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Dedication ((optional))

Abstract: The plant *Psychotria kirkii* hosts an obligatory bacterial symbiont, *Candidatus* Burkholderia kirkii, in nodules on their leaves. Recently, a glucosylated derivative of (+)-streptol, (+)-streptol glucoside, was isolated from the nodulated leaves and was found to possess a plant growth inhibitory activity. To establish a structure activity relationship study, a convergent strategy was developed to obtain several pseudosugars from a single synthetic precursor. Furthermore, the glucosylation of streptol was investigated in detail and conditions affording specifically the α or β glucosidic anomer were identified. Although (+)-streptol was the most active compound, its concentration in *P. kirkii* plant leaves extract was approximately 10 fold lower than that of (+)-streptol glucoside. These results provide compelling evidence that the glucosylation of (+)-streptol protects the plant host against the growth inhibitory effect of the compound, which might constitute a molecular cornerstone for this successful plant-bacteria symbiosis.

Bacteria are well known to establish special relationships with other organisms leading to either beneficial (symbiosis) or detrimental (parasitism) interactions with their hosts. The study of such systems led to the discovery of several bioactive compounds produced by the bacterial symbiont.[1] In some cases, it was found that the microorganism protects the host against predators by providing chemical defense.[2] The study of these natural products is particularly challenging because the bacterial symbionts often lost the ability to grow outside of its host; to overcome this difficulty, these natural products can be produced *via* heterologous expression or organic synthesis.[3]

The obligatory symbiosis of the plant *Psychotria kirkii* (*P. kirkii*) with its symbiont (*Candidatus* Burkholderia kirkii) represents an example where the bacterial symbiont cannot be cultivated without its host. The leaf nodule symbiosis was described more than 100 years ago[4] and has been investigated at a biological and genomic level.[5] The sequencing and bioinformatic analysis of the bacterial genome identified a putative 2-epi-5-epi-valiolone synthase.[6] which is known to be involved in the biosynthesis of C_7N aminocyclitols and other pseudosugars,[7] and is present in the genome of many prokaryotic and eukaryotic organisms.[8] By applying an NMR-guided fractionation of crude extracts of *P. kirkii* leaves, a novel aminocyclitol kirkamide (**1**) possessing insecticidal activities was isolated and characterized.[9] Interestingly, **1** and its potential gene cluster were also detected in the nodulated leaves of another plant of the *Rubiaceae* family.[10] An extensive analysis of the biological activities of *P. kirkii* leaf crude extract led to the discovery of the novel plant growth inhibitor (+)-streptol glucoside (**2**), which was isolated and its structure elucidated by NMR and mass spectrometry analysis.[10] The aglycon of this natural product is composed of the plant growth inhibitory (+)-streptol (**3**, known also as valienol), which was previously isolated from *Streptomyces sp*.[11] Furthermore, a detailed comparison of the chemical shift and coupling constant of the anomeric proton (4.30 ppm, $^3J_{H\text{-}H}$ = 7.9 Hz), in DMSO-d_6, with known natural products allowed the determination of the β configuration of the glucose moiety.[10]

Interestingly, the diastereoisomer of (+)-streptol glucoside A-79197-2 (**4**) was also isolated from bacteria living on the leaves of a different plant.[12] We hypothesized that the glucose attached to streptol plays an important role in the relationship between the host and the bacteria. To evaluate effects of glucosylation and configuration on the growth inhibitory activity of streptol, we embarked on the development of a convergent strategy to obtain (+)-streptol glucoside (**2**), (+)-streptol (**3**), A-79197-2 (**4**), (–)-streptol glucoside (**5**), (–)-streptol (**6**) and the diastereoisomer **7**of A-79197-2.

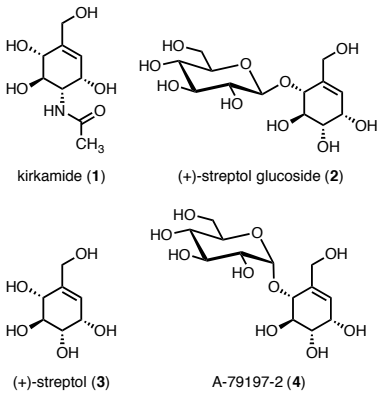

Figure 1. Constitution and configuration of the natural products kirkamide (**1**), (+)-streptol glucoside (**2**), (+)-streptol (**3**) and A-79197-2 (**4**).

