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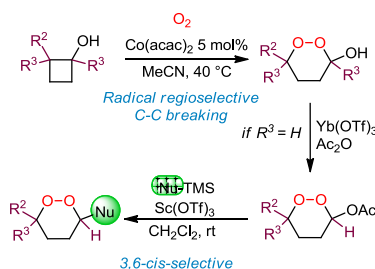
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Oxidative Ring Expansion of Cyclobutanols: Access to Functionalized 1,2-Dioxanes

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Supporting Information Placeholder



ABSTRACT: Cyclobutanols undergo an oxidative ring expansion with $\text{Co}(\text{acac})_2$ and triplet oxygen to give 1,2-dioxanols. The formation of an alkoxy radical drives the regioselective cleavage of the ring on the more substituted side before insertion of molecular oxygen. The reaction is particularly effective on secondary cyclobutanols but works also on certain tertiary alcohols. Further substitution with neutral nucleophiles under catalytic Lewis acid conditions led to original 1,2-dioxanes with a preferred 3,6-*cis*-configuration.

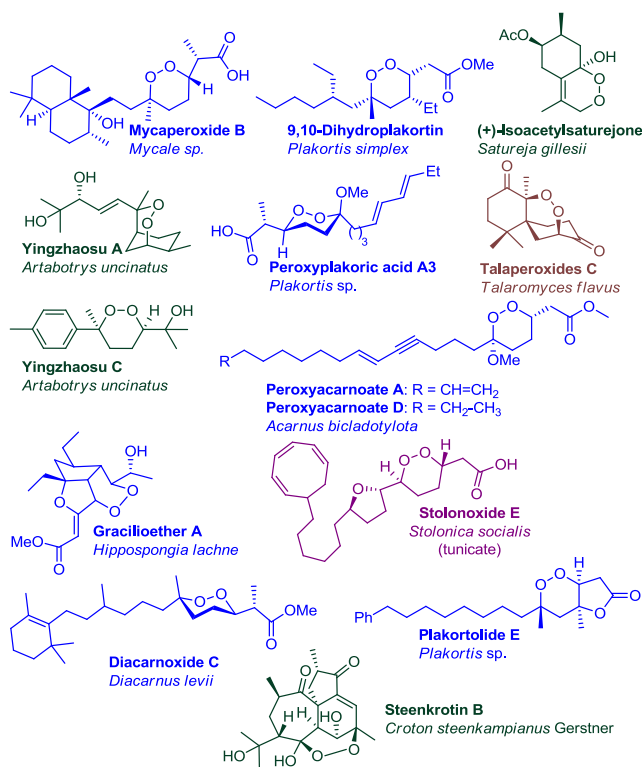


Figure 1. 1,2-Dioxane natural products involved in total synthesis studies (In blue, isolated from sponges; in purple, from other marine species, in green, from plants; in brown from fungi).

1,2-Dioxanes are a particular example of endoperoxides, which can be found in many natural products. They are mainly isolated from various sponges but also from other marine species, plants, and fungi.¹ Most of natural dioxanes display anti-parasitic, antifungal, or cytotoxic activities. Although hundreds of these natural substances were reported with more or less variety in their structures, relatively few works were driven towards their total synthesis.

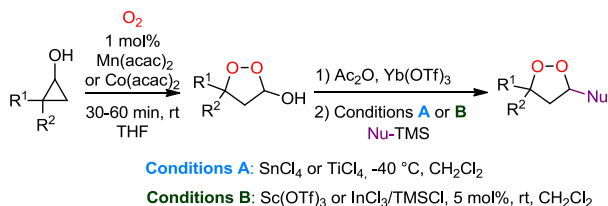
Many of these synthetic studies were targeting natural products isolated from marine species, and more specifically marine sponges. Indeed, sponges are known to be a tremendous pool for endoperoxides, and 1,2-dioxanes represent a large part of them. Nevertheless, other natural products with a 1,2-dioxane scaffold, produced by other marine species, fungi or plants, were studied for their total synthesis. Indeed, synthetic works toward mycaperoxyde B,² 9,10-dihydro-plakortin,³ peroxyplakoric acid A3,⁴ peroxyacarnate A&D,⁵ graciloether A,⁶ diacarnoxide C,⁷ plakortolide E,^{8,9} stolonoxides,¹⁰ talaperoxides and other derivatives of the chamigrane family,¹¹ isoacetylaturejone,¹² yingzhaosu A^{13,14} & C,^{15,16} and steenkrotin B¹⁷ were accomplished using different strategies to build the key 1,2-dioxane ring (Figure 1).¹⁸

