Tetrahedron Letters 57 (2016) 5286–5289

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 3,5-disubstituted-1,2-dioxolanes: access to analogues of mycangimycin and some rearrangement products

Thuy Linh Nguyen [a,b], Laurent Ferrié [a,*], Bruno Figadère [a,*]

[a] BioCIS, Univ. Paris-Sud, CNRS, Université Paris-Saclay, 92290 Châtenay-Malabry, France
[b] Institute of Marine Biochemistry-Vietnam Academy of Science and Technology (VAST), Cau Giay, Hanoï, Viet Nam

ARTICLE INFO

Article history:
Received 15 September 2016
Revised 7 October 2016
Accepted 14 October 2016
Available online 15 October 2016

Keywords:
Peroxide
Kulinkovich reaction
Natural product
Fatty acid
Anti-malarial

ABSTRACT

Mycangimycin is a eicosa-heptenic acid containing an unprecedented 3,5-disubstituted-1,2-dioxolane ring with promising anti-fungal and antimalarial activity. Most reported methods to prepare 1,2-dioxolanes are targeting 3,3,5,5-tetrasubstituted or 3,3,5-trisubstituted 1,2-dioxolanes. Thus, some methods for synthesizing these unusual 3,5-disubstituted 1,2-dioxolanes were investigated. The most promising approach was the use of a Kulinkovich reaction followed by an oxidative ring opening of the cyclopropanol with $Co(acac)_2$ to reach the peroxy-hemiketal structure. Successive triflic acid mediated silane reduction of the corresponding peroxy-hemiketal afforded the expected 3,5-disubstituted-1,2-dioxolane ring. Through our studies, some unprecedented rearrangements of 1,2-dioxolane rings were observed, which will be discussed in this Letter. Finally, two saturated analogues of mycangimycin were synthesized.

Peroxide rings are primary targets in pharmaceutics since the discovery of the bioactivity of artemisinin **1**, one of the most potent anti-malarial drug.[1] From this discovery, many efforts were conducted in the exploration of analogues and the development of chemical methods to supply the world demand. The search of some synthetic antimalarial peroxide compounds such as arterolane **2** (in phase III clinical trials) is still ongoing (Fig. 1).[2]

More recently, a new peroxide containing fatty acid, called mycangimycin **3**, was isolated from the southern pine beetle (*Dendroctonus frontalis*).[3] This compound is not produced by the insect itself, but rather by a bacterial symbiont, which helps the beetle to resist to some antagonistic fungi such as *Ophistoria minus*. By consequence, mycangimycin **3** exhibited a potent anti-fungal activity against a variety of fungi, with some efficiency similar to amphotericin B. Additionally, mycangimycin **3** displayed some promising anti-malarial activity, similar to **1** (EC_{50} = 17 ng/mL vs EC_{50} = 10 ng/mL for artemisinin **1**, chloroquine, pyrimethamine, or mefloquine) (Fig. 1).

The chemical structure of mycangimycin **3** is particularly original. It is an unprecedented C-20 heptenic fatty acid containing a 3,5-disubstituted-1,2-dioxolane ring between position 3 and 5 with a *cis* relative configuration and a 3*S*, 5*S* absolute configuration. The double bonds are all conjugated between C-7 and C-20 with a (*Z*, *Z*, *E*, *E*, *Z*, *E*) stereochemical pattern. It should be noted it is not the first 1,2-dioxolane containing fatty acid to be reported. Indeed, prostaglandin H_2 is an arachidonic acid derivative and a precursor of all other prostaglandins.[4] Also, plakinic acids **4a**–**g** were extensively studied, however, their 1,2-dioxolane ring is 3,3,5,5-tetrasubstituted.[5] This difference is of great importance in the synthesis of the 1,2-dioxolane ring moiety and also could be the origin of the difference of biological activity between mycangimycin **3** and plakinic acids **4a**–**g** (indeed, **4a**–**g** are not reported to exhibit an antimalarial activity). Also in a recent report, most of 1,2-dioxolane ring analogues of arterolane **2** showed no antimalarial activity, while only few got a moderate one.[6] The degree of substitution of the 1,2-dioxolane ring is also important in a synthetic point of view, because only few examples of preparation of 3,5-disubstituted-1,2-dioxolane ring were reported in the literature (Fig. 1).[7]

