIBN, PhH, 80 °C, 3 h, 14%; e) NaHMDS, DME, 85 °C, 50 min, 67%; f) TiCl₃, Zn/Cu, DME, 0 °C, 36 h, 60%. DME = dimethoxyethane, DMF = *N,N*-dimethylformamide.

Despite the industrial interest in terpene natural products, most of the naturally occurring germacrenes and their congeners are not easily available in bulk quantities due to a variety of challenges associated with their synthesis and/or isolation: germacrenes featuring a cyclodecadiene core are notoriously unstable to acidic and thermal conditions (leading to cyclized and/or rearranged products) and can often exist as conformationally semistable isomers at ambient temperature, thus creating complications with regard to purification and product analysis.^[4]

Although the total synthesis of sesquiterpenes has been an area of intense research efforts for decades,^[4] there is still no reliable synthetic pathway to rapidly forge the ten-membered germacrene carbocycle. The most effective synthetic approaches published to date (Scheme 1 B) suffer from serious drawbacks, such as low overall yield and poor step economy, and/or are impractical to perform on large scale. In addition, these syntheses either yield racemic products or start from chiral-pool starting materials. Whereas Nature's *cyclase* enzymes can efficiently overcome the entropic barrier

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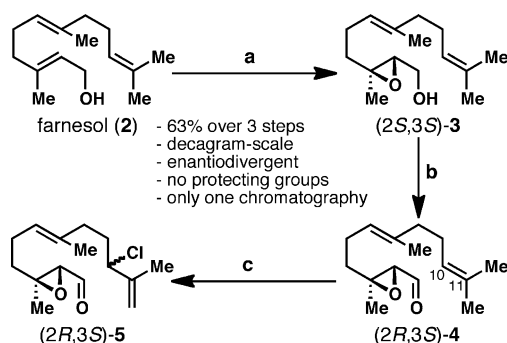
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for the formation of medium-sized carbocycles, direct ring closures from acyclic precursors remain a challenge in organic synthesis and are especially difficult to perform on larger scale (e.g., due to the need for high-dilution techniques). Finally, terpenes often occur in opposite enantiomeric forms in various organisms, and the programmed synthesis of either antipode of germacrenes and their congeners is a problem that has yet to be solved.

Our synthesis started with the readily available C₁₅ building block farnesol (**2**, < \$1.00/gram, Scheme 2), which was transformed in two known steps (Sharpless epoxidation^[6]



Scheme 2. Enantioselective synthesis of the coupling precursor **5** (shown for the (2*R*,3*S*)-enantiomer). Reagents and conditions: a) 4 Å MS, Ti(O*i*Pr)₄ (0.1 equiv), (+)-DET (0.12 equiv), TBHP (2 equiv), CH₂Cl₂, -50 °C, then **2** (1 equiv), 2 h, *ee* = 90%; b) SO₃·py (4 equiv), *i*Pr₂NEt (5 equiv), DMSO (10 equiv), CH₂Cl₂, 0 °C, 0.5 h; c) PhSeCl (0.12 equiv), NCS (1.1 equiv), CH₂Cl₂, RT, 1 h, 63% over 3 steps. DET = diethyl tartrate, TBHP = *tert*-butyl hydroperoxide, DMSO = dimethyl sulfoxide, NCS = *N*-chlorosuccinimide.

and Parikh–Doering oxidation) to epoxy aldehyde **4**.^[7] The crude material was used directly in the next step, a regioselective chlorination with concomitant transposition of the internal 10,11-double bond to the terminal position according to a protocol invented by Tunge et al.^[8] The chlorinated epoxy aldehyde **5** was thus obtained in 63% overall yield in three steps on decagram-scale from farnesol (**2**), with only one chromatographic purification. The route is amenable to produce both enantiomers of **5** and the most efficient route to a cyclization precursor in the context of germacrene total synthesis.

