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Regio- and stereoselective oxidative difunctionalization of alkylidene cyclohexenes

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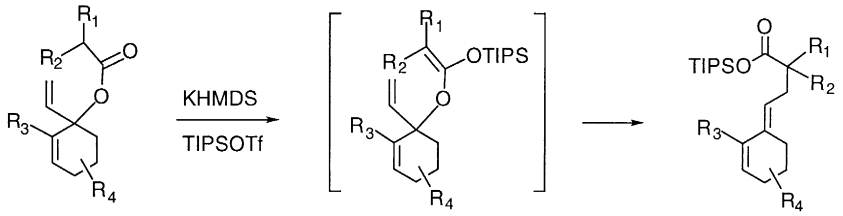
Abstract

Stereo- and regioselective oxidation of alkylidene cyclohexenes affords novel γ-lactones, δ-lactones and related structures.

Keywords: dienes; lactones; lactonization; oxidation.

As part of a general program directed toward the synthesis of a variety of natural products, we have begun developing stereoselective approaches to alkylidene cycloalkenes.[1] For example, we have previously shown that Ireland Claisen rearrangement of bis-allyl silylketene acetals derived from readily accessible bis-allylic esters proceeds exclusively via the *exo* alkene to yield alkylidene cyclohexenes (Scheme 1).[1] We envisioned that oxidation of the diene could be used to install the requisite functionality of various natural product targets[2–4] in a regio- and stereocontrolled manner.



Scheme 1.

Oxidation of cyclic and acyclic dienes to afford 1,2- or 1,4-difunctionalized alkene adducts has been employed extensively in the preparation of a variety of synthetically useful building blocks.[5–11] All possible modes of addition (1,2 and 1,4; *syn* and *anti*) have been observed depending upon the reagent(s) and reaction conditions (Scheme 2).[5–11]

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† Author to be contacted regarding X-ray crystallographic analyses.

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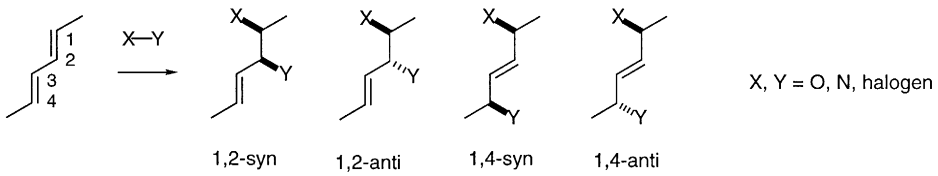
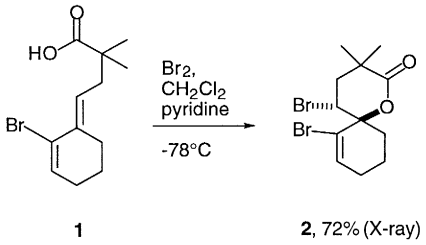


Scheme 2.

Oxidation involving the *exo* double bond of alkylidene cycloalkenes has the potential for control of the relative stereochemistry between the cycloalkene ring and the pendant side chain.[12] We report herein the realization of this approach to the synthesis of 1,2- and 1,4-difunctionalized cyclohexene lactones and related structures.

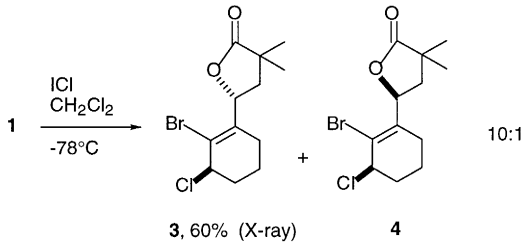
To simplify the initial studies of the oxidation chemistry, an achiral diene with electronically differentiated alkenes was employed. Reaction of various electrophilic oxidants with bromodiene **1**[1] would be expected to occur at the more nucleophilic *exo* alkene (Scheme 3).[13]

Halolactonization of alkenoic acids is a well established method for the synthesis of lactones.[14] Halolactonization of γ–δ enoic acids may afford either γ- or δ-lactones with poor to excellent selectivity depending upon the substitution pattern and reaction conditions.[14] Halolactonization of γ,ε-dienic acids, however, has received very little attention.[15] Bromolactonization of diene **1** afforded exclusively δ-lactone **2** via 6-endo cyclization (Scheme 3).[16]



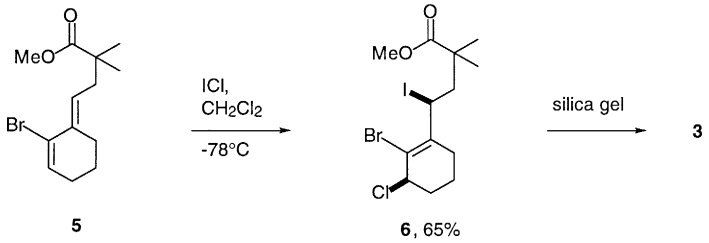
Scheme 3.

