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Total Synthesis of (−)-Strictosidine and Interception of Aryne Natural Product Derivatives "Strictosidyne" and "Strictosamidyne"

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Supporting Information

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Detailed experimental procedures and compound characterization data (PDF)

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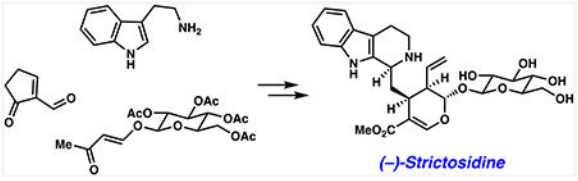
Abstract

Monoterpene indole alkaloids are a large class of natural products derived from a single biosynthetic precursor, strictosidine. We describe a synthetic approach to strictosidine that relies on a key facially selective Diels–Alder reaction between a glucosyl-modified alkene and an enal to set the C15–C20–C21 stereotriad. DFT calculations were used to examine the origin of stereoselectivity in this key step, wherein two of 16 possible isomers are predominantly formed. These calculations suggest the presence of a glucosyl unit, also inherent in the strictosidine structure, guides diastereoselectivity, with the reactive conformation of the vinyl glycoside dienophile being controlled by an exo-anomeric effect. (−)-Strictosidine was subsequently accessed using late-stage synthetic manipulations and an enzymatic Pictet–Spengler reaction. Several new natural product analogs were also accessed, including precursors to two unusual aryne natural product derivatives termed “strictosidyne” and “strictosamidyne”. These studies provide a strategy for accessing glycosylic natural products and a new platform to access monoterpene indole alkaloids and their derivatives.

Graphical Abstract



INTRODUCTION

Monoterpene indole alkaloids (MIAs) are a large class of natural products, many of which possess valuable pharmacological properties. To date, more than 3000 MIAs have been identified with diverse structures and bioactivities, which are exemplified by three of the most well-known members: quinine (**1**), strychnine (**2**), and vinblastine (**3**) (Figure 1).[1–3] Quinine (**1**) belongs to the family of *Cinchona* alkaloids and is an antimalarial drug;[4–6] strychnine (**2**), one of the most complex *Strychnos* alkaloids, is a potent toxin;[7–9] and vinblastine (**3**), a *Vinca* alkaloid, is a frontline anticancer therapeutic and one of the most expensive small-molecule, off-patent drugs on the pharmaceutical market.[10–13]

An active area of research is the development of new strategies to access complex MIAs, such as vinblastine (**3**), through a combination of isolation from natural sources, biosynthesis, and total synthesis.[1,14–31] We identified the natural product (−)-strictosidine (**4**) as an attractive entryway to access MIAs and derivatives.[1] (−)-Strictosidine (**4**) is the last common biosynthetic precursor to all MIAs. It was first isolated in 1968 and contains nine stereocenters, a highly congested dihydropyran ring, a glucosyl moiety, and a bis(acetal) linkage.[32] Despite its importance in MIA biosynthesis and being known for over 50 years,

(−)-strictosidine (**4**) has remained challenging to access. Isolation of **4** from natural sources is unreliable, and its complete biosynthesis has proven difficult to engineer.[32] Seminal efforts in this field include O'Connor and co-workers' breakthrough in the biocatalytic production of strictosidine in yeast, albeit with a modest titer,[1,33] and our groups' finding of prevalent shunt pathways in the bioengineering of the early steps in *S. cerevisiae.*[34,35] Furthermore, **4** has been largely overlooked by the synthetic community until very recently. The first total synthesis of strictosidine (**4**) was published during the course of our studies by Ishikawa and co-workers.[36,37]

Our laboratories sought to achieve the synthesis of (−)-strictosidine (**4**) using a blend of synthetic chemistry and biocatalysis and then use our approach as a platform for the preparation of new, unnatural derivatives thereof. Herein, we report: (a) a facially selective Diels–Alder reaction to access the dihydropyran moiety of **4**, including the C15–C20–C21 stereotriad, (b) a computational analysis of this key step, (c) access to (−)-strictosidine (**4**) and an unnatural C15 epimer via enzymatic and nonenzymatic late-stage Pictet–Spengler reactions, and (d) the preparation and interception of "strictosidyne" and "strictosamidyne," which are aryne derivatives of natural products.

RESULTS AND DISCUSSION

Retrosynthetic Analysis.

Our retrosynthetic analysis of (−)-strictosidine (**4**) is shown in Scheme 1. We envisioned (−)-strictosidine (**4**) would be obtained from its biosynthetic precursors (−)-secologanin (**6**) and tryptamine (**5**) via an enzymatic Pictet—Spengler reaction.[33] This known step would build the tetrahydro-β-carboline ring, establish the stereochemistry at the C3 stereocenter, and provide a platform for the synthesis of unnatural strictosidine analogs. It should be emphasized that secologanin derivatives have been popular synthetic targets, yet only one synthesis of this compound exists, as reported by Ishikawa in 2019.[37–45] (−)-Secologanin (**6**) could be obtained from vinylogous ester **7** through a series of manipulations, including introduction of the terminal olefin and oxidative cleavage of the five-membered ring. In a key step, the dihydropyran of vinylogous ester **7** could be accessed by an inverse electron-demand hetero-Diels–Alder reaction between enal **8** and enol ether **9**. Enabled by the presence of the acetylated glucose moiety, this transformation would set three key stereocenters (C15, C20, C21). Whereas enal **8** can be obtained from cyclopentenone using known chemistry,[46] we envisioned enol ether **9** to be accessible from glucose.[47,48]

Substrate Synthesis and Experimental and Computational Studies of Facially Selective Diels–Alder Reaction.

To initiate our synthetic effort, we prepared enol ether **9** using the sequence shown in Scheme 2. Known vinylogous ester **10**[48] underwent silylation/Rubottom oxidation to give an intermediate α-siloxy ketone.[49] Subsequent ketone reduction and acetylation[50,51] provided allylic acetate **11** as a 1:1 diastereomeric mixture in 56% yield over the two steps. Next, substantial effort was put forth to reductively remove the acetoxy group, which proved quite challenging. Reductions of allylic acetates bearing oxygen on the vinylic carbon are precedented on cyclic systems,[52–59] but the corresponding reduction on linear substrates is

rare and gives poor *E/Z* selectivity.[60] Ultimately, we optimized nickel-catalyzed allylic reduction conditions reported by Yin, which afforded enol ether **9**.[60] Of note, the position and *E* geometry of the olefin was maintained.[61,62]

With enol ether **9** in hand, we sought to assess its viability as a dienophile in the key inverse electron-demand hetero-Diels–Alder reaction with known enal **8**[46] (Scheme 3).[63,64] Of note, a successful Diels–Alder cycloaddition would lead to the introduction of three new stereocenters, where we hoped selectivity would be guided by the sugar moiety in **9**. Moreover, in considering the formation of these stereocenters and regioselectivity possibilities, 16 isomers of the Diels–Alder cycloadduct could arise. After examining a variety of reaction conditions (i.e., solvents, Lewis acids, and temperatures),[65] we identified optimal reaction conditions, which involved heating **8** and **9** in hexafluoroisopropanol (HFIP) at 50 °C for 16 h. This gave rise to cycloadducts **7a** (desired) and its C15 epimer, **7b**, as the major productsin a 1:1 ratio (55% combined yield).[66] Sugars have rarely been employed to dictate stereochemistry in intermolecular inverse electron-demand hetero-Diels–Alder reactions, where the sugar resides on the dienophilic component.[67–80] Furthermore, in the present example, the sugar is not used as a chiral auxiliary, but it is a component of both (−)-secologanin (**6**) and (−)-strictosidine (**4**). Thus, our approach involving early introduction of the sugar to guide stereochemical outcomes represents a useful strategy for accessing single enantiomers of glycosylated natural products.

