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

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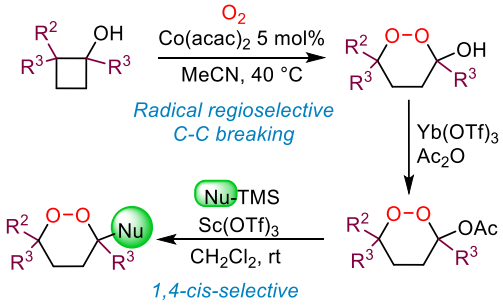


ABSTRACT: Cyclobutanols undergo an oxidative ring expansion into 1,2-dioxanols by using $Co(acac)_2$ and triplet oxygen ($^3O_2$) as radical promoters. The formation of an alkoxy radical drives to the regioselective break of the strained ring with stabilization of a new radical on the most substituted side. The radical traps then oxygen to form 1,2-dioxanols. The reaction is particularly effective on secondary cyclobutanols but can work also on tertiary alcohols. Further acetylation generates peroxycarbenium species under catalytic Lewis acid conditions, which react with neutral nucleophiles. Many original 1,2-dioxanes, which would be difficult to prepare by another method, were then obtained with a preferred 3,6-*cis*-configuration. This method provides an interesting access to the total synthesis of many natural endoperoxides.

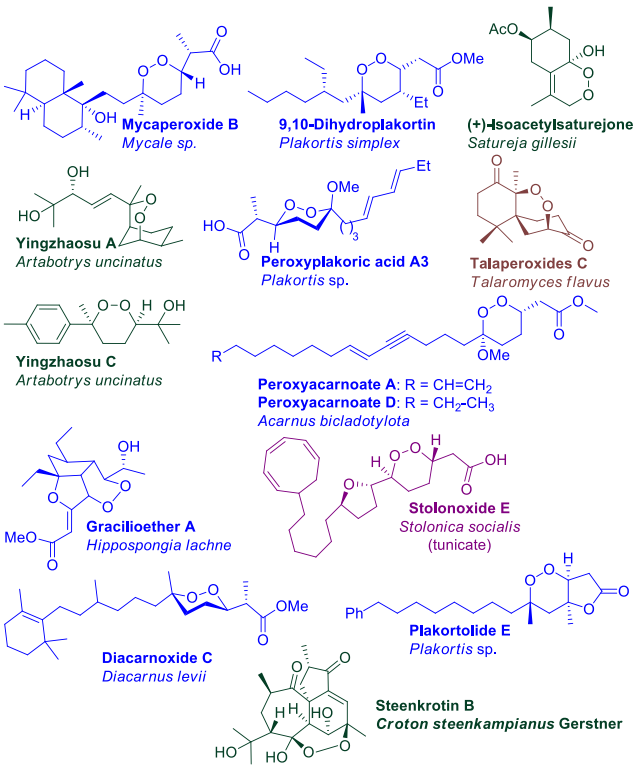


Figure 1. 1,2-Dioxane natural products involved in total synthesis studies (In blue, isolated from sponges; in purple, from other marine species, in green, from plants; in brown from fungi).

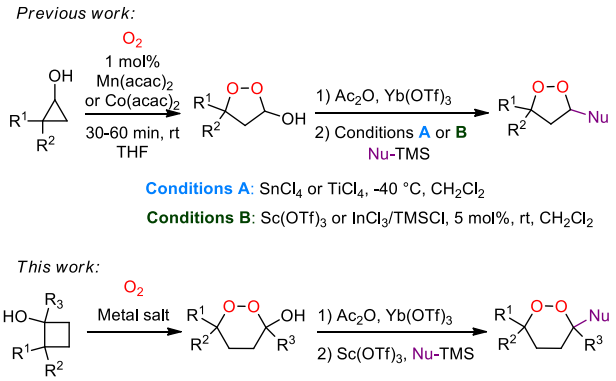
1,2-Dioxanes are a particular example of endoperoxides, which can be found in many natural products. They are mainly isolated from various sponges but also from other marine species, plants, and fungi.[1] Most of natural dioxanes display antiparasitic, antifungal, or cytotoxic activities. Although hundreds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

