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Synthesis of Macrocyclic Ketones through Catalyst-Free Electrophilic Halogen-Mediated Semipinacol Rearrangement: Application to the Total Synthesis of (±)-Muscone

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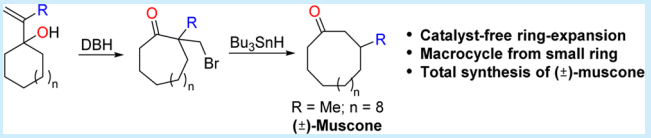
Supporting Information

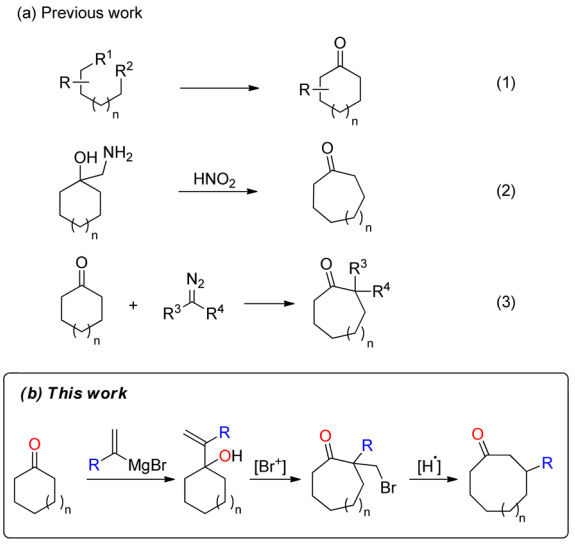
ABSTRACT: A series of macrocycles were successfully prepared using electrophilic halogen-mediated semipinacol rearrangement under mild conditions. Although the expansion from small ring to medium ring is an energetically unfavorable process, the electrophilic halogenation was found to be powerful enough to override such an energy barrier. The rearranged products could further undergo Dowd–Beckwith rearrangement to give the corresponding one-carbon ring-expanded ketones. This approach has been applied to the total synthesis of the natural product (±)-muscone, which is widely used in modern perfumery and medicines, in a two-step sequence.



Medium-ring and macrocyclic ketones have been found to be widely present as fundamental structures in plenty of biologically active natural products and clinic drugs.[1] In these biologically active chemical entities, the medium-ring and macrocyclic ketone structural cores have proven indispensable for their excellent pharmaceutical properties.[2] Over the past decades, chemists devoted significant effort toward the construction of these ketones. Ring-closing strategies including Dieckmann condensation,[3] radical initiated ring closing reactions,[4] ring-closing metathesis,[5] and intramolecular cross-coupling reactions (e.g., Stille coupling,[6] Sonogashira coupling,[7] Heck coupling[8]) have been widely applied to construct complicated macrocyclic ketone structures (Scheme 1, eq 1). However, these traditional methods generally require harsh reaction conditions (e.g., strong bases and/or high temperatures) and the use of expensive metal catalysts. In addition, a high dilution environment is usually required to avoid intermolecular head-to-tail coupling. Applications of one-carbon ring-expansion reactions in the preparation of medium-ring and macrocyclic ketones have emerged in recent years, partly due to the availability of substrates and potential in the development of asymmetric variant. For instance, Tiffeneau–Demjanov rearrangement[9] and homologation of cyclic ketones with diazo compounds[10] have been reported (Scheme 1, eqs 2 and 3). However, Tiffeneau–Demjanov rearrangement requires strong acidic conditions, which suffers from low functional group compatibility.[11] Ring expansion of ketone with diazo compounds might also suffer from uncontrolled multiple homologations, which could lead to a complicated product mixture.[12] Hence, it remains highly desirable to develop a new and efficient methodology to access medium-ring and macrocyclic ketones.

