Total Synthesis

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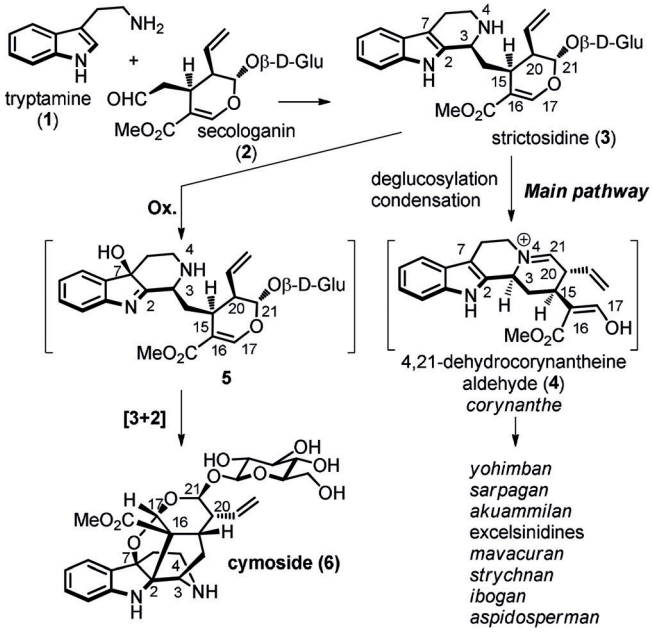
Enantioselective Total Synthesis of Cymoside through a Bioinspired Oxidative Cyclization of a Strictosidine Derivative

*Yingchao Dou, Cyrille Kouklovsky, Vincent Gandon, and Guillaume Vincent**

Abstract: *The first total synthesis of the caged monoterpene indole alkaloid cymoside is reported. This natural product displays a unique hexacyclic-fused skeleton whose biosynthesis implies an early oxidative cyclization of strictosidine. Our approach to the furo[3,2-b]indoline framework relied on an unprecedented biomimetic sequence which started by the diastereoselective oxidation of the indole ring into a hydroxyindolenine which triggered the addition of an enol ether and was followed by the trapping of an oxocarbenium intermediate.*

The very large family of monoterpene indole alkaloids, which encompasses more than 3000 compounds, is biosynthetically derived from an enzyme-catalyzed Pictet–Spengler reaction between secologanin (**2**), a glycosylated monoterpene, and tryptamine (**1**) to deliver strictosidine (**3**).[1] From this point, divergent biosynthetic pathways lead to several sub-families with skeletons of high structural diversity (Scheme 1). The main biosynthetic routes imply a cyclization event between the quinolizidine nitrogen N4 and an aldehyde arising from the deglucosylation of the secologanin subunit. For instance, strictosidine (**3**) is transformed into 4,21-dehydrocorynantheine aldehyde (**4**) and the *corynanthe* skeleton through the condensation of the released aldehyde at C21 with N4. Then, oxidative cyclization and/or skeletal rearrangement could occur to produce the *yohimban*, *sarpagan*, *akuammilan*, excelsidines, *mavacuran*, *strychnan, ibogan* or a*spidosperman* alkaloids among others. For instance, we have recently described the bioinspired divergent oxidative cyclization of the geissoschizine *(corynanthe)* skeleton into the excelsinidine or *mavacuran* frameworks.[2]

In contrast to this general pathway, an oxidative cyclization of strictosidine could also take place as observed from the frameworks of few monoterpene indole alkaloids.[3,4] Among them, cymoside (**6**) caught our attention owing to its unique structure, although no biological activity has been reported.[4] This natural product was isolated by Kritsanida, Grougnet, and co-workers from crushed leaves collected from the tree *Chimarrhis cymosa* (Rubiaceae) in the French Caribbean island Martinique. Cymoside (**6**) displays an unprecedented caged hexacyclic fused-skeleton which still possesses the glucose moiety and encompasses a rare furo[3,2-*b*]indoline motif. In natural products, the latter is only related to the benzofuro[3,2-*b*]indoline of phalarine[5] or the furo[3,2-*b*]indolone of lapidilectin B, grandilodine C and their congeners.[6,7] Biosynthetically, this high degree of complexity was proposed to arise from the intramolecular oxidative coupling between the enol ether of the monoterpene subunit and the indole by oxidation of the latter into hydroxyindolenine intermediate **5**.[4]



Scheme 1. Biosynthesis of monoterpene indole alkaloids and of cymoside.

