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# Formal Synthesis of Racemic Herbertene, α-Herbertenol, β-Herbertenol and Herbertenone *via* Gold(I)-Catalyzed Cyclization of 5-Phenyl-5-siloxy-3-en-1-ynes

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Herbertenes are a family of sesquiterpenoid natural products containing 1-aryl-1,2,2-trimethylcyclopentane backbones possessing two quaternary carbon centers (Figure 1).[1] Herbertene (**1**: also known as isocuparene)[2] was first isolated in 1981 by Matsuo from the liverwort *Herberta adunca* (Dicks) S. Gray belonging to the family herbertaceae. This natural product is structurally close to cuparene (**4**),[3] which has been reported first by Erdtman and co-workers in 1958. Since the discovery of herbertene, a number of structurally related phenolic herbertenes have been reported, including herbertenones (compound **5** and **6**).[4] More recently, more diverse structures have been revealed including hydroxylated herbretenes such as herbertene-1,14-diol (**7**).[5] Even though the natural products are structurally simple, generation of the cyclopentane structure possessing two quartenary carbon centers is quite challenging. These structural features and the reported biological activities[5] of the herbertene compounds attracted the synthetic chemists.[6] Although the synthesis of herbertene itself (compound **1**) has been reported several times, limited number of methods have been reported for the synthesis of other member of this family. For examples, the synthesis of herbertenones A and B (**5** and **6**) was first reported in 2008 by Srikrina and coworkers.[7]

We recently reported the synthesis of cyclopenten-2-ones possessing a quartenary carbon center by the gold(I)-catalyzed cyclization of the 5-siloxy-1-yne substrates **8** (Scheme 1). Notably, the siloxy group can attack the alkyne in the presence of highly electrophilic cationic gold(I) complexes to generate oxonium ion intermediate **9**, which produces **11** *via* formation of the carbocation intermediate **10**.[8] The cyclopentenone product **12** arises from the intermediate **11** with the assistance of the alcohol additive. We envisioned that herbertene natural products shown in Figure 1 can be easily accessed *via* this method.[9]

Initially, we planned the cyclization of 5-siloxypen-1-ynes **14** aiming at the synthesis of herbertene **1**, because this reaction provides a shorter route for the synthesis of the key cyclopentanones.[7,10] We envisiond that compound **14** could be accessed from easily available alkynol **13** by the two-step protocol involving Al-mediated reductive halogenation and subsequent Sonogashira coupling reaction. However, all our extensive efforts for the synthesis of compound **14** were fruitless, due to the chemical instability of the vinyl halide intermediate under the reaction condition.

Thus, we switched to an alternative route starting from

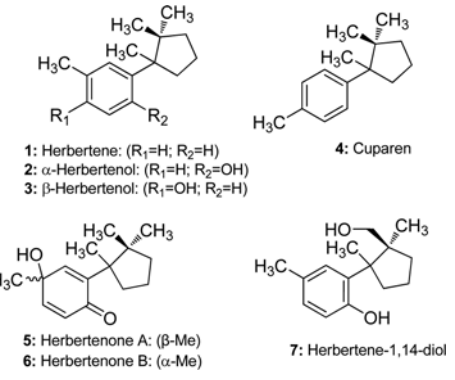
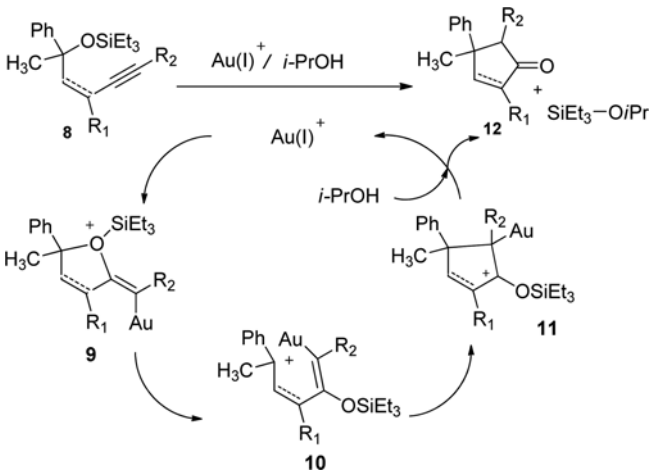
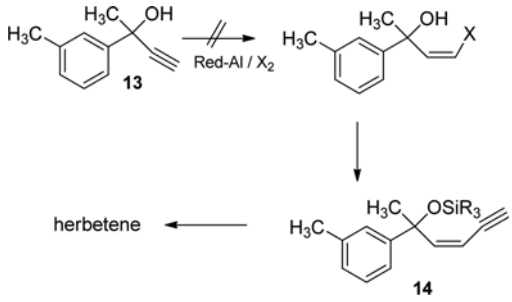



