ACADÉMIE
DES SCIENCES
INSTITUT DE FRANCE

Comptes Rendus
Chimie

Thierry Lequeux and Emmanuel Pfund

Fluoroalkenes as biomolecules isosteres; preparation and application: a personal account

Volume 27 (2024), p. 205-215

Online since: 26 September 2024

https://doi.org/10.5802/crchim.337

The Comptes Rendus. Chimie *are a member of the Mersenne Center for open scientific publishing*
www.centre-mersenne.org — e-ISSN : 1878-1543

ACADÉMIE DES SCIENCES
INSTITUT DE FRANCE

Comptes Rendus. Chimie
2024, Vol. 27, p. 205-215
https://doi.org/10.5802/crchim.337

Account

Fluoroalkenes as biomolecules isosteres; preparation and application: a personal account

Thierry Lequeux [*,a] **and Emmanuel Pfund** [a]

[a] Laboratoire de Chimie Moléculaire et Thioorganique LCMT UMR 6507 ENSICAEN, UNICAEN, CNRS, Normandie Université, 6 Bd. du Maréchal Juin, 14050 Caen, France

E-mail: Thierry.Lequeux@ensicaen.fr (T. Lequeux)

Abstract. Fluoroalkenes have been known for decades, but their preparation is still a hot topic. Indeed, the olefination reactions of carbonyl compounds with fluorinated derivatives are not trivial. For that reason, new tools have been developed to efficiently access tri- and tetrasubstituted alkenes. We report our contribution in this field and their interest will be illustrated by the preparation of dipeptide isosteres and acyclonucleoside analogues.

Keywords. Monofluoroalkenes, Olefination, Dipeptides, Acyclonucleosides.

Funding. Excellence laboratory LabEx SYNORG (ANR-11-LABX-0029), Conseil Régional de Normandie and European FEDER.

Manuscript received 5 July 2024, revised and accepted 6 September 2024.

1. Introduction

The introduction of a fluorine atom into a biologically active molecule significantly modifies its physicochemical properties. This modification has been widely used for the preparation of pharmaceuticals, agrochemicals and materials [1–4].

In this field, the synthesis of fluorinated carbon–carbon double bonds has been the source of a considerable and increasing interest in recent years (Figure 1) [5,6]. It has been found that fluoroalkenes have similar steric and electronic properties compared to amides and can therefore act as peptidomimetics [7]. For example, fluoro-olefin **2** was found to be an excellent DPP IV inhibitor with a constrained conformation.

The most common method for the synthesis of alkenes containing an [(Alk)CF=] moiety is the reaction of an aldehyde or ketone with fluorinated Horner–Wadsworth–Emmons (HWE) reagents such as Ph_3P=CHF or $(EtO)_2(O)PCHFCOOEt$ [8–12]. While, this approach is very efficient for the preparation of fluoroalkenes bearing electron withdrawing groups, it is not well suited for the synthesis of fluoroalkylidenes. Numerous efforts have been made in order to develop alternative methods and to overcome these drawbacks [5,6]. In this context, the modified Julia reaction (or Julia–Kocienski reaction) [13], has emerged as one of the most effective methods since our pioneering work [14]. This reaction developed by S. Julia was extended by our group and others to fluorinated series in order to easily access fluoroalkenes from aldehydes or ketones in one step (Scheme 1) [15–18]. This story began with the preparation of the potent insecticide precursor **3** from the pyrethrin family [14]. This first example has stimulated the preparation of new fluoroalkenes such as vinyl fluorides, which were later reported from the corresponding monofluoromethylsulfone [19,20].

In this account, we will focus on the preparation of fluoroalkenes via the modified Julia reaction that was reported by our group. The aim is to report the main methods for the preparation of di-, tri- and tetrasubstituted alkenes, with a particular emphasis

* Corresponding author

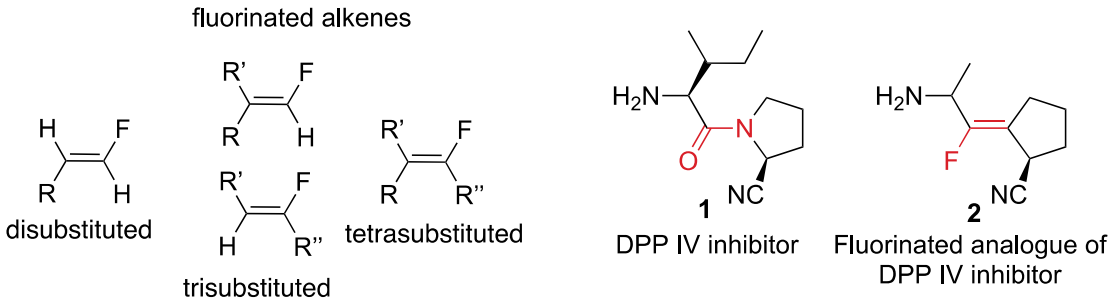
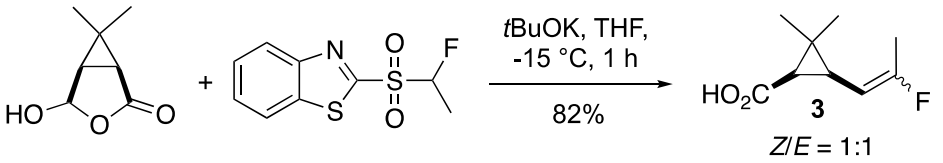


Figure 1. Fluoroalkenes as amide isosteres.



Scheme 1. Preparation of an insecticide precursor.

on highly functionalized fluoroalkylidenes acting as peptidomimetics and nucleoside surrogates.

2. Synthesis of fluoroacrylate derivatives

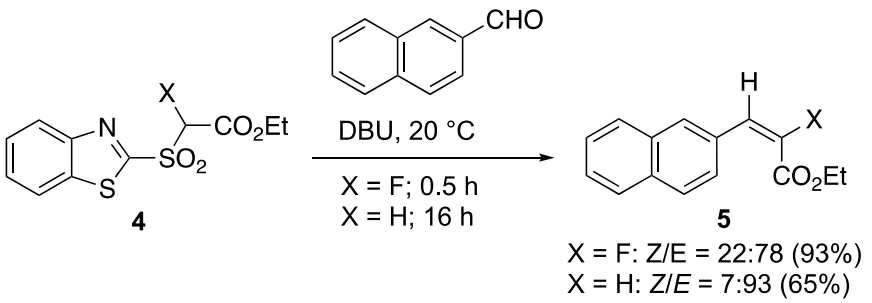
The effect of the fluorine was important for the preparation of acrylate derivatives **5** (Scheme 2). Indeed, the destabilization of the intermediate carbanion by the fluorine atom increased the reaction rate. The reaction with fluorosulfone **4** is 30 times faster than with the corresponding non-fluorinated sulfone [21,22]. It was completed in only 30 minutes with the fluorosulfone at 20 °C, whereas the same reaction took at least 16 h with the non-fluorinated sulfone.

