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Synthesis of 3-oxo oxacycloalkenes by ring closing metathesis

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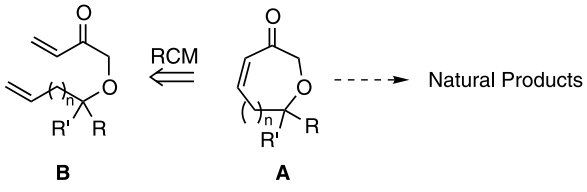
Abstract—The synthesis of six-, seven- and eight-membered 3-oxo oxacycloalkenes by using ring-closing metathesis has been achieved from 1-(ω-alkenyloxy)-but-3-en-2-ones.

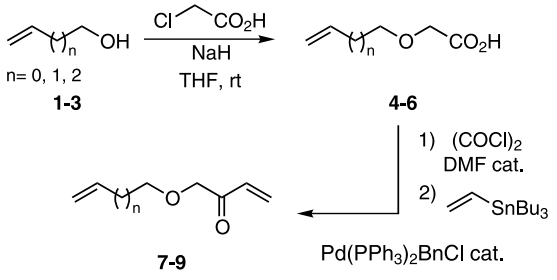
Cyclic ether-containing natural and non-natural products represent architecturally challenging and biologically important molecules[1,2] that have stimulated the development of an array of methods for their synthesis.[3] The number of methods available for the construction of cyclic ethers has steadily increased and among them, ring closing metathesis has proven to be efficient.[3e,4] The aim of this study was to identify a general strategy for the synthesis of functionalized 3-oxo oxacyclic compounds of type **A** as these compounds can be the precursors of cyclic skeleton of a large number of natural products (Scheme 1).[2] Although very few examples of ring-closing metathesis (RCM) reactions involving conjugated ketones were reported,[5] we have decided to examine the reactivity of 1-(ω-alkenyloxy)-but-3-en-ones in the metathesis process for obtaining six-, seven- and eight-membered 3-oxo oxacycloalkenes. Thus, we required a general route to synthesize a broad range of acyclic α-alkoxy enones of type **B** (Scheme 1).

The synthesis of compounds of type **B**, when R = R′ = H, has been accomplished by condensing ω-unsaturated alcohols **1**–**3** with chloroacetic acid under basic conditions (NaH, 2.2 equiv.) in THF at rt (Scheme 2). The corresponding α-alkoxy acetic acids **4**–**6** were obtained in yields greater than 50%. The transformation of the acids to α-alkoxy enones **7**–**9** was achieved in two steps via the acyl chlorides **4**–**6** [$(COCl)_2$, cat. DMF, benzene, rt, 1 h] which were then treated with tri-*n*-butylvinyltin in the presence of $Pd(PPh_3)_2BnCl$ (0.4 mol%) in HMPA (60°C, 45 min)[6] to afford the desired α-alkoxy enones **7**–**9** in yields greater than 35% (Table 1).

Compounds of type **B**, where R = alkyl or aryl and R′ = H or alkyl, could not be obtained from secondary and tertiary alcohols by using the previous sequence as the coupling reaction of the acyl chlorides with the tri-*n*-butylvinyltin did not lead to the desired α-alkoxy enones of type **B** but to decomposed products. Thus, α-alkoxy enones of type **B** were prepared via the stabilized phosphoranes **15**–**19** (Scheme 3). These latter compounds were obtained by alkylation of the secondary and tertiary alcohols **10**–**14** by using sodium hydride (4 equiv.) with triphenylchloroacetonylphosphorane in THF in yields greater than 48%.[7] The obtained phosphoranes **15**–**19** were converted, respectively, to the α-alkoxy enones **20**–**24** in more than 50% yield by condensation with formaldehyde (Table 2).[7,8] It is worth noting that the access to linear α-alkoxy enones **7**–**9** also proved to be effective by using this methodology.



Scheme 1.



Scheme 2.

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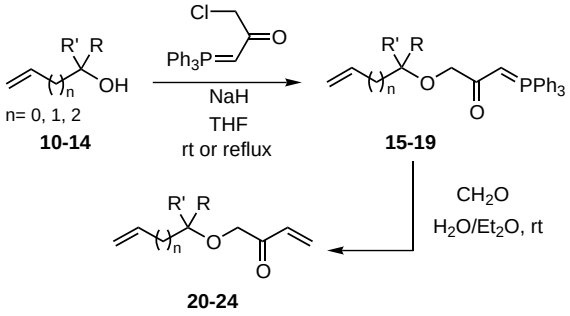
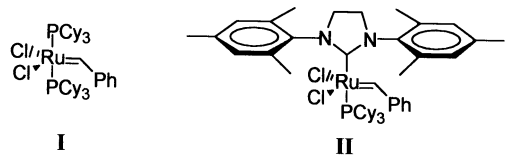
Table 1.

Entry	Alcohol	α-Alkoxy acetic acid		α-Alkoxy enone	
	1–3	Product	Yield (%)	Product	Yield (%)
1	**1** ($n=0$)	**4**	70	**7**	37
2	**2** (n = 1)	**5**	56	**8**	58
3	**3** (n = 2)	**6**	51	**9**	51



Scheme 3.

