OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Total Syntheses of Resin Glycosides Murucoidins IV and V

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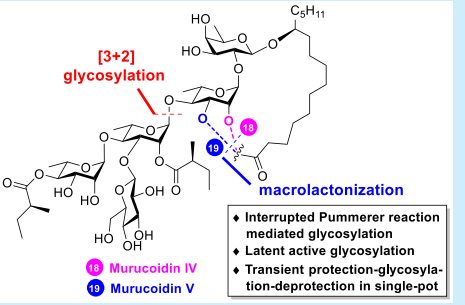
Supporting Information

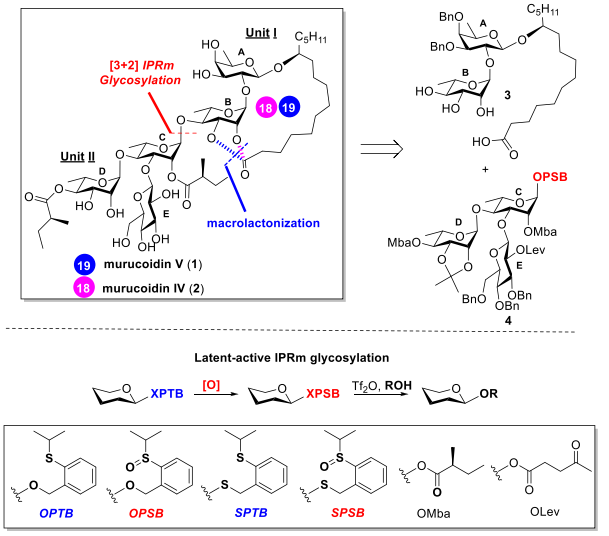
ABSTRACT: Murucoidins IV and V, two bioactive resin glycosides with complex yet similar structures isolated from the morning glory family, were synthesized in a convergent manner. All of the glycosylations in these syntheses including the key [3 + 2] coupling were achieved by our recently developed interrupted Pummerer reaction mediated (IPRm) glycosylations. The broad functional group compatibility of IPRm glycosylation allowed us to employ a latent-active concept and a single-pot transient protection−glycosylation−deprotection strategy which significantly improved the global synthetic efficiency.



Resin glycosides, as plant glycolipids or lipo-oligosaccharides, are important ingredients of secondary metabolites of the morning glory family, Convolvulaceae. Most of the resin glycosides have been found to exhibit unique bioactivities, for example, cytotoxic, ionophoretic, antiserotonic, antimicrobial, and phytogrowth-inhibitory activities.[1] Among them, non-cytotoxic resin glycoside murucoidin V (**1**) has been found to exhibit significant multidrug resistant (MDR) reversal activity, which was able to enhance the susceptibility of vinblastine by 255-fold via the inhibition of the efflux pump of vinblastine-resistant human breast carcinoma cells (MCF-7/Vin).[2] Murucoidins IV and V and their analogues were isolated from the flowers of *Ipomoea murucoides* by Pereda-Miranda in 2006.[3] Murucoidins IV (**2**) and V (**1**) present very similar structures, containing the same hydrophilic oligosaccharide chain consists of several rare deoxy sugars and a hydrophobic hydroxy fatty acid aglycone chain (Scheme 1). The only difference lies in the macrolactone rings in which murucoidin V (**1**) possesses a 19-membered ring while murucoidin IV (**2**) contains an 18-membered ring. The intriguing structural properties and our interest in discovering natural product based MDR inhibitors encouraged us to develop novel synthetic strategies toward the modular synthesis of these natural products.

Although hundreds of resin glycosides have been isolated, only a limited number of them have been synthesized or attempted to be synthesized as in work by Kitagawa,[4] Schmidt,[5] Yu and Hui,[6] Heathcock,[7] Fürstner,[8] Sakairi,[9] Postema,[10] Yang,[11] O'Doherty,[12] and Shi[13] due to their structure complexity and diversity.[14] Among these syntheses, the oligosaccharide chains were normally assembled by classical glycosylation reactions, typically, activation of trichloroacetoimidate glycosyl donors or thioglycosyl donors. Recently, we have developed two interrupted Pummerer reaction mediated (IPRm) glycosylation reactions.[15] Within them, the latent glycosides could be easily oxidized to the active glycosyl donors for the subsequent glycosylations with high efficacy. This advantage significantly streamlined the intricate oligosaccharide assembly process by avoiding the complex anomeric leaving group manipulation.[16] Herein, we report the first syntheses of murucoidins IV and V by application of the IPRm glycosylations and a sequential transient protection−glycosylation−deprotection protocol.

