

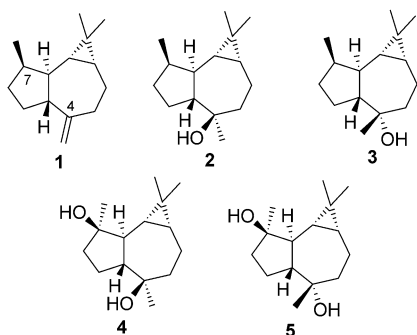
## Natural Product Synthesis

# Gold(I) as an Artificial Cyclase: Short Stereodivergent Syntheses of (–)-Epiglobulol and (–)-4 $\beta$ ,7 $\alpha$ - and (–)-4 $\alpha$ ,7 $\alpha$ -Aromadendranediols\*\*

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**Abstract:** Three natural aromadendrane sesquiterpenes, (–)-epiglobulol, (–)-4 $\beta$ ,7 $\alpha$ -aromadendranediol, and (–)-4 $\alpha$ ,7 $\alpha$ -aromadendranediol, have been synthesized in only seven steps in 12, 15, and 17% overall yields, respectively, from (*E,E*)-farnesol by a stereodivergent gold(I)-catalyzed cascade reaction which forms the tricyclic aromadendrane core in a single step. These are the shortest total syntheses of these natural compounds.

**A**romadendranes are a family of hydroazulenes named after (+)-aromadendrene (**1**, Figure 1), the main component in the essential oil from *Eucalyptus* trees. The related sesquiterpenoids (–)-globulol (**2**), (–)-epiglobulol (**3**), (–)-4 $\alpha$ ,7 $\alpha$ -aromadendranediol (**4**), and (–)-4 $\beta$ ,7 $\alpha$ -aromadendranediol (**5**)



**Figure 1.** Naturally occurring aromadendranes.

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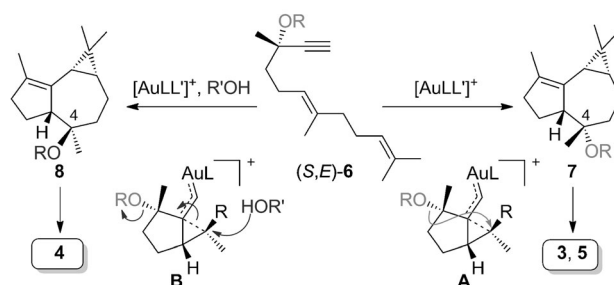
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are widespread in plant species<sup>[1]</sup> and display antifungal,<sup>[2]</sup> antibacterial,<sup>[3]</sup> antiviral,<sup>[4]</sup> cytotoxic,<sup>[5]</sup> and other activities.<sup>[6]</sup> Interestingly, the antipodes of **1** and other aromadendrenes have been isolated from corals.<sup>[7]</sup> Aromadendranes with amino, isonitrile, isothiocyano, and urea functionalities at C4 have been found in sponges.<sup>[8]</sup> Diterpenoids with an aromadendrane structure are also natural products.<sup>[9]</sup>

The synthesis of members of this family of tricyclic sesquiterpenes has attracted significant interest.<sup>[10]</sup> (–)-Epiglobulol (**3**), isolated in hop<sup>[11]</sup> and many essential oils,<sup>[12]</sup> was prepared from **1** or the corresponding ketone (apoaromadendrone).<sup>[13]</sup> A first total synthesis of **3** from the chiral pool was accomplished in eight steps (4% overall yield).<sup>[14]</sup> A recent synthesis of (±)-epiglobulol in 18 steps used a rhodium(I)-catalyzed hydroacylation/cycloisomerization as the key step.<sup>[15]</sup>

(–)-4 $\alpha$ ,7 $\alpha$ -Aromadendranediol (**4**) was isolated from a marine coral *Sinularia may*<sup>[7]</sup> and the leaves of the Amazonian tree *Xylopiya brasiliensis*.<sup>[2]</sup> A semisynthesis of **4** from (+)-spatulanol<sup>[7]</sup> and one total synthesis have been reported.<sup>[16]</sup> This total synthesis involved a three-reaction sequence in a three-component reaction to generate four stereogenic centers in one step and required ten steps to produce **4** in 23% overall yield. (–)-4 $\beta$ ,7 $\alpha$ -Aromadendranediol (**5**) has been isolated from the leaves of *Chloranthus glaber*.<sup>[17]</sup> A semisynthesis of **5** from (+)-spatulanol has been reported.<sup>[7]</sup>

