Natural Product Synthesis

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Gold(I) as an Artificial Cyclase: Short Stereodivergent Syntheses of (−)-Epiglobulol and (−)-4β,7α- and (−)-4α,7α-Aromadendranediols**

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Abstract: *Three natural aromadendrane sesquiterpenes, (−)-epiglobulol, (−)-4β,7α-aromadendranediol, and (−)-4α,7α-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.*

Aromadendranes are a family of hydroazulenes named after (+)-aromadendrene (**1**, Figure 1), the main component in the essential oil from *Eucaliptus* trees. The related sesquiterpenoids (−)-globulol (**2**), (−)-epiglobulol (**3**), (−)-4α,7α-aromadendranediol (**4**), and (−)-4β,7α-aromadendranediol (**5**) are widespread in plant species[1] and display antifungal,[2] antibacterial,[3] antiviral,[4] cytotoxic,[5] and other activities.[6] Interestingly, the antipodes of **1** and other aromadendrenes have been isolated from corals.[7] Aromadendranes with amino, isonitrile, isothiocyano, and urea functionalities at C4 have been found in sponges.[8] Diterpenoids with an aromadendrane structure are also natural products.[9]

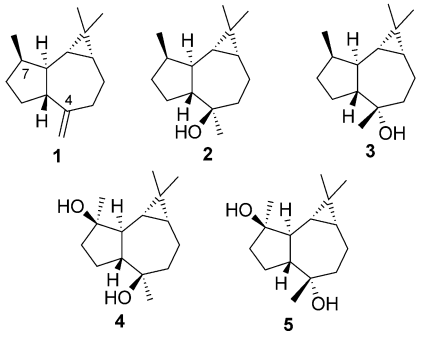
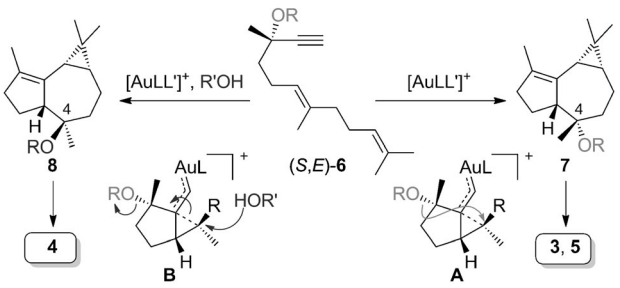


Figure 1. Naturally occurring aromadendranes.

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

(−)-4α,7α-Aromadendranediol (**4**) was isolated from a marine coral *Sinularia may*[7] and the leaves of the Amazonian tree *Xylopia brasiliensis*.[2] A semisynthesis of **4** from (+)-spathulenol[7] and one total synthesis have been reported.[16] 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. (−)-4β,7α-Aromadendranediol (**5**) has been isolated from the leaves of *Chloranthus glaber*.[17] A semisynthesis of **5** from (+)-spathulenol has been reported.[7]

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).[18] 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.

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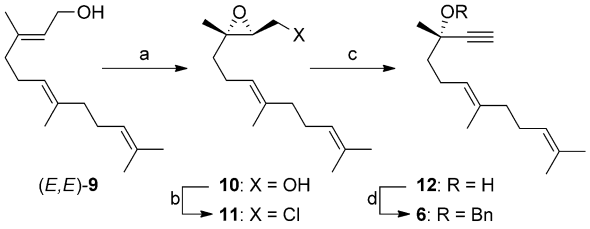
a strategy based on a gold(I)-catalyzed cyclization/1,5-OR migration/intermolecular cyclopropanation for the first total synthesis of (+)-schisanwilsonene A. As part of our program on the synthesis of terpenoids by using new gold-catalyzed cyclization cascades,[19] we decided to target **3**, **4**, 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.[20]

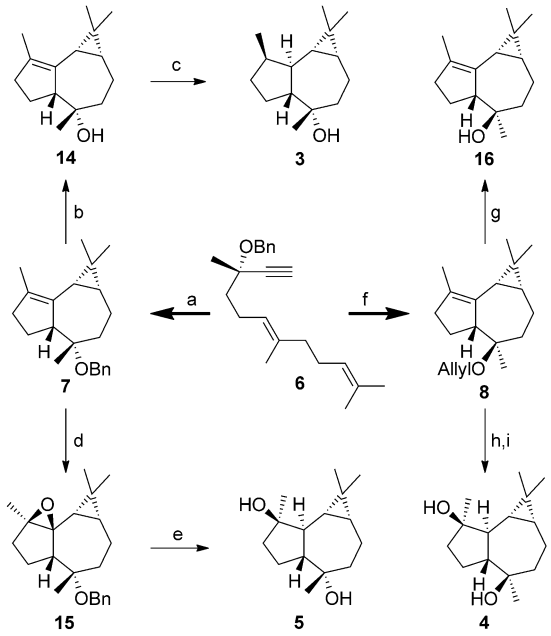
Herein we report a simple solution to this problem and it allows general access to this class of sesquiterpenes from (*S*,*E*)-**6** as a common precursor by means of a stereodivergent gold(I)-catalyzed cascade process. The reaction can take place intramolecularly by 1,5-migration of OR in **A** and 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 aromadendranes 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.[18] In these transformations, gold(I) acts as an artificial cyclase,[21] 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.[22,23]

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.[19a,24] 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.)[25,26] (Scheme 2). Substitution of the primary alcohol by chloride with CCl_4 and PPh_3 gave **11**, which was treated with *n*BuLi to yield the propargylic alcohol **12**. Finally, benzylation under standard reaction conditions gave (*S*,*E*)-**6**.



