# Metathesis reactions of β-acyloxysulfones: synthesis of 1,6- and 1,7-dienes

Gregory W. O'Neil *, Daniel J. Moser, Erasmus O. Volz

Department of Chemistry, Western Washington University, Bellingham, WA 98225-9150, USA

## ARTICLE INFO

## ABSTRACT

A novel alkene-masking strategy has been developed that allows for a metathesis approach to 1,6- and 1,7-dienes. This method was successfully applied to the synthesis of a long-chain alkenone natural product.

© 2009 Elsevier Ltd. All rights reserved.

Over the last decade, alkene metathesis has emerged as a powerful carbon–carbon bond-forming reaction in both organic and polymer chemistry.[1] While the reaction has had enormous success in the preparation of a wide range of structurally diverse compounds, only a selected number of examples in polyene systems can be found.[2] This can be attributed to problems of chemoselectivity, specifically the engagement by the metathesis catalyst of one olefin in the presence of another. Several strategies have been employed to overcome this shortcoming, typically by steric and/or electronic deactivation of one or more alkenes toward metathesis.[3] An alternative solution would be to 'mask' an alkene as an inert functional group to be revealed post-metathesis (Fig. 1).[4]

β-Acyloxysulfones are well known intermediates in the classical Julia reaction that can be eliminated to the corresponding predominantly trans di-, tri-, and tetra-substituted alkenes.[5] Metathesis reactions of *alkene*-containing acyloxysulfones **1** followed by elimination would provide diene subunits that are difficult to obtain by standard metathesis technology.

1,6- and 1,7-dienes, important substrates for a variety of cycloisomerization reactions,[6] were chosen as initial targets for this reaction sequence. These compounds are particularly challenging to prepare by cross-metathesis due to a competing rapid ring closure (Fig. 2).[7]

The requisite alkenyl-acyloxysulfones were conveniently prepared by the addition of lithiated sulfone **2** or **3** to an aldehyde followed by in situ acylation of the intermediate alkoxide, affording substrates of type **4** and **5** as approximately 1:1 mixtures of diastereomers (Scheme 1). Benzoic anhydride (Bz$_2$O) was chosen as a trapping agent to allow for a mild and selective elimination with SmI$_2$.[8]

Grubbs' second-generation catalyst **6**[9] proved capable of effecting the desired cross-metathesis, affording exclusively (*E*)-alkenyl-acyloxysulfone adducts as detectable by NMR. Reductive elimination then completed our metathesis approach to 1,6-
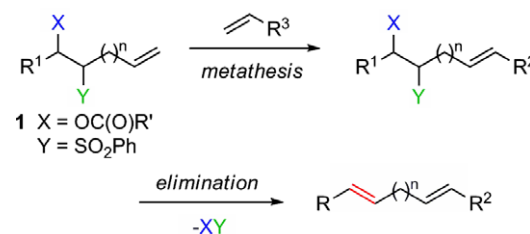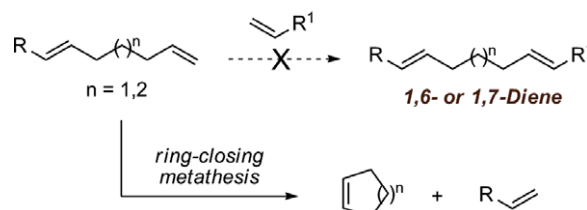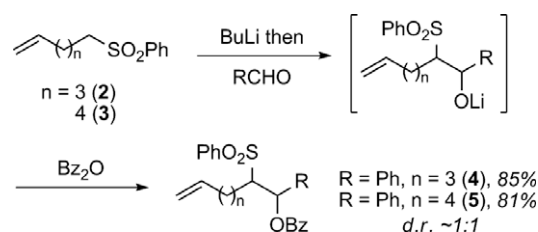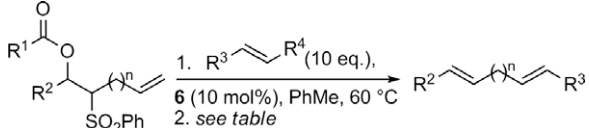


**Figure 1.** Masked diene metathesis.



**Figure 2.** Competing ring-closing metathesis.



**Scheme 1.** Alkenyl-acyloxysulfone synthesis.

($n = 3$) and 1,7-dienes ($n = 4$) as summarized in Table 1. The use of additives such as HMPA along with SmI$_2$ greatly accelerated

* Corresponding author. Tel.: +1 360 650 6283; fax: +1 360 650 2826.
E-mail address: oneil@chem.wwu.edu (G.W. O'Neil).