With the epoxy chloro aldehyde **5** in hand, cyclization conditions were explored to furnish the desired medium-sized germacrene ring system. Inspired by previous work of Shibuya et al.,^[5b] who performed a similar ring closure under Nozaki–Hiyama–Kishi (NHK) conditions using CrCl₃–LiAlH₄ (Scheme 1B, path b), the development of a robust, scalable, and diastereoselective cyclization was pursued. While several of the attempted reductive NHK-type or Barbier-type coupling conditions using Cr^{II}, Zn⁰, Sn⁰, In⁰, Ba⁰, Ni⁰, or Mn⁰ yielded the desired cyclized product, none of them proceeded with acceptable yield or selectivity. After an extensive screening of conditions, the intramolecular coupling of aldehyde **5** succeeded through a Pd-catalyzed umpolung allylation^[9] reaction. Using Pd(PPh₃)₄ and Et₂Zn in THF, we obtained intermediate **1** in varying yields of 10–30% (see

Table 1, entries 1 and 2). It was found that only 1.5 equiv of Et₂Zn (entry 2) is needed instead of 4 (entry 1). Interestingly, by switching the catalyst from [Pd(PPh₃)₄] (20 mol%) to [Pd(PPh₃)₂Cl₂] (10 mol%) and adding K₂CO₃ to the reaction

Table 1: Key ring closure of **5** through an umpolung allylation.

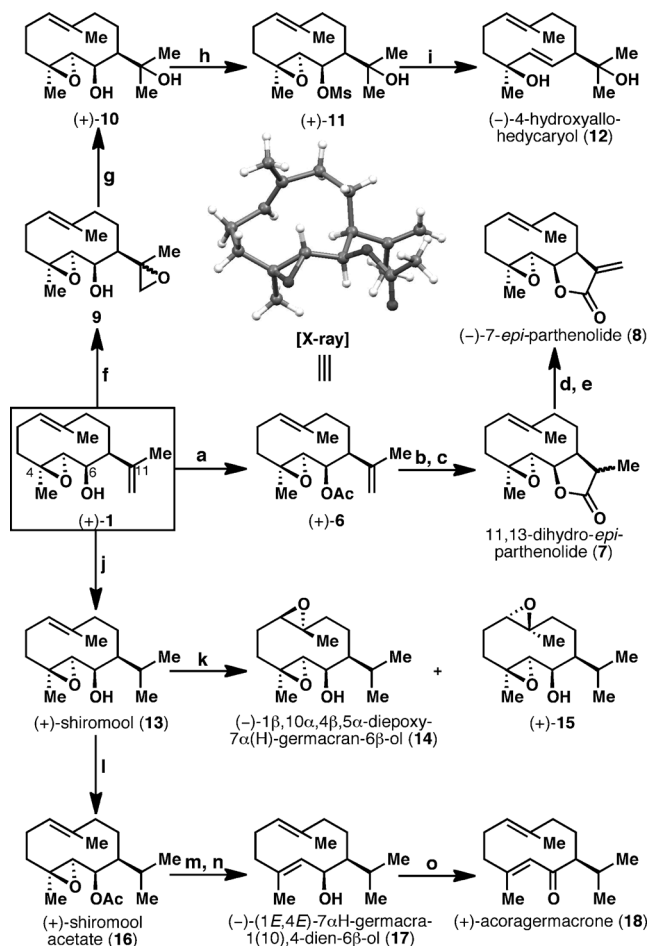
Entry	Catalyst	Ligand	Reduct.	Solv.	Base	1 ^[a]
1	[Pd(PPh ₃) ₄] ^[b]	–	Et ₂ Zn ^[c]	THF	–	19
2	[Pd(PPh ₃) ₄] ^[b]	–	Et ₂ Zn	THF	–	10–30
3	[PdCl ₂ (PPh ₃) ₂]	–	Et ₂ Zn	THF	K ₂ CO ₃	13–42
4	[PdCl ₂ (PPh ₃) ₂]	–	Et ₂ Zn	DMF	K ₂ CO ₃	32
5	[PdCl ₂ (PPh ₃) ₂]	–	Et ₂ Zn	DMA	K ₂ CO ₃	42 ^[d]
6	[PdCl ₂ (PPh ₃) ₂]	–	Et ₂ Zn	DMA	–	33
7	[PdCl ₂ (PPh ₃) ₂]	–	Me ₂ Zn	DMA	K ₂ CO ₃	0
8	[PdCl ₂ (PPh ₃) ₂]	–	Bu ₂ Zn	DMA	K ₂ CO ₃	31
9	Pd(OAc) ₂	PPh ₃	Et ₂ Zn	DMA	K ₂ CO ₃	15

