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Macrolide Core Synthesis of Calysolin IX *via* Intramolecular Glycosylation Approach

Mirosław Nawój,[a] Artur Grobelny[a] and Jacek Mlynarski*[b]

Abstract: The utility of intramolecular glycosylation for the synthesis of 27-membered macrocyclic ring is highlighted in this first total synthesis of the most complex resin glycoside isolated to date - Calysolin IX. Oligosaccharide-containing macrolides core was effectively constructed by TfOH/NIS-promoted intramolecular glycosylation of thioglycosyl donor. As the glycosidic bond must be created *en route* to target structure, we show that this unusual yet efficient approach can effectively reduce the number of steps in total synthesis of complex natural macrolides. This attempt is documented as an efficient tool in the synthesis of gigantic macrolide rings thus proving their practical utility in the total synthesis of sugar-containing targets.

Introduction

Achieving high efficiency and stereocontrol in glycosylation reactions is arguably still the major effort in the synthesis of widely distributed carbohydrate containing oligomers.[1] While intermolecular formation of glycosidic bond has reached a satisfactory level of development, the intramolecular glycosylation strategy is still not broadly used and accepted in the synthesis.[2] As a result, construction of the macrocyclic rings by means of glycosylation is not seen as an efficient tool in the synthesis of macrocyclic compounds[3] and therefore practically neglected in the literature.[4] This is particularly inconvenient in the synthesis of various structurally complex macrocyclic glycolipids being a central part of resin glycosides. Taking these compounds as an excellent example, resin glycosides are conjugates between complex oligosaccharide part and hydroxy fatty acid as an aglycon moiety. The latter chain is attached to sugars to form a specific macrolactone ring linking two or more sugar units of the backbone. Not surprisingly, known studies revealed that the construction of the cyclic macrolide core of resin glycosides is a crucial step eventually determining synthetic strategy and overall efficiency.[5] In most cases, this was carried out by intramolecular esterification between the aglycon carboxylic acid and a sugar hydroxy group under high-dilution conditions.[6]

Alternatively, Fürstner developed an elegant approach employing ring closure metathesis (RCM) for macrolide cyclization, which was applied to the synthesis of various resin glycosides.[7] This strategy was also utilized in the total synthesis of Woodrosin I (**1**, Figure 1) - one of the most complex resin glycosides known to date - isolated from *Convovulacaeae* plant family.[8] The molecule comprises of 11-(*S*)-hydroxyhexadecanoic acid (jalapinolic acid) as an aglycon, which is tied back to form a characteristic macrolide ring that spans two sugar units of their tetrasaccharide backbones.

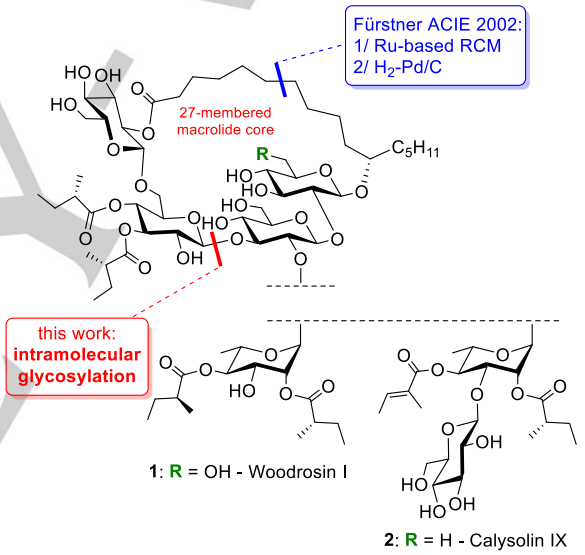

Figure 1. Structure of Woodrosin I (**1**) and Calysolin IX (**2**).

It is obvious that such strategy requires the use of additional steps, particularly the ring closing metathesis followed by hydrogenation of thus created double bond, not to mention multistep synthesis of two separated macrolide-precursors containing orthogonally protected sugar moieties. This caused the lower overall yield, and require application of Ru-catalyst.

