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Stereoselective gold-catalyzed cycloaddition of functionalized ketoenynes: synthesis of (+)-orientalol F†‡

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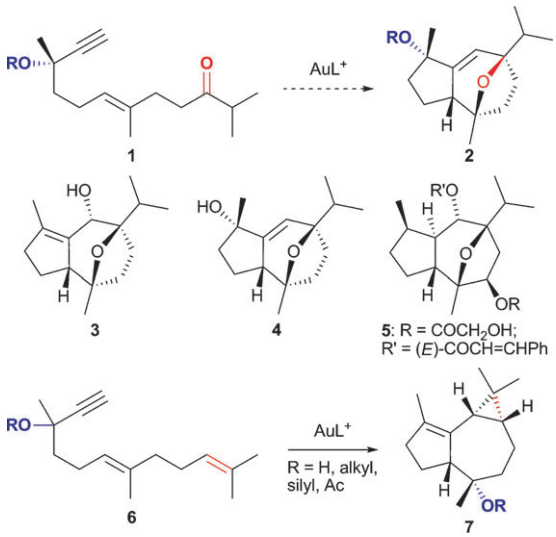
A stereoselective gold-catalyzed [2 + 2 + 2] cycloaddition of ketoenynes substituted at the propargylic position with OR groups has been applied for the synthesis of (+)-orientalol F and pubinernoid B.

1,6-Enynes with a carbonyl group at the alkenyl side chain react in the presence of Au(I) catalysts to give oxatricyclic skeletons by a domino process in which two C–C and one C–O bonds are assembled by a formal [2 + 2 + 2] alkyne/alkene/carbonyl cycloaddition.[1] The cyclization of ketoenynes **1** functionalized at the propargylic position for the synthesis of **2** would allow a direct entry into natural products such as orientalol F (**3**),[2] pubinernoid B (**4**),[3] or englerin A (**5**), a sesquiterpene that has been shown to selectively inhibit the growth of renal cancer cell lines at the nanomolar level.[4]

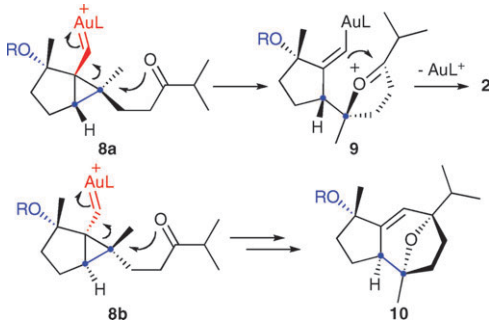
Although enynes react with gold, platinum, and other electrophilic metal catalysts to form a diversity of structures, tolerance to functional groups and stereochemical issues have not yet been examined in much detail.[5] The functionality of **1** posed a challenge since propargylic alcohols are prone to undergo Meyer–Schuster rearrangement or suffer nucleophilic attack with gold catalysts[6,7] and propargylic carboxylates readily undergo metal-catalyzed 1,2- or 1,3-acyl migrations.[5,8] In addition, we have recently found that propargyl alcohols, ethers, and silyl ethers **6** react by a new type of gold(I)-catalyzed intramolecular 1,5-migration of OR groups to give products **7** (Scheme 1).[9]

Therefore, for the desired cyclization of **1** to form **2**, the intramolecular attack of the carbonyl group should be faster than the migration of the OR group. Furthermore, the cyclization should proceed stereoselectively through **8a** and **9**, since the cyclization of the alternative intermediate **8b** would give rise to **10** with the undesired relative configuration (Scheme 2).

Here we report that the [2 + 2 + 2] gold-catalyzed cycloaddition of substrates **1** takes place stereoselectively *via* intermediates of type **8a**, which allows the first syntheses of (+)-orientalol F (**3**), the structure originally proposed for pubinernoid B (**4**), and the corrected structure of this sesquiterpene. This work also sheds light on the relative rates of competitive pathways occurring after the initial formation of the cyclopropylgold carbene[1a,10] in enyne cyclizations.



Scheme 1



Scheme 2

The cyclization proceeded more satisfactorily with TES-protected substrate **1** (Table 1). Whereas AuCl was inefficient as the catalyst (Table 1, entry 1), reaction with cationic Au(I) complexes **12**,[11] **13a**, and **13b**[12] gave oxatricyclic derivative **(±)-2b** as a single stereoisomer, along with rearranged ketone **11**[1,13] (Table 1, entries 2–4). The use of silver-free gold(I) catalysts was essential to obtain **2** in consistent yields. Although the reaction was faster with phosphine–gold catalyst **12**, the best result was obtained with NHC–gold complex **13b**, which gave **(±)-2** in 65% yield. No reaction was observed with a complex formed from $PtCl_2$ and P(*o*-Tol)$_3$ (Table 1, entry 5), whereas platinacycle **14**[14] gave rearranged ketone **11** as the major product (Table 1, entry 6). The cyclization with the free

