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1,4-Dioxene in Organic Synthesis: Rapid Access to the Oxabicyclo[4.2.1]nonene System

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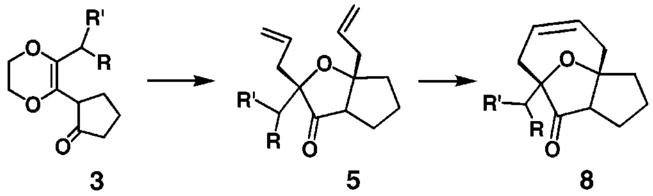
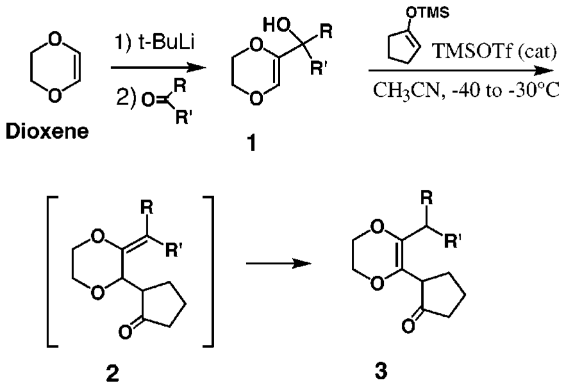
ABSTRACT



Oxidation of 2,3-disubstituted 1,4-dioxenes 3 with *m*-chloroperbenzoic acid in methanol followed by nucleophilic addition of allyltrimethylsilane in the presence of $TiCl_4$ afforded dienes 5, which have been converted to oxabicyclo[4.2.1] nonenes 8 in excellent yield by olefin ring-closing metathesis reaction.

Oxabicyclic compounds have become increasingly important in organic synthesis. Not only are they synthetically useful in their own right, but they might also be used as templates to control the regio- and stereoselectivity in polyfunctionalized cycloalkenes.[1] While a variety of methods for the preparation of oxabicyclo[2.2.1] and oxabicyclo[3.2.1] compounds are reported, few reliable methods for the synthesis of oxobicyclo[4.2.1]nonanes have been published.[2] A ring-opening strategy would result in the conversion of these substrates into functionalized eight-membered ring found in many natural products.[3] In this communication we describe a new approach to 9-oxabicyclo[4.2.1]nonenes based on the chemistry of 1,4-dioxene. Earlier disclosures from this laboratory have demonstrated the utility of 1,4-dioxene (2,3-dihydro-1,4-dioxin) in the formation of carbon−carbon bonds with rapid elaboration of useful functional groups.[4] Thus, addition of dioxenyllithium to ketones and aldehydes leads to allylic alcohols **1**[5] which may be transformed into variety of functionalized compounds via, for example, dehydration, oxidation, or hydrolysis. We recently reported the behavior of **1** toward nucleophilic displacement reactions in the presence of a Lewis acid. For instance, **1** reacts with 1-(trimethylsilyloxy)cyclopentene in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to furnish exclusively **2** as the sole regioisomer which led, after isomerization of the double bond, to 2,3-disubstituted 1,4-dioxene **3** in good yield (Scheme 1).[6]

Scheme 1



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(1) For a recent review, see: Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1−85.

(2) For recent examples, see: Rainier, J. D.; Xu, Q. *Org. Lett.* **1999**, *1*, 1161−1163. Blake, A. J.; Higton, A. J.; Magid, T. N.; Simpkins, N. S. *Org. Lett.* **1999**, *1*, 1787−1789.

(3) For reviews, see: Petasis, N. A.; Patane, M. A. *Tetrahedron*, **1992**, *48*, 5757−5821. Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930.

