Article

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

Sarah M. Anthony,[§] Veronica Tona,[§] Yike Zou,[§] Lucas A. Morrill, John M. Billingsley, Megan Lim, Yi Tang,* K. N. Houk,* and Neil K. Garg*
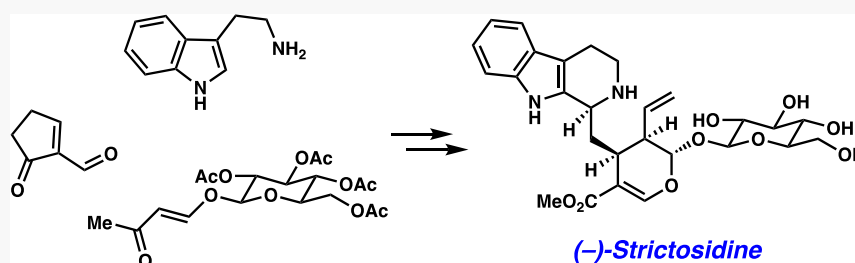
Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

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−Spenger 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.

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 biosyn-

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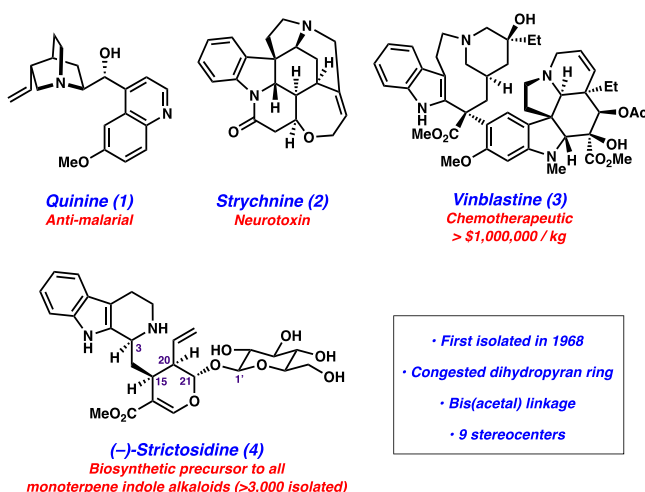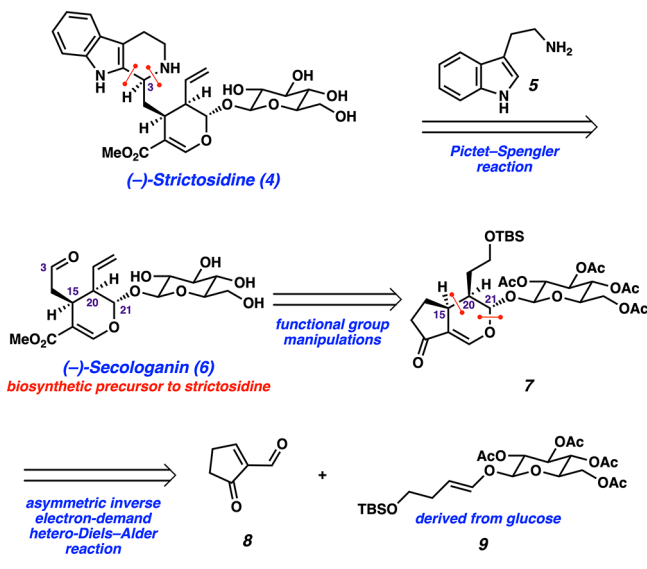
Figure 1. Strictosidine (**4**) and select natural products biosynthetically derived from **4**.

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–Spenger 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

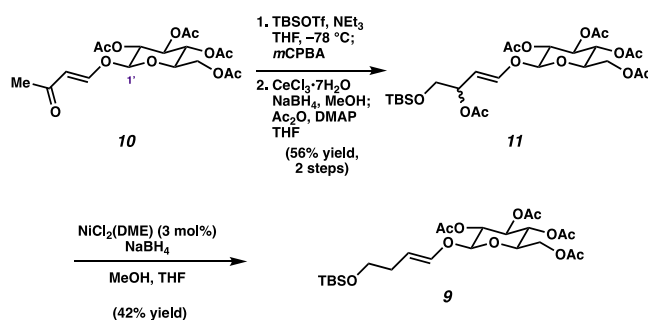**Scheme 1. Retrosynthetic Analysis of (−)-Strictosidine (4)**

(−)-strictosidine (**4**) would be obtained from its biosynthetic precursors (−)-secologanin (**6**) and tryptamine (**5**) via an enzymatic Pictet–Spenger 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
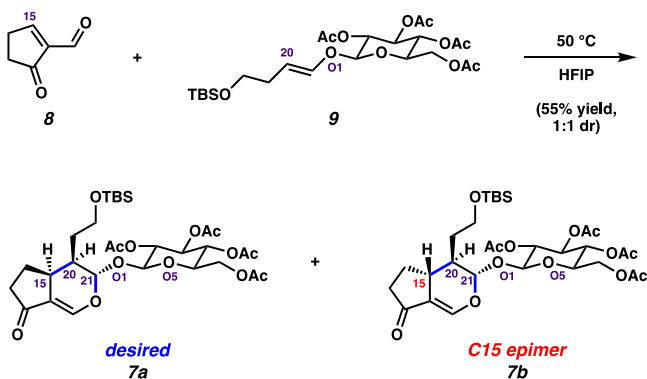
Scheme 2. Synthesis of Enol Ether 9

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 products in 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