Considering the promising anti-malarial activity of mycangimycin **3**, probably due to the 1,2-dioxolane moiety, and also considering that mycangimycin **3** could be relatively unstable due to the polyenic chain, we were interested to explore some chemical routes to synthesize more simple analogues of mycangimycin **3**. Because of the absence of general methods to obtain 3,5-disubstituted-1,2-dioxolanes, many routes from the literature describing the access to 3,3,5,5-tetrasubstituted or 3,3,5,-trisubstituted-1,2-dioxolanes were explored in order to obtain analogues of mycangimycin **3**.

The chemistry of peroxonium ions was first investigated, from the works of Woerpel or Dussault.[8] However, the application of

* Corresponding authors.

http://dx.doi.org/10.1016/j.tetlet.2016.10.051
0040-4039/

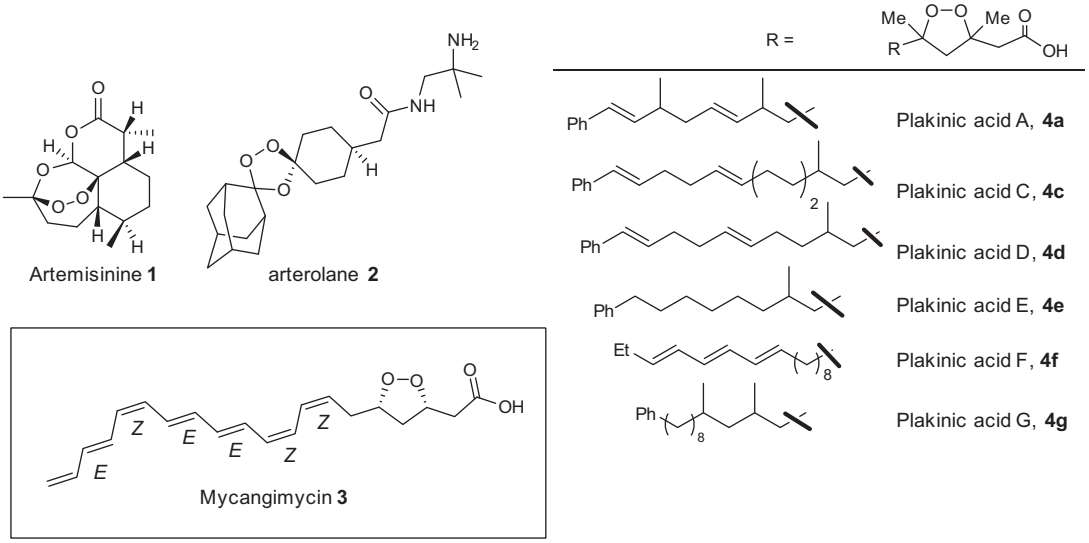


Figure 1. Structure of artemisinin, arterolane, plakinic acids A–G, and mycangimycin.

this method to some peroxy-acetal derivatives was unsuccessful probably due to a lower reactivity of these species compared to some reported peroxy-ketal derivatives, as the stabilization into peroxonium species is partly dependent on the substitution. Some radical pathways under oxygen were also investigated, but again, due to the absence of substitutions compared to the original methods, expected compounds could not be obtained, considering that radicals needed stabilization.[9] Incorporation of hydroperoxy group via a S_N2 process on a secondary position proved to be particularly difficult, in contrast to some reported methods, where the addition of hydrogen peroxide to secondary or tertiary carbon was possible through a S_N1 fashion pathway and a stabilization of an intermediate carbocation.[10]

