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Asymmetric syntheses of 8-oxabicyclo[3.2.1]octane and 11-oxatricyclo[5.3.1.0]undecane from glycals†

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Herein, we describe an efficient method to prepare enantiomerically pure 8-oxabicyclo[3.2.1]octanes via gold(I)-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement of glycal derived 1,6-enoate bearing propargylic carboxylates. The resultant compounds could then undergo interrupted Nazarov cyclization to afford diastereomerically pure 11-oxatricyclo[5.3.1.0]undecanes.

Chiral 8-oxabicyclo[3.2.1]octane and 11-oxatricyclo[5.3.1.0]-undecane are common structural motifs featured in many classes of natural products (Fig. 1), some of which show interesting biological activities. Englerin A, a potential anti-tumor reagent, is isolated from *Phyllanthus engleri* in Tanzania and shows selective activity to renal cancer cell lines at the nanomolar level.¹ Balsamiferine J, isolated from *Blumea balsamifera*, represents a novel type of sesquiterpenoids with NO inhibitory activity against murine microglial cell lines.² Homalomenol C, isolated from the roots of *Homalomena aromatic*, is reported as the bioactive component of the Vietnamese traditional medicine as an anti-inflammatory agent.³

Driven by their important bioactivities, many chemists are interested in the synthesis of this type of natural products. Attempts to gain access to this unique 8-oxabicyclo[3.2.1]-octane ring asymmetrically include [4 + 3],⁴ [5 + 2],⁵ [3 + 2]⁶ cycloadditions and cascade reactions.⁷ Despite achieving moderate to good diastereoselectivities, these methods suffer from the drawbacks of requiring expensive chiral metal

catalysts, requiring installation of non-atom economical auxiliaries and tedious chiral substrate synthesis. However, to our knowledge, there is still no report on the asymmetric synthesis of 11-oxatricyclo[5.3.1.0]undecane.

Tandem and sequential reactions are useful synthetic approaches as they offer the advantages of efficiency as well as reduction of cost and waste.⁸ Gold-catalyzed transformations of 1,6-enoate bearing propargylic carboxylates to form complex molecules have progressed rapidly in the past decade and an impressive series of transformations have been reported.⁹ It is well established that the propargylic esters could undergo 1,2- or 1,3-acyloxy migration to give the corresponding gold vinyl carbenoid or allene intermediates¹⁰ and these two intermediates could initiate further transformations depending on the reaction conditions and properties of substrates.¹¹ Hence, we envisaged that the glycal linked 1,6-enoate bearing propargylic carboxylates **1** could undergo the 1,3-acyloxy migration and the resulting intermediate would be prone to subsequent Ferrier rearrangement, thus furnishing the enantiomerically pure disubstituted 8-oxabicyclo[3.2.1]octanes **2**. If successful, this tandem 1,3-acyloxy migration/Ferrier rearrangement would set the stage for a subsequent Nazarov cyclization¹² to form the 11-oxatricyclo[5.3.1.0]undecane derivatives **3** (Scheme 1). To the best of our knowledge, this mode of reactivity is unprecedented in reactions involving 1,6-enoate bearing propargylic carboxylates. Furthermore, this glycal derived 1,6-enoate could be synthesized from readily available glycals through simple steps, making this chirality source cheap and atom economical.

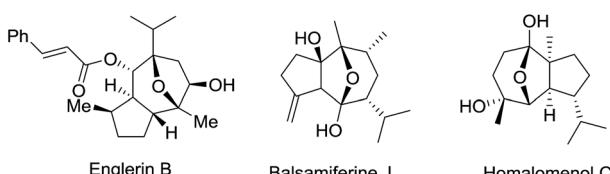
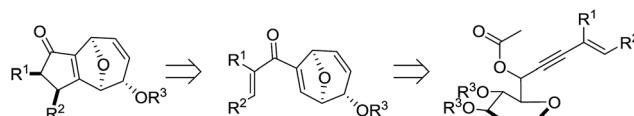


Fig. 1 Selected natural products containing 8-oxabicyclo[3.2.1]octane core structures.

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† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for all compounds are provided. CCDC 1436794 and 1520731. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7sc02625k



Scheme 1 1,3-Acyloxy migration/Ferrier rearrangement and Nazarov cyclization sequence.



