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Synthesis of Reverse Glycosyl Fluorides and Rare Glycosyl Fluorides Enabled by Radical Decarboxylative Fluorination of Uronic Acids

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03514 Read Online

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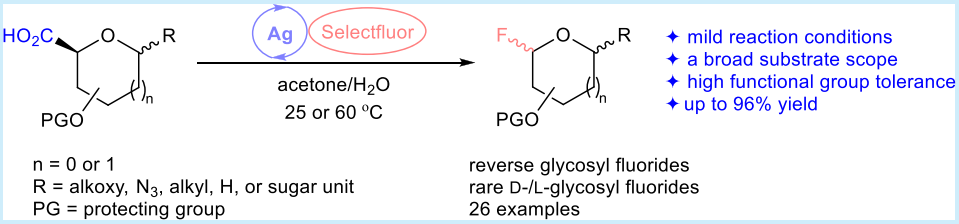
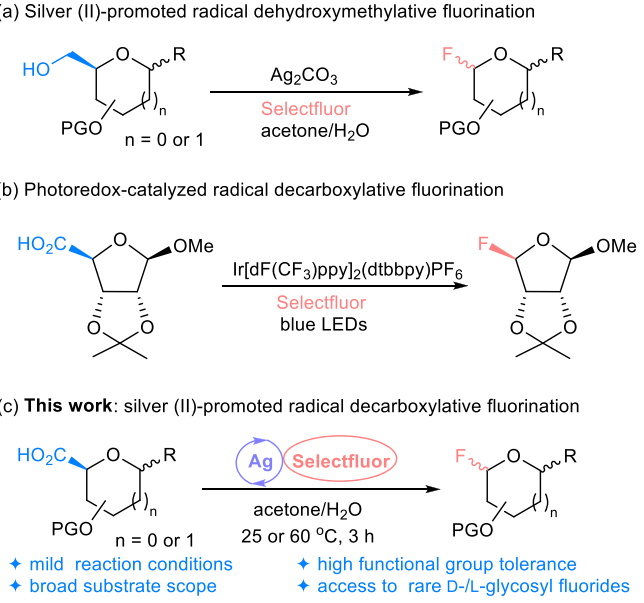


ABSTRACT: An efficient protocol for synthesizing reverse glycosyl fluorides is described, relying on silver-promoted decarboxylative fluorination of structurally diverse pentofuran- and hexopyranuronic acids under the mild reaction conditions. The potential applications of the reaction are further demonstrated by converting readily available D-uronic acid derivatives into uncommon D-/L-glycosyl fluorides through a C1-to-C5 switch strategy. The reaction mechanism is corroborated by 5-*exo*-*trig* radical cyclization of allyl α-D-C-glucopyranuronic acid triggered by decarboxylative fluorination.

Reverse glycosyl fluorides (RGFs)—namely, furanos-4-yl- and pyranos-5-yl fluorides—are the essential constituents of either naturally occurring nucleosides and drug candidates.[1] RGFs have been found to be probes of carbohydrate processing enzymes of particular biological importance.[2] The very recent work reported by Zhou and Plavec has revealed that 4′-fluorinated RNA can serve as a promising probe and exhibits wide applications in structural elucidation and functional clarification for RNA by ^{19}F NMR spectrometry.[3] As such, numerous methods relying on a nucleophilic or electrophilic fluorination process have been developed to get access to structurally unique RGFs.[2,4] In this context, we recently reported Ag_2CO_3/Selectfluor-promoted radical dehydroxymethylative fluorination of carbohydrates to afford RGFs with one carbon less sugar chain than the starting materials in aqueous solvent under mild reaction conditions (see Scheme 1a).[5] The mechanistic studies revealed that the reaction involves β-fragmentation of primary alkoxy radicals. Furthermore, our work also demonstrates that RGFs are valuable platforms for divergent elaborations of carbohydrates through C−F bond functionalization. Despite enjoying good substrate scope, the reaction of dehydroxymethylative fluorination shows some limitations: both benzyl group-protected sugars and certain oligosaccharides containing hex*p*-(1 → 4)-hex*p* moiety are problematic, likely the result of alkoxy radicals with relatively high tendency to engage in 1,*n*-hydrogen atom transfer (n = 5, 6, 8, etc.).[6]

