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FULL PAPER

Bioinspired Divergent Oxidative Cyclization from Strictosidine and Vincoside Derivatives: Second Generation Total Synthesis of (–)-Cymoside and Access to an Original Hexacyclic-Fused Furo[3,2-*b*]indoline

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Dedication ((optional))

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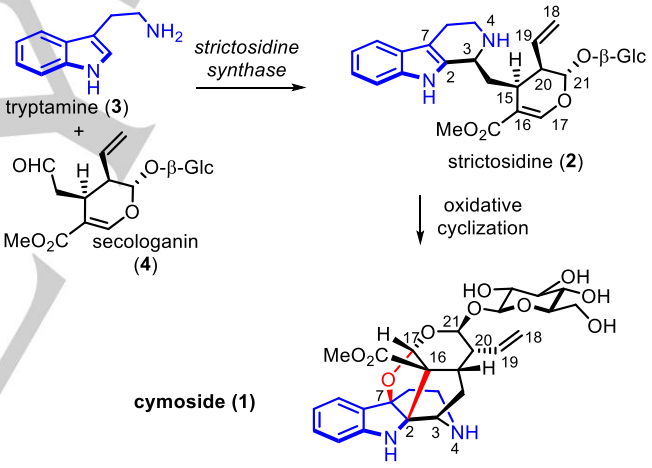
Abstract: We report our second generation synthesis of (–)-cymoside as well as the formation of a new hexacyclic-fused furo[3,2-*b*]indoline framework. After a Pictet-Spengler condensation between secologanin tetraacetate and tryptamine, the course of the cyclization of the 7-hydroxyindolenine intermediate generated by oxidation with an oxaziridine, depends on the stereochemistry of the 3-position. The 3-*(S)*-strictosidine stereochemistry delivered efficiently the scaffold of cymoside via intramolecular coupling with the C16-C17 enol ether, while the 3-*(R)*-vincoside stereochemistry directed towards the reaction with the C18-C19 terminal alkene and the formation of the unexpected caged compound.



Scheme 1. Biosynthesis of cymoside.

Introduction

Cymoside (–)-**1** is one of the 3000 known monoterpene indole alkaloids[1] and it possess a highly unusual and intricate structure with a fused-hexacyclic skeleton encompassing a furo[3,2-*b*]indoline moiety.

This natural product was isolated from the tropical tree *Chimarrhis cymosa* (Rubiaceae) found in Martinique in the French Antilles and its structure was elucidated by Kritsanida, Grougnet and co-workers.[2] Cymoside biosynthetically arises from a rare direct oxidative cyclization of strictosidine (**2**), the common biosynthetic precursor of all monoterpene indole alkaloids, which itself has for origin an enzymatic Pictet-Spengler reaction between tryptamine (**3**) and secologanin (**4**) (Scheme 1).

In line with our interest in furoindoline moieties[3] and in the total synthesis of monoterpene indole alkaloids,[3a,4] we recently performed the total synthesis of cymoside (–)-**1**[5] by mimicking the biosynthetic intramolecular oxidative coupling[6] between the indole nucleus and the enol ether part of the terpenic dihydropyrane to complete the furo[3,*2*-*b*]indoline core (Scheme 2).[7-9]

The N-*p*-nitrophenylsulfonyl ethylether aglycone of racemic strictosidine (±)-**6** was subjected to oxidation with oxaziridine **7** to presumably form 7-hydroxyindoline **A** with assistance of the N-sulfonyl group to control the diastereoselectivity.[10] Subsequent (3+2) annulation proceeds via successive addition of the enol ether to the imine and interception of the incipient oxocarbenium **B** by the hydroxy group.