Considering the number of steps, the most efficient strategy would be however to close the ring by intramolecular glycosylation reaction between sugar units, which in fact, must be done during the synthesis, anyway. Such a general concept assuming intramolecular glycosylation to create 27-membered ring as a crucial step was, however, perilous due to the lack of literature reports on this subject.[10] To prove this hypothesis we present herein such approach for the synthesis *of the most complex resin glycosides isolated to date* – Calysolin IX (**2**, Figure 1). This new resin glycoside having 27-membered ring macrolactone structure (jalapins) was isolated from the leaves, stems, and roots of *Calystegia soldanella* (*Convolvulaceae*).[9]

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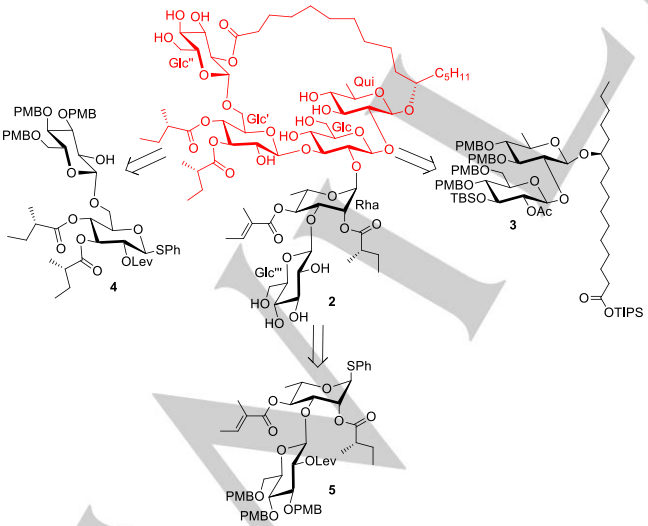
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

The sugar moiety of **2** was found to exist in partially acylated forms comprising (2*S*)-methylbutyric acid and tiglic acid. All those feature make Calysolin IX an extremely exciting synthetic target. Efficient macrolactonization, but also proper planning of orthogonally protected monosaccharides would be an exciting trial by fire for our concept.

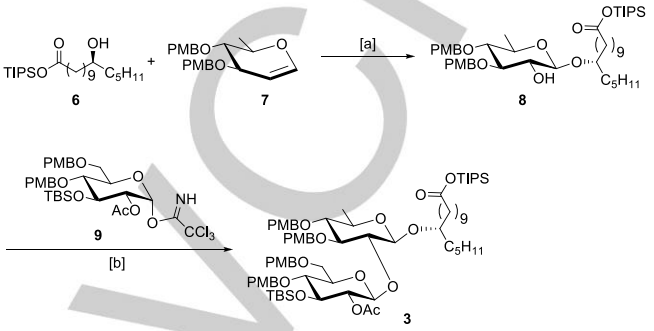
Results and Discussion

The target Calysolin IX (**2**) differs from formerly synthesized Woodrosin I (**1**) by number and kind of sugar units. Particular synthetic challenges arise from the 27-membered macrolide ring spanning three glucose and one 6-deoxyglucose (Quinovose). Peripheral disaccharide unit comprises of glucose and rhamnose (**5**) can be attached to central tetrasaccharide core at the late stage of synthesis, according to our retrosynthetic plan outlined at Scheme 1. This risky approach allows however to focus on the construction of macrolide core at the first steps. A key disconnection is obviously the glycosidic linkage between the Glc and Glc' rings. This bond would be formed by intramolecular coupling of glucose-glucose disaccharide glycosyl donor **4** with a glucose-quinovose disaccharide glycosyl acceptor **3**. To execute this key step, both disaccharide fragments must be linked by using 11-(*S*)-hydroxyhexadecanoic acid (jalapinolic acid). This requires efficient method for the formation of ester bond between carboxyl function in **3** and 2-OH of glucose ring. While it looks straightforward on paper, the implementation of this plan requires more careful choice of protecting groups in sugar molecules as two kind of ester-type residues and lactone ring are inherently present in final molecule. The occurrence of double bond in tiglic acid residue made the global application of benzyl groups unsuitable for this synthesis, of course. For this reason, after several simulations, we found to use the PMB ethers as the most promising candidates for the hydroxyl groups protection and final, last-stage deprotection.



