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Computation assisted chemical study of photo-induced late-stage skeleton transformation of marine natural products towards new scaffolds with biological functions

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ABSTRACT

A computer-assisted chemical investigation of an intriguing photoreaction of norditerpenoids (**3**–**7**) has been first reported, leading to not only their biomimetic conversion, but also the generation of several new products with uncommon 4,14-dioxabicyclo[10.2.1]pentadecane scaffold (**8**, **9**, **12**–**14**). In bioassay, compounds **10** and **15** exhibited significant stimulation of GLP-1 secretion. This study has given an insight for the application of computational methods on the late-stage skeleton transformation of complex natural products towards new bioactive compounds.

Late-stage skeleton transformation (LSST) of natural products, especially those with biological activities, is an effective strategy for constructing valuable derivatives compared to stepwise synthetic approaches. In recent years, selective C-H activation and biocatalysis strategies have developed rapidly, enabling efficient late-stage editing of natural products [1-7]. Such skeleton transformation often undergoes the breaking and reorganization of bonds, sometimes involving complex cascade reactions [8]. It is worth mentioning that although the LSST strategies for natural products are fascinating organic transformation process, the relevant strategies are limited [9].

Photochemical reaction can offer unique opportunities to achieve fast and efficient skeleton transformation of natural products by unlocking site-specific reactivities under generally mild reaction conditions [10]. Undoubtedly, the use of photochemical reaction is a powerful strategy that allows the transformation between two highly different natural product skeletons in a single step. To our knowledge, although some meaningful derivatives have been obtained by photochemical reaction of natural products in recent years [9,11-12], there are still some issues need to be addressed on the photochemical study of natural products. This is mainly due to the complex structure of natural products, which leads to the multiple possible photoreaction sites [9,13-15]. Therefore, it is important to understand the reaction mechanism for further prediction of possible products.

Polycyclic furanobutenolide-derived norcembrane diterpenoids are a small class of marine natural products with multiple remoted stereogenic centers in their macrocyclic ring and a wide range of biological activities, mainly isolated from soft corals of the genus *Sinularia* [16-19]. These bioactive metabolites have attracted extensive interests for total syntheses in recent years [20-22]. In our previous investigation of the chemical composition of Hainan soft coral *Sinularia* sp., norcembrane diterpenoid yonarolide

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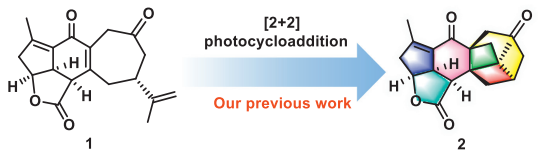


Fig. 1. Our previous work on [2+2] photoreaction from **1** to **2**.

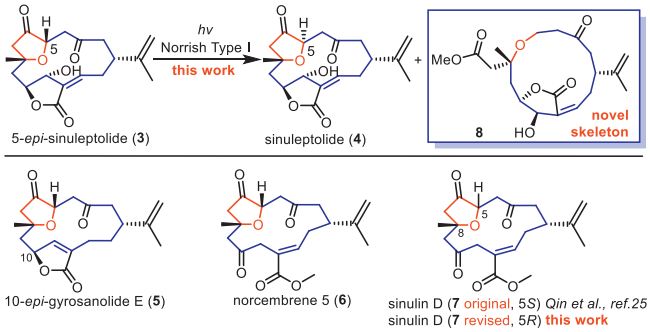


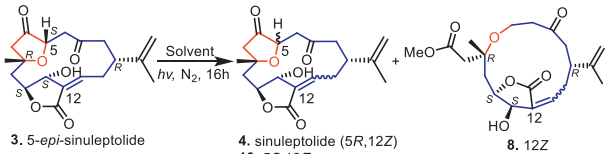
Fig. 2. Late-stage skeleton transformation of compound **3** and the structures of compounds **3**–**8** in this study.

