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Efficient one-pot *trans*-dihydroxylation of 2*H*-pyrans using dimethyldioxirane (DMD): synthesis of *trans*-3,4-dihydroxy-3,4-dihydro-*O*-methyloctandreolones, orixalone D, and *trans*-3,4-dihydroxy-3,4-dihydromollugin natural products

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Abstract—An efficient one-pot formation of *trans*-diols on 2*H*-pyranyl rings was achieved by dimethyldioxirane in wet acetone. This new methodology was applied to the synthesis of natural products containing *trans*-diol on the pyranyl rings such as *trans*-3,4-dihydroxy-3,4-dihydro-*O*-methyloctandreolones, orixalone D, and *trans*-3,4-dihydroxy-3,4-dihydromollugin.

1. Introduction

Molecules with a *cis*-(**1**–**7**) or *trans*-dihydroxyl group (**8**–**14**) on their 2*H*-pyranyl rings are distributed widely in nature (Fig. 1).[1] These compounds have a variety of interesting biological activities and potential medical applications.[2] This range of important biological activities and properties has stimulated research into the synthesis of molecules with *cis*- or *trans*-dihydroxy groups on the 2*H*-pyranyl ring. In particular, the development of a series of benzopyran-based potassium channel activators has generated considerable interest in the synthesis of *trans*-diols on the 2*H*-pyranyl rings.[3]

We recently reported that $Yb(OTf)_3$ or ethylenediamine diacetate-catalyzed reactions of 1,3-dicarbonyl compounds or resorcinol with α,β-unsaturated aldehydes provide a rapid route to 2*H*-pyrans or benzopyrans.[4] These reactions involve the formal [3+3] cycloaddition for constructing 2*H*-pyran rings. The synthesized

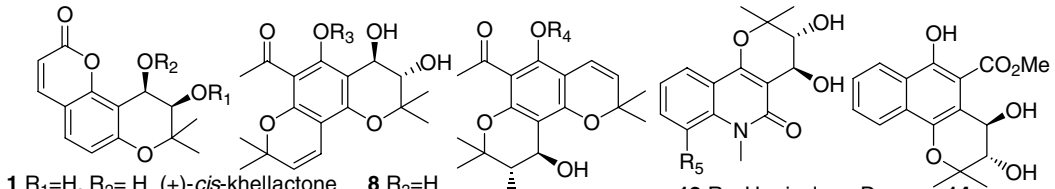

Figure 1. Naturally occurring molecules with *cis*- and *trans*-diol on the pyranyl rings.

Keywords: *trans*-Dihydroxylation; Dimethyldioxirane; *trans*-3,4-Dihydroxy-3,4-dihydro-*O*-methyloctandreolones; Orixalone D; *trans*-3,4-Dihydroxy-3,4-dihydromollugin.
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2*H*-pyrans or benzopyrans appear ideal for making natural products or biologically active materials with *cis*- or *trans*-diols on the pyranyl rings. This Letter reports an efficient and convenient one-pot synthesis of *trans*-diols on the pyranyl rings using dimethyldioxirane. As an application of this methodology, we report the synthesis of biologically interesting natural products as racemates, *trans*-3‴,4‴-dihydroxy-3‴,4‴-dihydro-*O*-methyloctandreolone (**9**),[5] *trans*-3″,4″-dihydroxy-3″,4″-dihydro-*O*-methyloctandreolone orixalone D (**11**),[6] and *trans*-3,4-dihydroxy-3,4-dihydromollugin (**14**).[7]