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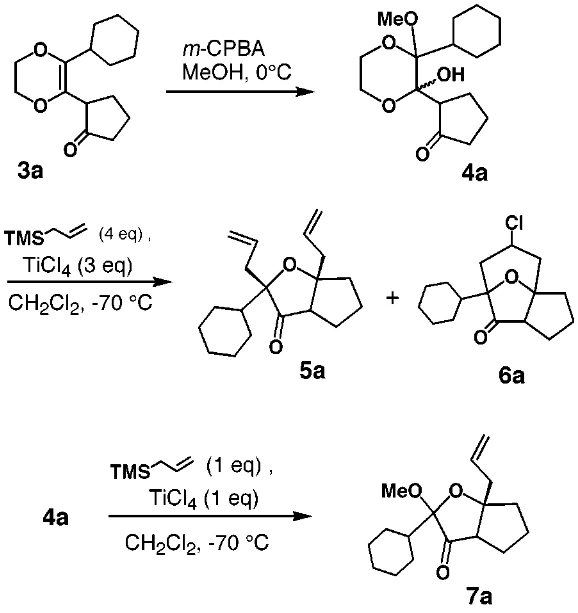
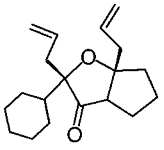
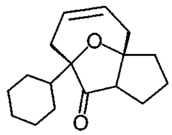
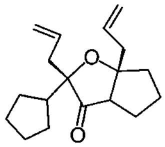
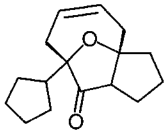
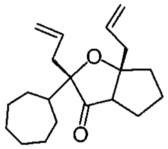
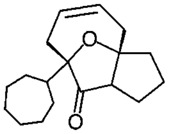
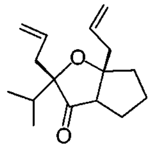
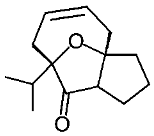
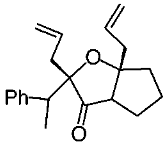
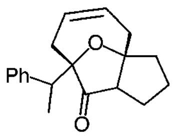
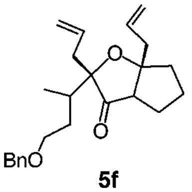
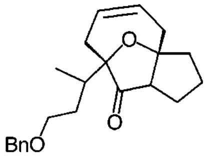
On the basis of a preceding work,[7] we anticipated that Lewis acid-mediated addition of allyltrimethylsilane to acetal **4**, readily prepared from **3**, would release the oxygen funtionalities present in the dioxene ring with simulaneous introduction of new carbon−carbon bonds.[8,9] Initial experiments were carried out on 2-cyclohexyl-3-(ketocyclopentyl) dioxene **3a**. Oxidation of **3a** with *m*-chloroperbenzoic acid (*m*-CPBA) in methanol at 0 °C gave almost exclusively only one acetal as shown by ^{1}H and ^{13}C NMR of the crude product. However, these data did not allow the unambiguous determination of the regiochemistry of the reaction. Structure **4a** was tentatively assigned and was confirmed later in the synthesis (Scheme 2). Treatment of **4a** with excess allyltrimethylsilane (5 equiv) in the presence of titanium tetrachloride ($TiCl_4$) (2.2 equiv) in dichloromethane at −70 °C afforded the syn diallyl product **5a** as *a single diastereoisomer* in 54% overall yield from **3a**. Besides **5a**, a minor product was isolated in 8% yield, and its structure **6a** was assigned on the basis of its spectroscopic data. It is worthy of note that when the allylation reaction was carried out with equimolecular amount allyltrimethylsilane and $TiCl_4$, the monoallyl product **7a** was isolated as the major component (Scheme 2). This result is in agreement with the postulated structure of **4a**.

Scheme 2



Under the same conditions, 2.3-disubstituted 1,4-dioxenes (**3b**−**e**) bearing cyclopentyl, cycloheptyl, isopropyl, or 2-phenethyl groups undergo *m*-CPBA oxidation followed by allylation to give compounds **5b**−**e**, respectively, in 50−55% overall yield from **3** (Table 1). However, with 2-(4-benzyloxybutyl) as substituent, a complex mixture was obtained, from which the expected diallyl compound **5f** was isolated only in poor yield (15−20%).

Table 1. 9-Oxabicyclo[4.2.1] Nonenes 8 from 2,3-Disubstituted-1,4-dioxenes 5 by Ring-Closing Olefin Metathesis

Diene	Product	Yield %
 **5a**	 **8a**	95
 **5b**	 **8b**	94
 **5c**	 **8c**	96
 **5d**	 **8d**	92
 **5e**	 **8e**	97
 **5f**	 **8f**	78

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(4) For a review of the chemistry of 1,4-dioxene, see: Fétizon, M.; Goulaouic, P.; Hanna, I. *Heterocycles* **1989**, *28*, 521−527. For examples on the use of dioxene in synthesis, see: (a) Hanna, I.; Prangé, T.; Zeghdoudi, R. *Tetrahedron Lett.* **1996**, *37*, 7013−7016 and references cited threin. (b) Boger, D.; Zhu, Y. *J. Org. Chem.* **1994**, *59*, 3453−3458. (c) Horito, S.; Amano, M.; Hoshimoto, H. *J. Carbohydr Chem.* **1989**, *8*, 681−684.