Scheme 3. Facially Selective Hetero-Diels−Alder Reaction Affords Cycloadducts 7a (Desired) and 7b out of 16 Possible Isomers
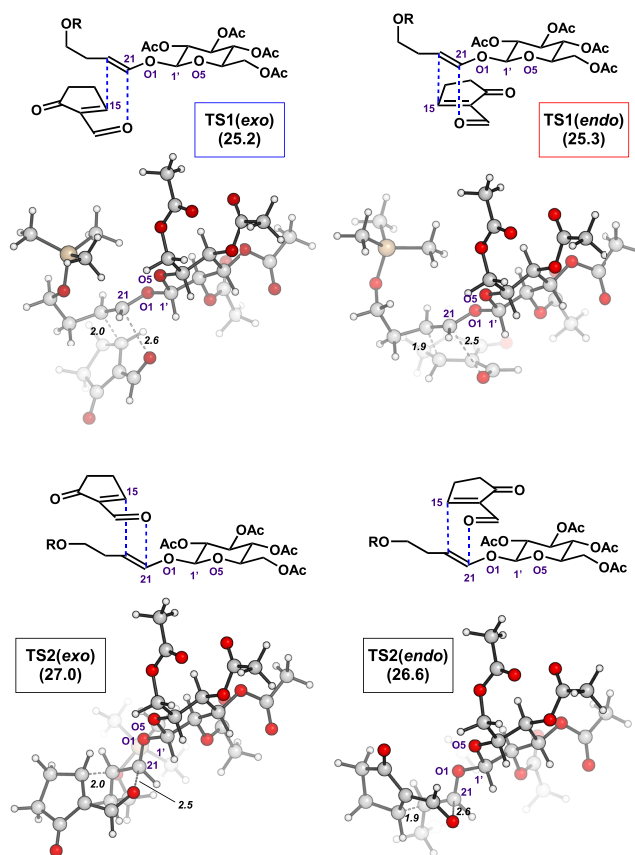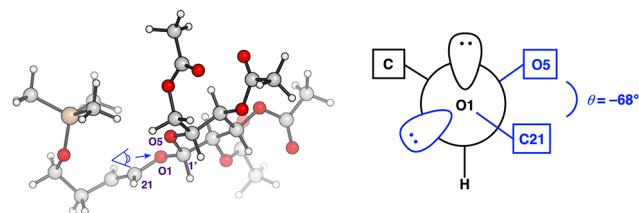

Figure 2. Four stereoisomeric transition states of the hetero-Diels−Alder reaction, with activation energies shown in kcal/mol. **TS1**(*exo*) and **TS2**(*endo*) correspond to observed products **7a** and **7b**, respectively. R = TBS in experimental work. R = TMS in calculated structures.

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 stereo-isomeric 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

a. Conformation and Newman projection of dienophile 9

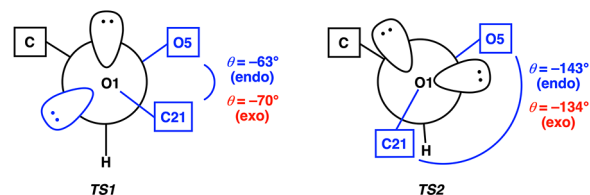**b. Newman projections for *TS1* and *TS2* (C21−O1 to C1'−O5)**

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

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
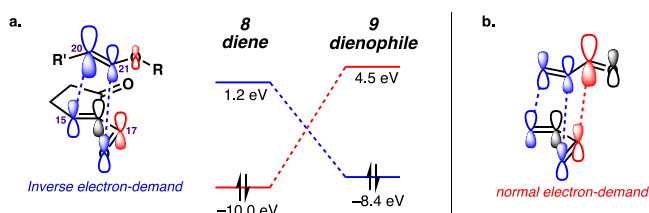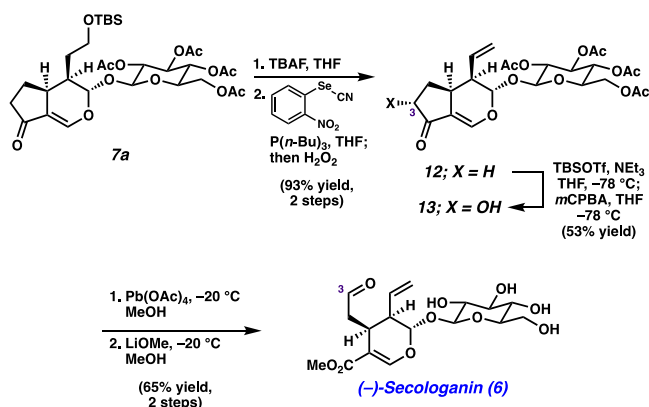

Figure 4. (a) Frontier orbital interactions in the inverse electron-demand Diels−Alder reaction of **8** with **9**. Orbital energies were calculated with HF/6-31G(d,p)/SMD(toluene).[93,94] HOMO−LUMO energies are shown with the inverse electron-demand pathway in blue (HOMO−LUMO gap = 9.6 eV) and the 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).

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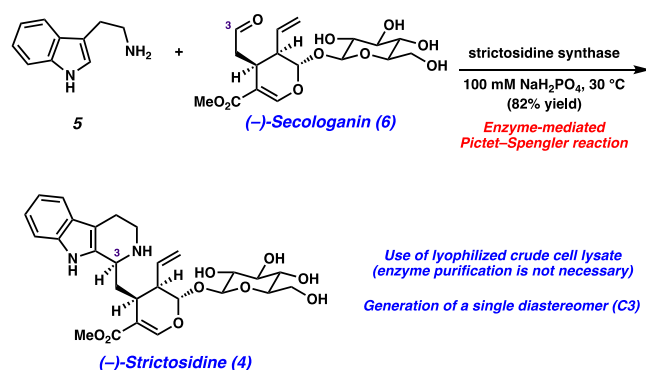
Scheme 4. Synthesis of (−)-Secologanin (6)

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.
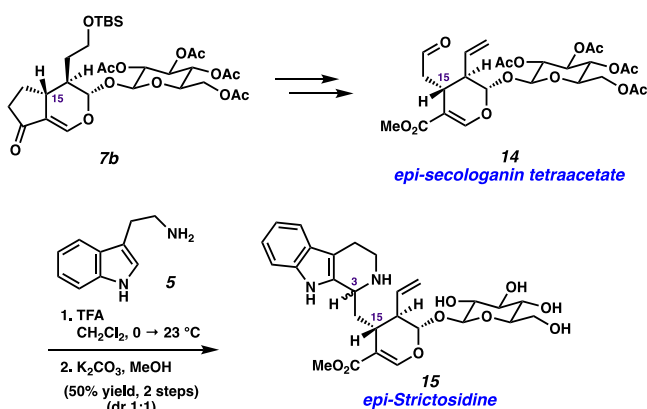
To access (−)-strictosidine (**4**), we turned to the late-stage enzymatic Pictet−Spengler reaction between (−)-secologanin (**6**) and tryptamine (**5**) (Scheme 5). The natural biocatalyst