To date, several synthetic approaches have been designed to obtain streptol (**3**). Routes towards racemic material used methylene cyclohexene,[13] *para*-benzoquinone[14] and *myo*-inositol[15] as starting materials and enantioselective syntheses were developed using diverse strategies such as a retro Diels-

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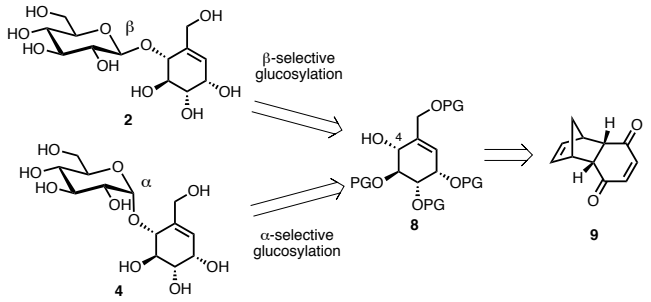
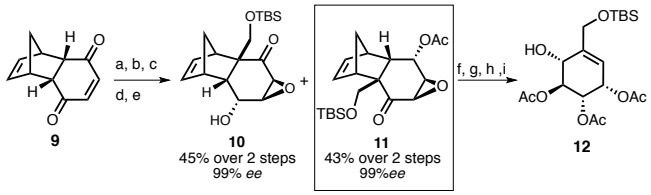
Alder reaction,[16] a Baylis-Hillman reaction followed by ring-closing metathesis (RCM),[17] and Horner-Wadsworth-Emmons (HWE)[18] and intramolecular aldol reactions.[19] We envisaged that both streptol glucoside and A-79197-2 could be derived from a protected streptol **8**. The glucosyl moiety can be attached in the last stage of the synthesis allowing for diversification by selective α or β glucosylation (Scheme **1**).



Scheme 1. Retrosynthetic route of (+)-streptol glucoside (**2**) and A-79197-2 (**4**) (PG = protecting group)

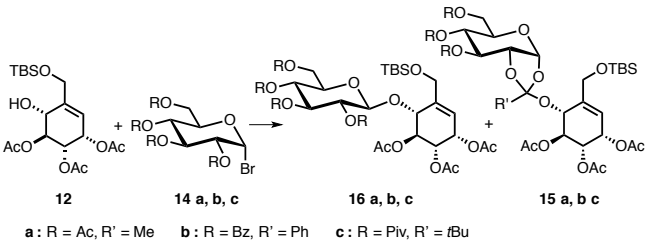
The compound **8** was chosen as the key intermediate for the synthesis. It could be prepared enantioselectively from the norbornene **9** according to a known procedure.[16] The selected route furnished the two key intermediates **10** and **11**, which can be separated by enzymatic kinetic resolution and used for the synthesis of both enantiomer of streptol. The synthesis features several key steps such as epoxidation, aldol reaction and an acetate-assisted epoxide opening reaction affording the protected streptol **12** (Scheme **2**).



Scheme 2. Synthetic strategy to obtain the protected streptol **12**. Reaction conditions: a) H_2O_2, Na_2CO_3; b) DBU, formalin; c) TBSCl, Imid, 84% over 3 steps; d) $NaBH_4$; e) Amano Lipase PS-IM, vinyl acetate 45% over 2 steps, 99% ee; f) $BF_3{\cdot}OEt_2$; g) NaOAc, Ac_2O, 76% over 2 steps; h) Ph_2O, 230°C, 98%; i) $NaBH_4$, $CeCl_3{\bullet}7H_2O$, 77%. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, TBS: *tert*-butyldimethylsilyl.