Electrophilic halogen-initiated semipinacol rearrangement is a useful one-carbon ring-expansion strategy, which has been applied as the key step in the total synthesis of various natural products.[13] However, its application on the synthesis of medium and large cyclic ketones is uncommon.[14] Due to the high ring strain in the small ring systems (e.g., 3 and 4-membered rings), the ring-expansion reactions from small to 5- or 6-membered rings are usually energetically favorable and relatively easier to be performed. In contrast, ring expansion from 6-membered rings to medium rings or from medium rings to macrocycles needs to overcome the increase in ring strain,

Scheme 1. Strategies in the Synthesis of Marcocyclic Ketones



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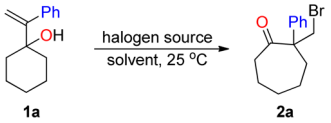
which is an uphill process.[15] For instance, the energy difference between 6- and 7-membered cyclic ketones is around 6 kcal/mol.[16] It remains unclear whether electrophilic halogen-initiated semipinacol rearrangement is powerful enough to overcome the ring-strain barrier in the synthesis of medium rings and marcocycles.[17] Herein, we are pleased to report our recent success in utilizing a catalyst-free electrophilic halogen-initiated semipinacol rearrangement protocol in the preparation of medium rings and marcocycles from smaller ring systems. In addition, the ring-expanded products contain a halogen handle, which allows for further radical-initiated one-carbon ring expansion to give an even larger ring system.

Initially we began our studies using 1-vinylcyclohexan-1-ol **1a** and dichloromethane as the substrate and solvent, respectively. First, electrophilic fluorinating agents such as selectfluoro and *N*-fluorobenzenesulfonimide (NFSI) in dichloromethane were examined. However, no reaction was observed even when Lewis basic catalyst triphenylphosphine sulfide was applied (Table 1, entries 1−3). The ring expansion using *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS) in the presence of a Lewis basic catalyst also returned sluggish reactions (entries 4−5). Interestingly, the ring expansion could proceed readily when using the halogen sources under catalyst-free conditions; a 69% yield of the ring-expanded product **2a** was obtained when using 1,3-dibromo-5,5-dimethylhydantoin (DBH) as the electrophilic halogenating agent (entries 6−9). A brief survey on solvents revealed the superior performance of chloroform, which gave **2a** in 74% yield (entries 10−12). The yield slightly decreased when conducting the reaction at 50 °C, potentially due to the decomposition of DBH at elevated temperature (entry 13).

Table 1. Conditions Optimization[a]



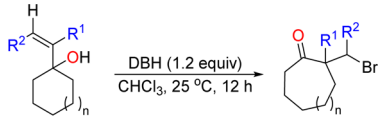
1a **2a**

entry	halogen source	solvent	catalyst	yield (%)[b]
1	Selectfluoro	CH_2Cl_2	–	trace
2[c]	Selectfluoro	CH_2Cl_2	Ph_3PS	trace
3[c]	NFSI	CH_2Cl_2	Ph_3PS	trace
4[c]	NCS	CH_2Cl_2	Ph_3PS	trace
5[c]	NIS	CH_2Cl_2	Ph_3PS	trace
6	NCS	CH_2Cl_2	–	19
7	NBS	CH_2Cl_2	–	20
8	NBP	CH_2Cl_2	–	33
9	DBH	CH_2Cl_2	–	69
10	DBH	THF	–	22
11	DBH	PhMe	–	68
12	DBH	$CHCl_3$	–	74
13[d]	DBH	$CHCl_3$	–	66

[a]Reactions were performed with **1a** (0.2 mmol) and a halogen source (0.24 mmol) in solvent (0.04 M) at room temperature for 12 h in the absence of light. [b]The yields were isolated yields. [c]10 mol % of catalyst was used. [d]The reaction was carried out at 50 °C.

With the optimal conditions in hand, the substrate scope was examined and the results are shown in Table 2. A range of substrates **1** with different ring sizes was investigated. Other than the six- to seven-membered ring expansion (**1a** → **2a**), the reaction protocol could be applied to the preparation of **2b** (8-membered), **2c** (9-membered), **2d** (10-membered), **2e** (11-membered), **2f** (13-membered), and **2g** (16-membered) from the corresponding one-carbon less substrates **1** (Table 2, entries 1−7). Substrates **1** that have different aryl substituents were also investigated. To our delight, electron-rich aryl substituted substrates **1h** and **1i** were well-tolerated under the optimized conditions, giving the ring-expanded products **2h** and **2i** in good yields (entries 8−9). Although the electron-deficient aryl substituents could deactivate the olefin in the ring-expansion process, the 3-fluorophenyl substituted **1j** and 4-fluorophenyl substituted **1k** could smoothly undergo the ring expansion to furnish marcocyclic ketones **2j** and **2k**, respectively, in appreciable conversions (entries 10−11).

