Collective synthesis of highly oxygenated (furano)germacranolides from *Elephantopus mollis* and *Elephantopus tomentosus*

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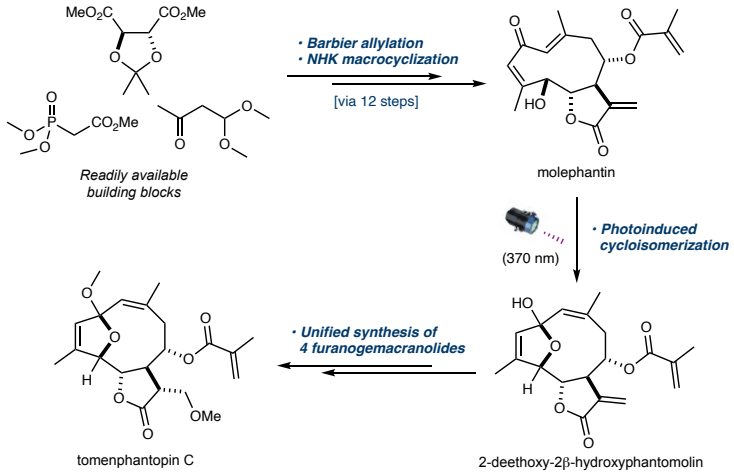
Abstract: Germacranolides, secondary metabolites produced by plants, have garnered academic and industrial interest due to their diverse and complex topology as well as a wide array of pharmacological activities. Molephantin, a highly oxygenated germacranolide isolated from medicinal plants, *Elephantopus mollis* and *Elephantopus tomentosus*, has exhibited *anti*-tumor, inflammatory, and leishmanicidal activities. Its chemical structure is based on a highly strained ten-membered macrocyclic backbone with an (*E*,*Z*)-dienone moiety, which is fused with an α-methylene-γ-butyrolactone and adorned with four successive stereogenic centers. Herein, we report the first synthesis of molephantin via 12 steps starting from readily available building blocks. The synthesis is featured by the highly diastereoselective intermolecular Barbier allylation of the β,γ-unsaturated aldehyde with optically active 3-bromomethyl-5*H*-furan-2-one intermediate and ensuing intramolecular Nozaki-Hiyama-Kishi (NHK) macrocyclization for the construction of the highly oxygenated ten-membered macrocyclic framework. This synthetic route enabled to craft another germacranolide congener, tomenphantopin F. Furthermore, cycloisomerization of molephantin into 2-deethoxy-2β-hydroxyphantomolin could be facilitated by irradiation with ultraviolet A light (λ_{max} = 370 nm), which opened a versatile and concise access to the related furanogermacranolides such as EM-2, phantomolin, 2-*O*-demethyltomephantopin C, and tomenphantopin C.

TOC graphics



Introduction

The diverse family of sesquiterpene lactones (germacranolides), which are plant secondary metabolites, has captured considerable attention from the natural product chemistry, medicinal chemistry, and synthetic chemistry communities over the years.[1-3] Molephantin (**1**), a highly oxygenated germacranolide, was first isolated in 1973 from a medicinal herb, *Elephantopus mollis*, by Lee,[4] and then, found in 2012 from *Elephantopus tomentosus* by Liu and Dai[5] (**Figure 1A**). Molephantin (**1**) is known to exhibit strong *in vivo anti*-tumor activity in Ehrlich and Walker 256 carcinosarcoma tumors[6] as well as *anti*-inflammatory and leishmanicidal activities.[7,8] The molecular structure of molephantin (**1**) consists of a 10-membered macrocyclic core with an (*E*,*Z*)-dienone moiety (C10-1-4), which is fused with an α-methylene-γ-butyrolactone and adorned with four successive stereogenic centers (C5-8). Tomenphantopin F (**2**), isolated in 2012 from *Elephantopus tomentosus* by Liu and Dai, is structurally analogous to molephantin (**1**).[9] Its structure is based on the same 10-membered macrocyclic core with an α-(*S*)-methyl-γ-butyrolactone moiety and a free hydroxyl group at C8. Other topologically relevant constituents found in *Elephantopus mollis* and *Elephantopus tomentosus* include furanogermacranolides such as EM-2 (2-deethoxy-2β-methoxyphantomolin) (**3**),[10] phantomolin (**4**),[11] 2-*O*-demethyltomenphantopin C (**5**),[7] and tomenphantopin C (**6**).[5,12] Notably, EM-2 (**3**) has been observed to render breast cancer cells more susceptible to epirubicin when both are co-administered, primarily by inhibiting the cells' protective autophagy pathway.[13] Their 10-membered macrocyclic core contains a (*Z*,*Z*)-skipped diene centered on a C2 (hemi)ketal carbon. While the biosynthetic routes of these highly oxygenated (furano)germacranolides remain unclear,[14] we posited that molephantin (**1**) could be a biosynthetic precursor of EM-2 (**3**) and other furanogermacranolides. This hypothesis is based on their intriguing topological similarity, suggesting a potential synthetic route involving *E*/*Z*-isomerization of the C1-C10 double bond of molephantin (**1**) to the (*Z*,*Z*)-dienone congener **A** and its successive (hemi)ketalization with the C5-hydroxyl group.