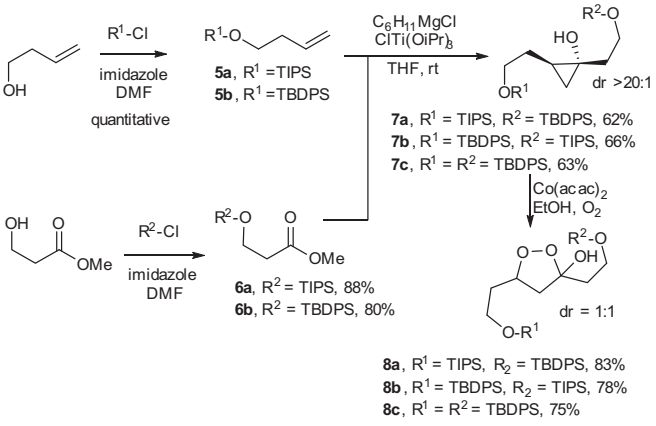
After many disappointed attempts, our most promising strategy was to use a cyclopropanol intermediate in order to perform an oxidative ring opening of the cyclopropyl ring affording the expected 1,2-dioxolane ring.[11]

Cyclopropanols were easily prepared from a Kulinkovich coupling reaction between appropriate terminal olefins **5a–b** and esters **6a–b** in the presence of chlorotitanium triisopropoxide and cyclohexylmagnesium chloride.[12] Thus, three different cyclopropanols **7a–c** were prepared in a 62–66% yield range (dr = 20 > 1) with a combination of different silyl protecting groups for the hydroxyl at terminal position. Oxidative ring opening of the cyclopropanol moiety was performed in the presence of air and a catalytic amount (5 mol %) of $Co(acac)_2$,[13] which gave us the best conversion rates. Thus, expected 3-hydroxy-1,2-dioxolanes **8a–c** were obtained in 75–83% yield and as a 1:1 mixture of diastereomers (Scheme 1).

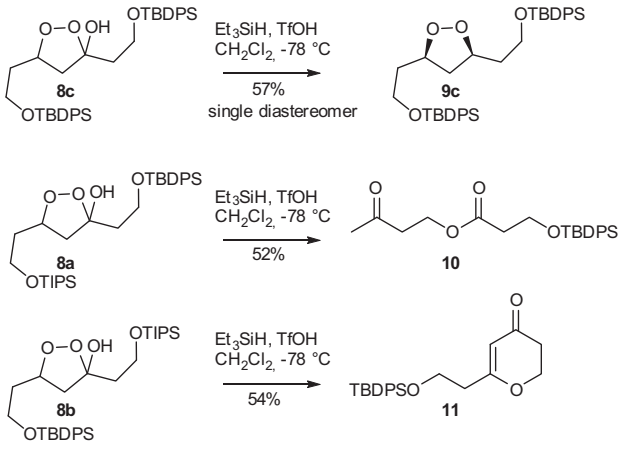
The next step was the reduction of the hydroxyl group under acid conditions, by using triethylsilane with triflic acid at −78 °C in dichloromethane.[14] When this reaction was performed on compound **8c**, expected compound **9c** was obtained in 57% yield and as a single *cis* diastereomer.

Interestingly, some surprising results were obtained with compounds **8a** and **8b**. Indeed, under the same reaction conditions, ketoester **10** was obtained from compound **8a** in 52% yield. Whereas, when **8b** was treated under these reaction conditions, new compound **11** was obtained in 54% yield (Scheme 2).

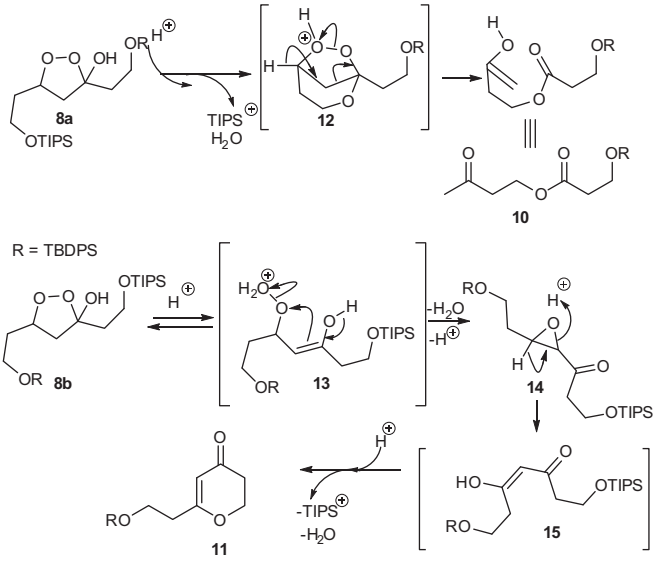
It appears that absolutely no reduction was performed in these two last reactions, even in the presence of a silane, but rather a rearrangement of the 1,2-dioxolane ring, which was the consequence of a deprotection of the TIPS group with TfOH, yet considered robust under acidic condition. A mechanism for the formation of compounds **10** and **11** is proposed in Scheme 3. In the presence of an acid, the TIPS cleavage and peroxyketal metathesis takes place for compound **8a** to produce bicyclic intermediate **12**. Under