These last years, our group was involved in a scientific program towards the total synthesis of mycangimycin, a polyunsaturated fatty acid containing an uncommon disubstituted 1,2-dioxolane ring.¹⁹ Our strategy was to build the endoperoxide through an oxidative ring expansion of a cyclopropanol to a 1,2-dioxolan-3-ol.^{20,21} We discovered that the corresponding acetate can react with various silylated nucleophiles through either Sakurai or Mukaiyama reactions, catalyzed by strong Lewis acids such as TiCl_4 or SnCl_4 in

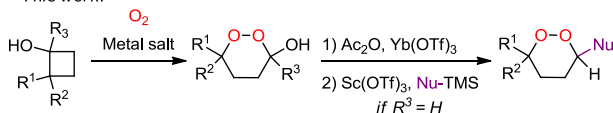
quasi-stoichiometric amounts.²² The process was further improved by the use of milder catalysts, such as $\text{Sc}(\text{OTf})_3$ or $\text{InCl}_3/\text{TMSCl}$ in catalytic amount, which allows one to run the reactions at room temperature with an expanded reagent scope (Scheme 1).²³

Scheme 1. Oxidative ring expansion of strained cycloalkyl alcohols and further functionalization of the endoperoxyacetals.

Previous work:



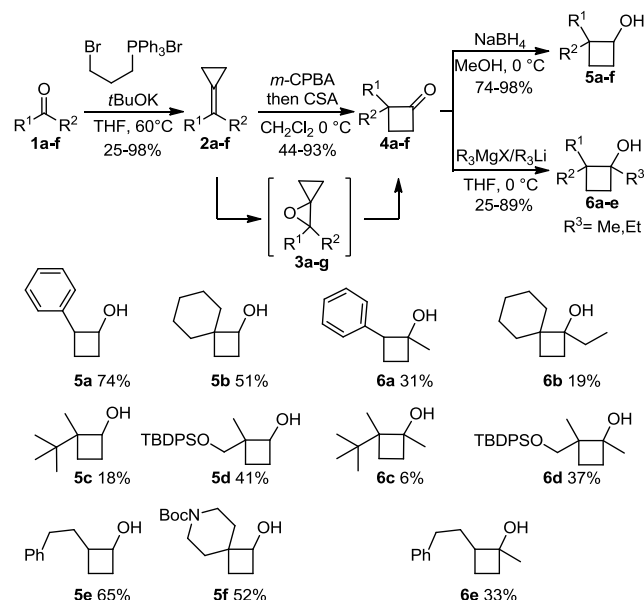
This work:



On the basis of this work, we were wondering if we could apply this strategy to the synthesis of functionalized 1,2-dioxanes. Indeed, Dussault earlier reported the nucleophilic substitution on 6-membered endoperoxyketal rings on 1,2-dioxene derivatives in some pioneering studies.²⁴ In contrast, oxidative ring expansion of cyclobutanols under radical conditions was relatively unknown, and there was concerns that the difference of kinetics between cyclopropoxyl and cyclobutoxyl radicals, by analogy with the cyclopropylmethyl radicals²⁵ and cyclobutylmethyl radicals,²⁶ might not allow the expected transformation in our favor. Nevertheless, a few examples of ring opening of cyclobutoxyl radicals were reported in the literature, driving to the formation of 1,4-diketones under oxidative conditions,²⁷ or to 4-substituted ketone derivatives when the radical is trapped with some good radical acceptors.²⁸ It is also important to note that during the total synthesis of graciloether A, the last key step included a radical transformation of a particularly strained cyclobutane ring into a 1,2-dioxane (Scheme 1).⁶