Despite the landmark studies in the synthesis of highly oxygenated germacranolides isolated from different plant species such as eremantholide,[15-17] diversifolin,[18,19] and goyazensolide,[20] to the best of our knowledge, total synthesis of (furano)germacranolides derived from *Elephantopus* species has not been reported (**Figure 1B**). The exception to this gap is the synthesis of nordeoxyelephantopin, an unnatural analogue of deoxyelephantopin derived from *Elephantopus scaber*.[21,22] Motivated by the unique topological complexity and therapeutic potential of the *Elephantopus*-derived (furano)germacranolides, we embarked on the development of a collective synthetic strategy that enables divergent preparation of these congeners.[23] The details of our synthetic studies are reported herein.

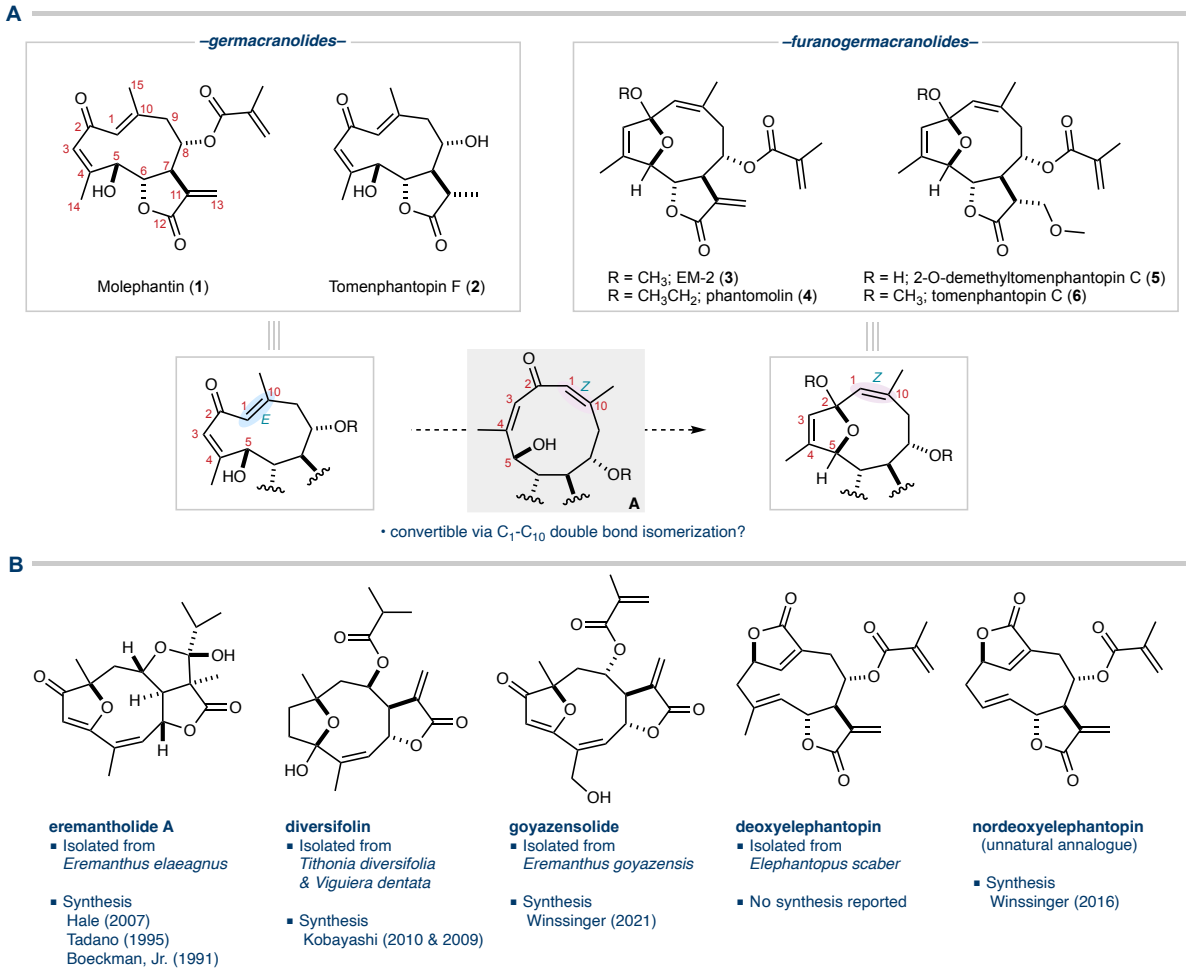


Figure 1. A. Germacranolides and furanogermacranolides isolated from *Elephantopus mollis and tomentosus*. **B.** Highly oxygenated germacranolides derived from different plants.

Result and discussion

