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Research paper

Toward synthesis of thioglycosyl-phosphonate analogues of lipid II

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Abstract

Although a multitude of epidemics has already been eradicated with the use of modern antibiotics, in the 20th century, a new and increasingly serious phenomenon has arisen - the resistance against antibiotic therapies, necessitatingthe need for the development of novel antibiotic compounds. Transglycosylases are key enzymes in the biosynthesis of the bacterial cell wall, and currently, there is no approved drug in human use against them, so they are an excellent target for further antibiotic development. During our research, the main goal was to synthesize compounds that are structurally similar to lipid II, the substrate of bacterial transglycosylases, however, with significant modifications, such as the incorporation of an α-thioglycosidic unit instead of the α-*O*-glycosidic bond and an alkylphosphonate unit instead of the pyrophosphate part, making the molecules suitable to act as enzyme inhibitors. The key step of our work is the stereoselective construction of the 1,2-*cis*-α-thioglycosidic bond by photoinitiated thiol ene coupling reaction. In this paper, the novel synthesis route is described which can be applied to furnish different lipid II analogues, for example synthesis of a D-glucose derivative.

1. Introduction

By 2050, the estimated deaths associated with antimicrobial resistance are up to 8.2 million worldwide.[1] Since the profitability of antibiotic drug development is continually dropping in the pharmaceutical industry, the rising resistances are becoming more and more difficult to overcome, therefore the need for novel antibiotics is ever increasing. One promising target in the therapy can be the bacterial cell wall, as it is essential for the survival of the microorganism, however, human cells do not have this organelle, therefore the side effect profile of the cell wall targeting drugs can be significantly more favorable in comparison to the ones of other antibiotic groups.[2] Starting with the discovery and use of penicillin in 1928 as the groundbreaker in antibiotic therapy[3],

inhibition of the bacterial transpeptidase enzyme (which is responsible for the formation of the short peptide chains between the polysaccharide subunits) has always been a widely targeted goal.[4] During the process of the cell wall formation, the building block lipid II (**Figure 1.**) is synthesized in the inner leaflet of the cytoplasmic membrane[5], then is transported to the cell wall synthesis site, where it is coupled to the growing peptidoglycan chain by the transglycosylase enzymes.[6] Inhibition of these transglycosylase enzymes is yet to be broadly utilized, and although it is an extremely promosinigtarget, currently no transglycosylase enzyme inhibitor antibiotics are used in human therapy. In this research, a reaction route for the synthesis of novel potential drug candidates are described on the example of a simple monosaccharide.

By the time of writing, the only naturally occurring antibiotics that target the transglycosidase enzymes are the moenomycins, phosphoglycolipide molecules isolated from *Streptomyces ghanaensis* bacteria, however, due to their side effect profile they are only in veterinary use.[7] While the exact process of inhibition is still not completely determined, so far it has been established that moenomycins inhibit the transglycosylase (also known as peptidoglycan glycosyl transferase) enzymes *via* binding to the binding domains, them being structural analogues of the natural substrates, rendering the enzymes unable to perform the catalyzing processes.[8] There are several subclasses of synthetic transglycosylase inhibitors as well, the chief ones being the lipid II analogues. These compounds are designed to be structurally similar to the natural substrate, lipid II (**Figure 1.**).