Table 2. Synthesis of Medium-Ring and Marcocyclic Ketones[a]



1 **2**

entry	substrate	*n*, R^1, R^2	product	yield (%)
1	**1a**	1, Ph, H	**2a**	74
2	**1b**	2, Ph, H	**2b**	80
3	**1c**	3, Ph, H	**2c**	84
4	**1d**	4, Ph, H	**2d**	87
5	**1e**	5, Ph, H	**2e**	71
6	**1f**	7, Ph, H	**2f**	86
7	**1g**	10, Ph, H	**2g**	90
8	**1h**	7, 3-Me-Ph, H	**2h**	79
9	**1i**	7, 4-Me-Ph, H	**2i**	75
10	**1j**	7, 3-F-Ph, H	**2j**	65
11	**1k**	7, 4-F-Ph, H	**2k**	62
12	**1l**	1, Me, H	**2l**	79
13	**1m**	2, Me, H	**2m**	81
14	**1n**	3, Me, H	**2n**	85
15	**1o**	4, Me, H	**2o**	86
16	**1p**	7, Me, H	**2p**	82
17	**1q**	10, Me, H	**2q**	86
18[b]	**1r**	2, $(CH_2)_2OH$, H	**2r**	53
19[b]	**1s**	7, $(CH_2)_2OTBS$, H	**2s**	45
20[c,d]	**1t**	7, H, Me	**2t**	39
21[e]	**1p**	7, Me, H	**2p**	79

[a]Reactions were carried out with **1** (0.2 mmol), DBH (0.24 mmol) in $CHCl_3$ (4 mL) at 25 °C in the absence of light. The yields were isolated yields. [b]1.5 equiv of K_2CO_3 was added. [c]1.2 equiv of *N*-bromophthalimide was used instead of DBH. [d]The product dr is 5:1. [e]The reaction was conducted at 5 mmol scale.

Besides the aryl substituents, substrates **1l−q** with a methyl group as the alkyl substituent were also studied (Table 2, entries 12−17). It was found that the corresponding alkyl substituted medium ring to macrocyclic ketones **2l−q** could be obtained readily and the reaction efficiency is similar to that of the aryl substituted substrates. For substrates **1r** and **1s** that contain a hydroxyl group and a silyl ether, respectively, moderate yields of the cyclized products **2r** and **2s** were furnished and the functional groups were intact (entries 18 and 19). When using the 1,2-disubstituted *cis*-olefinic substrate **1t**, appreciable cyclized product **2t** was still obtained (entry 20). Finally, the reaction was readily scalable without significant diminishment of the product yield (entry 21).

The macrocyclic ketone products **2** contain a carbonyl group and a methylene bromide moiety, which allow for further ring

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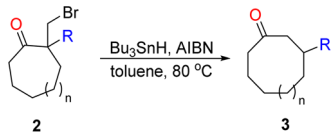
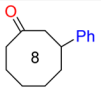
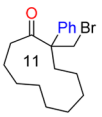
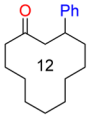
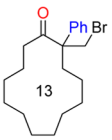
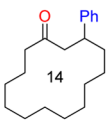
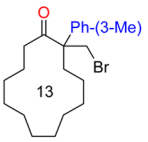
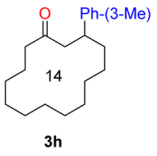
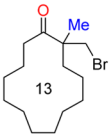
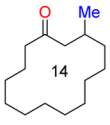
expansion through Dowd–Beckwith rearrangement.[18] By treating **2** with tri-*n*-butyltin hydride and azobis(isobutyronitrile) (AIBN) in toluene at 80 °C, the one-carbon ring-expanded macrocyclic ketones **3** could be furnished readily (Table 3). It is noteworthy that the preparation of *β*-keto-substituted macrocyclic ketones usually required multiple synthetic steps,[19] but they can be prepared using the newly developed strategy of a consecutive one-carbon ring-expansion sequence.