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] peroxyacarnoate A&D,[5] graciloether A,[6] diacarnoxide C,[7] plakortolide E,[8,9] stolenoxides,[10] talaperoxides and other derivatives of the chamigrane family,[11] isoacetylsaturejone,[12] yingzahosu A[13,14]&C,[15,16] and steenkrotin B[17] were accomplished using different strategies to build the key 1,2-dioxane ring.[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 $Sc(OTf)_3$ or $InCl_3$/TMSCl in catalytic amount, which allows to run the reactions at room temperature with an expanded reagent scope (Scheme 1).[23]

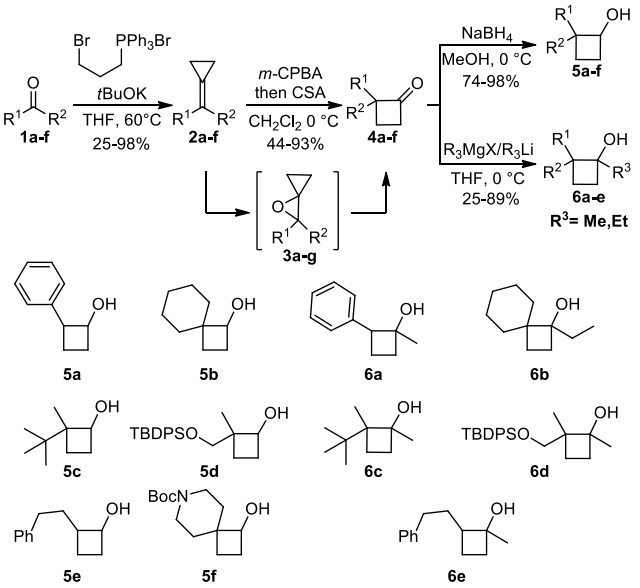
Scheme 1. Oxidative ring expansion of strained cycloalkyl alcohols and further functionalization of the endoperoxyacetals.



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 the difference of kinetics between cyclopropoxy and cyclobutoxy radicals, by analogy with the cyclopropylmethyl radicals[25] and cyclobutylmethyl radicals,[26] might not allow the expected transformation in our favor. Nevertheless, a few examples of ring opening of cyclobutyloxy 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 dioxolane (Scheme 1).[6]

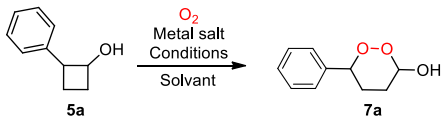
To study the oxidative ring expansion of cyclobutanols into 1,2-dioxolan-3-ols, the desired starting materials were first prepared. For this purpose, we found that the most general route was based on a Wittig olefination of ketones or aldehydes **1a-f** with a cyclopropyl ylide. Further epoxidation with *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**.



A first investigation of the oxidative ring expansion of cyclobutanols was conducted on cyclobutanol **5a**. This substrate was particularly interesting to start the study with, as a driving force of the C-C bond cleavage would be the stabilization of the new radical[29] 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	Solvant	Yield[a] (%)
1	$Mn(acac)_2$	1	rt, 48h	THF	No reaction
2	$Mn(acac)_2$	5	rt, 48h	THF	No reaction
3	$Co(acac)_2$	1	rt, 24h	THF	23[b]
4	$Co(acac)_2$	5	rt, 48h	THF	84[b]
5	$Co(acac)_2$	5	rt, 48h	MeCN	61
6	$Co(acac)_2$	5	40 °C, 8 h	MeCN	76
7	$Co(acac)_2$	100	rt	MeCN	56
8	$Co(acac)_3$	5	rt, 48h	MeCN	traces

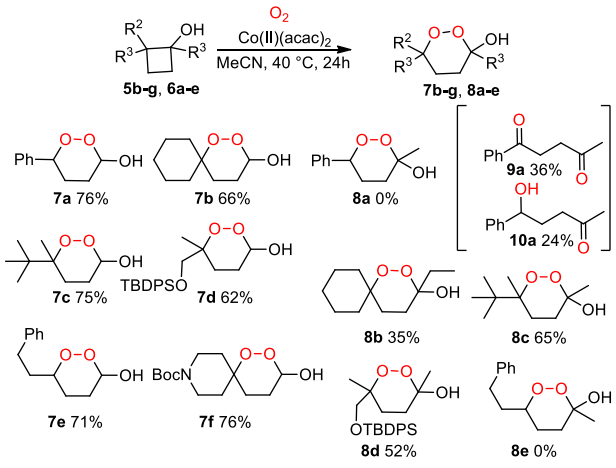
[a]Isolated yield as a 60:40 mixture of diastereomers.[b] Yield was overestimated due to THF peroxides byproducts contamination.