To explore the factors that control selectivity in the Diels–Alder reaction, we undertook density functional calculations (DFT) with the M06–2X functional. This method is known to give reliable energetics of stereoisomeric transition states of Diels–Alder reactions.[81–83] Transition states were calculated for stepwise and concerted pathways, and the latter were found to be more favorable. As such, the *E* geometry in dienophile **9** leads to the *trans* relationship between C20 and C21 in the products **7a** and **7b** (see Scheme 3). Four possible stereoisomeric transition states, corresponding to *endo/exo* pathways and different facial approach, were investigated, with bond formation occurring between C15 and C20 and O17 and C21 of the reactants. These are shown in Figure 2.[84–88] **TS1**(*exo*) and **TS1**(*endo*) were energetically most favorable and correlate to the two major products isolated experimentally, **7a** and **7b**, respectively. **TS2**(*exo*) and **TS2**(*endo*) were found to have higher activation barriers, and the corresponding products were not isolated experimentally.

Two key factors that were investigated are the conformation of the glucosyl moiety and the adjacent reactive double bond (Figure 3a). Although the conformation of the glucosyl unit in dienophile **9** was found to be similar to that in all stereoisomeric transition states (i.e., **TS1** and **TS2**), the orientation of the adjacent reactive olefin is more variable and is believed to dictate the stereochemical outcome of the reaction.

On dienophile **9**, the C21 alkene adopts an exo-anomeric conformation (Figure 3).[89] The dihedral angle between C21–O1 and C1'—O5 is −68°. Here, one lone pair on exocyclic oxygen O1 overlaps with the C1'—O5 σ^* antibonding orbital and stabilizes itself by negative hyperconjugation as shown in the Newman projection in Figure 3a. The glucosyl enol ether is s-*trans* in order to avoid steric repulsion of the glucosyl group that would occur in the s-*cis* conformation that is normally favored for enol ethers.[90,91] Each acetate is *syn*

with the C=O aligned with the axial CH of the ring, similar to the XRD structure of an acetylated glucose.[67]

In each **TS1**, approach of the heterodiene occurs *anti* to the face of pyranyl oxygen O5 (*re* face) (Figure 2). The C21–O1 and C1'–O5 dihedral angles are −63° and −70°, respectively, for **TS1**(*endo*) and **TS1**(*exo*), indicating exo anomeric preferences in the transition states, similar to the orientation present in dienophile **9** (Figure 3b).[92] This stabilizing effect imparted by the glucosyl ring leads to the face *anti* to pyranyl oxygen O5 (*re* face) being more accessible to the diene. In **TS2**(*endo*) and **TS2**(*exo*), involving *si* facial approach, some rotation around the C1'–O1 bond from the stable *exo*-anomeric conformation is required (C21–O1 and C1'–O5 dihedral angles are −143° and −134°, respectively). As a result, **TS2**(*endo*) and **TS2**(*exo*) are 1.3 and 1.8 kcal/mol higher in free energies than the corresponding **TS1**(*endo*) and **TS1**(*exo*) facial approaches. The computationally predicted activation energies for **TS1**(*endo*) and **TS1**(*exo*) correlate to the experimentally observed ratio of products **7a** and **7b**.

This hetero-Diels–Alder reaction is inverse electron-demand, since the LUMO of the heterodiene and the HOMO of the dienophile have a lower energy gap (9.6 eV) than the opposite HOMO–LUMO pair (14.5 eV) as shown in Figure 4a. There is a strong preference for one regioisomer involving the union of the nucleophilic carbon (C20) of the enol ether with the electrophilic carbon (C15) of the α,β-unsaturated aldehyde heterodiene due to a larger HOMO coefficient at C20 than C21. The frontier orbital interactions involving the π orbitals of the enal **8** and enol ether **9** are shown in Figure 4a. *Endo/exo* selectivity is not observed experimentally. The π lone pair of O1 mixes slightly with the alkene HOMO, but the coefficient is small, and the stabilizing secondary orbital interaction in the *endo* transition state is small. By contrast in a normal Diels–Alder reaction, such as that of butadiene plus acrolein, the large coefficient on the carbonyl carbon in the LUMO gives strong secondary orbital stabilization of the *endo* transition state (Figure 4b).

Elaboration to (−)-Secologanin and (−)-Strictosidine.

As shown in Scheme 4, Diels–Alder adduct **7a** was elaborated to (−)-secologanin (**6**). Deprotection of **7a** afforded the corresponding free alcohol, which underwent elimination under standard Grieco-olefination conditions.[95] This sequence gave olefin **12** in 93% yield over two steps. Next, **12** was converted to the corresponding TBS enol ether, which set the stage for a Rubottom oxidation. The corresponding α-hydroxy ketone **13** was obtained in 53% yield as a single diastereomer. This intermediate was subjected to lead tetraacetate in methanol[36,96] to effect oxidative cleavage[97] and introduce the necessary aldehyde and methyl ester groups. Lastly, global acetyl removal gave (−)-secologanin (**6**) in 65% yield over 2 steps.[40] Overall, (−)-secologanin (**6**) was accessed in nine steps from known materials.

To access (−)-strictosidine (**4**), we turned to the late-stage enzymatic Pictet–Spengler reaction between (−)-secologanin (**6**) and tryptamine (**5**) (Scheme 5). The natural biocatalyst for this transformation, strictosidine synthase, has previously been used successfully in the laboratory setting to prepare **4**.[33,98–103] As a practical advance, we sought to use crude cell

lysate from an *Escherichia coli* BL21 overexpressing the strictosidine synthase strain in place of purified enzyme. The lyophilized crude lysate was found to be a stable white powder that could be easily weighed on the benchtop.[104] To test the key biocatalytic step, (−)-secologanin (**6**) and tryptamine (**5**) were combined in an aqueous phosphate buffer with the crude lysate containing strictosidine synthase. This procedure delivered the natural product, (−)-strictosidine (**4**), in 82% yield, as a single C3 epimer, for which the spectral data are consistent with the published data.[105] Overall, (−)-strictosidine (**4**) was accessed in 10 steps from known materials, utilizing a blend of chemical synthesis and enzymatic catalysis.

Synthesis of *epi*-Strictosidine, “Strictosidyne”, and “Strictosamidyne”.

Our next objective was to prepare new, unnatural analogs of strictosidine (**4**).[106–109] This was pursued via two complementary strategies, the first of which is highlighted in Scheme 6 and involves the use of one of our synthetic intermediates that would not be readily accessible by other means. Specifically, **7b**, the C15 epimer of the desired product of the Diels–Alder reaction was elaborated to an unnatural secologanin derivative **14** by applying a similar synthetic sequence as that from **7a** to **6** (Scheme 3). The enzymatic Pictet–Spengler reaction of **14** with strictosidine synthase was attempted, but unfortunately, it led to the return of starting material, thus highlighting the substrate specificity of the enzyme.[110] We were delighted to find that treatment of **14** with TFA and tryptamine (**5**) generated the desired tetrahydro-beta-carboline ring system (1:1 diastereomeric ratio (dr) with respect to C3).[111–113] Subsequent removal of the acetates afforded *epi*-strictosidine isomers **15**. It is worth noting that isomers **15** would not be readily accessible from epimerization of strictosidine (**4**) or by manipulating the biosynthetic pathway.[114]

The second strategy we pursued for analog synthesis involved varying the tryptamine fragment using a new and unconventional building block (Figure 5). Specifically, we questioned if tryptamine derivative **17** could be accessible. In turn, **17** could serve as a masked synthetic equivalent of “tryptaminyne” **18**, which itself could find use in aryne trapping experiments or, for the purposes of our current study, be used in Pictet–Spengler reactions to make unique strictosidine derivatives. Of note, tryptamine is a prevalent precursor in both biosynthesis and chemical synthesis, [1,115,116] so the previously unknown “tryptaminyne” precursor could prove generally useful. We were delighted to find that commercially available indolyne precursor **16** could be elaborated to silyltriflate **17** in four steps.[117]

With silyl triflate **17** in hand, we attempted the Pictet–Spengler reaction using (−)-secologanin (**6**). Attempts to promote the desired reaction with strictosidine synthase were unsuccessful and only led to unreacted starting material. However, we found that the use of TFA led to the desired fragment coupling and annulation. “Strictosidyne” precursor **19** was obtained in 52% yield. The C3 epimer was also observed (16% yield, not depicted).[118] We also took advantage of the opportunity to make new derivatives of strictosamide, a related natural product.[119–121] As such, a single diastereomer of **19** (as depicted) was treated with sodium carbonate to afford **20**, which we envisioned serving as a precursor to the aryne derivative of strictosamide we term “strictosamidyne”.