Standard conditions unless otherwise stated: cat. (10 mol%), ligand (20 mol%), K₂CO₃ (1.5 equiv), solvent (0.033 M overall), **5** (100–600 mg scale, 1.0 equiv, 0.05 M, slow addition over 1.5 h), reductant (1.5 equiv, slow addition over 1.5 h), *T* = 50 °C. [a] Isolated yield. [b] Cat. (20 mol%). [c] 4 equiv of Et₂Zn. [d] Reproduced on six occasions, 42% was obtained for gram-scale. THF = tetrahydrofuran, DMF = *N,N*-dimethylformamide, DMA = *N,N*-dimethylacetamide.

mixture, the reaction proceeded more cleanly, which simplified the purification of the product (entries 3–6). Finally, changing solvents from THF to DMF then to DMA gave the best yield of 42% for cyclized product **1** (entries 4 and 5). Attempts to vary the reductant from Et₂Zn to Me₂Zn (entry 7), Bu₂Zn (entry 8), Et₃B, InI, or SnCl₂ also failed to improve the results (see Supporting Information, Table 1 for further details).

With optimized conditions in hand, the reaction was ultimately performed on gram-scale, by the dropwise addition of both substrate and Et₂Zn to a solution of [PdCl₂(PPh₃)₂] and K₂CO₃ in DMA, giving (+)-**1** in 42% yield, as the only diastereomer, opposite in stereoselectivity to that in the previously described conditions of Shibuya et al.^[5b] Overall, this diastereoselective ring closure strategy provides efficient access to the optically active germacrene-type key intermediate **1** reproducibly on gram-scale. In retrospect, it is not surprising that this ring closure was the only method that worked well, given the pioneering findings of Trost on medium and macrocyclic ring formation through π -allyl palladium catalysis.^[10]

With the supply problem solved, our attention turned to exploring the innate reactivity of **1** and its conversion to other natural products. Thus, acetylation of (+)-**1** with DCC, DMAP, and AcOH proceeded in quantitative yield to give (+)-**6** (Scheme 3). The stereochemistry of (+)-**1** was unambiguously established from the X-ray crystallographic analysis^[11] of acetate **6**, revealing the *cis* relationship between the 6-OH group and isopropylidene group in the 7-position. Hydroboration followed by oxidative work up of acetate **6** furnished the desired diol product, which was immediately