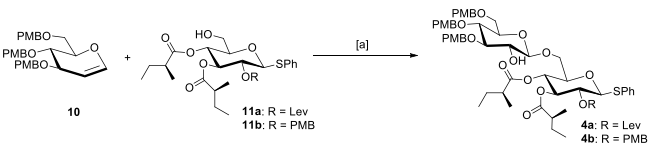
Scheme 1. Retrosynthetic analysis of Calysolin IX (**2**).

Leaving disaccharide fragment **5** to be attached at the very end, we envisaged that the macrolactone precursor itself can be assembled in a highly convergent manner from the disaccharide building blocks **3** and **4** (Scheme 1), which were obtained as described in Schemes 2 and 3. A detailed description of the synthesis of these fragments can be found in the Supporting Information material.



Scheme 2. Synthesis of disaccharide **3**. [a] i) Oxone®, acetone, DCM/$NaHCO_{3(aq)}$, 0 °C to rt, 3 h; ii) 1M $ZnCl_2{\cdot}OEt_2$, MS 4Å , THF, -78 °C to rt, 48 h, 71 %. [b] 0.1 M TMSOTf (cat.), MS 4Å, DCM, -20 °C, 3 h, 83 %.

The most efficient approach to disaccharide part **3** began with the synthesis of jalapinolic ester **6** from undecyne and hexanal. Enantioselective reduction of alkynone with (*S,S*)-Noyori catalyst resulted in the alcohol with high *ee*.[11] Thus obtained aglycone was used for the one-pot formation of β-glycoside from 6-deoxyglucal (**7**). This protocol not being widely used in the glycosylation turned out to be method of choice for the preparation of target β-glycoside. Efficient, stereoselective synthesis of epoxide ring by using Oxone,[11] followed by zinc chloride-promoted opening of oxirane ring[12] resulted in desired glycoside **8** with free OH group at the C-2 position suitable for next glycosylation step. This was done by using trichloroacetimidate **9** in the presence of a catalytic amounts of TMSOTf to give disaccharide **3** in 83% yield (Scheme 2).

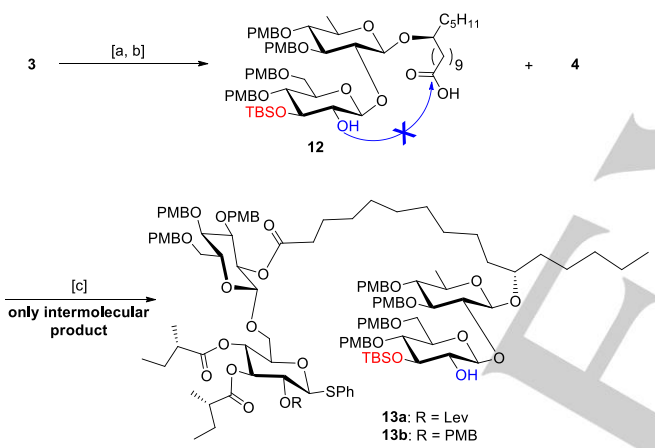


Scheme 3. Synthesis of disaccharides **4**. [a] i) Oxone®, acetone, DCM/$NaHCO_{3(aq)}$, 0 °C, 2 h; ii) 1M $ZnCl_2{\cdot}OEt_2$, MS 4Å , THF, -78 °C to rt, 36 h, **4a**: 71 %; **4b**: 78 %.

The same efficient protocol (Oxone, $ZnCl_2$) was used for the synthesis of second disaccharide fragment **4** (Scheme 3) from glucal **10** and thioglycoside **11**. The application of sugar with SPh group, which will be needed in the macrolide ring closing step reaction, does not interfere with the glycosylation reaction at this stage. Two different protecting groups at 2-OH of

Glc' ring have been used for testing two synthetic strategies, which will be revealed later.