By contrast, treatment of diene **1** with ICl yielded solely γ-lactones **3** and **4** as a 10:1 mixture (Scheme 4). The stereochemistry of lactones **2** and **3** were determined unambiguously by X-ray crystallographic analysis.



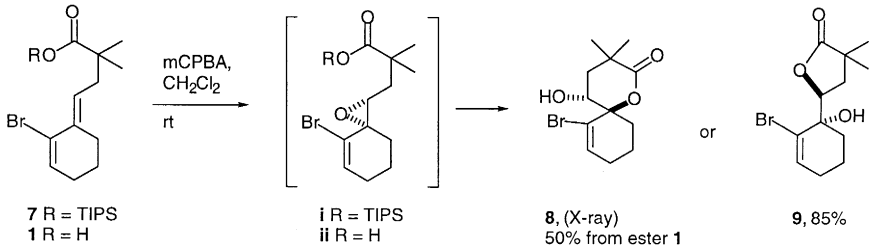
Scheme 4.

The regiochemical outcome of the chlorolactonization reaction apparently resulted from an initial regioselective and *syn*-stereoselective iodochlorination of the diene followed by cyclization via S_N2 displacement of the iodide.[9a,12a] This mechanism was supported by isolation of 1,4-*syn* iodochloride **6** upon treatment of dienic ester **5** under identical conditions (Scheme 5). The *syn* stereochemistry of iodochloride **6** was further supported by its partial lactonization to 1,4-*anti* chlorolactone **3** during silica gel chromatography.



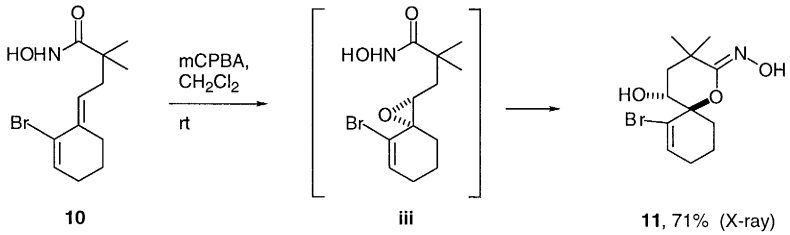
Scheme 5.

Reaction of dienes **1** and **7**[1] with *m*-CPBA led initially to *exo* epoxides **i** and **ii**, respectively, based on ^{1}H NMR analysis of the reaction mixtures (Scheme 6). In situ lactonization occurred over 1 h at rt for acid **ii**, while TIPS ester **i** required ca. 16 h for complete cyclization. Dienic acid **1** yielded only γ-lactone **9** via 5-*exo* cyclization, whereas dienic TIPS ester **7** afforded only δ-lactone **8** via 6-endo cyclization.[17] The structure of lactone **8** was verified by X-ray crystallographic analysis.



Scheme 6.

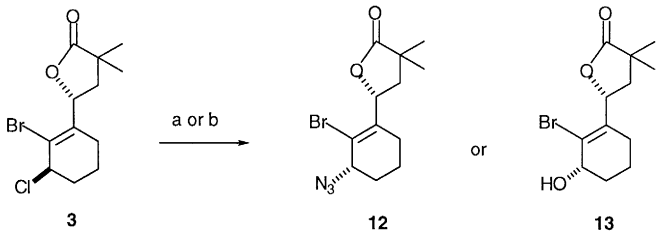
Interestingly, epoxidation of hydroxamic acid **10**, prepared from acid **1** via the corresponding acyl chloride, ultimately afforded (*Z*)-lactone oxime **11** in good yield (Scheme 7). Rapid formation of vinyl epoxide **iii** was followed by in situ cyclization to the oxime over 3 h at rt. This procedure may open a new entry to the synthesis of hydroxylated lactone oximes, which have previously been employed as 1,3-dipoles[18a] and as intermediates in the synthesis of glycosylidene carbenes.[18b]



Scheme 7.

We were also interested in using the oxidation chemistry for the stereoselective preparation of 1,4-diols and 1,4-aminoalcohols. Thus, chlorolactone **3** was converted to 1,4-*syn* azide **12** upon treatment with NaN_3 with 20:1 regioselectivity (ipso versus allylic substitution). Similarly, treatment of chlorolactone **3** with NaOAc and H_2O afforded 1,4-*syn* alcohol **13** with 10:1 regioselectivity (Scheme 8).

In summary, we have demonstrated that oxidation of alkylidene cyclohexenes can be employed in a systematic fashion to obtain 1,2- and 1,4-difunctionalized adducts. Use of the method in the synthesis of various natural products will be reported in due course.



Scheme 8. (a) NaN_3, DMF, rt, 67%; (b) NaOAc, DMF, H_2O, 120°C, 54%

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