C-Glycosylation

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Synthesis of the Pluramycins 1: Two Designed Anthrones as Enabling Platforms for Flexible Bis-C-Glycosylation**

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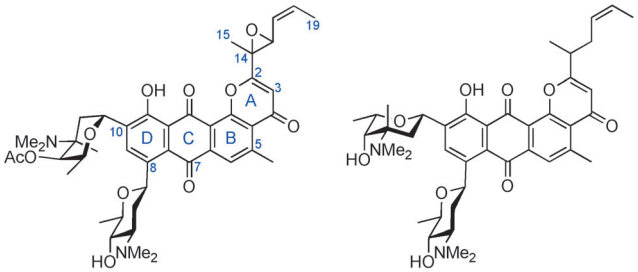
Dedicated to Professor Teruaki Mukaiyama

Abstract: *Two effective tricyclic platforms are reported for the installation of the two constituent sugars,* L*-vancosamine and* D*-angolosamine, in a regio- and stereoselective manner for the synthesis of the pluramycin class of bis-C-glycoside antitumor antibiotics. Two complementary protocols are now available that differ in the order in which the two sugar moieties are installed. Sc(OTf)$_3$ was effective as the Lewis acid.*

Among the aryl *C*-glycoside antibiotics, the pluramycins share the unique structural feature of two amino *C*-glycosides attached to an anthrapyranone chromophore (Scheme 1).[1]



Scheme 1. Bis-C-glycoside antibiotics of the pluramycin-class. The natural product numbering has been adopted herein.

The antitumor activity of these compounds is attributed to intercalation with DNA, whereby the two *C*-glycosides are responsible for the sequence selectivity.[2] The significant bioactivity as well as the challenging structures of the pluramycins have attracted considerable attention to their synthesis.

Two key synthetic challenges are 1) the regio- and stereoselective installation of two different *C*-glycosides[3] and 2) the effective assembly of the tetracyclic framework. However, it is difficult to find a coherent solution for these issues. The pioneering synthesis of isokidamycin by Martin and co-workers has been the only example of a completed total synthesis.[4]

Previous approaches for installing the bis-*C*-glycosides can be classified in three categories: 1) In early-stage approaches, simple mono- or bicyclic compounds are used to regioselectively connect two sugars. An inevitable issue, however, is that a linear strategy would be required for the construction of the tetracyclic core.[5–7] 2) In late-stage approaches, a pyranoanthracene tetracycle is used for bis-C-glycosylation; in this case, problems arise in terms of regioselectivity and/or yield.[8] 3) In their unique approach, Martin and co-workers[4] used a *C*-glycosyl furan derivative, which was converted into a tetracycle amenable to a second C-glycosylation.

Seeking a simple, general solution, we focused on *tricycles*. Among other structures, anthrones **1** and **2** were considered as potential platforms for bis-C-glycosylation according to the following reasoning. First, anthraquinone **A**, the intact BCD framework in the targets, was excluded by consideration of its electron poorness, which would be inappropriate for a Friedel–Crafts reaction or O→C-glycoside rearrangement.[3,9] Second, inspiration from type-II polyketide biosynthesis [Scheme 2, Eq. (1)][10] suggested that anthrone **B**, which lacks the C7 oxygen functionality, would be endowed with the necessary reactivity. Omission of the C7 carbonyl group would also help minimize the possible photodegradation known for the pluramycins [Scheme 2, Eq. (2)].[11] However, an issue in **B** was the equivalency of the B/D rings: Non-selective, multiple C-glycosylation reactions may occur at both rings. Finally, tricycles **1** and **2** emerged as the candidates for further investigation. In these compounds, the non-aromatic B ring would enable discrimination between the B/D rings. Furthermore, the carbonyl group in the B ring would be useful for the formation of the A ring. Herein, we report the excellent performance of tricycles **1** and **2** as platforms for the installation of two sugar groups in a complementary fashion, thus providing a firm basis for the general synthesis of the pluramycins.[12]

The reactivity of tricyles **1** and **2**[13] as *C*-glycosyl acceptors was studied extensively under a variety of Lewis acidic conditions. We employed three glycosyl donors for the constituent sugars: D-angolosamine precursors **3a** and **3b**,[5b,14] and L-vancosamine precursor **4** (Scheme 3),[15] and established two efficient protocols for their installation on the tricyclic platforms.

