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Programmable One-Pot Synthesis of Heparin Pentasaccharide Fondaparinux

Supriya Dey, Hong-Jay Lo, and Chi-Huey Wong*

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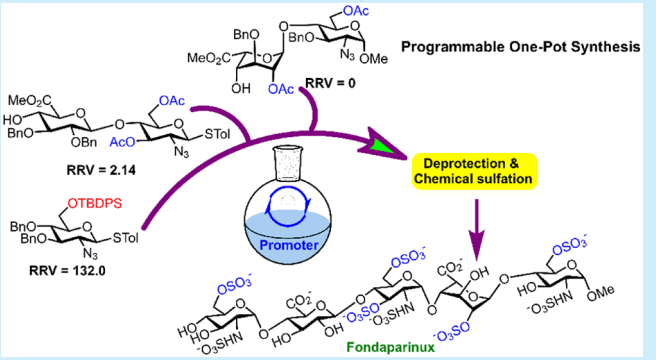
ABSTRACT: The clinically approved Fondaparinux (Arixtra) has been used for the treatment of deep vein thrombosis and acute pulmonary embolism since 2002 and is considered to be better than the low-molecular weight heparin in terms of anticoagulation response, duration of action, and biosafety. However, the synthetic methods previously developed for its manufacture are relatively complicated, thus restricting its extensive use. We report here a potentially scalable and programmable one-pot synthesis of Fondaparinux using the [1,2,2] strategy and designed thioglycosides with well-defined reactivity as building blocks.



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Fondaparinux **1**, a synthetic pentasaccharide with the brand name Arixtra, is a heparin-based anticoagulant that has been used for the treatment of deep vein thrombosis (DVT) and acute pulmonary embolism (PE) since 2002. Two types of heparins, namely, high-molecular weight heparin (HMWH) and low-molecular weight heparin (LMWH), have been used as injectable anticoagulants that bind to antithrombin III (AT) and exhibit selective inhibition of factor Xa and thrombin in the blood clotting cascade.[1] However, active monitoring is required for the patients to which heparins have been administered as serious complications like heparin-induced thrombocytopenia bleeding may occur. The sulfate-containing synthetic pentasaccharide **1** with the sequence D-GlcNS6S-α-(1,4)-D-GlcA-β-(1,4)-D-GlcNS3,6S-α-(1,4)-L-IdoA2S-α-(1,4)-D-GlcNS6S-OMe was identified as the AT-binding sequence[2] and later was introduced into the market in 2002 with the trade name "Fondaparinux (Arixtra)" (Figure 1).[3] Fondaparinux was shown to have a faster anticoagulation response, higher and more predictable anti-Xa activity, a longer half-life, a longer duration of action, a lower risk of heparin-induced thrombocytopenia (HIT), and better biosafety compared to those of LMWH, making it a more acceptable anticoagulant.[4] In addition, the contamination in naturally occurring heparins that caused several deaths[5] in 2008 led to the increasing clinical use of Fondaparinux as an alternative and perhaps better anticoagulant.

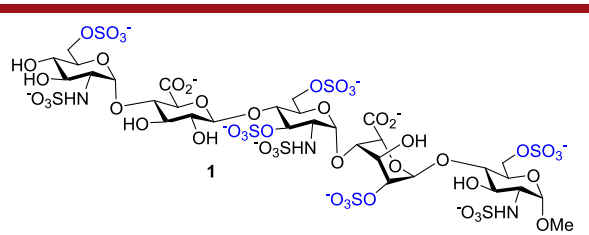

Figure 1. Structure of Fondaparinux.

For the treatment of DVT and acute PE, the recommended dose of **1** ranges from 5 to 10 mg/day based on body weight. However, the high-cost treatment ($600−1400 in the United States), mainly due to its complicated and high-cost manufacturing process, has limited the availability of Fondaparinux.

Thus, development of an efficient and cost-effective synthesis of **1** is highly desirable to meet the clinical demand. The synthesis of Fondaparinux is very challenging due to the difficulty in the regio- and stereoselective glycosylation among the glucosamine, glucuronic acid, and iduronic acid building blocks and the strategic installation of OSO_3^- and $NHSO_3^-$ groups. In particular, the 1,2-*cis* or α-glycosylation between a glucosamine and a uronic acid building block without the formation of the unwanted β-isomer as well as improvement of the overall yield via the shortest possible synthetic route represents a major challenge. In the past years, many groups, including those of Petitou,[6] Lin,[7] Hung,[8] Wang,[9] Qin,[10] Manikowski,[11] and Ding,[12] have reported the synthesis of

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Fondaparinux, but the procedures still encounter problems such as a long stepwise process, non-stereoselective glycosylation and low yield and efficiency. Zhao and co-workers recently reported a preactivation-based iterative one-pot synthesis of Fondaparinux with a <40% yield.[13] We thought the method of programmable one-pot synthesis of oligosaccharides using designed thioglycoside building blocks with defined relative reactivity values (RRVs) developed by us[14,15] could be useful for the practical synthesis of **1**.

