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One-pot reductive cleavage of *exo*-olefin to methylene with a mild ozonolysis-Clemmensen reduction sequence

Shu Xu, Takayuki Toyama, Jun Nakamura, Hirokazu Arimoto *

Graduate School of Life Sciences, Tohoku University, Katahira 2-1-1, Aoba, Sendai 980-8577, Japan

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A B S T R A C T

A one-pot *exo*-olefin reductive cleavage was for the first time developed. The reaction could proceed under a mild condition avoiding the use of hazardous and expensive reagents. Meanwhile, a TMSCl-mediated Clemmensen reduction in alcoholic solvent was also examined.

Reductive cleavage of *exo*-olefin to methylene is an important transformation in organic synthesis (Fig. 1).[1] So far it can only be achieved by multistep operations, for example, usually first oxidative cleavage of the olefins to ketones and then deoxygenation to the methylene groups. For the former oxidative olefin cleavage, ozonolysis and Os/Ru-IO_4^- method are the two regular techniques. Whereas, for the latter ketone carbonyl deoxygenation, many more variety of methods have been applied, including Clemmensen reduction[2] and its Yamamura modification,[3] thioacetal-based reduction, Wolff–Kishner reduction and its Caglioti modification,[4] and transformation to alcoholic derivatives followed by Barton–McCombie deoxygenation or hydride reduction.

Step[5] and atom economy[6] are the current and future trends of synthetic chemistry, which have received greater attention from both industrial and academic communities. Thus, to avoid the above-mentioned tedious procedures and hazardous expensive reagents, a one-pot atom-economic method is urgently desired for the *exo*-olefin reductive cleavage. This promoted us to study on the transformation by designing a cascade sequence with the combination of ozonolysis and Clemmensen reduction, the two least costly and most atom-economic conditions among the above. Ozonolysis is a well-studied reaction, popularly applied in the organic synthesis field. Zinc metal is a textbook reductant for the quench of the reactive ozone adduct. Also, so far zinc metal is the only suitable reductant for the Clemmensen reduction. Thus it may possibly be a good bridge to join the former oxidative olefin cleavage and the latter carbonyl deoxygenation reactions.

Clemmensen reduction[2] is a historically important reaction. However, because of its original harsh conditions (aqueous HCl, reflux) with toxic Hg reagent, it is seldom applied in the modern organic synthesis. In the late 1960s, Yamamura et al. developed an excellent modification of the Clemmensen reduction with a very mild condition (activated zinc, saturated HCl in Et_2O at 0 °C), which avoids the utility of toxic Hg.[3] Unfortunately, this work went largely unnoticed by our chemical community and further systematic development of this methodology was not continued since then. Therefore, in our research of the one-pot olefin reductive cleavage, we started from the modification of the Yamamura method, because Et_2O, the most successful solvent in the Yamamura condition, is not suitable for ozonolysis.

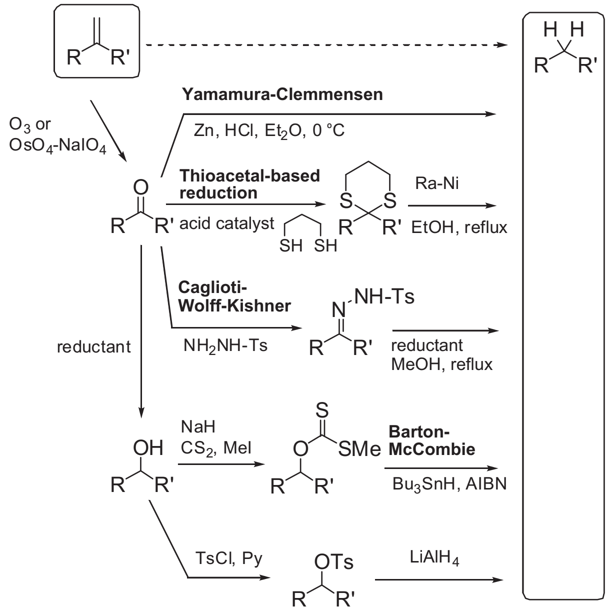

Figure 1. The reductive cleavage of *exo*-olefin to methylene and its typical methodologies and conditions.