D-Glucal derived 1,6-enyne bearing propargylic carboxylates **1a** was selected as the starting material to commence the investigation of this gold-catalyzed tandem reaction.¹³ To our delight, the reaction could go smoothly with compound **1a** as the starting material in the presence of AuCl_3 to give the desired product **2a** in 69% yield within 5 min (Table 1, entry 1). Other commercially available gold catalysts could also promote this reaction, further proving the feasibility of our strategy (Table 1, entries 2 and 3). Activated $\text{Ph}_3\text{PAuSbF}_6$ generated *in situ* from $\text{Ph}_3\text{PAuCl}/\text{AgSbF}_6$ was found to be most suitable for this reaction (Table 1, entry 4). Subsequently, the counter-ion effect was investigated through examining various silver salts and the AgSbF_6 presented the best performance (Table 1, entries 4–6). Attempt to employ the Brønsted acid catalyst, *p*-TsOH resulted in decomposition of the starting material (Table 1, entry 7). Notably, Ph_3PAuCl and AgSbF_6 were found to be inactive when they were employed individually (Table 1, entries 8 and 9). Solvent screening showed that CH_2Cl_2 was superior to other commonly used solvents (Table 1, entries 10–13). To demonstrate the utility of this method, a reaction on a larger scale (0.5 mmol) was carried out and **2a** was afforded in 81% yield (Table 1, entry 14). Interestingly, when the propargylic ester group was switched from acetyl group to pivaloyl or benzoyl groups, no significant change was observed (Table 1, entries 15 and 16).

Using the optimal conditions, a range of the glycal derived 1,6-enyne bearing propargylic carboxylates were investigated to demonstrate the wide application of this transformation. In general, the desired products were rapidly obtained in good to

Table 1 Optimization of gold-catalyzed reaction of **1a**

Entry ^a	Catalyst	Solvent	Time	Yield ^b
1	AuCl_3	CH_2Cl_2	5 min	69%
2	AuCl	CH_2Cl_2	5 min	42%
3	$\text{Ph}_3\text{PAuNTf}_2$	CH_2Cl_2	5 min	72%
4	$\text{Ph}_3\text{PAuCl}/\text{AgSbF}_6$	CH_2Cl_2	5 min	80%
5	$\text{Ph}_3\text{PAuCl}/\text{AgClO}_4$	CH_2Cl_2	5 min	62%
6	$\text{Ph}_3\text{PAuCl}/\text{AgOTf}$	CH_2Cl_2	5 min	68%
7	<i>p</i> -TsOH	CH_2Cl_2	—	Trace
8	Ph_3PAuCl	CH_2Cl_2	—	n.r.
9	AgSbF_6	CH_2Cl_2	—	n.r.
10	$\text{Ph}_3\text{PAuCl}/\text{AgSbF}_6$	DCE	5 min	76%
11	$\text{Ph}_3\text{PAuCl}/\text{AgSbF}_6$	Toluene	2 h	52%
12	$\text{Ph}_3\text{PAuCl}/\text{AgSbF}_6$	CH_3NO_2	5 min	66%
13	$\text{Ph}_3\text{PAuCl}/\text{AgSbF}_6$	CH_3CN	1 h	48%
14 ^c	$\text{Ph}_3\text{PAuCl}/\text{AgSbF}_6$	CH_2Cl_2	5 min	81%
15 ^d	$\text{Ph}_3\text{PAuCl}/\text{AgSbF}_6$	CH_2Cl_2	5 min	79%
16 ^e	$\text{Ph}_3\text{PAuCl}/\text{AgSbF}_6$	CH_2Cl_2	5 min	72%

^a Reaction conditions: propargylic ester **1** (0.1 M in CH_2Cl_2), 5 mol% gold catalyst, 10 mol% silver catalyst. ^b Isolated yield. ^c Reaction was carried out on scale of 0.5 M of **1a**. ^d Pivaloyl ester substrate. ^e Benzoyl ester substrate. DCE = $\text{ClCH}_2\text{CH}_2\text{Cl}$, n.r. = no reaction.

excellent yields. The stereochemistry was unambiguously confirmed by X-ray analysis of compound **2b**.¹⁴ A comparison of the *para*-substituents of aryl substrates showed that those with electron donating aryl substituents (**2b, c**) afforded higher yields than those with electron withdrawing substituents (**2d, e**). Replacing the aryl substituent at the alkyne position with less bulky alkyl substituents, such as cyclohexyl, *n*-butyl and methyl substituent (**2f–h**) furnished the corresponding products in good yields. Alkene substituents were also tolerated (**2i–m**), but the yield decreased when the reaction was carried out on a larger scale (0.5 M). It should be noted that the reaction proceeded readily to give the rearranged products when the benzyl group was changed to methyl or methoxymethyl groups (**2n–r**). To the best of our knowledge, methoxy group has never been used as the leaving group for Ferrier rearrangement. When L-glycal derived propargylic acetates were tested for this reaction, similar results were obtained (*ent*-**2a**, **2b** and **2g**). As expected, D-galactal derived substrate led to a diminished yield due to the steric effect between benzyl group and propargylic ester (*epi*-**2a**). Notably, complete diastereoselectivity was detected in all the examples (Table 2).

