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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*Received October 10, 2012, Accepted October 21, 2012*

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 quaternary 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 cyclo-

pentenone 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
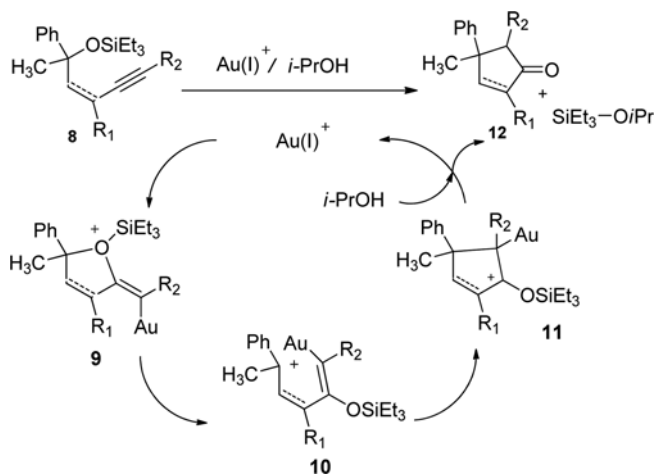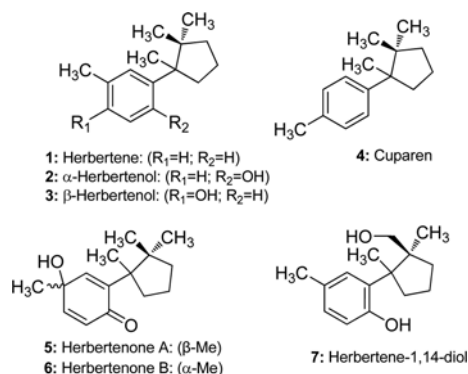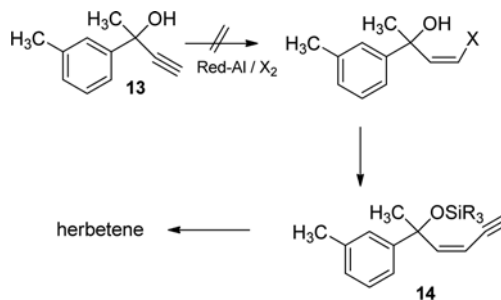

Scheme 1. Synthesis of herbertene natural products.

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

Figure 1. Structure of herbertene natural products.

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)$_3$Cl] (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.
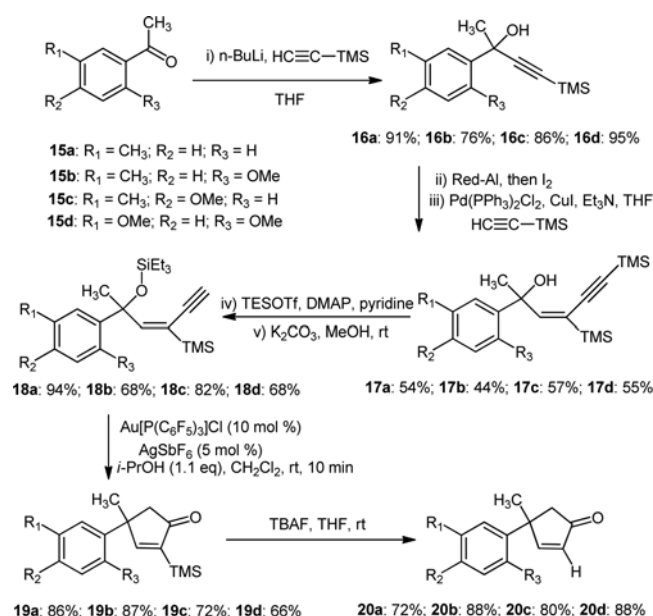
Experimental

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}. ^{1}H 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$_2$SO$_4$ 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). ^{1}H 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]

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

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Scheme 3. Formal synthesis of various Herbertene natural products.

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