A racemic formal total synthesis of clavukerin A using gold(I)-catalyzed cycloisomerization of 3-methoxy-1,6-enynes as the key strategy

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Abstract
An efficient formal total synthesis of (±)-clavukerin A was accomplished via a gold-catalyzed cycloisomerization of a 3-methoxy-1,6-enyne 5 as the key strategy followed by Rh-catalyzed stereoselective hydrogenation of the cycloheptenone 4.

Findings
Clavukerin A is a member of marine trinorguaiane sesquiterpene natural products. It was first isolated in 1983, by the group of Kitawara, from the Okinawa soft coral Clavularia koellikeri. The structure of clavukerin A was established by CD spectra and X-ray diffraction [1]. The first total synthesis of clavukerin A was reported by Asaoka in 1991, which was followed by several other racemic and enantioselective syntheses [2-14].

Herein, we report a short formal total synthesis of racemic clavukerin A employing the gold(I)-catalyzed cycloisomerization of a 3-methoxy-1,6-enyne as the key strategy, which was recently developed by us [15]. This reaction provides cycloheptane frameworks in a unique manner and illustrates the utility of the gold-catalyzed reactions [16-23].

From a retrosynthetic point of view, we envisioned two different approaches to the key enone intermediate 1 [3] to clavukerin A, starting from the cycloheptenone 4 (Scheme 1). In the first approach, enone 1 could be prepared by the sequential cyclization and the chemo- and stereoselective hydrogenation from cycloheptenone 4 (path A). Alternatively, enone 1 could be accessed by the hydrogenation of 4 and the subsequent cyclization (path B). The cycloheptenone 4 could then be synthesized from the enyne substrate 5 by gold(I)-catalyzed cycloisomerization.

The synthesis of enyne substrate 5 commenced with the alkylolation of methyl acetoacetate with the known bromide 6 [24] to
provide compound 7 in 55% yield (Scheme 2). Propargylation of 7 followed by the decarbomethoxylation with LiCl [25] gave the ketone 8 in 51% yield (over two steps). Addition of the vinyl group to this ketone gave the alkynol 9 in 90% yield as an inseparable 3:1 mixture of diastereomers. The diastereomeric ratio was determined by integration of the 1H NMR spectrum of the crude reaction product. Subsequent methylation gave the 1,6-enyne 5 in 88% yield.

We then investigated the gold-catalyzed cycloisomerization of enyne 5 using the optimized conditions from our previous study [15]. The use of the pre-generated complex Au[P(C_6F_5)_3]^+SbF_6^- (2 mol %) provided the relatively unstable enol ether 12, which was then immediately treated with aqueous silica gel to give the ketone 4 in 93% yield over two steps. Formation of 12 was unambiguously confirmed by the analysis of 1H NMR data of the crude reaction mixture. From a mechanistic viewpoint, the reaction presumably proceeds via the initial heterocyclization intermediate 10 and the subsequently rearranged intermediate 11 (Scheme 3). Notably, when the gold(I)-catalyzed reaction was carried out on a multi-mmol scale, there was no decrease in the yield at the same catalyst loading.

With ketone 4 in hand, the final stage in the formal synthesis of clavukerin A was explored. We first investigated the cyclization-hydrogenation strategy (path A in Scheme 4). Deprotection of 4 and the aldol condensation of the resulting diketone under basic conditions proceeded smoothly to give the enone 2 in good yield. However, extensive attempts at the chemoselective hydrogenation of the trisubstituted olefin 2 gave only compound 1 with poor selectivity. For example, various metal (Pd
or Rh)-catalyzed hydrogenations resulted in a mixture of 1 and 3. This problem was also noted in another work on the synthesis of clavukerin A [13].

Thus, we decided to investigate the alternative strategy that involved sequential hydrogenation–cyclization of 4. Initial efforts using various Pd catalysts or Wilkinson catalyst again showed poor stereoselectivity for the hydrogenation. However, with a Rh/alumina catalyst the selectivity was significantly improved and afforded the cis-ketone 3 in 94% yield with ~13:1 selectivity. The structure of 3 was unambiguously confirmed by comparison of the 1H and 13C data with those in the literature [3]. Because the ketone 3 was previously transformed into the enone 1 [3], synthesis of 3 represents the completion of the formal synthesis of clavukerin A.

In summary, a formal synthesis of racemic clavukerin A was accomplished via the gold(I)-catalyzed cycloisomerization of a 3-methoxy-1,6-ene as the key strategy and stereoselective Rh-catalyzed hydrogenation. Notably, the gold(I)-catalyzed reaction was compatible with the acid-sensitive functional group. Further application of the gold(I)-catalyzed cycloisomerization reaction of 3-methoxy-1,6-enynes to the enantioselective synthesis of more structurally complex cycloheptane natural products is in progress, and will be reported in due course.

Supporting Information
Supporting Information File 1
Experimental section for the preparation of compounds 2–12, and 1H and 13C NMR spectra for all new compounds. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-84-S1.pdf]

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