In order to control the geometry of the newly formed carbon–carbon double bond, we found that the reaction had to be carried out in the presence or absence of metalated bases (Scheme 3). Indeed, in the presence of DBU, the *(E)*-alkene was the main product, whereas the *(Z)*-alkene was mainly obtained in the presence of NaHMDS [23]. The selectivity is strongly dependent on the nature of the aromatic sulfone, and in particular on the π-deficient character of the heterocycle. In this way it is possible to control the geometry of the carbon–carbon double bond by replacing the benzothiazolyl (BT) [21,23] **6** with a pyrimidine (Pym) **8** [24] or a *bis*-trifluoromethylphenyl (BTFP) [25] ring **7**.

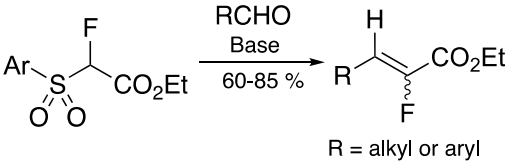
Other electron-deficient fluoroalkenes were prepared by the modified Julia reaction using BT [26,27] or BTFP [25] fluorosulfones. Depending on the experimental conditions *Z* isomers were preferentially obtained. For example, fluorinated Weinreb amides **10** were formed from *bis*-trifluoromethylphenylsulfones **9** and aldehydes with an excellent *Z*-selectivity in contrast to α,β-unsaturated fluoroacrylates reported in the same work (Scheme 4) [25].

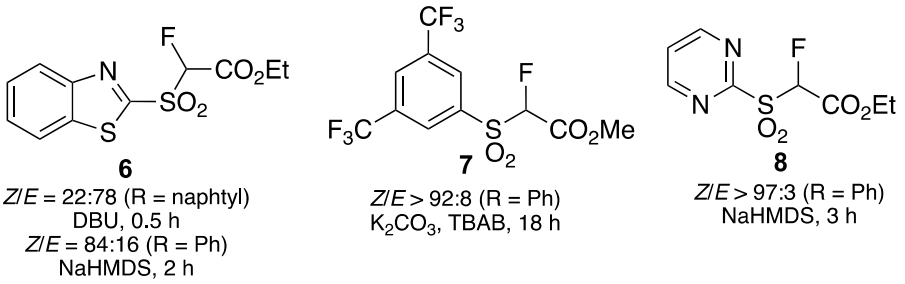
3. Fluoroalkylidenes substituted by an aromatic ring

The most important advance in the field of the preparation of fluoroalkenes has been the use of the modified Julia reaction to prepare fluoroalkylidenes that cannot be obtained directly from carbonyl compounds (Scheme 5). Indeed, our initial work on the modified Julia reaction opened up an easy access to tri- and tetra-substituted fluoroalkenes bearing an aryl ring, alkyl chain or an alkylamine. The main difficulties encountered were in the preparation of the fluorosulfones involved in this reaction. As mentioned above, the *Z*/*E* selectivity is strongly dependent on the nature of the carbonyl compound, the sulfone and the experimental conditions. In general, bulky substituents on both reagents favoured the formation of the *(Z)*-alkenes.

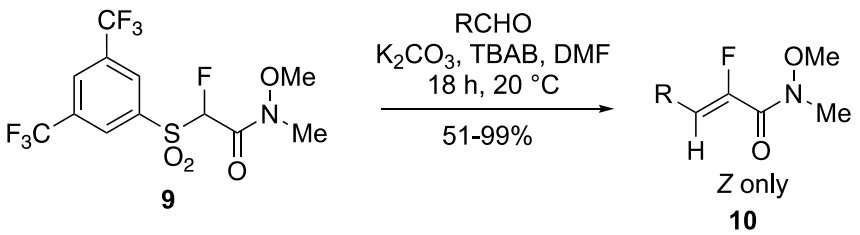


Scheme 2. Yields and ratios for the olefination of fluorinated and non-fluorinated aldehydes.

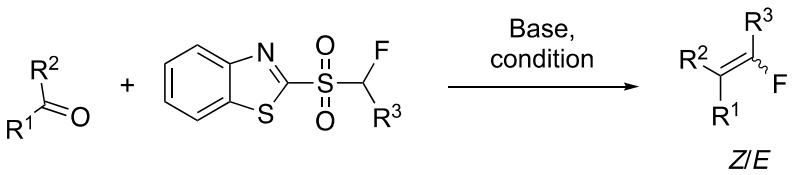




Scheme 3. Control of the carbon–carbon double bond geometry.

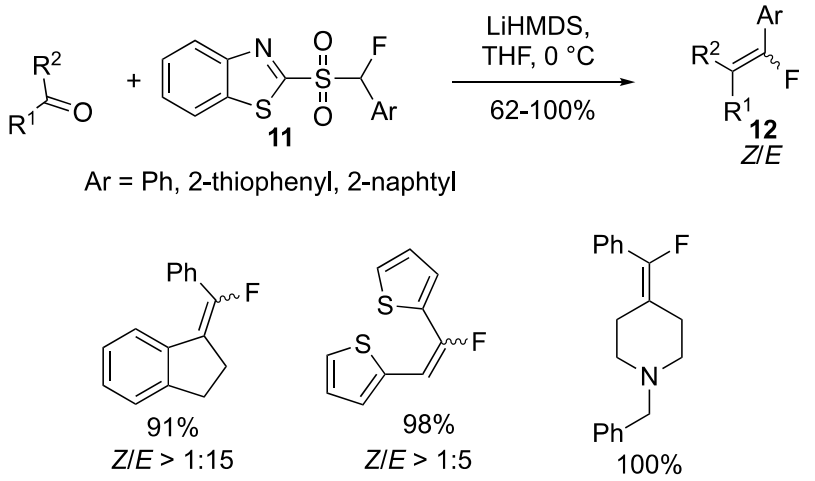


Scheme 4. Selective formation of unsaturated Weinreb amides.