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

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

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

14
epi-secologanin tetraacetate

15
epi-Strictosidine

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
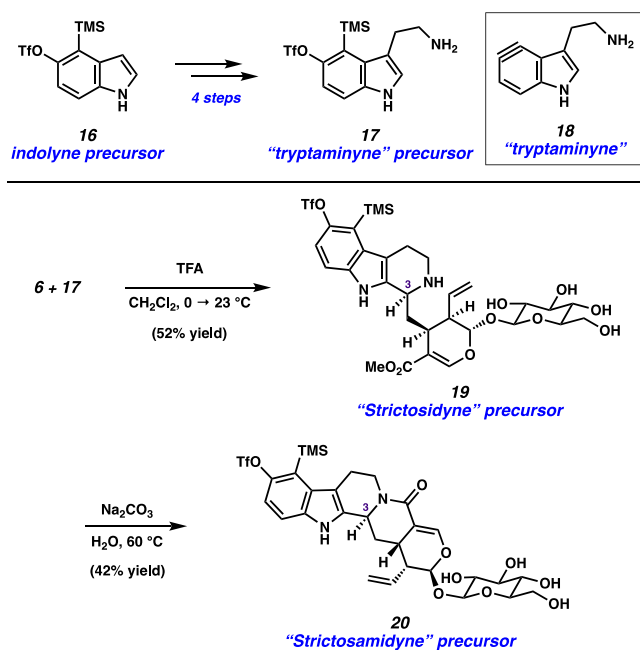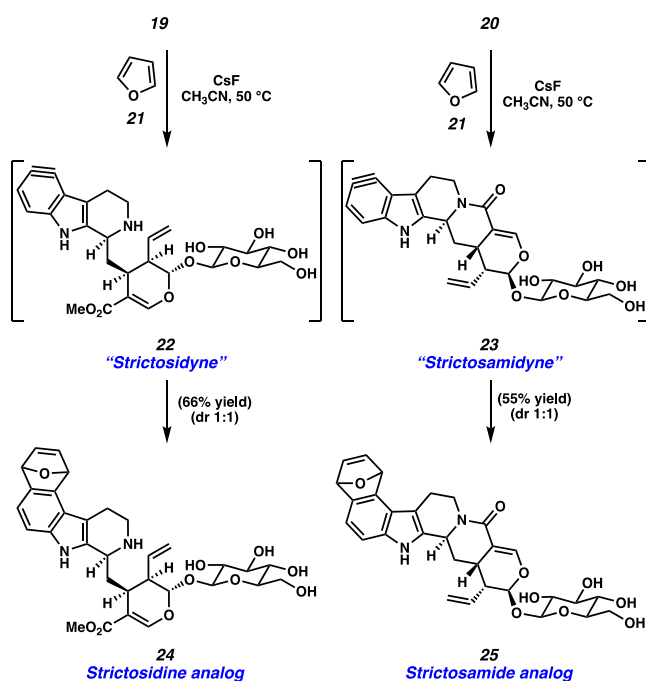

16
indolyne precursor

17
"tryptaminyne" precursor

18
"tryptaminyne"

19
"Strictosidyne" precursor

20
"Strictosamidyne" precursor

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

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

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

22
"Strictosidyne"

23
"Strictosamidyne"

24
Strictosidine analog

25
Strictosamide analog

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 (−)-secologanin 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.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c02004.

> Detailed experimental procedures and compound characterization data (PDF)

AUTHOR INFORMATION

Corresponding Authors

Yi Tang − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States*; Email: yitang@ucla.edu

K. N. Houk − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States*; Ⓘ orcid.org/0000-0002-8387-5261; Email: houk@chem.ucla.edu

Neil K. Garg − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States*; Ⓘ orcid.org/0000-0002-7793-2629; Email: neilgarg@chem.ucla.edu

Authors

Sarah M. Anthony − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States*; Ⓘ orcid.org/0000-0001-9101-9097

Veronica Tona − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States*

Yike Zou − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States*; Ⓘ orcid.org/0000-0003-4380-7827

Lucas A. Morrill − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States*

John M. Billingsley − *Department of Chemical and Biomolecular Engineering, University of California, Los Angeles, California 90095, United States*; Ⓘ orcid.org/0000-0001-9300-9378

Megan Lim − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States*

Complete contact information is available at:
https://pubs.acs.org/10.1021/jacs.1c02004

Author Contributions

§These authors contributed equally.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) O'Connor, S. E.; Maresh, J. J. Chemistry and biology of monoterpene indole alkaloid biosynthesis. *Nat. Prod. Rep.* **2006**, *23*, 532−547.

(2) Pan, Q.; Mustafa, N. R.; Tang, K.; Choi, Y. H.; Verpoorte, R. Monoterpenoid indole alkaloids biosynthesis and its regulation in *Catharanthus roseus*: a literature review from genes to metabolites. *Phytochem. Rev.* **2016**, *15*, 221−250.

(3) De Luca, V.; Salim, V.; Thamm, A.; Masada, A. S.; Yu, F. Making iridoids/secoiridoids and monoterpenoid indole alkaloids: progress on pathway elucidation. *Curr. Opin. Plant Biol.* **2014**, *19*, 35−42.

(4) Kaufman, T. S.; Rúveda, E. A. The quest for quinine: those who won the battles and those who won the war. *Angew. Chem., Int. Ed.* **2005**, *44*, 854−885.

(5) Nicolaou, K. C.; Snyder, S. A. *Classics in total synthesis II: more targets, strategies, methods*; Wiley-VCH: Weinheim, Germany, 2003; Ch. 15. pp 443−462.

(6) Souza, K. A. F. D.; Porto, P. A. History and epidemiology of science in the classroom: The synthesis of quinine as a proposal. *J. Chem. Educ.* **2012**, *89*, 58−63.

