Synthesis of 3,5-Disubstituted 1,2-Dioxolanes through the Use of Acetoxy Peroxyacetals

Alexis Pinet, Thuy Linh Nguyen, Guillaume Bernadat, Bruno Figadère,
Laurent Ferrié

► To cite this version:

Alexis Pinet, Thuy Linh Nguyen, Guillaume Bernadat, Bruno Figadère, Laurent Ferrié. Synthesis of 3,5-Disubstituted 1,2-Dioxolanes through the Use of Acetoxy Peroxyacetals. *Organic Letters*, 2019, 21 (12), pp.4729-4733. 10.1021/acs.orglett.9b01616 . hal-02271180

HAL Id: hal-02271180

<https://hal.science/hal-02271180>

Submitted on 26 Aug 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Synthesis of 3,5-Disubstituted 1,2-Dioxolanes Through the Use of Acetoxy-Peroxyacetals

Alexis Pinet,[†] Thuy Linh Nguyen,^{†,‡} Guillaume Bernadat,[†] Bruno Figadère,[†] Laurent Ferrié.^{†,*}

[†] BioCIS, Université Paris-Sud, CNRS, Université Paris-Saclay, Chatenay-Malabry, 92290 (France).

[‡] Institute of Marine Biochemistry-Vietnam Academy of Science and Technology (VAST), Cau Giay, Hanoi, Vietnam.

Supporting Information Placeholder

ABSTRACT: The synthesis of acetoxy-endoperoxyacetal derivatives allowed the formation of functionalized 3,5-disubstituted-1,2-dioxolanes through the formation of reactive peroxycarbenium species under Lewis acid mediation. The introduction of a neutral nucleophile such as allylsilanes, silanes, or silyl enol ethers was accomplished with moderate to good yields. The two studied Lewis acids, TiCl₄ and SnCl₄, gave contrasted results. The higher diastereoselectivity towards the *trans* diastereomer in experiments with TiCl₄ as Lewis acid was explained by a faster degradation of the *cis* isomer product, conducting generally to lower yields. A rationalization of this result was supported by calculation.

Organic peroxides are uncommon moieties for natural products.¹ Nevertheless, this pharmacophore is often source of potent biological properties due to the relative reactivity of peroxides. Besides the famous anti-malarial agent, artemisinin, isolated from *Artemisia annua* plant,² many other organisms produce peroxide containing natural products. Particularly, plakinic acids, isolated from sponges *Plakortis* sp., exhibit a fatty acid structure with a 1,2-dioxolane ring between positions 3 and 5 (Figure 1).³ Another characteristic of plakinic acids is that the 1,2-dioxolane ring is 3,3,5,5-tetra-substituted. More recently, we investigated the synthesis of simpler analogues of mycangimycin,⁴ a new peroxide isolated from *Streptomyces* sp. living in symbiosis with insect *Dendrocton frontalis*.⁵ Mycangimycin has a very similar structure compared to plakinic acids but beside its highly conjugated fatty chain, the 1,2-dioxolane ring is only 3,5-disubstituted (Figure 1). This difference of structure is detrimental for the synthesis of this compound. Indeed, the substitution pattern present in the dioxolane ring of plakinic acids facilitates the preparation of such compounds due to the enhanced stabilization of intermediate carbenium or radical species necessary to provide the expected structure.⁶ Precursor of 3,5-tetrasubstituted dioxolane rings can also be double bonds though peroxymercuration,⁷ and here again, the substitution of starting olefins for mycangimycin derivatives is detrimental to the reactivity of the required olefin. For these reasons,

relatively few examples of preparation of 3,5-disubstituted 1,2-dioxolanes are found in the literature.⁶