Lastly, we demonstrated that “strictosidyne” (**22**) and “strictosamidyne” (**23**) could be generated from precursors **19** and **20**, respectively, by performing Diels–Alder trapping experiments (Scheme 7). Each silyltriflate was independently subjected to furan (**21**) and cesium fluoride in acetonitrile at 50 °C.[122] To our delight, this gave cycloadducts **24** and **25** in 66% and 55% yield (both 1:1 dr), respectively. The chemoselectivity in both reactions is noteworthy, given that the highly reactive aryne moieties could be generated and trapped in the presence of nucleophilic groups, such as unprotected amines and the four free alcohols on the glucosyl unit. To our knowledge, **19** and **20** are the first silyl triflate derivatives of complex alkaloids. Likewise, **22** and **23** are the first aryne derivatives of such complex naturally occurring structures.[123] We expect the ability to use and intercept aryne derivatives of complex natural products will prove useful in future efforts, especially those geared toward late-stage structural diversification.

CONCLUSIONS

In summary, we have completed the total synthesis of (−)-strictosidine and several unnatural analogs thereof. Our stereospecific approach features a facially selective Diels–Alder reaction to access the C15–C20–C21 stereotriad. As shown by DFT calculations, stereoselectivity in this key step is ultimately controlled by the glucosyl unit present in both the dienophile and (−)-strictosidine itself as a result of an *exo*-anomeric effect. This key step permits access to (−)-secolo- ganin and an unnatural derivative, which are subsequently employed in enzymatic or reagent-based Pictet–Spengler reactions, to give (−)-strictosidine and an unnatural epimer. Moreover, by accessing a “tryptaminyne” precursor, two unusual aryne natural product derivatives termed “strictosidyne” and “strictosamidyne” were generated and intercepted in Diels–Alder cycloadditions. These studies not only provide a means to access strictosidine and new derivatives thereof but also showcase the ability of a glucosyl unit to guide stereoselectivity through conformational effects, the synergy between synthetic chemistry, biocatalysis, and computations, and the use of “tryptaminyne” chemistry as a strategy to access derivatives of complex alkaloids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(117). See the Supporting Information for more details.

(118). Reagent-based Pictet–Spengler reactions of secologanin derivatives often give 1:1 dr. However, we found that shorter reaction times (i.e., 20 min) led to roughly 2:1 dr with respect to C3 based on ^{1}H NMR analysis of crude reaction mixtures. Similarly, we have observed that the TFA-promoted Pictet–Spengler reaction of **5** and **6** to give strictosidine (**4**) similarly favors the natural C3 epimer at shorter reaction times.

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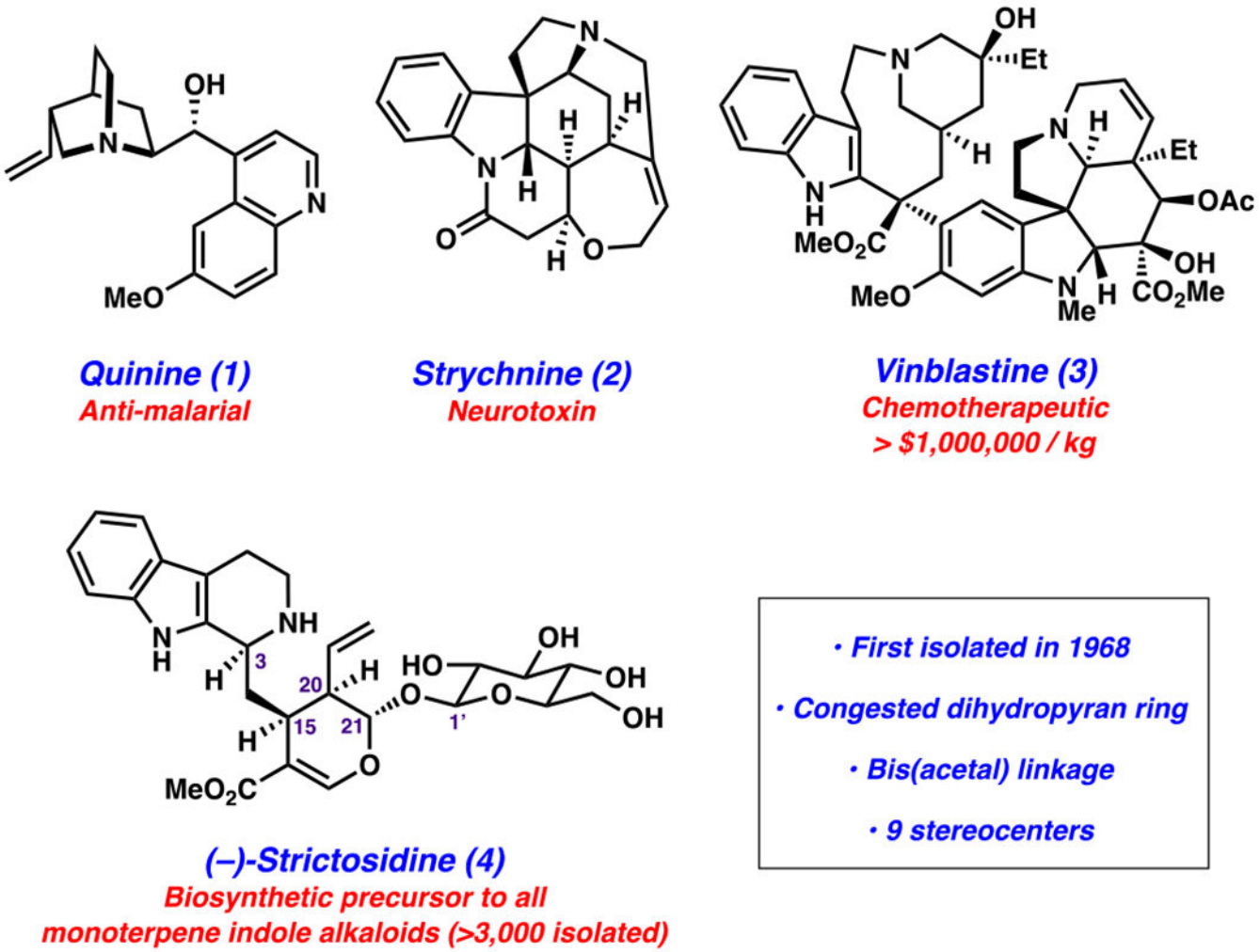


Figure 1.
Strictosidine (**4**) and select natural products biosynthetically derived from **4**.