(**1**) was found to be easily converted into yonarolide A (**2**), featuring an unprecedented 5/6/4/4/7 pentacyclic ring skeleton, through a [2+2] photocycloaddition reaction under sunlight (Fig. 1) [23]. As a continuation of our previous work, we further investigated the chemical composition of Hainan soft coral *Sinularia* sp., and five polycyclic furanobutenolide-derived norditerpenoids were obtained, including 5-*epi*-sinuleptolide (**3**) [24], sinuleptolide (**4**) [24], 10-*epi*-gyrosanolide E (**5**) [23], norcembrene 5 (**6**) [23], and sinulin D (**7**) (Fig. 2) [23,25].

Herein, inspired by our previous study of the photoreaction of **1** *via* a [2+2] photocycloaddition towards **2** (Fig. 1), we report the LSST of **3** to **4** by a Norrish type I reaction, along with the acquisition of a novel product **8** with new 4,14-dioxabicyclo[10.2.1]pentadecane scaffold (Fig. 2), the reaction mechanism study by deuterium experiment and detailed density functional theory (DFT) calculation, as well as the substrate scope examination leading to the late-stage modification of these intriguing natural products and the configuration revision of sinulin D (**7**).

To explore potantial new photo-products of polycyclic furanobutenolide-containing norditerpenoids, we first irradiated **3** in MeOH under 250 W long arc mercury lamp for 16 h, and a total of five products were obtained, with the yields shown in Table 1. Their structures were determined by 1D and 2D nuclear magnetic resonance (NMR) (the structure of **9** was determined by comparing ^{1}H NMR with **8** and the structure of **11** was determined by comparing ^{1}H NMR with **10**). It is worth mentioning that **8** and **9** featuring a new 4,14-dioxabicyclo[10.2.1] pentadecane scaffold, which is a nice example of using the LSST strategy to obtain new natural products derivatives. In addition, we consider that in all photo-products, the Δ^{12} *E*/*Z* isomerization is due to the photoexcitation of Δ^{12}, on the other hand, the photoexcitation of the C-6 carbonyl group lead to the C-5 chiral epimerization (products **4** and **11**) and tetrahydrofuran ring opening (products **8** and **9** in methanol), which was consistent with the Norrish type I reaction. In fact, Norish type I cleavage occurs at the α-position of the excited carbonyl group, which generates acyl and alkyl radicals, followed by a series of reactions [26,27]. We next performed trapping experiment with 2,2,6,6-tetramethylpiperidinooxy (TEMPO) (Table S2 in Supporting information) and confirmed that our reaction involves radical intermediates, which is consistent with the feature of the Norrish type I reaction. Subsequently we investigated the effect of solvent on the reaction, dichloromethane

Table 1
The effects of solvent system on the reaction.[a]



Entry	Solvent	Yields (%)					
		3[c]	**4**	**10**	**11**[d]	**8**	**9**[d]
1	MeOH	7	7	27	10[b]	20	9[b]
2	MeCN	37	30	10	6[b]	0	0
3	DCM	41	13	27	Trace	0	0

[a] All reactions were carried out under N_2 protection with a 250 W long arc mercury lamp for 16 h in room temperature, except that different solvents were used.
[b] Yields were calculated by ^{1}H NMR spectrum.
[c] Recovered **3** at the end of the reaction.
[d] Isolated as a mixture, the structure was determined by comparing ^{1}H NMR spectrum.

