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Total synthesis of orientalol F *via* gold-catalyzed cycloisomerization of alkynediol†

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The total synthesis of orientalol F has been achieved starting from 1,4-dioxaspirodecan-8-one **11** in 13 steps. The key steps in this synthesis feature: (1) gold-catalyzed tandem cycloisomerization of alkynediol **10** for the formation of its seven-membered oxa-bridged bicyclic skeleton **9** of orientalol F, (2) visible-light-promoted organocatalytic aerobic oxidation of silyl enol ether **16** to enone **17**, (3) Barbier-type butenylation for the diastereoselective synthesis of allylic alcohol **18** from enone **17**, and (4) substrate-controlled Pd-catalyzed hydrogenation of **20** for the stereoselective installation of the C1 stereogenic center of **8**.

Introduction

Orientalol F (**1** in Fig. 1), which was isolated from the rhizomes of *Alisma orientalis*, is a typical representative of the sesquiterpene family of guaianolides **2–7** in Fig. 1.[1,2] These compounds have a characteristic 5,7 bicyclic ring system, an oxygen bridge in the seven-membered ring that can have different oxidation levels, and relative stereochemistry at the ring-fusion position.

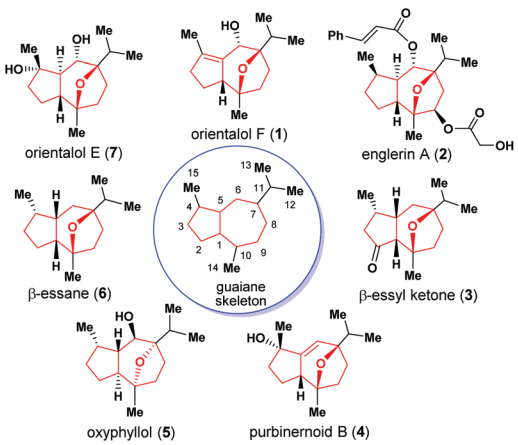

Fig. 1 Naturally occurring oxo-bridged guainane-type natural products.

Guainalides have diverse biological activities, *e.g.*, englerin A[3] (**2** in Fig. 1) is a potent and selective inhibitor of renal cell carcinoma,[4] and orientalol F (**1**) has been used as a folk medicine in East Asia for the treatment of diabetes.[1] However, the amounts of orientalol F in natural sources are small, with only 1 ppm in the corresponding dried plants, and this has hampered detailed biological research into its properties.

Because of their biological importance, much effort has been devoted to the total syntheses of these natural products,[5] and various synthetic methods[6] have been developed.

Gold(I)-catalyzed alkyne-based cycloisomerization reactions are powerful tools for the stereoselective construction of complex carbon skeletons.[7] These transformations have been used as key steps in the total syntheses of a range of natural products.[8,9] Echavarren's group[10] reported a tandem process for the simultaneous formation of two C–C bonds and one C–O bond by a gold(I)-catalyzed [2 + 2 + 2] alkyne/alkene/carbonyl cycloaddition of 1,6-enynes bearing a carbonyl group (Fig. 2, eq. 1). This reaction has been successfully used for the total syntheses of the natural products orientalol F (**1**) and englerin A (**2**).

In 2015, we reported a new type of tandem reaction for the formation of oxabicyclic scaffolds **G** involving the gold(I)-catalyzed cycloisomerization of alkynediols **D**. This reaction proceeds *via* the formation of a highly strained oxonium ion **E**, formed by the nucleophilic addition of a hydroxyl group[11] in **D** to the gold-activated alkyne, followed by a double migration to afford the highly strained intermediate **F**. The reaction continues *via* a semi-pinacol-type 1,2-alkyl migration to afford oxabicyclic compound **G** (Fig. 2, eq. 2), achieving the formation of two C–O bonds and one C–C bond in a single step. This proposed mechanism was supported by density functional theory calculations.[9c] This method has been used for the formal

