Highly efficient synthesis of medium-sized lactones *via* oxidative lactonization: concise total synthesis of isolaurepan†

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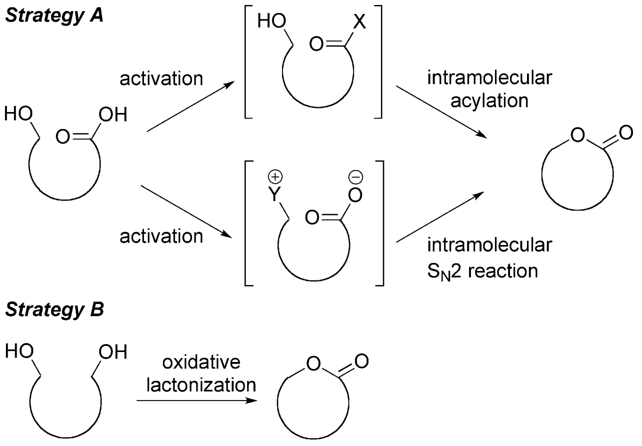
A catalytic amount of TEMPO in the presence of PhI(OAc)$_2$ effected oxidative lactonization of 1,6- and 1,7-diols, directly affording seven- and eight-membered lactones, respectively, in good yields.

Lactone is a common structural motif widely found in biologically active natural products and pharmaceuticals. In addition, a number of synthetic methods for functionalization of lactones are currently available, making them especially useful synthetic intermediates for the preparation of cyclic ethers.[1] Thus, the development of practical synthetic methods for lactones continues to be an important and fundamental research in organic synthesis.[2]

A variety of methods for the synthesis of medium-sized lactones *via* the formation of the ester linkage have been reported, which generally involve activation of an ω-hydroxy acid precursor (Scheme 1, strategy A). However, ω-hydroxy acids are often prepared from differentially protected α,ω-diols *via* multi-step synthesis including oxidations and protective group manipulations. In contrast, the synthesis of lactones *via* oxidative lactonization of α,ω-diols represents a more direct and step-economical strategy due to the fact that oxidation and lactonization occur in a single flask and that protecting group chemistry is not necessary (Scheme 1, strategy B).[3,4] In fact, there has been growing interest in oxidative lactonization of α,ω-diols in recent years. There are a number of precedents that describe oxidative lactonization of 1,4- and 1,5-diols, although most of the reported examples utilized *meso*-diols. In contrast, there are only a few specific examples for oxidative lactonization of seven- and eight-membered lactones[5] presumably because of the increased enthalpic and entropic penalties associated with their formation.[6] Thus, the development of a practical and efficient method for oxidative lactonization of α,ω-diols remains a significant challenge for organic chemists.



Scheme 1 Schematic presentation of lactonization strategies for the synthesis of medium-sized lactones

Herein we report that oxidative lactonization of 1,6- and 1,7-diols using a catalytic amount of TEMPO and PhI(OAc)$_2$ as stoichiometric oxidant[7] proceeds efficiently to provide synthetically useful seven- and eight-membered lactones, respectively, in good yields.[8] The remarkable efficiency of the TEMPO/PhI(OAc)$_2$-mediated oxidative lactonization strategy was highlighted by its successful implementation to a concise total synthesis of (±)-isolaurepan.[9,10]

Piancatelli, Margarita, and co-workers have reported that TEMPO/PhI(OAc)$_2$ oxidizes alcohols to carbonyl compounds in CH$_2$Cl$_2$ at room temperature.[7] Moreover, primary alcohols can be selectively oxidized in the presence of secondary alcohols under these conditions. Forsyth *et al.* have reported the synthesis of δ-lactones by TEMPO/PhI(OAc)$_2$ oxidation of 1,5-diols.[3j] Based on these precedents, we investigated the scope of the TEMPO/PhI(OAc)$_2$-mediated oxidative lactonization[8] by using various substrates with or without conformational constraint (Table 1). In contrast to the previous synthesis of **2**[11] that relied on Yamaguchi lactonization[12] of the corresponding hydroxy acid using a high-dilution technique, the TEMPO/PhI(OAc)$_2$-mediated oxidative lactonization directly afforded **2** from 1,6-diol **1** in 93% yield under non-high-dilution conditions (0.1 M) (entry 1). Even under a higher concentration (0.3 M) and on a large scale, **2** was isolated in 83% yield after single recrystallization, and the formation of dimer or higher oligomers was not observed (entry 2). Hence we were able to synthesize >15 grams of **2** in a single experiment. Importantly, **2** is a versatile intermediate in the synthesis of marine polycyclic ethers.[13] A variety of 1,6-diols **3**, **5**, **7**, **9**, **11**, **13**, and **15** could be cleanly oxidized under the TEMPO/PhI(OAc)$_2$ conditions to afford the respective seven-membered lactones **4**, **6**, **8**, **10**, **12**, **14a**,**b**, and **16**[4n] in good to excellent yields (entries 3–10).‡ Oxidative lactonization of 1,6-diol **17** required some optimization. Treatment of **17** with 10 mol% of TEMPO and 2.5 equiv of PhI(OAc)$_2$ in CH$_2$Cl$_2$ (0.1 M, room temperature) gave the desired lactone **18** in 40% yield (entry 11). Increasing both the amount of the reagents and the concentration of the reaction mixture was beneficial, giving **18** in 69% yield (entry 12). Thus, it seems that TEMPO/PhI(OAc)$_2$-mediated oxidative lactonization is generally applicable to the synthesis