Our retrosynthetic approach toward molephantin (**1**) began with the construction of the highly strained C(sp^2)-rich ten-membered ring framework. This involves the construction of the C2-C3 bond through the intramolecular Nozaki-Hiyama-Kishi (NHK)[24] macrocyclization of *E*-enal **I** tethered with a *Z*-iodoalkene, followed by oxidation of the resulting secondary alcohol (**Figure 2**).[25] The stereoselective construction of the α-methylene-γ-butyrolactone moiety of **I** would be achieved by forging the C7-C8 bond through the Barbier allylation of β,γ-unsaturated aldehyde **II** with optically active 3-bromomethyl-5*H*-furan-2-one **III**.[26-28] We envisioned that the preparation of aldehyde **II** could be started from commercially available trimethylphosphonoacetate (**7**) and 4,4-dimethoxy-2-butanone (**8**), whereas 3-bromomethyl-5*H*-furan-2-one **III** was anticipated to be synthesized from dimethyl 2,3-*O*-isopropylidene-L-tartrate (**9**) derived from L-tartaric acid as a cheap chiral source of C5 and C6, ensuring the potential scalability of the developed synthetic route.

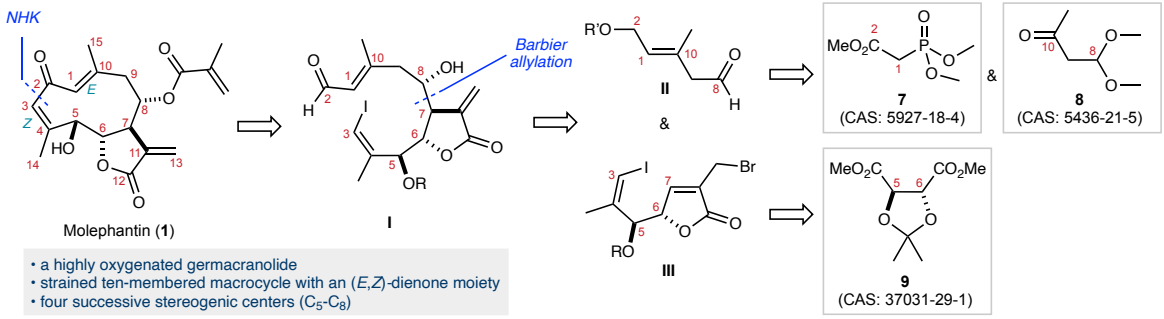


Figure 2. Retrosynthetic analysis of molephantin (1)