However, this first generation total synthesis suffers from some downsides. We synthesized secologanin aglycon derivative (±)-**5** in a racemic manner by reproducing the work of Tietze via a Knoevenagel condensation and hetero Diels-Alder cycloaddition sequence.[11] This aldehyde was engaged in a Pictet-Spengler reaction with tryptamine to deliver strictosidine aglycon derivative (±)-**6a** with a modest diastereoselectivity. The fact that the key bioinspired cyclization was performed on the racemic aglycon derivative (±)-**6a** is the major drawback since only half of this material could lead to the enantiopure natural product. After a low

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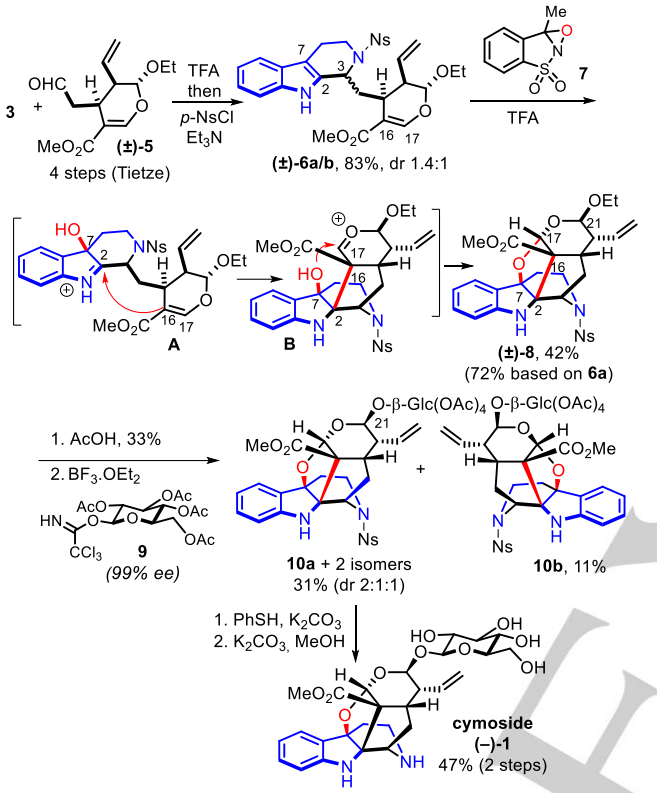
yielding hydrolysis of the acetal part of (±)-**8**, the glycosylation with the enantiopure (D)-glucose derivative **9** was effected on the racemic cymoside aglycon (±)-**8** leading to a mixture of two major β-glucosylated diasteroisomers: cymoside precursor **10a** and the coupling product **10b** from the enantiomeric skeleton of cymoside. Two minor diastereoisomers, resulting from an inefficient stereocontrol at the anomeric positions, were also obtained. Overall, cymoside (–)-**1** was obtained in a 1.7% yield from the racemic ethyl ether secologanin aglycone (±)-**5**.

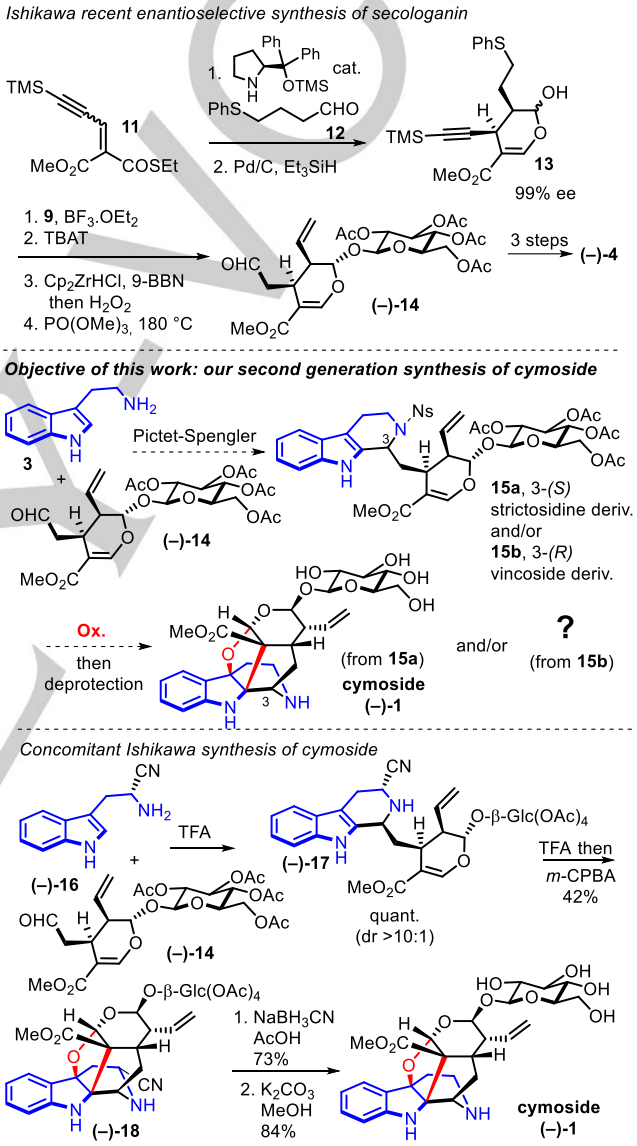


Scheme 3. Our first generation synthesis of cymoside (–)-**1** via a racemic synthesis of the cymoside backbone (–)-**8**.