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* Corresponding author. Tel.: +81 22 217 6201; fax: +81 22 217 6204.
E-mail address: arimoto@biochem.tohoku.ac.jp (H. Arimoto).

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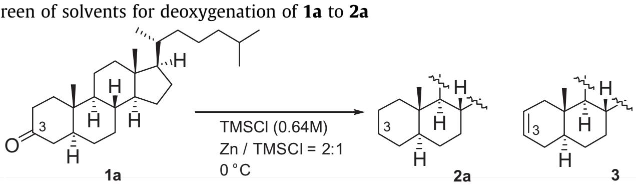
Table 1
Screen of solvents for deoxygenation of **1a** to **2a**

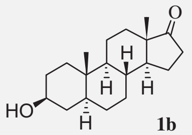
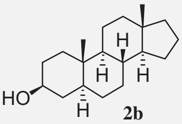
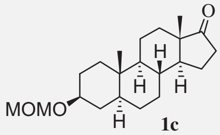
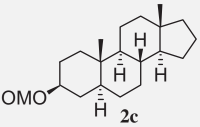
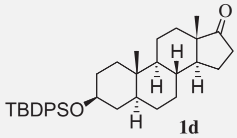
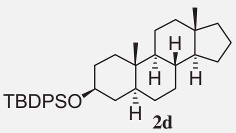
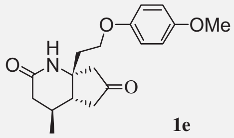
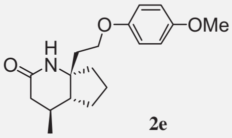
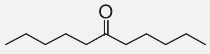
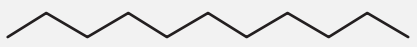
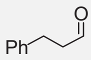
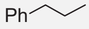


1a **2a** **3**

Entry	Solvent	Condition	Ratio of **2a** and **3**[a]	Yield[b] (%)
1	DCM	H_2O (3 equiv), 3 h	3:5[c]	n.d.
2	*i*PrOC(O)*i*Pr	H_2O (3 equiv), 0.5 h	4:1	n.d.
3	EtOAc	H_2O (3 equiv), 1 h	20:1	n.d.
4	DMA	H_2O (6 equiv), 10 h[d,e]	50:1	n.d.
5	THF	H_2O (3 equiv), 1 h	>50:1	82
6	MeOH	6 h	>50:1[f]	n.d.
7	*i*PrOH	1.5 h	>50:1	79
8	*i*PrOH	H_2O (4.5 equiv), 3 h[g]	>50:1	73
9	*i*PrOH[h]	3 h[g]	>50:1	86
10	*t*AmylOH	6 h[d]	>50:1	84
11	*i*PrOH/DCM (1:1)	2.5 h[g]	>50:1	81
12	*i*PrOH/DCM (3:1)	3 h	>50:1	86
13	EtOH/DCM (3:1)	5 h[d]	>50:1	84
14	MeOH/DCM (3:1)	8.5 h[i]	>50:1	79

[a] Determined by the integration in ^1H NMR of crude products.
[b] Isolated yield, n.d. = not determined.
[c] Determined by GC–MS.
[d] 1.27 M of TMSCl was used.
[e] The reaction was conducted at room temperature.
[f] Compound **1a** could not be fully consumed with a ratio of 1:4 to compound **2a** determined by GC–MS.
[g] 0.93 M of TMSCl was used.
[h] Dehydrated solvent was used.
[i] 1.87 M of TMSCl was used.