To circumvent these limitations, we turned our attention to decarboxylation of acyloxy radicals, based on the following salient features of the species:

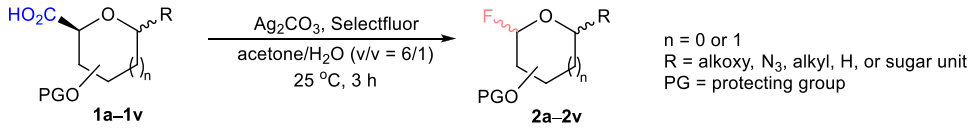
Scheme 1. Methods for Synthesis of RGFs through a Radical Process

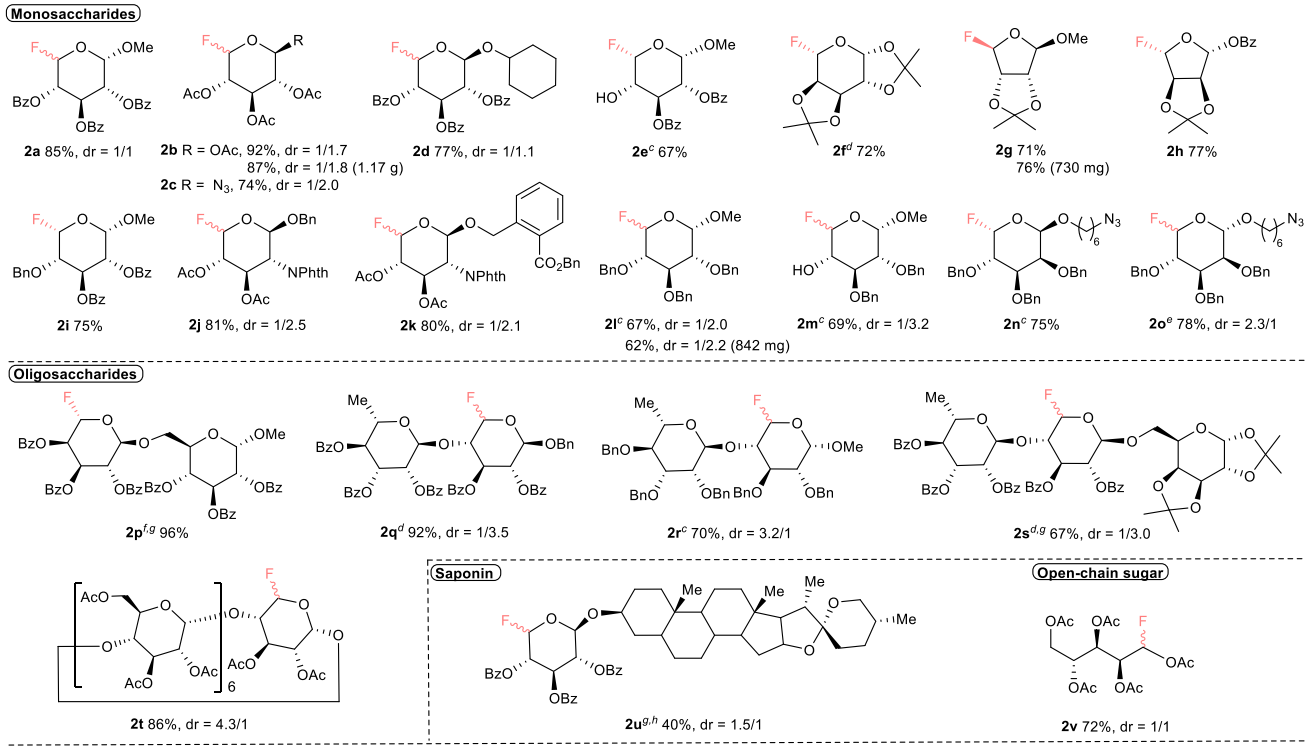


Received: October 24, 2020

https://dx.doi.org/10.1021/acs.orglett.0c03514
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope of Decarboxylative Fluorination[a,b]





