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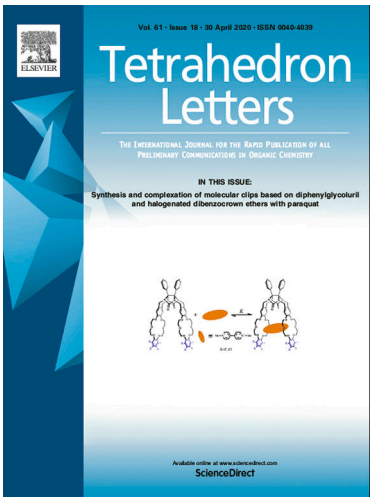

Versatile approach to densely substituted isoxazolines and pyrazolines: focus on a quaternary carbon center as a constitutive feature

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Versatile approach to densely substituted isoxazolines and pyrazolines: focus on a quaternary carbon center as a constitutive feature

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Abstract
A new family of isoxazolines has been obtained *via* 1,3-dipolar cycloaddition in good to high yields under mild conditions. Our approach focused on construction of the heterocyclic ring and direct access to a quaternary carbon center at position 5. The methodology has also been extended to pyrazoline analogues. The antibacterial activity of these compounds was evaluated, showing specific antibacterial activity against *Staphylococcus aureus*. Six members of these heterocycles exhibited MIC values of 4 µg/mL.

Keywords:1,3-Dipolar cycloaddition, Isoxazolines, Pyrazolines, Staphylococcus aureus

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1. Introduction

Isoxazolines are partially hydrogenated five-membered heterocycles containing neighbouring oxygen and nitrogen atoms. Members of this family are key scaffolds of numerous naturally occurring and synthetic biologically active compounds.[1] The steady interest of the scientific community for modulating biological properties has resulted in the development of effective and appealing synthetic procedures towards densely substituted isoxazolines.[2-10] The incorporation of more diverse molecular functionalities to the isoxazoline core as well as the construction of targets displaying a quaternary center in position 5 are among the current challenges in this domain. Indeed, the C-5 site is crucial to tether isoxazoles to podophyllotoxin or coumarin derivatives in the elaboration of molecular architectures which display potent insecticide, acaricide or anticancer properties.[11, 12] Moreover, the presence of a quaternary carbon center at position 5 of the isoxazoline ring prevents aromatization of the heterocycle into the related isoxazoles. Furthermore, the joint presence of a quaternary center and a functional group (CF_3)[5] were revealed to be crucial to the enhancement of the biological properties of isoxazoline derivatives. Access to differently substituted isoxazoline cores is reported through two main methodologies: cyclisation at the remote position or ring construction from oxime derivatives (Fig. 1).

Metal-mediated oxyhalogenation or oxidation of tertiary C-H bonds and photoredox processes are elegant procedures for promoting cyclisation at remote positions and thus the formation of isoxazolines. Such methods are especially useful to produce quaternary carbon centers substituted by aryl and alkyl groups as well as halides and di(tri)fluoromethyl groups.[6-10] Ring construction *via* conjugate addition or cycloaddition from oxime derivatives and nitrile oxide intermediates is a convenient approach allowing the formation of tertiary or quaternary C-5 centers mainly functionalized by alkyl, aryl or CF_3 groups.[2-5] However, the installation of carboxylic ester, sulfanyl or phosphonate groups at the C-5 position of the heterocycle remains less reported using both of the aforementioned strategies.[13] In most of these examples such functional groups substitute tertiary C-5 centers, with carboxylic esters being rarely found at a quaternary C-5 center.