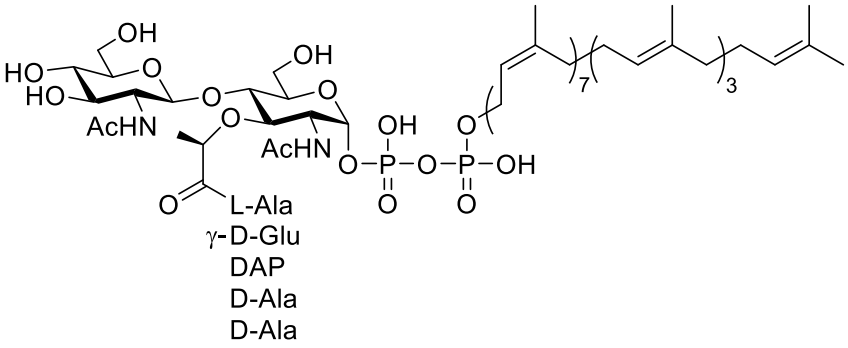

***Figure 1**.:* The structure of lipid II

Development of novel lipid II analogues has a decades-long history, among others mono-and disaccharide derivatives resembling both the moenomycins and lipid II have been synthesized,[9] as well as *N*-acetyl-glucosamine-thiazoline lipid II hybrids. In more recent research, iminosugar *C*-glycosides,[10] iminocyclitol type derivatives,[11] lipid II *C*-glycosides,[12] modified lipid II analogues such as *N*-deacetylated lipid II and a lipid II 4-hydroxy epimer,[13] and a novel anhydromuropeptide[14] were also described as potential

drug candidate compounds. In our research group, a β-1-thioglycoside type derivative has already successfully been synthesized and described,[15] in this paper, a continuation and broadening of that work is discussed.

2. Materials and methods

2,2-Dimethoxy-2-phenylacetophenone (DPAP), 4-methoxyacetophenone (MAP), and thioacetic acid (97%) were purchased from Sigma Aldrich Chemical Co. 2-acetoxy-D-glucal (**1**)[16] and vinylidene bisphosphonate (**4**)[17] were synthesized according to literature methods. The photoinitiated reactions were carried out in a borosilicate vessel by irradiation with a UV lamp (125 W) giving maximum emission at 365 nm. TLC was performed on Kieselgel 60 F_{254} (Merck) with detection by UV-light (254 nm) and immersing into sulfuric acidic ammonium-molibdenate solution, sulfuric acid and,4-anisaldehyde solution in 5% ethanol, or 5% ethanolic sulfuric acid followed by heating. Flash column chromatography was performed on Silica gel 60 (Merck 0.040-0.063 mm). ^{1}H and J-modulated ^{13}C NMR spectra were recorded with Bruker DRX-400 (1H: 400 MHz; ^{13}C: 100 MHz) and Bruker DRX-500 (1H: 500 MHz; ^{13}C: 125 MHz) spectrometers at 25 ºC. Chemical shifts are referenced to Me_4Si (0.00 ppm for ^{1}H) and to the residual solvent signals ($CDCl_3$: 77.16 for ^{13}C). MALDI-ToF MS analyses of the compounds were carried out in the positive reflectron mode using a BIFLEX III mass spectrometer (Bruker, Germany) equipped with delayed-ion extraction. 2,5-Dihydroxybenzoic acid (DHB) was used as a matrix and $F_3CCOONa$ as a cationising agent in DMF.

2. Chemical Synthesis

2,3,4,6-Tetra-*O*-acetyl-1-*S*-acetyl-1-thio-α-D-glucopyranose (**2**)[18]

Compound **1** (330 mg, 1.0 mmol), thioacetic acid (6.0 equiv, 6.0 mmol, 0.42 mL), DPAP (0.1 equiv, 0.1 mmol, 25 mg) and MAP (0.3 equiv, 0.3 mmol, 45 mg), were dissolved in 96% acetic acid (1.5 mL). The reaction mixture was cooled to -80 °C and was irradiated with UV light for 60 minutes. After irradiation, another 6.0 equiv. of thioacetic acid and 0.1 equiv. of DPAP were added and the irradiation was continued for 60 min. The addition of 6.0 equiv. of thioacetic acid and 0.1 equiv. of DPAP, and the 60 min irradiation was repeated one more time. The solvent was evaporated in vacuo and the crude product was purified by flash column chromatography (*n*-hexane:acetone 85:15) to give compound **2** (328 mg, 81%) as white crystals.

