

Total Synthesis of Sculponin U through a Photoinduced Radical Cascade Cyclization

Wei Cao, Zhen Wang, Yan Hao, Tianli Wang, Shaomin Fu,* and Bo Liu*

In memory of Professor Wei-Shan Zhou

Abstract: We have accomplished the total synthesis of sculponin U, a polycyclic C-20-oxygenated kaurane diterpenoid featuring a 7,20-lactone-hemiketal bridge, through a radical cascade cyclization triggered by photo-induced electron transfer (PET) of a silyl enolate to form the cyclohexanone-fused bicyclo[3.2.1]octane skeleton. Other key points in our synthetic strategy encompass a Diels–Alder reaction to construct the middle six-membered ring of sculponin U, and an intramolecular radical cyclization induced by iron-catalyzed hydrogen atom transfer to close the western cyclohexane ring. Successful preparation of the enantiopure silyl enolate as the PET precursor enables the asymmetric total synthesis of sculponin U, opening a new avenue for divergent syntheses of structurally related C-20-oxygenated kaurane congeners and pharmaceutical derivatives thereof.

Ent-kaurane-type diterpenoids have been continuously isolated and identified from *Isodon* and other genera since the isolation of *ent*-kaurene (Figure 1), the first family member,^[1] more than sixty years ago. This natural product family encompasses a diverse array of intriguing tetracyclic molecular structures^[2] and exhibits notable antibacterial, antitumor and other bioactivities.^[3] These fascinating motifs and bioactivities have stimulated extensive interest in the synthetic community, fostering a multitude of successful and impressive total syntheses with innovative synthetic strategies.^[4–7] These *ent*-kaurane diterpenoid members can be classified into several subgroups based on their respective structural features, among which the C-20-oxygenated variants represent a substantial group.^[2c] Aiming at the unique structural features of C-20-oxygenated *ent*-kaurane diterpenoids, synthetic chemists have developed distinctive and efficient synthetic routes other than those developed for the classical kaurane diterpenoids,^[7] including the semisyntheses^[7a,c] from polycyclic natural terpenoids^[8] and the total syntheses from commercially available small

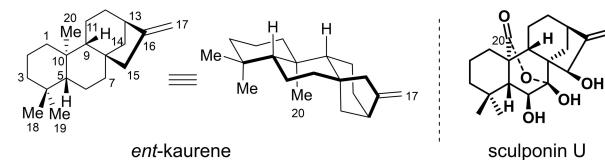
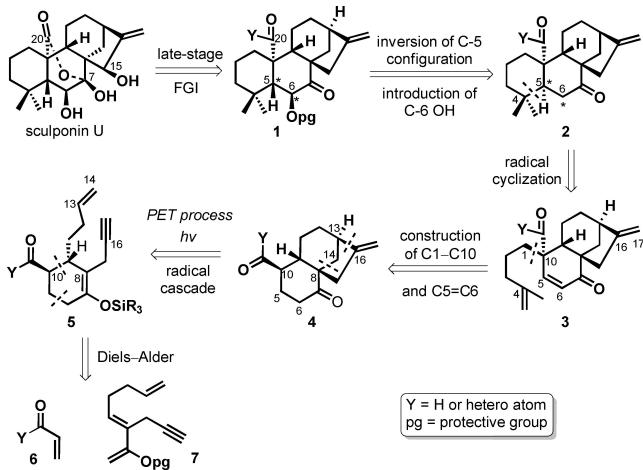


Figure 1. Molecular structures of *ent*-kaurene (1), a classic kaurane diterpenoid, and sculponin U (2), a C-20 oxygenated kaurane diterpenoid.