We embarked on our studies with the synthesis of aldehyde **II**, containing the C8-10-1-2 fragment, that could be achieved via the following three steps (**Figure 3A**): (i) the Horner-Wadworth-Emmons reaction of ketone **8** with phosphonoacetate **7**, providing the trisubstituted alkene **10** as an *E*/*Z*-mixture (71:29); (ii) DIBAL reduction of the ester moiety of **10** to give allylic alcohol **11**, where the desired *E*-**11** could be separated from *Z*-**11** through the silica gel column chromatography; (iii) treatment of *E*-**11** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of 2,6-lutidine[29] to afford β,γ-unsaturated aldehyde **12** bearing a trimethylsilyl ether moiety. Due to instability of **11**, it was utilized without purification for the next step (**Figure 4A**).

In parallel, optically active 3-bromomethyl-5*H*-furan-2-one **III** was synthesized in five steps from dimethyl 2,3-*O*-isopropylidene-L-tartrate (**9**) (**Figure 3B**). Nucleophilic acyl substitution at one of the methoxy carbonyl groups of **9** with MeLi allowed for the construction of methyl ketone **13** and subsequent Wittig iodoalkenylation proceeded stereoselectively to afford the desired (*Z*)-iodoalkene **14** (>98% purity).[30] This two-step sequence was scalable to a multi decagram scale. Upon mono-hydride reduction of the ester moiety of **14** with diisobutylaluminum hydride (DIBAL), the resulting crude aldehyde was treated with methyl acrylate in the presence of 1,4-diazabicylo[2,2,2]octane (DABCO), yielding α-methylene-β-hydroxyester **15** as an inconsequential mixture of diastereoisomers.[31] Following the protocol developed by Winssinger,[32] treatment of **15** with aqueous HBr enabled the construction of optically active 3-bromomethyl-5*H*-furan-2-one **16** as the major product, along with 3-bromomethyl-5,6-dihydro-2*H*-pyran-2-one **16'** as the minor component. After the isolation of pure **16** through reprecipitation from diisopropylether, its free hydroxy group was protected as a methoxymethyl (MOM) ether, resulting in **17**.