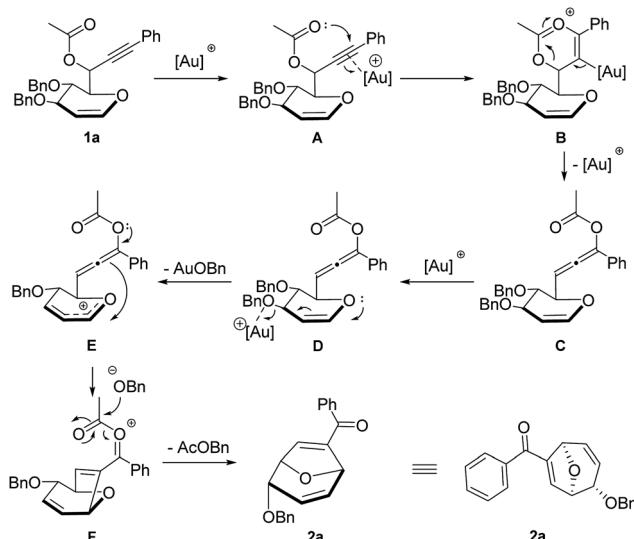
Based on the experimental results, a plausible mechanism for the formation of disubstituted 8-oxabicyclo[3.2.1]octane

Table 2 Substrate scope of gold-catalyzed synthesis of **2**

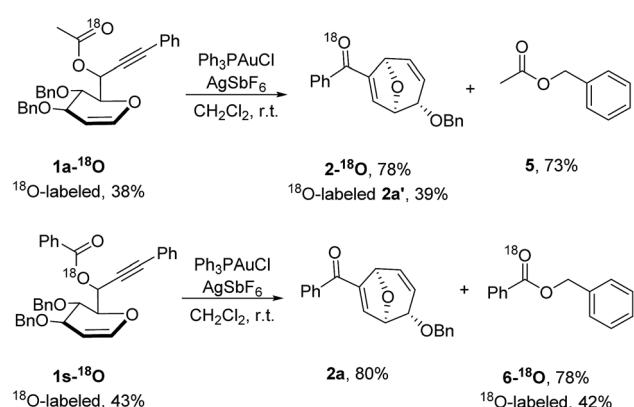
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product is proposed with compound **1a** (Scheme 2). The gold catalyst is proposed to have dual role in this transformation. Firstly, it helps to transform the propargylic ester motif of compound **1a** into the nucleophilic allenic intermediate **C** through gold-catalyzed 1,3-acloxy migration. Secondly, it serves as Lewis acid to facilitate the intramolecular Ferrier reaction by promoting the departure of benzyl group and leading to the formation of allylic oxocarbenium ion **E**.¹⁵ Subsequently, electrophilic attack of the allylic oxocarbenium motif to the allene generated oxa-bridged 7-membered ring intermediate **F**. Finally, the leaving group of Ferrier rearrangement attacks the oxonium species to generate the desired disubstituted 8-oxabicyclo[3.2.1]octane product **2a** with benzyl acetate as the byproduct. The complete diastereoselectivity is attributed to *cis* face attack of allenic ester at C-5 position of glycal derived propargylic esters.

To confirm the mechanism, isotopic labeling experiments were conducted (Scheme 3). When the propargylic acetate **1a-¹⁸O** with an ¹⁸O-enriched carbonyl oxygen atom was synthesized and subjected to the optimized reaction conditions, ¹⁸O-

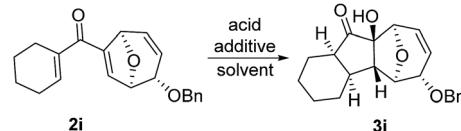


Scheme 2 Plausible mechanism for the formation of **2a**.



Scheme 3 Isotope labeling experiments.