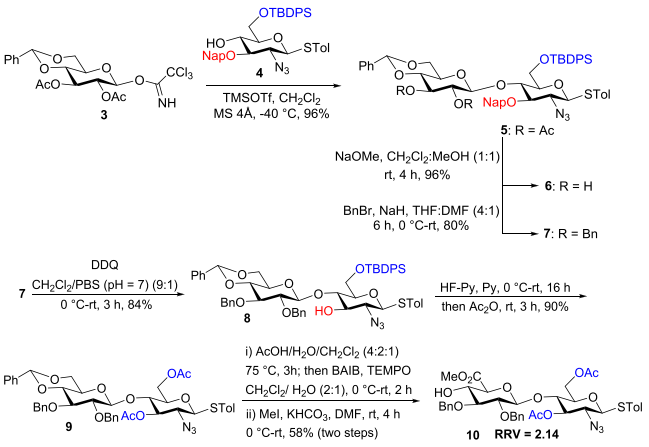
The concept of RRV is based on the quantitative determination of the reactivity of a thioglycoside donor with methanol as compared to the reactivity of the thioglycoside donor of *per*-acetyl mannose. RRV is measured using HPLC to determine the amount of leaving group released and the starting donor left during the reaction time course. With the RRVs of various thioglycoside building blocks (BBLs) available, one can design computer software to guide the selection of appropriate BBLs with well-differentiated RRVs for the one-pot assembly of oligosaccharides. We developed the first computer program, Optimer, in 1999[14] as a database search tool for the rapid one-pot assembly of large numbers of linear and branched complex oligosaccharides including *N*-glycans[15] and glycosaminoglycans.[16] In 2018, we reported an upgraded version of this software, Auto CHO, with a library of 150 BBLs with experimentally measured RRVs and 50000 BBLs with RRVs predicted by machine learning (including those with RRVs predicted by chemical shifts by NMR)[14] to diversify the applicability of the software for the synthesis of oligosaccharides. To use either Optimer or Auto CHO, the user needs to input the desired oligosaccharide structure, and then the software will generate one or more synthetic routes based on the RRVs of the BBLs needed for the synthesis of the oligosaccharide as output. Once the user chooses a specific synthetic route from the output, BBLs are required to be synthesized in the laboratory and then one-pot synthesis can be performed by sequential addition of BBLs starting from the most reactive from the nonreducing end unit toward the less reactive, least reactive, and so on in the reducing end. The one-pot strategy was successfully applied to the synthesis of heparin-like oligosaccharides[16a,b] and the heparin-based anticoagulant Idraparinux.[16c]

The building blocks used in this one-pot strategy allow differential removal of the protecting groups for the regioselective introduction of sulfate groups to evaluate their role in biological functions. Following this strategy, we report here an efficient and scalable programmable one-pot synthesis of Fondaparinux **1** using the [1,2,2] strategy and designed thioglycosides (**2**, **10**, and **18**) as building blocks.

All of the building blocks can be readily attained from commercially available monosaccharides. The synthetic design involves the use of our established programmable one-pot method to conduct highly α-selective glycosylation using TBDPS and Ac groups at *O*6 and late stage introduction of the acidic functionalities (glucuronic and iduronic). For the selective installation of the 3-SO_3^- group, we masked the C3-hydroxyl group (C3-OH) with an orthogonal protecting group, namely, 2-naphthylmethyl ether (Nap). The synthesis of 2-azido thioglycoside donor **2** was achieved from D-glucosamine hydrochloride using our previously reported procedure (Scheme S1).[16b] The RRVs of the newly synthesized building blocks were measured by HPLC analysis in a competition assay with a reference thioglycoside donor with a known RRV (Supporting Information).[14,15]

The synthesis of disaccharide **10** involved the glycosylation between glycosyl trichloroacetimidate **3**[17] and thioglycoside acceptor **4**[18] in the presence of TMSOTf to generate **5** in 96% yield. Zémplen deacetylation gave **6**, and *O*-benzylation of 2′,3′-OH led to the formation of **7** in 80% yield. Removal of the 2-Nap protecting group using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[19] furnished disaccharide **8** with a free hydroxyl group at C3 in 84% yield. Removal of the silyl protecting group under a F^- source (HF-Py) followed by protection of 3,6-OH as acetyl ester using Ac_2O/py led to **9** in 90% yield. Hydrolysis of the 4′,6′-*O*-benzylidene acetal using an AcOH/H_2O/CH_2Cl_2 (4:2:1) mixture produced the crude dihydroxy derivative for the selective oxidation of the primary hydroxyl group to carboxylic acid using (2,2,6,6-tetramethylpiperidin-1-yl)oxyl or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO)/diacetoxyiodo benzene (BAIB) and subsequent esterification with MeI/$KHCO_3$ to give disaccharide acceptor **10** in 58% yield (Scheme 1).