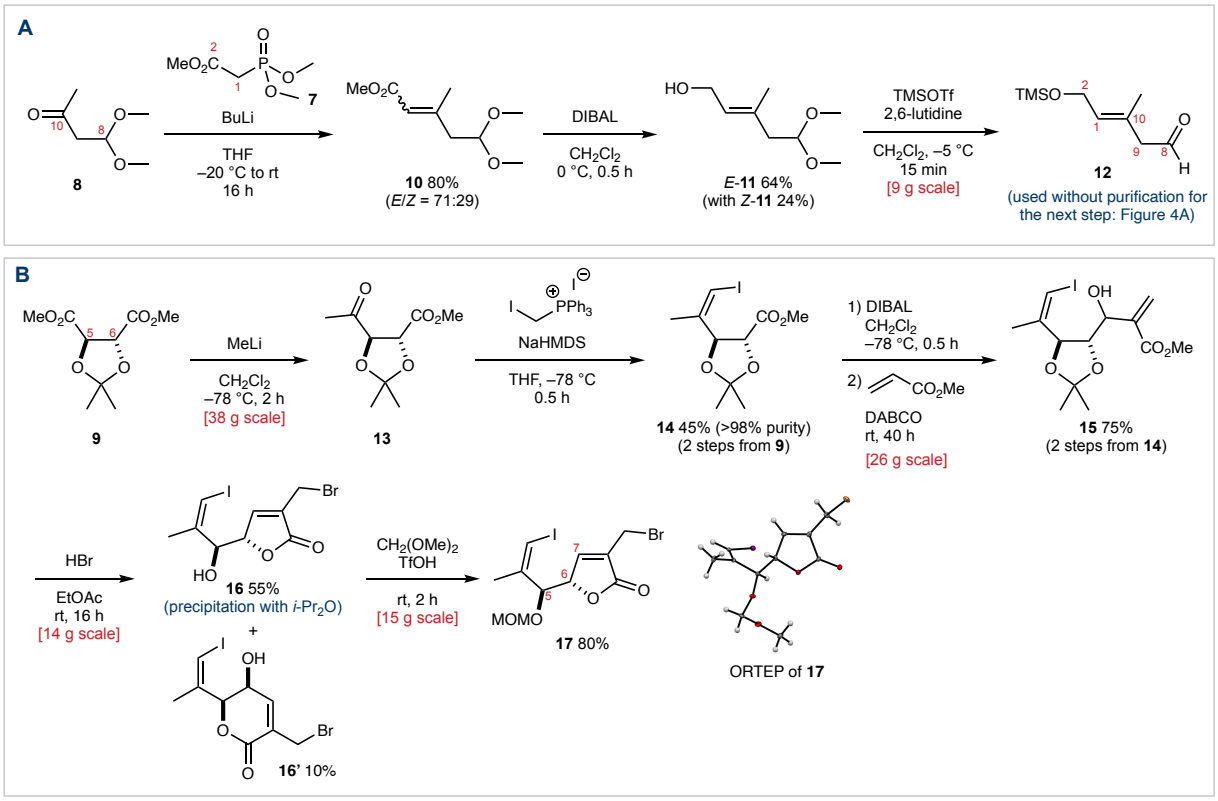


Figure 3. Preparation of the two key intermediates. A. Synthetic route of the aldehyde fragment **12**. **B.** Synthetic route of the key 3-bromomethyl-5*H*-furan-2-one **17**.

With the two key fragment parts, β,γ-unsaturated aldehyde **12** and 3-bromomethyl-5*H*-furan-2-one **17** in hand, their coupling via the intermolecular Barbier allylation was performed by treating a mixture of **12** (ca. 2 equiv) and **17** with chromium(II) chloride ($CrCl_2$) in dimethylformamide (DMF), affording α-methylene-γ-butyrolactone **18** having the desired stereochemistry at C7 and C8 with an excellent selectivity (no other diastereomers detected in 400 MHz ^{1}H NMR spectroscopy scale). The workup with aqueous acid resulted in concomitant deprotection of the trimethylsilyl ether at the C2 position (**Figure 4A**). This stereocontrol could be rationalized by the Zimmerman-Traxler pseudo-chair transition state **B** between aldehyde **11** and allylchromium species derived from **17**, in which aldehyde **11** predominantly approached from the top face of the sp^2-hybridized C7, opposite to the C5-C6 bond.[33] The C2-allylic alcohol moiety of **18** was then chemoselectively oxidized by manganese dioxide (MnO_2), resulting in α,β-unsaturated aldehyde **19**. Extensive screening of the reaction conditions for the NHK macrocyclization of **19** (see the Supporting Information) revealed that treatment of **19** with $CrCl_2$ (4 equiv) and $Ni(acac)_2$ (2 mol%) in DMSO (5 mM) at 25 °C afforded the desired 10-membered macrocycle **20** in 51% yield as a single diastereomer. The structure of **20** could unambiguously be confirmed by the single X-ray crystallographic analysis. MnO_2 oxidation of the bis-allylic alcohol moiety of **20** furnished dienone **21** and subsequent acylation of the remaining C8 hydroxyl group with methacrylic

anhydride gave **22**. Finally, the MOM ether at C5 was deprotected using trifluoroacetic acid (TFA) to give molephantin (**1**), with its spectral data matching the reported values.[9] Furthermore, we took advantage of 10-membered macrocyclic intermediate **20** for the synthesis of tomenphantopin F (**2**) (**Figure 4B**). Treatment of **20** with sodium borohydride ($NaBH_4$) in MeOH enabled diastereoselective reduction of the *exo*-methylene moiety, providing α-(*S*)-methyl-γ-butyrolactone **23** as a single stereoisomer. The stereochemistry of **23** was verified by the X-ray diffraction analysis. Subsequent MnO_2 oxidation of **23** facilitated the construction of dienone **24**, and the ensuing MOM deprotection with TFA delivered tomenphantopin F (**2**).

