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Synthesis of a Small-Molecule Library with Skeletal Diversity from Hemslecin A via the Reaction-Discovery Strategy

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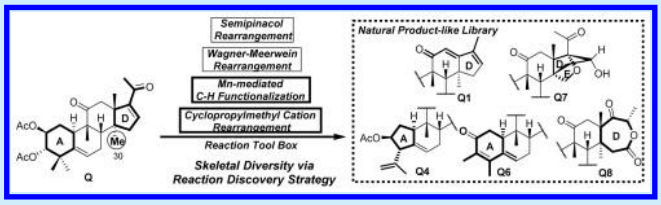
Supporting Information

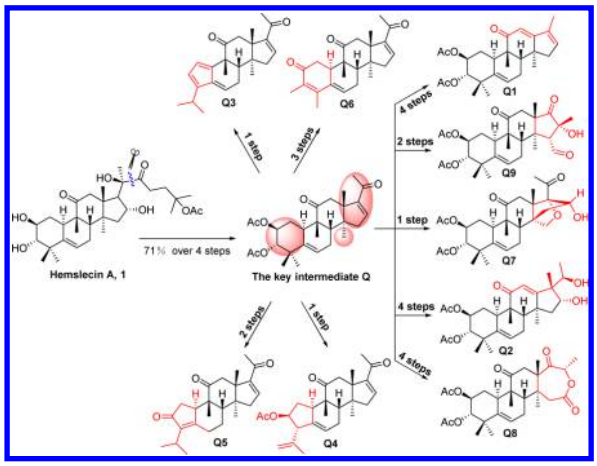
ABSTRACT: An efficient reaction tool box was developed for the synthesis of skeletally diverse and stereochemically complex templates for a small-molecule library based on the common synthon **Q**, which was prepared from hemslecin A in four steps. The reaction tool box comprises three acid-promoted rearrangements: semipinacol, Wagner−Meerwein, and cyclopropylmethyl cation rearrangements. More importantly, a Mn-mediated C−H oxidation was developed to achieve a high level of complexity, which provides a new entry for C−H functionalization of inert angular methyl groups in the chemistry of triterpenes. Our reaction-discovery strategy based on hemslecin A provides a basis for the inherent chemistry of triterpenes and could be applied for the further transformation of triterpenes.



Diversity-oriented synthesis (DOS) has become different to break through the limitation of traditional library synthesis by sampling new chemical space for small-molecule collections that exhibit a range of bioactivities.[1] The objective of DOS is to develop a synthetic scheme whereby each step opens up multiple opportunities for diversification that could be used to create natural product-like and/or drug-like small molecules with diverse molecular structures, each substantially different from the parent compound.[1−3] An approach involving the Beckmann rearrangement and Beckmann fragmentation to complex natural products (steviol and isosteviol) has been demonstrated by the Georg group.[4] Hergenrother et al. reported that tetracyclic diterpene gibberellic acid and steroid adrenosterone could be converted into a small collection of complex and diverse scaffolds using a ring-distortion strategy.[5] Moreover, fumagillol has been selectively remodeled into a series of perhydroisoindoles and perhydroisoquinolines through sequential ring-opening reactions with amines using a reaction-discovery-based strategy by the Porco and Snyder groups.[2a,c] These methods are inspired by nature's approach to creating certain complex natural products using a common intermediate to generate scores of compounds that differ substantially from one another.

Hemslecin A (**1**), a highly oxygenated tetracyclic triterpene,[6,9] is characterized by its densely functionalized and stereochemistry-rich framework, which includes five contiguous stereogenic centers and carbocyclic moieties with each bearing reactive functional groups (Scheme 1). Additionally, hemslecin A exhibits diverse pharmacological activities, such as cytotoxicity,[7,9] anti-HBV activity,[8] anticancer activity,[7] and anti-inflammatory activity.[7,8] Thus, far, most studies of hemslecin A have been focused on the transformations of functional groups;[6,8,9] skeletal transformations applied to hemslecin A have rarely been reported, likely because of the synthetic challenges arising from its structural complexity and its multiple reactive functionalities. Inspired by Porco's and Snyder's work[2] and by our continuous investigation of the bioactive diversity of terpenes,[10] we herein disclose a concise synthesis of structurally complex and diverse derivatives of hemslecin A by an efficient reaction tool box that includes a number of rearrangement reactions and a Mn-mediated C(sp^3)−H oxidation.