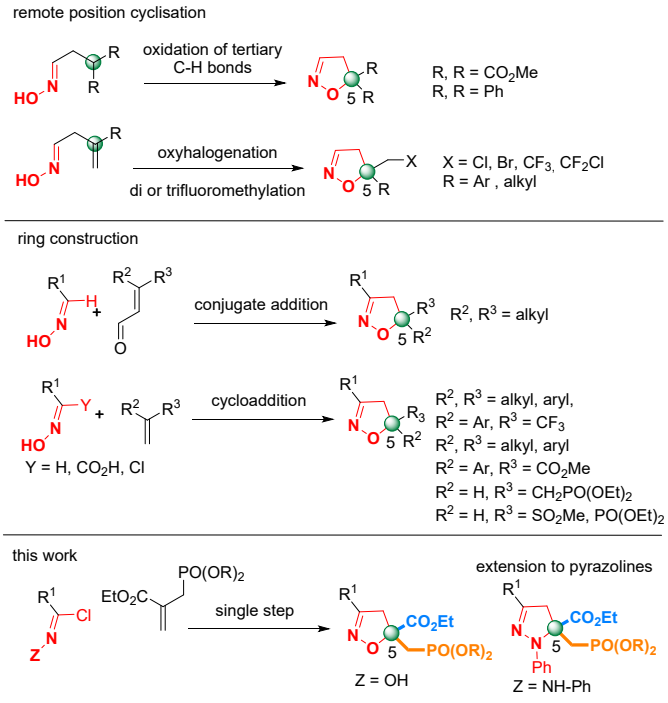


Figure 1. Overview of literature methods and the construction of isoxazolines containing a quaternary C-5 center.

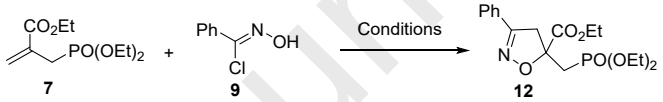
In this paper we have focused on the installation of two different functional groups, namely ethoxycarbonyl and phosphonomethyl at the quaternary C-5 center of isoxazolines. Our approach is based on the use of ethoxycarbonyl allylphosphonate[14] and nitrile oxides as the starting materials *via* a single step 1,3-dipolar cycloaddition under mild conditions. Our general methodology was further extended to the preparation of pyrazolines[15] from the same phosphonate precursor and nitrile imines. In this family of heterocycles, access to quaternary C-5 centers bearing valuable functional groups such as CO_2R and $CH_2PO(OR)_2$ remains a challenge. In addition, the preliminary biological activities of both isoxazolines and pyrazolines against *Staphylococcus aureus* have been evaluated for the development of potential new antibacterial agents.

2. Results and Discussion

1,3-Dipolar cycloaddition of alkenes to nitrile oxides, generated *in situ* from *N*-hydroximoyl chlorides, has been widely used for the synthesis of various heterocyclic structures.[16] We initially chose allylphosphonate **7** and hydroximoyl chloride **9** as model substrates to optimize the reaction conditions by testing several bases and solvents (Table 1). The reaction carried out in absence of a base led to the unchanged allylphosphonate **7** (Entry 1). We then decided to prepare the corresponding nitrile oxide *in situ* by treatment of chlorooxime **9** in the presence of a base. In addition, we were inspired by the reported methods for oxime cycloadditions, to use amine-type bases to access isooxazoline **12**. Initially, we observed that protic or aprotic solvents had no significant effect on the reaction time or yield (Entries 2 and 5). Increasing the temperature reduced the reaction time, but unfortunately led to the formation of several by-products. Consequently, isoxazoline **12** was obtained with a poor yield (Entry 4).

Bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine and Et_3N were successively tested (Entries 6-9). A significant increase in the yields and in allylphosphonate conversion was observed, after 18-24 h, when Et_3N was used (Entries 2, 5, 8, 9). It should be noted that using more than 1.1 equivalent of Et_3N has no significant effect on the reaction yield. Although only small differences were observed between the use of CH_2Cl_2 and $CHCl_3$, the latter led to cleaner crude material avoiding the presence of unidentified side-products. Thus, $Et_3N/CHCl_3$ was determined as the most suitable base/solvent combination for the cycloaddition.

Table 1. Preparation of 5-phosphonomethylisoxazoline **12**.

