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Exploratory studies toward a synthesis of flavaglines. A novel access to a highly substituted cyclopentenone intermediate

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ABSTRACT

The gold(I)-catalyzed intramolecular siloxycyclization developed by Rhee and collaborators was shown to operate also on alkyl ethers to generate a highly substituted 2-cyclopentenone **8**, extending the application of this reaction. Conversion of **8** to known anticancer natural products following a reported strategy was examined.

Isolated from medicinal plants of the genus *Aglaia*, flavaglines have attracted considerable attention due to their remarkable structural complexity and unique biological activities, which include a strong cytotoxicity that is specific to cancer cells.[1–5] In the course of our medicinal program aiming at developing flavaglines with enhanced pharmacological properties,[5,6] we considered to prepare novel flavaglines using a strategy developed by Ragot and coll. at Bayer (Scheme 1).[7] These authors achieved the synthesis of the flavagline core **3** in three steps from cyclopentenone **1a**, using an intramolecular hydroxy epoxide opening in the key step.

Although the disclosed preparation of unsubstituted cyclopentenone **1a** could be achieved in 4 steps with an overall yield of 14%, the introduction of substituents necessary for the anticancer activity (e.g., R = OMe) was not reported. In order to synthesize pharmacologically active flavaglines, we considered to prepare **1b** by another approach. While symmetrical 3,4-diaryl-cyclopent-2-enones can easily be obtained from α,β-diketones, the synthesis of cyclopentenones substituted by different aryl moieties is more tedious.

At the heart of our approach to prepare **1b** is the Rautenstrauch rearrangement, which is particularly efficient to prepare variously substituted cyclopentenones.[8] To test the viability of this strategy, we first examined the reactivity of the Rautenstrauch's substrate **7**.

Our attempt of synthesis of ester **7** is depicted in Scheme 2. Perkin condensation of acid **4** and benzaldehyde followed by the conversion to an acyl chloride and a Sonogashira coupling conveniently afforded ketone **5** as a sole *E* isomer. Condensation with lithiated trimethoxybenzene gave adduct **6** in 71% yield.

With carbinol **6** in hand, we tested many esterification protocols.[9] However, all our attempts were unsuccessful due to lack of reactivity or high instability of expected ester **7**.

This failure led us to explore another strategy based on the recently described gold(I)-catalyzed synthesis of highly substituted cyclopentenones by an intramolecular siloxycyclization process developed by Rhee and coll. (Scheme 3).[10] The utility of this approach was validated with the total synthesis of herbertene natural products.[11] Although this reaction was described exclusively with tertiary silyl ethers (R^1 = $SiEt_3$, R^2 and $R^3 \neq H$), we considered that the phenyl and the trimethoxyphenyl groups of substrate **11** should sufficiently stabilize the carbocationic intermediate to allow the reaction to proceed (Scheme 4). This hypothesis was supported by Toste's report of a related Au(I)-catalyzed carboxyalkoxylation using benzylic ethers as substrates to synthesize indenyl ethers.[12] Thus, the silyl ether was replaced by an ethoxy group due to its easier preparation.

Indeed, the direct molybdenum(VI)-catalyzed transposition and etherification of allylic alcohol **6** at 50 °C afforded a 1:1 mixture of ethers **9** and **10** in a 55% yield.[13] Gratifyingly, increasing the temperature to 65 °C improved the ratio to 1:3 in favor of the desired ether **10** in a 85% yield. Increasing the temperature further promoted the decomposition of this product. Desilylation provided alkyne **11**, which gratifyingly proved to be a good substrate for the Rhee's annulation reaction. The attempt to perform this reaction on silylated alkyne **10** also afforded **8** (58%).