Scheme 1. Concise Synthesis of a Small-Molecule Library from Hemslecin A



As illustrated in Scheme 1, the general synthetic strategy to achieve these molecules started from the preparation of the

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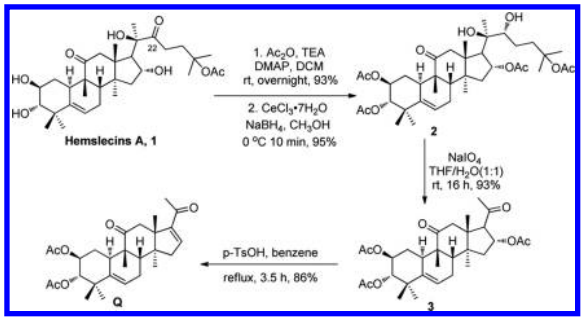
requisite intermediate **Q** using hemslecin A as the starting material. The functional groups of the key intermediate **Q** provide a wide and controlled synthetic platform that can be strategically manipulated to synthesize novel, diverse, and complex chemical scaffolds within four steps (**Q1**−**Q9**).

The synthesis commenced with **1**, which is naturally abundant and commercially available (Scheme 2). Treatment of **1** with

Scheme 2. Synthesis of Key Intermediate Q

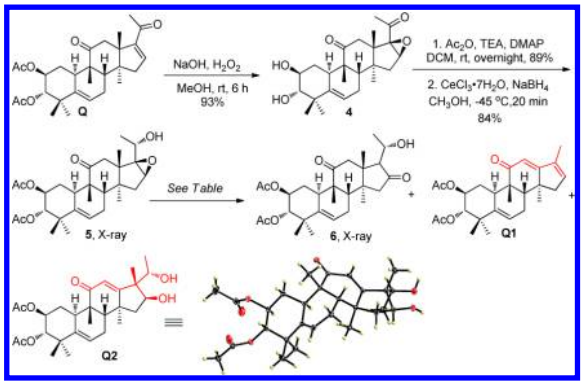


Ac_2O in the presence of 4-dimethyl-aminepyridine (DMAP) at room temperature (rt) afforded a triacylated intermediate. Subsequent regioselective and stereoselective reduction of the C22-carbonyl group with $NaBH_4$ in MeOH at 0 °C gave the vicinal diol **2** in 88% yield over two steps. Oxidative cleavage of the diol on the side chain was then induced using $NaIO_4$ in THF/H_2O (1:1, v/v) to give ketone **3** in 93% yield,[9] which subsequently underwent a smooth β-elimination in the presence of catalytic amounts of *p*-TsOH in refluxing benzene, readily resulting in the corresponding intermediate **Q** in 86% yield.[11] Thus, the common synthon **Q** with the necessary functional groups was prepared in 71% yield over four steps.

With the critical intermediate **Q** in hand, we initiated a reaction-discovery-based strategy to rapidly create complex and diverse small molecules focusing on ring D. Epoxidation of the enone **Q** under the conditions of H_2O_2 (30%)/NaOH at rt provided the desired epoxide **4** (93%),[12] which was followed by acetylation with Ac_2O and consequent reduction with $NaBH_4$ in MeOH at −45 °C to yield α-hydroxy epoxide **5** in 75% yield over two steps (Table 1). Treatment of **5** with $BF_3{\cdot}Et_2O$ in dry DCM at 0 °C to rt for 30 min gave a mixture of epoxide-rearranged products **Q1** (37%), **Q2** (33%), and **6** (21%) (Table 1, entry 1). We propose that the plausible mechanism of epoxide rearrangement was an oxonium-promoted Wagner−Meerwein rearrangement[13] to form **Q2**, with further release of acetaldehyde to give **Q1** (Path a, Scheme 3). By contrast, a 3-*exo* rearrangement[14] followed by semipinacol rearrangement[13a] under acidic conditions gave compound **6** (Path b, Scheme 3). In comparison, when THF was used as solvent, **6** was obtained as the major product in 70% yield (Table 1, entry 2). Interestingly, treatment of **5** with TFA in DCM at 0 °C to rt resulted in the formation of **Q1** as the major product in 68% yield (Table 1, entry 3). Additionally, when THF was again used as a solvent in the presence of TFA, compound **Q2** was the major product, with a 74% yield (Table 1, entry 4). The structure of **Q2** was unequivocally determined by X-ray crystallographic analysis. Moreover, **Q2** could be obtained as a single product with an 82% yield in $NaIO_4/H_5IO_6$ and THF/H_2O (1:1, v/v) (Table 1, entry 5).

