Carreras, Javier and Livendahl, Madeleine and McGonigal, Paul R. and Echavarren, Antonio M. (2014) 'Gold(I) as an artificial cyclase: short stereodivergent syntheses of (−)-epiglobulol and (−)-4,7- and (−)-4,7-aromadendranediols.', Angewandte Chemie international edition., 53 (19). pp. 4896-4899.

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https://doi.org/10.1002/anie.201402044

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

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

Aromadendrane sesquiterpenes are a family of hydroazulenes named after (+)-aromadrene (1, Figure 1), the main component in the essential oil from Eucaliptus trees. The related sesquiterpenoids (−)-globulol (2), (−)-epiglobulol (3), (−)-4α,7α-aromadendraniol (4), and (−)-4β,7α-aromadendraniol (5) are widespread in plant species and display antifungal, antibacterial, antiviral, cytotoxic, and other activities.

Interestingly, the antipodes of 1 and other aromadendrane have been isolated from corals. Aromadendrane sesquiterpenoids with amino, isonitrile, isothiocyanato, and urea functionalities at C4 have been found in sponges. Diterpenoids with an aromadendrane structure are also natural products.

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

(−)-4α,7α-Aromadendraniol (4) was isolated from a marine coral Sinularia may and the leaves of the Amazonian tree Xylopia brasiliensis. A semisynthesis of 4 from (±)-spathulenol and one total synthesis have been reported. 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-Aromadendraniol (5) has been isolated from the leaves of Chloranthus glaber. A semisynthesis of 5 from (±)-spathulenol has been reported.

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 aromadendrane sesquiterpenes (Scheme 1).

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

Figure 1. Naturally occurring aromadendranes.
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, 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 diene (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)-farnesol (9), the starting material, (E,Z)-farnesol, required for the synthesis of (Z)-6 is not commercially available.

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 aromadendrines 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. In these transformations, gold(I) acts as an artificial cyclase, thus mimicking the action of terpene cyclases forming polycyclic skeletons by the selective activation of the alkene terminus of a diene, to readily build a tricyclic skeleton with enantiocoretocontrol.

The diene (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. The epoxidation of (E,E)-farnesol (2) for 5 minutes at room temperature gave a mixture of geometric isomer (S,Z)-6, which was treated with nBuLi to yield the propargylic alcohol 11, which was treated with nBuLi 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$_6$ (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$_3$)$_2$BAr$_5$ (15 mol %), H$_2$ (80 atm), CH$_2$Cl$_2$, 40 °C, 4 days (40%); d) oxone, NaHCO$_3$, 18-crown-6, 1:2 acetone/CH$_2$Cl$_2$/H$_2$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$_3$)$_2$] (5 mol %), K$_2$CO$_3$, MeOH, reflux 72 h (72%); h) mCPBA, CH$_2$Cl$_2$, 0 to 23 °C (83%); i) Li, EDA, 50 °C, 1 h (62%).

The relative configuration of 7 (racemic series) was confirmed by X-ray diffraction. 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$_3$)$_2$]BAr$_5$ catalyst under high pressure of H$_2$ to give 3 in 40% yield (95:5 e.r.). The synthesis of 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 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 diene (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 catalyzed after crystallization. The synthesis of 3 from 9 required seven steps and proceeded in 12% overall yield.

Scheme 2. a) 1,4-DIP, Ti(OiPr)$_2$, 18BuOH, 4 Å M.S., CH$_2$Cl$_2$, −48 °C, 88% ee.[25] b) PPh$_3$, NaHCO$_3$, CCl$_4$, reflux, 6 h, 94%; c) nBuLi, THF, −40 °C, 2 h, 82%; d) BrBN, NaH, Bu$_3$NI, THF, 23 °C, 12 h, 91%. DIP = diisopropyl tartrate, M.S. = molecular sieves, THF = tetrahydrofuran.

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$_3$)$_2$BAr$_5$ (15 mol %), H$_2$ (80 atm), CH$_2$Cl$_2$, 40 °C, 4 days (40%); d) oxone, NaHCO$_3$, 18-crown-6, 1:2 acetone/CH$_2$Cl$_2$/H$_2$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$_3$)$_2$] (5 mol %), K$_2$CO$_3$, MeOH, reflux 72 h (72%); h) mCPBA, CH$_2$Cl$_2$, 0 to 23 °C (83%); i) Li, EDA, 50 °C, 1 h (62%).
Gold(I)-catalyzed addition of allyl alcohol to (S,E)-6. 

Table 1: Gold(I)-catalyzed addition of allyl alcohol to (S,E)-6. 

| Entry | AllylOH (equiv) | T [°C] | t [min] | 7/8 | 3/6 |
|-------|----------------|--------|---------|-----|-----|
| 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     | 20             | -30    | 30      | 33:67 |

[a] 0.05 m. [b] Determined by GC-MS. [c] 1 mol %.

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 crystal diffraction in the racemic series (Figure 2). Although 4 could be synthesized from 16, a more direct carbothylation, 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- aromadendractadiol (4), and (−)-4β,7α-aromadendractadiol (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.

Keywords: cyclization · gold · natural products · terpenoids · total synthesis

Received: February 3, 2014
Published online: April 1, 2014