Scheme 1. Synthesis of the D-Glc-β-(1→4)-D-GlcN_3 Disaccharide Building Block



For the synthesis of Ido-GlcN_3 disaccharide derivatives (**17** and **18**), we used commercially available diacetone glucose **11** that was converted to α-L-idopyranoside **12** using known procedures.[20] The 2-OH group of **12** was protected as both benzoyl (Bz) and acetyl ester (Ac) to generate **13**[16b] and **14** in 80% and 95% yields, respectively. *N*-Iodosuccinimide (NIS)/TMSOTf-mediated glycosylation of **13** with α-methyl acceptor **19**[16b] generated disaccharide **15** in 94% yield. The 4′,6′-*O*-benzylidene acetal was hydrolyzed using 80% AcOH-H_2O; the crude dihydroxy derivative was treated with TEMPO/BAIB to oxidize the primary hydroxyl group to acid, and subsequent esterification of the acid with MeI/$KHCO_3$ generated L-iduronic acid-containing disaccharide acceptor **17** in 58% yield (Scheme 2). We have also reported the synthesis of **17** using a different synthetic route previously.[16b]

We measured the RRVs of glycosyl donors (**2** and **10**)[14,15] and found that the RRV of **2** was 132.0 whereas that of **10** was 2.14. After synthesizing all of the required building blocks (**2**, **10**, and **17**), we attempted the programmable one-pot synthesis of the protected pentasaccharide **20**. However, the yield was only 26%. To improve the yield of the one-pot synthesis, we changed the disaccharide acceptor from **17** to **18**, in which the 2-OH is protected as acetyl ester. The 2-*O*-acetyl-protected donor **14** was coupled with α-methyl acceptor **19** in the presence of NIS/TMSOTf to generate disaccharide **16** in

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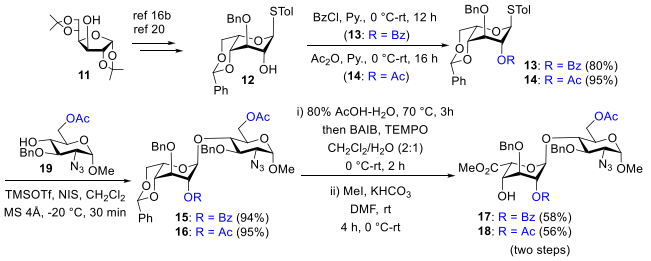
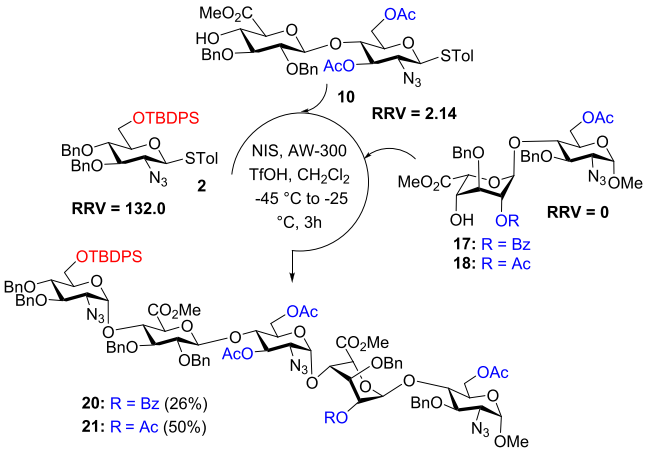
Scheme 2. Synthesis of the L-Ido-α-(1→4)-D-GlcN$_3$ Disaccharide Building Block



95% yield. Hydrolysis of the 4′,6′-*O*-benzylidene acetal, TEMPO/BAIB oxidation of the primary alcohol to acid, and subsequent esterification of the acid using MeI/KHCO$_3$ generated **18** (56%) (Scheme 2) that was then used in the one-pot synthesis of protected Fondaparinux **21** in 50% yield (Scheme 3). The concept of RRV is based on the