To study the oxidative ring expansion of cyclobutanols into 1,2-dioxolan-3-ols, the desired starting materials were first prepared. For this purpose, we found that the most general route was based on a Wittig olefination of ketones or aldehydes **1a-f** with a cyclopropyl ylide. Further epoxidation with *m*-CPBA provided unstable spiro-epoxycyclopropanes **3a-f**, which were converted into cyclobutanones **4a-f** through a pinacol rearrangement promoted by acid catalysis.²⁹ On one hand, further reduction with NaBH_4 gave cyclobutanols **5a-f** as a mixture of diastereoisomers. Tertiary alcohols **6a-e** were also synthesized, on the other hand, by addition of an organolithium or organomagnesium reagent onto cyclobutanones **4a-e** (Scheme 2).

Scheme 2. Preparation of 2-substituted cyclobutanols **5a-f** and **6a-e**. Final yields over 4 steps.



A first investigation of the oxidative ring expansion of cyclobutanols was conducted on cyclobutanol **5a**. This substrate was an excellent choice to start the study with, as a driving force of the C-C bond cleavage would be the stabilization of the new radical²⁹ into the intermediate opened product, and a benzene substituent could play perfectly this role.

Table 1. Screening of conditions for oxidative ring expansion of cyclobutanol **5a** into 1,2-dioxane **7a**.

| Entry | Metal salt | (mol%) | Conditions | Solvent | Yield ^a (%) |
|-------|----------------------------|--------|--------------------------|---------|------------------------|
| 1 | $\text{Mn}(\text{acac})_2$ | 1 | rt, 48h | THF | No reaction |
| 2 | $\text{Mn}(\text{acac})_2$ | 5 | rt, 48h | THF | No reaction |
| 3 | $\text{Co}(\text{acac})_2$ | 1 | rt, 24h | THF | 23 ^b |
| 4 | $\text{Co}(\text{acac})_2$ | 5 | rt, 48h | THF | 84 ^b |
| 5 | $\text{Co}(\text{acac})_2$ | 5 | rt, 48h | MeCN | 61 |
| 6 | $\text{Co}(\text{acac})_2$ | 5 | 40°C , 8 h | MeCN | 76 |
| 7 | $\text{Co}(\text{acac})_2$ | 100 | rt | MeCN | 56 |
| 8 | $\text{Co}(\text{acac})_3$ | 5 | rt, 48h | MeCN | traces |

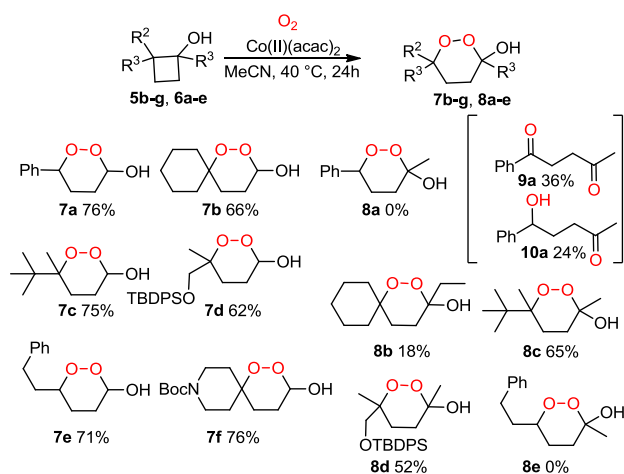
^aIsolated yield as a 60:40 mixture of diastereomers. ^bYield was overestimated because of THF peroxides byproducts contamination.

By using reported conditions for the oxidative ring expansion of cyclopropanols,²⁰⁻²³ it was observed that cyclobutanol **5a** did not react in presence of $\text{Mn}(\text{acac})_2$ (Table 1, entries 1 and 2). Gratifyingly, $\text{Co}(\text{acac})_2$ proved to promote strained cycle cleavage and be able to deliver a small amount of desired product over 48 h (Table 1, entry 3). Almost full conversion was attained with more cobalt salt (Table 1, entry 4), but yield was overestimated because of a large production of THF peroxide byproducts, which contaminated the desired product. These side-products were not observed, in contrast, on the ring expansion of cyclopropanols because of the fast scission process. To overcome this problem we switched THF for MeCN,

which seemed inert to oxidation and allowed the transformation to occur, providing dioxane **7a** in 61% yield after 48 h at room temperature (Table 1, entry 5). Increasing the temperature to 40 °C could decrease significantly the reaction time to 8 h improving the overall process (Table 1, entry 6). Using stoichiometric amount of cobalt(II) salt did not improve significantly the kinetic of the reaction, but lowered the yield due to the appearance of some degradations (Table 1, entry 7). Co(II) salt was essential to this reaction since starting directly from a source of Co(III) proved to be unproductive (Table 1, entry 8).