[a]Unless otherwise noted, the reaction was conducted with 0.1 mmol of the uronic acid, 0.5 equiv of Ag_2CO_3, and 5.0 equiv of Selectfluor, 25 °C, 3 h. [b]The diastereomeric ratio (dr) value refers to the ratio of 5*R*-/5*S*-isomer determined by ^{1}H NMR spectroscopy. [c]2.0 equiv of Selectfluor, 0.2 equiv of Ag_2CO_3, and 2.0 equiv of KF·2H_2O was used. [d]1.0 equiv of Ag_2CO_3 was used. [e]5.0 equiv of KF·2H_2O was added. [f]2.0 equiv of Ag_2CO_3 was used. [g]Reaction temperature = 60 °C. [h]Acetone/H_2O (v/v = 30:1) as the solvent.

(i) compared to primary alkoxy radicals, the corresponding acyloxy radicals are less electrophilic due to the presence of electron-withdrawing carbonyl group, thus decreasing, even eliminating, the tendency of hydrogen atom abstraction of the intermediates; and

(ii) decarboxylation of acyloxy radicals has been found to be several orders of magnitude faster than β-cleavage of primary alkoxy radicals.

This statement is supported by rate constant for decarboxylation of alkyl acyloxy radicals, ~1.0×10^{10} s^{-1} vs 1.8×10^5 s^{-1} for β-fragmentation of *tert*-butyloxyl radical, which is recognized to be more inclined to β-scission than primary alkoxy radicals.[7] With these results in mind, we thereby undertook radical decarboxylative fluorination of uronic acids with the hope to find a more general method for synthesizing RGFs.

Alongside the well-established functionalization of aliphatic carboxylic acids through decarboxylation of acyloxy radicals,[8] radical decarboxylation of uronic acids and derivatives under oxidative or reductive conditions has proven to be a powerful tool to enable elaborations of carbohydrates by constructing either carbon−carbon or carbon−heteroatom linkages.[9,10] Among these impressive works, MacMillan and co-workers reported a single example that dealt with conversion of ribofuranuronic acid into D-erythros-4-yl fluoride through visible-light photoredox-catalyzed radical decarboxylative fluorination (see Scheme 1b).[10c] However, the reaction was not found to bring about the transformation of glucopyranuronic acid, which is a typically representative hexopyranuronic acid. Herein, we would like to unveil our finding of silver-promoted radical decarboxylative fluorination of various uronic acids, providing a complementary and more general methodology for the synthesis of RGFs (see Scheme 1c). The reaction works well under the mild reaction conditions and accommodates structurally diverse and densely functionalized carbohydrates, such as those having benzyl protecting groups. The present transformation also provides a novel protocol for the synthesis of rare D-/L-configured glycosyl fluorides from easily available D-uronic acid derivatives through a C1-to-C5 switch strategy.[11]

Uronic acids can be readily prepared using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)/[bis(acetoxy)iodo]benzene (BAIB)-mediated oxidization of carbohydrate-based primary alcohols, which features a wide substrate scope and good chemoselectivity.[12] Inspired by silver-catalyzed decarboxylative fluorination of aliphatic carboxyl acids[13] and driven by our previous works on the synthesis of C-glycosylated phenanthandines and isoquinolines relying on silver-mediated decarboxylative functionalization of uronic acids,[14] we commenced our studies with glucopyranuronic acid **1a** as a model substrate to establish the optimal reaction conditions.

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Scrupulous evaluation of the reaction parameters revealed that treatment of **1a** with 5.0 equiv of Selectfluor in the presence of 0.5 equiv of Ag_2CO_3 afforded **2a** in 85% yield at 25 °C for 3 h in acetone/H_2O (v/v = 6/1) (see Table S1 in the Supporting Information (SI)). Given that carbohydrates are densely functionalized molecules, we selected the recipe as the optimal reaction conditions attributable to its mildness.