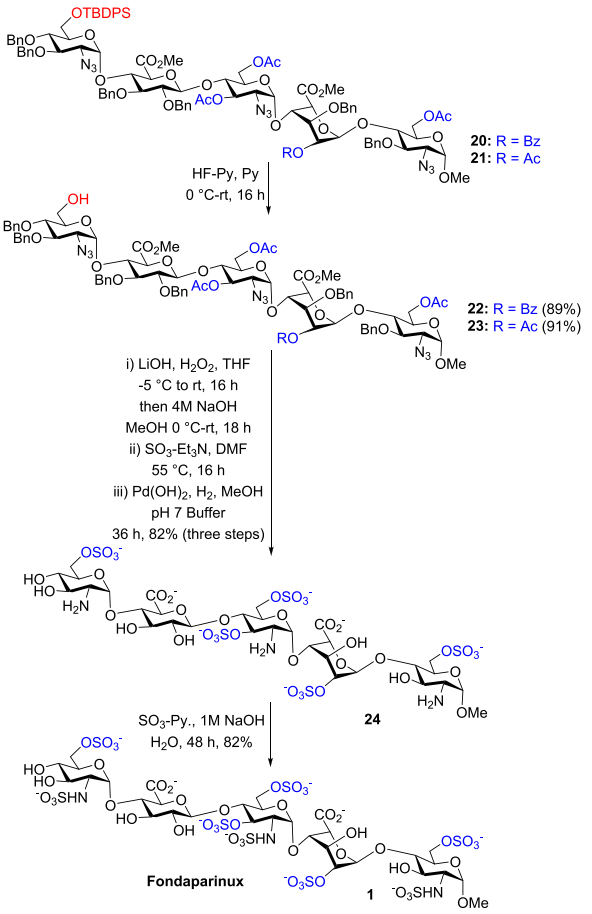
Scheme 3. One-Pot Synthesis of Protected Fondaparinux



measurement of the reactivity of the thioglycoside donor. Both **17** and **18** are glycosyl acceptors without a leaving group, so the RRVs were not measured and assigned to "zero". Thus, it was difficult to foresee the lower yield (26%) of pentasaccharide **20** using 2-*O*-Bz-protected disaccharide **17** (Scheme 3) and the higher yield of **21** (50%) using 2-OAc-containing disaccharide **18**.

We used the protected pentasaccharides **20** and **21** for differential deprotection and chemical sulfation. The silyl group (TBDPS) in **20** and **21** was removed using HF-Py to generate compounds **22** and **23** in 89% and 91% yields, respectively. Protection group free *O*-sulfated pentasaccharide **24** was obtained in three steps. Saponification of **22** and **23** using LiOH/H$_2$O$_2$[21] in the presence of NaOH/MeOH hydrolyzed all ester functional groups. For the installation of the OSO_3^- groups, it was further treated with excess SO$_3$-Et$_3$N followed by unmasking of all *O*-benzyl groups and reduction of N$_3$ to amine under catalytic hydrogenation with Pd(OH)$_2$/C to give **24** in 82% yield. The selective *N*-sulfation was performed at pH 9.5 with SO$_3$-Py, and the pH of the reaction was controlled by slow addition of 1 M NaOH(aq) from time to time. The crude product was passed through size-exclusion (Sephadex G-25) and ion-exchange (Dowex 50WX8Na$^+$) columns to furnish Fondaparinux **1** (Scheme 4). The reported NMR and mass spectrometry data are well matched with the

Scheme 4. Synthesis of Fondaparinux



reported values.[7−13] All newly synthesized derivatives were characterized by ^{1}H and ^{13}C NMR spectra and high-resolution mass spectra (HRMS). $^1J_{C-H}$ coupling constants were measured via two-dimensional NMR to determine the α- and β-linkages between the building blocks (Supporting Information).

In conclusion, we have developed a programmable one-pot synthesis of the clinically important anticoagulant Fondaparinux using designed thioglycoside building blocks with well-defined RRVs for α-selective glycosylation guided by silyl ether and acetyl ester functionality at *O*6 in the one-pot sequence. The introduction of 3-OSO_3^- was performed with the aid of 2-naphthylmethyl ether (Nap). The carefully selected orthogonal protecting groups that can be differentially deprotected and readily accessible thioglycoside building blocks in the one-pot synthesis effectively reduce the number of synthetic steps and eliminate the multiple purification steps. In addition, the advantage of a programmable approach is to allow a pre-evaluation of the building blocks to be used in a one-pot manner. The total synthesis was accomplished in the 22 longest linear route with 4.2% overall yield from diacetone glucose, which is a very significant improvement compared to previously reported synthetic methodologies. The protected pentasaccharide was synthesized in >200 mg and can be performed on a gram scale. The synthetic route reported here is scalable and should be useful for the synthesis of Fondaparinux and closely related structures decorated with regiodefined *O*- and *N*-sulfation.[16b]

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01386.

Experimental and purification procedures, characterization data (^{1}H and ^{13}C and high-resolution mass spectra), and copies of ^{1}H and ^{13}C spectra for all newly synthesized compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Chi-Huey Wong − *Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, United States;* orcid.org/0000-0002-9961-7865; Email: wong@scripps.edu, chwong@gate.sinica.edu.tw

Authors

Supriya Dey − *Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, United States*

Hong-Jay Lo − *Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, United States;* orcid.org/0000-0001-9906-0975

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01386

Author Contributions

S.D. and H.-J.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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