Having both disaccharides in hand, we started to explore the foremost, risky part of connection the macrolide ring. First, TIPS-ester hydrolysis of **3** followed by deacetylation reaction by using DIBAL liberated both OH and COOH groups (Scheme 4). A standard deacetylation reaction under Zémplan protocol (MeONa/MeOH) or other deprotection methods realized by treatment with basic reagents caused a *trans*-3,2-TBS group migration, leading to a mixture of 2'-*O*- and 3'-*O*-silyl protected compounds in a (1:1) ratio. Thus obtained 2'-*O*-TBS derivative is much less prone to react with the Olah's reagent used in the further step. This made carboxyl group in disaccharide **12** ready for esterification with free OH in **4**. However, the presence of a hydroxyl group in the substrate **12** could enable intramolecular esterification. Anticipating this, we applied sterically hindered *tert*-butyldimethylsilyloxy protection at neighboring C-3 position to prevent undesired side reaction *i.e.* the intramolecular cyclization. This assumption turned out to be correct and disaccharide **12** was smoothly esterified with alcohol **4** in the presence of DIC and a catalytic amount of DMAP (Scheme 4)



Scheme 4. Synthesis of **13**. [a] KCN, MeOH/DCM (1:1), rt, overnight; [b] 1M DIBAL, DCM, -78 °C, 2.5 h, 82 % (over both steps). [c] DIC, DMAP (cat.), DCM, rt; conditions and yields see Table 1.

Only 1.25 equivalents of disaccharide **4a** was enough to obtained good yield of the desired tetrasaccharide **13a** (Table 1, entry 1). High regioselectivity and reitarability of the reaction deserved further investigation and the results are collected in Table 1. Although the application of 5 equivalents of **4a** resulted in the best reaction yield (94%, entry 4), we decided to use 2.5 equivalents of acid (78%, entry 3), mostly due to the highest overall reaction economy. Thus, the same conditions have been applied for the synthesis of PMB-protected **13b** from **4b** (83%, entry 5).

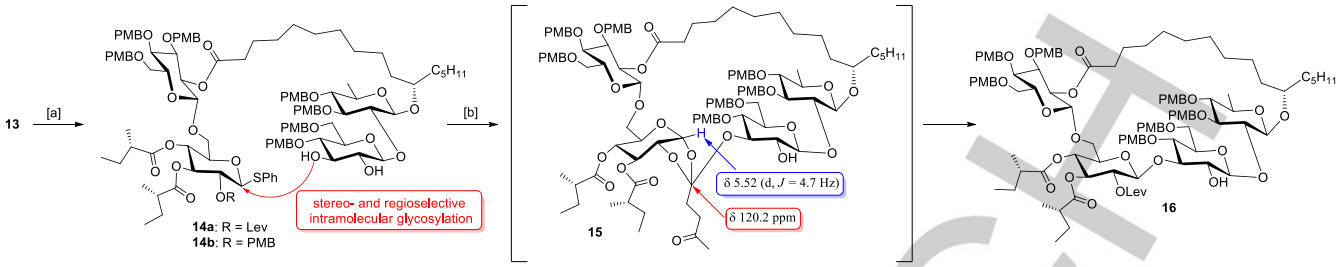
The next stage of the synthesis required the efficient assembly of the two terminus of each disaccharide to the tetrasaccharide macrolide core of Calysolin IX. Deprotection of the silyl group from **13a** was easy and resulted in the thioglycoside **14a** with two free hydroxyl groups ready for glycosidic bond formation. Scheme 5 presents required route to macrolide core *via* stereo- and regioselective glycosylation. Such a strategy, if efficient, would allow the formation of a macrolide ring and leave a free hydroxyl group at C-2 of Glc ready for final attachment of disaccharide 5 (Scheme 1). For steric reasons, equatorially placed 3-OH group should be more accessible allowing regioselective glycosylation, however, this endeavor turned out to be far from trivial.

Table 1. Intermolecular esterification.

Entry[a]	Substrate	Equivalents of substrate	Time	Yield[b]
1	**4a**	1.25	40 h	60 %
2	**4a**	1.5	18 h	73 %
3	**4a**	2.5	18 h	78 %
4	**4a**	5.0	18 h	94 %
5	**4b**	2.5	36 h	83 %

[a] Performed in DCM in the presence of DIC and catalytic amount of DMAP at rt. [b] Isolated yields.

At the beginning we checked the reactivity of compound **4b** where thioglycoside was additionally activated in the presence of benzyl-type PMB ether attached to C-2 position of Glc' ring. Unfortunately, no attempt to activate SPh, including triflic acid/NIS (Table 2, entry 1) was effective. Therefore the alternative approach for the glycosidation steps was explored by using ester-type levulinic protecting group at C-2 of Glc' in the substrate **14a** allowing the orthoester formation at the crucial step. This additional step forces the approximation of the acceptor hydroxyl group to the activated glycosyl donor part. Proving this concept required additional evidence for the *in situ* formation of orthoester intermediate from **14b**. This was possible by using NMR of reaction mixture. Most indicative was a doublet in the ^{1}H NMR at 5.52 ppm of anomeric proton and corresponding signal in ^{13}C NMR spectrum at 120.2 ppm which confirm the newly formed orthoester junction (Scheme 5).