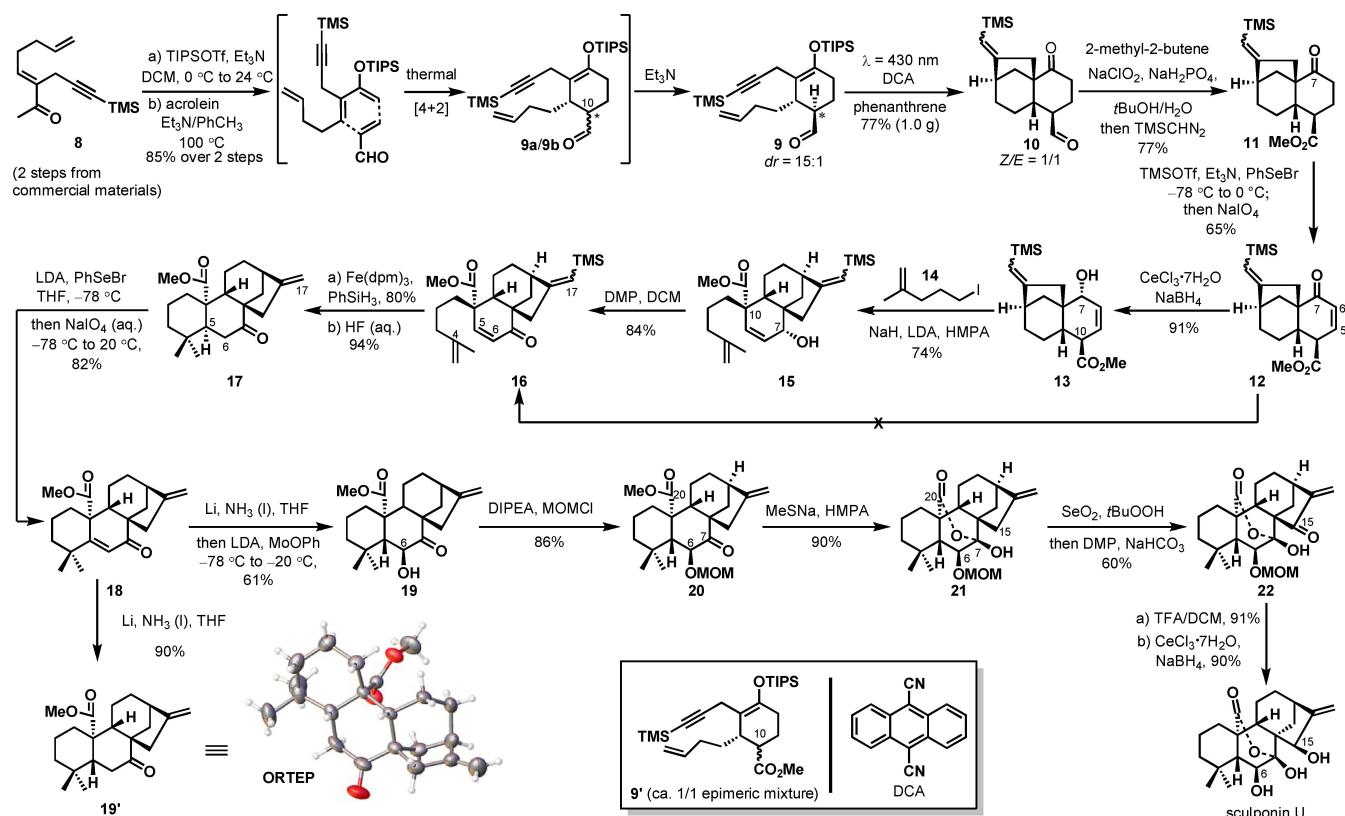
molecules.^[7b-d,f-i] Since our group has a long-standing passionate enthusiasm for the total syntheses of terpenoids, involving several diterpenoids, we herein present our achievement in the total synthesis of sculponin U, a C-20 oxygenated kaurane diterpenoid isolated from *Isodon sculponeatus*.^[9]

Retrosynthetically, sculponin U could be synthesized from compound 1 through global deprotection and functional group interconversion (FGI), which involves the introduction of a C-16 hydroxy and the formation of a bridge of 7,20-lactone-hemiketal functionality (Scheme 1). Compound 1 could be obtained from compound 2 by inverting the absolute configuration at C-5 and installing a hydroxy group at C-6 sequentially. The connection between C-4 and C-5 could be realized by utilizing a radical cyclization from compound 3, where the chemo-selectivity issue must be considered due to the coexistence of the C16=C17 double bond. The cyclization precursor 3 could be



Scheme 1. Retrosynthetic analysis.