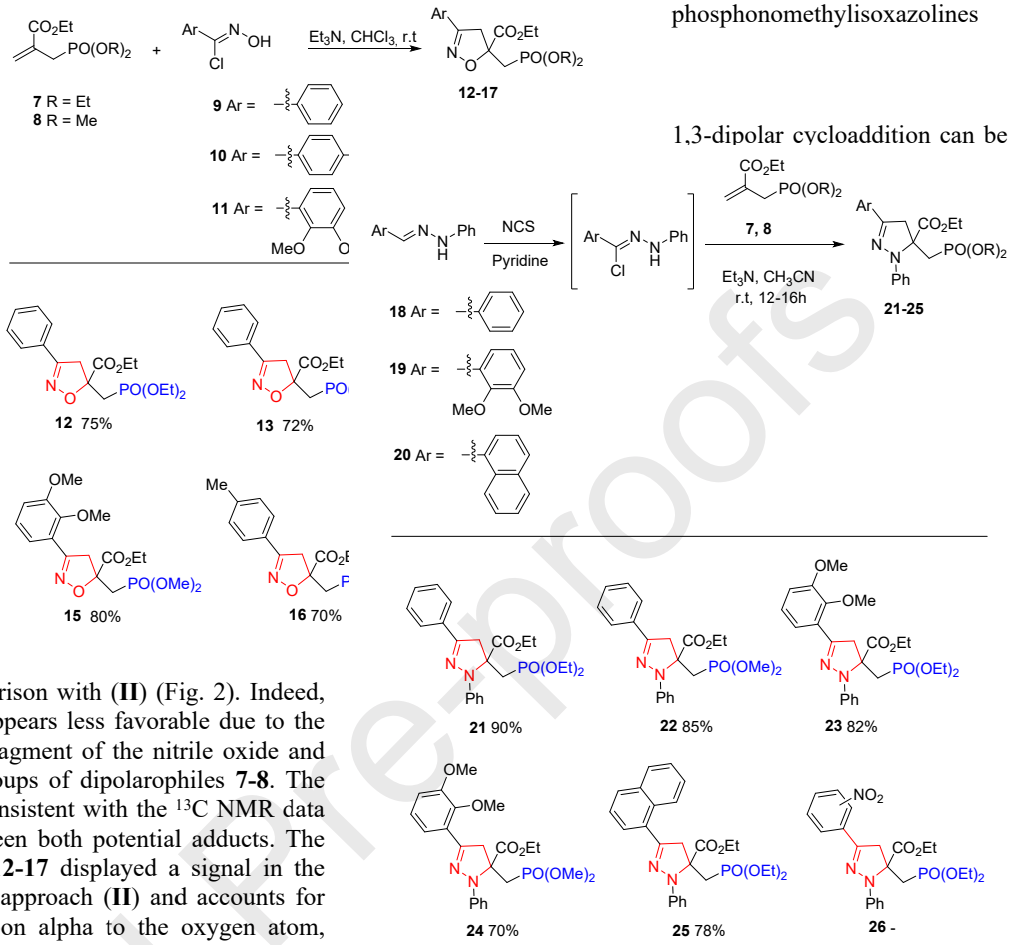


Entry	Conditions[a]	Time (h)[b]	Yield **12** (%)
1	CH_2Cl_2, r.t	72	--
2	Et_3N, CH_2Cl_2, r.t	20	72
3	Et_3N, CH_3CN, r.t	22	68
4	Et_3N, CH_2Cl_2, reflux	10	35
5	Et_3N, C_2H_5OH, r.t	24	68
6	DBU, $CHCl_3$, r.t	72	50
7	pyridine, CH_3CN, r.t	72	52
8	**Et_3N, $CHCl_3$, r.t**	**18**	**75**
9	Et_3N, $CHCl_3$, reflux	18	70

[a] Reaction was carried out using **7** (1 mmol), **9** (1.1 mmol) and base (1.1 mmol) in solvent (2 mL).
[b]Reactions were monitored by TLC.

V -17 in 67-82% yield (Scheme 1).

Scheme 1. Cycloaddition of allylphosphonates **7-8** towards **12-17**.