Scheme 5. Synthesis of **16**. [a] HF·Py, THF, 0 °C to rt, 48 h, **14a**: 76 %; **14b**: 72 %. [b] Conditions and yields see Table 2.

Table 2. Results of intramolecular glycosylation.

Entry[a]	Substrate	Conditions[b]	Concentration of substrate[c]	Time	Yield
1	**14b**	TfOH (0.25 eq.)/NIS, DCM, -20 °C to 0 °C	4.5 mM	40 h	No reaction[b]
2	**14a**	TMSOTf (0.25 eq.)/NIS, Hx/DCM (2:1), -20 °C to rt	4.5 mM	24 h	No reaction
3	**14a**	TMSOTf (0.65 eq.)/NIS, Hx/DCM (2:1), 0 °C	4.5 mM	18 h	Deprotection of PMB group
4	**14a**	MeOTf (5.0 eq.), Hx/DCM (2:1), 0 °C	4.5 mM	2 h	Deprotection of PMB group
5	**14a**	TfOH (0.1 eq.)/NIS, $CHCl_3$, 0 °C	10 mM	16 h	No reaction
6	**14a**	TfOH (0.1 eq.)/NIS, DCM, -40 °C to 0 °C	45 mM	14 h	13 %
7	**14a**	TfOH (0.1 eq.)/NIS, DCM, -20 °C to 0 °C	10 mM	16 h	45 %
8	**14a**	TfOH (0.15 eq.)/NIS, DCM, -20 °C to 0 °C	4.5 mM	40 h	58 %

[a] All reaction was performed with molecular sieves 4 Å under strictly anhydrous conditions. [b] Further addition of TfOH caused deprotection of PMB group.

Nonetheless, the implementation of this strategy required very careful optimization of the glycosylation conditions. Table 2 presents more informative steps showing the impact of the applied conditions, kind of activators and substrate concentration on the reaction outcome. Under most efficient conditions described in entry 8 intramolecular glycosylation of **14a** using similar TfOH/NIS was found to proceed smoothly in DCM at the substrate concentration of 4.5 mM, giving protected macrolide core of Calysolin IX **16** in 58% yield. It is noteworthy, that the transformation of orthoester into final macrolide required prolonged reaction time at 0 °C. Another interesting observation shows that a similar yield can be achieved under 10 and 4.5 concentration. This shows that intramolecular glycosylation is tolerant to broader concentration and reaction conditions and thus hypothetically useful for similar macrolide synthesis.

Conclusions

We have succeeded in the first total synthesis of macrolide ring of the most complex resin glycoside Calysolin IX known through intramolecular glycosylation approach. Our work shows not only the relevance of glycosylation to macrolide ring construction, but also present usefulness of an orthoester-strategy to catch the two ends of the ring, which supports closing the macrolide core. With macrolide **16** in hand, the introduction of the missing disaccharide Glc'''-Rha moiety will be investigated in due course and soon presented.

Acknowledgements

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Keywords: natural products • macrolide • carbohydrates • intramolecular glycosylation • total synthesis

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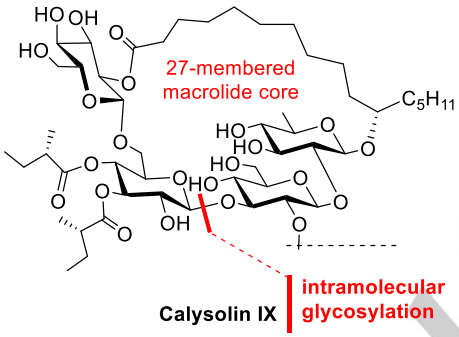
COMMUNICATION

Intramolecular glycosylation as an efficient tool for the synthesis of 27-membered macrocyclic ring is highlighted in the first total synthesis of the most complex resin glycoside isolated to date - Calysolin IX.



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