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InI₃-catalyzed polyene cyclization of allenes and its application in the total synthesis of seven abietane-type diterpenoids†

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A novel polyene cyclization using the allene group as the initiator has been successfully developed. This methodology provides an efficient strategy for the construction of an abietane-type tricyclic skeleton with a functionalizable C2–C3 double bond and features a wide substrate scope and excellent stereoselectivities. Potential utility of this approach has been well demonstrated by the collective total synthesis of seven abietane-type diterpenoids. Specifically, (±)-2,3-dihydroxyferruginol and (±)-2,3-dihydroxy-15,16-dinor-ent-pimar-8,11,13-triene were synthesized for the first time.

Introduction

Polyene cyclization, as one of the most powerful synthetic strategies, has been widely applied to the synthesis of complex polycyclic natural products and bioactive molecules.¹ Since the elegant strategy was first successfully introduced for synthesizing diterpenes, many synthetic chemists have strived to explore more convenient and general synthetic approaches toward biologically active polycyclic terpenes² or the key 6/6/6 tricyclic skeleton.³ During the process, many functional groups have been used as initiators to trigger this kind of cyclization procedure, such as alkene⁴ or alkyne,⁵ epoxide,⁶ allylic alcohol,⁷ propargylic ester⁸ and carbonyl-related groups.⁹ Nevertheless, it is still highly desirable to develop new activation patterns that can spontaneously introduce functional groups on the resulting polycyclic products to facilitate subsequent synthetic manipulations, in particular, the synthesis of corresponding bioactive molecules (Fig. 1).

Based on the pioneering work of polyene cyclization and in connection with our research interests in the development of efficient synthetic methodologies toward the synthesis of bioactive molecules, an Au(I)-catalyzed polyene cyclization strategy using propargylic ester as the initiator was developed by our group recently. In this procedure, an enol ester moiety at the C2–

C3 site of the key 6/6/6 tricyclic skeleton can be readily installed and used as a functional handle for subsequent synthetic transformations (Scheme 1a), which has been shown through the divergent synthesis of five abietane-type diterpenoids encouraging us to carry out further investigation in this field.⁸ Over the past decades, the allene group, as a typical versatile synthon, has attracted broad attention from chemists.¹⁰ In particular, it has been applied to a series of cyclization modes to construct various ring systems with an alkene moiety.¹¹ Inspired by these results, we envisioned that it should be viable to develop a new polyene cyclization mode using the allene functional group as the initiator to afford a 6/6/6 tricyclic cyclization product with a double bond at the C2–C3 position (Scheme 1b). Since the double bond can be readily transformed to structural moieties like vicinal diol or enone, realization of such a methodology should lead to a new synthetic strategy toward the collective total synthesis of some biological abietane-type diterpenoids with substituents at both C2 and C3-positions, such as (±)-shonanol, (±)-2,3-dihydroxy-

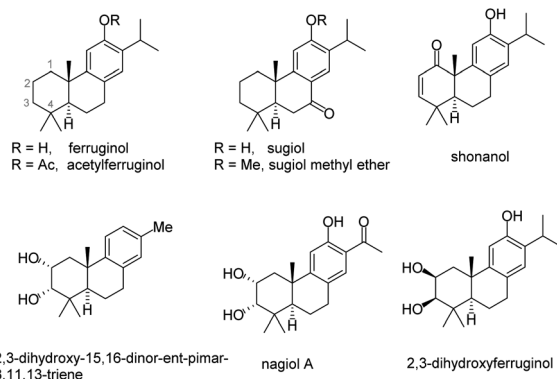


Fig. 1 Selected abietane-type diterpenoids.

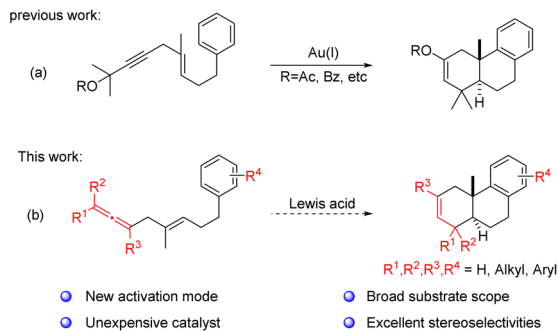
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Scheme 1 Background information and the synthetic strategy.

15,16-dinor-*ent*-pimar-8,11,13-triene, and (\pm)-2,3-dihydroxyferruginol (Fig. 1). Herein, we present an InI_3 -catalyzed polyene cyclization of allenes and its application to the total synthesis of seven abietane-type diterpenoids.