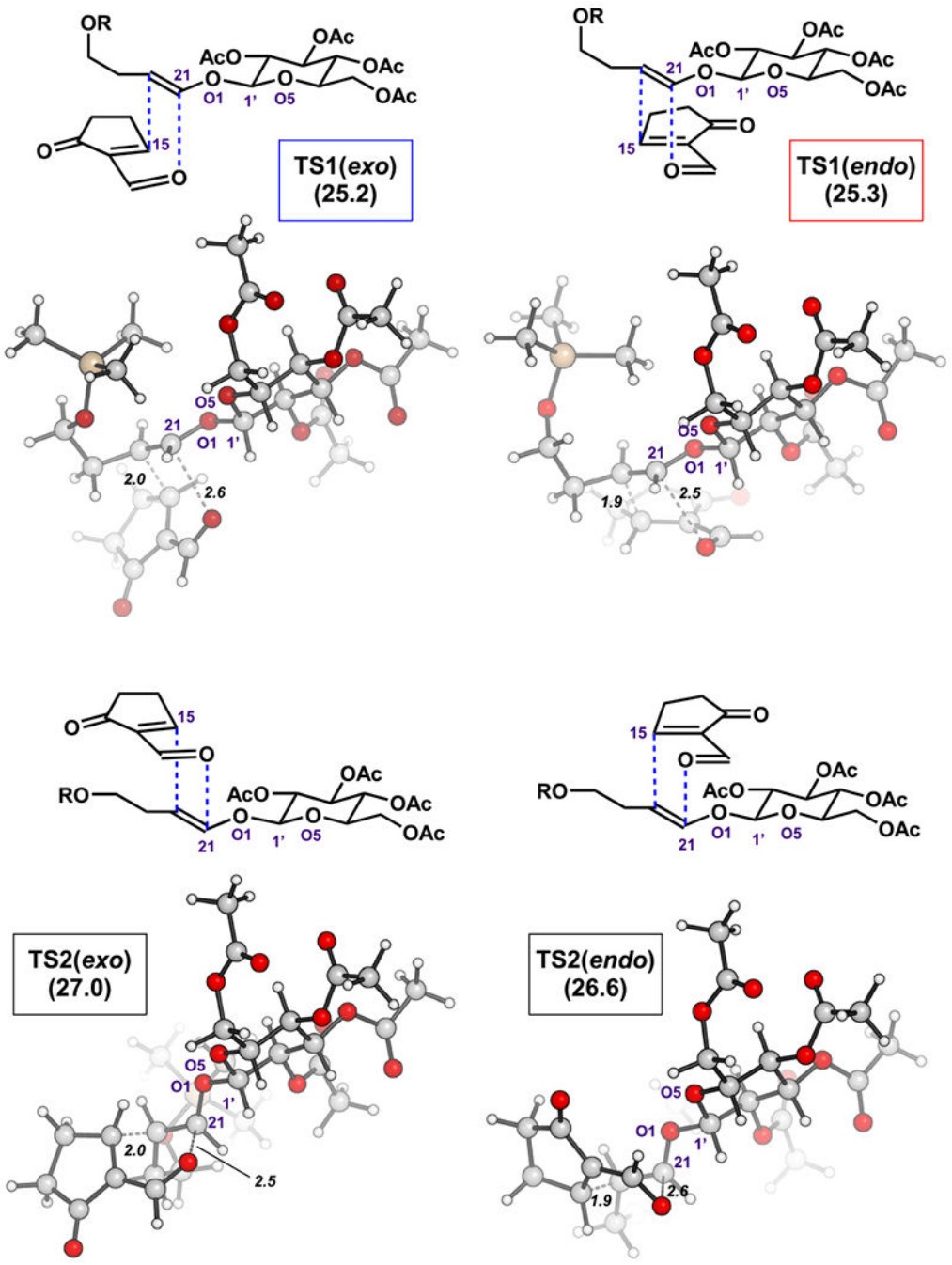


Figure 2.

Four stereoisomeric transition states of the hetero-Diels–Alder reaction, with activation energies shown in kcal/mol. **TS1**(*exo*) and **TS2**(*endo*) correspond to observed products **7a** and **7b**, respectively. R = TBS in experimental work. R = TMS in calculated structures.

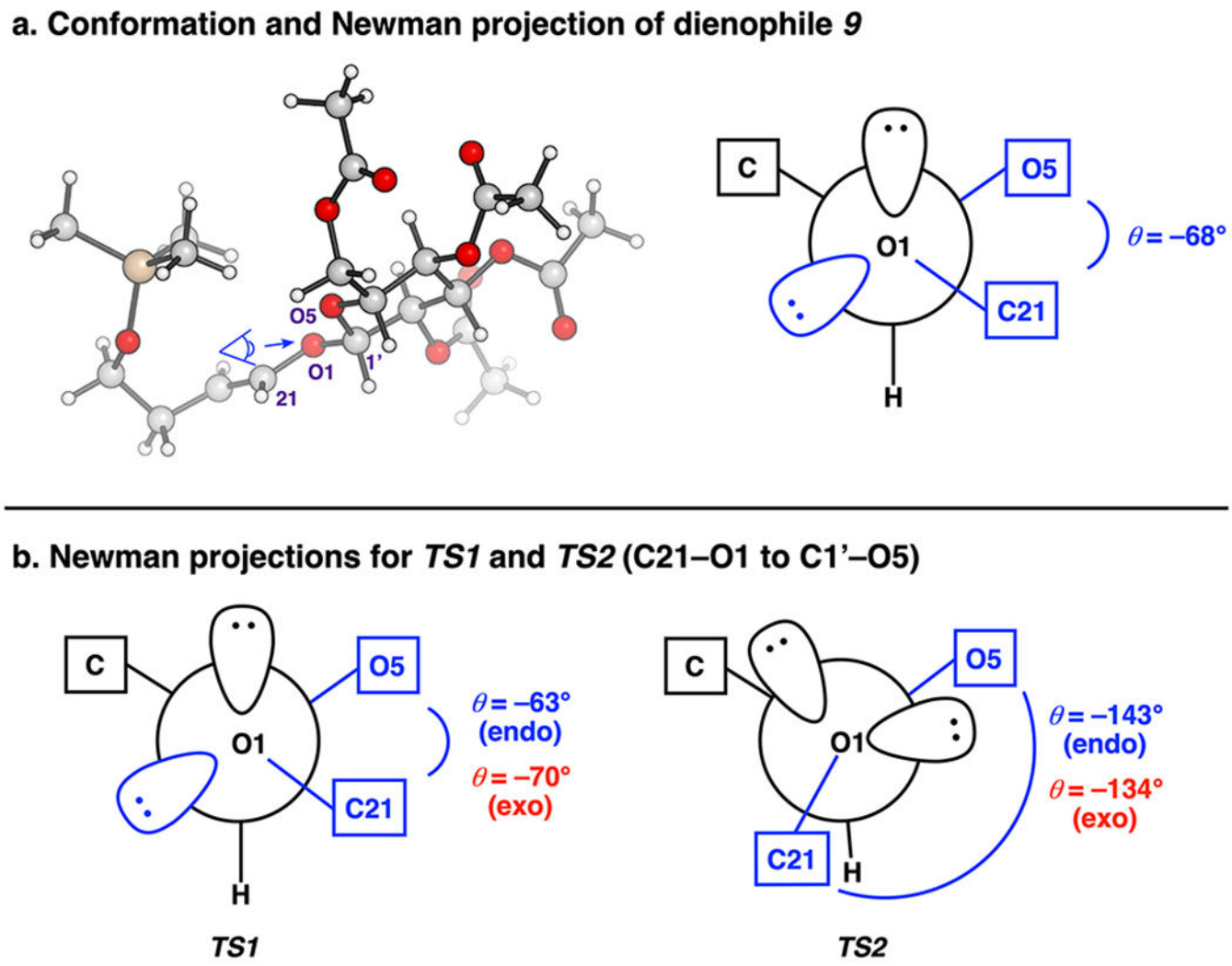


Figure 3.
(a) Conformation and Newman projection of dienophile **9**. (b) Newman projections for **TS1** and **TS2**.