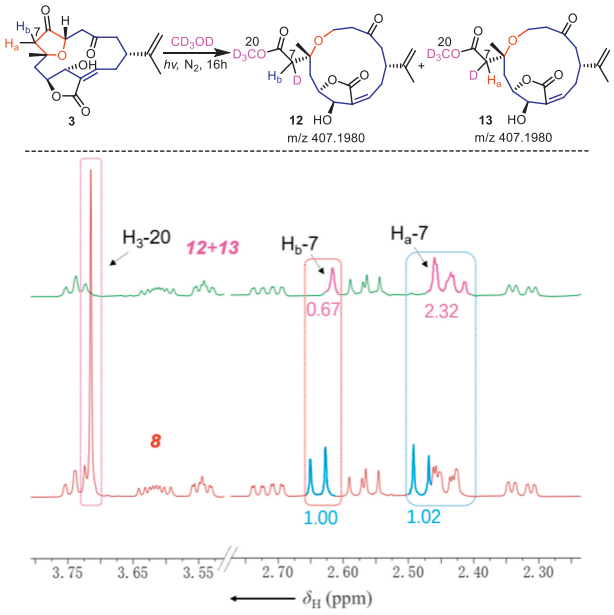


Fig. 3. Deuterium experiment of Norrish type I reaction. The reaction was carried out under N_2 protection with a 250 W long arc mercury lamp for 16 h in room temperature, methanol-d_4 was used as solvent. **8** refers to purified compound **8**.

(DCM) was shown to be more likely than MeCN to generate the Δ^{12} *E*/*Z* isomerization product **10**, which was further confirmed by examining the product when the reaction underwent for 2 h (Fig. S1 in Supporting information). We also periodically monitored the ^{1}H NMR spectra of the reaction when methanol and acetonitrile was used as the solvent (Figs. S2 and S3 in Supporting information). The gradual appearance process of each product within 16 h was visualized.

To further investigate the generation mechanism of **8**, we performed a deuterium experiment, and obtained a mixture of the deuterated products **12** and **13**. By comparing the ^{1}H NMR spetra of **12** and **13** with **8** (Fig. 3), the disappearance of H_3–20 at 3.71 ppm (the chemical shift of H_3–20 in **8**) in ^{1}H NMR confirmed that the methoxy group (CH_3–20) in **8** was derived from the solvent methanol. In addition, the integral ratio of the H_2–7 (chemical shift H_a-7: 2.46 ppm and H_b-7: 2.62 ppm) decreased from the original 2 to 1, which confirmed that the proton of methanol was transferred to one of the H_2–7. Meanwhile, the integral ratio of H_b-

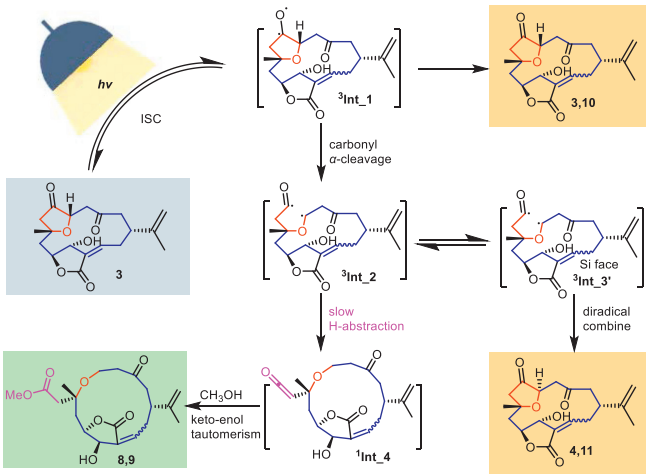
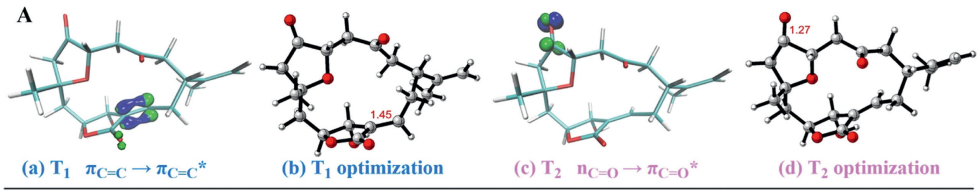


Fig. 4. Proposed isomerization process of **3** under irradiation.