(7) Nicolau, K. C.; Sorensen, E. J. *Classics in total synthesis: targets, strategies, methods*. VHC: Weinheim & New York, 1996; Ch. 2. pp 22−40.

(8) Cannon, J. S.; Overman, L. E. Is there no end to the total syntheses of strychnine? Lessons learned in strategy and tactics in total synthesis. *Angew. Chem., Int. Ed.* **2012**, *51*, 4288−4311.

(9) He, W.; Wang, P.; Chen, J.; Xie, W. Recent progress in the total synthesis of *Strychnos* alkaloids. *Org. Biomol. Chem.* **2020**, *18*, 1046−1056.

(10) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. Total synthesis of vinblastine, vincristine, related natural products, and key structural analogues. *J. Am. Chem. Soc.* **2009**, *131*, 4904−4916.

(11) Datta, A.; Srivastava, P. S. Variation in vinblastine production by *Catharanthus roseus* during in vivo and in vitro differentiation. *Phytochemistry* **1997**, *46*, 135−137.

(12) Miettinen, K.; Dong, L.; Navrot, N.; Schneider, T.; Burlat, V.; Pollier, J.; Woittiez, L.; Krol, D. v. d.; Lugan, R.; Ilc, T.; Verpoorte, R.; Oksman-Caldentry, K.-M.; Martinoia, E.; Bouwmeester, H.;

Goossens, A.; Memelink, J.; WerkReichhart, D. The seco-iridoid pathway from Catharanthus roseus. *Nat. Commun.* **2014**, *5*, 3606.

(13) Mehrotra, S.; Mishra, S.; Srivastava, V. *Hairy root cultures for monoterpene indole alkaloid pathway: investigation and biotechnological production*; Springer: Singapore, 2018; pp 95−121.

(14) Kries, H.; O'Connor, S. Biocatalysts from alkaloid producing plants. *Curr. Opin. Chem. Biol.* **2016**, *31*, 22−30.

(15) Zhu, H.; Kerčmar, P.; Wu, F.; Rajendran, C.; Sun, L.; Wang, M.; Stöckigt, J. Using strictosidine synthase to prepare novel alkaloids. *Curr. Med. Chem.* **2015**, *22*, 1880−1888.

(16) Leonard, E.; Runguphan, W.; O'Connor, S.; Prather, K. J. Opportunities in metabolic engineering to facilitate scalable alkaloid production. *Nat. Chem. Biol.* **2009**, *5*, 292−300.

(17) Caputi, L.; Franke, J.; Farrow, S. C.; Chung, K.; Payne, R. M. E.; Nguyen, T.-D.; Dang, T.-T. T.; Carqueijeiro, I. S. T.; Koudounas, K.; de Bernonville, T. D.; Ameyaw, B.; Jones, D. M.; Vieira, I. J. C.; Courdavault, V.; O'Connor, S. E. Missing enzymes in the biosynthesis of the anticancer drug vinblastine in Madagascar periwinkle. *Science* **2018**, *360*, 1235−1239.

(18) Tanifuji, R.; Minami, A.; Oguri, H.; Oikawa, H. Total synthesis of alkaloids using both chemical and biochemical methods. *Nat. Prod. Rep.* **2020**, *37*, 1098−1121.

(19) Liu, X.-Y.; Qin, Y. Indole alkaloid synthesis facilitated by photoredox catalytic radical cascade reactions. *Acc. Chem. Res.* **2019**, *52*, 1877−1891.

(20) Saya, J. M.; Ruijter, E.; Orru, R. V. A. Total synthesis of *Aspidosperma* and *Strychnos* alkaloids through indole dearomatization. *Chem. - Eur. J.* **2019**, *25*, 8916−8935.

(21) Tokuyama, H. The total synthesis of biosynthetically related monoterpene indole alkaloids. *Yuki Gosei Kagaku Kyokaishi* **2015**, *15*, 1120−1129.

(22) Dou, Y.; Kouklovsky, C.; Vincent, G. 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. *Chem. - Eur. J.* **2020**, *26*, 17190−17194.

(23) Zhang, B.; Wang, X.; Li, C. Enantioselective total synthesis of (+)-corymine and (−)-deformylcorymine. *J. Am. Chem. Soc.* **2020**, *142*, 3269−3274.

(24) Dou, Y.; Kouklovsky, C.; Gandon, V.; Vincent, G. Enantioselective total synthesis of cymoside through a bioinspired oxidative cyclization of a strictosidine derivative. *Angew. Chem., Int. Ed.* **2020**, *59*, 1527−1531.

(25) Jarret, M.; Turpin, V.; Tap, A.; Gallard, J.-F.; Kouklovsky, C.; Poupon, E.; Vincent, G.; Evanno, L. Bioinspired oxidative cyclization of the geissoschizine skeleton for enantioselective total synthesis of mavacuran alkaloids. *Angew. Chem., Int. Ed.* **2019**, *58*, 9861−9865.

(26) Liu, Y.; Wang, H. Unified enantioselective total syntheses of (−)-scholarisine G, (+)-melodinine E, (−)-leuconoxine and (−)-mersicarpine. *Chem. Commun.* **2019**, *55*, 3544−3547.

(27) Mason, J. D.; Weinreb, S. M. Total syntheses of the monoterpenoid indole alkaloids (±)-alstoscholarisine B and C. *Angew. Chem., Int. Ed.* **2017**, *56*, 16674−16676.

(28) Liang, X.; Jiang, S.-Z.; Wei, K.; Yang, Y.-R. Enantioselective total synthesis of (−)-alstoscholarisine A. *J. Am. Chem. Soc.* **2016**, *138*, 2560−2562.

(29) Piemontesi, C.; Wang, Q. W.; Zhu, J. Enantioselective total synthesis of (−)-terengganensine A. *Angew. Chem., Int. Ed.* **2016**, *55*, 6556−6560.

(30) Xu, Z.; Bao, X.; Wang, Q.; Zhu, J. An enantioselective total synthesis of (−)-isoschizogamine. *Angew. Chem., Int. Ed.* **2015**, *54*, 14937−14940.