We envisaged the attachment of the sugar moiety by the Koenigs-Knorr method[20] using a neighboring group participation strategy to ensure a selective β-glucosylation. The ester group at the 2-position of the glucose donor stabilizes the intermediate oxocarbenium ion forming a bicyclic intermediate **13** (**supporting information**).[21]

Readily available acetoxybromo-D-glucose (**14a**) was originally selected as the glucosyl donor for this reaction. However, preliminary screening of reaction conditions showed no product formation (Table **1**, entry 1-7). Interestingly, under AgOTf mediated conditions and in the presence of 2,6-di-*tert*-butyl-4-methylpyridine as an acid scavenger, the orthoester **15a** was isolated as the exclusive product (Table **1**, entry 7). We focused on optimizing these reaction conditions and adjusted the protecting groups on the glucosyl donor by introducing more sterically hindered substituents like benzoyl or pivaloyl in an attempt to prevent the orthoester formation. Unfortunately, the benzoylbromo-glucose **14b** did not provide the desired glucosidic product, and only the orthoester **15b** was observed**.** However, the use of pivaloylated bromo-D-glucose **14c** as glucosyl donor afforded the glucosidic product **16c** in 80% yield (Table **1**, entry 10).[22] Performing the reaction at lower temperature (– 5°C) decreased the rate of decomposition of the starting material and, using these conditions, we were pleased to observe an excellent yield (98%, Table **1**, entry 11). Other glucosylation methods did not give the desired product.



Scheme 3. Reaction screening for the selective β-glucosylation of the protected streptol **12**. Conditions are described in table **1**.

Table 1. Screening conditions for the selective β-glucosylation of the protected streptol (**12**)

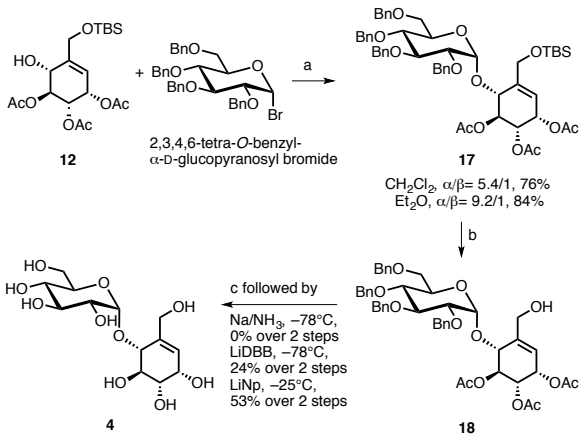
Entry[a]	R =	Promoter	Base	Time (h)	Yield (%)[b]
1[c]	Ac, **14a**	$Hg(CN)_2$	TMU	12	nd
2	Ac, **14a**	$Sn(OTf)_2$	TMU	12	nd
3	Ac, **14a**	Ag_2CO_3		12	nd
4	Ac, **14a**	Ag_2O		12	nd
5	Ac, **14a**	AgOTf	TMU	12	nd
6	Ac, **14a**	AgOTf	lutidine	12	nd
7	Ac, **14a**	AgOTf	DTBMP	12	89, **15a**
8	Ac, **14a**	$HgBr_2$	HgO	12	40, **15a**
9	Bz, **14b**	AgOTf	DTBMP	15	63, **15b**
10	Piv, **14c**	AgOTf	DTBMP	15	80, **16c**
11[d]	Piv, **14c**	AgOTf	DTBMP	24	98, **16c**

[a] Reactions were performed, unless stated otherwise, with 10 mg of alcohol with a concentration of 0.025 M, 3.0 equiv. of Br-glucose, the promoter, the base, MS 4Å, CH_2Cl_2 as solvent and at rt. [b] Yield of isolated product was determined by column chromatography. [c] The solvent of the reaction was CH_3CN. [d] The temperature of the reaction was –5°C. TMU: tetramethylurea, DTBMP: 2,6-di-*tert*-butyl-4-methylpyridine, nd: not determined, Ac: acetyl, Bz: benzoyl, Piv: pivaloyl

Finally, the substituents on the disaccharide **16c** were sequentially deprotected. The TBS group was removed using a TBAF solution and the ester groups were hydrolyzed in LiOH solution to afford the desired (+)-streptol glucoside (**2**), which was then purified by reverse phase HPLC (RP-HPLC). The configuration of the anomeric center of the glucopyranosyl moiety was confirmed as β by the analysis of its typical proton chemical shift and coupling constant ($^3J_{H\text{-}H}$ = 7.9 Hz). To our delight, the