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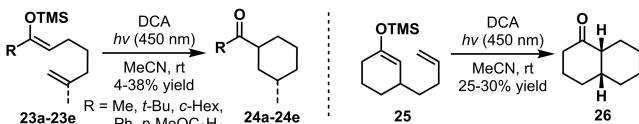
Scheme 2. Racemic Total synthesis of sculponin U.

constructed from compound **4** through the formation of a C1–C10 single bond and a C5=C6 double bond. Compound **4** might be secured from compound **5** through a radical cascade cyclization of an enolate showcased by us in this work, on the basis of the discovery of PET process of enolate by the Mattay group.^[10] The cyclohexene **5** should be attainable through Diels–Alder cycloaddition between the dienophile **6** and the diene **7**.

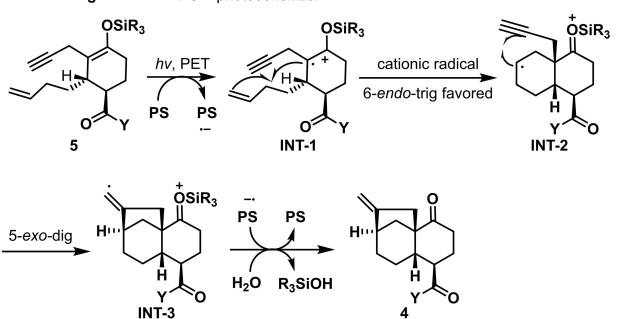
Our total synthesis of sculponin U commenced with compound **8** (Scheme 2), synthesized in 66 % yield over two steps from commercially available starting materials.^[12] Treatment of **8** with triisopropylsilyl triflate generated a silyl enolate, which acted as a diene and underwent a thermal Diels–Alder reaction with acrolein. The in situ-generated [4 +2] cycloadduct yielded an epimeric mixture at C-10, which equilibrated in the presence of triethylamine to afford the thermodynamically stable **9** with a 15:1 *dr* value. Notably, the 1:1 epimeric mixture **9'** from the [4+2] cycloaddition between **8** and methyl acrylate was inconvertible to each other, even in the presence of strong bases such as 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) or lithium diisopropylamide (LDA).

Using 9,10-dicyanoanthracene (DCA) as a photosensitizer, the Mattay group selectively induced an intramolecular 6-*endo*-trig cyclization of silyl enolates (e.g., **23a–23e** and **25**) upon excitation with light at 450 nm, albeit in moderate to low yields (Scheme 3A). Importantly, neither the 5-*exo*-trig cyclization nor a mixed 6-*endo*-trig/5-*exo*-trig pathway was observed, despite their prevalence in classical radical

A. Mattay and co-workers' findings:



B. Our design:



Scheme 3. Mattay's discovery of the preference of 6-*endo*-trig cyclization over 5-*exo*-trig cyclization through PET-triggered cationic radical intermediates from silyl enolates and our synthetic design of a PET cascade cyclization toward the bridged tricycle **4**.