**Figure 1.** Structure of herbertene natural products.




**Scheme 1.** Synthesis of herbertene natural products.

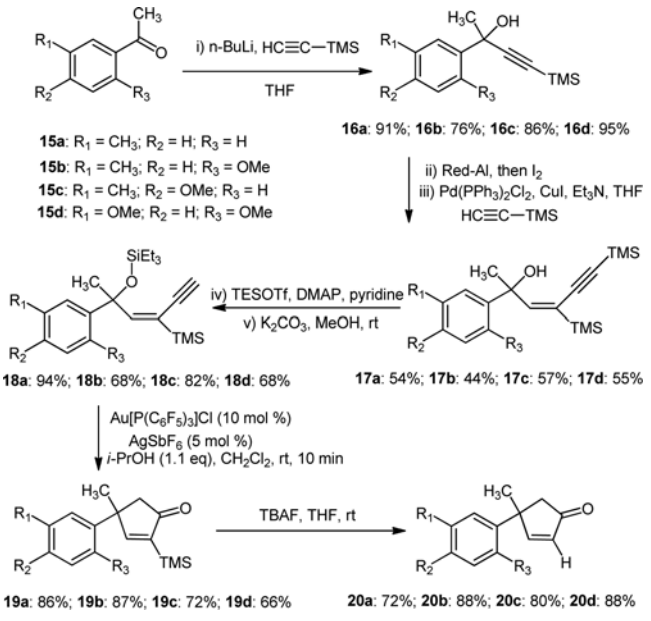



**Scheme 2.** A failed attempt for the synthesis of herbertene *via* the intermediates **13** and **14**.

trimethylsilyl-derived alcohol **16a**, which could be easily obtained from the commercially available ketone **15a** in good 91% yield (Scheme 3). Unlike the terminal alkyne 13, the following reductive iodination using Red-Al and iodine also went smoothly at room temperature to give the unstable iodovinylsilane in 57% yield with complete stereocontrol. The subsequent sonogashira coupling gave the enyne **17a** in 94% yield (54% over two steps). Protection of the tertiary alcohol using TESOTf and excess pyridine followed by the chemoselective removal of the alkynyltrimethylsilyl group using $K_2CO_3$ in methanol gave the substrate **18a** in 94% yield (two step yield). Treatment of this compound with $Au[P(C_6F_5)_3Cl]$ (10 mol %)/$AgSbF_6$ (5 mol %) and isopropyl alcohol (1.1 eq) gave the desired ketone **19a** in 86% yield. Removal of the trimethylsilyl group with TBAF gave the key cyclopentenone **20a** in 72% yield, thereby completing the formal synthesis of racemic herbertene. Overall, the key ketone **20a** could be obtained from the acetophenone **15a** in 7 steps over 29% yield.[11]

As depicted by Scheme 3, this method was successfully expanded to the synthesis of the key precursor to the formal synthesis of other herbertene compounds. For example, the synthesis of ketone **20b**, which was accomplished from **15b** (17% yield over 7 steps), represents a formal synthesis of racemic α-herbertenol. Moreover, the key precursors to racemic β-herbertenol (ketone **20c**) and herbertenone (ketone **20d**) was obtained from **15c** and **15d** in 23% and 21% yield, respectively. Finally, it should be noted that the aryl groups had no significant effect on the conversion and the yield of the key gold-catalyzed transformations.

In summary, we have developed a new catalytic synthetic pathway for the synthesis of herbertene natural products. The key step involves gold(I)-catalyzed cyclization of the 5-phenyl-5-siloxy-3-en-1-ynes. The synthetic method established in this study can be extended for other synthesis of related cyclopentene natural products.




**Scheme 3.** Formal synthesis of various Herbertene natural products.

## Experimental

Synthesis of **19a** from **18a**: To a stirred solution of gold complex $Au[P(C_6F_5)_3]Cl$ (13.0 mg, 0.017 mmol) and $AgSbF_6$ (3.0 mg, 0.0087 mmol) was added $CH_2Cl_2$ (3 mL) and the solution was stirred for 10 min. The resulting solution was filtered through a pad of Celite and concentrated. The residue was dried over high vacuum for 2 h. To this residue was added a solution of **18a** (63.4 mg, 0.17 mmol) and *i*-PrOH (14 μL, 0.19 mmol) in $CH_2Cl_2$ (3.5 m). After stirring at room temperature for 30 min, the mixture was passed through a pad of Celite and concentrated. The residual oil was purified by flash chromatography on silica gel (hexane: ethyl acetate = 95:5) to give the compound **19a** a as a yellow oil (37.7 mg, 0.15 mmol, 86% yield). IR (NaCl): 2959, 1699, 1248, 840 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 0.23 (s, 9 H), 1.58 (s, 3 H), 2.35 (s, 3 H), 2.53 (d, $J$ = 18.5 Hz, 1 H), 2.67 (d, $J$ = 18.5 Hz, 1 H), 7.02–7.06 (m, 3 H), 7.21 (d, $J$ = 7.2 Hz, 1 H), 7.67 (s, 1 H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ –2.1, 6.8, 7.3, 21.9, 30.2, 79.4, 82.8, 88.5, 120.9, 122.6, 126.2, 127.5, 127.9, 137.5, 148.3, 156.8. HRMS (EI) calcd for $C_{16}H_{22}OSi$: 258.1440. found: 258.1439.

Synthesis of **20a** from **19a:** To a solution of cyclopentenone **19a** (15 mg, 0.058 mmol) was added tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 0.12 mL, 0.12 mmol) at room temperature. The mixture was stirred at rt until the disappearance of the starting material. After 6 h, water (10 mL) was added and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over anh. $Na_2SO_4$ and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate = 95:5) to give the compound **20a** a as a yellow oil (7.8 mg, 0.41 mmol, 72% yield). $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.62 (s, 3 H), 2.35 (s, 3 H), 2.54 (d, $J$ =18.7 Hz, 1 H), 2.65 (d, $J$ = 18.6 Hz, 1 H), 7.05-7.07 (m, 3 H), 7.20–7.23 (m, 1 H), 7.68 (d, $J$ = 5.5Hz, 1 H).$^{13}C$ NMR (75 MHz, $CDCl_3$) δ 21.8, 27.4, 48.4, 52.1, 122.9, 126.7, 127.7, 128.8, 131.8, 138.6, 145.4, 171.8. The spectral data are in complete agreement with the literature value.[7,10c]

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**Supporting Information.** Spectral data for the compounds **16-20**.

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