By using reported conditions for the oxidative ring expansion of cyclopropanols,[24-27] it was observed that cyclobutanol **5a** did not react in presence of $Mn(acac)_2$ (Table 1, entries 1 and 2). Gratifyingly, $Co(acac)_2$ 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 due to 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 (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).

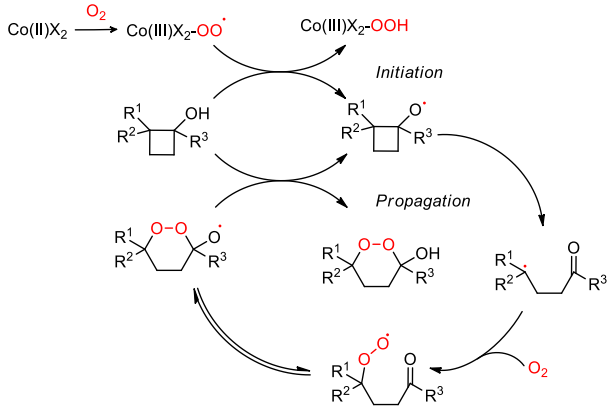
Oxidative ring expansion was then applied to other cyclobutanols **5b-f** and **6a-e**. Secondary alcohols **5b-f** are, in general, best substrates for such a transformation. Indeed, the reaction works well, with 2,2-disubstituted cyclobutanols **5b-d** and **5f**, affording isolated yields above 60%. 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 substrates; meaning heating is a mandatory in that case. Tertiary alcohols **6a-e** were also examined, and first trials were disappointing. 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 kinetic of this process 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 cyclobutoxy radical rather than a decrease of the kinetic of the cyclobutyloxy 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.[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. These species seem then able to abstract an hydrogen from an hydroxy group to produce a new alkoxyradical, which can initiate the strained ring scission with stabilization of the radical at position 4. Regioselectivity in the carbon-carbon bond cleavage is dependant 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 $^3O_2$ is then trapped by the radical, making a new peroxyradical, which can evolve between the opened form and the closed one. One or the other form might abstract a hydrogen from a new cyclobutanol to propagate the reaction. In this case superoxocobalt(III) radical seems to work as an initiator of the reaction rather than a catalyst (Scheme 4).

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

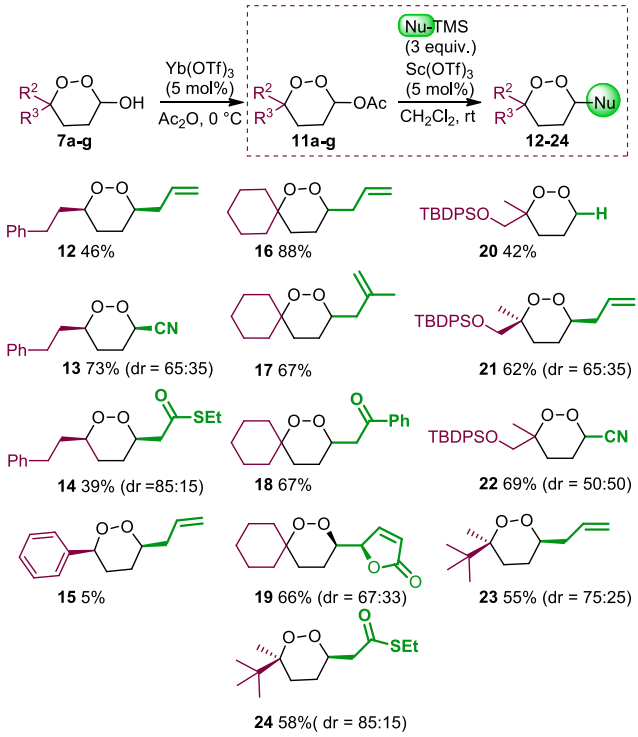


The so obtained 1,2-dioxanols **7a-g** were then acylated using $Yb(OTf)_3$ as a Lewis acid catalyst to produce different acetate derivatives **11a-g**.[26,27] Further functionalization of these compounds was initiated with different silylated nucleophiles. The catalytic version of the nucleophilic substitution using $Sc(OTf)_3$[27] was chosen for this screening for a better convenience. The reaction 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 *cis:trans* 65:35 ratio, 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.[26] Sakurai reaction 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.[31] Reduction of acetal **11d** with triethylsilane furnished compound **20** in moderate yield. With unsymmetrical dialkylated dioxanes **11c** and **11d,** the diasteroselectivity 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).

