



Synthesis of a Seco iso -Secologanin Aglycone Analogue of Interest toward Secoiridoids and Monoterpene Indole Alkaloids

Hussein Abou-Hamdan, Régis Guillot, Cyrille Kouklovsky, Guillaume Vincent

► To cite this version:

Hussein Abou-Hamdan, Régis Guillot, Cyrille Kouklovsky, Guillaume Vincent. Synthesis of a Seco iso -Secologanin Aglycone Analogue of Interest toward Secoiridoids and Monoterpene Indole Alkaloids. Journal of Organic Chemistry, 2021, 86 (13), pp.9244-9252. 10.1021/acs.joc.1c00916 . hal-03286160

HAL Id: hal-03286160

<https://hal.science/hal-03286160>

Submitted on 13 Jul 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

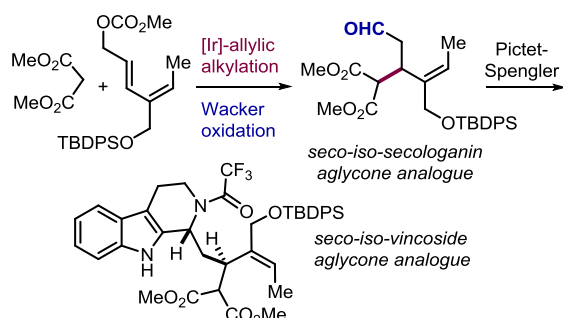
L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Synthesis of a *seco iso*-secologanin aglycone analogue of interest towards *seco*-iridoids and monoterpene indole alkaloids

Hussein Abou-Hamdan, Régis Guillot, Cyrille Kouklovsky, Guillaume Vincent*

Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO), Université Paris-Saclay, CNRS, 91405, Orsay, France
guillaume.vincent@universite-paris-saclay.fr