R_f = 0.20 (*n*-hexane:acetone = 8:2) $[\alpha]_D^{20}$= +132.8 (*c* = 0.28 in $CHCl_3$, lit.[18] $[\alpha]_D^{20}$= +135; m. p.: 128-129 °C, lit.[18] m. p.: 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.22 (d, *J* = 5.2 Hz, 1H, H-1), 5.24 (dd, *J* = 10.1, 5.1 Hz, 1H, H-2), 5.18 (t, *J* = 9.5 Hz, 1H, H-3*), 5.10 (t, *J* = 9.5 Hz, 1H, H-4*), 4.28 (dd, *J* = 12.5, 4.1 Hz, 1H, H-6a), 4.05 (dd, *J* = 12.5, 2.2 Hz, 1H, H-6b), 3.96 (ddd, *J* = 9.9, 4.0, 2.3 Hz, 1H, H-5), 2.43 (s, 3H, AcC*H*$_3$), 2.08 (s, 3H, AcC*H*$_3$), 2.03 (s, 3H, AcC*H*$_3$), 2.02 (s, 3H, AcC*H*$_3$), 2.02 (s, 3H, AcC*H*$_3$) ppm. *interchangeable signals ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.7, 170.1, 169.5, 169.4 (4C, 4xAc*C*O), 80.5 (1C, C-1), 71.6, 71.3, 69.2, 68.0 (4C, skeletal carbons), 61.7 (1C, C-6), 31.6 (1C, SAc*C*H$_3$), 20.8, 20.7, 20.7 (4C, 4xOAc*C*H$_3$) ppm.; MALDI-ToF-HRMS: *m/z* calcd for $C_{16}H_{22}NaO_{10}S$ $[M+Na]^+$ 429.0831, found 429.0826.

2,3,4,6-Tetra-*O*-acetyl-1-thio-α-D-glucopyranose (**3**)

Compound **2** (406 mg, 1.0 mmol) was dissolved in dry methanol (10 mL), then the solution was deoxygenated *via* argon bubbling. The reaction mixture was cooled to 0 °C, and then 0.95 equiv (0.95 mmol, 51 mg) of NaOMe was added in the form of freshly prepared stock solution in methanol. The reaction mixture was stirred at 0 °C until no starting material was observed on TLC (45 minutes). The solution was neutralized using Amberlite IR 120 H^+ ion exchange resin, the resin was filtered off, and the solution was concentrated under reduced pressure. The crude product was purified by flash column chromatography (*n*-hexane:acetone 8:2) to give compound **3** (335 mg, 92%) as colourless foam. The compound was stored under an argon atmosphere until use. R_f = 0.26 (n-hexane:acetone 8:2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (t, *J* = 5.6 Hz, 1H, H-1), 5.38 (t, *J* = 9.8 Hz, 1H, H-3), 5.12 - 5.04 (m, 2H, H-2, H-4), 4.44 (ddd, *J* = 10.3, 4.4, 2.3 Hz, 1H, H-5), 4.30 (dd, *J* = 12.4, 4.2 Hz, 1H, H-6a), 4.11 (dd, *J* = 12.4, 2.3 Hz, 1H, H-6b), 2.09 (s, 6H, 2xAcCH_3), 2.04 (s, 6H, 2xAcCH_3), 1.92 (d, *J* = 5.6 Hz, 1H, S*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.9, 169.7, 169.6 (4C, 4xAcCO), 77.1 (1C, C-1), 70.3 (1C, C-2), 69.9 (1C, C-3), 68.3 (2C, C-4, C-5), 61.7 (1C, C-6), 20.7, 20.7, 20.7, 20.6 (4C, 4xAcCH_3) ppm. MALDI-ToF-HRMS: *m/z* calcd for $C_{14}H_{20}NaO_9S$ $[M+Na]^+$ 387.0726, found 387.0710.

α-1-Thioglucopyranosyl bisphosphonate conjugate (**5**)

Compound **3** (2.0 mmol, 728 mg) and compound **4** (1.0 equiv, 2.0 mmol, 600 mg) were dissolved in dry dichloromethane (20 mL) under an inert argon atmosphere. The

reaction mixture was stirred at rt for 16 hours. After completion, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography (*n*-hexane:acetone 7:3) to give compound **5** (510 mg, 38%) as yellow syrup. The product was used in the following step without characterization.