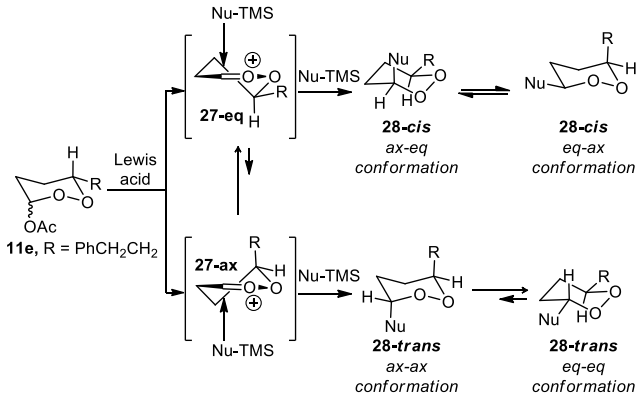
The diastereoselectivity in this nucleophilic substitution leads to the 1,4-*cis* diastereomer as a major product, in an analogous manner to 4-substituted tetrahydropyranyl acetals.[32,33] If we consider dioxanyl acetate **11e** for example, reaction with a

Lewis acid drives to the formation of peroxycarbenium species, which adopt a half-chair like conformation.[34] 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, although **11c** gave decent selectivity's due to the bulky *t*-butyl group (75:25 and 85:15 selectivity for **23** and **24,** respectively). (Scheme 6).

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



Scheme 6. Rationalization of the observed selectivity towards the 1,4 *cis*-diasteroisomer 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. The oxidation is regioselective and its kinetic seems dependant 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 1,4-*cis* diastereoisomers. This new method is able to provide quickly functionalized 1,2-dioxanes, which would be difficult to obtain by another method. Indeed, it 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, dihydroxyplakortides, diacarnoxide C and many others, whose structures seem to correspond to potential targets for its use.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

N.J. and A.P. thank the Ministère de l'Enseignement Superieur, de la Recherche et de l'Innovation (MESRI) for a PhD fellowship. M. M. M. thank th European Union for . We thank Nina Cooper (Université Paris-Saclay) for exploratoring studies, Karine Leblanc for HRMS analysis (BioCIS, Châtenay-Malabry) and Jean-Christophe Jullian (BioCIS, Châtenay-Malabry) for NMR services.

REFERENCES

(1) (a) Liu, D.-Z.; Liu, J.-K. Peroxy Natural Products. *Nat. Prod. Bioprospect.* **2013**, *3* (5), 161–206. https://doi.org/10.1007/s13659-013-0042-7.(b) Casteel, D. A. Peroxy Natural Products. *Nat. Prod. Rep.* **1999**, *16* (1), 55–73. https://doi.org/10.1039/A705725C.

(2) Silva, E. M. P.; Pye, R. J.; Brown, G. D.; Harwood, L. M. Towards the Total Synthesis of Mycaperoxide B: Probing Biosynthetic Rationale. *Eur. J. Org. Chem.* **2012**, *2012* (6), 1209–1216. https://doi.org/10.1002/ejoc.201101477.

(3) Gemma, S.; Gabellieri, E.; Sanna Coccone, S.; Martí, F.; Taglialatela-Scafati, O.; Novellino, E.; Campiani, G.; Butini, S. Synthesis of Dihydroplakortin, 6-Epi-Dihydroplakortin, and Their C10-Desethyl Analogues. *J. Org. Chem.* **2010**, *75* (7), 2333–2340. https://doi.org/10.1021/jo1001559.

(4) Xu, C.; Schwartz, C.; Raible, J.; Dussault, P. H. Asymmetric Synthesis of 1,2-Dioxanes: Approaches to the Peroxyplakoric Acids. *Tetrahedron* **2009**, *65* (47), 9680–9685. https://doi.org/10.1016/j.tet.2009.09.068.