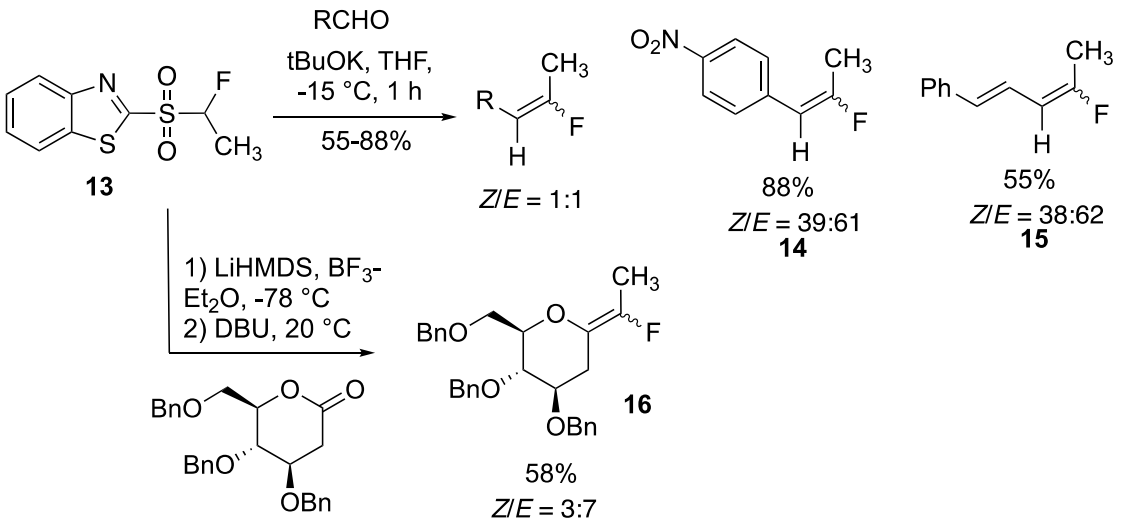


Scheme 5. One step synthesis of fluoroalkylidenes.

The preparation of monofluoroalkenes substituted by an aryl was reported by the group of Zajc from monofluorosulfones **11** (Scheme 6) [28,29]. (*E*)-alkenes **12** were the main product of the reaction,



Scheme 6. Fluoroalkenes substituted by an aromatic ring.



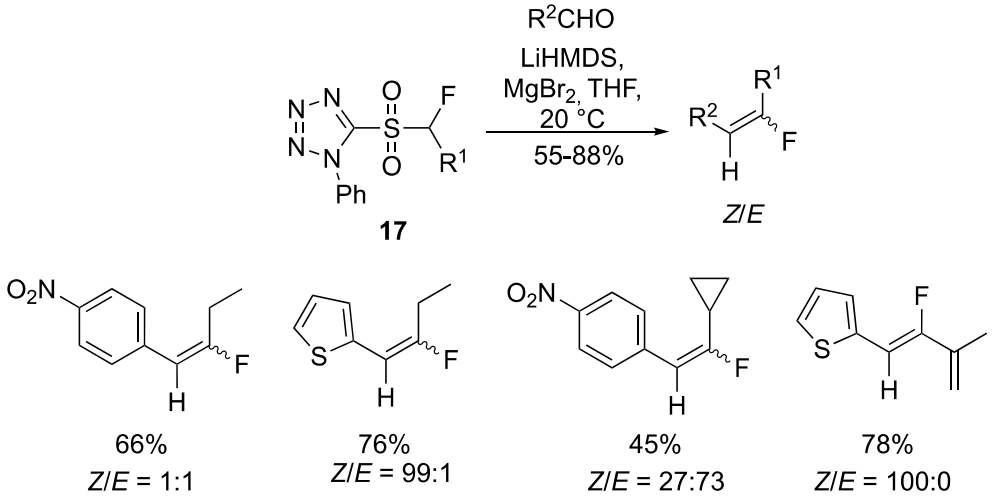
Scheme 7. Preparation of fluoroethylidene derivatives.

and the use of polar solvents (DMF:DMPU) could drive the reaction in favour of the *Z* isomers. This reaction can also be carried out from ketones.

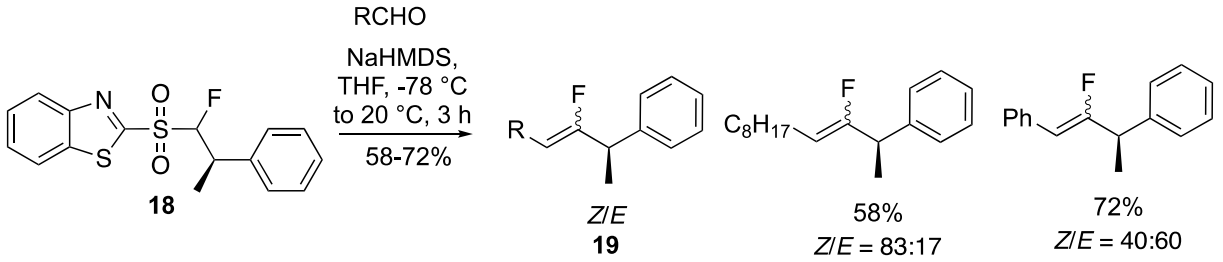
4. Fluoroalkenes substituted by an alkyl chain or a saturated ring

The synthesis of fluoroalkylidenes is the most challenging topic. As mentioned above, the fluoroolefination reactions of carbonyl compounds were limited and the modified Julia reaction opened a new way to access a wide range of fluoroalkenes.

Our first example on the pyrethrin analogue was the cornerstone of the fluoroolefination of carbonyl compounds based on the modified Julia reaction [14]. For example, the expected alkenes **14** and **15** were obtained in high yield but with a moderate *Z*/*E* selectivity (Scheme 7). This olefination reaction was applied to the synthesis of exo-glycals which were obtained in moderate to good yields and with moderate selectivity. Importantly, the reaction carried out with lactones required a stepwise process. In this case, the alcoholate intermediate had to be captured before the Smiles rearrangement could be



Scheme 8. Preparation of fluoroalkylidenes with tetrazolyl sulfones.