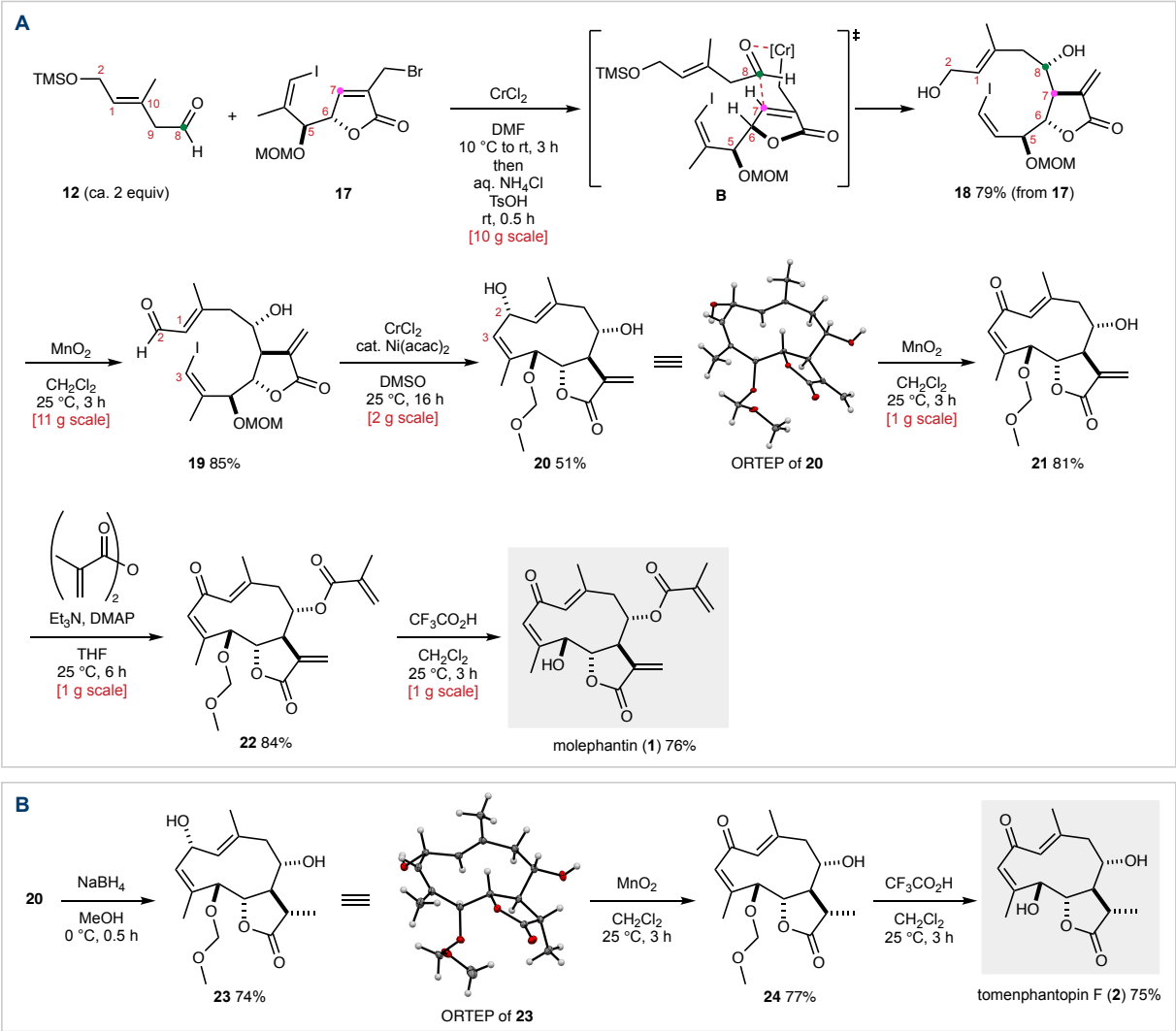


Figure 4. A. Synthesis of molephantin (**1**). **B.** Synthesis of tomenphantopin F (**2**).