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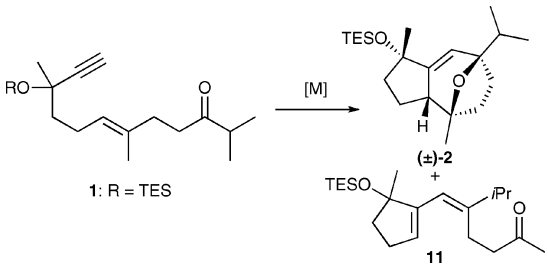
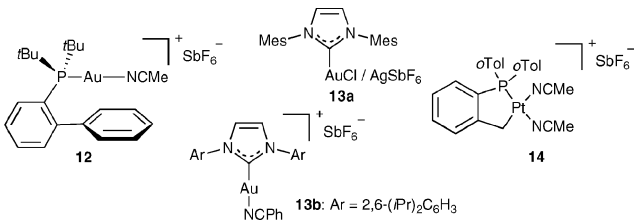
‡ Electronic supplementary information (ESI) available: Synthesis of starting substrates, characterization and X-ray crystallographic data. CCDC 747563 and 747564. See DOI: 10.1039/b920119j

Table 1 Cyclization of enyne **1** with metal catalysts[a]



Entry	[M]	*t*	Products (yield, %)
1	AuCl	24 h	—[b]
2	**12**	20 min	**2** (14) + **11** (34)
3	**13a**	3 h	**2** (25) + **11** (12)
4	**13b**	3 h	**2** (65) + **11** (4)
5[c]	$PtCl_2$/(P*o*-Tol_3)	24 h	—[b]
6	**14**	1 h	**2** (28) + **11** (42)

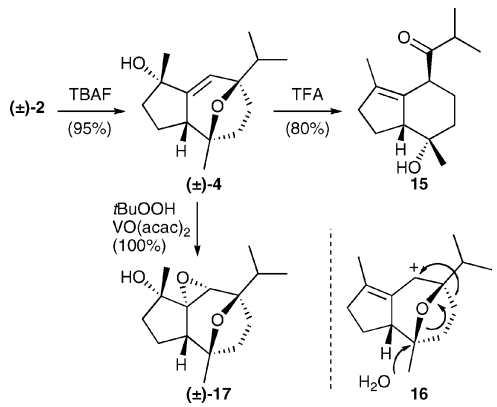
[a] Reactions in CH_2Cl_2 with 3 mol% catalyst and 4 Å molecular sieves at 23 °C. [b] Starting material was recovered. [c] Reaction in 1,2-dichloroethane at 70 °C.



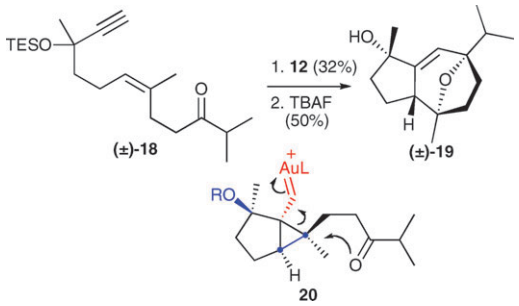
alcohol (**1**, R = H) or other protected derivatives gave low yields of the desired compounds.

Deprotection of **(±)-2** with TBAF gave **(±)-4** (95% yield) whose ^{1}H NMR (800 MHz) spectrum was clearly distinct from that reported for pubinernoid B.[3] Thus, the olefinic hydrogen appeared at δ 5.72 (d, J = 2.6 Hz), whereas for the natural product this signal was reported at δ 6.07 (br, s). An allylic rearrangement from **(±)-2** to give **(±)-3** failed using Re_2O_7.[15] Indeed, alcohol **(±)-2** is labile in the presence of acids. Treatment of **(±)-2** with TFA in CH_2Cl_2 at −20 °C gave **15** (80% yield), presumably *via* allylic carbocation **16** (Scheme 3). The configuration assigned to **(±)-2** was confirmed by X-ray diffraction of epoxide **(±)-17**.‡

Analysis of the ^{1}H NMR data reported for pubinernoid B[3] and comparison with those of the synthetic compounds