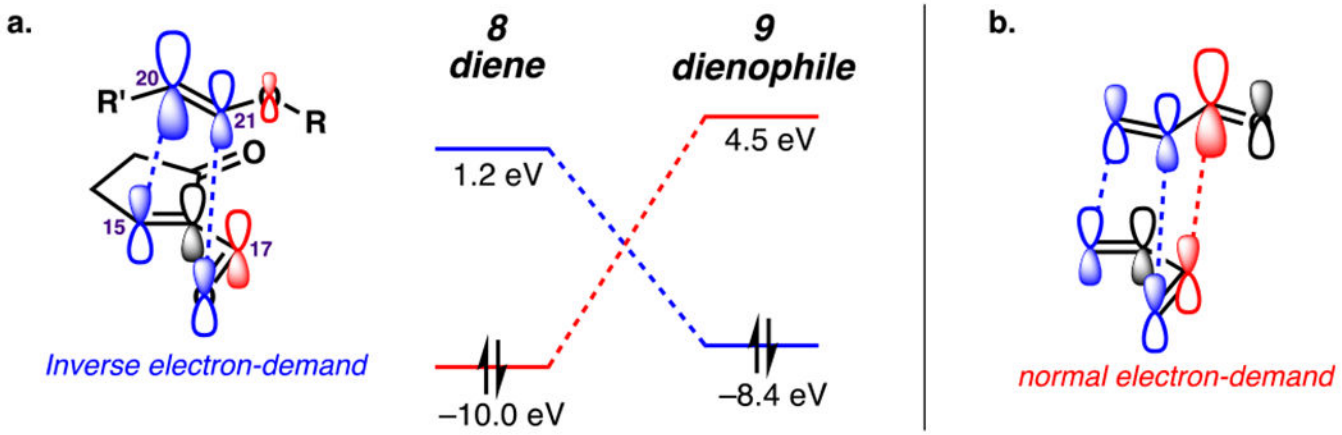


Figure 4.

(a) Frontier orbital interactions in the inverse electron-demand Diels–Alder reaction of **8** with **9**. Orbital energies were calculated with HF/6-31G(d,p)/SMD(toluene).[93,94] HOMO–LUMO energies are shown with the inverse electron-demand pathway in blue (HOMO–LUMO gap = 9.6 eV) and the normal electron-demand pathway in red (HOMO–LUMO gap = 14.5 eV). (b) Schematic representation of the strong *endo*-stabilizing secondary orbital interactions in a normal electron-demand Diels–Alder reaction (compared to weak interactions for the inverse electron-demand case studied here).

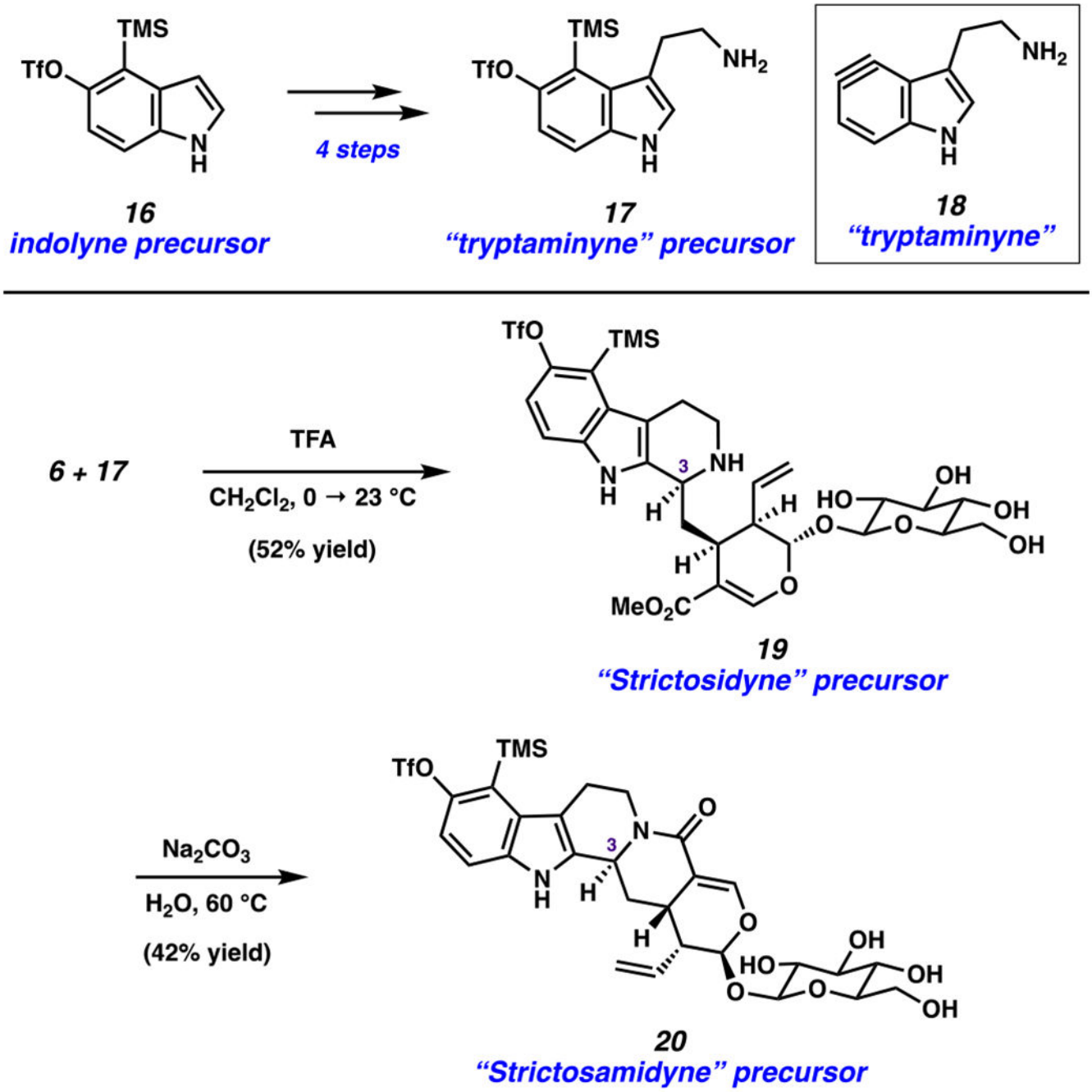
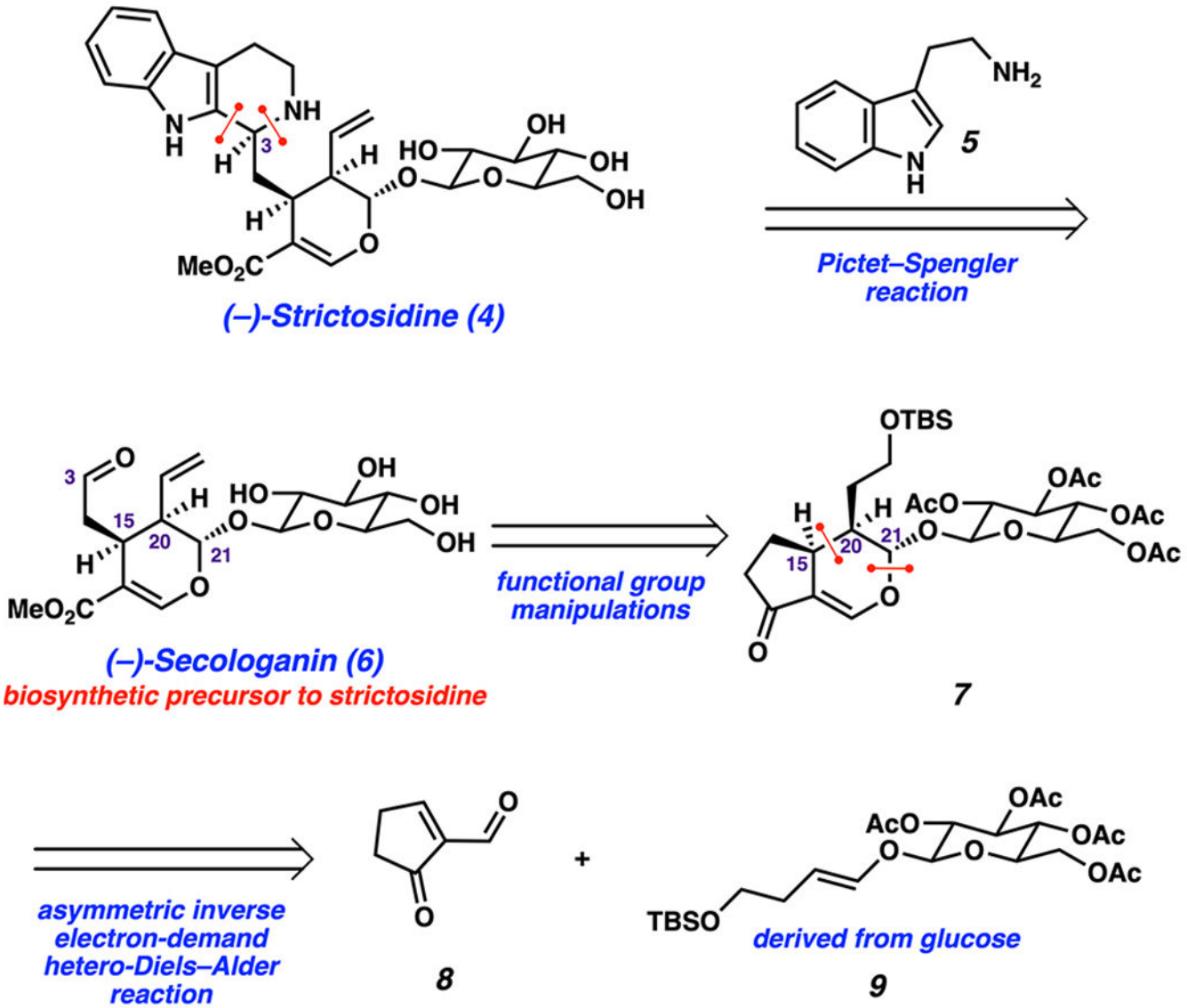
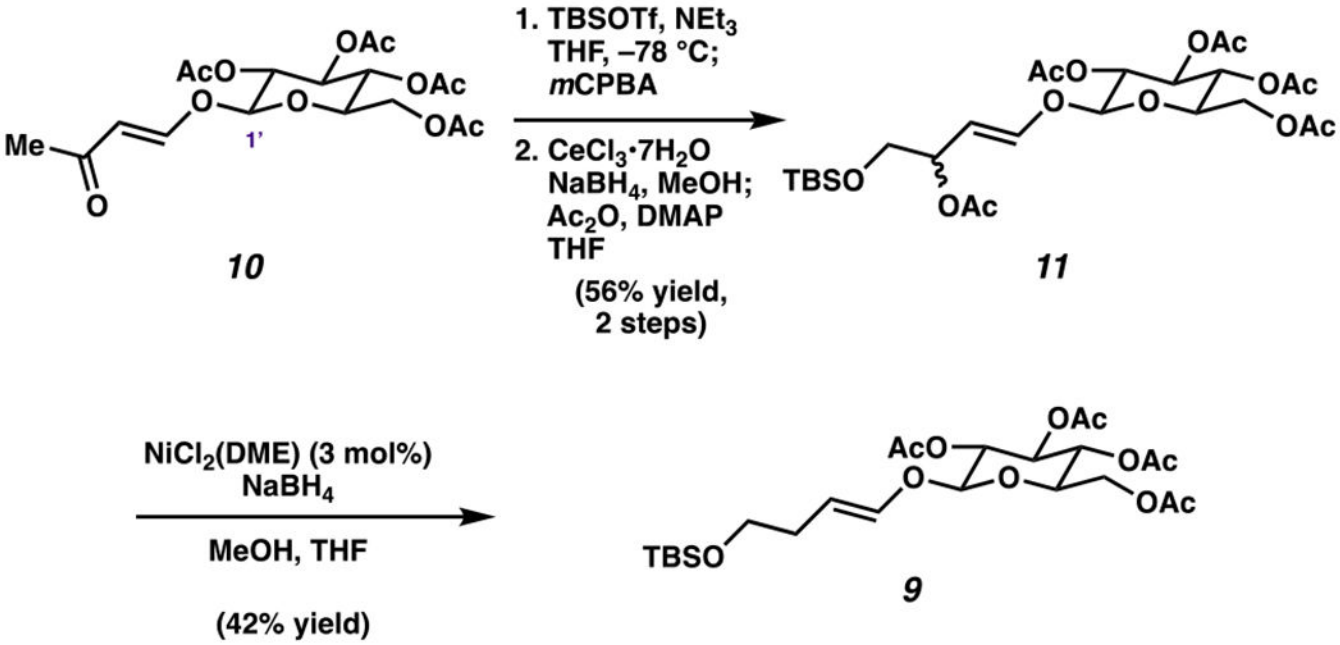