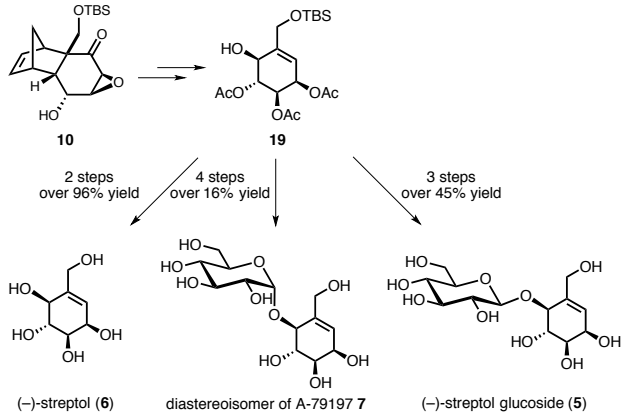
data for the fully synthetic streptol glucoside was in complete agreement with those obtained for the isolated natural product (**Supporting information**).

We then turned our attention on the preparation of A-79197-2 (**4**), which bears a glucose in α configuration (Scheme **4**). Readily available 2,3,4,6-tetra-*O*-benyzl-α-D-glucopyranosyl bromide was used as the glucosyl donor for this α-glucosylation reaction. As the OBn group at the C-2 position of the sugar does not participate as a neighboring group, the more thermodynamically stable α-product is formed, due to the anomeric effect.[23] Performing the reaction under our previously optimized conditions (AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2) at lower reaction temperature (–78°C), gave the product in good yield but with an α/β ratio of only 5.4/1. Changing the reaction solvent to Et_2O, pleasingly delivered the desired glucosidic product **17** in good yield with improved selectivity (α/β=9.2/1).[24] With this pseudodisaccharide in hand, we embarked on the sequential removal of the hydroxyl protecting groups. The TBS substituent on the aglycone was efficiently removed under standard conditions (TBAF) to yield the hydroxy **18**. However, the acetyl followed by the benzyl groups deprotection was proved considerably more challenging. Conventional methods using Birch conditions[25] (Na/NH_3 at –78°C) did not result in any product. The milder conditions of lithium di-*tert*-butylbiphenyl (LiDBB)[26] at –78°C provided A-79197-2 (**4**) but in a rather low 24% yield over 2 steps. A more successful debenzylation was achieved using lithium naphthalenide (LiNp),[27] which prevented the cleavage of the allylic alcohol and gave the product **4** in reasonable yield (53% over 2 steps). The resulting residue was purified by RP-HPLC to give A-79197-2 (**4**). Other debenzylation methods such as BCl_3 delivered the product in low yield accompanied by an inseparable impurity.[28] The configuration of the anomeric center of the glucopyranosyl moiety was confirmed as α by the analysis of its typical proton chemical shift and coupling constant.



Scheme **4**. Synthesis of A-79197-2 (**4**). a) DTBMP, AgOTf, –78°C to rt; b) TBAF, THF, 90%; c) NaOMe, MeOH.

In addition to the natural enantiomeric series, we are also interested in the biological properties of (–)-streptol (**6**), (–)-streptol glucoside (**5**) and the diastereoisomer of A-79197-2 **7**. The biological properties of these compounds would help to establish a structure-activity relationship (SAR) study. The enantioselective synthesis of (–)-streptol (**6**) was achieved using the previously obtained intermediate **10**, which was acetylated and converted to the protected (–)-streptol **19** following the route displayed in scheme **2**. Using our developed synthetic route, **19** was used for the synthesis of (–)-streptol (**6**), (–)-streptol glucoside (**5**) and the diastereoisomer **7** of A-79197-2.



Scheme **5**. (–)-Streptol (**6**), the diastereoisomer of A-79197-2 **7** and (–)-streptol glucoside (**5**) synthesized following the developed procedures.