Cymoside (**6**) appeared to us as a challenging target in relation with our interest in dearomatization of indoles.[8–12] Notably, we have recently developed bioinspired oxidative strategies to access the iso-chromeno[3,4-*b*]indoline and benzofuro[2,3-*b*]indoline moieties of bipleiophylline.[9] Closer to our target, we reported the synthesis of the benzofuro[3,2-*b*]indoline framework of phalarine through an oxidative coupling between *N*-Ac indoles and phenols[10] or an interrupted Fischer indolization.[11] We accessed, as well, the furano[3,2-*b*]indoline skeleton encountered in cymoside through a [3+2] annulation between *N*-Ac indoles and oxyallyl cations.[12]

In this context, we decided to adopt a bioinspired approach toward cymoside (Scheme 2). We planned to obtain the furo[3,2-*b*]indoline-containing hexacyclic fused-

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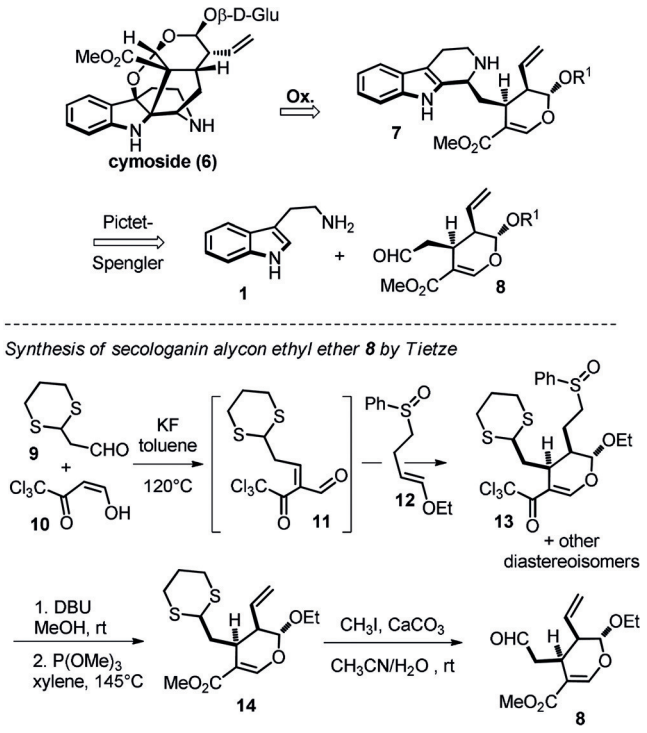
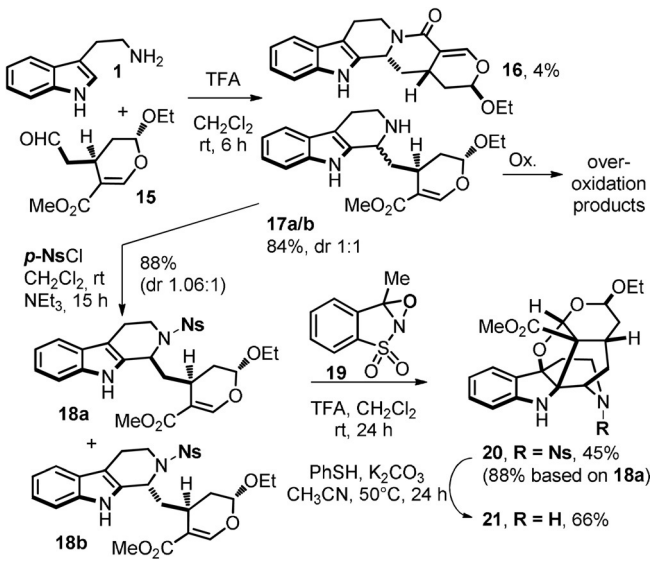


Scheme 2. Bioinspired retrosynthesis of cymoside.