cyclization.^[10a–d] They inferred that the selectivity of 6-*endo*-trig cyclization over 5-*exo*-trig cyclization be ascribed to the relative stability of the newly formed secondary radical carbon with partially cationic character in the 6-*endo*-trig transition state, as its precursor could be a cationic radical of silyl enolate generated by PET.^[10g] Therefore, we proposed

that a cyclohexanone-fused bicyclo[3.2.1]octane motif be constructible from compound **5** (Scheme 3B), although a bridged polycyclic framework has not yet been previously explored in this type of reaction.^[11] In our proposal, upon excitation with a photosensitizer, PET could generate a cationic radical **INT-1**, that would undergo *6-endo*-trig cyclization to afford the bicyclic **INT-2**. Subsequent intramolecular capture of the radical by the terminal alkyne in a *5-exo*-dig fashion could accordingly deliver the tricyclic intermediate **INT-3**. Final electron transfer and aqueous quenching could give rise to the bridged tricyclic compound **4**. Based on this design, we used compound **27** as a substrate and attempted various conditions to obtain the corresponding PET cascade product **28** (Table 1).^[12] We first evaluated 0.1 equivalent of various photosensitizers without a co-sensitizer under photoirradiation at the respectively appropriate wavelengths (entries 1–7).^[13] Although organic dyes

such as Mes-Acr⁺BF₄⁻, TPT⁺BF₄⁻ and eosin Y as photo-redox catalysts did not initiate the PET reaction (entries 1–3), employment of 4CzIPN produced the desired product **28** in 33 % yield (entry 4). Remarkably, DCA provided **28** with a better yield of 53 % (entry 7), whereas the application of two structurally similar photosensitizers, TXO and DCN, proved to be futile (entries 5 and 6). By increasing the amount of DCA from 10 mol % to 40 mol %, we could shorten the reaction time from 24 hours to 4 hours (entry 8). Mechanistically, to enhance the efficacy of the PET reaction, minimizing electron transfer from the excited photosensitizer (anionic radical) back to the excited substrate (cationic radical) such as **INT-1** in Scheme 3B is crucial.^[14] Among the different aromatic co-sensitizers examined, chrysene, triphenylene and naphthalene resulted in inferior yields albeit in shorter reaction time (entries 9–11).^[12] However, using phenanthrene as the co-sensitizer led to an excellent 86 % yield in 30 minutes (entry 12). Irradiation with light at 430 nm in the presence of both DCA and phenanthrene proved to be the optimal condition, as irradiation at other wavelengths gave lower yields (entries 13–15).

Using the optimized conditions, we explored the substrate scope of this PET cascade reaction (Table 2). The installation of a trimethylsilyl group onto the alkyne as in compound **9** did not affect the reaction efficiency, affording the desired compound **10** in 78 % yield as a 1:1 mixture of *Z/E* isomers. Transforming the aldehyde group of **27** to an

Table 1: PET-triggered cascade cyclization.^[a]

En-Photosensitizer (equivalent)	Co-sensitizer ^[b]	Light source	Yield/t ^[c]	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem>		
				<chem>Mes-Acr^+BF_4^-</chem>	<chem>TPT^+BF_4^-</chem>	<chem>4CzIPN</chem>
1 Mes-Acr ⁺ BF ₄ ⁻ (0.1 equiv)	—	450 nm LED	NR/24 h			
2 TPT ⁺ BF ₄ ⁻ (0.1 equiv)	—	430 nm LED	NR/24 h			
3 Eosin Y (0.1 equiv)	—	450 nm LED	NR/24 h			
4 4CzIPN (0.1 equiv)	—	430 nm LED	33 %/8 h ^[d]			
5 TXO (0.1 equiv)	—	419 nm Ryonet light	NR/24 h			
6 DCN (0.1 equiv)	—	350 nm Ryonet light	NR/24 h			
7 DCA (0.1 equiv)	—	430 nm LED	53 %/24 h ^[d]			
8 DCA (0.4 equiv)	—	430 nm LED	53 %/4 h ^[d]			
9 DCA (0.4 equiv)	chrysene	430 nm LED	36 %/30 min			
10 DCA (0.4 equiv)	triphenylene	430 nm LED	44 %/30 min			
11 DCA (0.4 equiv)	naphthalene	430 nm LED	39 %/30 min			
12 DCA (0.4 equiv)	phenanthrene	430 nm LED	86 %/30 min ^[d]			
13 DCA (0.4 equiv)	phenanthrene	419 nm Ryonet light	NR/30 min			
14 DCA (0.4 equiv)	phenanthrene	440 nm LED	54 %/30 min			
15 DCA (0.4 equiv)	phenanthrene	450 nm LED	44 %/30 min			

[a] 20 mg scale. [b] No co-sensitizer or 10 equivalent of co-sensitizer was used. [c] NMR yield unless otherwise stated; NR = no reaction; NP = no product. [d] Isolated yield.