Table 2
Clemmensen reduction with various ketones using TMSCl–Zn in alcoholic solvents[a]

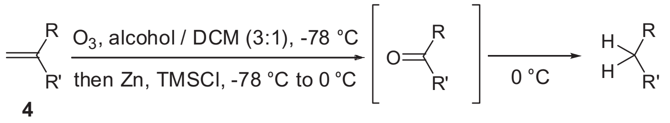
Entry	Ketone	Product	Solvent	Yield[b] (%)
1	 **1b**	 **2b**	MeOH/DCM 1 h	82
2	 **1c**	 **2c**	MeOH/DCM 1 h	94
3	 **1d**	 **2d**	EtOH/DCM 1 h	90
4	 **1e**	 **2e**	*i*PrOH/DCM 1.5 h	77
5	 **1f**	 **2f**	MeOH/DCM 0.5 h	98[c]
6	 **1g**	 **2g**	*i*PrOH/DCM 3 h	28[c]

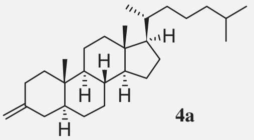
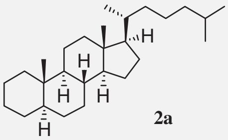
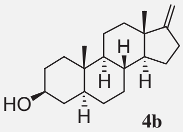
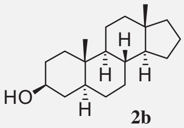
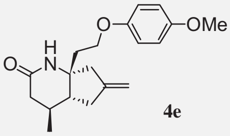
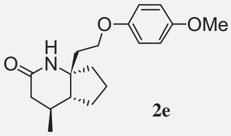
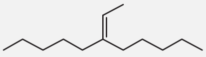
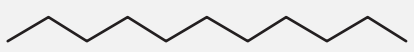
[a] Typical procedure: To ketone (0.20 mmol) in alcohol/DCM (3:1, 20 mL), were added zinc powder (20 mmol) and dropwise TMSCl (20 mmol) under ice-water bath. The reaction mixture was then stirred at 0 °C for the given reaction time. $NaHCO_3$ (24 mmol) was added. After stirring for 5 min, the reaction mixture was filtered and the filtrate was concentrated. The residue was partitioned with $CHCl_3$ and saturated aqueous NH_4Cl. The organic layer was dried with Na_2SO_4, filtered, concentrated, and purified by silica gel column chromatography to afford the pure product.
[b] Isolated yield.
[c] Determined by GC–MS.

Chlorotrimethylsilane (TMSCl) with the combination of Zn in dehydrated THF has been used for the reduction of carbonyl compounds to alkenes.[7] In a specific case, this condition was reported to give the Clemmensen products in low yields (∼30%).[8] We found that with some proton sources as the additive, TMSCl–Zn in fact could be an excellent reagent pair for the Clemmensen reduction, even without pre-activation of the zinc metal. A screen of solvents was carried out with cholestan-3-one **1a** as the substrate and the results are summarized in Table 1.[9] With H_2O as the proton source, in aprotic solvents such as dichloromethane (DCM), isopropyl isobutylate (*i*PrOC(O)*i*Pr), EtOAc, and *N*,*N*-dimethylacetamide (DMA), the alkene byproduct **3** could always be detected. In THF (entry 5), the desired compound **2a** was almost the sole product with good isolated yield. Unfortunately, we failed to apply THF as the common solvent also for ozonolysis, because, as one of the typical ether-type solvent, its oxidative decomposition could not be ignored as expected.