Next, the reaction-discovery strategy was tested on ring A. Schmalz et al.[15] reported a cyclopropyl-methyl cation rearrangement method for tricyclo[4.4.1.0^{5,10}]undecane **I**, which easily

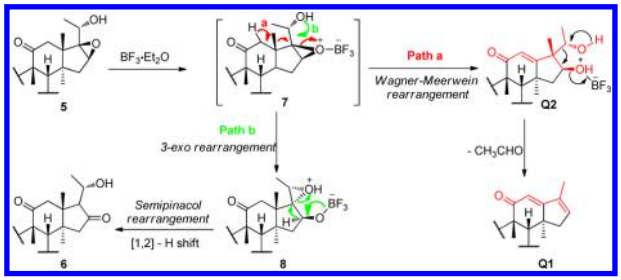
Table 1. Conditions and Optimization of Epoxide Rearrangement



entry	conditions	solvent	yield (%)[d] Q1	Q2	6
1[a]	$BF_3{\cdot}Et_2O$, 0 °C−rt, 30 min	DCM	37	33	21
2[a]	$BF_3{\cdot}Et_2O$, 0 °C−rt, 30 min	THF	12	15	70
3[b]	TFA, 0 °C−rt, 30 min	DCM	68	17	11
4[b]	TFA, 0 °C−rt, 30 min	THF	16	74	8
5[c]	$NaIO_4/H_5IO_6$, rt, 72 h	THF/H_2O (1:1, v/v)	nd[e]	82	nd

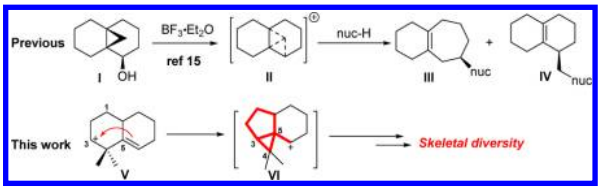
[a]Reaction conditions: **Q** (20 mg, 0.04 mmol); $BF_3{\cdot}Et_2O$ (6 μL, 0.048 mmol); corresponding solvent (3 mL) in table; 0 °C to rt. [b]Reaction conditions: **Q** (20 mg, 0.04 mmol); TFA (9 μL, 0.12 mmol); corresponding solvent (3 mL) in table; 0 °C to rt. [c]Reaction conditions: **Q** (20 mg, 0.04 mmol); H_5IO_6 (45 mg, 0.2 mmol); $NaIO_4$ (43 mg, 0.2 mmol); corresponding solvent (3 mL) in table; rt. [d]Yield of the isolated product after column chromatography. [e]Not detected.

Scheme 3. Proposed Mechanisms for the Formation of Q1, Q2, and 6



formed the bicyclic 6/7- and 6/6-fused compounds **III** and **IV** (Scheme 4). We envisioned the acid-promoted formation of the

Scheme 4. Rearrangement of Cyclopropyl Methyl Cation



C3 cation, which could be further trapped by C5 to generate the cyclopropyl-methyl cation intermediate **VI**. This intermediate could likely access the ring-A-contracted skeleton, resulting in further skeletal diversity. As expected, when the intermediate **Q** was treated with *p*-TsOH in benzene at 70 °C for 24 h, the ring-

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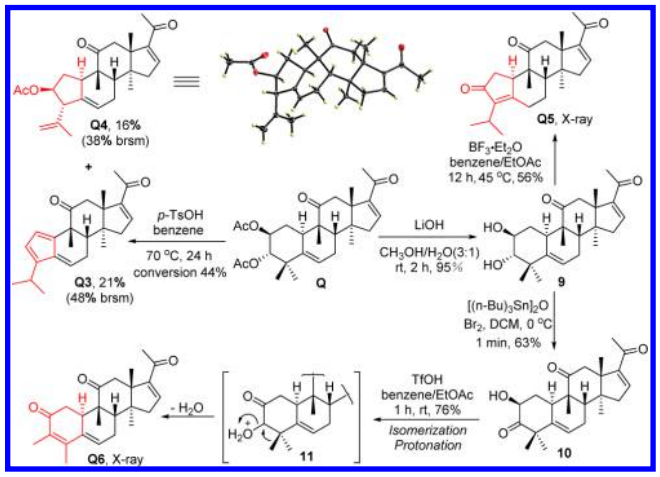
contracted products **Q3** and **Q4** were isolated in 21% (48% brsm) and 16% (38% brsm) yields, respectively (Scheme 5).