Hexyl chain bearing α-1-thioglucopyranosyl phosphonate derivatives (**6a** and **6b**)

Compound **5** (0.25 mmol, 167 mg) was dissolved in dry 1,4-dioxane (10 mL). NaH (1.2 equiv, 0.30 mmol, 7.24 mg in 12.4 mg 60% suspension) and *n*-hexanal (1.0 equiv, 0.25 mmol, 30 µL) were added, and the reaction mixture was stirred at rt for 120 minutes. After completion, 800 µL of 50% AcOH solution was added. The reaction mixture was concentrated under reduced pressure, dissolved in dichloromethane, and washed with water, the combined organic phase was dried over anhydrous Na_2SO_4, then filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (*n*-hexane:acetone 75:25) to give compounds **6a** and **6b** (51.5 mg, 34% combined yield, 3:1 ratio), both as colourless syrup.

Data for the major *Z* component **6a**: R_f = 0.28 (*n*-hexane-acetone 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (dt, *J* = 47.2, 7.7 Hz, 1H, PC=C*H*), 5.55 (d, *J* = 5.8 Hz, 1H, H-1), 5.39 (t, *J* = 9.8 Hz, 1H), 5.11 – 5.02 (m, 2H), 4.44 (ddd, *J* = 10.3, 4.7, 2.3 Hz, 1H), 4.31 (dd, *J* = 12.4, 4.7 Hz, 1H), 4.18 – 3.98 (m, 5H), 3.46 – 3.20 (m, 2H, SCH_2), 2.47 (m, 2H), 2.09 (s, 3H, AcCH_3), 2.04 (s, 3H, AcCH_3), 2.03 (s, 3H, AcCH_3), 2.01 (s, 3H, AcCH_3), 1.36 – 1.29 (m, 12H), 0.90 (t, *J* = 6.8 Hz, 3H, hexyl CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 169.1, 168.7 (4C, 4xAc*C*O), 150.5 (1C, P*C*=CH), 123.8, 122.4 (d, 1C, PC=*C*H), 79.2 (1C, C-1), 69.8, 69.6, 67.7, 66.8 (4C, skeletal carbons), 61.0 (1C, C-6), 60.8 (d, *J* = 5.3 Hz, 1C, O*C*H_2CH$_3$), 60.5 (d, *J* = 5.4 Hz, 1C, O*C*H_2CH$_3$), 32.3, 30.6, 29.5, 28.8, 28.5, 27.9, 21.6, 19.8, 19.7, 15.5, 13.1 (1C, hexyl *C*H$_3$). MALDI-ToF-HRMS: *m/z* calcd. $C_{26}H_{43}NaO_{12}PS$ $[M+Na]^+$ 633.2105, measured 633.2099.

Data for the minor *E* component **6b**: R_f = 0.26 (*n*-hexane-acetone 7:3); MALDI-ToF-HRMS: *m/z* calcd. $C_{26}H_{43}NaO_{12}PS$ $[M+Na]^+$ 633.2105, measured 633.2129.

3. Results and discussion

The goal of the research was to facilitate a general route (**Scheme 1**) from 2-substituted glycals to furnish lipid II analogue compounds bearing an α-thioglycosidic bond attached to alkylphosphonate units of various lenghth. In this paper, the route is demonstrated on the D-gluco example.