Scheme 1. Structures and Retrosynthetic Analysis of Murucoidins IV and V



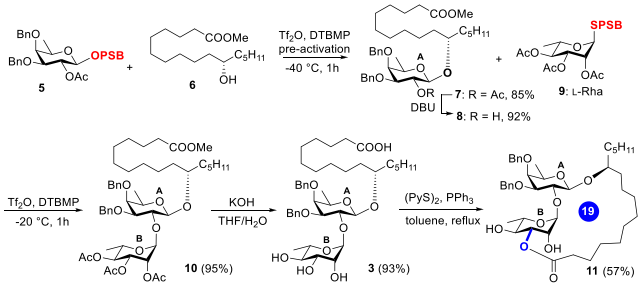
Received: June 11, 2019

DOI: 10.1021/acs.orglett.9b02004
Org. Lett. XXXX, XXX, XXX−XXX

Our retrosynthetic plans were outlined in Scheme 1. We envisioned that murucoidins IV and V could be assembled in a convergent manner via a [3 + 2] IPRm glycosidic coupling and a macrolactonization (Scheme 1). The assembly sequence of the two units was deemed to be critical for the global synthetic efficiency. In the literature, both early-stage[6,11a] and late-stage[7] macrolactonization strategies have been successfully used in the synthesis of complex resin glycosides. In our work, we intended to adopt the early-stage macrolactonization followed by the [3 + 2] IPRm glycosylation sequence because it was anticipated to be more straightforward, requiring less complex and tedious protecting group manipulations. Nevertheless, both sequences shared the same fragments **3** and **4**. Both fragments could be assembled from the corresponding monosugars and fatty acid chain via latent-active IPRm glycosylations.

The fatty acid chain of fragment **3** was introduced by glycosylation of glycosyl donor **5** with methyl 11(*S*)-jalapinolate **6**.[17] Due to the low reactivity of the long-chain alcohol, armed OPSB glycosyl donor **5** must be preactivated by Tf_2O at −40 °C prior to the addition of acceptor (Scheme 2).

Scheme 2. Synthesis of 19-Membered Macrolactone 11

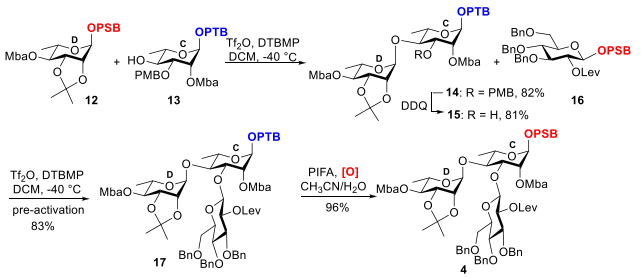


This procedure successfully produced **7** in 85% yield. Release of the C2-hydroxyl group of **7** gave acceptor **8** in 92% yield. Further coupling between disarmed *S*-2-(2-propylsulfinyl)-benzyl (SPSB) glycosyl donor **9** and **8** provided disaccharide **10** in 95% yield. Global saponification of all the ester groups under basic conditions furnished key intermediate **3**. The site-selective cyclization of **3** to form the 19-membered macrolactone is challenging due to the presence of three contiguous hydroxyl groups on the L-rhamnose moiety.[18] Fortunately, application of Corey−Nicolaou macrolactonization conditions[19] furnished the macrolactone **11** with C3-selectivity in 57% yield.

The synthesis of fragment **4** commenced from coupling of latent OPTB glycoside **13** with active OPSB glycosyl donor **12**, which furnished latent disaccharide **14** in 82% yield (Scheme 3). Further removal of the PMB protecting group of **14** and glycosylation with OPSB glycosides **16** produced trisaccharides **17** in good yield. The OPTB group of **17** was subsequently oxidized to an OPSB group, which offered active glycosyl donors **4** in excellent yields, ready for the following [3 + 2] glycosylation reactions.