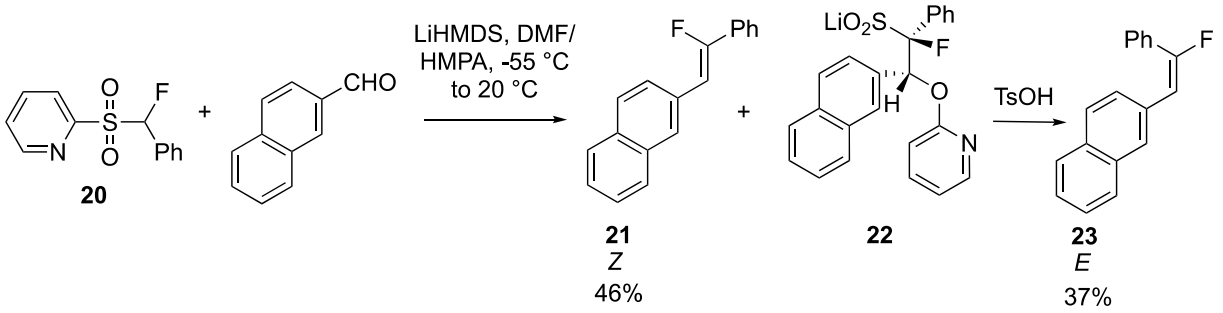
Scheme 9. Preparation of enantiopure allylic α-branched fluoroalkenes.

carried out at room temperature [30,31]. The modest selectivity observed in these examples was related to the small size of the methyl group even for the preparation of **16**. This reaction has been applied to the preparation of glucosidase inhibitors.

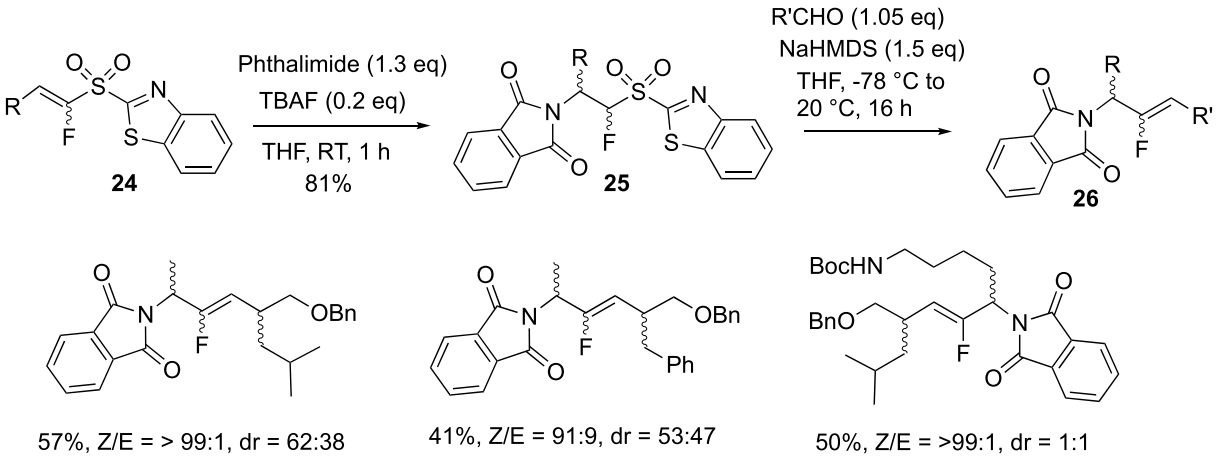
To partially address the stereoselectivity issue, phenyltetrazolyl sulfones **17** were tested instead of benzothiazolyl sulfones (Scheme 8) [32]. A rational analysis of the observed results was not easy to perform as the Z/E ratio was strongly dependent on the carbonyl compounds and the nature of the alkyl chain.

We have also reported the preparation of enantiomerically pure allylic α-branched fluoroalkenes from chiral fluorosulfones in the benzothiazolyl series (Scheme 9) [33]. The chiral sulfones **18** were prepared by a Mitsunobu reaction followed by a Krapcho decarbethoxylation reaction [34]. These sulfones were involved in the modified Julia reaction which, despite a moderate control of the carbon–carbon double bond geometry, provided an easy route to chiral fluoroalkenes **19**.

Notably, the group of J. Hu reported a rapid synthesis of *Z*- and *E*-fluoroalkenes by phase separation with pyridine sulfone **20** (Scheme 10) [35]. In this case, the *anti*-periplanar elimination is slow and depends on the relative configuration of the sulfinate intermediates. It has been suggested that the *anti*-lithium sulfinyl arylether, which gives gives the *(Z)*-alkene **21**, decomposes more rapidly than the *syn*-lithium sulfinyl arylether **22**, which gives the *(E)*-alkene **23**. Because of the aqueous solubility of the intermediate sulfinates, the kinetic control of the reaction allowed the *(Z)*-alkene to be extracted first with an organic solvent. The aqueous layer containing the *syn*-lithium sulfinyl arylether was then treated with an acid (TsOH) to give after extraction the corresponding *(E)*-alkene.



Scheme 10. Kinetic resolution for the synthesis of fluoroalkenes.

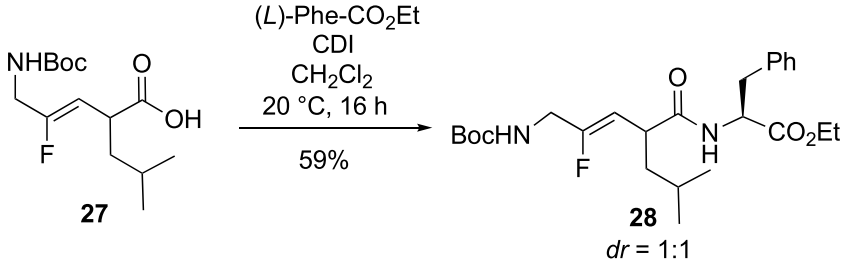


Scheme 11. Preparation of dipeptide isosteres.