Results and discussion

Initially, we attempted a model reaction of **1a** with various Lewis acids (see the ESI†). Fortunately, the desired product **2a** was obtained in 10% yield with $\text{In}(\text{OTf})_3$ (Table 1, entry 1), whereas other strong Lewis acids like $\text{Sn}(\text{OTf})_2$ and $\text{Zn}(\text{OTf})_2$ did not give product **2a** (Table 1, entries 2–3). Therefore, indium catalysts with different anions such as InCl_3 , InBr_3 , InI_3 were further screened. Fortunately, the use of InI_3 led to the best yield of 63% (Table 1, entry 6). Subsequently, several solvents were also tested, and

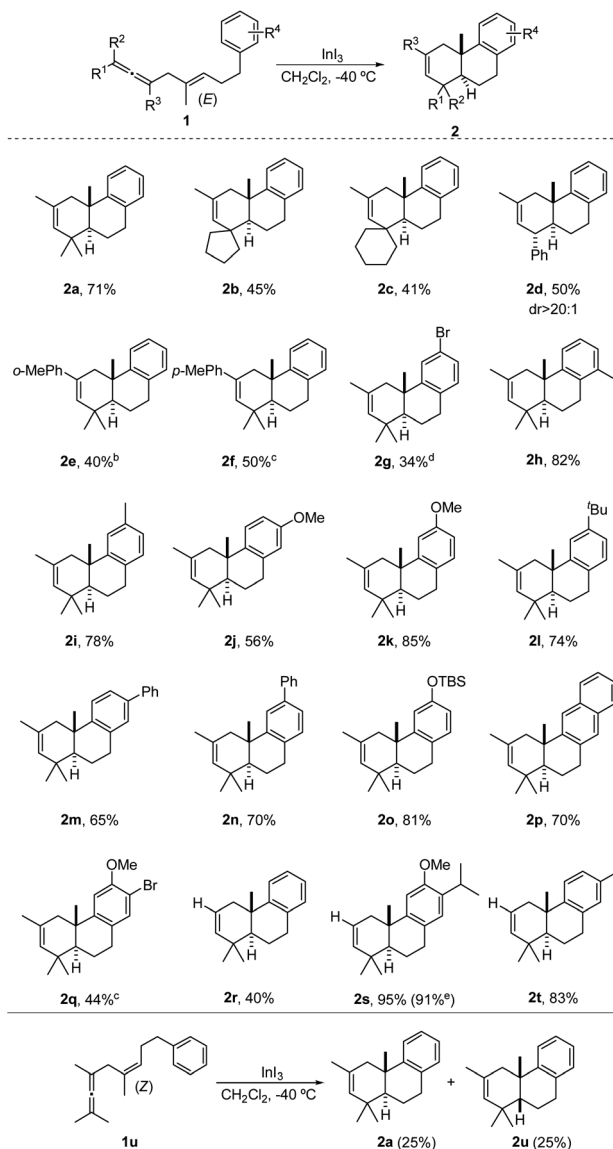
Table 1 Reaction condition optimization^a

Entry	Cat.	Equiv.	Sol.	<i>T</i> (°C)	<i>t</i> /h	Yield (%) ^b
1	$\text{In}(\text{OTf})_3$	0.2	DCM	r.t.	18	10
2	$\text{Sn}(\text{OTf})_2$	0.2	DCM	0	1	NR ^c
3	$\text{Zn}(\text{OTf})_2$	0.2	DCM	r.t.	120	NR ^c
4	InCl_3	0.2	DCM	r.t.	1	40
5	InBr_3	0.2	DCM	r.t.	1	40
6	InI_3	0.2	DCM	−20	4	63
7	InI_3	0.2	CH_3OH	r.t.	120	NR ^c
8	InI_3	0.2	DMF	r.t.	120	NR ^c
9	InI_3	0.2	DCE	−20	3	45
10	InI_3	0.2	Toluene	−20	3	20
11	InI_3	0.2	CH_3CN	r.t.	120	NR ^c
12	InI_3	0.2	THF	r.t.	120	NR ^c
13	InI_3	0.2	DCM	r.t.	0.5	45
14	InI_3	0.2	DCM	0	1.5	54
15	InI_3	0.2	DCM	−40	6	71
16	InI_3	0.2	DCM	−60	27	63

^a Unless specified, all reactions were carried out with **1a** (0.1 mmol, 1.0 equiv.) and solvent (2 mL) in reaction tubes. ^b Isolated yield of product **2a**. ^c NR = no Reaction.