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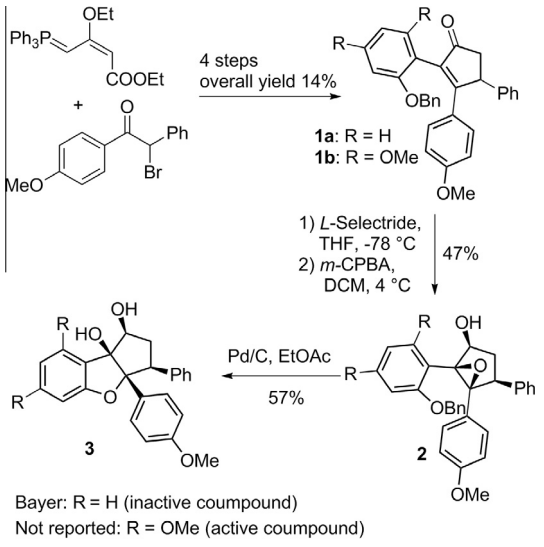
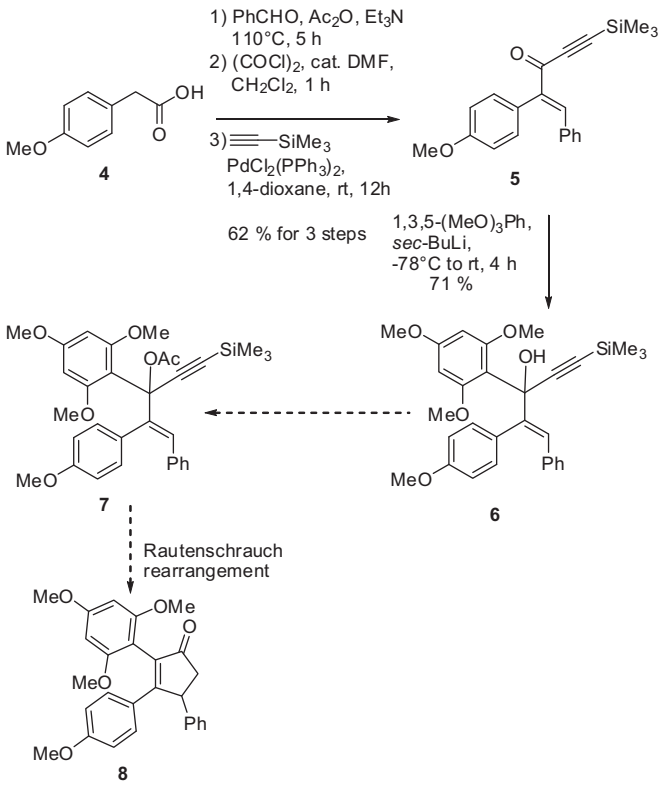


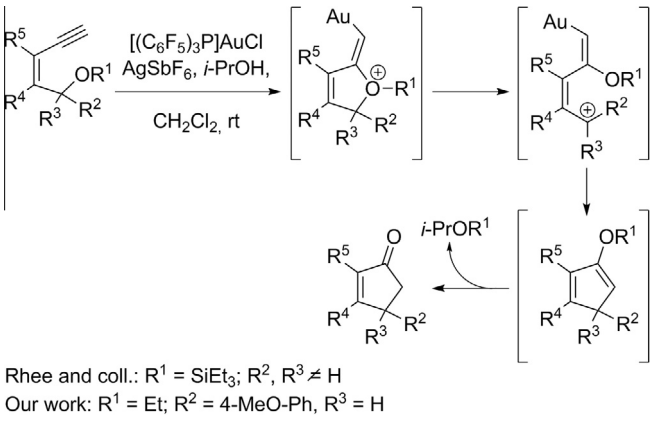
Scheme 1. Bayer synthesis of the flavagline core (the synthesis of pharmacologically active compounds (R = OMe) was not reported with this approach).[7]



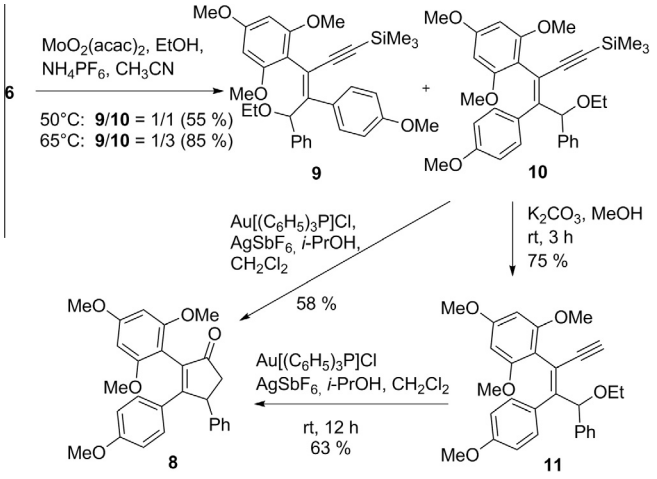
Scheme 2. Attempt synthesis of an advanced precursor of flavaglines.