7 and H_a-7 is 0.67 to 0.32 (2.32 includes the other two hydrogens), which means that the ratio of **12** to **13** is approximately 2 to 1. Furthermore, the 4 mass units more of **12** and **13** (407.1980 $[M+Na]^+$) than that of **8** (381.1908 $[M+H]^+$) in high resolution electrospray ionization mass spectroscopy (HR-ESI-MS) spectra confirmed that the H_3–20 and H-7_a (or H-7_b) were involved in the conversion process. Therefore, we confirmed the formation of product **8** through a ketene intermediate [28].

Based on the aforementioned experimental result, the isomerization process of **3** under irradiation was proposed (Fig. 4). In detail, the C-6 carbonyl group of **3** was excited under irradiation, and intersystem crossing (ISC) from $^1n-\pi^*$ to $^3n-\pi^*$, followed by conformational relaxation to the stable excited state **^{3}Int_1**. Then **^{3}Int_1** underwent α-cleavage to form acyl radicals and alkyl radicals by Norrish type I reaction to obtain diradical intermediate **^{3}Int_2**, with a Δ^{12} *E*/*Z* isomerization under irradiation at the same time. Subsequently, **^{3}Int_1** could spontaneously release energy to form **3** and **10**. **^{3}Int_2** could undergo C-C rotation to become **^{3}Int_3′** easily, then **^{3}Int_3′** could be transformed into **4** and **11** through a diradical combination. Furthermore, diradical **^{3}Int_2** underwent an internal hydrogen transfer to produce a ketene intermediate **^{1}Int_4**. **^{1}Int_4** is with high reactivity, which could easily undergo an addition reaction with methanol, and then, the addition product of enol type would undergo keto-enol tautomerization to yield more stable esters **8** and **9**.

To gain mechanistic insights into LSST of natural product **3**, DFT and time-dependent DFT (TD-DFT) calculations were performed (Fig. 5) [29]. The TD-DFT calculations performed by using different functionals (M06–2X, B3LYP and CAM-B3LYP), and the excitation types of $\mathbf{S_1}$, $\mathbf{T_1}$ and $\mathbf{T_2}$ were by analyzed electron-hole analysis (Fig. 5A and Fig. S11 in Supporting information) [30-32]. The



Method	S_1 excitation energy (eV)	*f*	T_1 excitation energy (eV)	T_1 characteristic	T_2 excitation energy (eV)	T_2 characteristic
M06-2X	4.086	0.0005	3.688	$n_{C=O} \rightarrow \pi_{C=O}^*$	3.771	$\pi_{C=C} \rightarrow \pi_{C=C}^*$
B3LYP	4.216	0.0014	3.425	$\pi_{C=C} \rightarrow \pi_{C=C}^*$	3.716	$n_{C=O} \rightarrow \pi_{C=O}^*$
CAM-B3LYP	4.348	0.0005	3.340	$\pi_{C=C} \rightarrow \pi_{C=C}^*$	3.805	$n_{C=O} \rightarrow \pi_{C=O}^*$