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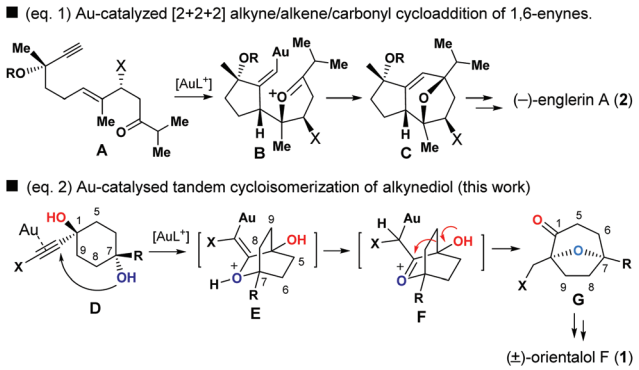
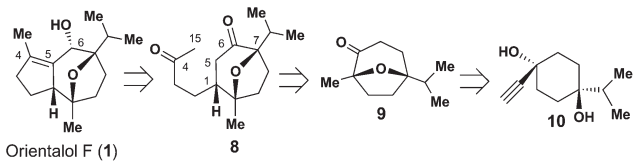


Fig. 2 Total syntheses of guainane-type natural products *via* gold-catalyzed cycloannulation.



Scheme 1 Retrosynthetic analysis of the total synthesis of orientalol F (**1**).

asymmetric total syntheses of (+)-cortistatins[9c] and asymmetric total synthesis of farnesiferol C.[9d]

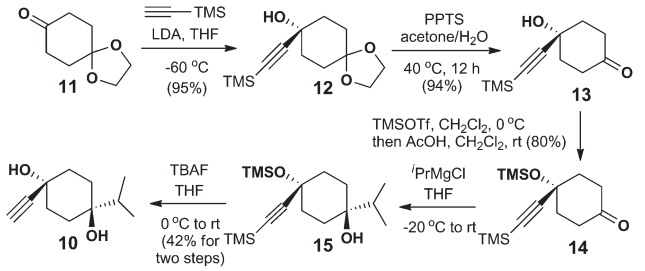
From a synthetic point of view, the primary challenge associated with the total syntheses of guainalide-type terpenoids is the construction of their oxygen-bridged seven-membered ring bearing the essential functionalities needed for their total syntheses. Here, we report the use of our recently developed gold(I)-catalyzed cycloisomerization of alkynediol **10** for the construction of the key intermediate **9** (Scheme 1), which enabled us to achieve the total synthesis of orientalol F (**1**).

Scheme 1 shows our retrosynthetic analysis of orientalol F (**1**). We expected that **1** could be synthesized from diketone **8** *via* a Robinson annulation.[12] We also envisioned that diketone **8** could be constructed *via* appropriate functional group interconversions from ketone **9**. Ketone **9**, in turn, can be synthesized from alkynediol **10** using our developed gold(I)-catalyzed cycloisomerization.[9c] This method provides an alternative strategy for the total syntheses of biologically important guainalide natural products.

Scheme 2 shows our synthesis of the key intermediate alkynediol **10**.

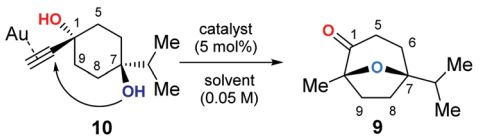
Ketone **11** was reacted with [(trimethylsilyl)ethynyl]lithium at −60 °C to give alcohol **12**, which, without purification, was treated with pyridinium *p*-toluenesulfonate [PPTS] in a mixed acetone/water solvent to give hydroxyl ketone **13** (89% yield) in two steps. Further reaction of **13** with isopropylmagnesium chloride in THF, followed by global desilylation, afforded alkynediol **10** in 42% yield in two steps.

With alkynediol **10** in hand, we then screened the reaction conditions to identify the optimum conditions; the results are shown in Table 1. The treatment of diol **10** with different gold



Scheme 2 Synthesis of alkynediol **10**.