(5) Fétizon, M.; Goulaouic, P.; Hanna, I.; Prangé, T. *J. Org. Chem.* **1988**, *53*, 5673−5679.

(6) Hanna, I. *Tetrahedron Lett.* **1999**, *40*, 863. Hanna, I.; Ricard, L. *Tetrahedron Lett.* **1999**, *40*, 2521.

(7) Hanna, I. *Tetrahedron Lett.* **1995**, *36*, 889−892.

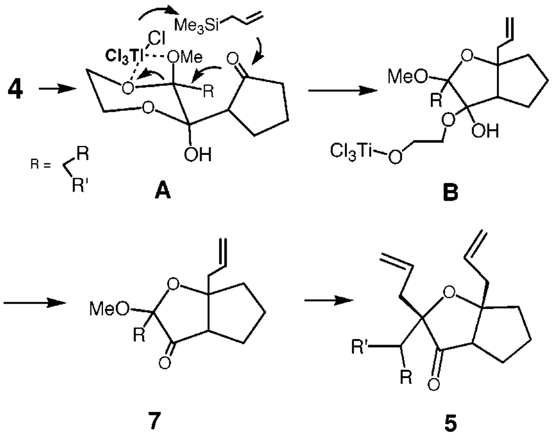
(8) For a review on Lewis acid-mediated addition to acetals, see: Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043−1054.

(9) For addition of allylsilane to α-diketone diketals, see: Pellissier, H.; Santelli, M. *J. Chem. Soc., Chem. Commun.* **1995**, 607−608.

A typical procedure is as follows: to a stirred solution of crude **4** (0.5 mmol) and allyltrimethylsilane (5 mmol) in dry CH_2Cl_2 (4 mL) at −70 °C was added a 1.0 M solution of $TiCl_4$ (1.1 mL). The reaction was monitored by TLC until complete conversion, and the mixture was then quenched with water, extracted with ether, and dried over $MgSO_4$. After evaporation of the solvent, the pure products **5** were isolated by flash chromatography [AcOEt/petroleum ether (1:9 v/v)].

The formation of **5** and **7** can be rationalized as indicated in Scheme 3. We assume that the first allylation of the ketal−Lewis acid complex **A** occurs on the carbonyl group and involves sequential cyclization and dioxane ring-opening leading to intermediate **B**, which could give rise to **7**. At this stage, in the presence of an excess of reagents, further allylation may take place to give the final product **5**.

Scheme 3



Having successfully achieved the $TiCl_4$-mediated domino allylation annulation of **4**, we turned to the carbocyclization of dienes **5** by ring-closing olefin metathesis. This reaction was carried out on **5** by the use of 5% Grubbs catalyst $[RuCl_2(CHPh)(Pcy_3)_2]$[10,11] in CH_2Cl_2 at room temperature (Table 1). In all cases, the expected 9-oxabicyclo[4.2.1]-nonene compounds (**8a**−**f**) were obtained in excellent yield (Table). These reactions also allow the stereochemical outcome of the allylation to be determined.

In conclusion, we found that $TiCl_4$-mediated reaction of allyltrimethylsilane and **4**, readily prepared from 2,3-disubstituted 1,4-dioxenes, provides stereoselectively the diallyl derivatives **5**. These products readily undergo ring-closing metathesis, leading to highly functionalized 9-oxabicyclo-[4.2.1]nonene compounds **8**. Cleavage of the oxa bridge of **8** should lead to the 5,8-fused ring system present in many natural products, in particular the ophiobolin and fusicoccin families.[3] Preliminary investigations have demonstrated the feasibility of this process using single-electron reducing reagents. Further studies are in progress and will be reported in due course.

Supporting Information Available: Spectroscopic data for compounds **5a**−**f**, **6a**, **7a**, and **8a**−**f**. This material is free of charge via the Internet at http://pubs.acs.org.OL005718Y

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[10] Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

[11] For recent reviews concerning ring-closure metathesis reactions, see (a) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.