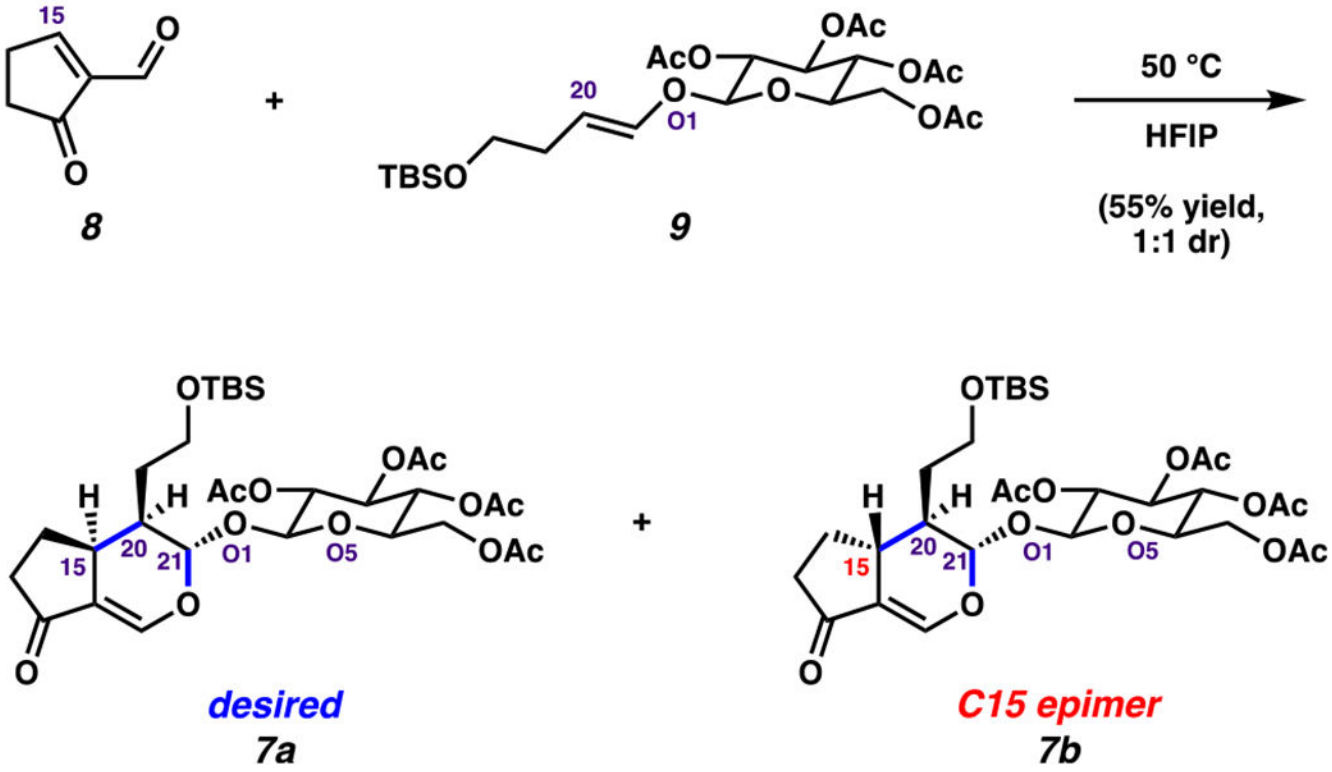
Figure 5.
Synthesis of tryptaminyne precursor **17**, "strictosidyne" precursor **19**, and "strictosamidyne" precursor **20**.