Scheme 3

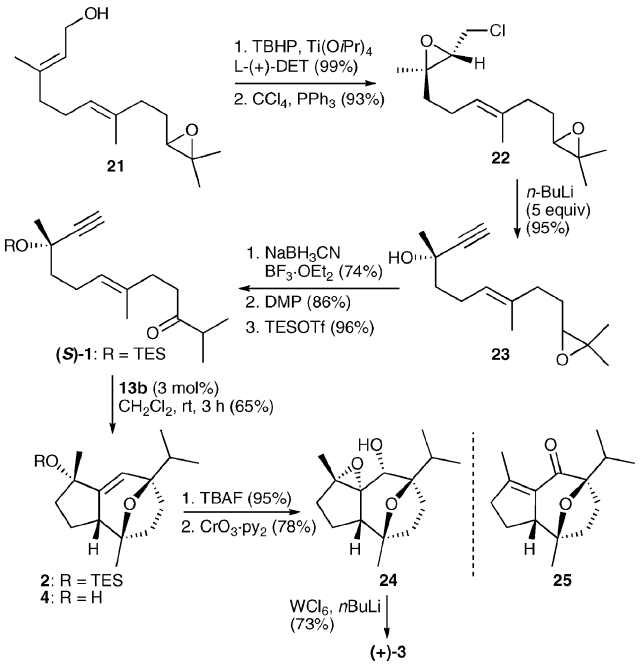


Scheme 4

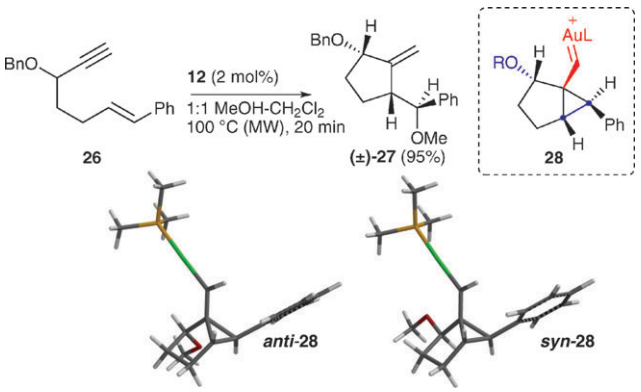
obtained in this work, suggested that this sesquiterpene might have instead a configuration opposite to that of **4** at the oxa bridge. Therefore, the synthesis of pubinernoid B required a substrate **18** with a *Z* configuration (Scheme 4). In the event, cyclization of ketoenyne **(±)-18** with catalyst **12** gave **(±)-19** in modest yield after desilylation of the major cyclization product in a reaction that presumably proceeds *via* intermediate **20**. Synthetic **(±)-19** showed NMR data identical to that reported for pubinernoid B.[3]

The synthesis of (+)-orientalol F (**3**) started from known (±)-epoxyfarnesol (**21**),[16] which furnished **22** by Sharpless epoxidation (99% yield) followed by treatment with CCl_4 and PPh_3 (93% yield). Reaction of **22** with 5 equiv. of *n*-BuLi furnished propargylic alcohol **23** in excellent yield. Regioselective reduction of the epoxide of **23** with $NaBH_3CN$ and $BF_3{\cdot}OEt_2$[17] gave the diol (74% yield), which, after oxidation with DMP (86%) and protection of the hydroxyl group with TESOTf (96%), provided (*S*)-**1**, with 95 : 5 enantiomeric ratio, which reflects the selectivity of the Sharpless epoxidation. Gold catalyzed cyclization of enantiomerically enriched (*S*)-**1** using catalyst **13b** (3 mol%) gave **2** in 65% yield. After desilylation of **2** (95% yield), the allylic alcohol **4** was treated with Collins reagent. Surprisingly, the oxidative allylic rearrangement led cleanly to *syn*-epoxy alcohol **24** (78% yield)[18] (Scheme 5). When PDC was used as the oxidant, a 74% yield of a 1 : 1 mixture of **24** and α,β-unsaturated ketone **25**, the product of the expected Dauben oxidation,[19] was obtained. (+)-Orientalol F (**3**) was obtained by reaction of **24** with WCl_6 and *n*-BuLi[20] (73% yield) or by Luche reduction of **25** (quantitative). Orientalol F (**3**) had NMR data identical to those reported.[2] Chiral-GC analysis showed an enantiomeric ratio of 94 : 6, that is, within experimental error, the same value determined for substrate **(*S*)-1**, which demonstrates that no racemization occurs in the gold-catalyzed process *via* a propargyl carbocation. Additionally, the structure of crystalline **(±)-3** was confirmed by X-ray diffraction.‡

The stereochemical control exerted by the tertiary propargyl stereocenter in the cyclization of substrates **1** is noteworthy. To clarify the origin of this stereocontrol, we examined the stereochemical outcome of the cyclization of a substrate such as **26** bearing a secondary OR at the propargylic position. The cyclization of **26** in the presence of MeOH and catalyst **12** gave product **27** exclusively (Scheme 6). The configuration of **27** was determined by NOE experiments and is consistent with a cyclization proceeding exclusively through intermediate **28** in which the OR group and the gold carbene are *anti* oriented, despite the fact that the bulky OR group is at the most



Scheme 5



Scheme 6

sterically hindered convex face of **28**. Accordingly, calculations§ show that *anti* intermediate *anti*-**28** (R = Me, L = PMe_3) is 2.3 kcal mol^{-1} more stable than *syn*-**28**.

In summary, the propargylic stereocenter controls the formation of three additional stereocenters in the Au(I)-catalyzed cyclization of ketoenynes through intermediates in which the OR group and the gold carbene are *anti*. This work shows that the attack of carbonyl groups on the cyclopropyl gold carbene is faster than the 1,5-migration of the OR groups. The stereoselective synthesis of (+)-orientalol F (**3**) illustrates the potential of the [2 + 2 + 2] gold-catalyzed cycloaddition for the synthesis of this class of substances. The synthesis of englerin A[21] along these lines is now in progress.

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Notes and references

§ M06 6-31G* (C,H,P), LANL2DZ (Au) (Spartan 08).

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