As reported in the literature, regioselective or lead to the formation of a mixture of regioisomers.[17] In our case, the cycloaddition was selective as only one adduct could be identified according to ^{1}H and ^{13}C NMR data. Similarly, proton decoupled ^{31}P NMR spectroscopy confirmed the presence of a single adduct for isoxazolines **12-17**, displaying a single signal in the range of 23-28 ppm. In our case, the steric effect may explain the regioselectivity of the reaction as previously noted in several 1,3-dipolar cycloadditions.[18] Plausibly, the formation of regioisomer (**I**) is favored in comparison with (**II**) (Fig. 2). Indeed, the formation of regioisomer (**II**) appears less favorable due to the steric hindrance between the aryl fragment of the nitrile oxide and the phosphonate-ethoxycarbonyl groups of dipolarophiles **7-8**. The formation of regioisomer (**I**) was consistent with the ^{13}C NMR data which allowed discrimination between both potential adducts. The ^{13}C NMR spectra of isoxazolines **12-17** displayed a signal in the range 84-85 ppm, which precludes approach (**II**) and accounts for the formation of a quaternary carbon alpha to the oxygen atom, consistent with the spectroscopic data of regioisomer (**I**). In addition, 2D HMBC NMR spectroscopy undoubtedly confirmed that only regioisomer (**I**) was obtained. Indeed, protons H^a and H^b are privileged spectators of the structure of the heterocycle and thus of the cycloaddition selectivity. As shown in the ESI, 2D HMBC NMR spectroscopy exhibited characteristic correlations between H^a and H^b in complete agreement with the structure of regioisomer (**I**). At the same time, no correlation between H^b and the (C=N) carbon of the heterocycle which potentially accounts for regioisomer (**II**) was observed.

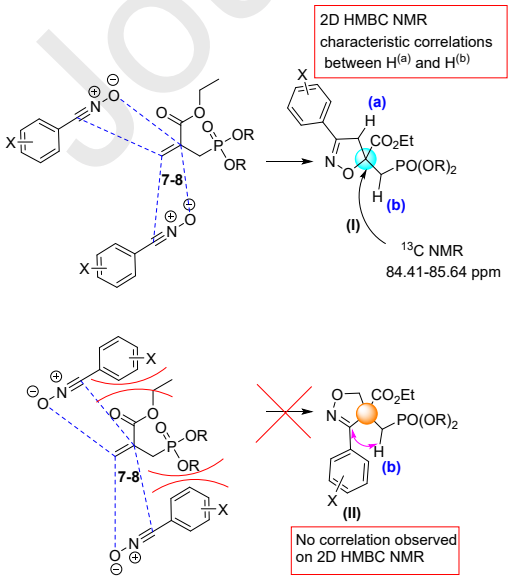


Figure 2. Proposed regioselectivity control for the 1,3-dipolar cycloaddition.

We next examined the transformation of allylphosphonates **7-8** into 5-phosphonomethylpyrazolines **21-25**. Several studies have shown that 1,3-dipolar cycloaddition between dipolarophiles and hydrazonyl chlorides, which are used as a source of nitrile imines, is an efficient approach to access 5- membered aza-heterocycles.[19, 20]

Scheme 2. Cycloaddition of hydrazonyl chlorides and allylphosphonates **7-8** towards 5-phosphonomethylpyrazolines **21-25**.

In our case, we chose to examine the cycloaddition between allylphosphonates **7-8** and hydrazonyl chlorides. The latter can be easily generated *in situ* from hydrazones **18-20**, using *N*-chlorosuccinimide (NCS) in pyridine (Scheme 2). The resulting hydrazonyl chlorides reacted smoothly with the allylphosphonates at room temperature to afford the expected pyrazoline derivatives. The cycloaddition process led to the formation of 5-phosphonomethylpyrazolines **21-25** in 70-90%

yi by phosphonomethyl, methylcarboxylate and nitrogen fragments. Surprisingly, the cycloaddition between allylphosphonates **7-8** and hydrazones bearing an electron-withdrawing nitro group in both the *meta* and *para* positions did not allow the formation of the corresponding pyrazolines, even with prolonged reaction times and at higher reaction temperatures. This might be attributed to either the instability of the hydrazonyl chloride intermediate or the lack of reactivity of hydrazones bearing electron-withdrawing groups precluding *in situ* formation of the hydrazonyl chloride at an early stage of the reaction.

