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A divergent approach to the synthesis of simplexides and congeners *via* a late-stage olefin cross-metathesis reaction†

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Simplexides constitute a unique group of immunosuppressive glycolipids that demonstrate antiproliferative activities against activated T-cell lymphocytes *via* a unique non-cytotoxic inhibition. To investigate the structure–activity relationship of the varied long-chain secondary alcohols on simplexides, we developed an efficient and divergent route to the synthesis of simplexides and congeners, taking advantage of a late-stage olefin cross-metathesis reaction.

Introduction

Simplexides, isolated as a mixture from the Caribbean sponge *Plakortis simplex* by Fattorusso *et al.*,[1–3] represent a new structural type of glycolipids that are composed of varied long-chain secondary alcohols and a conserved disaccharide consisting of glucose and galactose (Fig. 1). It was reported that simplexides strongly inhibited the proliferation of concanavalin-A activated T-cell lymphocytes *in vitro*.[1,4–6] A concentration of simplexides as low as 10 ng mL^{-1} could cause 43% antiproliferation of T-cells. In addition, an MTT assay indicated that this potent inhibition was through a unique yet unclear non-cytotoxic mechanism.[1] Given the critical role of T-cell lymphocytes in the immune system,[7] simplexides may serve as a promising lead for the development of novel immunosuppressive drugs.[8,9]

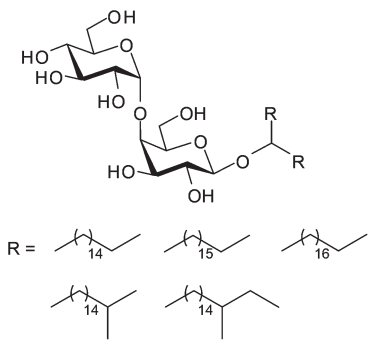

Fig. 1 Structure of simplexides.

Li *et al.* have reported the synthesis of several simplexide congeners by employing thioglycosides as the donors.[10] A fluorescent probe incorporated with a simplexide has also been synthesized.[11] However, there is little data about the structure–activity relationship of simplexides, apart from a couple of simplified analogues.[12] It has been revealed that immunological properties of glycolipids are usually modulated by the length and branching of their lipid chains.[13–15] Thus, it is necessary to investigate the structure–activity relationship of the long-chain secondary alcohols on simplexides to get a better comprehension of their immunosuppressive activities. Herein, we report the synthesis of simplexides and congeners with varied long-chain secondary alcohols *via* a divergent late-stage elaboration.[16]

As depicted in the retrosynthetic analysis (Scheme 1), we envisioned the use of an olefin cross-metathesis (CM) reaction as the key step to elaborate simplexides and congeners. In recent years, olefin metathesis has been widely employed in the synthesis of carbohydrate derivatives.[17–21] Due to the mild conditions and good tolerance to most of the functional groups, olefin metathesis has been proved to be an excellent and versatile tool in the diversity-oriented synthesis of glycolipids.[22–25] In our design, a variety of olefins **3** would be attached to the homoallyl group in disaccharides **2a**/**2b** *via* CM reaction at a late stage in the synthesis, giving variation by length and functionality of the long lipid chains. The acetyl group was chosen as protecting group for 6-OH in the glucose donor **4**, anticipating a remote participation in glycosylation with the galactose acceptor **5** to furnish the desired

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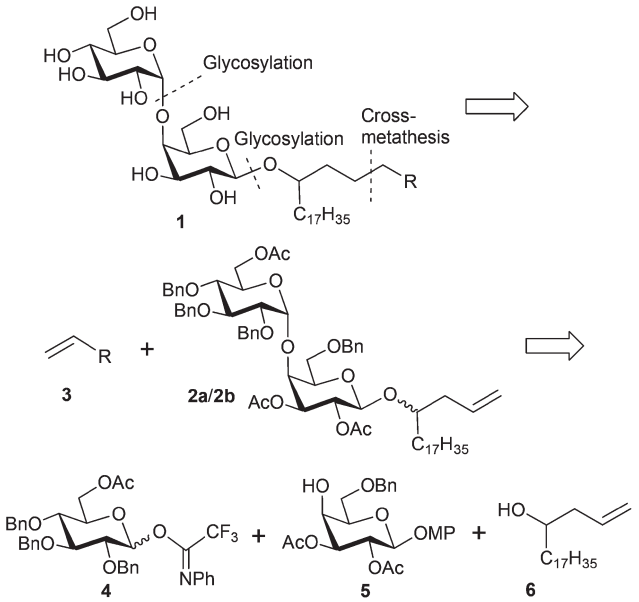


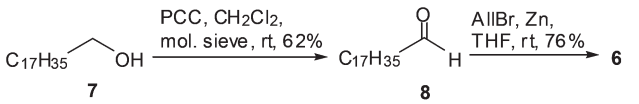
Scheme 1 Retrosynthesis of simplexides and congeners.