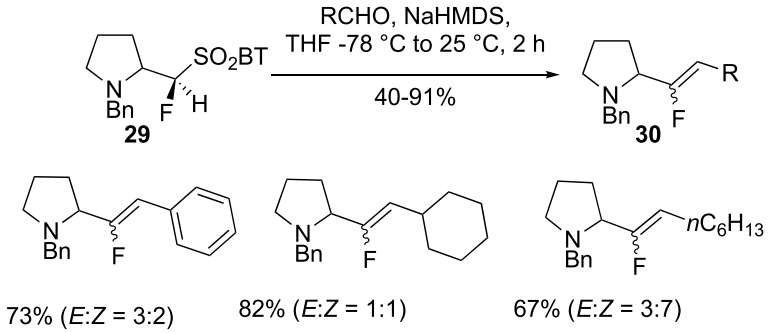
While the modified Julia reaction was efficient for the synthesis of fluoroalkenes, the preparation of functionalized fluoroalkenes was limited by the access to starting alkylfluorosulfones. In this area, we were focused on the challenging synthesis of nitrogen-containing fluoroalkenes. The preparation of aminosulfones was achieved from a fluorovinyl sulfone, and involved the olefination reaction. The aza-Michael addition of amines and amino acids to vinylsulfones **24** afforded the corresponding sulfones **25** as new fluoro-olefination reagents (Scheme 11) [36], whose reactivity in the modified Julia reaction was studied with carbonyl compounds and allowed us to prepare dipeptide isosteres **26** [37,38], and functionalized *exo*-glycal derivatives. Regarding the access to **26**, the *N*-terminal amino group was introduced by a conjugate addition of phtalimide onto fluorinated vinylsulfones containing an α-amino-acid side chain. The *C*-terminal motif was attached to the fluorovinylic peptide bond mimic *via* the Julia–Kocienski reaction between fluorosulfones and substituted aldehydes with α-amino-acid side chains (Scheme 11). In all cases, the diastereoselectivity was in favour of the *Z* isomers due to the steric demand of the bulky substituents.

Finally, the incorporation of monofluoroalkene-based dipeptide isosteres into peptide synthesis was tested (Scheme 12). A coupling reaction in solution between racemic Boc-Gly-ψ[CF=CH]-Leu **27** and (L)-phenylalanine ethyl ester was performed, yielding the corresponding tripeptide isostere Boc-Gly-ψ[CF=CH]-Leu-Phe-OEt **28**.

Following a similar approach, pyrrolidine fluorosulfone **29** was also prepared and used in the olefination of carbonyl compounds to give alkenes **30**



Scheme 12. Fluorinated tripeptide analogue.



Scheme 13. Pyrrolidine as potential proline isosteres.

in moderate to good yields with low E/Z selectivity (Scheme 13) [39].

Finally, this aza-Michael addition onto vinyl sulfones provided access to nucleic base-containing benzothiazolyl sulfones. For example, the thymine-derived sulfone **31** was used in the modified Julia reaction to prepare the acyclonucleoside precursor **33** (Scheme 14) [40].

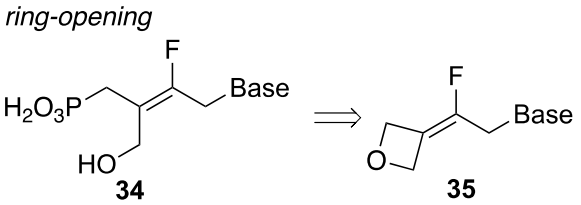


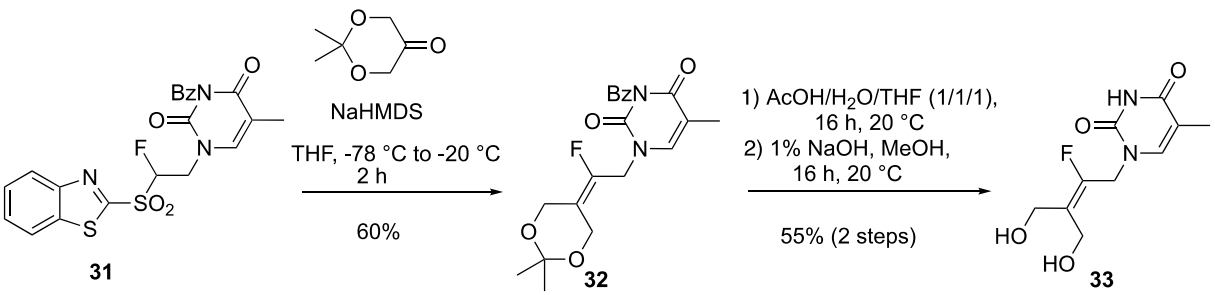
Figure 2. Ring–opening of oxetane derivatives.

5. Access trisubstituted fluoroalkenes for the preparation of acyclonucleosides

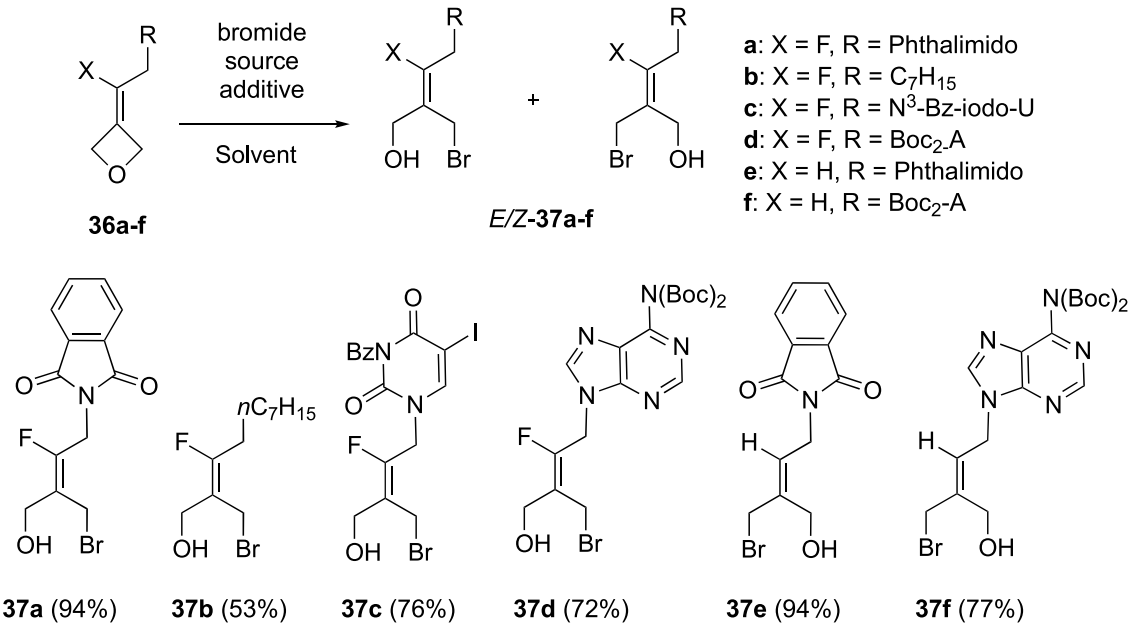
For the synthesis of trisubstituted fluoroalkenes, we explored another alternative route using alkylidene oxetanes **35** as key intermediates (Figure 2) [41]. The selective ring–opening reaction of fluoroalkylidene oxetanes was controlled by the presence of the fluorine atom, providing a two-step access to tetrasubstituted alkenes **34** with excellent geometry control (Figure 2) [42].