The growth inhibitory activity of the synthesized natural products and their analogs containing the enantiomeric form of streptol, was evaluated on lettuce seedlings by measuring the length of their roots after 5 days of incubation (Figure **2**). Interestingly the most active compound was (+)-streptol (**3**) with an IC_{50} value of 17 μM followed by (+)-streptol glucoside (**2**) and A-79197-2 (**4**), with IC_{50} values of 28 μM and more than 100 μM, respectively (see supporting information). Additionally, the enantiomer of the natural product **3**, *i.e.* (–)-streptol (**6**), and the glucosylated form, (–)-streptol glucoside (**5**) and the diastereoisomer of A-79197-2 **7**, were found to be inactive. Comparison of the biological activity based on the IC_{50} values alone seems challenging, due to a rather small difference between **2** and **3**. However, analysis of the phenotype shown in Figure **2** provides visual and compelling evidence (1) that the presence of the aglycon (+)-streptol (**3**) is important for the growth inhibitory activity and (2) that glucosyl residue, attached in α or β position of the anomeric center, decreases the potency of the compound. It is worth highlighting that the hypocotyl growth is affected by **3** as a consequence of root-growth inhibition, but no developmental defects were observed.

To investigate if not only (+)-streptol glucoside (**2**) but also (+)-streptol (**3**) was present in *P. kirkii* leaves extract, an HPLC/MS method to quantify the concentration of both compounds was developed. In agreement with a previous report,[29] 1.29% of (+)-streptol glucoside (**2**) was detected in the extract while, surprisingly, only 0.14% of (+)-streptol (**3**) were observed. These results further corroborate the hypothesis that (+)-streptol (**3**) is the active compound and glycosidation could protect the plant *P. kirkii* against the growth inhibitor effect of **3**.

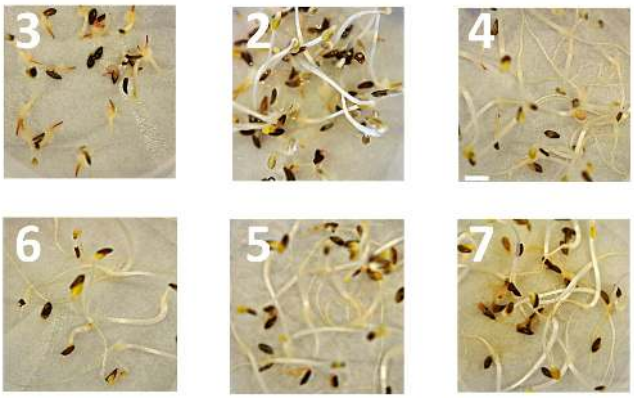


Figure **2**. Phenotype of lettuce seedlings after 5 days of compound treatment at 25 µM concentration. Root growth and development are altered in decreasing activity: (+)-streptol (**3**) > (+)-streptol glucoside (**2**) > A-79197-2 (**4**) and **5**, **6** and **7** showed no activity. Scale = 5 mm.

In conclusion, we developed a convergent synthetic route producing three natural products and their enantiomer or diastereoisomer form. The plant growth inhibitory activity of these compounds has been evaluated and (+)-streptol was found to possess the most potent activity, (+)-streptol glucoside and A-79197-2, which are produced by different plant-associated bacteria, were found to be less active than (+)-streptol. We suggest that the glucosylation of (+)-streptol is required to reduce the toxicity of the compound for the host plant and we are currently investigating this hypothesis.

Experimental Section

The experimental procedures and the characterization of the compounds are found in the supporting information.

Acknowledgements

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Keywords: streptol glucoside • A-79197-2 • streptol • *Psychotria kirkii* • *glucosylation*

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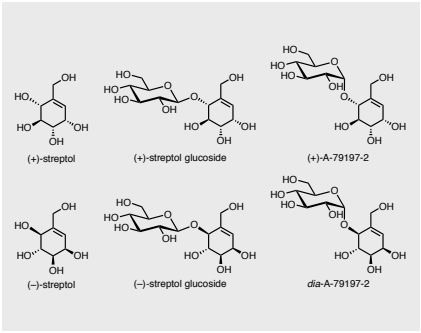
Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Protective glucosylation:

A convergent synthetic route was developed to obtain the novel growth plant inhibitor, streptol glucoside, recently isolated from *P. kirkii* plant leaves extract. The biological activity investigation of the natural product and its derivatives suggests that the glucose of streptol glucoside protects the plant against the potent growth inhibitor streptol.



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