Supporting Information Placeholder

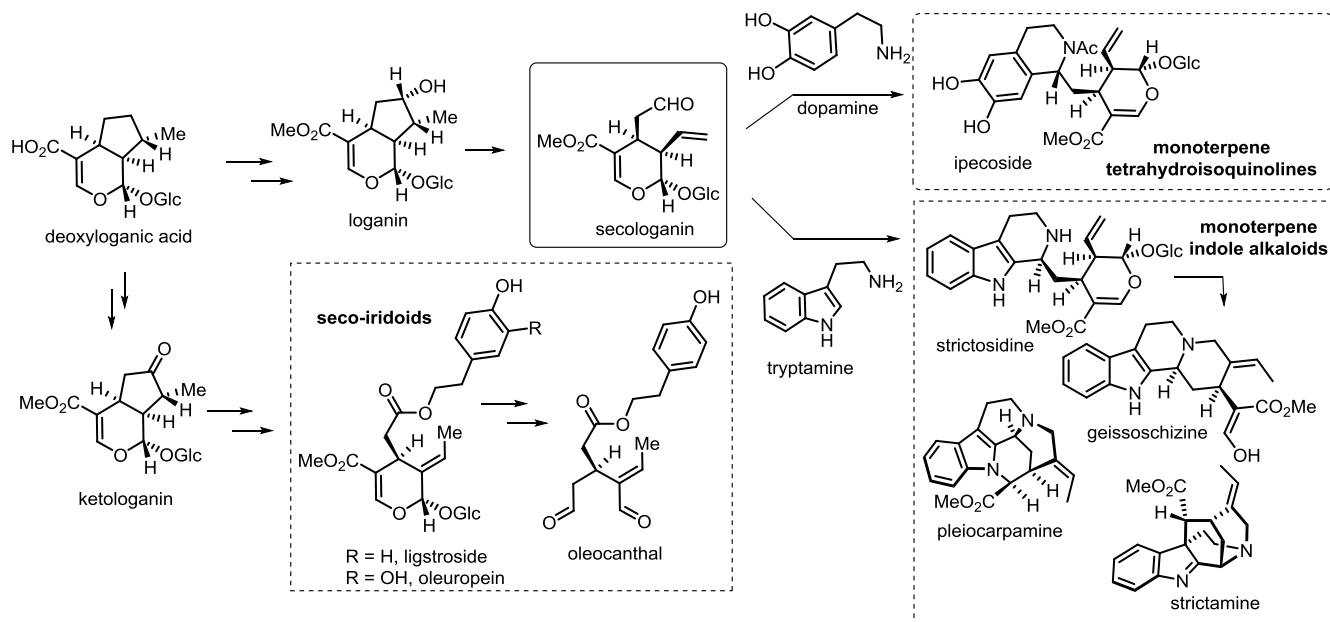


ABSTRACT: We report the access to an acyclic *iso*-secologanin aglycone analogue relevant to *seco*-iridois and monoterpene indole alkaloids. Its synthesis involved a regioselective allylic alkylation of a linear dienyln carbonate with dimethyl malonate catalyzed by an iridium complex and an anti-Markovnikov Wacker-type oxidation of the terminal alkene of the branched product obtained. The aldehyde thus formed was engaged in a Pictet-Spengler reaction with tryptamine towards monoterpene indole alkaloids.

Secologanin is a glucoside monoterpenoid¹ which is pivotal in the biosynthesis of monoterpene indole alkaloids (geissoschizine, pleiocarpamine, strictamine...)² and dopamine-derived tetrahydroisoquinolines.³ The biosynthesis of these compounds involves an enzymatic Pictet-Spengler reaction of secologanin with dopamine or tryptamine leading to

ipecoside or strictosidine respectively.^{2,3} Simple *seco*-iridoids⁴ such as oleocanthol⁵ or oleuropein⁶ are also apperanted to secologanin with a closely related biosynthesis involving the oxidative cleavage of ketologanin instead of loganin in the case of secologanin (Scheme 1).

Scheme 1. Biosynthesis of *seco*-iridoids, monoterpene tetrahydroisoquinolines and monoterpene indole alkaloids.



Indeed, the synthesis of simple seco-iridoids such as oleocanthal have been accomplished by Smith,⁷ Williams⁸ and Vidari.^{9,10} Several synthetic and hemisynthetic strategies have also been deployed to access the aglycone of secologanin by Tietze,^{11,12} Hutchinson and Partridge,¹³ Isoe,¹⁴ Chang¹⁵ or Tai.¹⁶ In 2019, Ishikawa achieved the first enantioselective total synthesis of secologanin itself via a key organocatalyzed *anti*-1,4-addition of an aldehyde onto a Michael acceptor.¹⁷ Very recently, Garg also reported the asymmetric total synthesis of secologanin via a hetero Diels-Alder cycloaddition.¹⁸

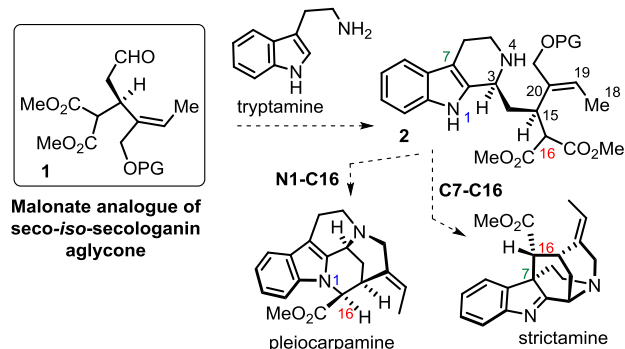
In the recent past, our group has been interested in the synthesis of monoterpene indole alkaloids such as cymoside, the mavacurane and the akuammilane sub-families.¹⁹ Noteworthy, we relied in the works of Tietze¹² and Ishikawa¹⁷ during our total syntheses of glycosidic cymoside.^{19a,b}

However, a very large number of monoterpene indole alkaloids lacks the glucose moiety due to a deglycosylation event by strictosidine glucosidase leading, via opening of the resulting hemiacetal, to a reactive dialdehyde which is subject to cyclization.² One other common features among several monoterpene indole alkaloids and simple seco-iridoids is the isomerization of the C18=C19 terminal alkene into a C19=C20 ethylidene.

We recently reported divergent Ma/Zhu oxidative cyclizations²⁰ from a truncated strictosidine model leading to the key N1-C16 bond of the mavacuranes or the C7-C16 bond of the akuammilanes.²¹ Conveniently, the C16-formyl ester was replaced by a dimethyl malonate. However, this strictosidine model, notably lacked the ethylidene part.