Peroxycarbenium ions have emerged as a powerful tool for the synthesis of organic peroxides.⁸ Nevertheless, the synthesis of 3,5-disubstituted 1,2-dioxolanes from the corresponding peroxyacetals is still an issue due to a reduced stabilization of the oxycarbenium ion as intermediate. Moreover, disfavoured withdrawing effect by induction of one oxygen atom to the other at the peroxide moiety reduces the ability to stabilize the peroxycarbenium compared to a classical acetal. Indeed, we planned to use in early experiments some reported methodologies from Dussault *et al.*^{8b} to perform the nucleophilic addition to peroxyacetal such as methoxyperoxyketal **6**, which has been prepared from hemiperoxyketal **4** by acid mediated metathesis with MeOH.⁹ However, to our disappointment, we were unable to prepare entity **7** from hemiperoxyacetal **5** (prepared from cyclopropanol by oxidative ring opening with triplet oxygen, see supporting information) and any simple alcohol. By analogy with tetrahydrofurans, we decided to activate the cyclic peroxyacetal as acetate, due to its known excellent leaving group ability.

In the first attempts, we experienced issues to obtain acetate **8** under classical conditions involving pyridine and Ac₂O, but only decomposition was observed, which can explain that a similar structure was scarcely reported.¹⁰ Fortunately the preparation of such a compound was possible by using Lewis acid-

catalysed acetylation condition. With rare earth triflates such as Yb(OTf)₃, we obtained expected acetate **8** in high yield. It is worth noting that stability of this compound is pretty high compared to THF acetate derivatives due to a reduced stabilization of the peroxy-carbenium compared to THF oxycarbeniums, and thus compound **8** can then be generally purified by flash chromatography on silica gel without notable decomposition.

Figure 1. Artemisinin, plakinic acids and mycangimycin

Scheme 1. Activation of endoperoxy-ketals and -acetals.

A Sakurai reaction between peroxyacetal **8** and allyltrimethylsilane **9** was then investigated, searching optimized reaction conditions. Dichloromethane was found to be the most suited solvent for this reaction. TMSOTf or BF₃·OEt₂ were ineffective promoters for this transformation, converting only small amounts of starting material (Table 1, entries 1 and 2). In contrast, SnCl₄ and TiCl₄ were far more promising. Indeed, SnCl₄ gave a high isolated yield of dioxolane **10** (Table 1, entry 4) at –40 °C. At lower temperature (entry 3), the reaction hardly proceeded with recovery of starting material after one hour. Extended reaction time did not improve significantly the yield and/or the diastereoselectivity. At higher temperature, the yields also decreased due to some degradations (Table 1, entries 5 and 6). The observed diastereoselectivity is moderated, in contrast to those observed on 2,4-disubstituted THF derivatives.¹¹ This limited selectivity could be attributed to a competition between two conformers of the peroxy-carbenium species. We also turned our attention to TiCl₄; similarly to SnCl₄ the reaction must be conducted at –40 °C (Table 1, entry 8) rather

than –78 °C (Table 1, entry 7). However, in contrast to SnCl₄, diastereoselectivity for 1,2-dioxolane **10** was largely improved up to 85:15, albeit with a lower yield. To explain this enhancement, we suspected reaction product **10** to endure a selective degradation of the *cis* isomer, therefore enriching the proportion of *trans* isomer but decreasing overall yield. Indeed, this hypothesis was confirmed by adjusting the number of equivalents of TiCl₄ to the reaction mixture. Increasing the stoichiometry of TiCl₄ to 1.1 equivalent decreased the yield but increased diastereoselectivity to 91:9 (Table 1, entry 9), while decreasing the amount of TiCl₄ to 0.7 equivalent improved the yield but decreased diastereoselectivity of **10** to 70:30 (Table 1, entry 10).

Table 1. Screening of Lewis acid, stoichiometry and temperature on the Sakurai reaction between acetoxyperoxyketal **8** and allylTMS **9**.