Scheme 1.
Retrosynthetic Analysis of (−)-Strictosidine (4)

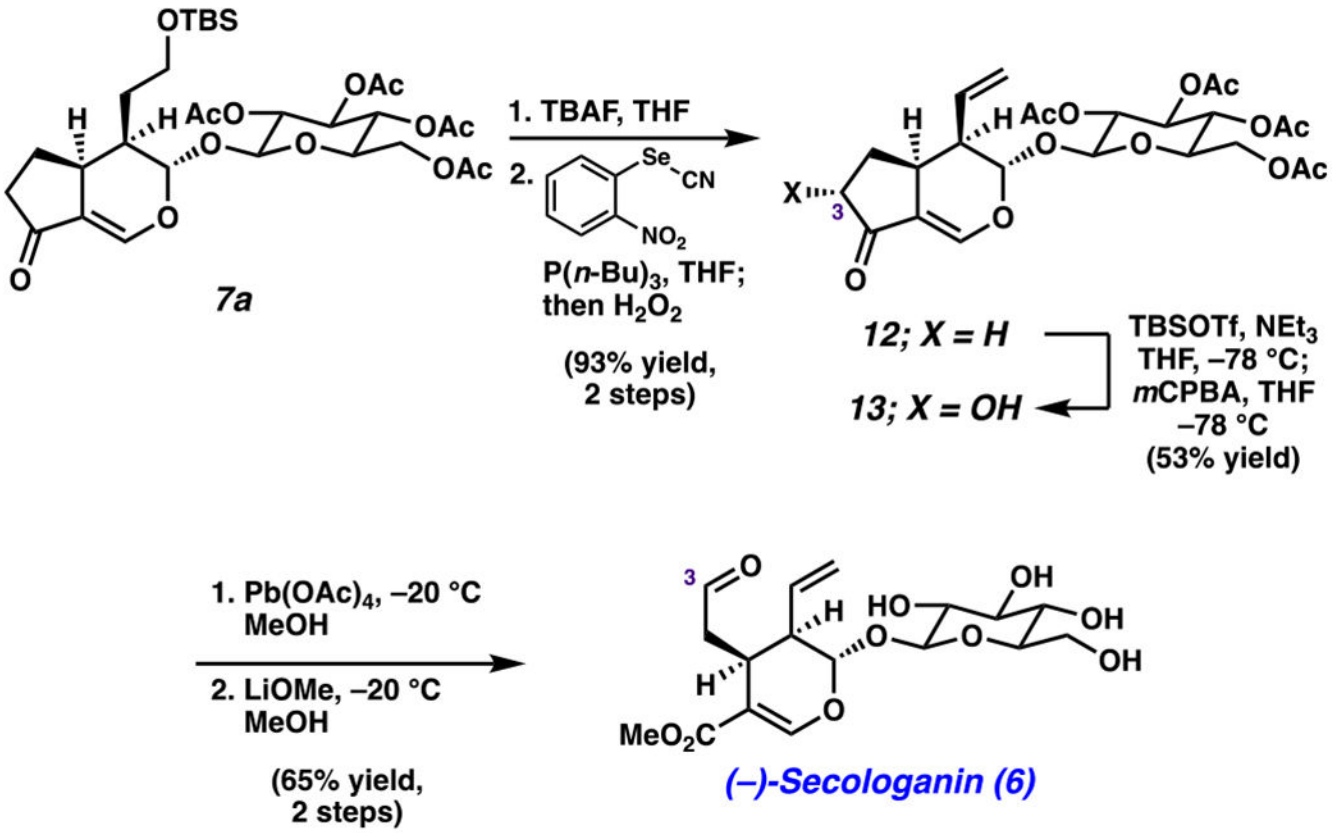


Scheme 2.
Synthesis of Enol Ether 9

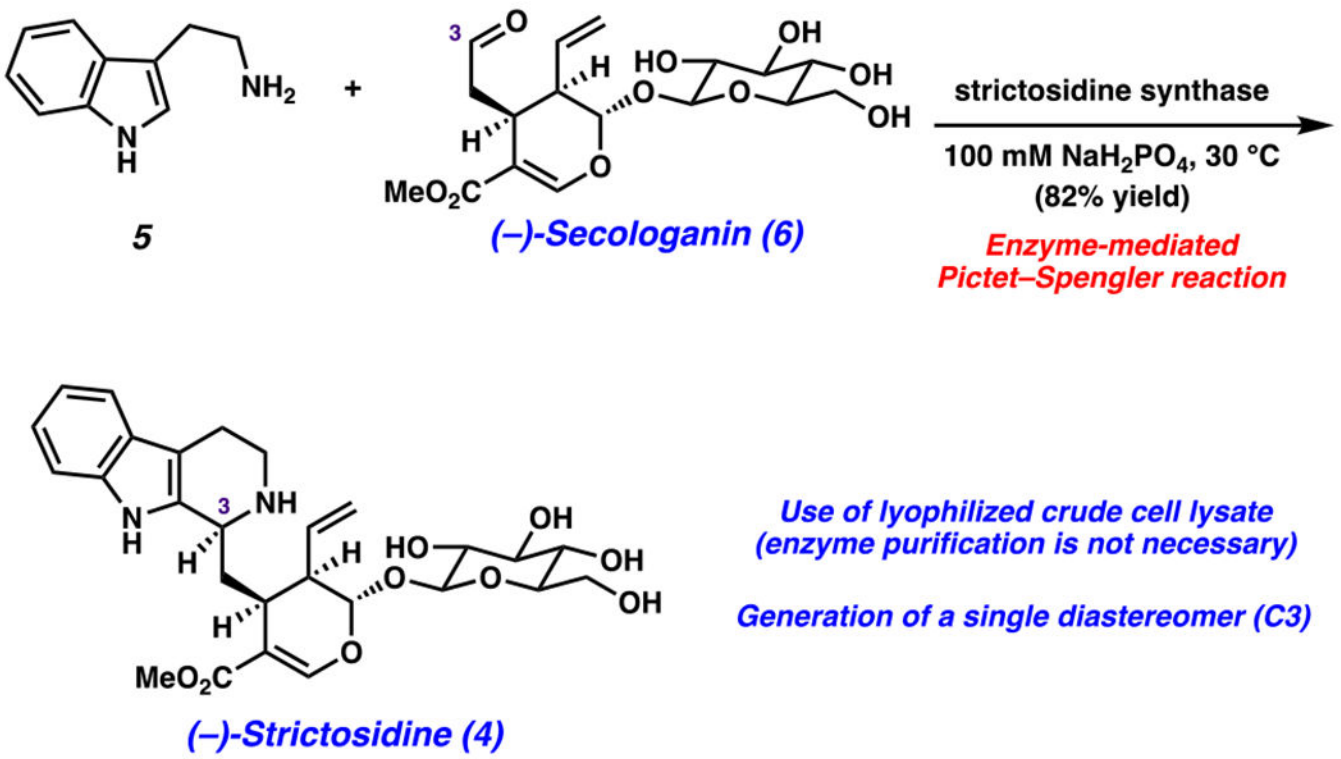


Scheme 3.