In order to improve the efficiency of the synthesis of cymoside (–)-**1**, it is, indeed, desirable to effect the bioinspired oxidative cyclization on an enantiopure strictosidine derivative and if possible already containing the β-(D)-glucose moiety. When we started to study the synthesis of cymoside, no enantioselective syntheses of secologanin (**4**) or strictosidine (**2**) were known, despite their pivotal role in the biosynthesis of monoterpene indole alkaloids.

However, at the end of our endeavour, the research group of Ishikawa filled this important gap and reported the first enantioselective synthesis of secologanin (–)-**4** (Scheme 3).[12] The authors cleverly took advantage of an organocatalyzed trans-selective Michael addition developed by Hong of aldehyde **12** onto 1-thioester acrylate **11**.[13] Reduction of the thioester, glycosylation of **13**, hydroboration and sulfoxide elimination delivered secologanin tetraacetate (–)-**14** and then secologanin (–)-**4**.

Therefore, after the completion of our first generation synthesis of cymoside (–)-**1**, it appeared evident to us that using enantiopure secologanin tetraacetate (–)-**14**, produced by the Ishikawa enantioselective synthesis, could greatly improve the efficiency of the enantioselective synthesis of cymoside (–)-**1** (Scheme 3). Pictet-Spengler reaction with tryptamine should deliver enantiopure protected stritosidine **15a** which would be submitted to our biosinspired oxidative cyclization and therefore avoid the low yielding hydrolysis of the acetal and glycosylation steps at a late stage of our first generation synthesis. More importantly, half of the cymoside aglycon would not be lost as it is the case in the racemic approach. In addition, obtaining the C3-epimer **15b** would also be an opportunity to study its oxidative cyclization.



Scheme 3. Synthetic approach towards the enantioselective synthesis of the cymoside backbone.

While we were finishing this second generation synthesis of cymoside (–)-**1**, Ishikawa published the realization of a similar approach for the total synthesis of cymoside (–)-**1** (Scheme 3).[14] He employed (R)-α-cyano tryptamine (–)-**16** for the Pictet-Spengler reaction with (–)-**14**, in order to ensure a high diastereoselectivity and the oxidative cyclization was performed on protonated strictosidine (–)-**17** with m-CPBA after prior

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protonation of the N4 amine. Reduction of the aminonitrile of (–)-**18** and deacetylation delivered cymoside (–)-**1**. The very recent publication of Ishikawa urged us to report our own approach herein.