**Table 1**
1,6- and 1,7-diene synthesis



| | n | R[1] | R[2] | R[3] | R[4] | Cond. | Yield[a] (%) | E,E:Z,E[b] |
|---|---|------|------|------|------|-------|-----------|-----------|
| 1 | 3 | Ph | Ph | CH$_2$OAc | CH$_2$OAc | A | 72 | 7:1 |
| 2 | 4 | Ph | Ph | CH$_2$OAc | CH$_2$OAc | A | 68 | 9:1 |
| 3 | 4 | Ph | Ph | CH$_2$OAc | CH$_2$OAc | B | 61 | 9:1 |
| 4 | 4 | Ph | Ph | H | (CH$_2$)$_5$CH$_3$ | B | 80 | 10:1 |
| 5 | 4 | Ph | Ph | H | (CH$_2$)$_2$C(O)Me | B | 70 | 7:1 |
| 6 | 3 | Ph | n-hex | CH$_2$OAc | CH$_2$OAc | C | 83 | 9:1 |
| 7 | 3 | Me | n-hex | CH$_2$OAc | CH$_2$OAc | C | 85 | 7:1 |
| 8 | 4 | Ph | Ph | CH$_2$OAc | CH$_2$OAc | C | 70 | 7:1 |

Elimination conditions: (A) SmI$_2$ (2 equiv), HMPA (6 equiv), THF −78 °C, 30 min; (B) SmI$_2$ (3 equiv), THF/DMPU (4:1), −78 °C, 1 h; (C) Na/Hg (5%), NaH$_2$PO$_4$, THF/MeOH, rt.
  [a] Yields are for two-steps.
  [b] Ratios determined by ^{1}H NMR.

the rate of elimination, giving the corresponding E,E-dienes in several minutes at −78 °C (entries 1 and 2).[10] Other additives such as DMPU were also suitable for promoting elimination, albeit requiring prolonged reaction times (entries 3–5). Interestingly, alkyl substrates proved less prone to elimination with SmI$_2$ (entries 6 and 7). The corresponding 1,6-dienes were best prepared by post-metathesis elimination with Na/Hg amalgam.[11] Exploitation of this differential reactivity for the preparation of complex intermediates is currently under investigation. Each of the elimination protocols proceeded with comparable yield and trans-selectivity (compare entries 2, 3, and 8).

As a demonstration of this method in the context of natural product synthesis, we set out to prepare one member of a class of natural products that are of great interest to paleoceanographers. Long-chain alkenones are among the most extensively studied class of lipids in marine geochemistry because of their use as proxies for past sea-surface temperatures and global CO$_2$ concentrations.[12] In 2001, Xu et al. reported the isolation of hexatriaconta(16E,21E)-diene-3-one (**7**) as the major component of a mixture of isomeric long-chain alkenone natural products from Holocene Black Sea sediments (Fig. 3).[13] Extensive purification, spectral analysis, and derivatization of **7** revealed an unusual structure with regard to chain-length, alkene location, and double bond spacing when compared to the more common dienones isolated from *Emiliania huxleyi* raising questions as to its origin and biosynthesis.[14]

Formation of the C$_{16}$–C$_{17}$ olefin was envisaged to occur by cross-metathesis. The remaining C$_{21}$–C$_{22}$ alkene would be masked
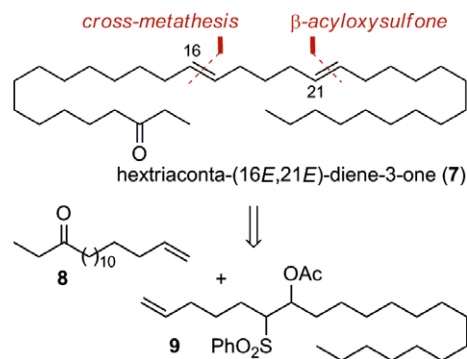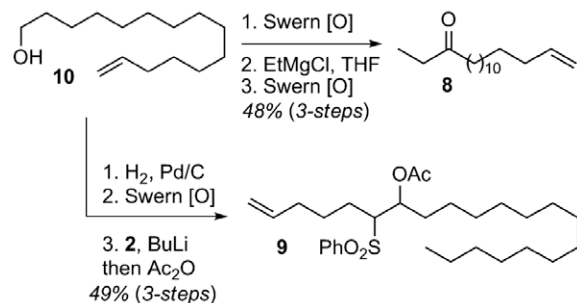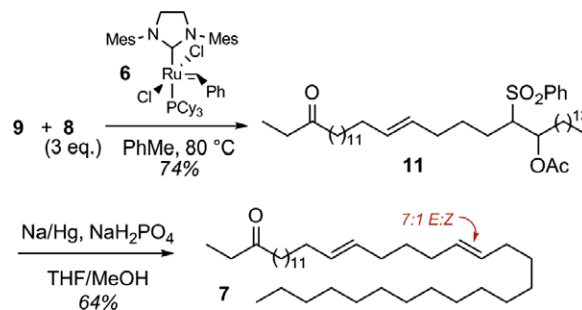


**Figure 3.** Long-chain alkenone natural product **7**.



**Scheme 2.** Fragment syntheses.



**Scheme 3.** Completion of the synthesis.

as the corresponding β-acyloxysulfone giving two key fragments **8** and **9**. Both compounds **8** and **9** were ultimately derived from the same alkenol starting material **10**[15] as depicted in Scheme 2. The synthesis of **8** from **10** was accomplished in three steps by oxidation, ethyl Grignard addition, and reoxidation providing the completed ethyl ketone fragment in 48% overall yield. Alternatively, hydrogenation of **10** followed by oxidation gave an intermediate aldehyde that was immediately treated with the Li anion of sulfone **2**. Trapping of the resulting alkoxide with acetic anhydride then gave an approximately 1:1 diastereomeric mixture of the desired alkenyl-acyloxysulfone **9** in 49% yield for the three steps.