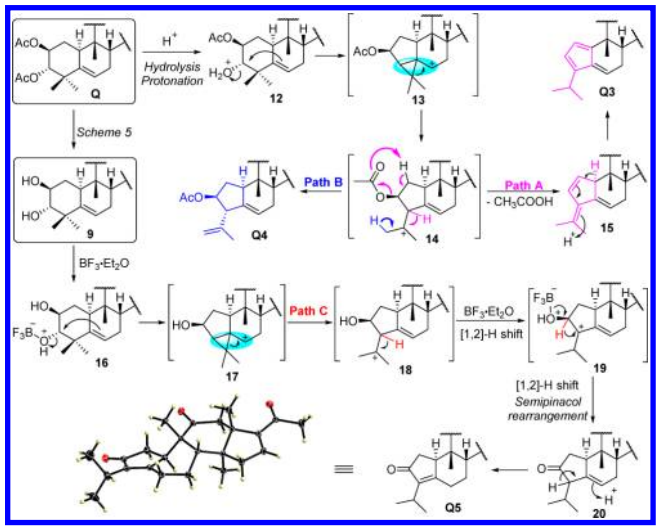
Scheme 5. Skeletal Diversity Based on Ring A Rearrangement



To further investigate the acid-promoted rearrangement of ring A, we prepared deacetylated substrate **9** in 95% yield. Regioselective oxidation of **9** using bis(tri-*n*-butyl-tin)oxide in the presence of bromine at 0 °C resulted in the α-hydroxyl ketone **10** in 63% yield.[16] Interestingly, when compound **9** was treated with $BF_3{\cdot}Et_2O$ in benzene/EtOAc (50:1, v/v) for 12 h, the cyclopentenone **Q5** was obtained in 56% yield. To our surprise, when compound **10** was treated with TfOH in benzene/EtOAc (50:1, v/v) at rt, a methyl [1,2]-shifted product **Q6** was obtained in 76% yield.

We propose that the transformation from **Q** to products **Q3**, **Q4**, and **Q5** was initiated by the formation of cyclopropyl-methyl cations **13** and **17**. The plausible pathway is shown in Scheme 6.

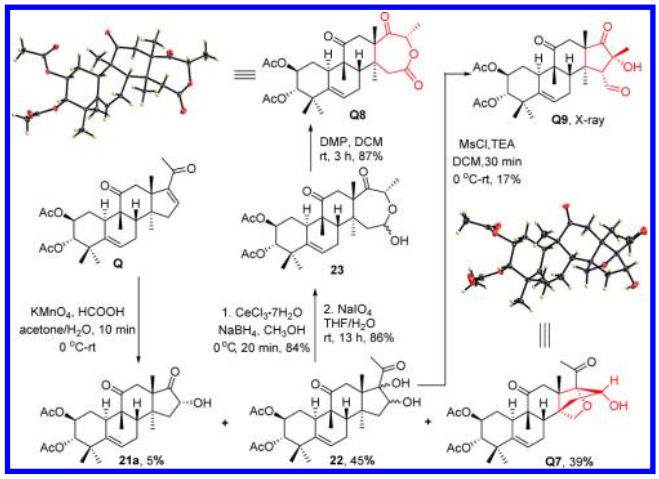
Scheme 6. Proposed Mechanisms for the Formation of Q3, Q4, and Q5



Hydrolysis and protonation of the intermediate **Q** under acidic conditions led to the formation of the cyclopropyl methyl cation **13**. The cation **13** underwent a ring-opening reaction to give the more stable tertiary cation **14**. Deprotonation and elimination of acetic acid from cation **14** gave the intermediate **15**, and the subsequent isomerization of **15** resulted in **Q3** (Path A), whereas deprotonation of the methyl group yielded **Q4** (Path B). For cation **17**, the reaction pathway likely involved two [1,2]-H shifts and subsequent isomerization to give **Q5** (Path C).

To access a high level of skeletal diversity, we exploited the α,β-unsaturated ketone at ring D of the intermediate **Q** (Scheme 7).