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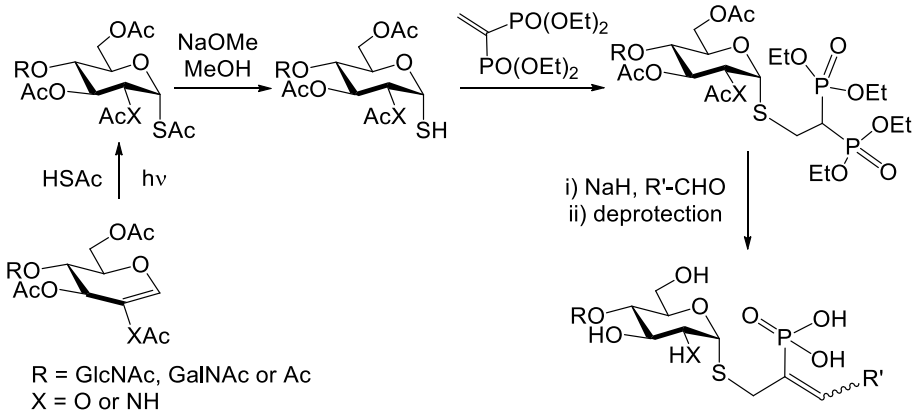
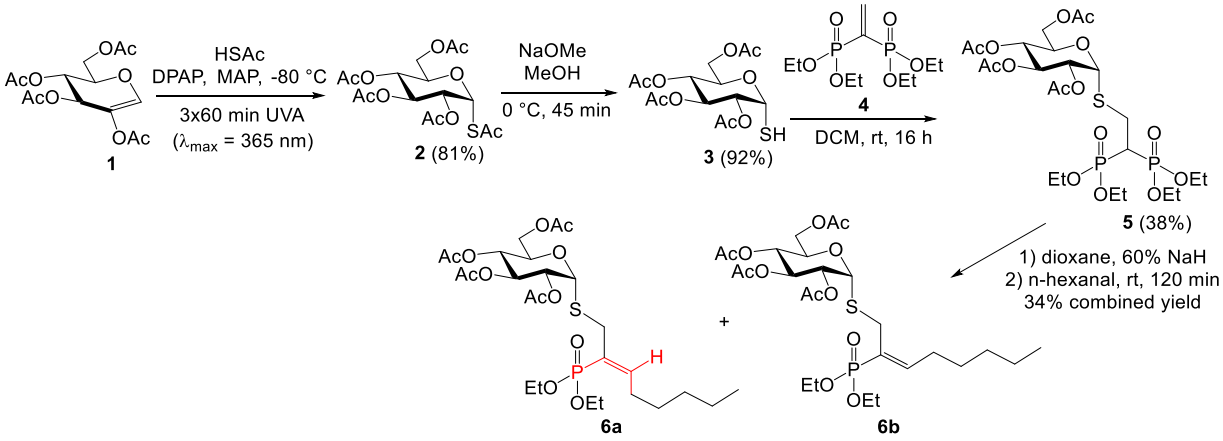


Scheme 1.: Planned synthesis route to α-thioglycoside anlogues of lipid II

The first step in this pathway is the synthesis of the 1,2-*cis*-α-1-thiosugars from 2-substituted glycals (mono- or disaccharides) using photoinitiated thiol-ene addition, followed by selective *S*-deacetylation. The radical-mediatedthiol-ene reaction can be performed on a wide variety of enoses, including 2-acetamido derivatives and disaccharides, which is noteworthy because those moieties are present in the naturally occurring lipid II. The thiosugars can then be converted to the planned alklylphosphonate derivatives in four steps including conjugated addition to ethylidene bisphosphonate, Wadsworth-Horner-Emmons reaction of the the thioglycosyl bisphophonates with long-chain aldehydes and two-step deprotection.[15]



Scheme 2.: Synthesis of lipid II analogue model compounds **6a** and **6b** from D-glucal and *n*-hexanal

Photoinitiated thiol-ene addition reaction has already been applied in carbohydrate chemistry to furnish stable thioconjugates.[19, 21-23] Recently, it has been shown that using 2-substituted glycals as alkene reactants, the method is suitable for stereoselective synthesis of 1,2-*cis*-α-thioglycosides and 1,2-*cis*-α-1-glycosyl thiols with good to exceptionally high yields in two steps from glycals.[20, 24, 25] The model reaction on 2-acetoxy-D-glucal (**1**) and thioacetic acid was carried out in 96% acetic acid with DPAP (2,2-dimethoxy-2-phenylacetophenone) as photoinitiator and MAP (4-

methoxyacetophenone) as photosensitizer, in which compound **2** was obtained with 81% isolated yield.