Scheme 1. Synthesis of peroxy-hemiketal rings through a Kulinkovich coupling.



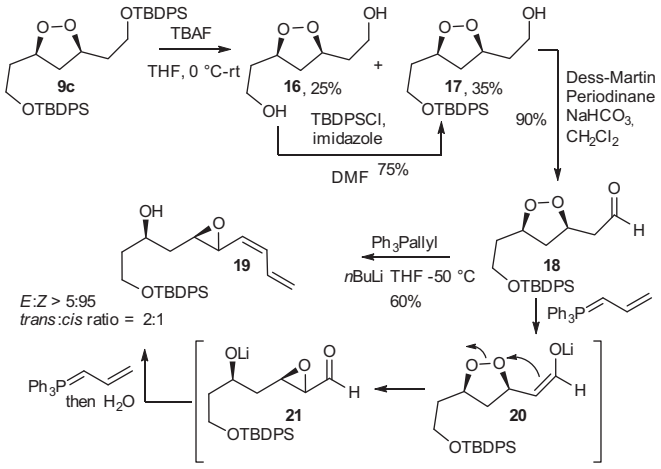
Scheme 2. Reduction of peroxy-hemiketal ring **8c** and unexpected rearrangement products **10** and **11**.



Scheme 3. Plausible mechanisms for the formation of compounds **10** and **11**.

acid catalysis a fragmentation of the 1,2-dioxolane ring **12** occurs with cleavage of a C—C bond, leading to ketoester **10**. This mechanism appears to share some similarities with the Hock cleavage, although some differences remains such as the presence of a hydroperoxide or the alkyl migration[15] but also with some base mediated fragmentation of ozonides.[16] Concerning the formation of compound **11**, it is important to note that some 2,3-dihydro-4*H*-pyran-4-ones were previously prepared using a similar strategy, through a Kulinkovich reaction-oxidative cyclopropane ring opening sequence. However, reductive cleavage of the intermediate 1,2-dioxolane and presence of a masked ketone were necessary.[17] From compound **8b**, the cyclization from the TIPS protected hydroxyl group is not possible, as it would make a 4-member ring. However, it appears that the formation of compound **11** could proceed through the opening of the hemi peroxy-ketal ring under acid catalysis, followed by formation of the enol form of the ketone (intermediate **13**), which then attacks the peroxide to produce epoxy-ketone intermediate **14** (this is a classical and known decomposition product of compounds **8a–c** under basic condition). Acid catalysis Meinwald rearrangement of epoxide **14** affords enol **15**,[18] which leads finally to product **11** after ketal metathesis with the hydroxyl group bearing the TIPS protection (TIPS group could be removed from any of the intermediates or starting material **13**, **14**, **15**).