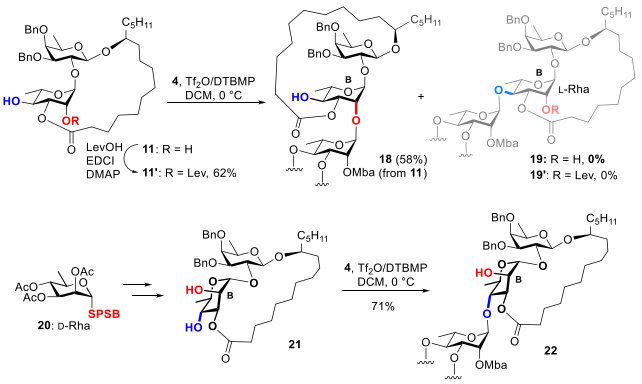
With an adequate amount of **4** and **11** in hand, we then endeavored to merge them to assemble the pentasaccharide core structure of murucoidin V by IPRm glycosylation. Given that the equatorial hydroxyl group was normally more active than the axial one in glycosylation reactions, we intended to directly couple OPSB glycoside **4** with macrolactone **11** without protecting the C2 axial hydroxyl group of L-rhamnose

Scheme 3. Synthesis of OPSB Glycoside 4



(sugar B), aiming to minimize the reaction steps. Surprisingly, the anticipated C4-glycosylated product **19** was not observed; instead, undesired C2 coupling product **18** was obtained in 58% yield (Scheme 4). The further deprotection of **18** revealed

Scheme 4. Problematic Site Selectivity of [3 + 2] Coupling



that the NMR spectral data were inconsistent with the natural murucoidin V (**1**) (see the Supporting Information). These results led us to conclude that the C2 axial hydroxyl group of L-Rha is more reactive or less hindered than the one at the C4 position. Then, to avoid the competing glycosylation, the C2 free hydroxyl group was protected as levulinate (Lev) ester **11′**. Unfortunately, glycosylation between trisaccharide donor **4** and disaccharide acceptor **11′** failed to give any [3 + 2] coupling product. We carefully analyzed the original NMR data of the natural murucoidin V again and confirmed that the bottom trisaccharide moiety was exactly attached to the C4 position rather than the C2 position. These failures made us wonder if the configuration of the L-rhamnose (sugar B) of murucoidin V was as proposed. Hence, a proposed 19-membered lactone **21** with a revised structure of sugar B (D-Rha) was prepared according to a similar procedure (see the Supporting Information). With this modification, the glycosylation has indeed occurred at the desired C4 position, thus producing **22** in 71% yield. However, this modification did not lead to the natural murucodin V as revealed by the NMR spectral data (see the Supporting Information). These results implied that the structure of murucodin V was possibly exactly as proposed; however, the C4 hydroxyl group was largely shielded by the lactone ring, which made the glycosylation impossible. A similar phenomenon was also observed by Heathcock during the synthesis of tricolorin A.[7a] To this point, we have to abandon the early-stage macrolactonization strategy.

The unsuccessful efforts for the employment of the early-stage macrolactonization compelled us to carry out the [3 + 2]

DOI: 10.1021/acs.orglett.9b02004
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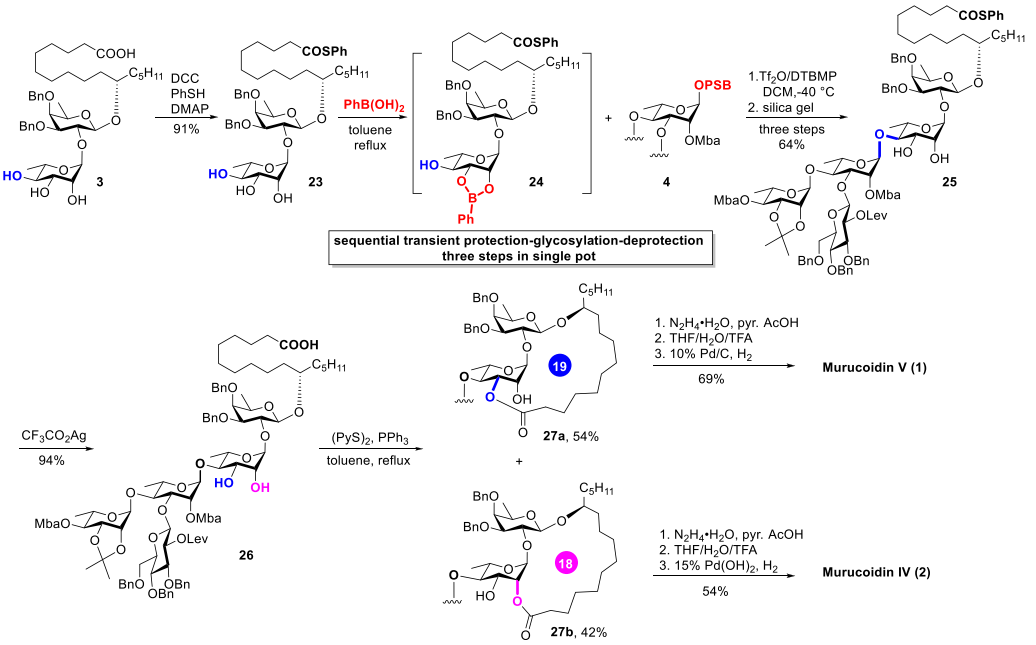
Scheme 5. [3 + 2] IPRm Glycosylation–Macrolactonization Assembly Sequence to Murucoidins IV and V