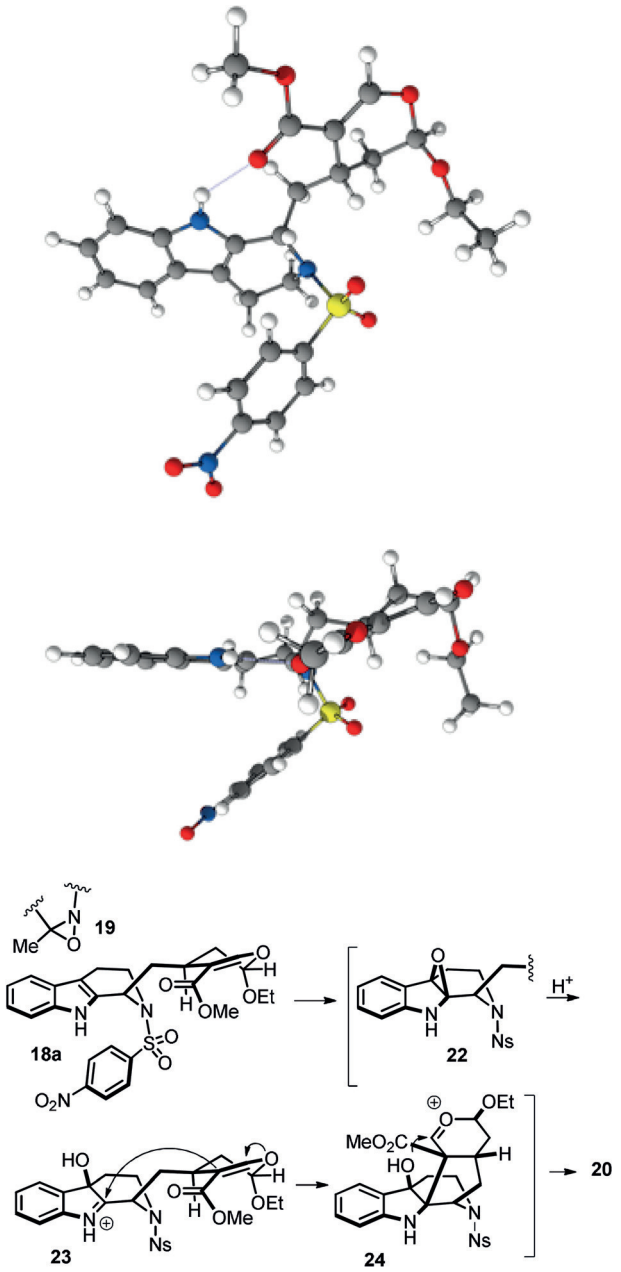
Scheme 3. Development of the key oxidative cyclization on a model substrate.

skeleton by an oxidative cyclization of a strictosidine derivative **7**.[13,14] Indeed, the latter would arise from the Pictet–Spengler reaction[15] of a secologanin derivative **8** which would be obtained as described by Tietze three decades ago.[16–18] It involved a domino sequence of a Knoevenagel condensation between monoprotected malondialdehyde **9** and 3-formyl-1,1,1-trichloroacetone **10** followed by an inverse-demand hetero Diels–Alder cycloaddition between generated enal **11** and enol ether **12**.[16a] Methanolysis, sulfoxide elimination, and release of the aldehyde from the dithiane furnished secologanin aglycon **8**.

In order to assess, the viability of the oxidative cyclization approach, we started to synthesize a simplified analog **17a** of secologanin lacking the vinyl substituent (Scheme 3). The Pictet–Spengler reaction between tryptamine **1** and secologanin analog **15** lacking the vinyl moiety[16b,c] delivered **17a,b** as a 1:1 ratio of epimers and **16** which arose from the lactonization of the undesired epimer. The observed diastereoselectivity is in accord with all observations in the literature since only the use of the enzyme *strictosidine synthase* can stereoselectively produce strictosidine derivatives.[15] With **17** in hand, the stage was set to evaluate the key oxidative cyclization. Unfortunately, the desired framework of cymoside could not be obtained despite intensive efforts. With most of the oxidants tried,[14] unidentified over-oxidation products were observed. The free secondary amine N4 appeared to be rather fragile to oxidative conditions. Therefore, we decided to protect it with a *para*-nosyl group to yield **18a** and its epimer **18b** as a 1.06:1 mixture. Subsequently, we were pleased to identify oxaziridine **19**[14b] in acidic conditions as a suitable oxidant to promote the desired oxidative cyclization of **18a** and deliver the intricate fused-hexacyclic skeleton **20** of cymoside in 45 % from the epimeric mixture of **18a**/**18b** which represents an 88 % yield from the adequate epimer **18a**.[19] It is presumed that oxaziridine **19** induced the epoxidation of the C2 = C7 double bond of the indole of **18a** which is followed by a cascade of cyclizations. The removal of the nosyl group is a trivial operation which delivered free secondary amine **21**.