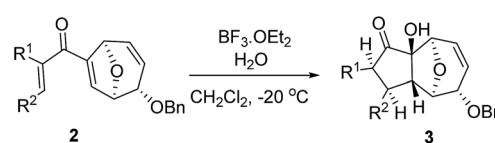
Table 3 Optimization studies of the Nazarov cyclization^a



Entry	Acid	Additive	Solvent	T/t (h)	Yield ^b
1	H ₂ SO ₄	—	MeOH	-40 °C/1	Mixture
2	BF ₃ ·OEt ₂	—	CH ₂ Cl ₂	-20 °C/2	Trace
3	BF ₃ ·OEt ₂	H ₂ O	CH ₂ Cl ₂	-20 °C/2	77%
4	CF ₃ SO ₃ H	—	CH ₂ Cl ₂	r.t./2	18%
5	CF ₃ SO ₃ H	H ₂ O	CH ₂ Cl ₂	r.t./2	32%
6	SnCl ₄	—	CH ₂ Cl ₂	-40 °C/1	Mixture
7 ^c	BF ₃ ·OEt ₂	H ₂ O	CH ₂ Cl ₂	-20 °C/2	78%

^a Reaction conditions: divinyl ketone **2i** (0.1 M in CH₂Cl₂), acid (2 equiv.), additive (1 equiv.). ^b Isolated yield. ^c Reaction was carried out on scale of 0.2 M of **2i**.

Table 4 Substrate scope of interrupted Nazarov cyclization



Entry	Starting material	Solvent	Yield ^b
1	2i		3i 78%
2	2j		3j 64%
3	2k		3k 75%
4	2l		3l Mixture
5 ^c	2m		3m 34%

^a Reaction conditions: divinyl ketone **2** (0.2 M in CH₂Cl₂), BF₃·OEt₂ (2 equiv.), H₂O (1 equiv.). ^b Isolated yield. ^c Reaction carried out at 0 °C.



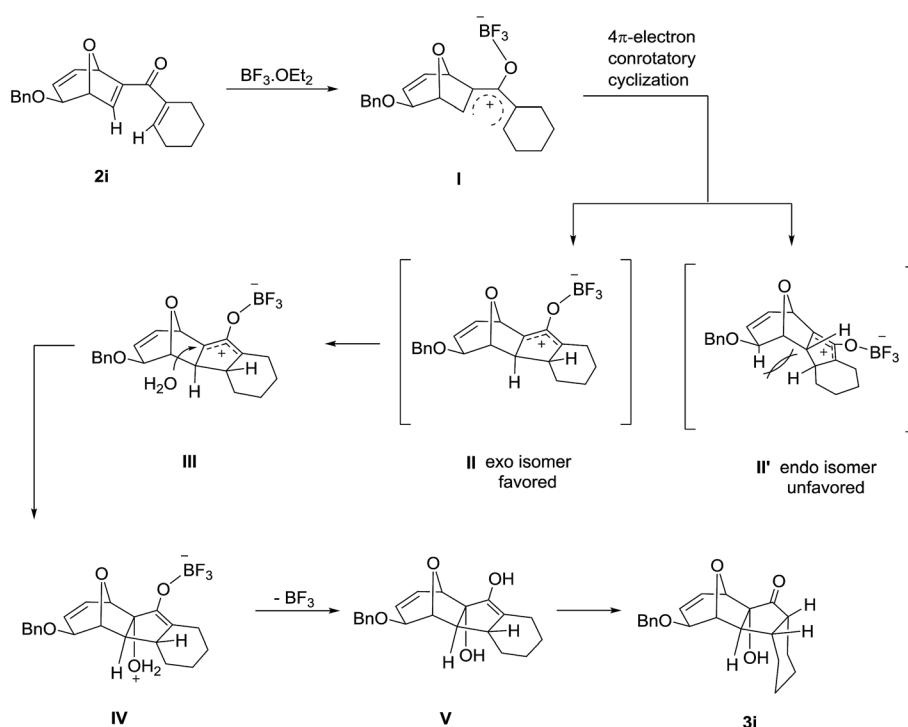
labeled 8-oxabicyclo[3.2.1]octane **2a-¹⁸O** was isolated in 78% yield and ¹⁸O containing carbonyl fragment was detected (PhC¹⁸O⁺ with *m/z* 107.0393). Conversely, ¹⁸O label was present in benzyl benzoate **6-¹⁸O** instead of 8-oxabicyclo[3.2.1]octane **2a-¹⁸O** when propargylic benzoate **1s-¹⁸O** with an ¹⁸O-enriched ester oxygen was used as the starting material. The following conclusions could be drawn from the isotopic labeling results detected by high-resolution mass spectrometry: firstly, 8-oxabicyclo[3.2.1]octane was generated exclusively from allene intermediate *via* gold-catalyzed 1,3-acyloxy migration rather than two sequential 1,2-acyloxy migration since scrambling of ¹⁸O-label was not detected in **5** or **2a**. Secondly, Ferrier rearrangement was initiated by gold-catalyzed 1,3-acyloxy migration and its byproduct benzyl oxoanion quenched the reaction, accounting for the high efficiency and rapid rate for this transformation.