Our next objective was to explore a method to convert molephantin (**1**) into the furanogermacranolides. The hypothetical skeletal transformation via isomerization of the (*E*,*Z*)-dienone moiety of **1** to the (*Z*,*Z*)-dienone [(*Z*,*Z*)-**1**] and its subsequent hemiketalization with the C5-hydroxyl group could afford 2-deethoxy-2β-hydroxyphantomolin (**25**), which was also isolated from *Elephantopus mollis* (**Figure 5A**).[34] Inspired by the previous studies on photochemical isomerization of dienone-based sesquiterpene natural products such as tagitinin C,[35] asteriscunolide D[36] and zerumbone[37,38] under irradiation with UV light, we investigated the analogous photochemical dienone-isomerization of molephantin (**1**). Indeed, we observed a weak absorption band at λ_{max} = 348 nm in the ultraviolet-visible (UV-vis) spectrum of molephantin (**1**) in CH_2Cl_2 (0.5 mM), which was characterized as the n-π* transition of the carbonyl group of the dienone moiety (see the Supporting Information).[39] We found that irradiation of a solution of **1** in degassed CH_2Cl_2 with ultraviolet A light (λ_{max} = 370 nm) could generate multiple alkene isomers within a few minutes, as confirmed by the ^{1}H NMR analyses, suggesting that the dienone isomers (*E*,*E*)-**1**, (*Z*,*E*)-**1** and (*Z*,*Z*)-**1** could be formed under photoequilibrium. We observed that these dienone congeners could eventually converge to **25** in a quantitative yield via hemiketalization of (*Z*,*Z*)-**1**.

Hemiketal **25** served as a primary scaffold to synthesize a set of other furanogermacranolides such as EM-2 (**3**) and phantomolin (**4**), through ketalization by the simple treatment of **25** with the corresponding alcohol in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH) (**Figure 5B**). On the other hand, the treatment of **25** with sodium methoxide (NaOMe) in methanol enabled the chemo- and diastereoselective addition of methanol to the *exo*-methylene-γ-butyrolactone moiety, yielding 2-*O*-demethyltomenphantopin C (**5**). In turn, after the addition of methanol to **25** under basic reaction conditions, acidification of the solution induced successive C2 ketalization to afford tomenphantopin C (**6**).