Entry	Lewis acid	Equivalent	Temperature	Yield ^a (%)	dr ^b (trans:cis)
1	TMSOTf	0.1 or 1	–78 °C to rt	<10	nd ^c
2	BF ₃ ·OEt ₂	1.0	–78 °C to rt	19	nd ^c
3	SnCl ₄	0.9	–78 °C	13 ^d	50:50
4	SnCl ₄	0.9	–40 °C	80	65:35
5	SnCl ₄	0.9	0 °C	31	78:22
6	SnCl ₄	1.0	rt	– ^e	– ^e
7	TiCl ₄	0.9	–78 °C	7 ^d	75:25
8	TiCl ₄	0.9	–40 °C	47	85:15
9	TiCl ₄	1.1	–40 °C	30	91:9
10	TiCl ₄	0.7	–40 °C	60	70:30

^aIsolated yield. ^bDiastereomeric ratios were determined by ¹H NMR. ^cNot determined. ^d50% of recovered starting material. ^eDecomposition.

Scheme 2. Partial degradation of dioxolane **10** using reduced amount of TiCl₄ under the reaction conditions of a Sakurai reaction

An additional experiment allowed us to confirm our hypothesis by applying Sakurai reaction conditions to dioxolane **10** with a reduced amount of TiCl₄ (0.4 equivalent). After 30 min, the reaction mixture was quenched and purified to afford starting material in 56% recovered yield but with an improved diastereoselectivity in favour of the *trans* compound (from 70:30 to 84:16, Scheme 2).

The mechanism of this TiCl₄ catalyzed degradation was further investigated and some major degradation products were identified. A TiCl₄ catalysed Kornblum-DeLaMare rearrangement¹² of dioxolane **10** afforded compounds **12** and **13** on one hand (Scheme 3, top route). On the other hand, TiCl₄ mediated fragmentation of dioxolane **10** also afforded aldehyde **14** and ketone **15** from intermediate **11a**. Under Sakurai reaction conditions, reactive species such as aldehyde **14** was converted into

allyl adduct **18** (Scheme 3, bottom route). Presumably, a similar process occurred from intermediate **11b** as well, but the expected degradation products were not produced in sufficient amount and also due to their relative volatility for some of them, side products **14**, **16**, **19**, **20** and **21** were only observed from GC/MS analysis of the crude material and were not isolated. The mechanism of this fragmentation is not completely clear on our system, since the possibility of a retro-aldol reaction from 1,3-hydroxyketones **12** and **13** cannot be completely excluded. However a similar fragmentation was studied on 3,3,4-trisubstituted 1,2-dioxolanes with TiCl_4 , affording ketones and aldehydes with migration of an alkyl group, an hydrogen or a deuterium.¹³ An analogous fragmentation was also observed in one of our previous work, where a bicyclic peroxyketal afforded a ketoester under triflic acid activation.⁴ These two examples show that a retro-aldol process might not occur since it cannot explain the formed product. Here, the migration of the proton from position 3 or 5 to the position 4 of the 1,2-dioxolane ring is probably concomitant with the peroxide bond and carbon-carbon bond cleavage (Scheme 3).

Scheme 3. Identification of TiCl_4 mediated degradation products of dioxolane **10.**

^a: Not isolated but observed by GC/MS.

Figure 2. Energy profiles of the TiCl_4 mediated Kornblum-DeLaMare rearrangements of model compound *cis* and *trans*-**22** at the B3LYP/(6-31+G(d,p), LanL2DZ) level of theory. Electronic energy along the coordinates is represented in kcal/mol relative to [*trans*-**22**+ TiCl_4 + Cl^-]. A chloride anion was used as a base to scavenge the proton freed in the reaction.