The preparation of a series of fluoroalkylidene oxetanes was realized from 3-oxetanone through an olefination reaction with benzothiazoyl sulfones (Scheme 15) [41]. With these fluoroalkylidene oxetanes **36a–f** in hand, the selectivity of the ring–opening reaction with bromide ion to access to tetrasubstituted fluoroalkenes was investigated.

The ring-opening reaction of oxetane **36a**, substituted by a phthalimido group, carried out with bromide ion sources (HBr 33 wt% in AcOH or Bu_4NBr in the presence of BF_3-Et_2O) afforded the corresponding *(E)*-alkene **37a** in an E/Z ratio of 89:11 (Scheme 15). This reaction was extended to other fluoroalkylidene oxetanes **36b–d** substituted with bulky substituents (an alkyl chain or a nucleic base) and different sources of bromide ions [42,43]. The ring-opening of these oxetanes to *(E)*-alkenes was also highly selective, thus confirming our initial observation. The reaction tested with oxetanes **36b–d** selectively gave the corresponding *E*-fluoroalkenes **37b–d**, in up to 9:1 E/Z ratios. On the other hand, when



Scheme 14. Preparation of an acyclonucleoside.



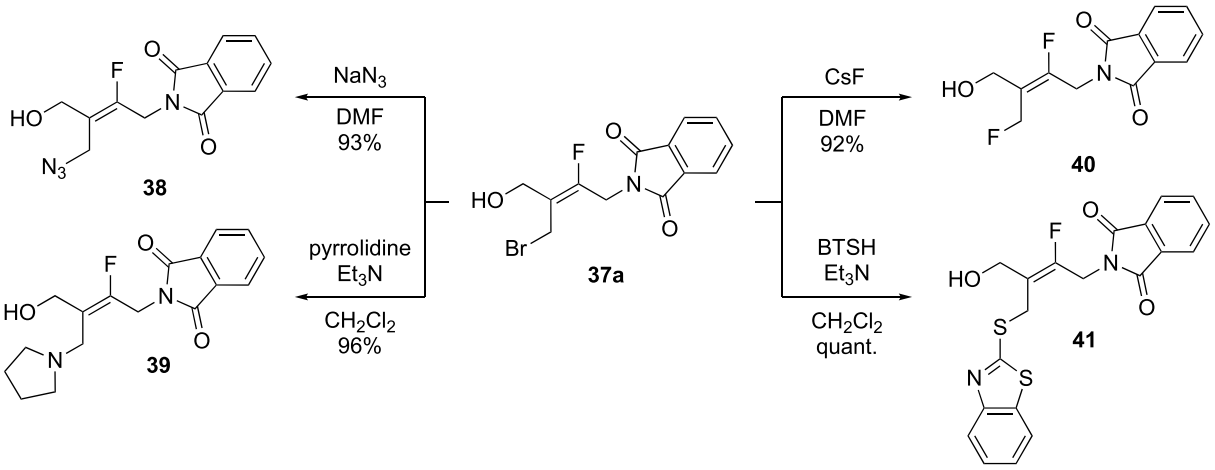
Scheme 15. Ring-opening reaction of alkylidene oxetanes.

the reaction with oxetanes **36e,f** was carried out in the absence of a fluorine atom, only *(E)*-alkenes **37e,f**, were formed. In this case, the attack of the bromide ion occurred on the opposite side of the bulky phthalimido or protected adenine substituents.

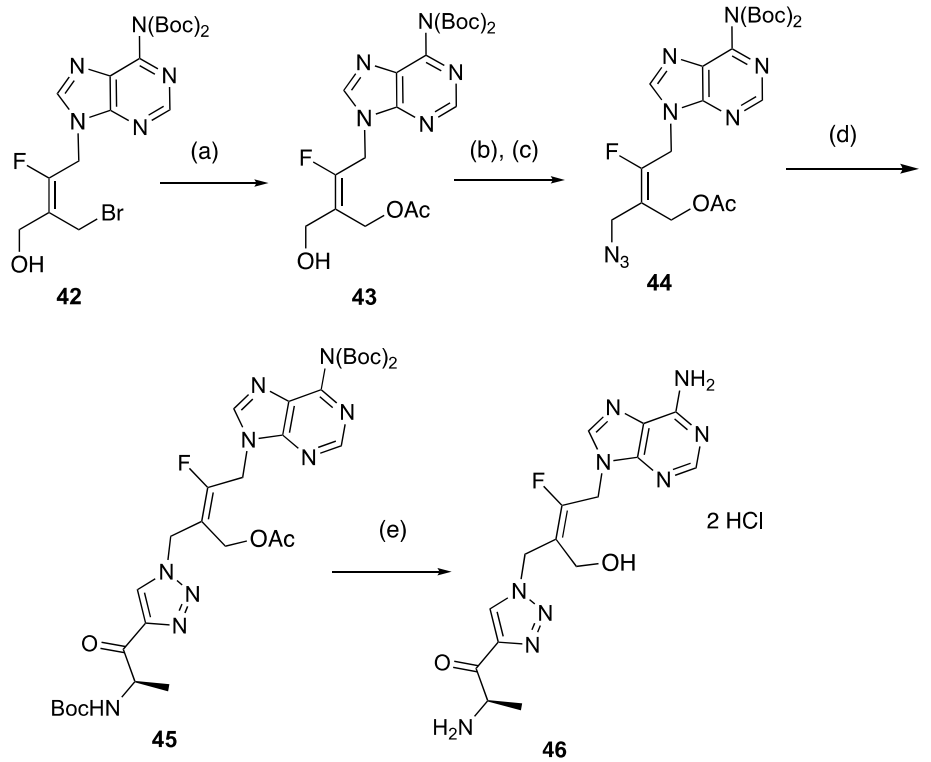
The functionalization of alkene **37a** allowed an easy access to a large series of tetrasubstituted fluoroalkenes. Indeed, the oxetane ring-opening reaction was restricted to the bromide ion (Scheme 16).