Therefore, the synthesis of acyclic secologanin aglycone analogue **1** would be of high interest to access seco-iridoids and monoterpene indole alkaloids in which the glucoside moiety is absent and displays an ethylidene rather than a terminal alkene (Scheme 2). In addition, the formyl ester would be replaced by a more stable malonate.²² A Pictet-Spengler reaction²³ would produce malonate analogue **2** of *seco-iso*-strictosidine aglycone as a precursor of pleiocarpamine and strictamine via our divergent oxidative cyclization strategy.²¹

Scheme 2. Synthetic plan toward pleiocarpamine and strictamine from a *seco-iso*-secologanin analogue via divergent oxidative cyclizations.



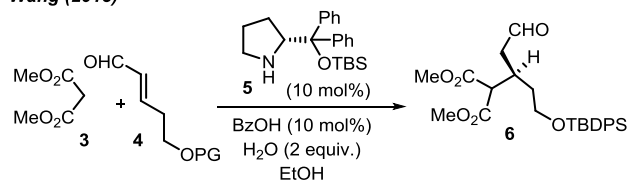
We initially planned to access this compound via the organocatalyzed 1,4-addition of dimethyl malonate **3** onto dienal **7** which contains the desired ethylidene. Following the work of Wang, this approach was successful in presence of proline-derived catalyst **5** to access analogue **6** from enal **4** in which the ethylidene part is missing (Scheme 3).²⁴

Unfortunately, despite intensive efforts, we were never able to observe the desired product of the addition of dimethyl

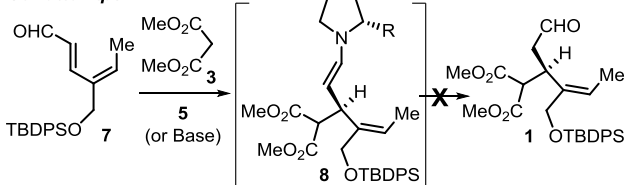
malonate **3** into dienal **7**.^{25,26} One explanation would be that the 1,4-addition to the enamine product intermediate **8** is reversible.^{27,28} Replacing the organocatalytic conditions with the use of a base (NaOMe) to deprotonate **3** also failed (Scheme 3).

Scheme 3. Failed attempts toward aldehyde **1 via 1,4-addition of dimethyl malonate onto dienal **7**.**

Wang (2013)

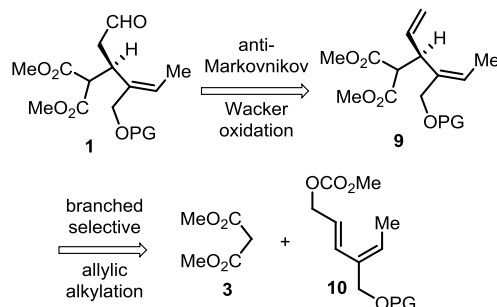


Our attempts



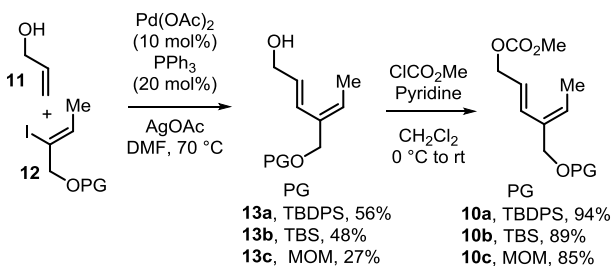
Therefore, we revised our strategy and thought that aldehyde **1** could be accessed from a regioselective anti-Markovnikov Wacker-type oxidation of terminal alkene **9**. An allylic alkylation of allylic carbonate **10** would deliver the branched-product **9** (Scheme 4).

Scheme 4. Retrosynthesis of aldehyde **1 via anti-Markovnikov Wacker-type oxidation and branched-selective allylic alkylation.**



In order to test this allylic alkylation/Wacker-type oxidation sequence, carbonates **10a-c** were prepared by the Heck reaction between vinylic iodides **12a-c** and allylic alcohols **11** followed by coupling of the obtained dienols **13a-c** with methyl chloroformate (Scheme 5).

Scheme 5. Preparation of dienyl carbonates via a Heck reaction.