(5) Xu, C.; Raible, J. M.; Dussault, P. H. Total Synthesis of Peroxyacarnoates A and D: Metal-Mediated Couplings as a Convergent Approach to Polyunsaturated Peroxides. *Org. Lett.* **2005**, *7* (12), 2509–2511. https://doi.org/10.1021/ol050291m.

(6) Li, Q.; Zhao, K.; Peuronen, A.; Rissanen, K.; Enders, D.; Tang, Y. Enantioselective Total Syntheses of (+)-Hippolachnin A, (+)-Gracilioether A, (−)-Gracilioether E, and (−)-Gracilioether F. *J. Am. Chem. Soc.* **2018**, *140* (5), 1937–1944. https://doi.org/10.1021/jacs.7b12903.

(7) Schneider, M.-A.; Seifert, K. Towards the Total Synthesis of the Norsesterterpene Diacarnoxide C. *Eur. J. Org. Chem.* **2017**, *2017* (45), 6739–6746. https://doi.org/10.1002/ejoc.201700922.

(8) Jung, M.; Ham, J.; Song, J. First Total Synthesis of Natural 6-Epiplakortolide E. *Org. Lett.* **2002**, *4* (16), 2763–2765. https://doi.org/10.1021/ol026285x.

(9) Barnych, B.; Vatèle, J.-M. Total Synthesis of Seco-Plakortolide E and (−)-Ent-Plakortolide I: Absolute Configurational Revision of Natural Plakortolide I. *Org. Lett.* **2012**, *14* (2), 564–567. https://doi.org/10.1021/ol203185f.

(10) Hu, L.; Lu, X.; Deng, L. Catalytic Enantioselective Peroxidation of α,β-Unsaturated Aldehydes for the Asymmetric Synthesis of Biologically Important Chiral Endoperoxides. *J. Am. Chem. Soc.* **2015**, *137* (26), 8400–8403. https://doi.org/10.1021/jacs.5b05345.

(11) Chen, H.-J.; Wu, Y. Expeditious Entry to the Chamigrane Endoperoxide Family of Natural Products. *Org. Lett.* **2015**, *17* (3), 592–595. https://doi.org/10.1021/ol503603t.

(12) Snider, B. B.; O'Neil, S. V. Synthesis of (−)-Acetylsaturejol and (+)-Isoacetylsaturejol. *Syn. Comm.* **1995**, *25* (7), 1085–1091. https://doi.org/10.1080/00397919508012671.

(13) (a) Xu, X.-X.; Zhu, J.; Huang, D.-Z.; Zhou, W.-S. Total Synthesis of (+)-Yingzhaosu A. *Tetrahedron Lett.* **1991**, *32* (41), 5785–5788. https://doi.org/10.1016/S0040-4039(00)93555-X. (b) Zhou, W.-S.; Xu, X.-X. Total Synthesis of the Antimalarial Sesquiterpene Peroxide Qinghaosu and Yingzhaosu A. *Acc. Chem. Res.* **1994**, *27* (7), 211–216. https://doi.org/10.1021/ar00043a005.

(14) Szpilman, A. M.; Korshin, E. E.; Rozenberg, H.; Bachi, M. D. Total Syntheses of Yingzhaosu A and of Its C(14)-Epimer Including the First Evaluation of Their Antimalarial and Cytotoxic Activities. *J. Org. Chem.* **2005**, *70* (9), 3618–3632. https://doi.org/10.1021/jo050074z.

(15) (a) Xu, X.-X.; Dong, H.-Q. Enantioselective Total Syntheses and Stereochemical Studies of All Four Stereoisomers of Yingzhaosu C. *J. Org. Chem.* **1995**, *60* (10), 3039–3044. https://doi.org/10.1021/jo00115a019. (b) Xu, X.-X.; Dong, H.-Q. Enantioselective Total Synthesis of All Four Stereoisomers of Yingzhaosu C. *Tetrahedron Lett.* **1994**, *35* (50), 9429–9432. https://doi.org/10.1016/S0040-4039(00)78561-3.

(16) (a) Boukouvalas, J.; Pouliot, R.; Fréchette, Y. Concise Synthesis of Yingzhaosu C and Epi-Yingzhaosu C by Peroxyl Radical Cyclization. Assignment of Relative Configuration. *Tetrahedron Lett.* **1995**, *36* (24), 4167–4170. https://doi.org/10.1016/0040-4039(95)00714-N.