(31) Wagnières, O.; Xu, Z.; Wang, Q.; Zhu, J. Unified strategy to monoterpene indole alkaloids: total syntheses of (±)-goniomitine, (±)-1,2-dehydroaspidospermidine, (±)-aspidospermidine, (±)-vincadifformine, and (±)-kopsihainanine A. *J. Am. Chem. Soc.* **2014**, *136*, 15102−15108.

(32) Smith, G. N. Strictosidine: a key intermediate in the biogenesis of indole alkaloids. *Chem. Commun. (London)* **1968**, 912−914.

(33) Brown, S.; Clastre, M.; Courdavault, V.; O'Connor, S. De novo production of the plant-derived alkaloid strictosidine in yeast. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 3205−3210.

(34) Billingsley, J. M.; DeNicola, A. B.; Barber, J. S.; Tang, M.-C.; Horecka, J.; Chu, A.; Garg, N. K.; Tang, Y. Engineering the biocatalytic selectivity of iridoid production in *Saccharomyces cerevisiae*. *Metab. Eng.* **2017**, *44*, 117−125.

(35) Yee, D. A.; DeNicola, A. B.; Billingsley, J. M.; Creso, J. G.; Subrahmanyam, V.; Tang, Y. Engineered mitochondrial production of monoterpenes in *Saccharomyces cerevisiae*. *Metab. Eng.* **2019**, *55*, 76−84.

(36) Ishikawa's route to strictosidine features an organocatalytic Michael reaction, Fukuyama reduction, cyclization cascade; see: Ishikawa, H.; Sakamoto, J.; Umeda, Y.; Rakumitsu, K.; Sumimoto, M. Total syntheses of (−)-strictosidine and related indole alkaloid glycosides. *Angew. Chem., Int. Ed.* **2020**, *59*, 13414−13422.

(37) For Ishikawa's route to secologanin; see: Rakumitsu, K.; Sakamoto, J.; Ishikawa, H. Total syntheses of (−)-secologanin, (−)-5-carboxystrictosidine, and (−)-rubenine. *Chem. - Eur. J.* **2019**, *25*, 8996−9000.

(38) Bernhardt, P.; O'Connor, S. E. Synthesis and biochemical evaluation of des-vinyl secologanin aglycones with alternate stereochemistry. *Tetrahedron Lett.* **2009**, *50*, 7118−7120.

(39) Bernhardt, P.; Yerkes, N.; O'Connor, S. E. Bypassing stereoselectivity in the early steps of alkaloid biosynthesis. *Org. Biomol. Chem.* **2009**, *7*, 4166−4168.

(40) Tietze, L.-F. Secologanin, a biogenetic key compound—synthesis and biogenesis of the iridoid and secoiridoid glycosides. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 828−841.

(41) Nakane, M.; Hutchinson, C. R. Stereoselective synthesis of (±)-1-*O*-methylloganin, 10-hydroxyloganin, secologanin, and sweroside aglucons from a common 1-hydroxy-4a,5,8,8-tetrahydroisochromene synthon. *J. Org. Chem.* **1980**, *45*, 4233−4236.

(42) Cheng, P. T. W.; McLean, S. A synthetic approach to secologanin: synthesis of a protected form of the secoxyloganin aglucone. *Tetrahedron Lett.* **1988**, *29*, 3511−3512.

(43) Isoe, S.; Katsumura, S.; Okada, T.; Yamamoto, K.; Takemoto, T.; Inaba, H.; Han, Q.; Nakatani, K. Novel synthesis of (−)-secologanin aglucon-O-silyl ether from (+)-genipin via oxidative fragmentation of γ-hydroxyalkylstannane. *Tetrahedron Lett.* **1987**, *28*, 5865−5868.

(44) Chang, N.-C.; Day, H.-M.; Lu, W.-F. Total synthesis of (±)-secologanoside O-methyl ether. *J. Org. Chem.* **1989**, *54*, 4083−4088.

(45) Tai, H.-M.; Huang, M.-H.; Yang, C.-C. Formal total synthesis of (±)-dimethyl secologanoside. *J. Chin. Chem. Soc.* **2003**, *50*, 441−444.

(46) Adary, E. M.; Chang, C.-W.; D'Auria, D. T.; Nguyen, P. M.; Polewacz, K.; Reinicke, J. A.; Seo, H.; Berger, G. O. Improved synthesis of and nucleophilic addition to 2-formyl-2-cyclohexenone. *Tetrahedron Lett.* **2015**, *56*, 386−389.

(47) Frank, R. L.; Varland, R. H. 1,3,5-Triacetylbenzene. *Org. Synth.* **1947**, *27*, 91.

(48) Gupta, R.; Harland, F. A.; Stoodley, R. J. An efficient enantiocontrolled synthesis of (+)-4-demethoxydaunomycinone. *Tetrahedron* **1984**, *40*, 4657−4667.

(49) Craita, C.; Didier, C.; Vogel, P. Short synthesis of the C16-C28 polyketide fragment of apoptolidin A aglycone. *Chem. Commun.* **2007**, 2411−2413.

(50) Jung, J.; Lehnemann, B. W. Preparation of cis-2-cyclopentene-1,4-diol. US Patent US 2009−663763. Dec 9, 2009.

(51) Nishiyama, S.; Ikeda, Y.; Yoshida, S.-I.; Yamamura, S. Synthetic study on breynin A: synthesis of breynolide sulfone. *Tetrahedron Lett.* **1989**, *30*, 105−108.

(52) Clark, J. S.; Romiti, F.; Sieng, B.; Paterson, L. C.; Stewart, A.; Chaudhury, S.; Thomas, L. H. Synthesis of the A-D ring system of the gambieric acids. *Org. Lett.* **2015**, *17*, 4694−4697.

(53) Fukumoto, S.; Ujikawa, O.; Morimoto, S.; Asano, Y.; Mikami, S.; Tokunaga, N.; Kori, M.; Imaeda, T.; Fukuda, K.; Nakamura, S.;

Iwanaga, K. Sulfonamide derivative and use thereof. International Patent WO 2012/137982 A2, October 11, 2012.