In order to investigate whether Nazarov cyclization could proceed sequentially after tandem 1,3-acyloxy migration/Ferrier rearrangement, a variety of Lewis and Brønsted acids were examined with **2a** but gave either intractable mixtures or incomplete consumption of starting material. To our delight, when the divinyl ketone derivative **2i** was used as the substrate instead, the interrupted Nazarov cyclization product **3i** was furnished. The stereochemistry of compound **3i** was confirmed by X-ray structure analysis of its derivative.¹⁶ Use of 2 equivalent $\text{BF}_3 \cdot \text{OEt}_2$ with 1 equivalent H_2O as additive produced the optimal yield of 11-oxatricyclo[5.3.1.0]undecane **3i** (Table 3, entry 3), while using $\text{CF}_3\text{SO}_3\text{H}$ or in absence of H_2O also effected conversion to **3i**, albeit in lower yield (Table 3, entries 2, 4 and 5). H_2SO_4 and SnCl_4 were examined but an intractable mixture was observed even when the reaction was conducted at a lower

temperature (Table 3, entries 1 and 6). Reaction on larger scale (0.2 M) also proceeded smoothly and afforded **3i** in 78% yield (Table 3, entry 7).

With the optimal interrupted Nazarov cyclization conditions in hand, five 8-oxabicyclo[3.2.1]octane derivatives **2** containing divinyl ketone motif were investigated. Similar with cyclohexenyl ketone **2i**, substituted cyclohexenyl ketone **2j** and cyclooctenyl ketone **2k** could also undergo conversion to the corresponding polycyclic products **3j** and **3k** in good yields (Table 4, entry 3 and 4). In addition, β -substituted ketone **2m** could be applied to form the 11-oxatricyclo[5.3.1.0]undecane **3l**, which was the core structure of homalomenol C (Table 4, entry 5). However, α -substituted ketone **2l** decomposed under the same condition (Table 4, entry 2).

The high degree of torque selectivity of 11-oxatricyclo[5.3.1.0]undecane **3** is quite interesting in this study and we proposed the mechanism as follow (Scheme 4): activated by the $\text{BF}_3 \cdot \text{OEt}_2$, the pentadienyl cation **I** was generated and following by a 4π conrotatory electrocyclization to afford the cyclopentenyl cation intermediate **II** with complete exo selectivity. The similar result about high exo selectivity for Nazarov cyclization of norbornene derivatives^{17b} and bicyclo[3.2.1]octane^{17g,h} were previously reported by West *et al.* and it was ascribed to the alkene predistortion such as transition state allylic bond staggering,^{17b} combination of alkene pyramidalization,^{17c} nonequivalent orbital extension,^{17d} steric crowding^{17e} and torsional strain.^{17f} Houk and co-workers have shown that bicyclo[3.2.1]octane derivatives without through-space interaction would reach quite high exo selectivity in electrocyclization in DFT calculations.^{17a} In our case, the nonconjugated alkene does not involve this reaction and the cycloalkene motifs create more



Scheme 4 Proposed mechanism of interrupted Nazarov cyclization.



steric repulsion and torsional strain in the transition state which further promote the exo stereoselectivity. Sequentially, the external H_2O trapped the cyclopentenyl cation **II** from the endo face of the polycyclic system which is less bulky after electrocyclization. Finally, the intermediate **IV** was transformed into 11-oxatricyclo[5.3.1.0]undecane 3 through hydrogen shift and enol–keto tautomerism.

Conclusion

In summary, a novel homogeneous gold-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement was developed successfully to access disubstituted 8-oxabicyclo[3.2.1]octane with high efficiency and complete diastereoselectivity using glycal-derived propargylic esters. The resultant products could then undergo an interrupted Nazarov cyclization serving as an efficient strategy for the facile synthesis of diastereomerically pure 11-oxatricyclo[5.3.1.0]undecanes which was applied to synthesize the core structure of homalomenol C. More studies on mechanism and natural product synthesis are currently in progress.

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13 Preparation of all the propargyl ester substrates **1** is included in Section B, general procedure A and B in the ESI†.

14 See Section E, Table 1 (**2b**, CCDC 1436794) in the ESI† for the crystal structure.

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