With the optimized conditions in hand, we set out to explore the scope of decarboxylative fluorination of uronic acids. The results are compiled in Scheme 2. Consistent with our expectations, decarboxylative fluorination is applicable to not only pyranosides and furansides equipped with acetate, benzoate, isopropylidene, or azido groups (**1b**−**1h**), but also those bearing a benzyloxy group at the C4 or the anomeric position (**1i**−**1k**). The latter are not amenable to dehydromethylative fluorination via β-scission of primary alkoxyl radicals.[5] Of particular note, the reaction exhibits good selectivity toward carboxylic acid over secondary hydroxyl groups, as exemplified by the preparation of **2e**, where the transformation selectively occurred to carboxylic acid with the C4 hydroxy group intact. Notably, **2k** might be an interesting fluoride, since (2-benzyloxycarbo-nyl)-benzyl glycosides could act as the precursor to (2-hydroxycarboxylic)-benzyl glycosides, which represent a class of proven and efficient glycosyl donors.[15]

Encouraged by these results, we turned our attention toward decarboxylative fluorination of more challenging uronic acids having multiple benzyl protecting groups (**1l**−**1o**). When 2,3,4-tri-*O*-benzyl-glucuronic acid **1l** was exposed to decarboxylative fluorination, the desired product **2l** was obtained in 48% yield under the standard conditions. The rapid decomposition of **2l** resulted in the moderate yield attributable to the presence of electron-donating benzyl ethers favoring C−F cleavage in the acidic reaction medium.[5,13a] To eliminate this unexpected reaction, we tried to use KF·2H_2O as the base to modulate the acidity of the reaction medium. To our delight, inclusion of 5.0 equiv of KF·2H_2O increased the yield of **2l** to 67%. Furthermore, it was found that the reaction could be conducted without erosion of yield and diastereochemistry by reducing molar equivalents of Ag_2CO_3, Selectfluor, and KF·2H_2O to 0.2, 2.0, and 2.0, respectively. Under these conditions, **2m** with the C4 hydroxy group free was smoothly obtained in 69% yield. The configuration of anomeric substituent might exert a profound influence to diastereoselectivity of the reaction. For instance, β-D-mannuronic acid **1n** afforded **2n** as the sole product, while its α-isomer **1o** resulted in **2o** as a diastereomeric mixture. Taken together, these results demonstrate that decarboxylative fluorination enjoys a broader substrate scope than dehydromethylative fluorination, providing thereby a complementary approach to various RGFs of importance. We assume that the diastereoselectivity of the reactions is governed by the preferential conformation of furanos-4-yl- and pyranos-5-yl radical intermediates coupled with the steric hindrance of substituents.[9b,c,14,16]

Oligosaccharides were also competent substrates for decarboxylative fluorination, as exemplified by uneventful synthesis of disaccharide fluorides **2p**−**2r**, trisaccharide fluoride **2s**, and cyclodextrin fluoride **2t** in yields of 63%−96%. Remarkably, access to benzoylated **2q** and benzylated **2r**, both of which have an α-L-rhamnosyl-(1 → 4)-β-D-glucoside backbone, illustrates another salient feature of decarboxylative fluorination, because such linkage impedes the dehydromethylative fluorination of primary alkoxy radical stemming from the competitive intramolecular hydrogen atom transfer.[6]

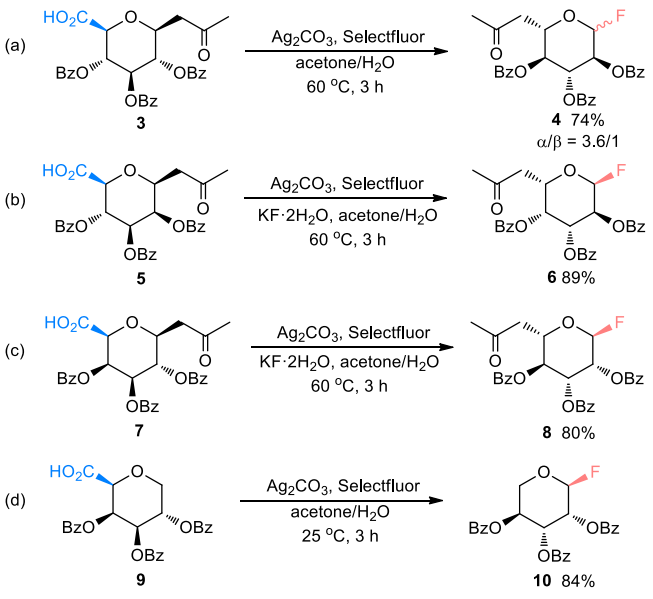
To assess the scalability of this method, we performed the scale-up reactions of **1b**, **1g**, and **1l**. All of the reactions performed at equal efficiency on the gram scale.