The arylsulfonyl protecting group of the quinolizidine nitrogen N4 is crucial to allow this complex transformation to happen. Indeed, the nosyl group masks the reactivity of N4 towards oxidants. Moreover, we postulate that it would also shield one of the faces to control the diastereoselectivity of the epoxidation. DFT-computations were carried out to determine the best possible conformation of **18a** (Scheme 4). This analysis shows that to minimize steric interactions between the nosyl group and the dihydropyran substituent at C3 of **18a**, the phenyl ring of the nosyl group is forced to lie under the indole ring without π-staking interactions. The structure is rigidified by an intramolecular hydrogen bond between the carbonyl of the methyl ester and the hydrogen borne by the indolic nitrogen. Consequently, the face encumbered by the nosyl group appears to be blocked and the epoxidation would occur on the less hindered face (Scheme 4). Therefore, after opening of epoxide **22** by the lone pair of the indolic nitrogen, the dihydropyran at C3 and the hydroxyl group at C7 of hydroxyindolenine **23** are *cis* to each other which is required to continue the domino cyclization. Accordingly with the biosynthetic hypothesis of Kritsanida and Grougnet, the enol ether could then add to the imine part of **23** and generate oxocarbenium **24** which could be trapped by the hydroxyl group at C7, thus completing the furo[3,2-*b*]indoline moiety of **20**.

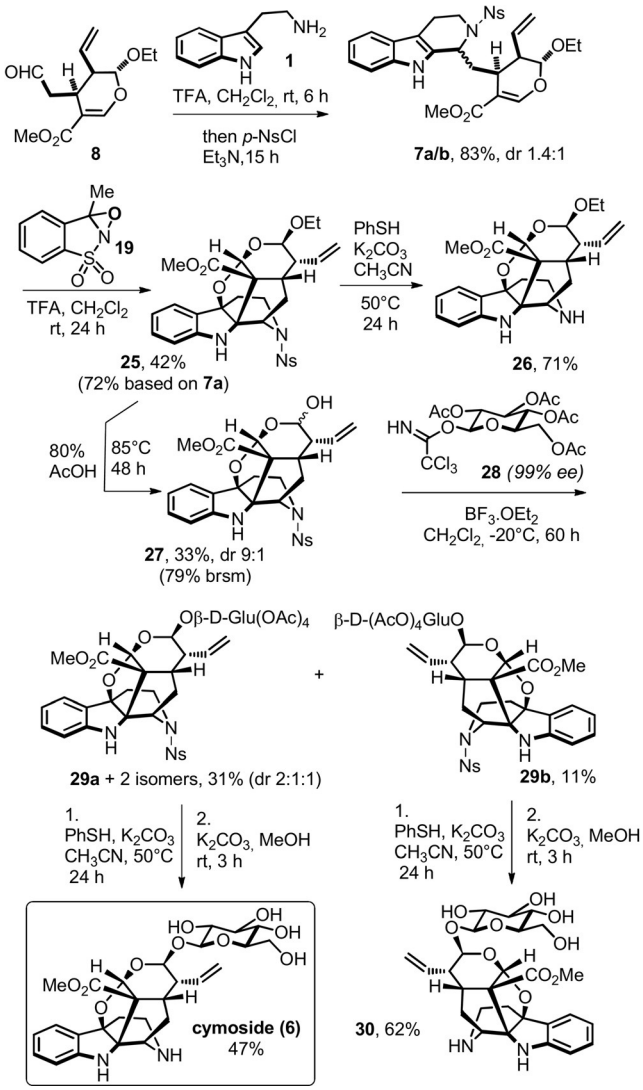
Having established the proof of concept of the key oxidative intramolecular coupling, we directed our efforts towards the total synthesis of cymoside (**6**) itself. Uneventfully, the Pictet–Spengler reaction of the Tietze secologanin aglycon **8** and tryptamine (**1**) followed by protection of the



Scheme 4. Bottom and side views of DFT-minimized conformation of **18a** in CH_2Cl_2 (Gaussian09 software package, M06 functional and 6-31G(d,p) basis set for all atoms) and mechanistic hypothesis for the conversion of **18a** into **20**.

secondary amine with a *para*-nosyl group yielded protected strictosidine aglycon ethyl ether **7a** in a 1.4:1 mixture with its epimer **7b**.