Finally, alcoholic solvents were found to be excellent for our TMSCl-mediated Clemmensen reduction. The byproduct **3** could only be detected in trace amount, if any. However, in MeOH (entry 6), the reaction was very slow. Even after 6 h, the starting material **1a** still remained in large amount. This might be due to the ketone–methyl acetal equilibrium, which retarded the desired deoxygenation. Though as far as we tried, in this compound case the corresponding methyl acetal could never be directly observed, the existence of acetal was partly supported when *i*PrOH was applied (entry 7). In this case, formation of the hindered isopropyl acetal is expected to be difficult. As a result, in accordance with the

Table 3
One-pot reductive cleavage of olefin with various substrates[a]



Entry	Olefin	Product	Solvent	Yield[b] (%)
1	 **4a**	 **2a**	*i*PrOH/DCM 0.5 h[c]	87
2	 **4b**	 **2b**	MeOH/DCM 1 h	75
3	 **4e**	 **2e**	*i*PrOH/DCM 0.75 h	72
4	 **4f**	 **2f**	MeOH/DCM 1 h	86[d]

[a] Typical procedure: O$_3$ was passed through a solution of olefin (0.20 mmol) in alcohol/DCM (3:1, 20 mL) at −78 °C. After the olefin was fully consumed by TLC check, excess O$_3$ was removed by a stream of Ar for 10 min. At −78 °C, zinc powder (20 mmol) was added followed by dropwise TMSCl (20 mmol). Then the reaction temperature was gradually increased to 0 °C and stirred at 0 °C for the given reaction time. The same workup procedure as in Table 2 was followed to afford the pure product.

[b] Isolated yield.

[c] Zn/TMSCl = 2:1, TMSCl (0.33 M).

[d] Determined by GC–MS.

hypothesis, **1a** was fully consumed within 1.5 h and **2a** could be isolated in good yield. In *tert*-Amyl alcohol (entry 10), **1a** could also be fully consumed, but the reaction became slower. Next, since the ozonolysis is usually conducted at low temperature such as −78 °C, for the solubility reason,[10] the mixed solvent system was studied. From entries 11–14, it was found that with DCM as the co-solvent, common alcoholic solvents all gave good yields without the loss of the selectivity.

The established condition was then applied to various carbonyl compounds to prove the scope and generality. As shown in Table 2,[9] good to excellent yields were obtained with different types of ketones by the appropriate choice of the alcoholic solvent. For compound **1d** (entry 3), the reaction did not complete with *i*PrOH as the co-solvent. Instead, in MeOH, though the reaction was fast, the TBDPS was partly deprotected. Finally, EtOH proved to be the suitable solvent and gave an excellent yield. Compound **1e** (entry 4) is an important synthetic intermediate in our total synthesis of pinnaic acid, a bioactive marine alkaloid.[11] The substrate had been shown to be sensitive to many deoxygenation conditions described in Figure 1. Only modest yield (60%) had been obtained with the two-step Caglioti-modified Wolff–Kishner reduction.[4] This time, by the application of our TMSCl-mediated Clemmensen condition with *i*PrOH, 77% yield of **2e** was achieved with simpler operations. Interestingly, unlike compound **1a**, when using MeOH as the co-solvent, in this case, the methyl acetal[12] was confirmed and could be isolated from the reaction system, which was perhaps because of the more stability of cyclopentaone acetal than that of cyclohexanone.

With the successful development of the TMSCl-mediated Clemmensen reduction, combination of it with ozonolysis for the one-pot olefin reductive cleavage was studied. The results are summarized in Table 3.[9] Good to excellent yields were obtained with multi-functionalized substrates. In the case of compound **4e** (entry 3), one-pot 72% yield was obtained compared to the previous three-step 49% result,[11] which showed the feasibility of our method in the complex natural product synthesis. In entry 4, an internal olefin **4f** could also be cleaved and reduced efficiently.

In summary, a one-pot *exo*-olefin reductive cleavage was for the first time developed. This reaction could proceed under a mild condition avoiding the use of hazardous and expensive reagents. During the research process, a TMSCl-mediated Clemmensen reduction in alcoholic solvent was also examined.

Acknowledgments

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9. All the reagents and solvents mentioned in this Letter were used as received from commercial suppliers.
10. At −78 °C, the substrate was poorly soluble in alcoholic solvent.
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12.