α-glycosidic linkage.[26–30] The neighboring group participation of 2-*O*-Ac in the galactose unit would secure a β-selective glycosylation with homoallyl alcohol **6**.[27,31]

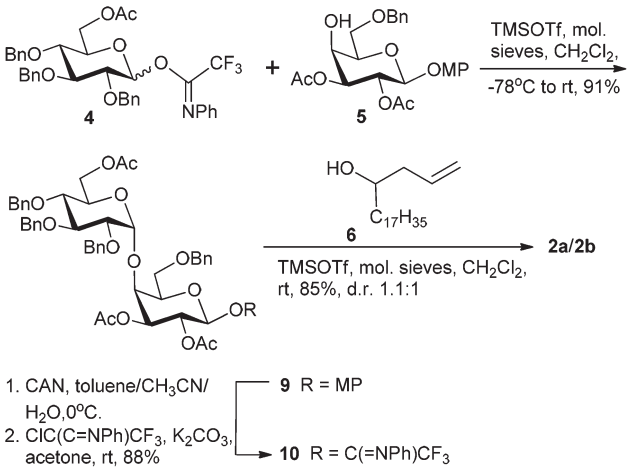
Results and discussion

Our synthesis commenced with the preparation of the three building blocks **4**, **5** and **6**. Treatment of commercially available alcohol **7** with PCC provided aldehyde **8**,[32] which was then converted into the desired racemic olefin **6** in the presence of allyl bromide and Zn powder in good yield (Scheme 2). In accordance with the literature, *N*-phenyltrifluoroacetimidate (PTFAI) donor **4** was prepared from the commercially available *per*-*O*-acetylated glucose (8 steps, 52%) in high yield.[33–37] Acceptor **5** was efficiently prepared from *per*-*O*-acetylated galactose *via* 5 steps in 49% overall yield.[38]

With the three building blocks in hand, we started the assembly process (Scheme 3). The challenging step was to create the α-glycosidic linkage with high selectivity between glucose donor **4** and galactose acceptor **5**. The formation of 1,2-*cis* glycosidic linkage remains a major subject of study in carbohydrate chemistry, and the α-selectivity in the glycosylation with glucose donors is still case-by-case.[27,39,40] One of those successful examples takes advantage of the acyl protecting group at 6-OH,[26–30,41] although the mechanism of



Scheme 2 Synthesis of olefinic alcohol **6**.

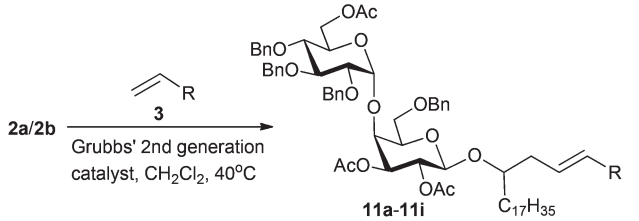


Scheme 3 Synthesis of homoallyl disaccharides **2a**/**2b**.

this α-directing effect is still controversial. As expected, the glycosylation of **4** and **5** catalyzed by TMSOTf proceeded smoothly to give the desired α-linked disaccharide **9** in excellent yield (91%), with no β-glycosidic product being obtained. It is particularly noteworthy that poor α-selectivity was observed in this glycosylation when replacing the acetyl group in donor **4** with benzyl. Selective removal of the anomeric *p*-methoxylphenyl (MP) group in **9** with CAN and subsequent activation with $ClC(C{=}NPh)CF_3$ provided PTFAI donor **10**.[42–46] Taking advantage of the neighboring group participation of the 2-*O*-Ac, glycosylation of donor **10** and acceptor **6** in the presence of a catalytic amount of TMSOTf gave fully the desired β-glycosidic products **2a**/**2b** in 85% yield. The resulting **2a**/**2b** were a pair of separable diastereoisomers with the absolute configuration at the alcoholic carbon uncharacterized. Nevertheless, both of the diastereoisomers were applied to the following transformations.