Antibacterial activity

The biological activities of nine compounds were evaluated for their antibacterial properties against several bacterial species; *Staphylococcus aureus* and *Enterococcus faecalis* classified as Gram-positive bacteria; *Escherichia coli* and *Pseudomonas aeruginosa* classified as Gram-negative bacteria. The antibacterial activity of isoxazolines **12-17** and pyrazolines **21-25** was assessed using the disc-diffusion and broth dilution methods.[21] Gram negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and *Enterococcus faecalis* Gram positive bacteria isolates showed no sensitivity to the tested compounds. Interestingly, growth inhibition was observed in the *Staphylococcus aureus* strain that exhibited susceptibility to most of the evaluated compounds, especially 5-phosphonomethylisoxazolines (**12**, **14** and **17**) and 5-phoshonomethylpyrazolines (**22**, **23** and **24**) which exhibited the lowest MIC values of 4 µg/mL (Table 2). According to the antibacterial test results, the synthesized isoxazolines and pyrazolines showed specific activity against *Staphylococcus aureus* Gram positive bacteria.

Table 2. Antimicrobial activity assays and minimal inhibitory concentrations (MIC) against *Staphylococcus aureus*.

Compounds	MIC (µg/mL)
12	4
14	4
15	32
17	4
21	16
22	4
23	4
24	4
25	32
Gentamicin	4

3. Conclusion

In the present work, we have prepared novel 5-phosphonomethyl-isoxazoline derivatives incorporating a quaternary carbon center at the C-5 position *via* 1,3-dipolar cycloaddition reactions from allylphosphonate precursors. This easy to implement and efficient strategy allowed the synthesis of densely functionalized isoxazolines. The cycloaddition process was shown to be highly selective, leading to a single adduct most plausibly due to steric factors. Our approach was also successfully extended to the preparation of 5-phosphonomethyl-pyrazolines starting from allylphosphonates. Biological activities of the synthesized isoxazolines and pyrazolines have been evaluated. Heterocycles bearing phosphonomethyl fragments exhibited specific activity against *Staphylococcus aureus* Gram positive bacteria. Functionalization of the phosphonated isoxazolines and pyrazolines as well as the study of its effect on their biological activities will be the subject of a forthcoming publication.

Acknowledgments

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References and notes

1. (a) Ajay Kumar, K.; Govindaraju, M.; Renuka, N.; Vasanth Kumar, G. *J. Chem. Pharm. Res*. **2015**, *7*, 250-257; (b) Lingaraju, G. S.; Balaji, K. S.; Jayarama, S.; Anil, S. M.; Kiran, K. R.; Sadashiva, M. P. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 3606–3612; (c) Znati, M.; Debbabi, M.; Romdhane, A.;