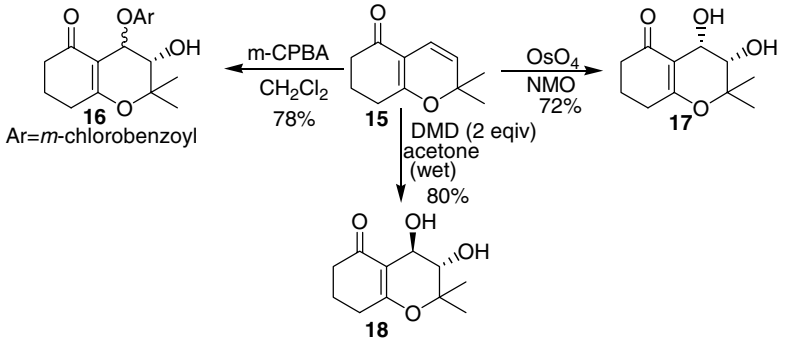
2. Results and discussion

The dihydroxylation of alkenes represents a unique synthetic method for generating 1,2-diols with a defined relative configuration.[8] A number of synthetic approaches for *cis*- and *trans*-dihydroxylation have been reported.[9–13] The most common protocol of *cis*-dihydroxylation is the use of OsO_4, $KMnO_4$, and RuO_4,[9] whereas that of *trans*-dihydroxylation is achieved by the treatment with a suitable peroxycarboxylic acid in a two-step reaction.[10] The reactions first produce an epoxide (oxirane), which then undergoes ring opening through the anti-attack of the corresponding nucleophiles to give *trans*-diols. However, in many cases, monoesters with a hydroxy group due to ring opening of the corresponding carboxylic acid are normally present in the reaction medium and are produced as a mixture of cis and trans-isomers.[10] The hydrolysis of this monoester provides the 1,2-diols as a mixture of cis and trans-isomers. In an attempt to prevent this, hydrogen peroxide and WO_3, SeO_2, V_2O_3, $VO(acac)_2$, and $MeReO_3$ as catalysts have been used as new oxidants to give the trans-diols.[11] An example of this is the reaction using $MMPP/H_2O_2$, which provides mainly *trans*-diols as a 9:1 mixture.[12] Furthermore, Sudalai also developed a 'transition-metal free' procedure for *trans*-dihydroxylation using $PhI(OAc)_2$/LiBr in a two-step reaction.[13] Only one example of dihydroxylation of hydroquinones using dimethyldioxirane is found in the literature.[14] However, in these reactions, 2,3-dihydroxycyclohexene-1,4-diones were obtained as a mixture of cis/trans-isomers along with quinones. In particular, there does not appear to be any efficient and general method for preparing *trans*-diols on the pyranyl rings as a one-pot procedure using dimethyldioxirane.

2*H*-Pyrans **15** and **19**–**28** are easily prepared by the ethylenediamine diacetate-catalyzed condensation of the corresponding 1,3-dicarbonyl compounds with 3-methyl-2-butenal according to a synthetic method reported by our group.[4] The reaction of compound **15** was first investigated using several oxidants (Scheme 1). The epoxidation of compound **15** using mCPBA at room temperature for 10 h in methylene chloride gave the hydroxyester **16** in 78% yield as a 1:1 mixture of cis and trans-isomers. Catalytic osmium tetroxide oxidation using 2 equiv of NMO in *t*-BuOH/THF/H_2O (10:3:1) at room temperature for 24 h gave the *cis*-diol **17** in 72% yield.[15] Interestingly, the treatment of compound **15** with 2 equiv of DMD in wet acetone at room temperature for 3 h provided the *trans*-diol **18** in 80% yield without any of the *cis*-diol **17**.[16] The stereochemical assignment of cis and trans products was easily defined by the observation of the coupling constants between the vicinal protons, H3–H4. The *J* value for this H3–H4 vicinal coupling in the cis-isomer **17** is 4.5 Hz, whereas it is 7.7 Hz for the trans-isomer **18**.[17]

In order to extend the utility of this methodology, further reactions of a variety of compounds containing 2*H*-pyranyl rings were investigated. The results are shown in Table 1. A reaction between compound **19** and DMD in wet acetone at room temperature for 3 h gave compound **29** in 83% yield (entry 1). The treatment of biologically active dehydro-α-lapachone (**20**), isolated from *Zeyhera tuberculosa*,[18] with DMD at room temperature for 3 h afforded compound **30** in 78% yield (entry 2). Similarly, a reaction with compound **21** at room temperature for 3 h gave product **31** in 63% yield (entry 3). In the cases of biologically interesting pyranocoumarins **22**–**23** and pyranoquinolinones **24**–**27**, the expected products **32**–**37** were produced in 66–90% yields (entries 4-9). In the case of precocene I (**28**), product **38** was obtained in 61% yield (entry 10). These reactions provide a rapid route for the synthesis of *trans*-diols on the 2*H*-pyranyl rings.

An attempt was made to synthesize the naturally occurring materials, *trans*-3‴,4‴-dihydroxy-3‴,4‴-dihydro-*O*-methyloctandreolone (**9**), *trans*-3″,4″-dihydroxy-3″,4″-dihydro-*O*-methyloctandreolone (**11**), orixalone D (**12**), and *trans*-3,4-dihydroxy-3,4-dihydromollugin (**14**) as racemates using this methodology. *trans*-3‴,4‴-Dihydroxy-3‴,4‴-dihydro-*O*-methyloctandreolone (**9**) are



Scheme 1.