We developed a gold(I)-catalyzed cascade cyclization of the dienyne **6**, a cascade consisting of a cyclization, 1,5-migration of the propargylic OR group, and intramolecular cyclopropanation, thus leading to tricyclic structures closely related to the aromadendrene sesquiterpenes (Scheme 1).<sup>[18]</sup> This reaction is stereospecific since (*E*)-**6** gave the tricyclic product **7** having the relative configuration of **3** and **5**, whereas the geometrical isomer of **6** led to **8**, the C4 epimer of **7**, having the configuration of **2** and **4**. We recently applied

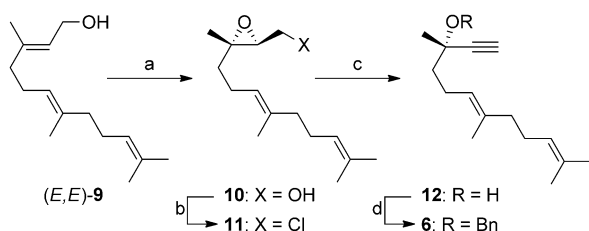


**Scheme 1.** Gold-catalyzed formation of tricyclic cores of the aromadendranes by cyclization/1,5-OR migration/intramolecular cyclopropanation.

a strategy based on a gold(I)-catalyzed cyclization/1,5-OR migration/intermolecular cyclopropanation for the first total synthesis of (+)-schisanwilsonene **A**. As part of our program on the synthesis of terpenoids by using new gold-catalyzed cyclization cascades,<sup>[19]</sup> we decided to target **3**, **4**, and **5**, each of which present six stereogenic centers in a tricyclic skeleton. In principle, **3** and **5** could be synthesized from the dienyne (*S,E*)-**6** (Scheme 1), whereas **4** would be prepared from geometric isomer (*S,Z*)-**6**. However, although enantioenriched (*E*)-**6** could be readily prepared from (*E,E*)-farnesol (**9**), the starting material, (*E,Z*)-farnesol, required for the synthesis of (*Z*)-**6** is not commercially available.<sup>[20]</sup>

Herein we report a simple solution to this problem and it allows general access to this class of sesquiterpenes from (*S,E*)-**6** as a common precursor by means of a stereodivergent gold(I)-catalyzed cascade process. The reaction can take place intramolecularly by 1,5-migration of OR in **A** and in the presence of an external nucleophile (via **B**), thus leading to **7** and **8**, respectively, having opposite configurations at C4 (Scheme 1). Starting from (*R,E*)-**6**, enantiomeric aromadenranes can be similarly obtained. This proposal is based on our initial mechanistic study in the *Z* series, in which we found that the cyclopropyl gold(I) carbene intermediate could be trapped with methanol to form an epimeric compound as a minor product.<sup>[18]</sup> In these transformations, gold(I) acts as an artificial cyclase,<sup>[21]</sup> thus mimicking the action of terpene cyclases forming polycyclic skeletons by the selective activation of the alkyne terminus of a dienyne, to readily build a tricyclic skeleton with exquisite stereocontrol.<sup>[22,23]</sup>

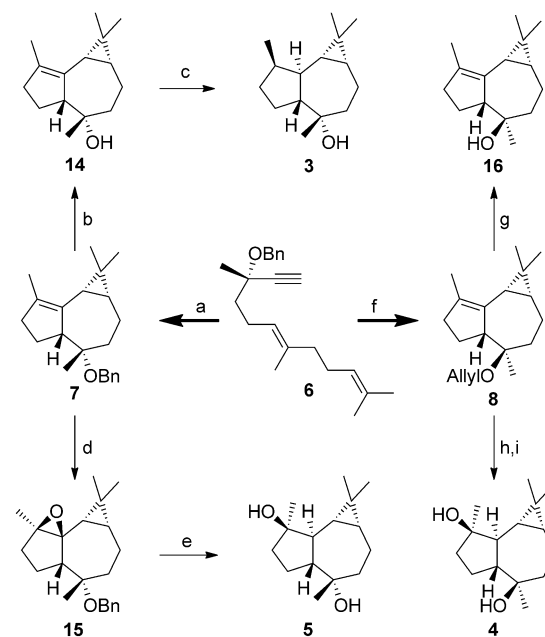
The dienyne (*S,E*)-**6** (R = Bn) was prepared in four steps and 62% overall yield by using a route similar to that used in the transformation of the lower homologue geraniol.<sup>[19a,24]</sup> The transformation involved the known Sharpless asymmetric epoxidation of (*E,E*)-farnesol (**9**) to give the epoxide (*S,S*)-**10** (88% yield, 91:9 e.r.)<sup>[25,26]</sup> (Scheme 2). Substitution of the