(17) Xuan, J.; Zhu, A.; Ma, B.; Ding, H. Diastereoselective Synthesis of the Hydroperoxide–Keto Form of (±)-Steenkrotin B. *Org. Lett.* **2018**, *20* (13), 4153–4156. https://doi.org/10.1021/acs.orglett.8b01875.

(18) Terent'ev, A. O.; Borisov, D. A.; Vil', V. A.; Dembitsky, V. M. Synthesis of Five- and Six-Membered Cyclic Organic Peroxides: Key Transformations into Peroxide Ring-Retaining Products. *Beilstein J. Org. Chem.* **2014**, *10* (1), 34–114. https://doi.org/10.3762/bjoc.10.6.

(19) Oh, D.-C.; Scott, J. J.; Currie, C. R.; Clardy, J. Mycangimycin, a Polyene Peroxide from a Mutualist Streptomyces Sp. *Org. Lett.* **2009**, *11* (3), 633–636. https://doi.org/10.1021/ol802709x.

(20) Kulinkovich, O. G.; Astashko, D. A.; Tyvorskii, V. I.; Ilyina, N. A. Synthesis of α,β-Epoxy Ketones from Alkyl- and Arylsubstituted Cyclopropanols. *Synthesis* **2001**, *2001* (10), 1453–1455. https://doi.org/10.1055/s-2001-16089.

(21) Nguyen, T. L.; Ferrié, L.; Figadère, B. Synthesis of 3,5-Disubstituted-1,2-Dioxolanes: Access to Analogues of Mycangimycin and Some Rearrangement Products. *Tetrahedron Lett.* **2016**, *57* (47), 5286–5289. https://doi.org/10.1016/j.tetlet.2016.10.051.

(22) Pinet, A.; Nguyen, T. L.; Bernadat, G.; Figadère, B.; Ferrié, L. Synthesis of 3,5-Disubstituted 1,2-Dioxolanes through the Use of Acetoxy Peroxyacetals. *Org. Lett.* **2019**, *21* (12), 4729–4733. https://doi.org/10.1021/acs.orglett.9b01616.

(23) Pinet, A.; Figadère, B.; Ferrié, L. Access to Functionalized 3,5-Disubstituted 1,2-Dioxolanes under Mild Conditions through Indium(III) Chloride/Trimethylsilyl Chloride or Scandium(III) Triflate Catalysis. *Adv. Syn. Cat.* **2020**, *362* (5), 1190–1194. https://doi.org/10.1002/adsc.201901145.

(24) Dussault, P. H.; Lee, I. Q.; Lee, H.-J.; Niu, Q. J.; Schultz, J. A.; Zope, U. R. Peroxycarbenium-Mediated C−C Bond Formation: Applications to the Synthesis of Hydroperoxides and Peroxides. *J. Org. Chem.* **2000**, *65* (25), 8407–8414. https://doi.org/10.1021/jo991714z.

(25) Beckwith, A. L. J.; Bowry, V. W. Kinetics of Reactions of Cyclopropylcarbinyl Radicals and Alkoxycarbonyl Radicals Containing Stabilizing Substituents: Implications for Their Use as Radical Clocks. *J. Am. Chem. Soc.* **1994**, *116* (7), 2710–2716. https://doi.org/10.1021/ja00086a003.

(26) (a) Tanko, J. M. Rearrangements of Cyclobutanes. In *The Chemistry of Cyclobutanes*; John Wiley & Sons, Ltd, 2006; pp 497–519. https://doi.org/10.1002/0470864028.ch11.(b) Beckwith, A. L. J.; Moad, G. The Kinetics and Mechanism of Ring Opening of Radicals Containing the Cyclobutylcarbinyl System. *J. Chem. Soc., Perkin Trans. 2* **1980**, No. 7, 1083–1092. https://doi.org/10.1039/P29800001083. (c) Ingold, K. U.; Maillard, B.; Walton, J. C. The Ring-Opening Reactions of Cyclobutylmethyl and Cyclobutenylmethyl Radicals. *J. Chem. Soc., Perkin Trans. 2* **1981**, No. 6, 970–974. https://doi.org/10.1039/P29810000970.