Table 2: Substrate scope of PET cascade cyclization.^[a]

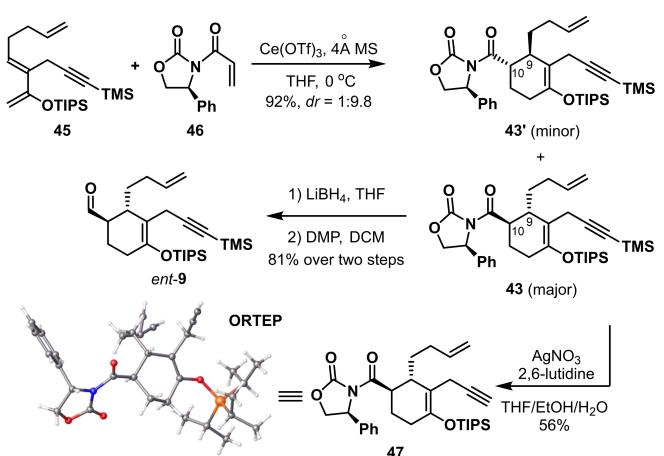
reactant	product	reactant	product
<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem>	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem> 28, 86%	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem>	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem> 10, 75% Z/E = 1:1
<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem>	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem> 30, 64%	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem>	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem> 32, 63%
<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem>	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem> 34, 73%	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem>	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem> 36, 71%
<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem>	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem> 38, 78% dr = 2:1 H	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem>	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem> 40, 81% dr = 1.4:1 H
<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem>	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem> 42, 70%	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem>	<chem>CC#C[C@H]1[C@@H](C[C@H]1C(=O)c2ccccc2)C[C@H]2[C@H]1C=CC(=O)N2</chem> 44, 53% ^[b]

[a] Reaction conditions: DCA (0.4 eq), phenanthrene (10 eq), *hν* (430 nm LED), MeCN, rt, *c* = 0.02 mol L⁻¹; Isolated yields. [b] Isolated yield over two steps including cascade cyclization and desilylation; Xp represents a chiral auxiliary (please see Scheme 4 for molecular structure).

acetate, a MOM ether and a methyl ester gave compounds **29**, **31** and **33**, respectively, which cyclized smoothly in decent yields to deliver compounds **30**, **32** and **34** respectively. Substitutions of the terminal alkene in **27** with 1,1-disubstituted alkene as in **35** and 1,2-disubstituted alkenes as in **37** and **39** were found to be all well tolerated in this reaction. Furthermore, compound **41** with one less substituent on the six-membered ring and compound **43** with an Evans auxiliary were also proved as appropriate substrates.