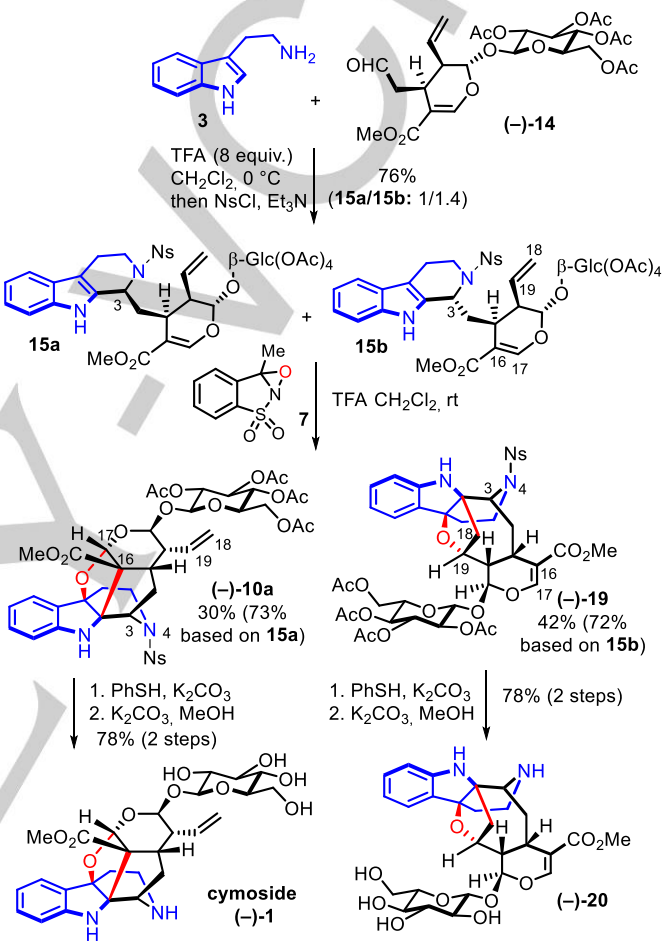
Results and Discussion

We started our study by the synthesis of secologanin tetraacetate (–)-**14** with slight modifications of the Ishikawa procedures (see SI). We then studied the Pictet-Spengler cyclization between tryptamine and secologanin tetraacetate (–)-**14** (Scheme 4).[15] The presence of the glucose moiety on (–)-**14** had an impact on the efficiency of the reaction in comparison with aglycon (±)-**5** since a low conversion was observed with 1.5 equivalent of TFA as in our previous conditions. The tetraacetateglycosyl of (–)-**14** offers several chemical functions which could be protonated and thus compete with activation of the imine to induce the Pictet-Spengler reaction. The reactivity was restored by increasing the amount of TFA to 8 equivalents with an excess of **3** and after one-pot nosylation of the N4-secondary amine, a 76% yield was obtained of a mixture of protected strictosidine **15a** and protected vincoside **15b**, its C3-epimer in a 1:1.4 ratio in favour of the latter. It is known that a diastereoselective Pictet-Spengler reaction could be performed in presence of the enzyme strictosidine synthase to obtain selectively the stereochemistry of strictosidine.[16] However this chemoenzymatic approach is not yet easily available to most organic chemistry labs.

Therefore, we envisioned to induce a diastereoselective Pictet-Spengler reaction with non-racemic chiral catalysts that are known to promote enantioselective Pictet-Spengler reactions.[17,18] Unfortunately, neither a cinchona-derived thiourea[17b,c,18] nor a squaramide,[17d,e,18] nor a binol-derived phosphoric acid[17f,18] were able to promote the conversion of the reaction. It is probably due to the presence of competitive protonatable functional groups. Mimicking strictosidine synthase with a simple organocatalyst able to induce a highly diastereoselective Pictet-Spengler reaction between tryptamine and secologanin remains a challenge. Ishikawa devised an elegant and efficient alternative by using α-cyanotryptamine (–)-**16** instead of tryptamine (see Scheme 3). Nevertheless, the latter is synthesized in three steps from tryptophan and the cyano group needs to be removed afterwards.

While the diastereoselectivity is not what we expected, this procedure from tryptamine is very straightforward and represents a fast access to protected strictosidine **15a** to pursue the total synthesis of cymoside (–)-**1**. In addition, the access to protected vincoside **15b** offered us an opportunity to study its oxidative cyclization.

The 1:1.4 diastereomeric mixture of **15a/b** was then subjected to the oxidative cyclization that we developed with oxaziridine **7** (Scheme 4).[5] We were delighted to observe that the presence of the glycosyl moiety at this stage did not affect the efficiency of the key bioinspired oxidative cyclization and the furo[3,2-*b*]indoline-containing hexacyclic fused-skeleton **10a** of cymoside was obtained in 30% yield from the mixture of diastereoisomers which represent a 73% yield from protected strictosidine **15a**. In fact, compound **10a** was an intermediate of our first generation total synthesis of cymoside (–)-**1**, that we intercepted in a much more efficient manner in this second generation approach. We were also thrilled to observe the transformation of protected vincoside **15b** into unexpected hexacyclic-fused compound (–)-**19** in 42% yield which represent a 72% yield from **15b**. 2D NMR analysis of this compound (Figure 1, see SI for details), notably showed HMBC correlations between the C18 and C19 atoms of the former terminal double bond with the C2 and C7 atom of the indoline ring. We were therefore able to assign the intricate furo[3,2-*b*]indoline-containing structure to (–)-**19**, which is the product of an oxidative cyclization between the indole moiety and the C18-C19 terminal alkene of **15b**.