Gratefully, the key biomimetic domino sequence of oxidation with oxaziridine **19** and cyclization of strictosidine derivative **7a** successfully proceeds in the presence of the vinyl substituent (Scheme 5). The complete framework **25** of cymoside was thus obtained in 42% from the epimeric mixture of **7a**/**7b** which represents a 72% yield from **7a**.[19] Indeed, the ethyl ether aglycon **26** of cymoside was obtained in 71% yield after removal of the nosyl group with thiophenol in basic conditions.



Scheme 5. Total synthesis of cymoside.

In order to achieve the total synthesis of **6**, the main event remaining was the introduction of the β-D-glucose moiety. This operation would also allow us to separate the two enantiomers of the racemic mixture of **25** since we would use a highly enantioenriched glycosyl reagent. Hydrolysis of the acetal of **25** produced hemiacetal **27** in a 9:1 mixture of epimers. The Schmidt glycosylation of **27** with glycosyl trichloroacetimidate **28**[20] in presence of trifluoroborane yielded the expected protected glycosylated compound **29a** in mixture with two minor isomers[21] (ratio 2:1:1) as well as the glycosylated product **29b** of the enantiomer of the cymoside scaffold. Finally, we achieved the first total synthesis of cymoside (**6**) after the successive removal of the nosyl group from the quinolizidine nitrogen and hydrolysis of the four acetates of the glycosyl moiety in 47% over two steps from the mixture of **29a** and its isomers.[22,23] It is noteworthy that we were also able to effect this double deprotection on **29b** to obtain **30** which is a diastereoisomer of cymoside.

In conclusion, we performed the first total synthesis of the caged natural product cymoside (**6**). Unlike many other

monoterpene alkaloids, the biosynthesis of hexacyclic-fused cymoside (**6**) involves a unique oxidative cyclization cascade from strictosidine. Inspired by this biosynthetic consideration, we achieved this unprecedented transformation from an adequately protected strictosidine aglycone in the presence of an oxaziridine. Key to the success of this biomimetic reaction is the use of a nosyl protecting group of the N4 secondary amine, which masks the reactivity of the latter and directs the facial selectivity of the oxidation of the indole nucleus into a hydroxyindolenine. Addition of the enol ether of the terpenic moiety to this imine was followed by the trapping of the generated oxocarbenium by the hydroxyl to deliver the furo[3,2-*b*]indoline framework of the natural product. The total synthesis of cymoside (**6**) was finally achieved by a late stage introduction of the β-D-glucose.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cymoside · furoindoline · monoterpene indole alkaloids · oxidative cyclization · total synthesis

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[21] We believe that one of them is epimeric to **30a** or **30b** at the anomeric position (α-D-glucose instead of β-D-glucose), while the second one might be an epimer of **30a** or **30b** at the C21 position.

[22] Despite the significant difference in the optical rotation ($[\alpha]^{D+}190$, $c = 0.011$ in MeOH for the natural product and $[\alpha]^{-D}6$, $c = 0.015$ in MeOH for our synthetic product), all the 1D and 2D NMR data as well as the HRMS data of our synthetic product are in accord with the data reported for natural cymoside. Unfortunately, natural cymoside is not available at the present time.

[23] In the isolation paper (ref [4]), it was hypothesized that cymoside was isolated as an ammonium salt by protonation of the N4 secondary amine. Our synthetic cymoside was not obtained as an ammonium salt, since it was isolated after a basic aqueous work-up. Since all the 1D and 2D NMR data of the natural and synthetic cymoside are concordant, we believe that the natural cymoside was isolated as a free base and not as an ammonium salt.

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