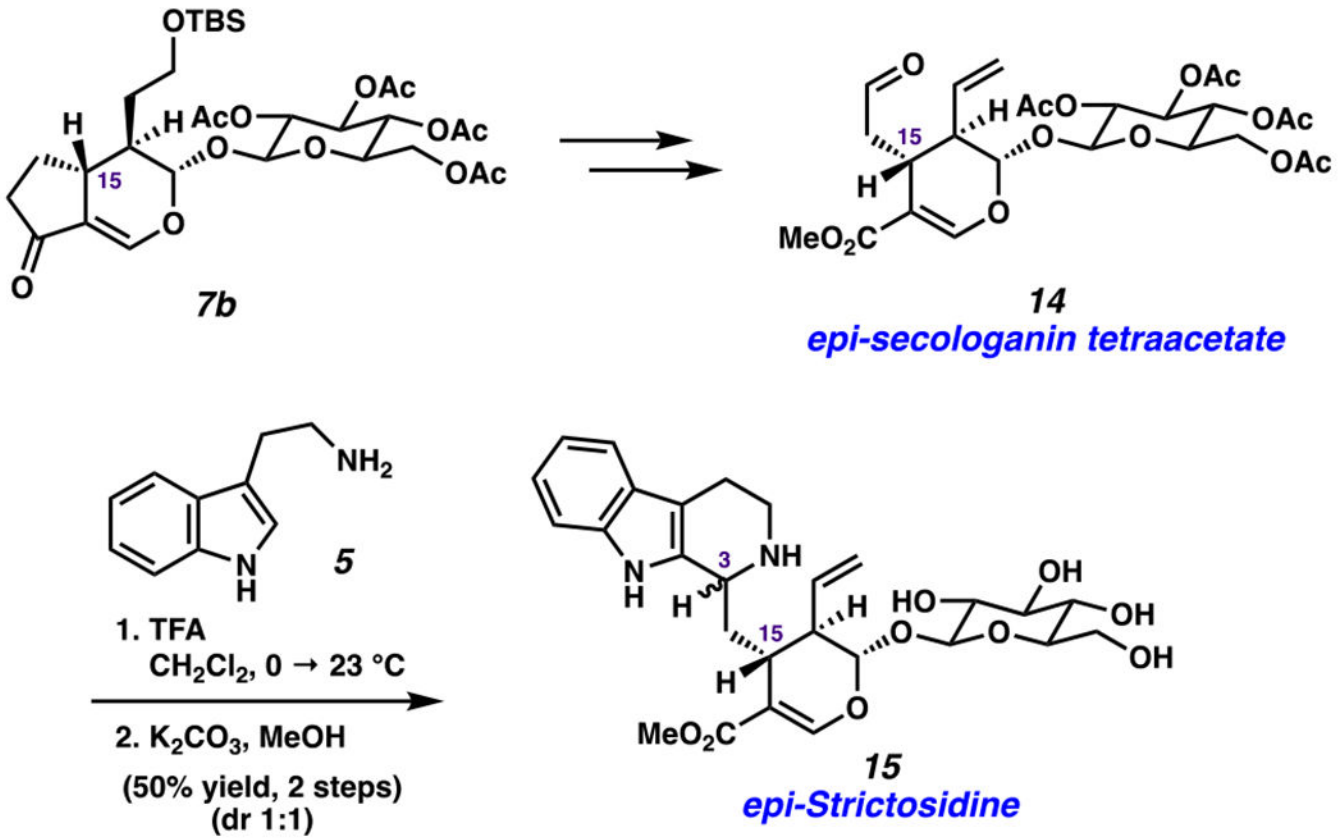
Facially Selective Hetero-Diels–Alder Reaction Affords Cycloadducts 7a (Desired) and 7b out of 16 Possible Isomers



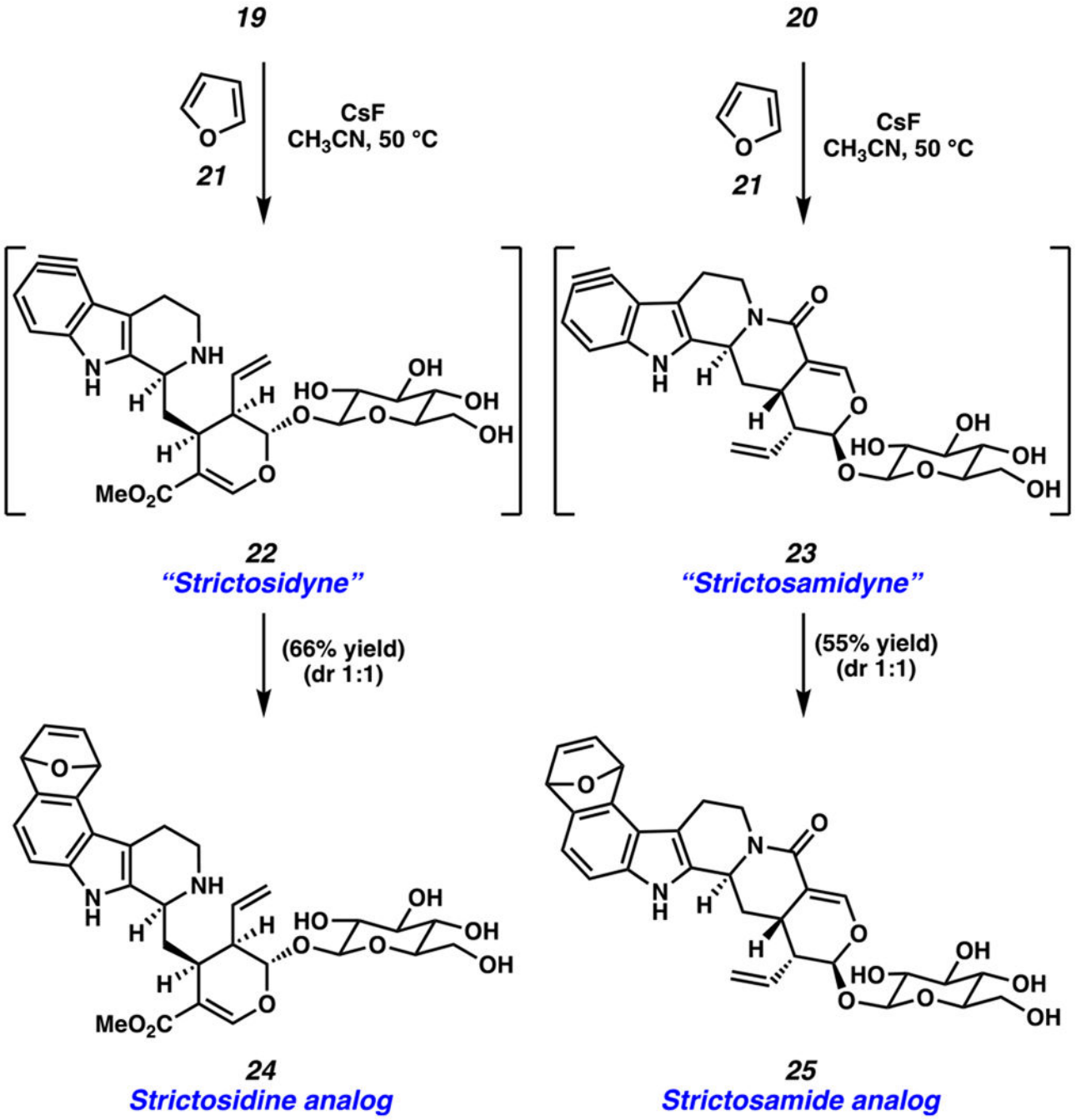
Scheme 4.
Synthesis of (−)-Secologanin (6)



Scheme 5.
Enzymatic Pictet–Spengler Reaction Provides (−)-Strictosidine (4)



Scheme 6.
Synthesis of Unnatural Derivative *epi*-Strictosidine 15



Scheme 7.
Trapping Experiments of Strictosidyne Precursor 19 and Strictosamidyne Precursor 20