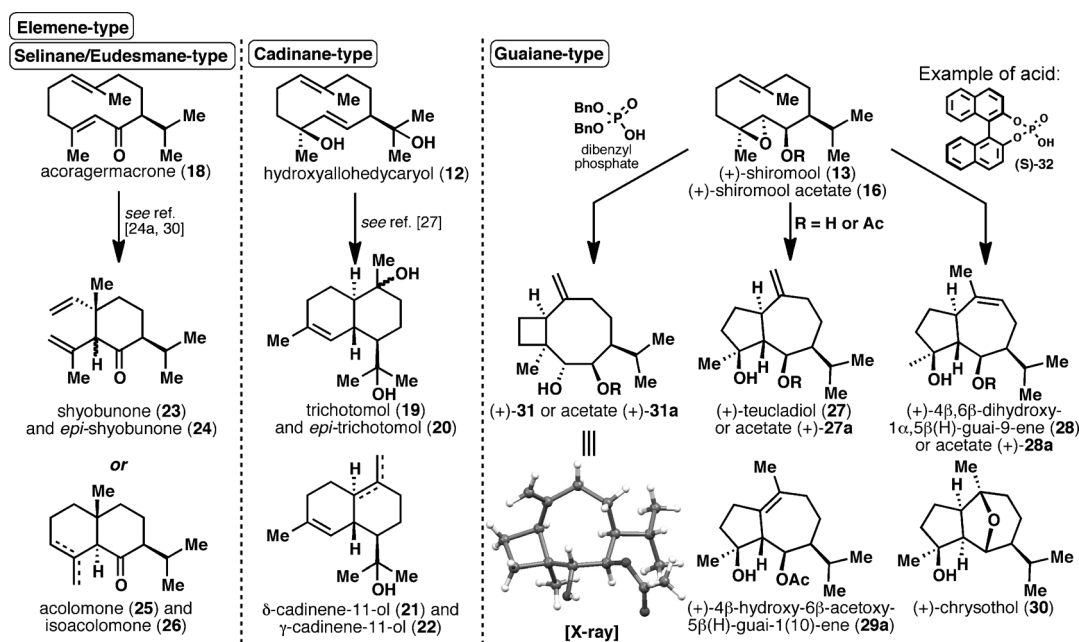
Scheme 3. Synthesis of germacrane-type sesquiterpenes. Reagents and conditions: a) DCC (3 equiv), DMAP (0.5 equiv), AcOH (3 equiv), CH₂Cl₂, RT, quant.; b) 9-BBN (2 equiv), THF, RT, 2 h, then EtOH, 6 h aq. NaOH, 35% aq. H₂O₂; c) TEMPO (0.5 equiv), PhI(OAc)₂ (4 equiv), CH₂Cl₂, RT, 4 h, 77% over 2 steps; d) LDA (3.6 equiv), THF, −78°C, 1 h, then CBr₄ (4 equiv), 0.5 h; e) TBAF (3 equiv), THF, RT, 1 h, 60% over 2 steps; f) VO(acac)₂ (0.27 equiv), TBHP (2.2 equiv), CH₂Cl₂, 0°C, 77%; g) LiAlH₄ (5 equiv), THF, 0°C, 20 min; h) MeSO₃Cl (3 equiv, as 2 portions), Et₃N (3 equiv, as 2 portions), CH₂Cl₂, −5°C, 0.5 h, 44% over 2 steps; i) lithium naphthalenide (10 equiv, as 2 portions), THF, −25°C, 20 min, 65% of **12**, 23% of **10**; j) Crabtree's cat. (7.5 mol%), 2,6-di-*tert*-butylpyridine (1 equiv), CH₂Cl₂, H₂ (1 atm), RT, 1 h, 65–84%; k) *m*CPBA (1.5 equiv), NaHCO₃ (2 equiv), CH₂Cl₂, −5°C, 30 min, 62% of **14**, 22% of **15**; l) DCC (3 equiv), AcOH (3 equiv), DMAP (0.5 equiv), CH₂Cl₂, RT, 2 h, quant.; m) WCl₆ (1.85 equiv), *n*BuLi (3.8 equiv), THF, −60°C to RT, 86%; n) K₂CO₃ (10 equiv), MeOH, 50°C, 1 h, 95%; o) IBX (4 equiv), DMSO, RT, 2 h, 90%. DCC = *N,N'*-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, BBN = borabicyclo[3.3.1]nonane, TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl, LDA = lithium diisopropylamide, TBAF = tetra-*n*-butylammonium fluoride, TBHP = *tert*-butyl hydroperoxide, *m*CPBA = *meta*-chloroperbenzoic acid, IBX = 2-iodoxybenzoic acid.