(27) Che, C.; Qian, Z.; Wu, M.; Zhao, Y.; Zhu, G. Intermolecular Oxidative Radical Addition to Aromatic Aldehydes: Direct Access to 1,4- and 1,5-Diketones via Silver-Catalyzed Ring-Opening Acylation of Cyclopropanols and Cyclobutanols. *J. Org. Chem.* **2018**, *83* (10), 5665–5673. https://doi.org/10.1021/acs.joc.8b00666.

(28) (a) Wang, S.; Guo, L.; Wang, H.; Duan, X.-H. Alkynylation of Tertiary Cycloalkanols via Radical C–C Bond Cleavage: A Route to Distal Alkynylated Ketones. *Org. Lett.* **2015**, *17* (19), 4798–4801. https://doi.org/10.1021/acs.orglett.5b02353.(b) Guo, L.-N.; Deng, Z.-Q.; Wu, Y.; Hu, J. Transition-Metal Free Alkylarylation of Acrylamides Initiated by Radical C–C Bond Cleavage of the Tertiary Cycloalkanols. *RSC Adv.* **2016**, *6* (32), 27000–27003. https://doi.org/10.1039/C6RA03431D. (c) Wang, J.; Huang, B.; Shi, C.; Yang, C.; Xia, W. Visible-Light-Mediated Ring-Opening Strategy for the Regiospecific Allylation/Formylation of Cycloalkanols. *J. Org. Chem.* **2018**, *83* (17), 9696–9706. https://doi.org/10.1021/acs.joc.8b01225. (d) Kurouchi, H.; Singleton, D. A. Labelling and Determination of the Energy in Reactive Intermediates in Solution Enabled by Energy-Dependent Reaction Selectivity. *Nature Chem.* **2018**, *10* (2), 237–241. https://doi.org/10.1038/nchem.2907.

(29) (a) Crandall, J. K.; Paulson, D. R. Small-Ring Epoxides. I. Synthesis and Reactions of a 4-Methylene-1-Oxaspiro[2.2]Pentane Derivative. *J. Org. Chem.* **1968**, *33* (3), 991–998. https://doi.org/10.1021/jo01267a011. (b) McCullough, D. W.; Cohen, T. Preparation of 2-Vinylcyclobutanones Viam-Chloroperbenzoic Acid Oxidation of Allylidenecyclopropanes. *Tetrahedron Lett.* **1988**, *29* (1), 27–30. https://doi.org/10.1016/0040-4039(88)80007-8.

(30) Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. Catalytic Oxidation of Alkylbenzenes with Molecular Oxygen under Normal Pressure and Temperature by N-Hydroxyphthalimide Combined with $Co(OAc)_2$. *J. Org. Chem.* **1997**, *62* (20), 6810–6813. https://doi.org/10.1021/jo9708147.

(31) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. Diastereoselectivity in the Directed Aldol Condensation of 2-Trimethylsiloxyfuran with Aldehydes. A Stereodivergent Route to Threo and Erythro δ-Hydroxy-γ-Lactones. *Tetrahedron Lett.* **1987**, *28* (35), 4037–4040. https://doi.org/10.1016/S0040-4039(01)83855-7.

(32) To determine the relative configuration of each diastereomers, we assumed that the protons at the foot of the peroxide function gives the highest coupling constant for *trans*-isomer, due to a higher probability to be in axial position (see Scheme 6). See also: Phillipson, D. W.; Rinehart, K. L. Antifungal Peroxide-Containing Acids from Two Caribbean Sponges. *J. Am. Chem. Soc.* **1983**, *105* (26), 7735–7736. https://doi.org/10.1021/ja00364a045.

(33) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. Stereochemical Reversal of Nucleophilic Substitution Reactions Depending upon Substituent: Reactions of Heteroatom-Substituted Six-Membered-Ring Oxocarbenium Ions through Pseudoaxial Conformers. *J. Am. Chem. Soc.* **2000**, *122* (1), 168–169. https://doi.org/10.1021/ja993366o.

(34) Woods, R. J.; Andrews, C. W.; Bowen, J. P. Molecular Mechanical Investigations of the Properties of Oxocarbenium Ions. 2. Application to Glycoside Hydrolysis. *J. Am. Chem. Soc.* **1992**, *114* (3), 859–864. https://doi.org/10.1021/ja00029a008.