Scheme 4. Divergent oxidative cyclization of **15a** and **15b**: total synthesis of cymoside (–)-**1** and synthesis of (–)-**20**.

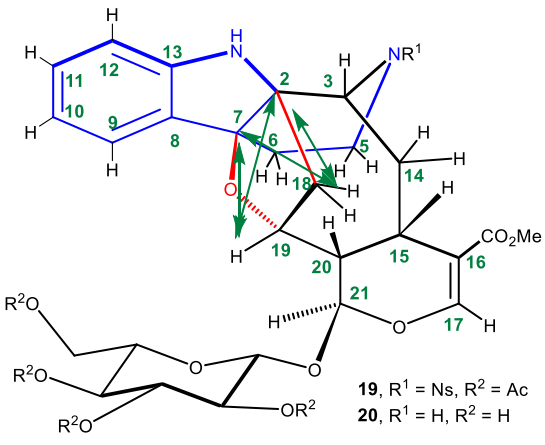


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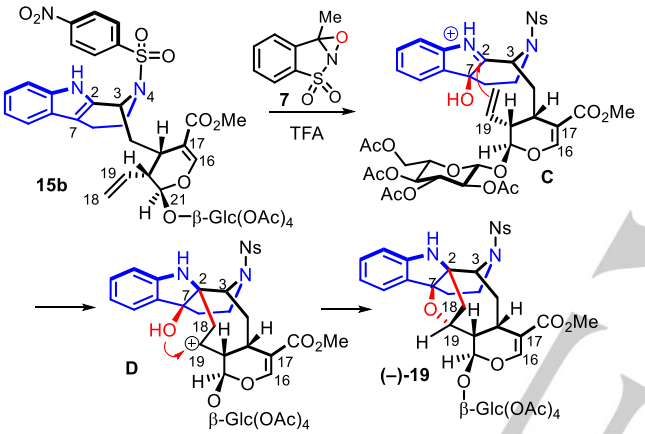
Figure 1. Key HMBC correlation of **19** and **20**.

In analogy with the formation of the cymoside skeleton (see Scheme 2), we can postulate that the indole moiety is oxidized into 7-hydroxyindolenine **C** (Scheme 5). We assume that to minimize steric interactions, the nosyl group blocks the face opposite to the one bearing the monoterpene part at C3. As a result, the oxidation is directed into the latter face which can allow the oxidative cyclization to happen. In contrast to the formation of the cymoside scaffold **10a** from protected strictosidine **15a**, the inversion of the configuration at C3 in vincoside derivative **15b** precludes the addition of the enol part to the C2-position. Alternatively, the terminal position of the C18-C19 alkene is poised to add onto the C2-iminium of **C** leading to the formation of the seven-membered ring of tertiary carbocation **D**. The latter would then be intercepted by the hydroxyl group at C7 to complete the synthesis of the five-membered ring of the furo[3,2-*b*]indoline moiety of (–)-**19**.



Scheme 5. Mechanistic hypothesis for the synthesis of (–)-**19**.

All what remained, was to achieve the two deprotection steps (Scheme 4). Attempts to effect this double deprotection in the same pot did not succeeded, therefore it was performed uneventfully in two steps. The nosyl group was removed from the secondary amine with thiophenol in presence of potassium carbonate and in a second operation the four acetyl groups were removed from the glucose moiety with potassium carbonate in methanol to finally deliver cymoside (–)-**1** in 78% yield. All spectra data of this synthetic cymoside (–)-**1** were in strong agreement with the ones of the natural substance as well as the synthetic products of our first generation synthesis as well as the Ishikawa synthesis. Slight differences of the ^{1}H and ^{13}C signals at positions in proximity of the N4 secondary amine were observed (see SI). It might be explained by the fact that traces of acid could influence the NMR chemical shifts of protons or carbons closed to the nitrogen lone pair. The optical rotation of the product obtained in this second generation synthesis ($[\alpha]^{D}$ -29.5 c 0.475 in MeOH) is also similar to the ones of our first generation ($[\alpha]^{D}$ -26.3, c 0.015 in MeOH)[5] and the Ishikawa ($[\alpha]^{D}$ -28.9, c 0.3 in MeOH)[14] syntheses. These three values significantly differ from the optical rotation reported in the isolation paper ($[\alpha]^{D}$ +190, c 0.011 in MeOH)[2] which we believe is not accurate.