Functionalization of alkene **37a** by displacement of the bromine atom, with nucleophiles such as CsF and NaN_3 afforded products **40** and **38** in 92% and 93% yields, respectively. Reactions with amines and thiols such as pyrrolidine and 2-mercaptobenzothiazole, afforded products **39** and **41** in high yield.

Finally, this rapid synthesis of tetrasubstituted alkenes by sequential ring-opening and nucleophilic substitution reactions was intended to test the robustness of a selective preparation of acyclonucleoside precursors. In connection with our work on the preparation of inhibitors of a protein involved in antibioresistance [44–46], we focused on the synthesis of acyclic analogues of functionalized adenosine derivatives as enzyme inhibitors. Our aim was to determine the influence of the replacement of the ribosyl ring by a fluoroalkenyl chain on the biological activity of the resulting nucleoside analogue



Scheme 16. Functionalization by substitution reaction of the bromide.



Scheme 17. Preparation of triazolyl derivatives in F-series. (a) KOAc, DMF, 20 °C, 16 h, 86%. (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, (c) NaN_3, DMF, 20 °C, 12 h, 74% (2 steps). (d) *N*-Boc-amino-pentynone, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, *t*-BuOH, H_2O, 40 °C, 24 h, 79%. (d) HCl_{aq} (3N), MeOH, 20 °C, 20 h, 76%.

(Scheme 17). To access the final target compound **46**, the preparation of fluorinated azide **44** was realized from the tetrasubstituted (*E*)-alkene **42**. The substitution of the bromine atom was carried out with KOAc to give the intermediate acetylated alcohol **43**, which was mesylated and then treated with

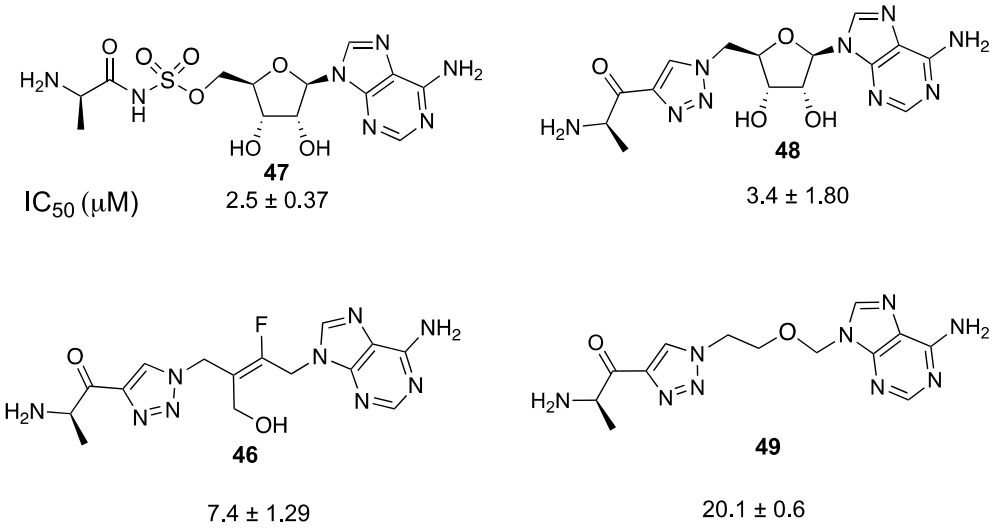


Figure 3. Measured IC_{50} values towards DltA of *E. faecalis*.

NaN_3 to produce azide **44** in 74% overall yield. Finally, the expected fluorinated triazolyl derivative **45** was obtained in 79% yield from **44** and *N*-Boc 4-amino-pentynone. Compound **45** was treated by an acidic methanolic solution to afford **46** in 76% yield (Scheme 17).

The inhibitory activity of **46** against the DltA enzyme (*Enterroccus faecalis*) was investigated and compared with that of nucleoside **47** (IC_{50} = 2.5 μM) and triazolyl derivative **48** (IC_{50} = 3.4 μM) (Figure 3) [46]. It appeared that the introduction of a triazolyl ring did interfere with the activity, and the replacement of the ribosyl ring by a fluoro *trans*-butenyl moiety was also well tolerated. Compound **46** exhibited an IC_{50} value of 7.4 μM, slightly higher than that observed with adenosine derivative **48**. This first example of the use of a fluoro *trans*-butenyl moiety shows that this moiety can be considered as a surrogate for the nucleoside ribosyl moiety. In the present case, the presence of a carbon–carbon double bond is important as reported for *trans*-butenyl substrates targeting thymidylate kinase [47,48], In contrast, the acyclic analogue **49** containing an alkyl ether chain (2-oxa-butyl) instead of a (fluoro)alkenyl chain was the less efficient inhibitor of the DltA enzyme with an inhibition constant of 20.1 μM. The loss of activity was probably related to the high flexibility of the alkyl chain, which allows conformational changes. The (*E*)-fluorobutenyl moiety appeared to be the best nucleoside mimic in the butenyl series.

6. Conclusion

The modified Julia reaction has contributed to the development of new approaches for the preparation of highly functionalized fluoroalkenes including fluoroalkylidenes. The discovery of this reaction and its application to the synthesis of fluorinated biomolecules has provided access to fluoroalkene motifs as mimics of dipeptides and acyclonucleosides.

Declaration of interests

The authors do not work for advise, own shares in, or receive funds from any organization that could benefit from this article, and have declared no affiliations other than their research organizations.

Funding

This work was supported by the excellence laboratory LabEx SYNORG (ANR-11-LABX-0029), the Conseil Régional de Normandie and the European FEDER funding.

References

[1] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315-8359.
[2] M. Inoue, Y. Sumii, N. Shibata, *ACS Omega*, 2020, **5**, 10633-10640.