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† Electronic supplementary information (ESI) available: Representative experimental procedure and spectroscopic data for all newly synthesized products. See DOI: 10.1039/b919673k

Table 1 Oxidative lactonization of various α,ω-diols

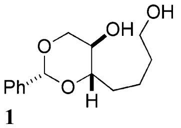
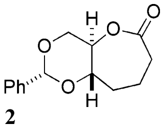
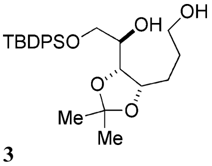
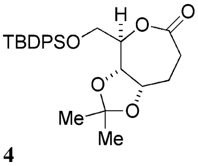
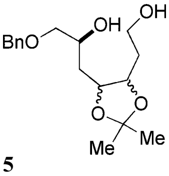
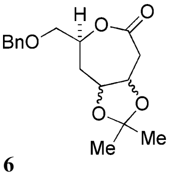
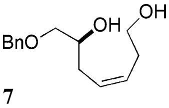
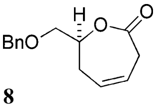
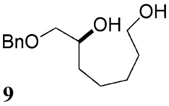
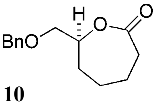
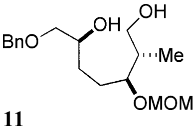
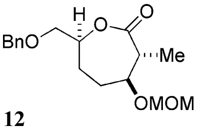
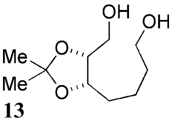
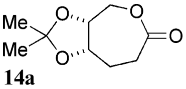
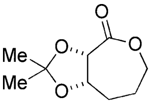
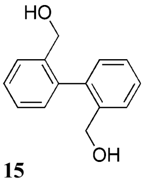
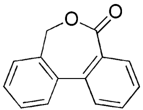
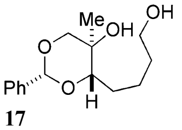
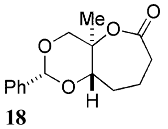
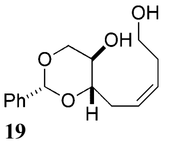
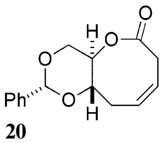
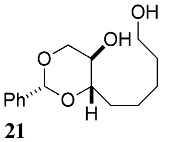
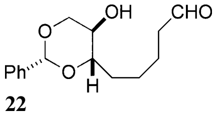
Entry	Diol	Lactone	Yield%
1[a]	 **1**	 **2**	93
2[b]			83
3[a]	 **3**	 **4**	95
4[a]	 **5**	 **6**	98
5[a]	 **7**	 **8**	85
6[a]	 **9**	 **10**	62
7[c]			76
8[a]	 **11**	 **12**	54
9[a]	 **13**	 **14a**  **14b**	100 (**14a**:**14b** = 51 : 49)
10[a]	 **15**	 **16**	63

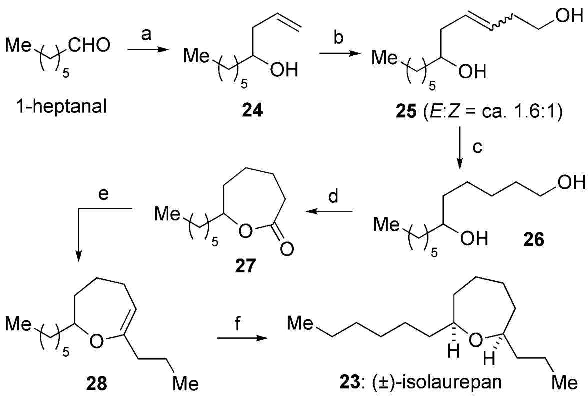
Table 1 (*Contd.*)

Entry	Diol	Lactone	Yield%
11[a]	 **17**	 **18**	40
12[d]			69
13[a]	 **19**	 **20**	67
14[a]	 **21**	 **22**	80