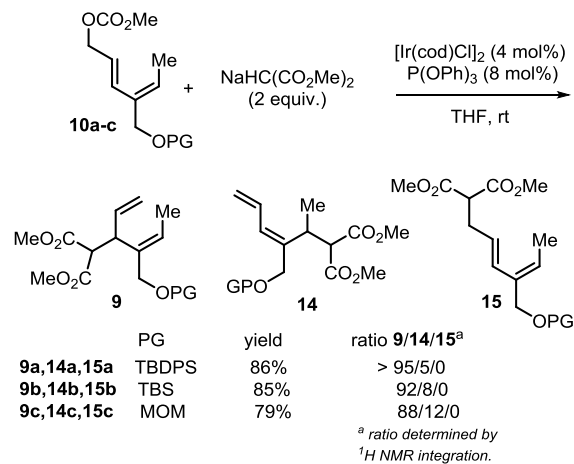


While, the palladium-catalyzed Tsuji-Trost reaction³⁰ of allylic electrophiles with one terminal substituent usually leads to the linear products, the use of other metal-complexes such as iridium or molybdenum can favor the formation the branched isomers.³¹ Indeed, the use of a dienic substrate in allylic substi-

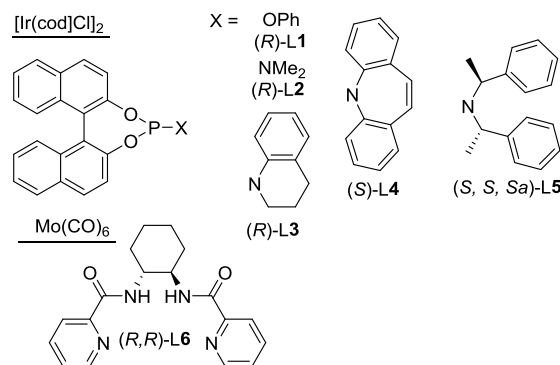
tution reactions increases the problems of regioselectivity and very few examples are described. In 1999 and 2000, Trost³² and Takeuchi³³ respectively reported highly regioselective allylic alkylation of dienyl carbonates or acetates with various nucleophiles by molybdenum or iridium complexes. In these studies, nearly perfect regioselectivities in favor of the branched products were observed. We therefore decided to apply the Takeuchi protocol with 4 mol% of [Ir(cod)Cl]₂ and 8 mol% of P(OPh)₃ in THF at room temperature to functionalized dienyl carbonates **10a-c** with sodium dimethyl malonate as nucleophile (Scheme 6). Good yields (79% to 86%) and regioselectivities for desired terminal alkenes **9a-c** were obtained. Minor amounts of regioisomers **14b,c** were observed in the cases of a TBS or MOM protecting group on the alcohol, resulting of the addition of the nucleophile to the carbon bearing the methyl group. Linear regioisomers **15a-c** were not observed in all cases. The presence of the bulkier TBDPS on the alcohol is optimal since only the desired non-conjugated divinyl compound **9a** is observed. The regioisomeric ratio seems therefore to be dependent to the size of the protecting group.

With the synthesis of racemic branched product **9a** in hand, we turned our attention toward an enantioselective version of this reaction. For this purpose, triphenyl phosphite was replaced by non-racemic chiral phosphoramidite ligands which are known to be the more efficient in Ir-catalyzed asymmetric allylic substitution reactions.³¹ Unfortunately and to our surprise, no reaction occurred with BINOL-derived phosphate **L1** or phosphoramidite ligands **L2-L5**. Despite extensive experimentations, only decarboxylation of the carbonate function was observed. The same disappointing result was observed with Mo(CO)₆ as the metal pre-catalyst and bis-pyridine **L6** as ligand.³²

Scheme 6. Regioselective allylic alkylation of dienyl carbonates with sodium dimethyl malonate.