Table 2. Addition of various nucleophiles to peroxyacetal **8^a**

$ \begin{array}{c} \text{Nu-SiR}_3 \text{ 24-31} \\ \text{SnCl}_4 \text{ or TiCl}_4 \text{ (0.9 equiv.)} \\ \text{CH}_2\text{Cl}_2 \text{ -40 }^\circ\text{C} \end{array} $				
entry	Nu-SiR ₃	Lewis acid	product	yield (%) ^b (dr <i>trans:cis</i>) ^c
1		SnCl_4		79 (40:60)
2		TiCl_4		15 (75:25)
3		SnCl_4		38 (80:20) ^d
4		TiCl_4		41 (83:17) ^d
5		SnCl_4		30 (80:20) ^e
6		TiCl_4		40 (92:08) ^e
7		SnCl_4		70 (35:65)
8		TiCl_4		43 (43:57)
9		SnCl_4		77 (40:60)
10		TiCl_4		16 (50:50)
11	TMS-CN 29	SnCl_4		87 (50:50)
12	TMS-N ₃ 30	SnCl_4		78 (50:50)
13		TiCl_4		32% (50:50)
14	Et ₃ Si-H 31	SnCl_4		66
15		TiCl_4		79

^aReaction conditions: **8** (1 equiv.), TiCl₄ or SnCl₄ (0.9 equiv.), nucleophile **24-31** (3 equiv.). ^bIsolated yield. ^cDiastereomeric ratios were determined by ¹H NMR. ^d*E:Z* ratio = 1:4 (¹H NMR). ^e*E:Z* ratio = 1:2 (¹H NMR).

Origin of the enhancement of the diastereoselectivity by degradation in the presence of TiCl₄ in favour of *trans* compound was then investigated at the B3LYP/(6-31+G(d,p), LanL2DZ)¹⁴ level of theory (Pople's basis set for organoelements and Los Alamos effective core potential for metallic centers). We focused our study on one of the two possible TiCl₄ mediated Kornblum-DeLaMare rearrangements, leading to intermediate **23** from dioxolane **22**, a simplified model of dioxolane **10** (Figure 2). Transition states starting from diastereoisomers *cis*-**22** and *trans*-**22** were localized on the potential energy surface. First attempts to search a pathway for the transition state from *cis/trans*-**22** and TiCl₄ only were unsuccessful. Introduction of a proton acceptor under the form of an additional chloride anion, which is likely to be found in the reaction medium, allowed the rearrangement to occur. The difference of activation energy $\Delta\Delta E^\ddagger$ between the two diastereomers was found to be 2.2 kcal/mol, in favour of isomer *cis*-**22**. This result is consistent with our observation about a faster degradation of *cis*-**10** compared to *trans*-**10** with TiCl₄ and subsequent enrichment of this latter. The energy for [*cis*-**22**+TiCl₄+Cl⁻] is higher by 3.7 kcal/mol compared to the *trans* isomer, probably due to steric interactions between the two alkyl groups at the backside of the 1,2-dioxolane ring, squeezed by TiCl₄ and chlorine placed on the front face. In contrast, the transition state for *cis*-**22** is only 0.7 kcal/mol higher due to the free field for proton trapping by chlorine anion at the front face of the dioxolane ring. In the meantime, a steric congestion exists between chlorine and one alkyl group in the transition state for *trans*-**22**, demanding more energy (2.9 kcal/mol) to perform the reaction (Figure 2).

Table 3. Use of various peroxyacetals 40-45 and peroxyketal 46 in the Sakurai reaction with allyltrimethylsilane 9.

entry	substrate	Lewis acid	product	yield (%) ^b (dr <i>trans</i> : <i>cis</i>) ^c
1		SnCl ₄		30 (60:40)
2		TiCl ₄		35 (80:20)
3		SnCl ₄		91 (60:40)
4		TiCl ₄		28 (85:15)
5		SnCl ₄		92 (60:40)
6		TiCl ₄		95 (60:40)
7		SnCl ₄		87 (50:50)
8		TiCl ₄		32 (85:15)
9		SnCl ₄		82 (70:30)
10		TiCl ₄		33 (83:17)
11		SnCl ₄		59 (50:50)

^aReaction conditions: **40-46** (1 equiv.), TiCl₄ or SnCl₄ (0.9 equiv.), allyltrimethylsilane (3 equiv.) in CH₂Cl₂ at -40 °C. ^bIsolated yield. ^cDiastereoselectivities were determined by ¹H NMR. ^dYield calculated over 2 steps from hemiperoxyketal precursor of acetate **46**.