[a] TEMPO (10 mol%), $PhI(OAc)_2$ (2.5 equiv), CH_2Cl_2 (0.1 M), room temperature. [b] TEMPO (20 mol%), $PhI(OAc)_2$ (2.2 equiv), CH_2Cl_2 (0.3 M), room temperature. [c] TEMPO (10 mol%), $PhI(OAc)_2$ (2.5 equiv), CH_2Cl_2 (0.5 M), room temperature. [d] TEMPO (30 mol%), $PhI(OAc)_2$ (5 equiv), CH_2Cl_2 (0.5 M), room temperature.

of seven-membered lactones from 1,6-diols. We were pleased to find that oxidative lactonization of 1,7-diol **19** proceeded to afford eight-membered lactone **20** in good yield (entry 13), which should be useful as an intermediate for the synthesis of eight-membered unsaturated cyclic ether *Laurencia* metabolites, as exemplified by (+)-laurencin.[14] However, 1,7-diol **21** did not give the corresponding eight-membered lactone; instead the hydroxy aldehyde **22** was isolated in 80% yield (entry 14).

The effectiveness of our developed TEMPO/$PhI(OAc)_2$-mediated oxidative lactonization strategy was demonstrated in a concise total synthesis of (±)-isolaurepan (**23**) (Scheme 2).



Scheme 2 Total synthesis of (±)-isolaurepan. *Reagents and conditions*: (a) allylMgCl, THF, 0 °C; (b) 3-buten-1-ol, Grubbs' 2nd-generation catalyst, CH_2Cl_2, 40 °C; (c) H_2, Pd/C, EtOAc, room temperature, 53% (three steps); (d) TEMPO (10 mol%), $PhI(OAc)_2$ (2.5 equiv), CH_2Cl_2 (0.1 M), room temperature, 73%; (e) KHMDS, $(PhO)_2P(O)Cl$, HMPA, THF, −78 °C; then *n*-PrMgBr, CuI, Me_2S, −30 °C; (f) TMSOTf, Et_3SiH, CH_2Cl_2, 0 °C, 74% (two steps).

The synthesis commenced with allylation of 1-heptanal to give homoallylic alcohol **24**. Olefin cross-metathesis[15,16] of **24** with 3-buten-1-ol afforded olefin **25** as a 1.6 : 1 mixture of *E*/*Z* isomers, which was hydrogenated to deliver diol **26** in 53% overall yield.[17] Treatment of diol **26** with 10 mol% of TEMPO and 2.5 equiv of $PhI(OAc)_2$ in CH_2Cl_2 (0.1 M) at room temperature directly afforded seven-membered lactone **27** in 73% yield. Introduction of a propyl side chain was achieved *via* the intermediacy of a lactone-derived enol phosphate. Thus, enolization of lactone **27** with KHMDS in the presence of $(PhO)_2P(O)Cl$ generated the corresponding enol phosphate, which without isolation was alkylated using an organocopper reagent.[18] The resulting enol ether **28** was sensitive to hydrolysis during chromatographic purification. Thus, upon isolation, **28** was immediately treated with TMSOTf/Et_3SiH to furnish (±)-isolaurepan (**23**) in 74% overall yield from **27** as a single diastereomer. The ^1H, ^{13}C NMR, and HRMS spectra of synthetic **23** matched those reported in the literature.[9,10] The present total synthesis proceeded in only six steps from 1-heptanal with an overall yield of 29%, which constitutes the most concise and high-yielding synthesis hitherto reported.

In summary, we have developed an efficient method for the synthesis of medium-sized lactones based on the TEMPO/$PhI(OAc)_2$-mediated oxidative lactonization of α,ω-diols, which is operationally simple and cost effective and proceeds cleanly even under high concentration conditions without the formation of dimer or higher oligomers. In addition, the TEMPO/$PhI(OAc)_2$-oxidative lactonization strategy alleviates protective group chemistry as well as separate oxidation steps. These features highlight the efficiency and practicality of the oxidative lactonization strategy, being suitable even for multi-gram scale preparation of synthetically useful medium-sized lactones. The remarkable efficiency of the synthesis of (±)-isolaurepan demonstrates the power and usefulness of the oxidative lactonization strategy in the synthesis of medium-sized cyclic ethers.

Acknowledgements

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Notes and references

‡ For oxidative lactonization of **9**, we have also evaluated other oxidation reagents such as Ag_2CO_3 on Celite, PCC, TPAP/NMO, Dess–Martin periodinane, and IBX and found that TEMPO/PhI(OAc)$_2$ is far superior to these oxidants.

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