Scheme 2. a) L-(+)-DIPT, Ti(O*i*Pr)$_4$, *t*BuOOH, 4 Å M.S., CH_2Cl_2, −48 °C, 88%, 82% *ee*;[25] b) PPh_3, $NaHCO_3$, CCl_4, reflux, 6 h, 94%; c) *n*BuLi, THF, −40 °C, 2 h, 82%; d) BnBr, NaH, Bu_4NI, THF, 23 °C 12 h, 91%. DIPT = diisopropyl tartrate, M.S. = molecular sieves, THF = tetrahydrofuran.

Exposing (*S*,*E*)-**6** to the cationic gold(I) complex [(JohnPhos)Au(MeCN)]SbF_6 (**13**) for 5 minutes at room temperature gave **7** in 60% yield (Scheme 3). Other gold(I) catalysts were also screened for this reaction, but the best results were obtained using complex **13**.[27] The relative configuration of **7** (racemic series) was confirmed by X-ray diffraction.[28,29] Debenzylation of **7** with H_2 (1 atm) and $Pd(OH)_2$/C gave the alcohol **14** (79% yield), which was hydrogenated with [Ir(cod)(PCy$_3$)py]BAr_F catalyst[30] under high pressure of H_2 to give **3** in 40% yield (95:5 e.r.). The synthesis **3** from **9** required seven steps and proceeded in 12% overall yield.

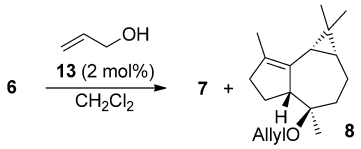


Scheme 3. Reagents and conditions: a) [(JohnPhos)Au(MeCN)]SbF_6 (**13**; 2 mol%), 23 °C, 5 min (60%); b) H_2, $Pd(OH)_2$/C, 1:1 MeOH/THF, 23 °C, 4 h (79%); c) [Ir(cod)(PCy$_3$)py]BAr_F (15 mol%), H_2 (80 atm), CH_2Cl_2, 40 °C, 4 days (40%); d) oxone, $NaHCO_3$, 18-crown-6, 1:1:2 acetone/CH_2Cl_2/H_2O, 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$_3$)$_4$] (5 mol%), K_2CO_3, MeOH, reflux 72 h (72%); h) *m*CPBA, CH_2Cl_2, 0 to 23 °C (83%); i) Li, EDA, 50 °C, 1.5 h (62%). BAr_F = 3,5-bis(trifluoromethyl)phenylborate, cod = 1,5-cyclooctadiene, EDA = ethylenediamine, JohnPhos = (2-biphenyl)-di-*tert*-butylphosphine; *m*CPBA = *m*-chloroperbenzoic acid.

Epoxidation of **7** with dimethyldioxirane yielded **15** stereoselectivily. Epoxide opening and ether cleavage with Li in ethylenediamine[31] 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**.[a]



Entry	AllylOH (equiv)	*T* [°C]	*t* [min]	**7**/**8**[b]
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[c]	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 $[Pd(PPh_3)_4]$ in MeOH gave the alcohol **16**, whose structure was confirmed by X-ray crystal diffraction[29] in the racemic series (Figure 2).[26] Although **4** could be synthesized from **16**, a more direct

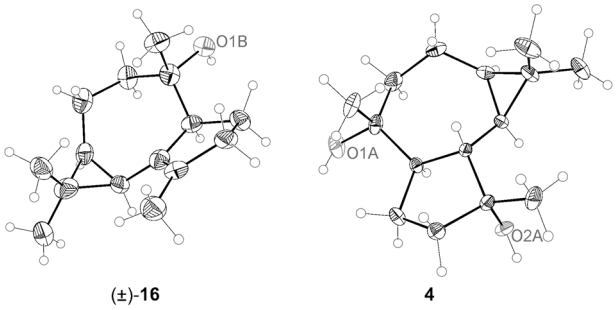


Figure 2. X-ray structures for (±)-**16** and **4**. Thermal ellipsoids are shown at 50% probability.

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 4α,7α-aromadendranediol matched those reported for the natural compound. The relative and absolute configuration of **4** were confirmed by X-ray diffraction (Figure 2).[29] The synthesis of (+)-4α,7α-aromadendranediol was similarly carried out from (*R*,*R*)-**10**.[27]

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**.[18,32] 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**), (−)-4α,7α-aromadendranediol (**4**), and (−)-4β,7α-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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[26] The syntheses of (±)-epiglobulol and (±)-4α,7α-aromadendranediol was also carried out from a 1.2:1 mixture of geranyl- and nerylacetone. See the Supporting Information for details.

[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.[27]

[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.

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