1410; (c) Fnan, I.; Boudjha, S.; Znati, M.; Bousejra-El Garah, F.; Jannet, H. B. *J. Enzym. Inhib. Med. Chem.* **2015**, *30*, 371–376.
2. (a) Pohjakallio, A.; Pihko, P. M.; Liu, J. *J. Org. Chem*. **2010**, *75*, 6712–6715; (b) Pohjakallio, A.; Pihko, P. M.; Laitinen, U. M. *Chem. Eur. J.* **2010**, *16*, 11325-11339.
3. (a) Han, L.; Zhang, B.; Zhu, M.; Yan, J. *Tetrahedron Lett*. **2014**, *55*, 2308–2311; (b) Li, Z.; Frings, M.; Yu, H.; Raabe, G.; Bolm, C. *Org. Lett*. **2018**, *20*, 7367-7370; (c) Zhao, S.; Jin, L.; Chen, Z-L.; Rui, X.; He, J-Y.; Xia, R.; Chen, K.; Chen, X-X.; Yin, Z-J.; Chen, X. *RSC Adv*. **2019**, *9*, 11585-1588; (d) Okusu, S.; Okazaki, H.; Tokunaga, E.; Soloshonok, V. A.; Shibata, N. *Angew. Chem. Int. Ed*. 2016, 55, 6744-6748.
4. Svejstrup, T. D.; Zawodny, W.; Douglas, J. J.; Bidgeli, D.; Sheikhc, N. S.; Leonori, D. *Chem. Commun*. **2016**, *52*, 12302 -12305.
5. Lahm, G. P; Cordova, D.; Barry, J. D.; Pahutski, T. F.; Smith, B. K.; Long, J. K.; Benner, E. A.; Holyoke, C. W.; Joraski, K.; Xu, M.; Schroeder, M. E.; Wagerle, T.; Mahaffey, M. J.; Smith, R. M.; Tong, M.-H. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 3001–3006.
6. Zhu, X. ; Wang, Y.-F. ; Ren, W. ; Zhang, F.-L. ; Chiba, S. *Org. Lett.* **2013**, *15*, 3214-3217.
7. Shi, D.; Qin, H.-T.; Zhu, C.; Liu, F. *Eur. J. Org. Chem*. **2015**, 5084–5088.
8. Zhu, M.; Fun, W.; Guo, W.; Tian, Y.; Wang Z.; Xu, C.; Ji, B. *Eur. J. Org. Chem*. **2019**, 1614–1619.
9. Dong, K.-Y.; Qin, H.-T.; Liu, F.; Zhu, C. *Eur. J. Org. Chem.* **2015**, 1419–1422.
10. Li, X.; Ding, Y.; Qian, L.; Gao, Y.; Wang, X.; Yan, X.; Xu, X. *J. Org. Chem.* **2019**, *84*, 12656−12663.
11. Yang. R.; Zhang, Y.; Xu, H. *Bioorg. Med. Chem. Lett*. **2018**, *28,* 1410–1416.
12. Lingarajua, G. S.; Balajib, K. S.; Jayaramab, S.; Anila, S. M.; Kirana, K. R.; Sadashivaa, M. P. *Bioorg. Med. Chem. Lett*. **2018**, *28*, 3606–3612.
13. (a) Liautard, V.; Christina, A. E.; Desvergnes, V.; Martin, O. R., *J. Org. Chem.* **2006**, *71*, 7337-7345; (b) Conti, P.; Pinto, A.; Tamborini, L.; Dunkel, P.; Gambaro, V.; Visconti, G. L.; De Micheli, C. *Synthesis* **2009**, *04*, 591-596; (c) Chalyk, B. A.; Sosedko, A. S.; Volochnyuk, D. M.; Tolmachev, A. A.; Gavrilenko, K. S.; Liashuk, O. S.; Grygorenko, O. O. *Org. Biomol. Chem.* **2018**, *16*, 9152-9164; (d) Perez, V.; Rabasso, N.; Fadel, A. *Eur. J. Org. Chem*. **2016**, *2016*, 320–324.
14. For recent applications of ethoxycarbonyl allylphosphonate, see: (a) Abdelli, A.; Gaucher, A.; Efrit, M. L.; M'rabet, H.; Prim, D. *Tetrahedron Lett*. **2015**, *56*, 1679-1681; (b) Abdelli, A.; Efrit, M. L.; Gaucher, A.; M'rabet, H.; Prim, D. *Tetrahedron Lett*. **2015**, *56*, 5397-5400; (c) Abdelli, A.; Bourdreux, F.; Gaucher, A.; Efrit, M. L.; M'rabet, H.; Prim, D. *Tetrahedron Lett*. **2016**, *57*, 379-382; (d) Boufroura, H.; Abdelli, A.; Bourdreux, F.; Gaucher, G.; Clavier, G.; Efrit, M. L.; M'rabet, H.; Prim, D. *RSC Adv*. **2017**, *7*, 18211-18216.