Oxidative ring expansion was then applied to other cyclobutanols **5b-f** and **6a-e**. Secondary alcohols **5b-f** are, in general, best substrates for such a transformation. Indeed, the reaction works well, with 2,2-disubstituted cyclobutanols **5b-d** and **5f**, affording isolated yields above 60%. Mono-substituted cyclobutanol **7e** were also able to undergo an oxidative ring extension but required a longer reaction time (up to 48 h). We also observed no reaction at room temperature with this last substrate, so heating was necessary in this case. Tertiary alcohols **6a-e** were also examined, and first trials did not lead to good results. Mono-substituted cyclobutanols **6a** and **6e** gave unsatisfactory results: no conversion into dioxane **8e** was observed from **6e**. Isolation of diketone **9a** and hydroxyketone **10a** in 36% and 24% yield, respectively, from cyclobutanol **6a** was experienced in place of dioxanol **8a**. Isolation of these two unexpected products means the reaction was probably working but compound **8a** might undergo a Kornblum-DeLamare rearrangement to form **9a** in one hand, because the benzylic position facilitates an elimination process. In the other hand, hydroxyketone **10a** might have been produced from 1,2-dioxane **8a** by homolytic cleavage of the peroxide bond, but the exact pathway is for the while unclear. In contrast, it was found that 2,2-disubstituted cyclobutanols **5b-d** and **5f** were better substrates for an oxidative ring expansion. However, the rate of the reaction was slower compared to secondary alcohols derivatives **6b-d**, affording the desired products in lower yields with sometimes recovery of unreacted starting materials. This observation was unexpected and might be attributed to steric hindrance for the formation of the cyclobutyloxy radical rather than a decrease of the kinetic of the radical scission. (Scheme 3).

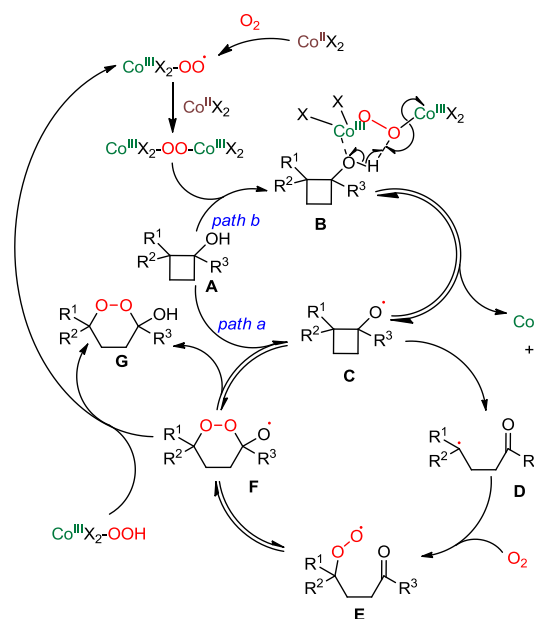
Scheme 3. Diverse attempts towards the synthesis of 1,2-dioxan-6-ols **7b-g** and **8a-e**.