We then turned our attention to the nature of the nucleophile being able to react on endoperoxyacetal **8**. The use of various allylsilanes proved to be successful (Table 2, entries 1-6). The selective degradation of *cis* diastereoisomer with TiCl₄ gave always better *trans* selectivity. Enol ethers were also screened as potent nucleophiles (Table 2, entries 7-10). The *cis* diastereoisomer was obtained as major product, although TiCl₄ mitigated this result due to a selective degradation of *cis* diastereoisomer. Cyanide **29** was a very effective nucleophile with SnCl₄ as well as azide **30** giving expected products **37** and **38** with excellent yields but no control of the diastereoselectivity. TiCl₄ was not able to improve this result, resulting only in decreased yield (Table 2, entries 11-13). Reduction of the endoperoxyacetal is also possible with triethylsilane **31**, producing 3-monosubstituted dioxolane **39** (entries 14 and 15).

Next, we explored substrates **40-46** (easily obtained as compound **8**, see Supporting Information) in the Sakurai reaction with allylsilane **9**. In order to improve the diastereoselectivity of the reaction, bulky dioxolanyl acetates **40-42** were studied (Table 3, entries 1-6). Unfortunately, these substrates did not improved diastereoselectivity compared to acetate **8** (Table 1), and a selective degradation of *cis* product was still observed when was used TiCl₄ in most of the cases. Nevertheless, high steric congestion of the *tert*-butyl group for compound **42** seemed to suppress degradation of product **49**, affording high yield of it using both Lewis acid. Benzyl substituted and protected alcohols are compatible in this reaction leading to good yield with SnCl₄ and improved *trans* diastereoselectivity with TiCl₄, as expected (Table 3, entries 7-11). Ketal derivative **46** was also examined with our protocol (Table 3, entries 13 and 14). Due to the improved stabilization of the peroxonium species with the methyl group, compound **46** proved to be unstable and could not be isolated cleanly. The crude material was used directly in the Sakurai reaction, meaning that the yield was calculated over two steps. Product **53** was obtained with a good selectivity with both SnCl₄ and TiCl₄. This result is comparable in yields (over 2 steps) with Dussault's procedure, meaning our methodology is not only limited to endoperoxyacetals.^{7e,15}

In conclusion, we developed a new method for the formation of 3,5-disubstituted 1,2-dioxolanes through the use of acetoxyperoxyacetals and the formation of peroxycabenium intermediate species under SnCl₄ or TiCl₄ activation. The formation of acetoxyperoxyacetal by using a Lewis acid catalysis proved to be essential for their formation and allowed a sufficient reactivity for further functionalization. SnCl₄ and TiCl₄ were found to be the best Lewis acids screened so far. A wide variety of substrates and nucleophiles were compatible with the reaction conditions. A variation of results was observed between these two reagents: SnCl₄ generally gave good yields but moderate selectivities, while TiCl₄ furnished higher selectivity towards the *trans* products but generally lower yields. In this case, a TiCl₄ mediated decomposition of the newly formed products takes place, where the *cis*-disubstituted dioxolane seems to decompose faster than the *trans* isomer, explaining improved selectivities and lower yields thus observed. Calculation

about towards one degradation pathway could rationalize why *cis*-1,2-dioxolanes decompose more easily under treatment with TiCl₄.

AUTHOR INFORMATION

Corresponding Author

* E-mail: laurent.ferrie@u-psud.fr

ORCID

Laurent Ferrié: 0000-0002-1171-205X

Bruno Figadère: 0000-0003-4226-8489

Guillaume Bernadat: 0000-0001-8955-0364

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

A.P. thanks the MESRI for a PhD fellowship, L.N. the USTH for a financial support. We thank Karine Leblanc and Jean-Christophe Jullian (BioCIS, Châtenay-Malabry) for HRMS analysis and NMR services, respectively. Leo Goehrs from Alionis is gratefully thanked for the donation of computing hardware.