15. For recent evaluation of the bioblogical activities of pyrazoline dereivatives, see: (a) ElBordiny, H. S.; El-Miligu, M. M.; Kassab, S. E.; Dabees, H.; Ali, W. A. M.; El-Hawash, S. A. M. *Eur. J. Med. Chem*. **2018**, *145*, 594-605; (b) Burmudžija, A.; Muškinja, J.; Ratković, Z.; Kosanić, M.; Ranković, B.; Novaković, S. B.; Bogdanović, G. A. *Inorg. Chim. Acta*. **2018**, *471*, 570-576; (c) Kumar. G.; Tanwar, O.; Kumar, J.; Akther, M.; Sharma, S.; Pillai, C.R.; Alam, M. M.; Zama, M.S. *Eur. J. Med. Chem*. **2018**, *149*, 139-147; (d) Chen, K.; Zhang, Y-L.; Fan, J.; Ma, X.; Qin, Y-J.; Zhu, H-L. *Eur. J. Med. Chem*. **2018**, *156*, 722-737; (e) Yang, R.; Lv, M.; Xu, H. *J. Agric. Food Chem.* **2018**, *66*, 11254–11264.
16. Kotyatkina, A. I.; Zhabinsky, V. N.; Khripach, V. A. *Russ. Chem. Rev.* **2001**, *70*, 641-653.
17. Aurell, M. J.; Domingo, L. R.; Pérez, P. *Tetrahedron* **2004**, *60*, 11503–11509.
18. (a) Efremova, M. M.; Molchanov, A. P.; Stepakov, A. V.; Kostikov, R. R.; Shcherbakova, V. S.; Ivanov, A. V. Tetrahedron **2015**, *71*, 2071-2078. (b) Sharipov, B. T.; Davidova, A. N.; Ryabova, A. S.; Galimzyanova, N. F.; Valeev, F. A. *Chem. Heterocycl. Compd.* **2016**, *52*, 31–40.
19. (a) Zou, H.; Zhu, H.; Shao, J.; Wu, J.; Chen, W.; Giulianotti, M. A.; Yu, Y. *Tetrahedron* **2011**, *67*,4887-4891; (b) Guo, C-X.; Zhang, W-Z.; Zhang, N.; Lu, X-B. *J. Org. Chem.* **2017**, *82*, 7637−7642; (c) Kawai, H.; Yuan, Z.; Tokunaga, E. *Org. Lett.* **2012**, *14*, 5330-5333.
20. (a) Espildora, E.; Delgado, J. L.; Cruz, P.; Hoz, A.; López-Arza, V.; Langa, F. *Tetrahedron* **2002**, *58*, 5821-5826.; (b) Cruz, P.; Díaz-Ortiz, A.; García, J.; Gómez-Escalonilla, M. J.; Hoz, A.; Langa, F. *Tetrahedron Lett*. **1999**, *40*, 1587-1590.
21. Balouiri, M.; Sadiki, M.; Ibn souda, S. K. *J. Pharm. Anal.* **2016**, *6*, 71-79.
22. Goering, B. K. Ph.D. Dissertation, Cornell University, 1995.
23. Haslam, E. *Shikimic Acid Metabolism and Metabolites*, John Wiley & Sons: New York, 1993.
24. Buchanan, J. G.; Sable, H. Z. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1972; Vol. 2, pp 1–95.
25. Lyle, F. R. U.S. Patent 5 973 257, 1985; *Chem. Abstr*. **1985**, *65*, 2870.

Supplementary Material

The supplementary material contains experimental procedures and spectroscopic data for all new compounds.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

TETL-D-20-00354R1

from a common alllyhosphonate starting material

- Easy access to C5 quaternary carbon center
- Selective 1,3-dipolar cycloaddition under mild conditions
- Specific antibacterial activity against *Staphylococcus aureus* strain.

Graphical Abstract