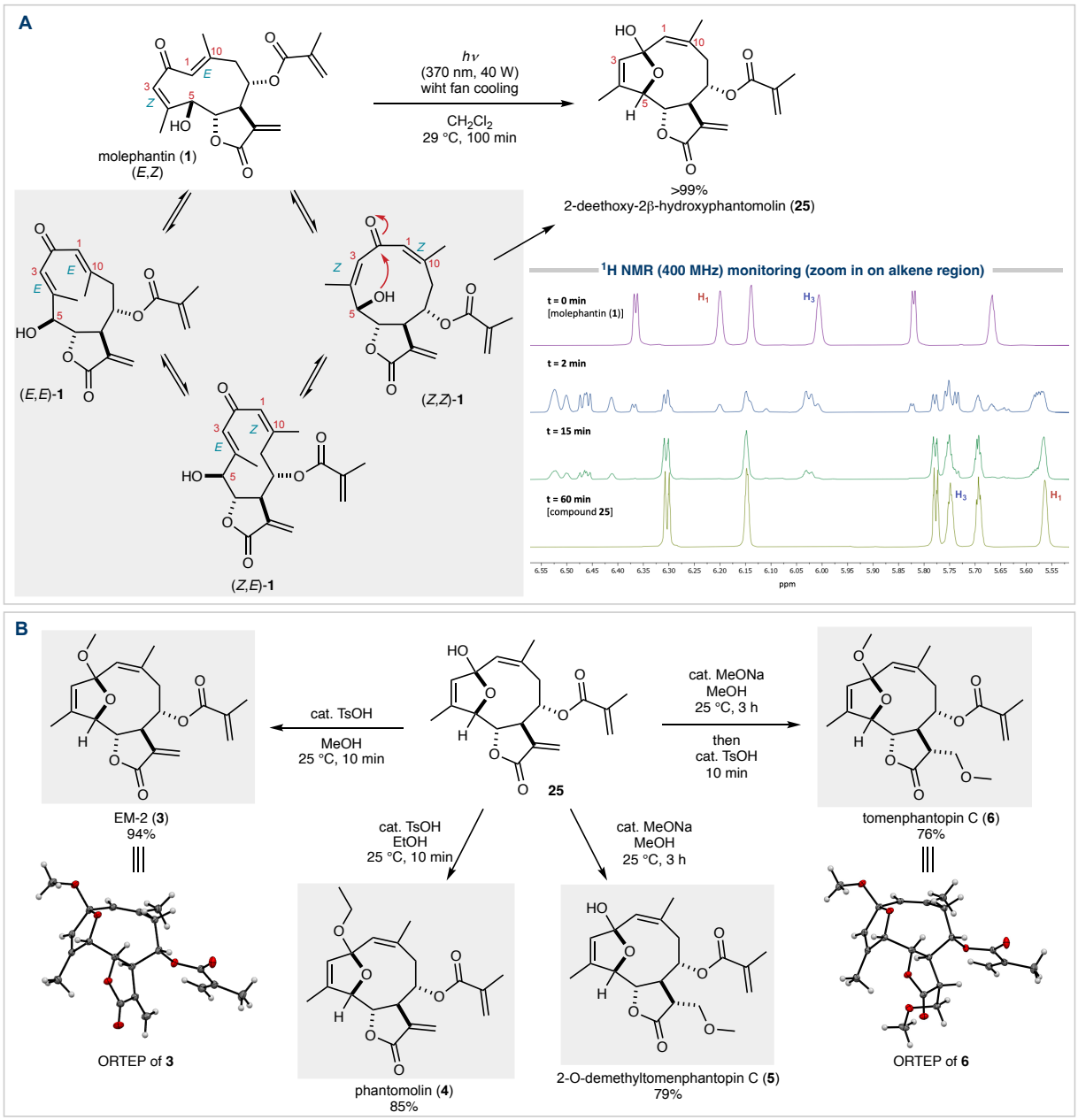


Figure 5. A. Photoinduced cycloisomerization of molephantin (**1**) to 2-deethoxy-2β-hydroxyphantomolin (**25**). **B.** Collective synthesis of furanogermacranolides**.**

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Conclusions

In this work, we have accomplished the first syntheses of (furano)germacranolides isolated from *Elephantopus mollis* and *Elephantopus tomentosus*. The key to the stereoselective assembly of highly oxygenated and strained ten-membered macrocyclic core of molephantin (**1**) and tomenphantopin F (**2**) was the employment of the highly diastereoselective intermolecular Barbier allylation, coupled with the intramolecular Nozaki-Hiyama-Kishi (NHK) macrocyclization. In addition, the photoinduced isomerization of the (*E*,*Z*)-dienone moiety of molephantin (**1**) to (*Z*,*Z*)-dienone followed by hemiketalization enabled the collective access to four furanogermacranolides, EM-2 (**3**), phantomolin (**4**), 2-*O*-demethyltomephantopin C (**5**), and tomenphantopin C (**6**). Our future research endeavors will focus on taking advantage of the developed synthetic strategies to craft other highly oxygenated (furano)germacranolides as well as various unnatural congeners of molephantin (**1**) for the structure-activity relationship studies.

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Author contributions

Conceptualization and Methodology, P.R. and S.C.; Investigation, P.R., N.C. and S.C.; Writing – Original Draft, P.R. and S.C.; Writing – Review & Editing, P.R., N.C. and S.C.; Funding Acquisition, Resources and Supervision, S.C.

Competing interests

The authors declare no competing interest.

Additional information

All data are available in the supplementary information.