In our total synthesis, the PET cascade cyclization of compound **9** was successfully conducted on a one-gram scale, yielding compound **10** in 77% yield (Scheme 2) comparable to that achieved on a small scale (Table 2). Subsequent Pinnick oxidation and esterification delivered compound **11**. Treatment with silyl triflate generated a silyl enolate intermediate, which was in situ transformed to the enone **12** with PhSeBr and NaIO₄. Luche reduction afforded the alcohol **13** stereoselectively. Formation of a dianion with excess LDA allowed for selective introduction of an aliphatic chain **14**^[15] at C-10 to give compound **15**, which was oxidized to afford compound **16**. Notably, the quaternary stereogenic center at C-8 in **13** exhibited significant steric hindrance on the concave face of the cyclohexene ring, which resulted in the convex alkylation product **15** with excellent stereoselectivity. However, direct installation of the aliphatic chain **14** at C-10 of **12** failed, necessitating the circuitous route via **13** and **15**. An iron-catalyzed radical cyclization through hydrogen atom transfer (HAT) was then utilized to construct the single bond between C-4 and C-5,^[12,16] followed by the cleavage of the TMS group, to give compound **17**. Importantly, existence of the bulky TMS group at C-17 is necessary to prevent hydrogenation of the C16=C17 double bond under the HAT conditions. Since the absolute configuration at C-5 was contrary to that in the target molecule, **17** was transformed to **18** by reconstruction of the C5=C6 double bond. Saturation of the alkene with Li/NH₃, followed by in situ installation of hydroxy at C-6, yielded compound **19**, which was subsequently protected to give **20**. Demethylation of compound **20** with MeSNa formed the cyclic hemiketal **21** with a bridge between C-7 and C-20, whereas smooth hydrolysis of the ester at C-20 failed under other conditions with various bases. Allylic oxidation at C-15 was realized to yield **22** after sequential treatment with SeO₂ and Dess–Martin periodinane. Final deprotection of MOM ether at C-6 and diastereoselective reduction of carbonyl at C-15 completed the first racemic total synthesis of sculponin U.

To demonstrate the feasibility of asymmetric total synthesis of sculponin U along our aforementioned synthetic strategy, enantiopure compound **9** was prepared (Scheme 4). Cerium triflate-catalyzed Diels–Alder cycloaddition between compound **45** and compound **46** furnished compound **43** as the major *exo*-diastereomer at 0°C. Subsequent reduction of the amide moiety to an alcohol followed by oxidation with Dess–Martin periodinane led to the aldehyde *ent*-**9**. X-ray crystallography of compound **47**,^[17] obtained by removing the trimethylsilyl group from **43**, confirmed the absolute configuration of the stereogenic centers at C-9 and C-10.^[12]



Scheme 4. Preparation of *ent*-**9** and confirmation of the absolute stereochemistry of **43**.

In conclusion, we developed a radical cascade cyclization protocol to expeditiously construct a bicyclo[3.2.1]octane skeleton, based on Mattay's discovery of PET-triggered cyclization of a silyl enolate favoring a 6-*endo*-trig pathway. This methodology was successfully utilized in the total synthesis of sculponin U, a natural C-20-oxygenated kaurane diterpenoid. Our total synthesis also features an efficient Diels–Alder/isomerization cascade to produce the PET reaction precursor **9**, a smooth HAT-initiated cyclization to complete the tetracyclic framework **17**, and a MeSNa-mediated demethylation to in situ generate the bridge of 7,20-lactone-hemiketal functionality in **21**. The success of total synthesis presented here makes it promising for the divergent total synthesis of other C-20-oxygenated kaurane and *seco*-kaurane diterpenoids, as well as the pharmaceutical derivatives possessing the related polycyclic skeletons.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Hydrogen Atom Transfer · Natural Products · Photoinduced Electron Transfer · Terpenoids · Total Synthesis

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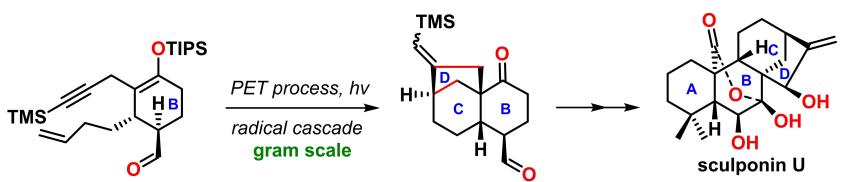
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Communications

Natural Products

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Total Synthesis of Sculponin U through a Photoinduced Radical Cascade Cyclization



The total synthesis of sculponin U, a C₂₀-oxygenated kaurane diterpenoid, was completed. The hexanone-fused bicyclo[3.2.1]octane skeleton was strate-

gically established by a photoinduced electron transfer, generating a cationic radical intermediate from a silyl enolate.