REFERENCES

- (1) (a) Casteel, D. A. *Nat. Prod. Rep.* **1999**, 16, 55-73. (b) Liu, D.-Z.; Liu, J.-K. *Nat. Prod. Bioprospect.* **2013**, 3, 161-206. (c) Vil, V. A.; Glorizova, T. A.; Terent'ev, A. O.; Savidov, N.; Dembitsky, V. M. **2019**, 103, 1627-1642. (d) Vil, V. A.; Terent'ev, A. O.; Savidov, N.; Glorizova, T. A.; Poroikov, V. V.; Pounina, T. A.; Dembitsky, V. M. *J. Steroid Biochem. Mol. Biol.* **2019**, 190, 76-87.
- (2) (a) Klayman, D. L. *Science* **1985**, 228, 1049-1055. (b) Tu, Y. *Nat. Med.* **2011**, 17, 1217-1220. (c) White, N. J. *Science* **2008**, 320, 330-334. (d) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, 47, 2945-2964. (e) Haynes, R. K. *Curr. Top. Med. Chem.* **2006**, 6, 509-537.
- (3) Rahm, F.; Hayes, P. Y.; Kitching, W. *Heterocycles*, **2004**, 64, 623-676.
- (4) Nguyen, T. L.; Ferrié, L.; Figadère, B. *Tetrahedron Letters* **2016**, 57, 5286-5289.
- (5) (a) Scott, J. J.; Oh, D.-C.; Yuceer, M. C.; Klepzig, K. D.; Clardy, J.; Currie, C. R. *Science* **2008**, 322, 63. (b) Oh, D.-C.; Scott, J. J.; Currie, C. R.; Clardy, J. *Org. Lett.* **2009**, 11, 633-636.
- (6) Terent'ev, A. O.; Dmitry, A. B.; Vera, A. V.; Dembitsky, V. M. *Beilstein J. Org. Chem.* **2014**, 10, 34-114.
- (7) Bloodworth, A. J.; Bothwell, B. D.; Collins A. N.; Maidwell, N. L. *Tetrahedron Lett.*, **1996**, 37, 1885-1888.
- (8) (a) Dussault, P. H.; Lee, H.-J.; Liu, X. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3006. (b) Dussault, P. H.; Lee, I. Q.; Lee, H.-J.; Lee, R. J.; Niu, Q. J.; Schultz, J. A.; Zope, U. R. *J. Org. Chem.* **2000**, 65, 8407. (c) Ramirez, A.; Woerpel, K. A. *Org. Lett.* **2005**, 7, 4617. (d) Dai, P.; Trullinger, T. K.; Liu, X.; Dussault, P. H. *J. Org. Chem.* **2006**, 71, 2283. (e) Dussault, P. H.; Liu, X. *Org. Lett.* **1999**, 1, 1391-1393.
- (9) Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Fares, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2013**, 135, 6677-6693.
- (10) (a) Witkowski, B.; Gierczak, T. *J. Mass Spectrom.* **2013**, 48, 79-88. (b) Baumstark, A. L.; Vasquez, P. C.; Chen, Y.-X. *J. Org. Chem.* **1994**, 59, 6692-6696.
- (11) Schmitt, A.; Reißig, H.-U. *Eur. J. Org. Chem.* **2000**, 3893-3901.
- (12) Yaremenko, I. A.; Vil', V. A.; Demchuk, D. V.; Terent'ev, A. O. *Beilstein J. Org. Chem.* **2016**, 12, 1647-1748.
- (13) Yoshida, M.; Miura, M.; Nojima, M.; Kusabayashi, S. *J. Am. Chem. Soc.* **1983**, 105, 6279-6285.
- (14) (a) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, 136, B864-B871. (b) Kohn, W.; Sham, L. J. *Phys. Rev.* **1965**, 140, A1133-A1138. (c) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648-5652. (d) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, 37, 785-789 (e) Hehre, W. J.; Radom, L.; Schleyer, P. V. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986. (f) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, 82, 270-283. (g) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, 82, 299-310.
- (15) Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, 130, 8134-8135