The potential of the present transformation in complex natural products was also explored. Fluorinated spirosaponin **2u** derived from tigogen-3-yl glucuronic acid **1u** was obtained with the spiroketal and tertiary C−H functionalities intact.

As a typical example of open-chain sugars, gluconic acid **1v** possesses more flexible conformation than the cyclic uronic acids. To our delight, **1v** underwent smooth decarcarboxylative fluorination to produce α-fluoroalkyl ester **2v** in 72% yield with a diastereomeric ratio of 1/1. α-Haloalkyl esters originated from carbohydrates are a class of interesting chiral synthons in organic synthesis. While α-bromo- and iodoalkyl esters are known,[17] the present transformation represents the first example of sugar-based α-fluoroalkyl ester synthesis.

L-Sugar moieties are frequently found as integral components of oligosaccharides, glycopeptides, saponins, and nucleosides of biological relevance.[11,18] Given the poorly commercial and natural availability of most of L-sugars and the related building blocks, a plethora of approaches to prepare these types of molecules have been devised.[11] Glycosyl fluorides have been established to be a class of glycosylating agents for chemical and enzymatic synthesis of oligosaccharides and glycoconjugates.[19] With the protocol established for the fragmentation of uronic acids to RGFs with one carbon less degradation, we envisaged that the transformation could permit conversion of readily available β-D-C-glycosides or 1,5-anhydroalditols into rare L-glycosyl fluorides, thus developing a novel route to L-configured sugar constructs through a C1-to-C5 switch strategy. To reduce this concept to practice, we set out to synthesize L-glycosyl fluorides. As shown in Scheme 3, uronic acid **3**, readily prepared by means of a four-step sequence of reaction in overall 54% yield using D-glucose and 2,4-pentane-dione as the starting materials,[20] was subjected to Ag_2CO_3-promoted decarboxylative fluorination in the presence of Selectfluor. Gratifyingly, the reaction proceeded smoothly at 60 °C to afford L-*gluco*-octopyranosyl

Scheme 3. Synthesis of L-Glycosyl Fluorides by Decarboxylative Fluorination



https://dx.doi.org/10.1021/acs.orglett.0c03514
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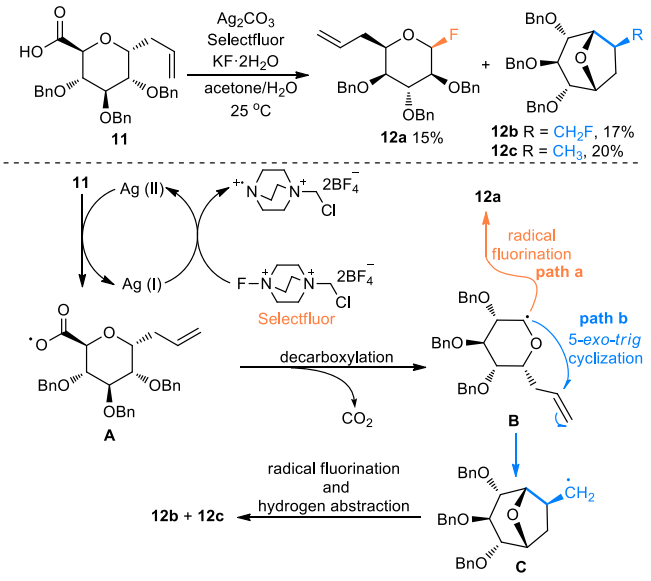
fluoride **4** in 74% overall yield as an anomeric mixture of α/β (3.6/1) (see Scheme 3a). Under the identical conditions benzoyl-protected uronic acids **5** and **7** derived from D-mannose and galactose, however, afforded L-*galacto*- and *manno*-octopyranosyl fluorides **6** and **8** in decreased yields of 44% and 26%. To our delight, the addition of KF·2H_2O greatly improve the outcome of both transformations, and glycosyl fluorides **6** and **8** were obtained in 89% and 80% yields with α-anomer as the sole product (see Schemes 3b and 3c). To further showcase the utility of the obtained glycosyl fluorides as glycosyl donors, the coupling of **4** with one of the alcohol acceptors was explored (see Table S2 in the SI). The octopyranside building blocks obtained might serve as valuable precursors to L-hexopyranoside constructs since shortening the side chain by two C atoms has been reported.[21]