CH_2Cl_2 was still the best choice after many trials, while other solvents were not efficient enough (Table 1, entries 7–12). Furthermore, examining different temperatures ranging from −60 °C to 0 °C revealed the best yield of 71% at −40 °C (Table 1, entries 13–16). Finally, the reaction was conducted in CH_2Cl_2 at −40 °C (Table 1, entry 15).

With the optimal reaction conditions in hand, the substrate scope of this reaction was then investigated. As shown in Scheme 2, switching the *gem*-dimethyl moiety to cyclopentane and cyclohexane rings was feasible, giving the desired products **2b** and **2c** in 45% and 41% yields, respectively. The slightly decreased yields might be attributed to the steric hindrance of these moieties. Notably, a mono phenyl substituted substrate **1d** could deliver **2d**

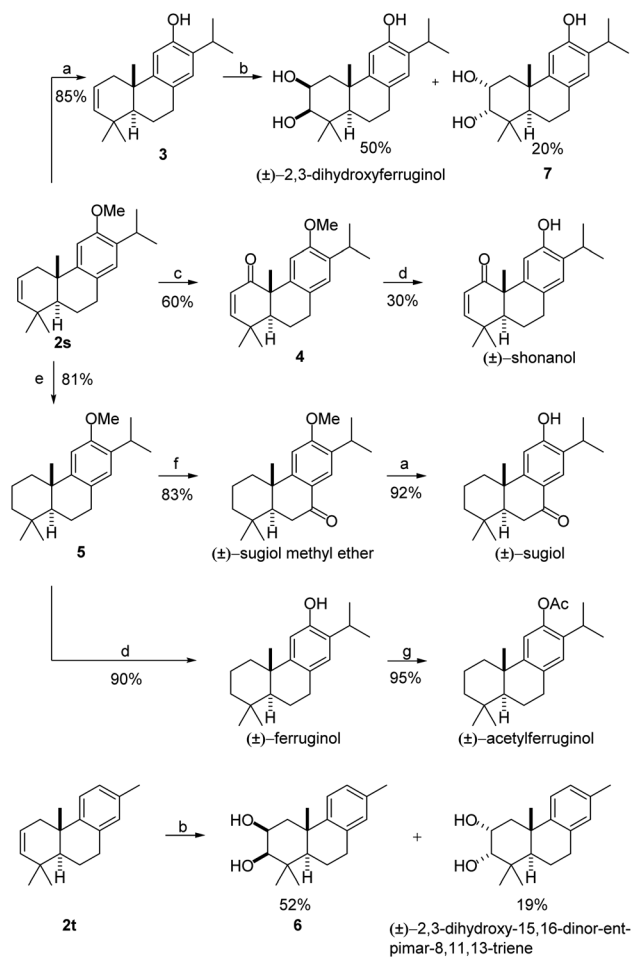


Scheme 2 Substrate scope investigation of the reaction^a. ^aUnless specified, all reactions were carried out with **1** (0.1 mmol, 1.0 equiv.), InI_3 (20 mol%) and CH_2Cl_2 (2 mL) in reaction tubes at −40 °C for 4 h. ^bReaction temperature was 0 °C. ^cReaction temperature was 25 °C. ^dReaction temperature was −20 °C. ^eYield obtained in a 2 mmol scale reaction.



smoothly in 50% yield with excellent diastereoselectivity, and the relative configuration of **2d** was further determined by X-ray crystal diffraction. Next, changing the R³ group of substrates from methyl to *o*-methylphenyl and *p*-methylphenyl was successful to give corresponding products **2e** and **2f** in moderate yields of 40% and 50% at 0 °C and room temperature, respectively. Subsequently, it was observed that bromo substituted substrate **1g** was amenable to this reaction, albeit giving **2g** with only 34% yield. Subsequently, substrates with electro-donating groups such as methyl, methoxy, *tert*-butyl and phenyl groups as R⁴ at different positions on the phenyl ring were also investigated. All these substrates could produce the expected products in moderate to good yields (**2h–2n**). Generally, electron-donating substituents were beneficial for better yields of corresponding products (**2g** vs. **2h–2n**). Consistent with the above observation, electron-donating substituents like TBS ether on the phenyl ring and the use of the naphthalene ring could also lead to the desired products **2o** and **2p** in good yields of 81% and 70%, respectively. It is worth mentioning that substrate **1r** with two electron-donating substituents gave the best yield of 95%, whereas **1q** bearing both electron-rich and electron-deficient substituents produced **2q** in only 44% yield. Moreover, the electronic effect was also shown by comparison between **2r** and **2t** (40% vs. 83%). To further demonstrate the potential practicality of this reaction, a 2 mmol scale reaction of **1s** was also conducted, and an excellent yield of 91% yield was obtained. Additionally, substrate **1u** with a (*Z*)-1,4-enallene moiety was also tested under the standard conditions, and an inseparable mixture of **2a** and **2u** was obtained in 50% total yield and 1 : 1 diastomeric ratio (*trans/cis*).^{12,4h,5e}