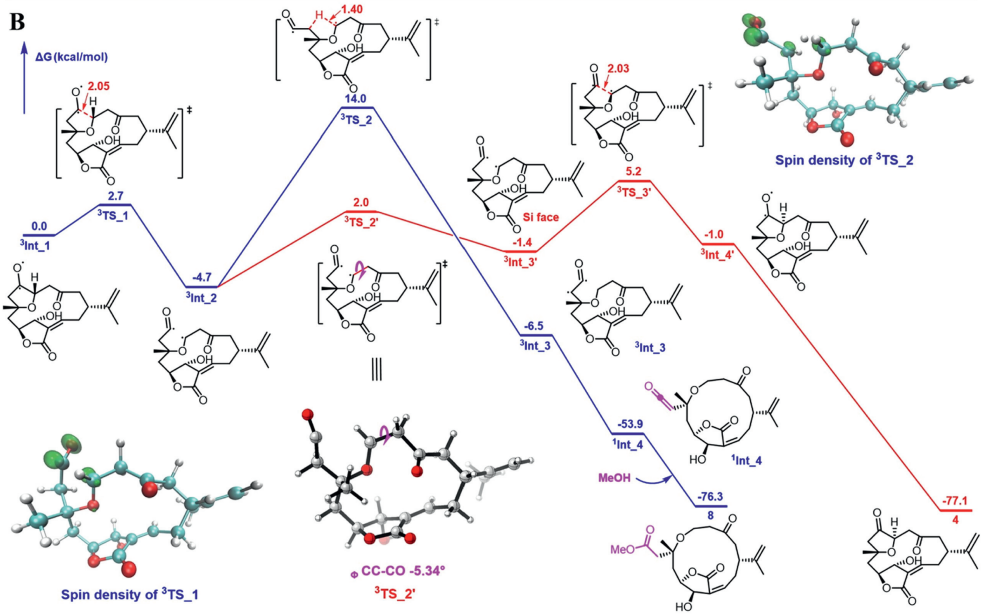


Fig. 5. (A) TD-DFT calculation the photoreactive site of compound **3** at the 6–311+G(d,p)/PCM(MeOH) level. (a) Excitation type of $\mathbf{T_1}$, (b) optimized $\mathbf{T_1}$, (c) excitation type of $\mathbf{T_2}$ and (d) optimized $\mathbf{T_2}$. (B) DFT calculated free energy surface for the C-5 chiral epimerization and H-abstraction process of **3** (at the (U)ωB97X-D/def2-TZVPP/PCM(MeOH)//(U)M06–2X/6–31G(d)/PCM(MeOH) level of theory).

results showed that Δ^{12} and C-6 carbonyl group can be easily excited, which means that they are the first or second triplet excited states, more likely to be obtained from $\mathbf{S_1}$ by ISC [33,34]. We consider that the excitation of Δ^{12} is responsible for the isomerization of the Δ^{12} of the photo-products, *e.g.*, **9**, **10** and **11**, and we further investigated the condition after the C-6 carbonyl group excitation (Fig. 5B). The carbonyl group of ^{3}**Int_1** underwent α-cleavage to give ^{3}**Int_2**, this process is controlled by transition structure ^{3}**TS_1** with free energy 2.7 kcal/mol above ^{3}**Int_1**, in the transition state ^{3}**TS_1**, the spin density was majorly shared by C5, C6, and O21. ^{3}**Int_3′** and ^{3}**Int_2** can be converted quickly by ^{3}**TS_2′**, with activation barrier 6.7 kcal/mol. The radical of ^{3}**Int_3′** attacks from the Si face to give ^{3}**Int_4′**. When the two electrons in ^{3}**Int_4′** spin in reverse to form open-shell singlet specie, the two radicals could directly combine and form **4**. For the formation of product **8**, the α hydrogen of the acyl radical in ^{3}**Int_2** was captured by the alkyl radical to form ^{3}**Int_3**, the transition state ^{3}**TS_2** of this process is with a free energy of 18.7 kcal/mol higher than ^{3}**Int_2**. In the transition state ^{3}**TS_2**, the spin density was majorly shared by C5, C6, C7 and O21. Then, the formation of the ketene intermediate ^{1}**Int_4** was accomplished by the release of energy in ^{3}**Int_3**. Finally, with the aid of methanol, ^{1}**Int_4** could be transformed into the thermodynamic product **8**.

In addition, we noted that the Δ^{12} excitation of compound **3** may also generate [2+2] photo-products similar to compound **2**, for which we also calculated the [2+2] photoreaction of compound **1** to **2** as well as compound **3** (Figs. S5–S9 in Supporting information). The results showed that for compound **1** to form **2**, the energy barrier is only 11.1 kcal/mol. However, for compound **3** to form [2+2] photo-product, the only feasible way need to overcome a high energy barrier of 23.5 kcal/mol (see Fig. S9 for detail). On the other hand, the calculations also showed that for compound **3**, the formation of [2+2] photo-product has a higher energy barrier compared to the Norrish type I products.