Scheme 7. Skeletal Diversity via Remodeling Ring D



The regioselective dihydroxylation of the C16−C17 double bond was first carried out in the presence of $KMnO_4$ (3 equiv)/HCOOH (5 equiv) in acetone/H_2O (4:1, v/v), which resulted in the expected dihydroxylated product **22** (45%, dr = 1:1, determined by ^{1}H NMR) and the C17−C20 cleavage product **21a** (5%). The reaction also furnished the C30-methyl-oxidized product **Q7** (39%) with a newly formed oxabicyclo[2.2.1]-heptane motif at ring D. To the best of our knowledge, site-selective aliphatic C−H oxidations of inert angular methyl C−H bonds using $KMnO_4$ for the construction of strained and transannulated tetrahydrofuran ring systems have rarely been reported, although such reactions are extremely interesting. To further explore the origins of the selectivity for C−H functionalization in this transformation and to improve the yield of **Q7**, a series of reaction conditions were examined (Table 2). Finally, we obtained **Q7** in a higher yield of 54% by adjusting the ratio of acetone and water (Table 2, entry 4). The stereochemistry of the product **Q7** was further clarified by X-ray crystallographic analysis. Subsequent treatment of compound **22** with $NaBH_4/CeCl_3{\cdot}7H_2O$ in MeOH was followed by treatment with $NaIO_4$ to give the ring-expanded hemiacetal **23** in 72% yield over two steps. Oxidation of the resulting hemiacetal **23** with Dess−Martin periodinane provided lactone **Q8** in 87% yield, the structure of which was also confirmed by X-ray crystallographic analysis. In addition, when compound **22** was treated with MsCl/TEA in DCM at 0 °C to rt for 30 min, the rearrangement product **Q9** was isolated in 17% yield. Thus, synthesis of a diverse range of compounds was achieved; investigations of their biological activities are now underway and will be reported in due course.

In summary, we have accomplished a facile chemical approach to a natural-product-like molecular library with complex diversity by using the common synthon **Q** derived from hemslecin A. Systematic modulation of the architecture of hemslecin A was achieved via oxonium-promoted semipinacol rearrangement, Wagner−Meerwein rearrangement, and a cyclopropyl-methyl cation rearrangement. Most importantly, this work led to the discovery of a Mn-mediated site-selective aliphatic C−H

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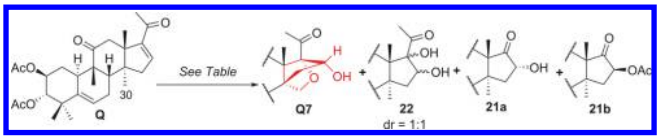
Table 2. Condition Screening for C(sp^3)−H Oxidation of the C30-Methyl Group



entry[a]	conditions	solvent	yield (%)[b] Q7	21a/21b	22
1	$KMnO_4$, HCOOH	acetone/H_2O (4:1, v/v)	39	5/nd[c]	45
2	$KMnO_4$, HCOOH	acetone/H_2O (2:1, v/v)	40	25/nd	35
3	$KMnO_4$, HCOOH	acetone/H_2O (1:1, v/v)	42	15/9	12
4	$KMnO_4$, HCOOH	acetone/H_2O (1:2, v/v)	54	nd/25	nd
5[d]	$KMnO_4$, HCOOH	18-crown-6 (1 equiv)/ acetone	37	nd/nd	51
6	$KMnO_4$, HCOOH	CH_3CN/H_2O (1:2, v/v)	36	24/17	11

[a]Unless otherwise noted, all reactions were carried out with **Q** (50 mg, 0.11 mmol), $KMnO_4$ (49 mg, 0.33 mmol), and HCOOH (21 μL, 0.55 mmol) in the corresponding solvent (4 mL) with the corresponding ratio listed in the table at 0 °C to rt. [b]Yield of the isolated product after column chromatography. [c]Not detected. [d]Reaction conditions: **Q** (50 mg, 0.11 mmol), HCOOH (21 μL, 0.55 mmol), 18-crown-6 (24 mg, 0.11 mmol), $KMnO_4$ (49 mg, 0.33 mmol) in acetone (4 mL) at 0 °C to rt.

oxidation of inert angular methyl groups, which could easily lead to a synthetically challenging oxabicyclo[2.2.1]heptane motif. These rearrangement reactions with Mn-mediated C−H oxidation could be used as a reaction tool box to remodel other related triterpene scaffolds and to access novel chemotypes and pharmacological tools.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01654.

Detailed experimental procedures; characterization data; copy of ^{1}H and ^{13}C NMR spectra for new compounds; and X-ray crystallographic data for compounds **5**, **6**, **Q2**, **Q4**, **Q5**, **Q6**, **Q7**, **Q8**, and **Q9** (PDF)
Crystallographic data for compound **5** (CIF)
Crystallographic data for compound **6** (CIF)
Crystallographic data for compound **Q2** (CIF)
Crystallographic data for compound **Q4** (CIF)
Crystallographic data for compound **Q5** (CIF)
Crystallographic data for compound **Q6** (CIF)
Crystallographic data for compound **Q7** (CIF)
Crystallographic data for compound **Q8** (CIF)
Crystallographic data for compound **Q9** (CIF)

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Notes

The authors declare no competing financial interest.

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