Exposure of alkenyl-acyloxysulfone **9** to catalyst **6** (10 mol %) in the presence of an excess of ketone **8** (3 equiv) in toluene at 80 °C generated the Δ$^{16,17}$-trans alkene affording compound **11** in an optimized 74% yield (Scheme 3). Gratifyingly, treatment of **11** with Na/Hg amalgam in a buffered THF/MeOH solution at room temperature for 1 h resulted in reductive elimination of the β-acyloxysulfone, installing the Δ$^{21,22}$ alkene with 7:1 (NMR) trans-selectivity and completing our synthesis of hexatriaconta(16E,21E)-diene-3-one (**7**). The ^{1}H and ^{13}C NMR data for our synthetic sample matched that reported in the literature thus confirming the structure of this rare natural product.[16]

In summary, a novel alkene-masking strategy has been employed that allows for a metathesis approach to 1,6- and 1,7-dienes. Specifically, metathesis reactions of alkenyl-β-acyloxysulfones followed by reductive elimination afford diene subunits thus circumventing chemoselectivity problems associated with polyene metathesis. This strategy was successfully applied to the synthesis of a long-chain alkenone that is amenable to other members of this class of climatologically interesting natural products. Current efforts are directed at extending this method to other polyene subunits currently unobtainable by standard metathesis technology.

### Acknowledgments

## Supplementary data

Supplementary data (complete analytical data and experimental procedures for the preparation of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.071.

## References and notes

1. (a) *Alkene Metathesis in Organic Synthesis*; Fürstner, A., Ed.; Springer: Berlin, 1998; (b) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003.
2. For select applications in natural product synthesis see: (a) Mitton-Fry, M. J.; Cullen, A. J.; Sammakia, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 1066; (b) Fürstner, A.; Nevado, C.; Waser, M.; Tremblay, M.; Chevrier, C.; Teplý, F.; A, C.; Moulin, E.; Müller, O. *J. Am. Chem. Soc.* **2007**, *129*, 9150.
3. (a) BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6*, 3465; (b) Ferrié, L.; Amans, D.; Reymond, S.; Bellosta, V.; Capdevielle, P.; Cossy, J. *J. Organomet. Chem.* **2006**, *691*, 5456; (c) Funk, T. W.; Efskind, J.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 187.
4. For a recent example of masked alkene metathesis see: Baird, L. J.; Timmer, M. S. M.; Teesdale-Spittle, P. H.; Harvey, J. E. *J. Org. Chem.* **2009**, *74*, 2271.
5. Dumeunier, R.; Markó, I. E. 'The Julia Reaction'. In *Modern Carbonyl Olefination*; Takeshi, T., Ed.; Wiley-VCH: Weinheim, 2004.
6. Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. and references cited therein.
7. Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.
8. (a) Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1990**, *31*, 7105; (b) Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194; (c) Markó, I. E.; Murphy, F.; Dolan, S. *Tetrahedron Lett.* **1996**, *37*, 2089; (d) Markó, I. E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* **2001**, *57*, 2609; (e) Jourdain, P.; Philippart, F.; Dumeunier, R.; Markó, I. E. *Tetrahedron Lett.* **2009**, *50*, 3366.
9. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
10. (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485; (b) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, *34*, 1717.
11. For a recent review of desulfonylation reactions see: Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547.
12. (a) Brassell, S. C.; Eglinton, G.; Marlowe, I. T.; Pflaumann, U.; Sarnthein, M. *Nature* **1986**, *320*, 129; (b) Prahl, F. G.; Wakeham, S. G. *Nature* **1987**, *330*, 367; (c) Jasper, J. P.; Hayes, J. M. *Nature* **1990**, *347*, 462; (d) Eglinton, G.; Bradshaw, S. A.; Rosell, A.; Sarnthein, M.; Pflaumann, U.; Tiedemann, R. *Nature* **1992**, *356*, 423; (e) Jasper, J. P.; Hayes, J. M.; Mix, A. C.; Prahl, F. G. *Paleoceanography* **1994**, *9*, 781.
13. Xu, L.; Reddy, C. M.; Farrington, J. W.; Frysinger, G. S.; Gaines, R. B.; Johnson, C. G.; Nelson, R. K.; Eglinton, T. I. *Org. Geochem.* **2001**, *32*, 633.
14. Rontani, J.-F.; Prahl, F. G.; Volkman, J. K. *J. Phycol.* **2006**, *42*, 800.
15. Hon, Y.-S.; Wang, Y.-C.; Chang, C.-P.; Hsieh, C.-H. *Tetrahedron* **2007**, *63*, 11325.
16. See Supplementary data for details.