Although similar oxidation was reported in the literature, the exact mechanism has never been determined on how are

formed peroxy radical species.²⁷ It seems plausible that Co(II)(acac)_2 is reacting with oxygen to form a superoxocobalt(III) radical and a μ -peroxocobalt(III) species.³⁰ Indeed the reaction mixture, in presence of oxygen, turns rapidly from light brown color to intense green, which is a characteristic of Co(III) ions. As well, the inability of Co(III)(acac)_3 to promote the reaction, (Table 1, entry 8) indicates the crucial role of these oxocobalt(III) species. Alkoxy radicals are less stable than peroxy radicals by about 4 kJ/mol,³¹ and by consequence makes hydrogen abstraction of a hydroxyl group from **A** an endothermic process. However the strain ring scission which follows, with stabilization of the radical at position 4, is highly exothermic, making the overall process highly favorable [about -71 KJ/mol for scission of *trans*-2-methylthylcyclobutyloxy radical (determined by calculation at B3LYP/6-31+G(d,p)³² level of theory]. Coordination of hydroxyl group to Co(III) species is also very plausible during the hydrogen abstraction step, facilitated by a directed process such as represented in **B**. Moreover, the observed difficulty applying the reaction to tertiary cyclobutanols is consistent with higher steric hindrance of these substrates, which strengthens the hypothesis of a coordination. Regioselectivity in the carbon-carbon bond cleavage to **C** is dependent of the ability of the new site to stabilize the new radical species. Therefore, this driving force explains some differences of reactivity between mono- and di-substituted cyclobutanols. A molecule of $^3\text{O}_2$ is then trapped by the radical, making new peroxy radical **D**, which can evolve between the opened form **E** and the closed one **F**. One or the other form might abstract a hydrogen atom from a new cyclobutanol to propagate the reaction such as in path a or a cobalt(III)hydroperoxide species could reinitiate the process from the beginning such as in path b (Scheme 4).

Scheme 4. Plausible mechanism of the cyclobutanol oxidative ring-expansion.

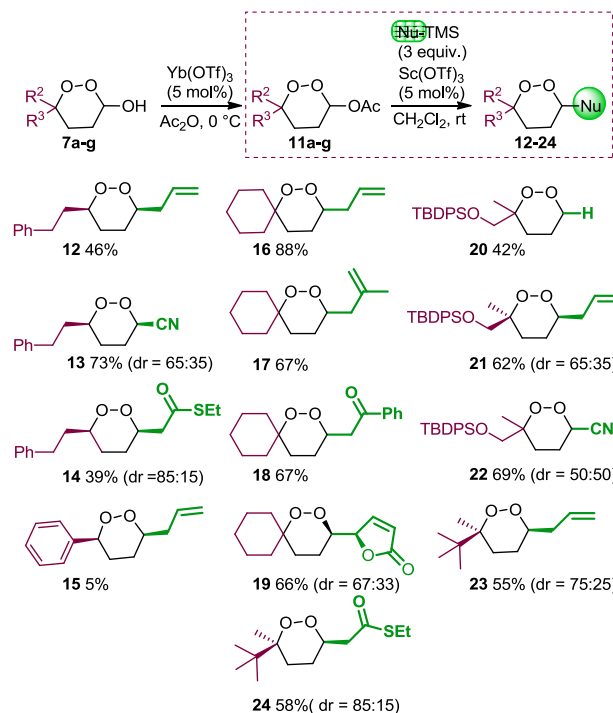


In order to prepare different 1,2-dioxanes, the so obtained 1,2-dioxanols **7a-g** were then acylated using Yb(OTf)_3 as a Lewis acid catalyst to produce different acetate derivatives **11a-g**.^{22,23} Further functionalization of these compounds was initiated with different silylated nucleophiles. The catalytic version of the nucleophilic substitution using Sc(OTf)_3 ²³ was chosen for this screening for a better convenience. The reac-