Table 3. Dowd–Beckwith Rearrangement in the One-Carbon Ring Expansion of 2[a]



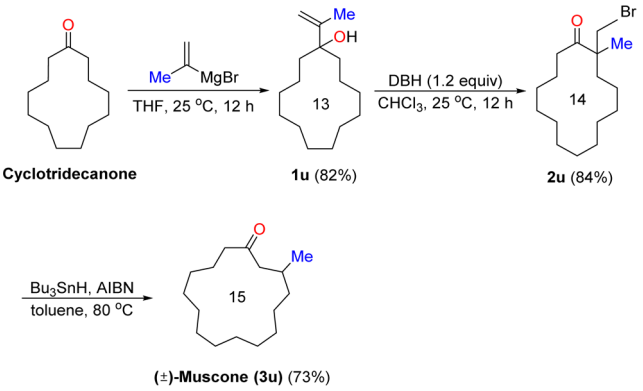
2 **3**

entry	substrate	product	yield (%)[b]
1	 **2a**	 **3a**	59
2	 **2e**	 **3e**	68
3	 **2f**	 **3f**	62
4	 **2h**	 **3h**	52
5	 **2p**	 **3p**	61

[a]Reactions were carried out with **2** (0.2 mmol), Bu_3SnH (0.6 mmol), AIBN (10 mg) in toluene (10 mL) at 80 °C. [b]Isolated yield.

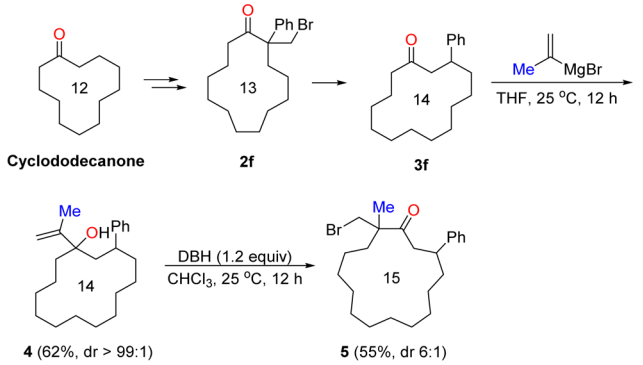
To further demonstrate the synthetic utility of this newly developed 1 + 1-carbon ring-expansion strategy, we attempted to prepare muscone (**3u**) from cyclotridecanone (Scheme 2). Muscone (**3u**) is a glandular secretion of the musk deer and has been widely used in perfumery and medicine.[20] Classically, multistep synthesis is required for the preparation of muscone.[21] On the other hand, under the catalyst-free electrophilic halogen-initiated semipinacol rearrangement of **1u** (prepared from the reaction between cyclotridecanone and 2-propenyl magnesium bromide), the 14-membered macrocyclic ketone **2u** could be furnished (84% yield). Subsequently, Dowd–Beckwith rearrangement of **2u** furnished muscone (**3u**) in 73% yield.

Scheme 2. Total Synthesis of (±)-Muscone (3u)



Since products **3** from the Dowd–Beckwith rearrangement contain the ketone functionality, they could potentially be converted into the corresponding allylic alcohols for further semipinacol rearrangement/ring expansion reaction. Preliminary study on the ring expansion of **3f**, which was derived from cyclododecanone, was performed (Scheme 3).[22] Reaction of **3f** with isopropenyl magnesium bromide gave **4** in 62% yield. Electrophilic halogen-initiated semipinacol rearrangement of **4** using the optimized conditions gave the 15-membered ring system **5**. This sequence of alternative semipinacol rearrangement/Dowd–Beckwith rearrangement executed the ring expansion from a 12-membered ring ketone to a 15-membered ring ketone system.

Scheme 3. Preliminary Result on the Consecutive Ring Expansion



In summary, we have developed an efficient strategy to prepare medium-ring and macrocyclic ketones that are deemed difficult to achieve using traditional synthetic methods due to the existence of high ring strain. The reaction conditions are mild and catalyst-free. This double one-carbon ring-expansion strategy has been applied to the total synthesis of (±)-muscone (**3u**).

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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