oxidized (without further purification) with TEMPO and PhI(OAc)₂ to 11,13-dihydro-*epi*-parthenolide^[12] (**7**) as a mixture of diastereomers. Converting **1** to acetate **6** is necessary for the hydroboration step, since less than 40% conversion was observed otherwise. α -Bromination of lactone **7** with LDA and CBr₄, followed by dehydrobromination with TBAF,^[13] gave rise to 7-*epi*-parthenolide (–)-**8** (60% over

2 steps), an unnatural epimer of the biologically active^[14] sesquiterpene lactone parthenolide.^[15] While parthenolide has been successfully isolated in quantity recently,^[16] none of its epimers have been synthesized to date, and thus the biological activity of **8** has not yet been explored. (–)-4-Hydroxyallohedycaryol (**12**) was obtained in a four-step sequence from (+)-**1** by: 1) directed epoxidation with VO(acac)₂ to give *bis*-epoxide **9** (77 % yield); 2) chemoselective reduction of the less-hindered epoxide to diol (+)-**10** with LiAlH₄; 3) mesylation of the secondary alcohol providing (+)-**11** (44 % over 2 steps); and 4) reductive elimination of the epoxy mesylate (+)-**11** with lithium naphthalenide to afford (–)-**12** in 65 % yield, together with recovered diol **10** in 23 % yield.

Chemoselective hydrogenation of the isopropylidene side chain in (+)-**1** using Crabtree's catalyst^[17] afforded (+)-shiomool^[18] (**13**) in good yield (65–84 %). It was found that the addition of 2,6-di-*tert*-butylpyridine was crucial to suppress side-product formation. Epoxidation of (+)-**13** with *m*CPBA led to a 4:1 diastereomeric mixture of (–)-1 β ,10 α ,4 β ,5 α -diepoxy-7 α (H)-germacran-6 β -ol (**14**) and (+)-**15** in 84 % combined yield, both of which are natural products.^[19] Acetylation of the 6-OH of (+)-**13** with AcOH, DCC, and DMAP furnished (+)-shiomool acetate^[20] (**16**) in quantitative yield. Reaction of (+)-**16** with WCl₆ and *n*BuLi;^[21] effected the removal of the 4,5-epoxide, followed by saponification of the acetate group with K₂CO₃/MeOH at 50 °C gave (–)-(1*E*,4*E*)-7 α H-germacra-1(10),4-dien-6 β -ol^[22] (**17**) in 82 % yield over two steps. Oxidation of this natural product (–)-**17** with IBX^[23] gave (+)-acoragermacrone^[24] (**18**) in 90 % yield.

In addition to the successful syntheses of sesquiterpenes **8–18** incorporating the 10-membered carbocycle, common bicyclic sesquiterpene frameworks were also accessed by transannular cyclizations (Scheme 4). It is known that transannular cyclization of compounds such as **12**, with the allohedycaryol framework, would give rise to cadinane-type sesquiterpenes. Depending on the acid used with ($\pm$)-**12**, trichotomol^[25] (**19**) and its C10-epimer **20**, δ -cadinene-11-ol^[26] (**21**) and γ -cadinene-11-ol (**22**) were obtained in varying ratios (Scheme 4).^[27] The elemene skeleton can be accessed by a Cope rearrangement of acoragermacrone (**18**), giving a 21:4 mixture of shyobunone^[28] (**23**) and its epimer **24**, respectively.^[24a] Alternatively, treating **18** with acid would afford selinane-type sesquiterpenes, acolamone^[29] (**25**; 55 % yield) and isoacolamone (**26**; 23 % yield).^[30] Likewise, the guaiane framework can be accessed by treating shiromool acetate (**16**) with dry HCl gas in Et₂O at 0°C to obtain an approximate 15:5:4 mixture of (+)-**27a**, (+)-**28a**, and (+)-**29a** respectively, with a preference for the exocyclic olefin.^[20] A similar outcome (5:2:1 mixture) was observed with *p*-TsOH (0.27 equiv) as the acid catalyst in CH₂Cl₂ at room temperature. The resulting major product (+)-**27a** was then converted to (+)-teucladiol^[31] (**27**) by saponification. At this point, we set out to investigate whether different acids would affect the regioselectivity of this cyclization, and if the same transformation could be performed directly on (+)-shiromool (**13**), in order to obtain the natural products **28** and **30** selectively (see Supporting Information, Table 9 for further