Table 1 Gold(I)-catalyzed cycloisomerization of alkynediol **10**[a]



Entry	Catalyst	Solvent	Time	Yield[b] (%)
1	$(Ph_3P)AuCl/AgBF_4$	DCM	2 h	75
2	$(Ph_3P)AuCl/AgOTf$	DCM	2 h	72
3	$(Ph_3P)AuCl/AgSbF_6$	DCM	2 h	80
4	$(Ph_3P)AuCl/AgNTf_2$	DCM	2 h	85
5	$IPrAuCl/AgNTf_2$	DCM	2 h	46
6	$(t\text{-}Bu)_3PAuCl/AgNTf_2$	DCM	2 h	50
7	$(Ph_3P)AuCl/AgNTf_2$	DCE	2 h	79
8	$(Ph_3P)AuCl/AgNTf_2$	THF	3 h	0
9	$(Ph_3P)AuCl/AgNTf_2$	CH_3CN	3 h	0
10	$(Ph_3P)AuCl/AgNTf_2$	Toluene	3 h	0
11	$(Ph_3P)AuCl$	DCM	3 h	Trace
12	$AgNTf_2$	DCM	3 h	0
13	$PtCl_2$	DCM	3 h	0
14	PTSA	DCM	3 h	0

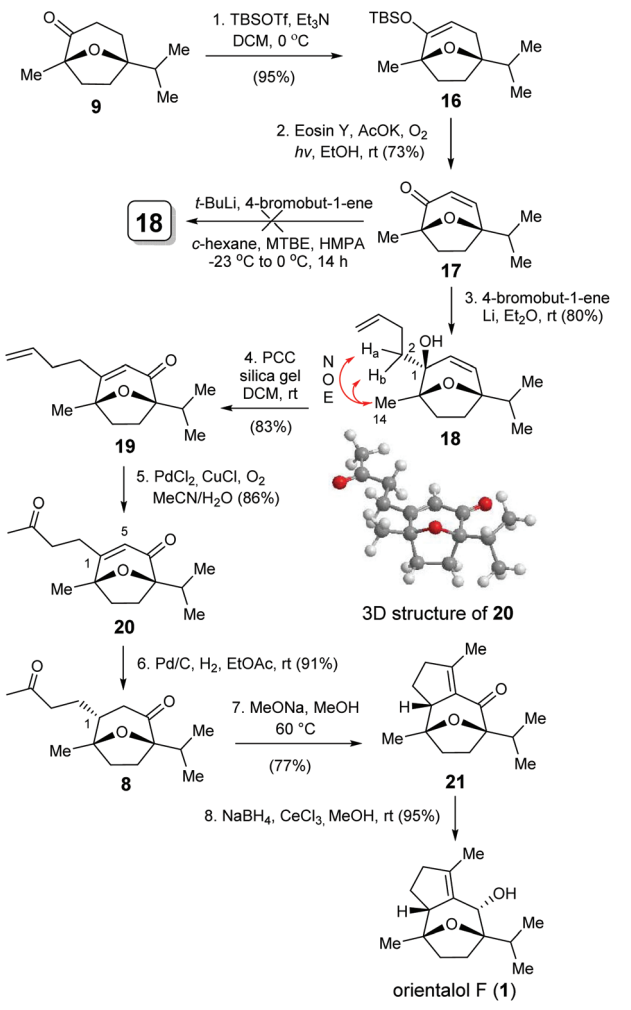
[a] Reaction conditions: A glass vial (10 mL) was filled with **1** (0.1 mmol) and a catalyst (5 mol%) in an appropriate solvent (2 mL); the mixture was stirred at room temperature for the indicated time. [b] Yield of the isolated product.

catalysts (5 mol%) in dichloromethane (DCM) for 2 h gave the desired 5-isopropyl-1-methyl-8-oxabicyclo[3.2.1]octan-2-one (**9**) in moderate to high yields (entries 1–6). $Ph_3AuCl/AgNTf_2$ (5 mol%) was the best gold catalyst, giving the desired product **9** in 85% yield (entry 4). The effects of various solvents on the outcome of the reaction were also studied (entries 7–10); DCM gave the best result. A control experiment performed in the absence of a gold catalyst gave none of the desired product, indicating that the use of $Ph_3PAuNTf_2$ is essential (entries 11 and 12). We also investigated the use of a platinum catalyst in this annulation reaction. However, only the starting material was recovered when $PtCl_2$ was used (entry 13). A Brønsted acid, namely *p*-toluenesulfonic acid, also had no effect on the reaction (entry 14). These results show that the optimum conditions for this reaction were $Ph_3PAuCl/AgNTf_2$ (5 mol%) in DCM at 25 °C. The experimental conditions were particularly practical because flame-dried glassware, an inert atmosphere, and carefully dried solvents were not required.