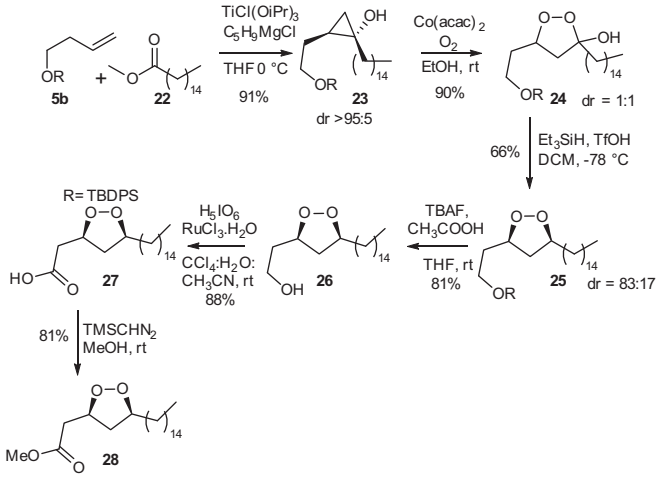
Nevertheless, further functionalization around the 1,2-dioxolane ring could be performed by using compound **8c**. Indeed, mono-deprotection of the TBDPS group was possible with TBAF in THF, by controlling the stoichiometry of the reagent, furnishing a mixture of diol **16** and mono-protected compound **17** in 25 and 35% yield, respectively along with 15% recovered starting material **9c**. Some diol **16** was also recycled by treatment with TBDPS chloride and imidazole in DMF affording product **17** in 75% yield. The free hydroxyl-group of compound **17** was then further oxidized into aldehyde **18** with Dess–Martin periodinane (90% yield), and in a second step, aldehyde **18** was subjected to Wittig olefination. Indeed, the olefination took place, but not exactly as expected since no 1,2-dioxolane ring was detected after reaction and mainly compound **19** was isolated in 60% yield (Scheme 4). It appears that the formation of epoxy-aldehyde **21** took place first, through the production of enolate **20**, which attacks the electrophilic peroxide, in a similar fashion than intermediate **13** in Scheme 3. Other olefination such as Wittig Horner or Julia-Kosciensky olefination and the



Scheme 4. Tentative of functionalization of 1,2-dioxolane **9c**.

use of less basic ylides led to similar observations, meaning this side reaction is faster than the olefination. In front of this failure, it was decided to functionalize as little as possible the 1,2-dioxolane ring by forming a C—C bond, but rather introducing the desired carbon chain at the stage of the Kulinkovich reaction.

Therefore, it was planned to synthesize as a first example of mycangimycin analogue, a completely saturated version, containing the C-20 carbon skeleton. Kulinkovich reaction between olefin **5b** and methyl palmitate **22** under optimized conditions, by using cyclopentylmagnesium chloride instead of cyclohexyl-magnesium chloride, afforded cyclopropanol **23** (dr >95:5) in an excellent 91% yield. Optimization of the cobalt catalyzed oxidative ring opening of the cyclopropanol by using pure oxygen afforded compound **24** with also an improved yield of 90%. Acid catalyzed silane reduction of peroxy-hemiketal **24** afforded expected 1,2-dioxololane ring in 66% yield ($dr_{cis:trans}$ = 83:17). Deprotection of the primary hydroxyl group was performed by the use of buffered TBAF to afford cleanly the desired alcohol **26** in 81% yield. However, prolonged exposure time of 1,2-dioxolane **25** to a slight excess of TBAF led to fragmentation of the 1,2-dioxolane ring into a β-hydroxyketone, known as the Kornblum-DeLaMare rearrangement.[15] Further oxidation with $RuCl_3$ hydrate and periodic acid in a 2:3:2 CCl_4/water/MeCN mixture was performed to give carboxylic acid **27** in 88% yield. Further derivatization of the acid into methyl ester **28** (81%) was performed (Scheme 5).



Scheme 5. Synthesis of saturated analogues of mycangimycin **27**, **28**.

In conclusion, we presented herein the first report toward the synthesis of mycangimycin **3**. This work focused particularly onto the synthesis of the 3,5-disubstituted-1,2-dioxolane ring, and showed that cyclopropanols can be good intermediates for the synthesis of this pattern through an oxidative ring opening process. The synthesis of two racemic saturated analogues of mycangimycin **3** was thus performed. The anti-malarial potential of these substances and some other peroxide containing intermediates or analogues is being evaluated and will be reported in due course. Some 1,2-dioxolane ring rearrangements were also discovered, depending on both reaction conditions and substrates. Although the access to rearranged products **10**, **11**, **19** through the pathways described in this paper has limited interest, these rearrangements are of particular interest for who is involved in the chemistry of peroxides and show the low tolerance of this class of substrates toward many reaction conditions.

Acknowledgments

We thank Vietnamese Government for a fellowship to T.L. Nguyen. We thank Karine Leblanc for HRMS analyses of all our compounds.

Supplementary data

Supplementary data (experimental data and copies of the ^{1}H, ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.10.051.