The synthesis of two other cyclopentenones was next examined (Scheme 5). The substrates of the Au-catalyzed cyclization were prepared from acyl chloride **12** through Suzuki coupling, ethynylation, rearrangement and desilylation of the alkyne. Enyne **13** harboring an unsubstituted phenyl afforded the desired cyclopentenone **15** in a satisfactory yield of 50%. Interestingly, introduction of a chlorine atom in the *para* position increased the yield to 75%, probably due to a higher stabilization of the carbocationic intermediate.

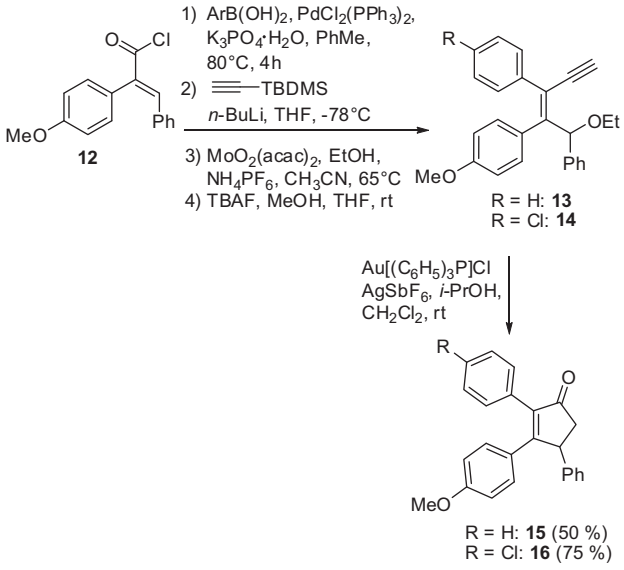
Thanks to the assistance of ketone, **8** was selectively monodemethylated upon treatment with BBr_3 in a 75% yield (Scheme 6).



Scheme 3. Proposed mechanism for the gold(I)-catalyzed cyclopentanone formation developed by Rhee and coll.[10]

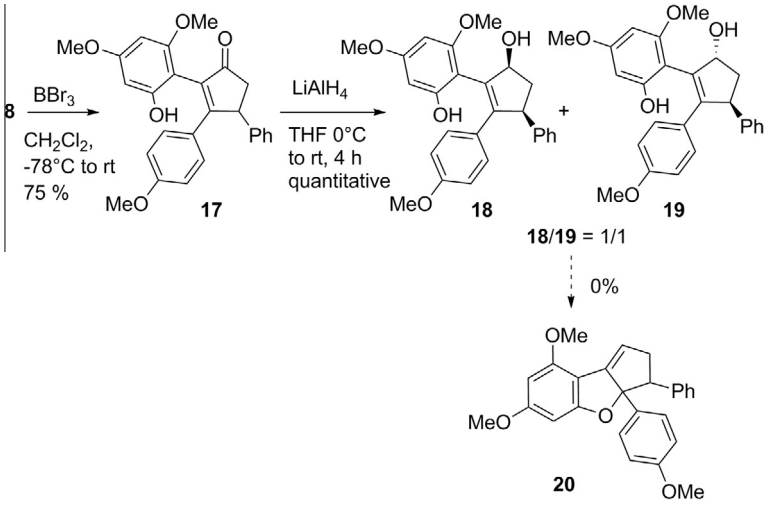


Scheme 4. Synthesis of cyclopentenone **8**.