glycosylation prior to the macrolactonization (Scheme 5). Hence, the fatty acid of **3** was specifically protected as the thioester in view of the existing several fatty acyl chains in murucoidins. To avoid interference of the terminal L-rhamnose moiety, the *cis*-dihydroxyl groups must be masked. Inspired by the idea of introducing transient masking groups in glycosylation reactions,[20] we intended to employ phenyl boronic acid as a protecting reagent to temporarily mask the *cis*-dihydroxyl groups of **23** by forming a cyclic boronic acid ester **24** (Scheme 5). This transient protecting group, which forced the subsequent glycosylation to occur at the C4 position, was proven to be stable in the IPRm glycosylation with OPSB glycoside **4**. Most interestingly, it was found that the cyclic boronic ester was efficiently cleaved during column chromatography on silica gel, thus omitting the introduction of additional steps. This single-pot, sequential, in situ transient protection–glycosylation–deprotection reaction significantly increased the synthetic efficiency, which produced the pentasaccharide **25** in 64% total yield. A similar strategy has also been recently applied to the modification of erythromycin by Nagorny et al.,[21] indicating its potential in assembly of complex oligosaccharides and glycoconjugates. The macrolactonization of **26** under Corey–Nicolaou conditions proceeded smoothly to furnish macrolactones **27a** and **27b** with 19- and 18-membered rings, respectively. Despite there being no selectivity obtained for this macrolactonization, the beneficial part was that both skeletons belong to the natural resin glycosides murucodins V and IV, respectively. Consequently, we did not make further efforts to optimize the conditions for higher selectivity. Finally, global removal of the protecting groups of **27a** and **27b** accomplished the divergent syntheses of murucodins V and IV. The NMR data were exactly matched with natural murucoidins V and IV, which endorsed the real structures of murucoidins V and IV (see the Supporting Information).

In summary, we have successfully accomplished the total syntheses of resin glycosides murucoidins IV and V in a convergent manner. During the syntheses, all sugars and fatty acid chain were assembled by our IPRm glycosylation strategy. The combination of IPRm glycosylation with a latent-active concept streamlined the first total syntheses of these structurally complex resin glycosides. Meanwhile, we found that the temporary *cis*-diol protecting group, phenyl boronic ester, was compatible with the IPRm glycosylation reactions and was easily removed during column chromatography. This observation let us introduce a single-pot transient protection–glycosylation–deprotection strategy in the syntheses to avoid complex protecting group manipulations. The syntheses not only supplied materials for further MDR reversal activity study but also paved the way for the synthesis of other resin glycosides. The relevant studies are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02004.

Detailed experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (21672077, 21761132014, 21772050,

DOI: 10.1021/acs.orglett.9b02004
Org. Lett. XXXX, XXX, XXX–XXX

21702068), the State Key Laboratory of Bioorganic and Natural Products Chemistry (SKLBNPC13425), the Wuhan Creative Talent Development Fund, the "Thousand Talents Program" Young Investigator Award, the Fundamental Research Funds for the Central Universities, HUST: 2019JYCXJJ046, and Huazhong University of Science and Technology is greatly appreciated. We thank Prof. Rogelio Pereda-Miranda (Universidad Nacional Autónoma de México) for providing original NMR spectra of murucoidin IV and V.

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DOI: 10.1021/acs.orglett.9b02004
Org. Lett. XXXX, XXX, XXX−XXX