References and notes

1. (a) Tu, Y. *Nat. Med.* **2011**, *17*, 1217–1220; (b) White, N. J. *Science* **2008**, *320*, 330–334; (c) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 2945–2964; (d) Haynes, R. K. *Curr. Top. Med. Chem.* **2006**, *6*, 509–537.
2. (a) Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Dong, Y.; Dorn, A.; Hunziker, D.; Matile, H.; McIntosh, K.; Padmanilayam, M.; SantoTomas, J.; Scheurer, C.; Scorneaux, B.; Tang, Y.; Urwyler, H.; Wittlin, S.; Charman, W. N. *Nature* **2004**, *430*, 900–904; (b) Valecha, N.; Looareesuwan, S.; Martensson, A.; Abdulla, S. M.; Krudsood, S.; Tangpukdee, N.; Mohanty, S.; Mishra, S. K.; Tyagi, P. K.; Sharma, S. K.; Moehrle, J.; Gautam, A.; Roy, A.; Paliwal, J. K.; Kothari, M.; Saha, N.; Dash, A. P.; Björkman, A. *Clin. Infect. Dis.* **2010**, *51*, 684–691; (c) Dong, Y.; Wittlin, S.; Sriraghavan, K.; Chollet, J.; Charman, S. A.; Charman, W. N.; Scheurer, C.; Urwyler, H.; Santo Tomas, J.; Snyder, C.; Creek, D. J.; Morizzi, J.; Koltun, M.; Matile, H.; Wang, X.; Padmanilayam, M.; Tang, Y.; Dorn, A.; Brun, R.; Vennerstrom, J. L. *J. Med. Chem.* **2010**, *53*, 481–491.
3. (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.
4. Van Der Donk, W. A.; Tsai, A.-L.; Kulmacz, R. J. *Biochemistry* **2002**, *41*, 14451–14458.
5. Rahm, F.; Hayes, P. Y.; Kitching, W. *Heterocycles* **2004**, *64*, 623–676.
6. (a) Wang, X.; Dong, Y.; Wittlin, S.; Creek, D.; Chollet, J.; Charman, S. A.; Santo Tomas, J.; Scheurer, C.; Snyder, C.; Vennerstrom, J. L. *J. Med. Chem.* **2007**, *50*, 5840–5847; (b) Martyn, D. C.; Ramirez, A. P.; Beattie, M. J.; Cortese, J. F.; Patel, V.; Rush, M. A.; Woerpel, K. A.; Clardy, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6521–6524.
7. Terent'ev, A. O.; Dmitry, A. B.; Vera, A. V.; Dembitsky, V. M. *Beilstein J. Org. Chem.* **2014**, *10*, 34–114.
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. (a) Feldman, K. S.; Simpson, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 4878–4886; (b) Zhao, Q.; Wong, H. N. C. *Tetrahedron* **2007**, *63*, 6296.
10. (a) Guerra, F. M.; Zubia, E.; Ortega, M. J.; Moreno-Dorado, F. J.; Massanet, G. M. *Tetrahedron* **2010**, *66*, 157; (b) Yan, X.; Qiao, C.; Guo, Z. *Synlett* **2013**, 502–506.
11. Kulinkovich, O. G.; Astashko, D. A.; Tyvorskii, V. I.; Ilyina, N. A. *Synthesis* **2001**, 1453.
12. (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244; (b) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198–4199.
13. Han, W.-B.; Li, S.-G.; Lu, X.-W.; Wu, Y. *Eur. J. Org. Chem.* **2014**, 3841–3846.
14. 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.
15. Yaremenko, I. A.; Vil', V. A.; Demchuk, D. V.; Terent'ev, A. O. *Beilstein J. Org. Chem.* **2016**, *12*, 1647–1748.
16. Hon, Y. S.; Lin, S. W.; Lu, L.; Chen, Y. J. *Tetrahedron* **1995**, *51*, 5019–5034.
17. Astashko, D. A.; Tyvorskii, V. I. *Tetrahedron Lett.* **2011**, *52*, 4792–4794.
18. (a) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 3070; (b) Meinwald, J.; Labana, S. S.; Chadha, M. S. *J. Am. Chem. Soc.* **1963**, *85*, 582.