Scheme 4. Transannular cyclization to cadinane-, selinane-, elemene-, and guaiane-type sesquiterpenes. Reagents and conditions: for **27**: a) **16** (1 equiv), *p*-TsOH (0.27 equiv), CH₂Cl₂, 40 min, 44% of **27a**, 7% of **29a**, 19% of **28a**; b) **27a** (1 equiv), K₂CO₃ (10 equiv), MeOH, 50 °C, 1 h, quant.; for **28**: **13** (1 equiv), Sc(OTf)₃ (1 equiv), CH₂Cl₂, 0 °C, 10 min, 67% of **28**; for **30**: **13** (1 equiv), **32** (0.2 equiv), CH₂Cl₂, RT, 1 h, 49% of **30**, 32% of **27** and **28**; for **31**: a) **16** (1 equiv), dibenzyl phosphate (1 equiv), CH₂Cl₂, RT, 30 min, 70% of **31a**; b) **31a** (1 equiv), K₂CO₃ (10 equiv), MeOH, 50 °C, 1 h, 78%.

details). Subjecting (+)-**13** to catalytic *p*-TsOH gave a 3:1 mixture of (+)-**28** and (+)-**27**, a selectivity opposite to that observed for the same reaction with acetate **16**. After further screening, it was found that adding Sc(OTf)₃ to (+)-**13** in CH₂Cl₂ at 0 °C gave a > 20:1 mixture of (+)-4β,6β-dihydroxy-1α,5β(H)-guai-9-ene^[32] (**28**) and (+)-**27** in 67% yield. A separate reaction of (+)-**13** with (*S*)-(+)-1,1'-binaphthalene-2,2'-diyl hydrogen phosphate (*S*)-**32** as acid catalyst in CH₂Cl₂ at room temperature gave a 11:5:2 mixture of (+)-chrysotol^[33] (**30**; 49% yield), **28**, and **27** (32% yield combined), respectively. Instead of the concomitant loss of proton after the acid-induced epoxide opening, as in the case in the formation of **27** and **28**, the ether linkage in (+)-**30** is formed by the trapping of the cation intermediate by the 6-OH group, which is not possible when (+)-shiromool acetate (**16**) is used as substrate. Using the above conditions, the 4,8-ring system (as in **31**) was not observed, which could potentially arise from the Markovnikov opening of the 4,5-epoxide of (+)-shiromool (**13**). However, when dibenzyl phosphate was used as the acid for cyclization of (+)-**13**, (+)-**31** was obtained, albeit with poor selectivity. Gratifyingly, using (+)-**16** instead of (+)-**13** as substrate under the same conditions afforded acetate (+)-**31a** in 70% yield, whose stereochemistry was unequivocally verified by X-ray crystallographic analysis.^[34] Acetate (+)-**31a** was subsequently converted to (+)-**31** in 78% yield upon treatment with K₂CO₃/MeOH at 50 °C.

The concise, scalable, enantioselective synthesis of epoxygermacrenol **1** through a unique Pd-catalyzed macrocyclization presents a viable solution to the longstanding problem of forming the 10-membered germacrane ring system. It has also enabled the rapid formation of a range of germacrane-type sesquiterpenes **8–18**, six of which are natural products. Of

these compounds, **12**, **18**, and **13** can be converted in a single step to give cadinane-, elemene- or selinane-, and guaiane-type frameworks, respectively. In particular, we have demonstrated that the cyclization of shiromool **13** to the guaiane-type natural products **27**, **28**, and **30** can be performed selectively, by varying either the substrate or the acid used. Finally, the divergent pathways to sesquiterpenes illustrated here nicely complement the recent elegant studies of Winsinger and co-workers.^[35]

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