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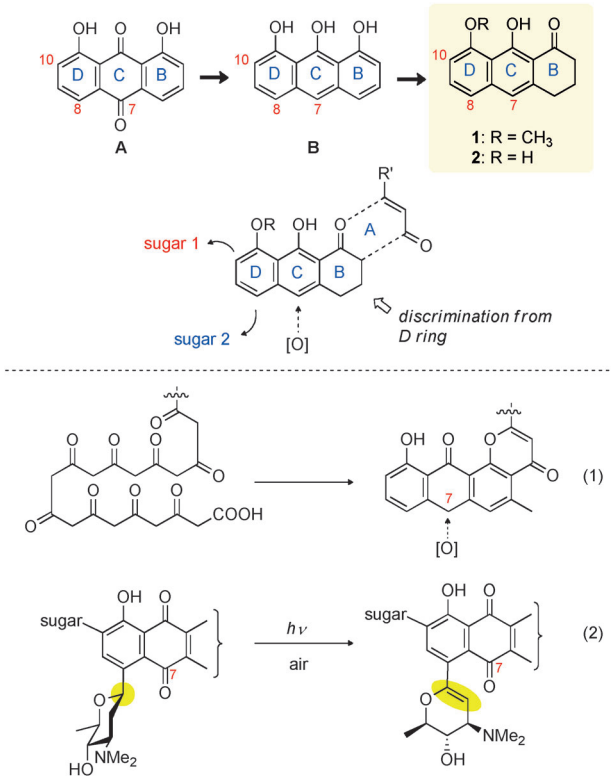


Scheme 2. Design of the enabling platform for bis-C-glycosylation.

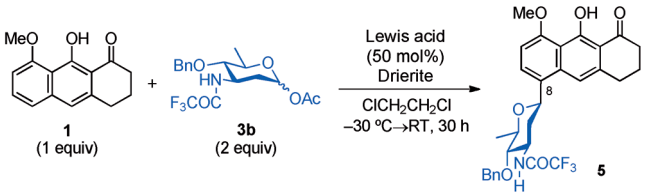
Scheme 3. Three glycosyl donors. Bn = benzyl.

Preliminary reactions of tricycle **1** with glycosyl donors **3a** and **3b** were examined under a specified set of conditions (50 mol% of a Lewis acid, 1,2-dichloroethane, Drierite, −30 °C→RT). The azido acetate **3a** failed to give any *C*-glycoside products owing to reactivity mismatching: Donor **3a** was rapidly activated by the Lewis acid at low temperature, at which the nucleophilicity of **1** was insufficient for the Friedel–Crafts reaction. Thus, donor **3a** was completely consumed, but did not take part in the productive pathway. Instead only unidentified decomposition products were obtained, with complete recovery of **1**.

By contrast, **3b** proved to be a viable glycosyl donor. The first trial with $Sc(OTf)_3$ gave the C8-linked *C*-glycoside **5**, albeit in 21% yield (Table 1, entry 1) along with decomposition products derived from **3b** and the recovery of **1**. Whereas other Lewis acids led to poor yields of **5** (Table 1, entries 2–4), Me_3SiOTf gave the *C*-glycoside **5** in promising yield (67%; Table 1, entry 5). In all experiments, the anomeric configuration of **5** was entirely D-β (^{1}H NMR and 2D ROESY spectroscopy).[16]

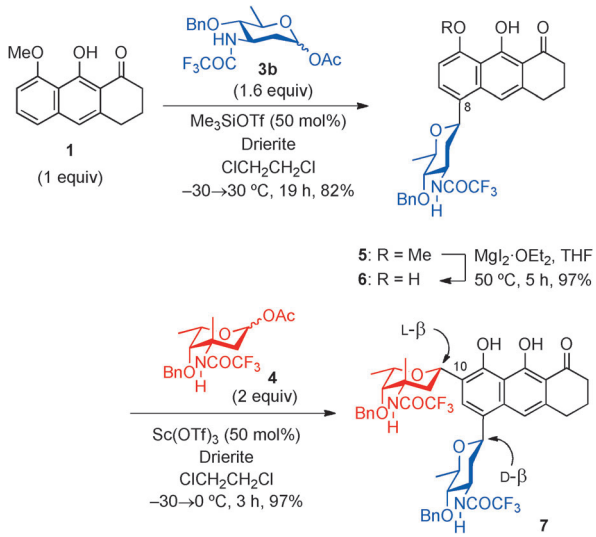
After further optimization, the reaction with Me_3SiOTf gave **5** in improved yield (82%; Scheme 4). Although it was good that the reaction of **1** rigorously stopped at the stage of mono-C-glycosylation at C8, we needed some means to promote the second C-glycosylation. An idea was to first remove the methyl protecting group in **5**, in the hope that the O→C-glycoside rearrangement would be effective.[9] $MgI_2{\cdot}OEt_2$ promoted this deprotection nicely:[17] The desired phenol **6** was formed in 97% yield.[18] Pleasingly, the second C-glycosylation was possible with phenol **6**. The reaction of **6** and L-vancosamine precursor **4** (2 equiv) with $Sc(OTf)_3$ occurred exclusively at the C10 position to give the bis-*C*-glycoside **7** cleanly in 97% yield. The anomeric centers in **7** both had the β configuration.[16]