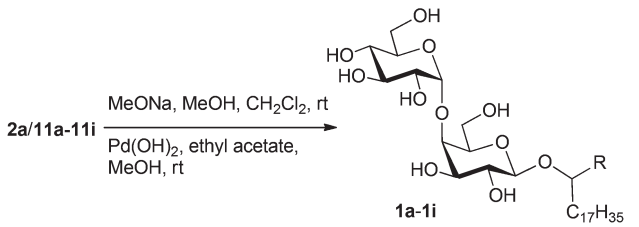
The next step was to examine the performance of CM reactions on disaccharides **2a**/**2b** (Table 1). Compared to that of ring-closing and ring-opening olefin metathesis, the application of CM reaction has been limited by its relatively poor chemoselectivity because undesired self-metathesis is always observed.[47] Fortunately, the discovery of more active catalysts helped to overcome this limitation and greatly extend the application of CM reactions in total synthesis. An evaluation of a relevant CM reaction with *C*-glycoamino acids as substrates has been reported by McGarvey *et al*. in 2005.[21] In the present studies, after examining a number of potential conditions,[48–51] we found that a catalytic amount of Grubbs' 2nd generation reagent at 40 °C in CH_2Cl_2 was highly efficient and universal for the coupling of homoallyl disaccharides **2a**/**2b** with an excess amount (9 equiv.) of the terminal olefins **3a–3g**. Thus, the desired simplexide precursors **11a–11i**, including two pairs of diastereoisomers (**11c**/**11d** and **11e**/**11f**) at the alcoholic carbon, were prepared in high yields with the corresponding self-metathesis products being well suppressed. It is noteworthy that the *E*-olefins turned out to be the major products, with only a few or even no *Z*-olefins being observed.

Table 1 Synthesis of simplexides precursors *via* CM reaction



Entry	Substrate	Olefins	Product (yield)
1	**2a**	**3a** C_4H_9	**11a** (86%)
2	**2a**	**3b** $C_{10}H_{21}$	**11b** (78%)
3	**2a**	**3c** $C_{14}H_{29}$	**11c** (80%)
4	**2b**	**3c** $C_{14}H_{29}$	**11d** (75%)
5	**2a**	**3d** $C_{16}H_{33}$	**11e** (76%)
6	**2b**	**3d** $C_{16}H_{33}$	**11f** (79%)
7	**2a**	**3e** Ph	**11g** (99%)
8	**2a**	**3f** OBz	**11h** (61%)
9	**2a**	**3g** OCH_3	**11i** (92%)

Table 2 Synthesis of simplexides and congeners **1a–1i**



Entry	Substrate	R	Product (yield)
1	**2a**	C_3H_7	**1a** (66%)
2	**11a**	C_7H_{15}	**1b** (61%)
3	**11b**	$C_{13}H_{27}$	**1c** (83%)
4	**11d**	$C_{17}H_{35}$	**1d** (91%)
5	**11e**	$C_{19}H_{39}$	**1e** (85%)
6	**11f**	$C_{19}H_{39}$	**1f** (90%)
7	**11g**	C_3H_7Ph	**1g** (67%)
8	**11h**	C_4H_8OH	**1h** (32%)
9	**11i**	$C_3H_6COOCH_3$	**1i** (99%)

The acyl groups in disaccharides **2a**/**11a–11i** were removed with MeONa in MeOH and CH_2Cl_2 (Table 2). Subsequent hydrogenolysis in the presence of $Pd(OH)_2$ led to the saturation of the olefins as well as the deprotection of the Bn groups. The target simplexides and congeners **1a–1i** were obtained in satisfactory yields. Among these compounds, **1e**/**1f** were a pair of the epimers at the alcoholic carbon in the lipid. Part of the allyl benzoate group on substrate **11h** was reduced to propyl in hydrogenolysis, so we only obtained the desired **1h** in 32% yield.

Conclusions

In summary, an efficient and concise route to the synthesis of simplexides and congeners *via* a late-stage olefin cross-metathesis reaction has been well established. A library of glycolipids with structural alternation in the lipid moieties has been successfully synthesized and characterized. The determination of the biological activities of these glycolipids is in progress and will be reported in due course.

Acknowledgements

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