To show the synthetic utility of the reaction, a collective total synthesis of seven abietane-type diterpenes, *i.e.*, (±)-2,3-dihydroxyferruginol,¹³ (±)-shonanol,¹⁴ (±)-2,3-dihydroxy-15,16-dinor-*ent*-pimar-8,11,13-triene,¹⁵ (±)-ferruginol,¹⁶ (±)-sugiol methyl ether,¹⁷ (±)-sugiol,¹⁸ and (±)-acetylferruginol,¹⁹ was then conducted from compounds **2s** and **2t**. As shown in Scheme 3, demethylation of **2s** delivered **3** in 85% yield in the presence of NaSEt, and (±)-2,3-dihydroxyferruginol was readily obtained through dihydroxylation of **3** in 50% yield along with its epimer **7**. The relative configuration of (±)-2,3-dihydroxyferruginol was confirmed by X-ray diffraction (see the ESI†). In another successful example, selective oxidation of **2s** with SeO₂ and further oxidation could give ketone **4** in 60% yield using DMP as the oxidant. Subsequently, the synthesis of (±)-shonanol was readily finished after simple demethylation, and the relative configuration was also confirmed by X-ray diffraction (see the ESI†). Other syntheses of abietane-type diterpenoids, such as (±)-ferruginol, (±)-sugiol methyl ether, (±)-sugiol, and (±)-acetylferruginol are also exhibited in Scheme 3 starting from a common advanced intermediate **5**, which was easily prepared through hydrogenation of **2s** in 81% yield. Next, (±)-ferruginol was obtained by demethylation of **5** in 90% yield in the presence of BBr₃. Acylation of (±)-ferruginol gave (±)-acetylferruginol in 95% yield. Alternatively, compound **5** could be oxidized with CrO₃ to give (±)-sugiol methyl ether in 83% yield, and demethylation of (±)-sugiol methyl ether with NaSEt afforded (±)-sugiol. Additionally, another natural product (±)-2,3-dihydroxy-15,16-dinor-*ent*-pimar-8,11,13-triene and its epimer **6** were



Scheme 3 Synthetic applications. (a) NaSEt, DMF, 140 °C; (b) OsO₄, NMO, citric acid, *t*-BuOH/acetone/H₂O = 1:1:1; (c) SeO₂, 1,4-dioxane, 100 °C, then DMP, DCM, r.t.; (d) BBr₃, DCM, -20 °C; (e) H₂, Pd/C, CH₃OH, r.t.; (f) CrO₃, AcOH, r.t.; (g) Ac₂O, Et₃N, DMAP, DCM, r.t.

also rapidly prepared in 71% total yield through a dihydroxylation of compound **2t**. These synthetic applications well exhibit the utility of our newly developed polyene cyclization mode, in particular the usefulness of the retained C2–C3 double bond for further functionalization.

Conclusions

In conclusion, a new mode of polyene cyclization initiated by the allene moiety has been successfully realized under the catalysis of InI₃, and the retained C2–C3 double bond provides the very crucial reaction site for further transformations, in particular, towards the synthesis of corresponding abietane diterpenes, such as (±)-2,3-dihydroxyferruginol, (±)-shonanol and (±)-2,3-dihydroxy-15,16-dinor-*ent*-pimar-8,11,13-triene. In addition, other diterpenes like (±)-ferruginol, (±)-sugiol methyl ether, (±)-sugiol, and (±)-acetylferruginol have also been collectively synthesized after simple operations. Currently, biological activity tests of these abietane diterpenes and their analogues along with the synthesis of other bioactive polycyclic



terpenes using the same strategy are ongoing in the same laboratory.

Data availability

Experimental data has been uploaded as part of the ESI.†

Author contributions

SHW and DYZ directed this project. CYH, TLZ, WHD, ZHZ and JDW performed the experiments. XMZ, XTX, DYZ and SHW prepared the draft and SHW revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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