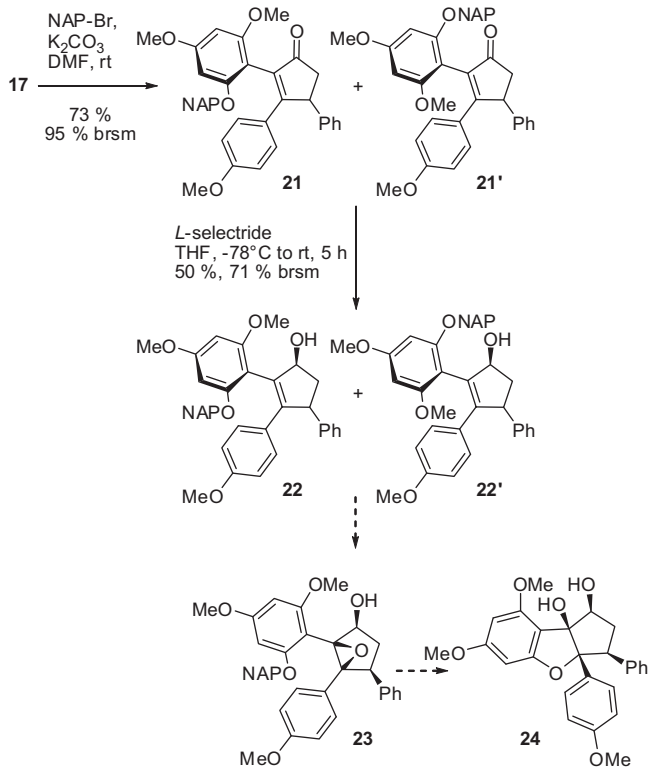


Scheme 5. Synthesis of cyclopentenones **15** and **16**.

Reduction of ketone **17** was not diastereoselective under various conditions (L-selectride; Red-Al; $NaBH_4$; $NaBH_4$, $CeCl_3{\cdot}7H_2O$). In addition, the mixture of **18** and **19** significantly degraded during



Scheme 6. Synthesis of the allylic alcohols **18/19** and attempts to generate the flavagline scaffold.



Scheme 7. Synthesis of the atropoisomeric allylic alcohols **22**/**22′** and epoxidation attempts to synthesize flavagline **24**.

purification steps. After extensive work, we eventually were able to quantitatively prepare a mixture of **18**/**19** in a 1/1 ratio using 4 equivalents of $LiAlH_4$.

With **18** and **19** in hand, we tried to convert these reactive allylic alcohols into the flavagline precursor **20** using many methods of activation of allylic alcohols ($Pd[P(OC_6H_5)_3]_4$, Na_2SO_4; PPh_3-AuCl, AgOTf, 4 Å MS; $Bi(OTf)_3$, KPF_6, $CaSO_4$; Ar-$B(OH)_2$; $FeCl_3$; $MoO_2(acac)_2$, NH_4PF_6; Re_2O_7).[14–18] Unfortunately, all of these assays only generated degradation products. Even though compounds similar to **20** have been described,[19–23] it is probable that the inherent ring strain of this product and the kinetic lability of the carbocationic intermediate prevent such a cyclization.

At this point, attempts at following Ragot's strategy using a protected phenol were examined (Scheme 7). 2-Naphthylmethyl (NAP) group was selected as the protecting group due to extremely mild conditions involved in its removal by catalytic hydrogenolysis.[24] The adduct was obtained as a pair of atropoisomers **21** and **21′**. As far as we know atropoisomerism for 1,2-diaryl cyclopentenes has not been reported hitherto.

Diastereoselective reduction with L-selectride afforded alcohols **22** and **22′** with 71% of conversion. Epoxidation of cyclopentenols **21/22′** under various conditions (*m*-CPBA, $NaHCO_3$; $VO(acac)_2$, *t*-BuO_2H; H_2O_2, NaOH; 4-nitroperbenzoic acid, $NaHCO_3$) provided none of the desired product probably due to the low reactivity of the sterically hindered alkene and instability of the product. Under Sharpless type conditions (*t*-BuO_2H, $Ti(Oi\text{-}Pr)_4$, 4 Å MS), formation of the ketone was predominant, probably due to ring strain release.

The inability to obtain substrate **23** suggests that the method reported by Bayer scientist is restricted to the synthesis of flavaglines that are not substituted by the functional groups necessary for the pharmacological activity. Indeed, none of the required decorations proposed in this Letter were described in Bayer patents.

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Supplementary data

Supplementary data (experimental procedures for the synthesis of compounds **5**, **6**, **8**, **10**–**16**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.093.

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