Table 1: Mono-C-glycosylation of tricycle **1**.



Entry	Lewis acid	Yield of **5** [%]
1	$Sc(OTf)_3$	21
2	$BF_3{\cdot}OEt_2$	14
3	$SnCl_4$	30
4	$[Cp_2HfCl_2]/AgOTf$[a]	21
5	Me_3SiOTf	67

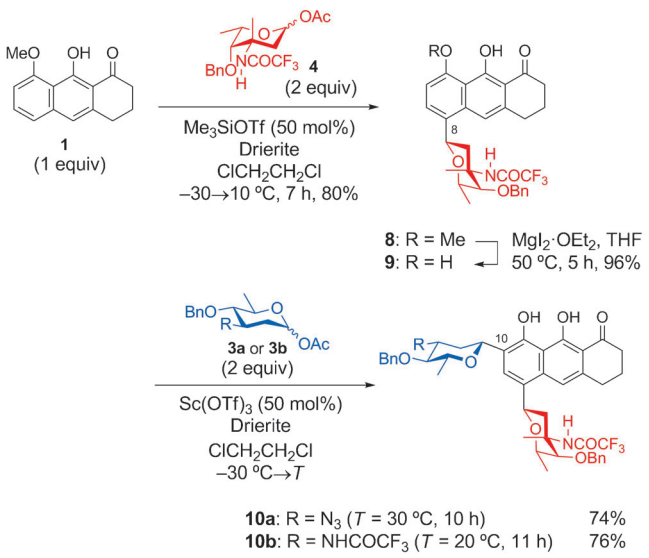
[a] Tf = trifluoromethanesulfonyl.



Scheme 4. Protocol for the bis-C-glycosylation of tricycle **1**.

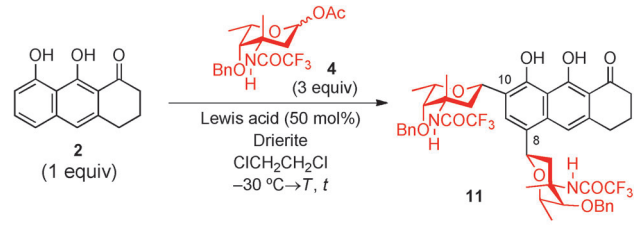
Thus, an efficient three-step protocol was established for the bis-C-glycosylation of tricycle **1**: 1) mono-C-glycosylation at C8, 2) deprotection, 3) a second C-glycosylation at C10. The generality of this approach was tested successfully in the synthesis of *C*-glycosides **10a** and **10b**, in which the positions of the two sugar moieties in **7** were exchanged (Scheme 5). Notably, the second *C*-glycosylation proceeded well with both glycosyl acetates, **3a** and **3b**. Such artificial bis-C-glycosides are potentially useful for biological studies.

We next focused on another substrate, **2**, with the C11 phenol unprotected. Tricycle **2** turned out to be much more reactive than **1**, and readily accepted two sugars at the C8 and



Scheme 5. Synthesis of bis-*C*-glycosides **10** with the opposite sugar substitution at C8 and C10 (with respect to **7**).

C10 positions, as exemplified by its reaction with glycosyl donor **4** (3 equiv; Scheme 6). The reaction promoted by Me_3SiOTf (50 mol%) cleanly gave bis-*C*-glycoside **11** in 89% yield, and $Sc(OTf)_3$ was also effective, with the formation of **11** in 95% yield. The anomeric centers in **11** both had the L-β configuration.[16]

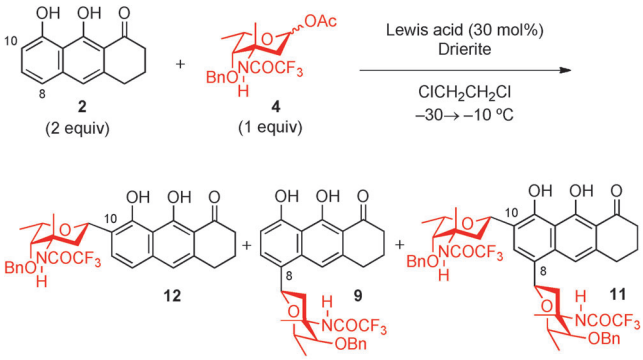


Lewis acid	*T* [°C]	*t* [h]	Yield of **11** [%]
Me_3SiOTf	5	3	89
$Sc(OTf)_3$	0	0.7	95

Scheme 6. One-pot bis-C-glycosylation of tricycle **2**.