(54) Hanessian, S.; Maianti, J. P.; Matias, R. D.; Feeney, L. A.; Armstrong, E. S. Hybrid aminoglycoside antibiotics via Tsuji palladium-catalyzed allylic deoxygenation. *Org. Lett.* **2011**, *13*, 6476−6479.

(55) Wyatt, P. G.; Coomber, B. A.; Evans, D. N.; Jack, T. I.; Fulton, H. E.; Wonacott, A. J.; Colman, P.; Varghese, J. Sialidase inhibitors related to zanamivir. Further SAR studies of 4-amino-4*H*-pyran-2-carboxylic acid-6-propylamides. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 669−673.

(56) Jung, M. E.; Trifunovich, I. D. Efficient Synthesis of 2′,3′-dideoxynucleosides and C-nucleosides from D-glucosamine. *Tetrahedron Lett.* **1992**, *33*, 2921−2924.

(57) Kovács, L.; Herczegh, P.; Batta, G.; Farkas, I. Thiazole-C-nucleosides IV. An entry to pent-1′-enopyranosylthazole derivatives. *Tetrahedron* **1991**, *47*, 5549−5560.

(58) Schreiner, E.; Zbiral, E. A convenient approach to 3-deoxy-D-glycero-D-galacto-nonulosonic acid (KDN), 5-Azido-5-deoxy-KDN and 5-deoxy-KDN, and their 4-methylumbelliferyl 2α-glycosides. *Liebigs Ann. Chem.* **1990**, *1990*, 581−586.

(59) Greenspoon, N.; Keinan, E. Selective deoxygenation of unsaturated carbohydrates with Pd(0)/Ph$_2$SiH$_2$/ZnCl$_2$. *J. Org. Chem.* **1988**, *53*, 3723−3731.

(60) Yin, B.-L.; Cai, C.-B.; Lai, J.-Q.; Zhang, Z.-R.; Huang, L.; Xu, L.-W.; Jiang, H.-F. Sodium borohydride-nickel chloride-methanol catalytic system for regioselective reduction of electron-rich conjugated dienes and reductive cleavage of allyl esters involving π-allylnickel intermediates. *Adv. Synth. Catal.* **2011**, *353*, 3319−3324.

(61) Several reductants were surveyed, including silanes and Lewis acid-promoted conditions. No other conditions gave the desired reduction. Inclusion of additional nickel catalyst gave the isomerized olefin and over-reduced products, which we inseparable from enol ether **9**.

(62) Other methods to construct the olefin were explored, such as a Wittig reaction, olefin metathesis, and olefin isomerization. Furthermore, constructing the C−O bond were also investigated, but no methodologies gave adequate yield of enol ether **9**.

(63) Tietze, L. F.; Meier, H.; Nutt, H. Synthesis of (±)-secologanin alucone O-ethyl ether and derivatives by tandem Knoevenagel hetero Diels-Alder reaction. *Liebig Ann. Chem.* **1990**, *1990*, 253−260.

(64) Tietze, L. F.; Meier, H.; Nutt, H. Inter- and intramolecular hetero Diels-Alder reactions, XXV. The tandem Knoevenagel hetero Diels-Alder reaction with a formylacetic acid equivalent. Synthesis of dihydropyrancarboxylates. *Chem. Ber.* **1989**, *122*, 643−650.

(65) See SI for the Diels−Alder reaction optimization details.

(66) Although we cannot rule out the formation of other possible isomers in trace quantities, based on ¹H NMR analysis of the crude reaction mixture, we estimate that any given byproduct is produced in less than 5% yield.

(67) For previous examples of glucose-directed inverse-electron demand Diels−Alder reactions see: Choudhury, A.; Franck, R. W.; Gupta, R. B. Cycloaddition of isoquinolinium salts: homochiral tetralins via dienophiles bearing chiral auxiliaries. *Tetrahedron Lett.* **1989**, *30*, 4921−4924.

(68) Normal demand Diels−Alder reactions with a glucosyl moiety are more common, see references[70−79] and: Lubineau, A.; Queneau, Y. Aqueous cycloadditions using glyco-organic substrates. 1. Stereochemical course of the reaction. *J. Org. Chem.* **1987**, *52*, 1001−1007.

(69) Larsen, D. S.; Stoodley, R. J. Asymmetric Diels−Alder reactions. Part 3. Influence of butadiene structure upon the diastereofacial reactivity of (*E*)-1-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyloxy)buta-1,3-dienes. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1841−1852.

(70) Beagley, B.; Curtis, A. D. M.; Pritchard, R. G.; Stoodley, R. J. Asymmetric Diels−Alder reactions. Part 6. Regio- and stereo-selective cycloadditions of 5-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyloxy)-1,4-naphthoquinone. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1981−1991.

(71) Larsen, D. S.; Lins, R. J.; Stoodley, R. J.; Trotter, N. S. Studies related to carba-pyranoses: a strategy for the synthesis of β-1,3-glycosidically linked aminomonocarba-disaccharides. *J. Chem. Soc. Perkin Trans. 1* **2001**, 2204−2212.

(72) Alves, M. J.; Almeida, I. G.; Fortes, A. G.; Freitas, A. P. Stereoselective cycloaddition of 1-glucosyl-1,3-butadienes with tert-butyl 2H-azirine-3-carboxylate, glyoxylates and imines. *Tetrahedron Lett.* **2003**, *44*, 6561−6565.

(73) Cousins, R. P. C.; Curtis, A. D. M.; Ding, W. C.; Stoodley, R. J. 1,5-asymmetric inductions in the reactions of 2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyloxy)benzaldehyde with Danishefsky's diene. *Tetrahedron Lett.* **1995**, *36*, 8689−8692.

(74) Pritchard, R. G.; Stoodley, R. J.; Yuen, W.-H. Studies related to carba-pyranoses: synthesis of acetylated derivatives of 4-amino-2,4-dideoxy-3-O-(β-D-glucopyranosyl)-β-L-(and β-D-) altrocarba-pyranose from a D-glucose template. *Org. Biomol. Chem.* **2005**, *3*, 162−171.