With the required 1-(ω-alkenyloxy)-but-3-en-2-ones in hand, we set out to investigate the ring-closing metathesis of these compounds. The initial tests were conducted on α-alkoxy enone **8**. With Grubbs' catalyst **I** (Scheme 4),[9] the formation of the cyclic enone was not observed in the absence or in the presence of $Ti(O\textit{i}\text{-}Pr)_4$.[5c,10] However, when **8** was treated with 15 mol% of Grubbs' catalyst **II** (Scheme 4) in refluxing dichloromethane,[11] the starting material was transformed to the cyclic enone **27** in 58% yield (Table 3, entry 3). It was found that 2.5 mol% of catalyst **II** was sufficient to provide **27** in 42% isolated yield (Table 3, entry 4).



Scheme 4.

The other substrates **7**, **9**, **20–24** were examined in the RCM reaction and the results are reported in Table 3. All the reactions were carried out with 2.5 to 10 mol% of Grubbs' catalyst **II**, at the indicated concentrations in refluxing dichloromethane (Scheme 5). In general, it was found that the RCM provided the cyclic compounds in good yields irrespective of the substitution pattern present in the substrates. In general, eight-membered rings are difficult to obtain by using RCM and we were particularly gratified that α-alkoxy enones **9** and **24** were equally effective substrates in the RCM as **31** and **32** were formed (Table 3, entries 8 and 9), even at a concentration of 10^{-2} M.[12]

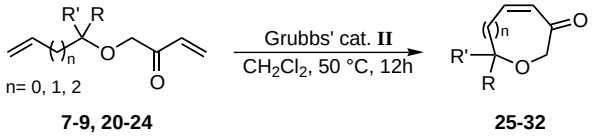
The above metathesis products are well-suited for further manipulations. To demonstrate this point, compound **29** was subjected to a dihydroxylation reaction (OsO_4 cat., NMO, acetone/H_2O) and diol **33** was isolated in 80% yield with a diastereomeric ratio of 95/5. Osmylation presumably occurs on the less hindered face *anti* to the phenyl group (Scheme 6).

To gain entrance to natural products, selective alkylations on **29** were also achieved (Scheme 7). When **29** was subjected to lithium dimethylcuprate, compound **34** was obtained in 60% yield with a diastereomeric ratio of 86/14,[13] and when **29** was treated with LDA in HMPA/THF followed by the addition of methyl iodide at −78°C the monomethylated product **35** was obtained in 48% yield, as a single isomer.[14]

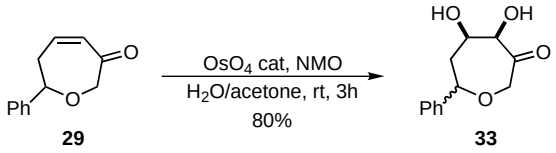
In conclusion, we have shown that 1-(ω-alkenyloxy)-but-3-en-2-ones can readily undergo RCM reaction affording six-, seven- and even eight-membered 3-oxo oxacycloalkenes in good yields. The use of this methodology is currently being investigated in our laboratory for the synthesis of natural products.

Table 2.

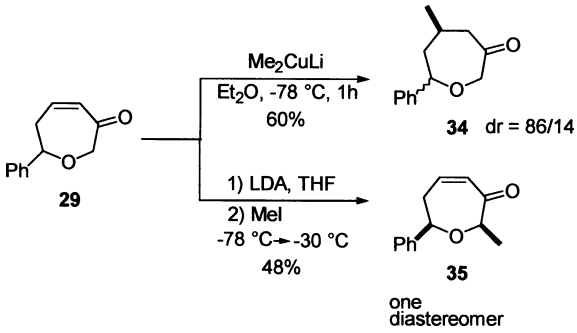
Entry	Alcohol	Conditions		Phosphorane		α-Alkoxy enone	
	10–14	Time (h)	Temp. (°C)	Product	Yield (%)	Product	Yield (%)
1	**10** ($n=0$, R = H, R′ = *i*-Pr)	5	70	**15**	94	**20**	67
2	**11** ($n=1$, R = H, R′ = *i*-Pr)	7	20	**16**	48	**21**	49
3	**12** ($n=1$, R = H, R′ = Ph)	12	20	**17**	70	**22**	73
4	**13** ($n=1$, R = R′ = Me)	1	70	**18**	82	**23**	49
5	**14** ($n=2$, R = H, R′ = *i*-Pr)	6	70	**19**	76	**24**	54



Scheme 5.



Scheme 6.



Scheme 7.

Acknowledgements

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Table 3.

Entry	α-Alkoxy enone	Catalyst II (mol%)	Concn. (mol.L^{-1})	3- Oxo oxacycloalkene Product	Yield (%)
1	**7** (n=0, R=R'=H)	2.5	2×10^{-2}	**25**	69
2	**20** (n=0, R=H, R'=*i*-Pr)	5	4×10^{-3}	**26**	87
3	**8** (n=1, R=R'=H)	15	2×10^{-2}	**27**	58
4	**8**	2.5	2×10^{-2}	**27**	42
5	**21** (n=1, R=H, R'=*i*-Pr)	5	1.3×10^{-2}	**28**	90
6	**22** (n=1, R=H, R'=Ph)	2.5	2×10^{-2}	**29**	93
7	**23** (n=1, R=R'=Me)	4	5×10^{-3}	**30**	67
8	**9** (n=2, R=R'=H)	10	1.3×10^{-2}	**31**	66
9	**24** (n=2, R=H, R'=*i*-Pr)	2.5	1×10^{-2}	**32**	35 + dimer (14%) + oligomers

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12. Head-to-tail oligomers were also observed.
13. The diastereomeric ratio was determined by ^{1}H NMR analysis.
14. Only one diastereomer was detected by ^{1}H and ^{13}C NMR analysis. The relative *cis* stereochemistry of **35** was determined by ^{1}H NMR–NOE analysis.