Although this one-pot bis-C-glycosylation of tricycle **2** proceeded in similar yields with Me_3SiOTf and $Sc(OTf)_3$, monitoring of the reaction by TLC suggested an interesting difference between these Lewis acids: In the reaction with Me_3SiOTf, two sugar moieties appeared to be installed in a random order, whereas the reaction with $Sc(OTf)_3$ initially led to glycosylation at C10. This observation was a promising clue for the next goal: the regioselective installation of two different sugars on tricycle **2**.

Indeed, the reaction of tricycle **2** and acetate **4** in a 2:1 molar ratio led to completely different results with the two Lewis acids. Me_3SiOTf gave a mixture of regioisomeric mono-C-glycosides **12** and **9**, along with bis-*C*-glycoside **11** (Scheme 7). On the other hand, $Sc(OTf)_3$ gave specifically the mono-C-glycoside **12** as the sole product. The anomeric configuration of **12** was L-β.[16,19]

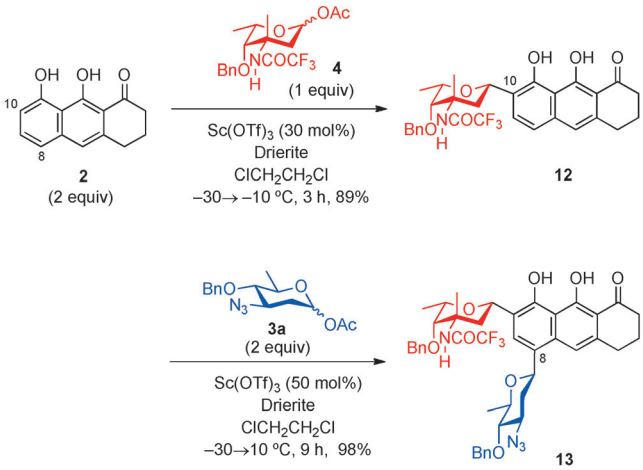


Lewis acid	*t* [h]	Combined yield [%]	**12** / **9** / **11**
Me_3SiOTf	3	82	52 : 27 : 21
$Sc(OTf)_3$	1.5	77	>95 : – : –

Scheme 7. Mono-C-glycosylation of tricycle **2**.

In this case, the intermediary *O*-glycoside was neither observed (TLC assay) nor isolated (early quenching). Elusiveness of the *O*-glycoside intermediate is a general trend for reactions of substrates with a phenol group hydrogen-bonded to a nearby carbonyl group,[5,9b] although the phenol apparently plays a key role in the reactivity and regioselectivity of the transformation. The mechanistic details of the process and special reactivity of $Sc(OTf)_3$ await further investigation.

A larger-scale reaction enabled the mono-*C*-glycoside **12** to be obtained in improved yield (89%). This product was then subjected to the second C-glycosylation (Scheme 8). The



Scheme 8. Protocol for the bis-C-glycosylation of tricycle **2**.

treatment of **12** with azido acetate **3a** in the presence of $Sc(OTf)_3$ led to smooth installation of the D-angolosamine moiety at the C8 position to give bis-*C*-glycoside **13** in excellent yield and stereoselectivity.[16]

In conclusion, two effective protocols have been established for site-selective, stepwise bis-C-glycosylation by the use of tricycles **1** and **2** as enabling platforms. These synthetic methods provide flexible access to pluramycin-related com-

pounds and enabled the first total synthesis of saptomycin B,[12] a member of this class of antibiotics.

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[18] Other reagents (BBr_3, BCl_3, and $CeCl_3$/NaI) induced side reactions, such as debenzylation and/or decomposition of the sugar moiety.

[19] $BF_3{\cdot}OEt_2$ and $[Cp_2HfCl_2]$/AgOTf also gave mixtures of **12**, **9**, and **11** in varying ratios. No reaction occurred with $Y(OTf)_3$ or $La(OTf)_3$.