**Scheme 2.** a) L-(+)-DIPT, Ti(O*i*Pr)<sub>4</sub>, *t*BuOOH, 4 Å M.S., CH<sub>2</sub>Cl<sub>2</sub>, -48 °C, 88%, 82% ee;<sup>[25]</sup> b) PPh<sub>3</sub>, NaHCO<sub>3</sub>, CCl<sub>4</sub>, reflux, 6 h, 94%; c) *n*BuLi, THF, -40 °C, 2 h, 82%; d) BnBr, NaH, Bu<sub>4</sub>NI, THF, 23 °C 12 h, 91%. DIPT = diisopropyl tartrate, M.S. = molecular sieves, THF = tetrahydrofuran.

primary alcohol by chloride with CCl<sub>4</sub> and PPh<sub>3</sub> gave **11**, which was treated with *n*BuLi to yield the propargylic alcohol **12**. Finally, benzylation under standard reaction conditions gave (*S,E*)-**6**.

Exposing (*S,E*)-**6** to the cationic gold(I) complex [(JohnPhos)Au(MeCN)]SbF<sub>6</sub> (**13**) for 5 minutes at room temperature gave **7** in 60% yield (Scheme 3). Other gold(I)



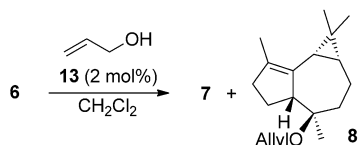
**Scheme 3.** Reagents and conditions: a) [(JohnPhos)Au(MeCN)]SbF<sub>6</sub> (**13**; 2 mol%), 23 °C, 5 min (60%); b) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, 1:1 MeOH/THF, 23 °C, 4 h (79%); c) [Ir(cod)(PCy<sub>3</sub>)py]BAR<sub>F</sub> (15 mol%), H<sub>2</sub> (80 atm), CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 4 days (40%); d) oxone, NaHCO<sub>3</sub>, 18-crown-6, 1:1:2 acetone/CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O, 23 °C, 1 h (51%); e) Li, EDA, 50 °C, 1 h (78%); f) allyl alcohol (20 equiv), **13** (2 mol%), -30 °C, 15 min (56% + 21% **7**); g) [Pd(PPh<sub>3</sub>)<sub>4</sub>] (5 mol%), K<sub>2</sub>CO<sub>3</sub>, MeOH, reflux 72 h (72%); h) *m*CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 0 to 23 °C (83%); i) Li, EDA, 50 °C, 1.5 h (62%). BAR<sub>F</sub> = 3,5-bis(trifluoromethyl)phenylborate, cod = 1,5-cyclooctadiene, EDA = ethylenediamine, JohnPhos = (2-biphenyl)-di-*tert*-butylphosphine; *m*CPBA = *m*-chloroperbenzoic acid.

catalysts were also screened for this reaction, but the best results were obtained using complex **13**.<sup>[27]</sup> The relative configuration of **7** (racemic series) was confirmed by X-ray diffraction.<sup>[28,29]</sup> Debenzylation of **7** with H<sub>2</sub> (1 atm) and Pd(OH)<sub>2</sub>/C gave the alcohol **14** (79% yield), which was hydrogenated with [Ir(cod)(PCy<sub>3</sub>)py]BAR<sub>F</sub> catalyst<sup>[30]</sup> under high pressure of H<sub>2</sub> to give **3** in 40% yield (95:5 e.r.). The synthesis **3** from **9** required seven steps and proceeded in 12% overall yield.

Epoxidation of **7** with dimethyldioxirane yielded **15** stereoselectively. Epoxide opening and ether cleavage with Li in ethylenediamine<sup>[31]</sup> yielded **5** in 78% (96:4 e.r.), which gave enantiopure material after crystallization. The synthesis of **5** from **9** was accomplished in seven steps with 15% overall yield.