The 1,2-*cis*-α-D-glucosyl thiol was then obtained using selective *S*-deacetylation, and was immediately used in the following reaction. On the activated double bond of the ethylidene bisphosphonate derivative, a conjugated thioladdition reaction was performed in dichloromethane. The reaction was completed in 16 hours at room temperature under an inert argon atmosphere with a 38% isolated yield. The low yield can be attributed to disulfide formation from the thiol as a by-product. As the last step of the reaction route, the Wadsworth-Horner-Emmonds reaction [26] was performed on the bisphosphonate derivative **5**. In dioxane, NaH was used as a base to furnish the carbanion intermediate, then n-hexanal was used in the same-pot condensation-elimination reaction to obtain the *Z* and the *E* alkyl monophosphonate derivatives in 34% total yield. The two isomers formed and have been isolated in approximately 3:1 ratio. It is noteworthy to mention that the major *Z* isomer (**6a**) can be identified by the characteristically high coupling constant of the anti-positionedproton to the phosphorous atom (highlighted in red in **Scheme 2**). The coupling constant $J_{P,H}$ of **6a** was measured to be 47.2 Hz, which corresponds to the value found in the case of the preceding β-D-glcNAc derivative (47.0 Hz).[15]

4. Conclusion

A reaction route for the synthesis of lipid II thioglycosidic mimetics has successfully been developed, using a simple α-D-glucose unit as a model compound in place of the glucosaminyl-β(1–4)-muramic acid disaccharide. A key step in this reaction route was the formation of the 1,2-*cis*-α-thioglycosidic bond, which was formed using a photoinitiated thiol-ene addition reaction, with full regio- and stereoselectivity. Following selective *S*-deprotection, the thiosugar was used in a conjugated addition step to furnish the desired bisphosphonate conjugate. This conjugate was then coupled to *n*-hexanal using Wadsworth-Horner-Emmons reaction, where the *Z* stereoisomer was found as the major product. Our method can be used in the future by varying the carbohydrate part and the alkyl chain to furnish a broad variety of different lipid II analogue compounds. Notably, in the future, 2-acetamido-D-gluco and -galacto type derivatives are planned to be synthesized, them being structurally most similar to the naturally occurring lipid II. Various disaccharides are also planned to be introduced to better mimic the disaccharide characteristic of the original lipid II molecule, and the effects of different alkyl side chains will be investigated as well.

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Data Availability Statement:

All measurement data are available at the corresponding author in case of further requests.

References

1. Kariuki S. Global burden of antimicrobial resistance and forecasts to 2050. The Lancet. 2024;404(10459):1172 - 1173.
2. Bugg TDH, Walsh CT. Intracellular steps of bacterial cell wall peptidoglycan biosynthesis: enzymology, antibiotics, and antibiotic resistance. Nat Prod Rep. 1992; 9:199-215.
3. Bennett JW, Chung K-T. Alexander Fleming and the discovery of penicillin. Adv Appl Microbiol. 2001;49:163-184.
4. Cochrane SA, Lohans CT, Breaking down the cell wall: Strategies for antibiotic discovery targeting bacterial transpeptidases. Eur J Med Chem. 2020;194:112262.
5. Karak M, Cloonan CR, Baker BR, Cochrane RVK, Cochrane SA. Optimizations of lipid II synthesis: an essential glycolipid precursor in bacterial cell wall synthesis and a validated antibiotic target. Beilstein J Org Chem. 2024;20(1):220-227.
6. Ostash B, Walker S. Bacterial transglycosylase inhibitors. COCHBI. 2005;9(5):459-466.
7. Ostash B, Doud E, Walker S. ABC Transporter Genes from Streptomyces ghanaensis Moenomycin Biosynthetic Gene Cluster: Roles in Antibiotic Production and Export. Arch Microbiol. 2012;194:915-922.
8. Ostash B, Makitrynskyy R, Yushchuk O, Fedorenko V. Structural diversity, bioactivity, and biosynthesis of phosphoglycolipid family antibiotics: Recent advances. BBA Advances. 2022;2:100065.
9. Garneau S, Qiao L, Chen L, Walker S, Vederas JC, Bioorg Med Chem, Synthesis of mono- and disaccharide analogs of moenomycin and lipid II for inhibition of transglycosylase activity of penicillin-binding protein 1b. 2004;12(24):6473-6494.
10. Tseng YY, Liou JM, Hsu TL, Cheng WC, Wu MS, Wong CH. Development of bacterial transglycosylase inhibitors as new antibiotics: moenomycin A treatment for drug-resistant Helicobacter pylori. Bioorg Med Chem Lett. 2014;24:2412−2414.
11. Shih HW, Chen KT, Chen SK, Huang CY, Cheng TJ, Ma C, Wong CH, Cheng WC. Combinatorial approach toward synthesis of small molecule libraries as bacterial transglycosylase inhibitors. Org Biomol Chem. 2010;8:2586−2593

