

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

Javier Carreras, Madeleine Livendahl, Paul R. McGonigal, and Antonio M. Echavarren*

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 *Eucalyptus* 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]

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 *Xylopi 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 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

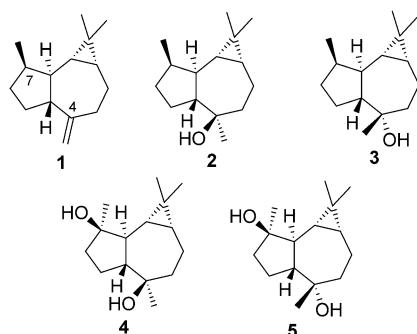
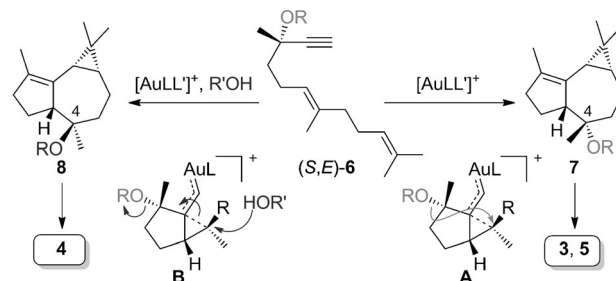


Figure 1. Naturally occurring aromadendranes.

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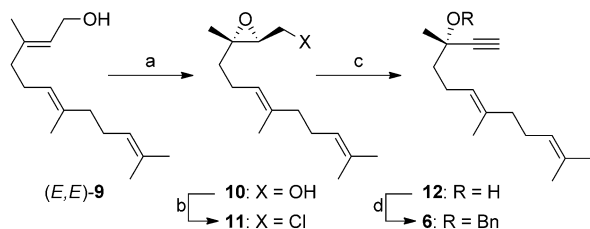


Scheme 1. Gold-catalyzed formation of tricyclic cores of the aromadendranes by cyclization/1,5-OR migration/intramolecular cyclopropanation.

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 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.^[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]

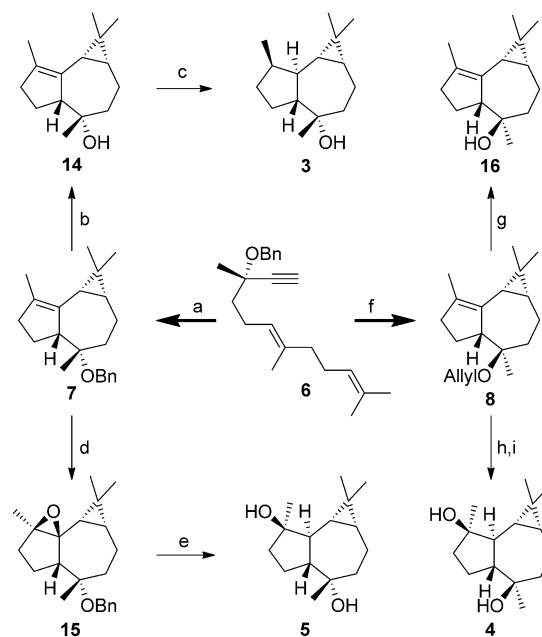
The dienyne (*S,E*)-**6** (*R* = Bn) was prepared in four steps and 62% overall yield by using a route similar to that used in the transformation of the lower homologue geraniol.^[19a,24] the transformation involved the known Sharpless asymmetric epoxidation of (*E,E*)-farnesol (**9**) to give the epoxide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



Scheme 2. a) L-(+)-DIPT, Ti(O*i*Pr)₄, *t*BuOOH, 4 Å M.S., CH₂Cl₂, –48 °C, 88%, 82% ee;^[25] b) PPh₃, NaHCO₃, CCl₄, reflux, 6 h, 94%; c) *n*BuLi, THF, –40 °C, 2 h, 82%; d) BnBr, NaH, Bu₄NI, THF, 23 °C 12 h, 91%. DIPT = diisopropyl tartrate, M.S. = molecular sieves, THF = tetrahydrofuran.

primary alcohol by chloride with CCl₄ and PPh₃ 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)]SbF₆ (**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

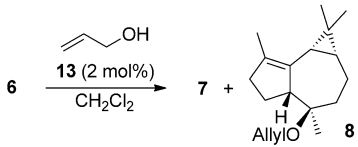


Scheme 3. Reagents and conditions: a) [(JohnPhos)Au(MeCN)]SbF₆ (**13**; 2 mol%), 23 °C, 5 min (60%); b) H₂, Pd(OH)₂/C, 1:1 MeOH/THF, 23 °C, 4 h (79%); c) [Ir(cod)(PCy₃)py]BAR_F (15 mol%), H₂ (80 atm), CH₂Cl₂, 40 °C, 4 days (40%); d) oxone, NaHCO₃, 18-crown-6, 1:1:2 acetone/CH₂Cl₂/H₂O, 23 °C, 1 h (51%); 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(PPh₃)₄] (5 mol%), K₂CO₃, MeOH, reflux 72 h (72%); h) *m*CPBA, CH₂Cl₂, 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.

diffraction.^[28,29] Debenzylation of **7** with H₂ (1 atm) and Pd(OH)₂/C gave the alcohol **14** (79% yield), which was hydrogenated with [Ir(cod)(PCy₃)py]BAR_F catalyst^[30] under high pressure of H₂ 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^[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 obtained in 56% yield, along with **7** (21% yield; Scheme 3). Removal of the allylic ether with [Pd(PPh₃)₄] in MeOH gave the alcohol **16**, whose structure was confirmed by X-ray

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**.

crystal diffraction^[29] in the racemic series (Figure 2).^[26] Although **4** could be synthesized from **16**, a more direct 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 ethyl-

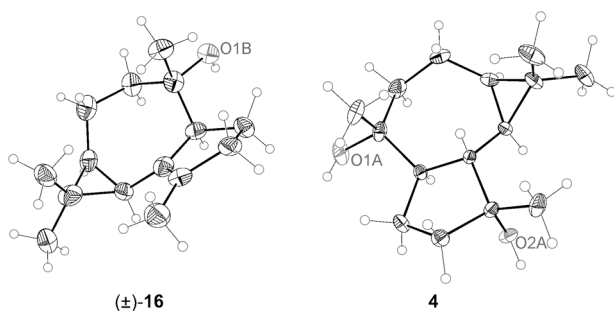


Figure 2. X-ray structures for (±)-**16** and **4**. Thermal ellipsoids are shown at 50 % probability.

enediamine 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 pre-

cursor 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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- [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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Communications



Natural Product Synthesis

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

Aromasynthesis: Aromadendrane ses-
quiterpenes (–)-epiglobulol, (–)-4 α ,7 α -
aromadendranediol, and (–)-4 β ,7 α -aro-
madendranediol are synthesized in only

seven steps from (*E,E*)-farnesol by a ster-
eodivergent gold(I)-catalyzed cascade
reaction.