(75) Luo, S.-Y.; Jang, Y.-J.; Liu, J.-Y.; Chu, C.-S.; Liao, C.-C.; Hung, S.-C. Carbohydrate-templated asymmetric Diels−Alder reactions of masked *ortho*-benzoquinones for the synthesis of chiral bicyclo[2.2.2]-oct-5-en-2-ones. *Angew. Chem., Int. Ed.* **2008**, *47*, 8082−8085.

(76) Helliwell, M.; Phillips, I. M.; Pritchard, R. G.; Stoodley, R. J. Asymmetric synthesis of (5S)-4-deoxy-5-C-(4-nitrophenyl)-L-*threo*-pentose and (5R)-5-C-(4-nitrophenyl)-L-arabinose. *Tetrahedron Lett.* **1999**, *40*, 8651−8655.

(77) Weng, C.-H.; Hsu, D.-S.; Liao, C.-C. Application of carbohydrate-templated asymmetric Diels−Alder reaction to the syntheses of *ent*-penicillones A and B. *J. Org. Chem.* **2016**, *81*, 11421−11426.

(78) Aucagne, V.; Avera, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Rollin, P.; Tatibouet, A. Sulfenic acids in the carbohydrate field. Synthesis of transient glycosulfenic acids and their addition to unsaturated acceptors. *J. Org. Chem.* **2002**, *67*, 6925−6930.

(79) Totani, K.; Takao, K.-i.; Tadano, K.-i. Sugar as a tool for asymmetric synthesis: some effective approaches. *Synlett* **2004**, *12*, 2066−2080.

(80) Kunz, H.; Ruck, K. Carbohydrates as chiral auxiliaries in stereoselective synthesis. New synthetic methods. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 336−358.

(81) Levandowski, B. J.; Hamlin, T. A.; Helgeson, R. C.; Bickelhaupt, F. M.; Houk, K. N. Origins of the *endo* and *exo* selectivities in cyclopropenone, iminocyclopropene, and triafulvene Diels-Alder cycloadditions. *J. Org. Chem.* **2018**, *83*, 3164−3170.

(82) Houk, K. N.; Luskus, L. J. Influence of steric interactions on endo stereoselectivity. *J. Am. Chem. Soc.* **1971**, *93*, 4606−4607.

(83) McCarrick, M. A.; Wu, Y. D.; Houk, K. N. Hetero-Diels−Alder reaction transition structures: reactivity, stereoselectivity, catalysis, solvent effects, and the exo-lone-pair effect. *J. Org. Chem.* **1993**, *58*, 3330−3343.

(84) TMS replaces TBS group in our models to restrict conformational flexibility. Due to the conformational flexibility of the glycosyl enol ether dienophile, we performed extensive conformational searches using metadynamics approaches in Grimme's program CREST. More than 1700 conformations were generated for the dienophile; in order to find what proved to be the most favored chair ⁴C1 conformation of the glycosyl group, manual adjustments of the glycosyl group to the lowest energy ⁴C1 conformation were also required. Low energy conformations were reoptimized with M06-2X.

(85) Grimme, S. Exploration of chemical compound, conformer, and reaction space with meta-dynamics simulations based on tight-binding quantum chemical calculations. *J. Chem. Theory Comput.* **2019**, *15*, 2847−2862.

(86) Pracht, P.; Bohle, F.; Grimme, S. Automated exploration of the low-energy chemical space with fast quantum chemical methods. *Phys. Chem. Chem. Phys.* **2020**, *22*, 7169−7192.

(87) Biarnés, X.; Ardevol, A.; Planas, A.; Rovira, C.; Laio, A.; Parrinello, M. The conformational free energy landscape of β-D-

glucopyranose. Implications for substrate preactivation in β-glucoside hydrolases. *J. Am. Chem. Soc.* **2007**, *129*, 10686−10693.

(88) Mayes, H. B.; Broadbelt, L. J.; Beckham, G. T. How sugars pucker: electronic structure calculations map the kinetic landscape of five biologically paramount monosaccharides and their implications for enzymatic catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 1008−1022.

(89) Lemieux, R. U.; Koto, S.; Voisin, D., The Exo-Anomeric Effect. In *Anomeric Effect*; American Chemical Society: 1979; Vol. 87, pp 17−29.

(90) Owen, N. L.; Sheppard, N. Infra-red spectra and structure of methyl vinyl ether. *Trans. Faraday Soc.* **1964**, *60*, 634−645.

(91) Capon, B.; Siddhanta, A. K. Simple enols. 3. Stereochemistry of simple enols in solution. *J. Org. Chem.* **1984**, *49*, 255−257.

(92) The s-*cis* conformation of the enol ether in **9** was found to be energetically disfavorable both in the ground state and transition state, presumably due to steric repulsion of the glucosyl group.

(93) The reaction conducted in toluene provided the same dr as in HFIP. See the Supporting Information for more details.

(94) TBS group was replaced by TMS group in the orbital calculations.

(95) Grieco, P. A.; Gilman, S.; Nishizawa, M. Organoselenium chemistry. A facile one-step synthesis of alkyl aryl selenides from alcohols. *J. Org. Chem.* **1976**, *41*, 1485−1486.

(96) Kou, K. G. M.; Kulyk, S.; Marth, C. J.; Lee, J. C.; Doering, N. A.; Li, B. X.; Gallego, G. M.; Lebold, T. P.; Sarpong, R. A unifying synthesis approach to the C18-, C19-, and C20-diterpenoid alkaloids. *J. Am. Chem. Soc.* **2017**, *139*, 13882−13896.

(97) Tietze, L. F. Fragmentation of hydroxyloganin derivatives. Easy access to secologanin type compounds. *J. Am. Chem. Soc.* **1974**, *96*, 946−947.

(98) Yang, L.; Zou, H.; Zhu, H.; Ruppert, M.; Gong, J.; Stockigt, J. Improved expression of His(6)-tagged strictosidine synthase cDNA for chemo-enzymatic alkaloid diversification. *Chem. Biodiversity* **2010**, *7*, 860−870.

(99) Pfitzner, U.; Zenk, M. H. Immobilization of strictosidine synthase from Catharanthus cell cultures and preparative synthesis of strictosidine. *Planta Med.* **1982**, *46*, 10−14.