12. Lin CK, Chen KT, Hu CM, Yun WY, Cheng WC. Synthesis of 1-C-Glycoside-Linked Lipid II Analogues Toward Bacterial Transglycosylase Inhibition. Chem Eur J. 2015; 21:7511−7519

13. Chen KT, Lin CK, Guo CW, Chang YF, Hu CM, Lin HH, Lai Y, Cheng TJR, Cheng WC. Effect of the lipid II sugar moiety on bacterial transglycosylase: the 4-hydroxy epimer of lipid II is a TGase inhibitor. Chem Commun. 2017;53(4):771-774.

14. Zhang XL, Báti G, Li C, Guo A, Yeo C, Ding H, Pal KB, Xu Y, Qiao Y, Liu XW. GlcNAc-1,6-anhydro-MurNAc Moiety Affords Unusual Glycosyl Acceptor that Terminates Peptidoglycan Elongation. J Am Chem Soc. 2024;146(11):7400-7407.

15. Borbás A, Herczegh P. Synthesis of lipid II phosphonate analogues. Carbohydr Res. 2011;346(12):1628-1632.

16. Rao DR, Lerner LM. Dehydrohalogenation of glycosyl halides with 1,5-diazabicyclo[5.4.0]undec-s-ene. Carbohydr Res. 1972;22:345-350.

17. Page PCB, Moore PGJ, Mansfield I, McKenzie MJ, Bowler WB, Gallagher JA. Synthesis of bone-targeted oestrogenic compounds for the inhibition of bone resorption. Tetrahedron. 2001;57:1837–47.

18. Sakata M, Haga M, Tejima S, Akagi M. Thiosugars. VI. Reaction Products of Potassium Alkyl- and Benzylxanthates with Acetylated Glucosyl Halides. Chem Pharm Bull. 1964;12:652-6.

19. Borbás A, Photoinitiated Thiol-ene Reactions of Enoses: A Powerful Tool for Stereoselective Synthesis of Glycomimetics with Challenging Glycosidic Linkages, Chem Eur J, 2020, 26, 6090-101

20. Kelemen V, Bege M, Eszenyi D, Debreczeni N, Bényei A, Stürzer T, Herczegh P, Borbás A. Stereoselective Thioconjugation by Photoinduced Thiol-ene Coupling Reactions of Hexo- and Pentopyranosyl D- and L-Glycals at Low-Temperature—Reactivity and Stereoselectivity Study. Chem Eur J. 2019;25:14555-71.

21. Fiore M, Marra A, Dondoni A. Photoinduced Thiol—Ene Coupling as a Click Ligation Tool for Thiodisaccharide Synthesis. J Org Chem. 2009;74(11):4422-5.

22. McSweeney L, Dénès F, Scanlan EM. Thiyl-Radical Reactions in Carbo-hydrate Chemistry: From Thiosugars to Glycoconjugate Synthesis. Eur J Org Chem. 2016; 2080−95.

23. Kelemen V, Borbás A. Glycomimetics with unnatural glycosidic linkages. Recent Trends in Carbohydrate Chemistry. Rauter AP, Christensen BE, Somsák L, Kosma P, Adamo R (Eds). 2020; Elsevier: Amsterdam, The Netherlands, 161–215.

24. Lázár L, Csávás M, Herczeg M, Herczegh P, Borbás A. Synthesis of S-Linked Glycoconjugates and S-Disaccharides by Thiol–Ene Coupling Reaction of Enoses. Org Lett. 2012;14(17):4650-3.

25. Eszenyi D, Kelemen V, Balogh F, Bege M, Csávás M, Herczegh P, Borbás A. Promotion of a Reaction by Cooling: Stereoselective 1,2-cis-α-Thioglycoconjugation by Thiol-Ene Coupling at −80 °C. Eur J Chem. 2018;24(18):4532-6.

26. Wadsworth WS. Synthetic Applications of Phosphoryl-Stabilized Anions. Org React. 1977;25(73):253.