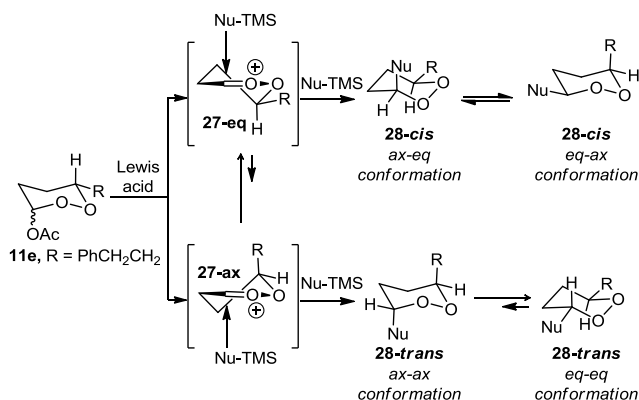
tion of acetate **11e** with allylTMS drove to compound **12** as a sole *cis*-product in 65% yield. In contrast, reaction of acetate **11e** with TMS cyanide was less selective and gave product **13** with only a 65:35 *cis:trans* ratio,³³ while Mukayama aldol reaction with a ketene TMS-thioethylacetal furnished 1,2-dioxane **14** with a quite good diastereoselectivity. The synthesis of allyl 1,2-dioxane **15** from **11a** was achieved in poor yield due to an elimination process, which might take place more easily at the benzylic position, and produced many degradation products.²² Sakurai reactions on acetate **11b** produced compounds **16** and **17** with pretty good yields. Mukaiyama reaction on acetate **11b** with silyl enol ether of acetophenone gave dioxane **18** in good yield, and a vinylogous process was also possible to produce **19** from TMS-siloxyfuran as a 2:1 mixture of diastereomers.³⁴ Reduction of acetal **11d** with triethylsilane furnished compound **20** in moderate yield. With unsymmetrical dialkylated dioxanes **11c** and **11d**, the diastereoselectivity is not as good as with mono-substituted compounds, but generally a major isomer is observed such as in the synthesis of 1,2-dioxanes **21-24**. Carbamate **7f** proved to be unreactive under our used Lewis acid catalysis, due to Lewis base properties of the nitrogen function (Scheme 5).

The diastereoselectivity in this nucleophilic substitution leads to the 3,6-*cis* diastereomer as a major product, in an analogous manner to 4-substituted tetrahydropyranyl acetals.^{35,36} If we consider dioxanyl acetate **11e** for example, reaction with a Lewis acid drives to the formation of peroxycarbenium species, which adopt a half-chair like conformation (Scheme 6).³⁷ This species can evolve between conformations **27-eq** and **27-ax**, depending if the substituent is placed in axial or equatorial position. Because alkyl substituents prefer to adopt an equatorial position, the major reactive conformer must be **27-eq**. A nucleophilic substitution takes then place preferentially to the axial position of the peroxycarbenium species, which lead **27-eq** to compound **28-cis**. In contrast, diastereoselectivity is poorer from 6,6-disubstituted-1,2-dioxannyl acetates where no high selective conformation of **27** could be adopted, excepted for **11c**, which gave decent selectivities due to the bulky *t*-butyl group (75:25 and 85:15 selectivity for **23** and **24** respectively, Scheme 5)

Scheme 5. Functionalization of 1,2-dioxanyl acetates **11a-g**.



Scheme 6. Rationalization of the observed selectivity towards the 3,6-*cis*-diastereoisomer in the nucleophilic substitution of 1,2-dioxanyl acetates.



In conclusion, we developed a new access to 1,2-dioxanes, by using an original approach involving an oxidative ring expansion of cyclobutanols under radical conditions.³⁸ The oxidation is regioselective and its kinetic seems dependent of the ability of the substituents to stabilize an intermediate alkyl radical. The process seems to work particularly well with secondary alcohols even if specific examples of tertiary alcohols can also moderately work sometimes. Further functionalization was then achieved. For instance, the corresponding acetates **11a-g**, by generating reactive peroxycarbenium species, react with neutral nucleophiles to afford expected 1,2-dioxanes, preferentially as the 3,6-*cis* diastereoisomers. This new method is able to provide quickly functionalized 1,2-dioxanes, which would be difficult to prepare by another method. Indeed, this approach would be very valuable for the synthesis of new endoperoxides, but in particular for the total synthesis of natural marine products containing a 1,2-dioxane moiety such as mycaperoxides, stolonoxides, dihydroxylakortides, diacarnoxide C and many others, whose structures seem to correspond to potential targets for its use.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI.

Experimental Procedures, characterization data, cartesian coordinates and energy diagram of *trans*-2-methylcyclobutoxyl radical, pentanal-4-yl radical and their transition state, and copies of ^1H and ^{13}C NMR spectra of all compounds. (PDF).

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Notes

The authors declare no competing financial interest.

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