We then began to explore the chemistry involved in the total synthesis of orientalol F (**1**). After examining various

approaches used for the total syntheses of guainalides, we decided to adopt the method developed by Iwasawa's[6l] and Hashimoto's groups[6k] in their total synthesis of (±)-englerin A (**2**) for the formation of the C ring of our target, orientalol F (**1**). Ketone **9** was treated with *tert*-butyldimethylsilyltrifluoromethane sulfonate (TBSOTf) in the presence of Et_3N, and the resulting silyl vinyl ether **16** was subjected to Saegusa oxidation[13] *via* treatment with $Pd(OAc)_2$ (10 mol%) in the presence of oxygen; however, under these reaction conditions, only a trace amount of enone **17** was obtained. We later found that enone **17** could be generated from **16** in 73% yield using our recently developed visible-light-promoted organocatalytic aerobic oxidation.[14] We therefore used this method for the synthesis of enone **17**, because of its green chemistry features.

We then moved to the butenylation stage for the conversion of enone **17** to allylic alcohol **18**. Initially, we attempted to use the method developed by Iwasawa's[6l] and Hashimoto's groups[6k] for the butenylation reaction. However, when enone **17** was treated with but-3-en-1-yllithium derived from *t*-BuLi and 4-bromobut-1-ene, allylic alcohol **18** was not obtained under the various screened conditions (Scheme 3).



Scheme 3 Total synthesis of orientalol F (**1**).

We then decided to use a Barbier-type butenylation[15] to achieve the conversion of enone **17** to allylic alcohol **18**. Lithium metal was added to a solution of enone **17** in ether at room temperature, and the resulting mixture was stirred at the same temperature; the desired allylic alcohol **18** was obtained in 80% yield as a single diastereoisomer. The stereochemistry of the newly generated stereogenic center at C1 was confirmed using 2D NMR spectroscopy, which indicated a nuclear Overhauser effect between the protons on C2 and C14 (see the ESI† for details).

Further treatment of **18** with pyridinium chlorochromate (PCC) afforded enone **19** *via* an oxidative 1,3-allylic rearrangement.[16] The terminal alkene group in substrate **19** was converted to the corresponding ketone moiety under Wacker conditions; product **20** was obtained in 71% yield in two steps.

We used Pd-catalyzed hydrogenation for the stereoselective saturation of the C1–C5 double bond in **20** because the catalyst could approach the double bond from its convex face. Enone **20** was treated with Pd/C in EtOAc under a balloon pressure of hydrogen at room temperature; ketone **8** was obtained in 91% yield as a single diastereoisomer. Next, the five-membered ring was constructed using the method reported by Nicolaou.[6d] Wacker oxidation of **19** followed by an intramolecular aldol condensation of the resulting diketone under basic conditions afforded the tricyclic enone **21**. The carbonyl group of **21** was then subjected to Luche reduction with $NaBH_4$ and $CeCl_3$ in MeOH at room temperature. The final product, orientalol F, was obtained in 95% yield as a single stereoisomer.

Conclusions

In conclusion, the total synthesis of orientalol F (**1**) from 1,4-dioxaspirodecan-8-one (**11**) was achieved in 13 steps. The key steps in this synthesis are (1) gold-catalyzed tandem cycloisomerization of alkynediol **10** to form the seven-membered oxa-bridged bicyclic skeleton **9** of orientalol F; (2) visible-light-promoted organocatalytic aerobic oxidation of silyl enol ether **16** to enone **17**; (3) Barbier-type butenylation for the diastereoselective synthesis of allylic alcohol **18** from enone **17**; and (4) substrate-controlled Pd-catalyzed hydrogenation of **20** for the stereoselective installation of the C1 stereogenic center of **8**. Further gold-catalyzed tandem cycloisomerizations of alkynediols to form eight-membered-ring-based oxa-bridged bicyclic natural products are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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