[3] N. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320-330.
[4] J. Han, A. M. Remete, L. S. Dobson, L. Kiss, K. Izawa, H. Moriwaki, V. A. Soloshonok, D. O'Hagan, *J. Fluor. Chem.*, 2020, **239**, article no. 109639.
[5] G. Landelle, M. Bergeron, M.-O. Turcotte-Savard, J.-F. Paquin, *Chem. Soc. Rev.*, 2011, **40**, 2867-2908.
[6] H. Yanai, T. Taguchi, *Eur. J. Org. Chem.*, 2011, **2011**, 5939-5954.
[7] S. Couve-Bonnaire, D. Cahard, X. Pannecoucke, *Org. Biomol. Chem.*, 2007, **5**, 1151-1157.
[8] D. J. Burton, Z. Yang, W. Qiu, *Chem. Rev.*, 1996, **96**, 1641-1715.
[9] Z. Xu, D. D. Desmarteau, *J. Chem. Soc. Perkin Trans.*, 1992, **1**, 313-315.
[10] G. Etemad-Moghadam, J. Seyden-Penne, *Bull. Soc. Chim. Fr.*, 1985, **3**, 448-454.
[11] J. R. Mc Carthy, E. W. Huber, T. Le, M. Laskovics, D. P. Matthews, *Tetrahedron*, 1996, **52**, 45-58.
[12] S. J. Veenstra, K. Hauseer, P. Felber, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 351-354.
[13] J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Tetrahedron Lett.*, 1991, **32**, 1175-1178.
[14] D. Chevrie, T. Lequeux, J. P. Demoute, S. Pazenok, *Tetrahedron Lett.*, 2003, **44**, 8127-8130.
[15] B. Zajc, R. Kumar, *Synthesis*, 2010, **11**, 1822-1836.
[16] E. Pfund, T. Lequeux, D. Gueyrard, *Synthesis*, 2015, **11**, 1534-1546.
[17] E. Pfund, T. Lequeux, *Synthesis*, 2017, **17**, 3848-3862.
[18] Q. luo, X. Wang, J. Hu, *Tetrahedron*, 2022, **113**, article no. 132694.
[19] L. Zhu, C. Ni, Y. Zhao, J. Hu, *Tetrahedron*, 2010, **66**, 5089-5100.
[20] G. K. S. Prakash, A. Shakhmin, M. Zibinsky, I. Ledneczki, S. Chacko, G. A. Olah, *J. Fluorine Chem.*, 2010, **131**, 1192-1197.
[21] S. Kake, B. Zajc, *Org. Lett.*, 2006, **8**, 4457-4460.
[22] P. R. Blakemore, D. K. H. Ho, W. M. Nap, *Org. Biomol. Chem.*, 2005, **3**, 1365-1368.
[23] E. Pfund, C. Lebargy, J. Rouden, T. Lequeux, *J. Org. Chem.*, 2007, **72**, 7871-7877.
[24] F. Larnaud, E. Pfund, B. Linclau, T. Lequeux, *Tetrahedron*, 2014, **70**, 5632-5639.
[25] D. A. Alonso, M. Fuensanta, E. Gomez-Bengoa, C. Nájera, *Adv. Synth. Catal.*, 2008, **350**, 1823-1829.
[26] A. K. Ghosh, S. Banerjee, S. Sinha, S. B. Kang, B. Zajc, *J. Org. Chem.*, 2009, **74**, 3689-3696.
[27] M. Chowdhury, S. K. Mandal, S. Banerjee, B. Zajc, *Molecules*, 2014, **19**, 4418-4432.
[28] S. M. Mandal, A. K. Gosh, R. Kumar, B. Zajc, *Org. Biomol. Chem.*, 2012, **10**, 3164-3167.
[29] A. K. Ghosh, B. Zajc, *Org. Lett.*, 2006, **8**, 1553-1556.
[30] S. Habib, F. Larnaud, E. Pfund, T. Lequeux, B. Fenet, P. Goekjian, D. Gueyrard, *Eur. J. Org. Chem.*, 2013, **2013**, 1872-1875.
[31] S. Habib, F. Larnaud, E. Pfund, T. M. Barragán, T. Lequeux, C. Ortiz Mellet, P. Goekjian, D. Gueyrard, *Org. Biomol. Chem.*, 2014, **12**, 690-699.
[32] A. K. Ghosh, B. Zajc, *J. Org. Chem.*, 2009, **74**, 8531-8540.
[33] F. Larnaud, J. Malassis, E. Pfund, B. Linclau, T. Lequeux, *Org. Lett.*, 2013, **15**, 2450-2453.
[34] C. Calata, J.-M. Catel, E. Pfund, T. Lequeux, *Tetrahedron*, 2009, **65**, 3967-3973.
[35] Y. Zhao, F. Jiang, J. Hu, *J. Am. Chem. Soc.*, 2015, **137**, 5199-5203.
[36] C. Calata, E. Pfund, T. Lequeux, *J. Org. Chem.*, 2009, **74**, 9399-9405.
[37] C. Calata, E. Pfund, T. Lequeux, *Tetrahedron*, 2011, **67**, 1398-1405.
[38] F. Larnaud, C. Calata, A. Prunier, C. Le Guen, R. Legay, E. Pfund, T. Lequeux, *Org. Biomol. Chem.*, 2022, **20**, 1205-1218.
[39] C. Le Guen, M.-L. TranDo, A. Chardon, C. Lebargy, J.-F. Lohier, E. Pfund, T. Lequeux, *J. Org. Chem.*, 2016, **81**, 6714-6720.
[40] A. Prunier, C. Calata, J. Legros, J. Maddaluno, E. Pfund, T. Lequeux, *J. Org. Chem.*, 2013, **78**, 8083-8097.
[41] R. Laporte, A. Prunier, E. Pfund, V. Roy, L. A. Agrofoglio, T. Lequeux, *Eur. J. Org. Chem.*, 2015, **2015**, 3121-3128.
[42] C. Q. Fontenelle, T. Thierry, R. Laporte, E. Pfund, T. Lequeux, Beilstein, *J. Org. Chem.*, 2020, **16**, 1936-1946.
[43] D. Leparfait, F. Xiao, D. Coupri *et al.*, *Eur. J. Org. Chem.*, 2023, **26**, article no. e202300258.
[44] D. Coupri, A. Budin-Vernueil, A. Hartke, A. Benachour, L. Léger, T. Lequeux, E. Pfund, N. Verneuil, *J. Antimicrob. Chemother.*, 2019, **74**, 3162-3169.
[45] D. Coupri, N. Verneuil, A. Hartke, A. Liebaut, T. Lequeux, E. Pfund, A. Budin-Vernueil, *J. Antimicrob. Chemother.*, 2021, **76**, 2778-2786.
[46] J. J. May, R. Finking, F. Wiegeshoff, T. T. Weber, N. Bandur, U. Koert, M. A. Marahiel, *FEBS J.*, 2005, **272**, 2993-3003.
[47] D. Topalis, H. Kumamoto, M.-F. A. Velasco *et al.*, *FEBS J.*, 2007, **274**, 3704-3714.
[48] D. Topalis, U. Pradère, V. Roy *et al.*, *J. Med. Chem.*, 2011, **54**, 222-232.