With the clear mechanism of the reaction in hand, we expected to increase the chemical diversity of photochemical products **8** and **9**, which are rare macrocyclic ethers. Therefore, the other four natural norditerpenoids **4**, **5**, **6**, and **7** were employed in an attempt to explore the universality of this reaction (Fig. 6A). Compounds **4**–**6** yield the photochemical ethers **8**, **14** and **15**. The structures of **8**, **14** and **15** were elucidated by 2D NMR spectroscopic data analysis. However, instead of the expected **16**, **7** produced **15**, whose structure was determined by X-ray diffraction analysis, indicating that the C-8 configuration of the original structure of **7** should be wrong. The X-ray diffraction analysis confirmed that the C-8 absolute configuration of **15** was *R*, which implied that **6** and **7** should be C-5 epimers. To further verify our hypothesis, quantum NMR calculation of **7** (revised) and **7** (original) was subjected to the GIAO method, at the mPW1PW91/6–31+G(d,p) level, with the PCM model in chloroform (Fig. 6B) [35,36]. The result indicated that the calculated NMR data of (1*R**, 5*R**, 8*R**)-**7** (revised) were consistent with the experimental data, with a correlation coefficient $R^2 = 0.9993$ and DP4+ probability of 100% [37-39]. Therefore, we proposed that the correct absolute configuration of sinulin D (**7**) should be 1*R*, 5*R*, 8*R*.

Glucagon-like peptide 1 (GLP-1) is a peptide hormone produced and secreted by intestinal L-cells, which lowering postprandial blood glucose by binding the GLP-1 receptor to stimulate the insulin secretion from beta cells. It is a currently popular target for the obesity and type diabetes related drug discovery [40-43]. In this study, the stimulation of GLP-1 secretion by the compounds **1**, **2**, **10**, **14**, and **15** at 20 μmol/L was evaluated and compared to that of INT777, a Takeda G-protein-coupled receptor 5 (TGR5, a GPCR receptor) agonist. Among these five compounds **10** and **15** could stimulate GLP-1 secretion significantly with no cell toxicity, and dose-dependently (Fig. 7 and Fig. S13 in Supporting information).