(100) Zou, H.-B.; Zhu, H.-J.; Zhang, L.; Yang, L.-Q.; Yu, Y.-P.; Stockigt, J. A facile chemoenzymatic approach: one-step syntheses of monoterpenoid indole alkaloids. *Chem. - Asian J.* **2010**, *5*, 2400−2404.

(101) Bernhardt, P.; Usera, A. R.; O'Connor, S. E. Biocatalytic asymmetric formation of tetrahydro-β-carbolines. *Tetrahedron Lett.* **2010**, *51*, 4400−4402.

(102) Pressnitz, D.; Fischereder, E.-M.; Pletz, J.; Kofler, C.; Hammerer, L.; Hiebler, K.; Lechner, H.; Richter, N.; Eger, E.; Kroutil, W. Asymmetric synthesis of (*R*)-1-alkyl-substituted tetrahydro- -carbolines catalyzed by strictosidine synthases. *Angew. Chem., Int. Ed.* **2018**, *57*, 10683−10687.

(103) Cai, Y.; Shao, N.; Xie, H.; Futamura, Y.; Panjikar, S.; Liu, H.; Zhu, H.; Osada, H.; Zou, H. Stereocomplementary chemoenzymatic Pictet−Spengler reactions for formation of rare azepino-indole frameworks: discovery of antimalarial compounds. *ACS Catal.* **2019**, *9*, 7443−7448.

(104) Standard methods were used to generate the strictosidine synthase *E. coli* expression strain. The lyophilized crude cell lysate was found to be stable for at least 6 months at 23 °C. See the Supporting Information for more details.

(105) Achenbach, H.; Benirschke, M. Confirmation of the absolute configuration of dolichantoside and isodolichantoside by synthesis from (−)-secologanin. *Phytochemistry* **1997**, *44*, 1387−1390.

(106) Most prior studies for analog synthesis have involved manipulating secologanin (**6**) or employing substituted tryptamines. For examples, see: McCoy, E.; Galan, M. C.; O'Connor, S. E. Substrate specificity of strictosidine synthase. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2475−2478.

(107) Most prior studies for analog synthesis have involved manipulating secologanin (**6**) or employing substituted tryptamines. For examples, references[108,109] and: Yerkes, N.; Wu, J. X.; McCoy, E.; Galan, M. C.; Chen, S.; O'Connor, S. E. Substrate specificity and

diastereoselectivity of strictosidine glucosidase, a key enzyme in monoterpene indole alkaloid biosynthesis. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3095−3098.

(108) Bernhardt, P.; McCoy, E.; O'Connor, S. E. Rapid identification of enzyme variants for reengineered alkaloid biosynthesis in periwinkle. *Chem. Biol.* **2007**, *14*, 888−897.

(109) Lee, H.-Y.; Yerkes, N.; O'Connor, S. E. Aza-tryptamine substrates in monoterpene indole alkaloid biosynthesis. *Chem. Biol.* **2009**, *16*, 1225−1229.

(110) Similarly, the deprotected derivative of **14** also failed to undergo the enzymatic PS reaction.

(111) Patty-Lukats, A.; Karolyhazy, L.; Szabo, L. F.; Podanyi, B. First direct and detailed stereochemical analysis of strictosidine. *J. Nat. Prod.* **1997**, *60*, 69−75.

(112) Patty-Lukats, A.; Kocsis, A.; Szabo, L. F.; Podanyi, B. Configurative correlation and conformational analysis of strictosidine and vincoside derivatives. *J. Nat. Prod.* **1999**, *62*, 1492−1499.

(113) Battersby, A. R.; Burnett, A. R.; Parsons, P. G. Alkaloid biosynthesis. Part XV. Partial synthesis and isolation of vincoside and isovincoside: biosynthesis of the three major classes of indole alkaloids from vincoside. *J. Chem. Soc. C* **1969**, 1193−1200.

(114) The C15 stereocenter is set early in the biosynthesis and is controlled by enzymes and a 5/6 fused ring system. For the full biosynthesis, see ref 33.

(115) For a review on chemical Pictet−Spengler reactions involving tryptamine derivatives, see: Royer, J.; Bonin, M.; Micouin, L. Chiral heterocycles by iminium ion cyclization. *Chem. Rev.* **2004**, *104*, 2311−2352.

(116) For a review on Pictet−Spenglerase enzymes and their applications in biocatalysis: Roddan, R.; Ward, J. M.; Keep, N. H.; Hailes, H. C. Pictet−Spenglerases in alkaloid biosynthesis: Future applications in biocatalysis. *Curr. Opin. Chem. Biol.* **2020**, *55*, 69−76.

(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.

(119) Strictosamide has recently been investigated for various biological activity. See: Candeias, M. F.; Abreu, P.; Pereira, A.; Cruz-Morais, J. Effects of strictosamide on mouse brain and kidney Na⁺, K⁺-ATPase and Mg²⁺-ATPase activities. *J. Ethnopharmacol.* **2009**, *121*, 117−122.

(120) Strictosamide has recently been investigated for various biological activity. See: Kuete, V.; Sandjo, L. P.; Mbaveng, A. R.; Seukep, J. A.; Ngadjui, B. T.; Efferth, T. Cytotoxicity of selected Cameroonian medicinal plants and Nauclea pobeguinii towards multi-factorial drug-resistant cancer cells. *BMC Complementary Altern. Med.* **2015**, *15*, 309.

(121) Strictosamide has recently been investigated for various biological activity. See: Yuce, I.; Agnaniet, H.; Morlock, G. E. New Antidiabetic and Free-Radical Scavenging Potential of Strictosamide in Sarcocephalus pobeguinii Ground Bark Extract via Effect-Directed Analysis. *ACS Omega* **2019**, *4*, 5038−5043.

(122) Silyl triflates **19** and **20** were employed in these experiments as single diastereomers.

(123) For reactions of natural products with arynes, see: Ross, S. P.; Hoye, T. R. Reactions of hexadehydro-Diels−Alder benzynes with structurally complex multifunctional natural products. *Nat. Chem.* **2017**, *9*, 523−530.