L-Lyxose, as a rare sugar, has been identified as a component of oligosaccharide antibiotics, including flambamycin, curamycin, avilamycin, and everninomicin.[22] There are sporatic reports describing synthesis of L-lyxose by chemical methods and biotransformations.[23] We were pleased to find that the exposure of D-1,5-anhydrogalactinol **9** to decarboxylative fluorination to generate α-L-lyxopyranosyl fluoride **10** in 84% yields (see Scheme 3d). This transformation not only provides valuable building blocks for synthesizing structurally unique antibiotics but also represents the first example of converting 1,5-anhydroaldotiols to usual pentopyranosyl fluorides. Distinct from the conventional methods to prepare glycosyl fluorides usually involving a polar pathway,[24] the present transformations represent a few of the examples wherein glycosyl fluorides were reached by using a radical reaction.[25]

To shed light on the reaction mechanism, a radical clock experiment was set up. As shown in Scheme 4, exposure of allyl

Scheme 4. Proposed Mechanism for Decarboxylative Fluorination of Uronic Acids



α-D-C-glucopyranuronic acid **11** to decarboxylative fluorination stereoselectively produced 15% of D-*ido*-configured glycosyl fluoride **12a**, along with the fluorinated oxa-[3,2,1]-bridged cycloheptane **12b** and its reduced analogue **12c**, in respective yields of 17% and 20%. Combining these observations and literature precedents,[13,26] a radical mechanism was proposed. Silver(II) species, generated by oxidation of silver(I) with Selecfluor, enables the decarboxylation of acid **11**, leading to the formation of the intermediate radical **B** through decarboxylation of the acyloxy radical **A**. Direct fluorination of carbon-centered radical **B** afforded the fluoride **12a** (path a). On the other side, the kinetically favored transannular 5-*exo-trig* addition of **B** to the C=C double bond located at the anomeric allyl group gives the primary radical **C**, and then it undergoes fluorination and hydrogen abstraction to eventually provide **12b** and **12c** (path b), respectively. The prevalence of combined **12b** (17%) and **12c** (20%), compared to **12a** (15%), implies that 5-*exo-trig* cyclization reaction of the intermediate **B** outcompetes the direct fluorination. Since D-*ido*-configured building blocks are attractive but challenging synthetic targets,[27] access to **12a**, albeit in the low yield, suggests the potential of decarboxylative fluorination in synthesis of this unique sugar. In addition, oxa-[3,2,1]-bridged cycloheptane skeleton is present in various natural products;[28] therefore, decarboxylative fluorination of uronic acids offers a carbohydrate-based approach to such architectures with novel structure and potential bioactivities.

In summary, a mild and operationally simple approach to RGFs has been developed, capitalizing on silver-promoted radical decarboxylative fluorination of structurally diverse uronic acids. The reaction is superior to dehydroxymethylative fluorination reported by us, with respect to substrate scope and functional group compatibility as exemplified by the successful transformation of sugars bearing benzyl groups and/or hex*p*-(1 → 4)-hex*p* moiety. The reaction also opens up a radical way to D-/L-glycosyl fluorides with uncommon configuration from easily accessible D-C-glycosides following a C1-to-C5 interchange strategy. The applications of the present method in the synthesis of structurally unique glycosyl fluorides and their incorporations in the related oligosaccharides are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03514.

Experimental procedures, characterization data for all new compounds, results of optimization and glycosylation, and NMR spectra for all compounds (PDF)

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https://dx.doi.org/10.1021/acs.orglett.0c03514
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of China (Nos. 21672194 and 21977088), the National Natural Science Foundation of China-Shandong Joint Fund (Nos. U1906213 and U1606403), the Shandong Provincial Natural Natural Science Foundation (No. ZR2018MB015), and the Central Public-interest Scientific Institution Basal Research Fund for Chinese Academy of Tropical Agricultural Sciences (No. 1630052019026).

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https://dx.doi.org/10.1021/acs.orglett.0c03514
Org. Lett. XXXX, XXX, XXX−XXX