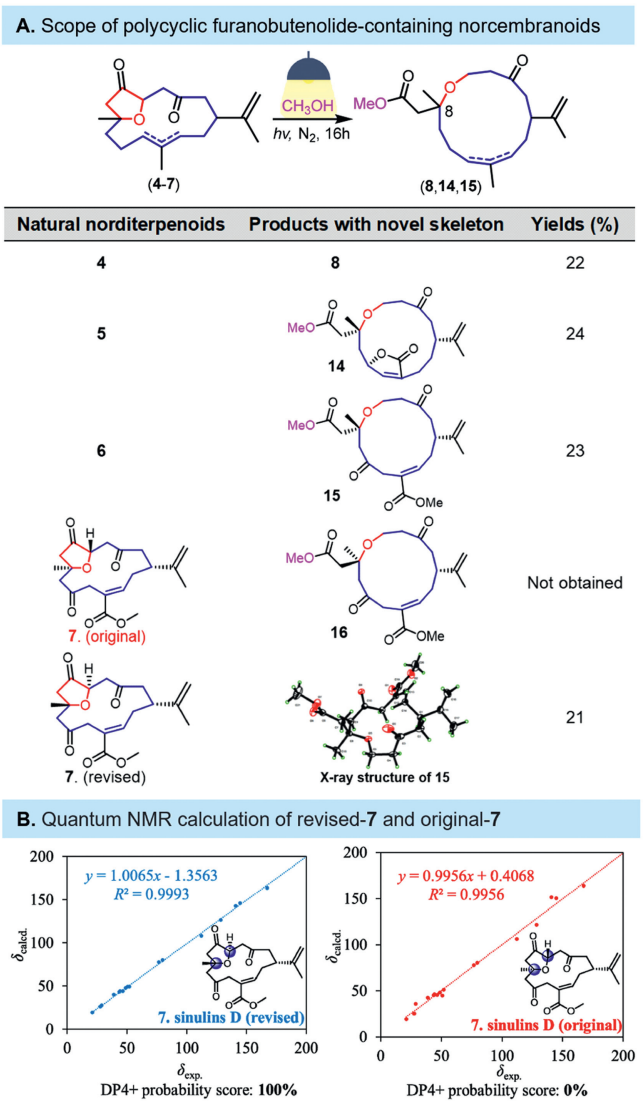


Fig. 6. (A) Scope of polycyclic furanobutenolide-containing norditerpenoids. All reaction details are described in Supporting information 1.3.5. (B) Parameters of the calculated chemical shifts of revised-**7** and original-**7**.

In the mechanism study, compounds **10** and **15** exhibited significant stimulation of GLP-1 secretion by increasing intracellular calcium concentration dependent on the protein kinase A (PKA) pathway (the details bioactivity results are described in Supporting information 1.7.3).

In summary, inspired by our previous study of the photoreaction of **1** *via* a [2+2] photocycloaddition towards **2**, we conducted a photo-induced late-stage skeleton transformation of the co-occurring compound **3** towards compounds **8** and **9** with new 4,14-dioxabicyclo[10.2.1]pentadecane skeleton. The biomimetic conversion of **3** to **4** was achieved meanwhile. A Norrish type I reaction mechanism was proposed based on the deuterium experiments and further confirmed by the DFT calculations. Subsequently, a substrate scope examination produced new skeleton derivatives **14** and **15**, and further confirmed that the correct absolute configuration of **7** is 1*R*, 5*R*, 8*R*. All these findings not only enlarged the chemical space, but also gave us a clue for obtaining more new derivatives of bioactive natural products. Intriguingly, compounds **10** and **15** were found to stimulate the intracellular calcium and promote GLP-1 secretion in the PKA-dependent pathway, which could inspire the discovery of new metabolic disease-related

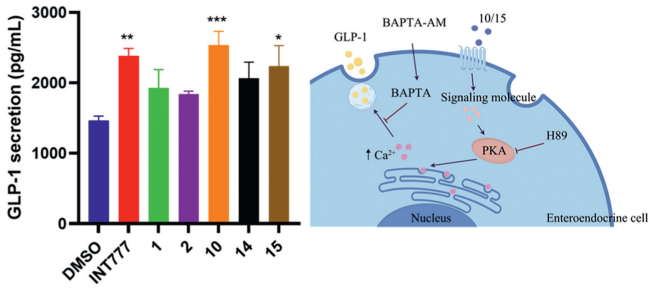


Fig. 7. Effects of compounds **1**, **2**, **10**, **14**, and **15** on GLP-1 secretion in STC-1 cells. Left: effect of **1**, **2**, **10**, **14**, and **15** on GLP-1 secretion at 20 μmol/L STC-1 cells. Right: proposed mechanism for **10** and **15**-stimulated secretion of GLP-1, drawn by Figdraw. The results are presented in the form of mean ± SEM ($n = 3$). The *t*-test was used to analyze the significance. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ *vs*. DMSO group. BAPTA-AM, a membrane permeable Ca^{2+} chelator; H89, a PKA inhibitor.

drug leads from marine sources. The present work forms the first paradigm for efficient construction photo-induced late-stage skeleton transformation strategy of complex natural products through combination of quataum chemistry calculation and experimental validation, which will give a perspective for efficient LSST of interesting natural products towards new bioactive compounds.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Quan Xu: Writing – original draft. **Ye-Qing Du:** Validation, Data curation. **Pan-Pan Chen:** Validation. **Yili Sun:** Validation. **Ze-Nan Yang:** Investigation. **Hui Zhang:** Data curation. **Bencan Tang:** Software. **Hong Wang:** Methodology. **Jia Li:** Funding acquisition. **Yue-Wei Guo:** Funding acquisition. **Xu-Wen Li:** Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110141.

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