The same deprotective sequence of two steps was also applied to (–)-**19** to deliver (–)-**20**. Worthy of note, we did not observe any lactamisation between the methyl ester at C16 and the N4-secondary amine after the removal of the nosyl group in basic conditions.

While the unique structure of (–)-**20** is not presently known among natural products, it is not unconceivable that it could be produced by Nature via an oxidative cyclization related to the one that we have uncovered (Scheme 5). Indeed, unlike (–)-**20**, most of the monoterpene indole alkaloids possess a *(S)*-configuration at the C3 position arising from strictosidine. However, there are few examples of monoterpene indole alkaloids that display a *(R)*-configuration at this position such as vincosamide or reserpine.

Conclusion

We significantly improved the synthesis of cymoside (–)-**1** that we published earlier this year by starting from enantiopure secologanin tetraacetate instead of its racemic aglycon. After the Pictet-Spengler reaction, the key bioinspired oxidative cyclization of strictosidine derivative **15a** between the indole and the C16-C17 enol ether proceeded well in presence of the glucose moiety. Cymoside (–)-**1** was synthesized in 4 steps and 18% yields from secologanin tetraacetate **14** obtained according to the synthesis of Ishikawa, while our first generation synthesis required 6 steps and 1.7 % yields from racemic secologanin aglycon (±)-**5**. In a divergent manner, the oxidation of the vincoside derivative **15b**, the 3-epimer of **15a**, yielded a new fused hexacyclic furo[3,2-*b*]indoline structure **20** via reaction with the terminal C18-C19 alkene instead of the C16-C17 enol ether. It was obtained in 4 steps and 25% yields from secologanin tetraacetate **14**. While unexpected, we think that this new skeleton is the more interesting part of our report since it expands the molecular diversity and complexity accessible from the strictosidine/vincoside skeleton. The mechanism of its formation might also be relevant from a biosynthetic point of view.

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Keywords: Total synthesis • Monoterperne indole alkaloids • Cymoside • Oxidative cyclisation • Furoindoline

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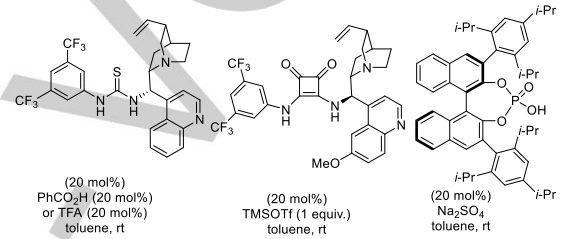

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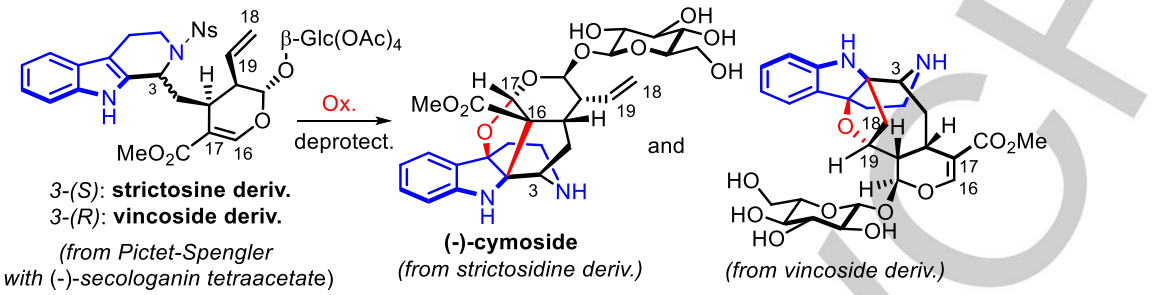

3-(S): **strictosine deriv.**
3-(R): **vincoside deriv.**
(from Pictet-Spengler with (-)-secologanin tetraacetate)

(-)-cymoside
(from strictosidine deriv.)

(from vincoside deriv.)

The oxidative cyclization of an enantiopure strictosidine derivative lead to the total synthesis of (–)-cymoside, while the corresponding 3-epimeric vincoside derivative deliver a new hexacyclic-fused furo[3,2-b]indoline framework.

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