When the gold-catalyzed reaction of dienyne (*S,E*)-**6** was performed in the presence of allyl alcohol as an external nucleophile, the allyl ether **8** was obtained with the opposite configuration at C4 compared to that of **7** (Table 1). While lowering the reaction temperature to -30 °C led to a 1:1 mixture of **7** and **8** (Table 1, entry 3), increasing the concentration of allyl alcohol to 20 equivalents favored the intermolecular pathway (Table 1, entry 5). Similar results were obtained with using only 1 mol% gold(I) catalyst (Table 1, entry 5). Under the optimized reaction conditions, **8** was

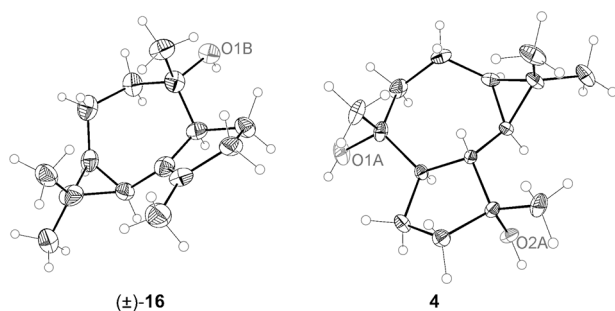
**Table 1:** Gold(I)-catalyzed addition of allyl alcohol to (*S,E*)-**6**.<sup>[a]</sup>



Entry	AllylOH (equiv)	T [°C]	t [min]	7/8 <sup>[b]</sup>
1	10	23	5	75:25
2	10	0	10	55:45
3	10	-30	15	50:50
4	20	-30	20	27:73
5 <sup>[c]</sup>	20	-30	30	33:67

[a] 0.05 M. [b] Determined by GC-MS. [c] 1 mol % **13**.

obtained in 56 % yield, along with **7** (21 % yield; Scheme 3). Removal of the allylic ether with [Pd(PPh<sub>3</sub>)<sub>4</sub>] in MeOH gave the alcohol **16**, whose structure was confirmed by X-ray crystal diffraction<sup>[29]</sup> in the racemic series (Figure 2).<sup>[26]</sup> Although **4** could be synthesized from **16**, a more direct



**Figure 2.** X-ray structures for (±)-**16** and **4**. Thermal ellipsoids are shown at 50% probability.

synthesis was completed from **8** by selective epoxidation with *m*CPBA from the convex face (83 % yield), followed by opening of the epoxide and allyl cleavage with Li in ethylenediamine to give **4** in 62 % yield (87:13 e.r.), yielding enantiopure **4** after crystallization. Spectral data and optical rotation of synthetic 4 $\alpha$ ,7 $\alpha$ -aromadendranediol matched those reported for the natural compound. The relative and absolute configuration of **4** were confirmed by X-ray diffraction (Figure 2).<sup>[29]</sup> The synthesis of (+)-4 $\alpha$ ,7 $\alpha$ -aromadendranediol was similarly carried out from (*R,R*)-**10**.<sup>[27]</sup>

The stereochemical divergent synthesis of **3** and **4** from (*S,E*)-**6** confirms the proposal that this cascade cyclization process proceeds by intra- or intermolecular reactions of cyclopropyl gold(I) carbene-like intermediates such as **A** or **B**.<sup>[18,32]</sup> The enantioselectivity is fully preserved in the formation of **3** and **5** via **7** by an intramolecular gold(I)-catalyzed 1,5-migration of a propargylic group. The intermolecular reaction of (*S,E*)-**6** with allyl alcohol occurs with high enantioselectivity (ca. 96 %). In this case, the slight racemization is due to the competitive formation of a propargyl

carbocation, presumably facilitated by the higher polarity of the reaction medium.

In summary, we have completed highly concise syntheses of three representative aromadendranes from a single precursor by a stereodivergent gold-catalyzed reaction which establishes four new stereogenic centers from a single one. The three natural sesquiterpenes (–)-epiglobulol (**3**), (–)-4 $\alpha$ ,7 $\alpha$ -aromadendranediol (**4**), and (–)-4 $\beta$ ,7 $\alpha$ -aromadendranediol (**5**) have been synthesized in seven steps in 12, 17, and 15 % overall yields, respectively, from commercially available (*E,E*)-farnesol (**9**), and constitutes the shortest total syntheses of these natural compounds. This route could be extended for the enantioselective synthesis of any enantiomer of other aromadendranes and non-natural analogues.

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- [27] See the Supporting Information for additional details.
- [28] Racemic **7** was prepared in four steps from a 1.2:1 mixture of geranyl- and nerylacetone.<sup>[27]</sup>
- [29] CCDC 983695 (**4**), 983696 [(±)-**7**], 983697 [(±)-**16**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
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