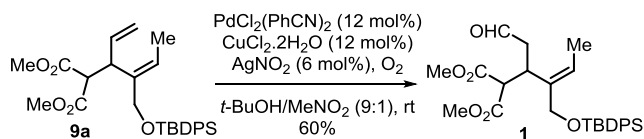


No reaction with the following combination of catalyst and chiral ligand



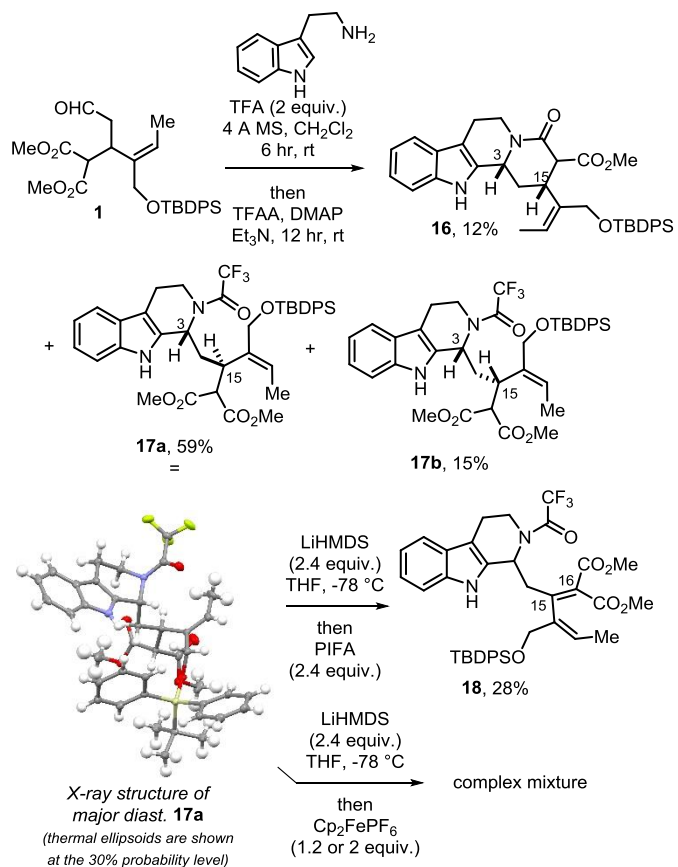
The next step of our strategy towards the seco-*iso*-secologanin aglycone target **1** involved the regioselective oxidation of the terminal alkene of **9a** into an aldehyde. Usually, the classical Wacker-type oxidations of terminal alkenes deliver the corresponding methyl ketones via a polar mechanism.³⁴ To overcome this Markonikov-type selectivity, Grubbs introduced the use of nitrite salts in *t*-butanol in order to potentially add a nitrite radical to the terminal position of the alkene.³⁵ Alternatively, the regioselectivity may be controlled by the addition of the bulky *t*-butyl alcohol to the less hindered carbon of the alkene.^{35d} Therefore, alkene **9a** was engaged with palladium dichloride bisbenzonitrile complex, copper dichloride and silver nitrite under an oxygen atmosphere in *t*-butanol to selectively deliver the desired aldehyde **1** in 60% yield (Scheme 7).

Scheme 7. Anti-Markovnikov Wacker oxidation.



With the desired seco-*iso*-secologanin aglycone analogue **1** in hand, we turned our attention to its utility in the synthesis of monoterpene indole alkaloids (Scheme 8).

Scheme 8. Pictet-Spengler reaction and attempts towards oxidative cyclizations.



To this end, we studied the Pictet-Spengler reaction of aldehyde **1** with tryptamine in order to access the corresponding seco-*iso*-strictosidine aglycone analogue **2**.²⁷ The reaction was carried out with 2 equivalents of trifluoroacetic acid (TFA) in dichloromethane. At the end of the reaction, the N4 piperidinic secondary amine was acylated with trifluoroacetic anhydride (TFAA) into seco-*iso*-secologanin aglycone analogue **17**. This one-pot protection prevents the spontaneous lactamization between the N4-secondary amine and one of the esters of the malonate of the Pictet-Spengler product leading to tetracycle **16**.^{26,36,37} This reaction gave us a mixture of two diastereoisomers **17a** and **17b** (dr 4:1) with 74% yield and lactam **16** with 12% yield. X-ray analysis of a crystal of the major diastereoisomer **17a** informed us that the relative stereochemistry does not correspond to the desired strictosidine relationship between the stereogenic centers at C3 and C15 but to the vincoside relationship.³⁸ This was confirmed by the *cis*-C3-C15 relative stereochemistry of lactam **16**.²⁶

Nevertheless, we tested the feasibility on major diastereoisomer **17a** of the divergent oxidative cyclizations developed by Ma and modified by Zhu and us (Scheme 8).^{20,21} After double deprotonation with LiHMDS, addition of PIFA as oxidant, which should lead to the formation of the N1-C16 bond of pleiocarpamine, only led to dehydrogenation of the C16-C15 bond into allylidenemalonate **18**. On the other hand, with the use of Cp_2FePF_6 as oxidant, the formation of a complex mixture was observed instead of the expected C7-C16 bond. Obviously, the presence of the ethylidene has a detrimental effect on these divergent oxidative cyclizations.

In conclusion, a racemic synthesis of seco-iridoid analogue **1** was achieved in 4 steps from known vinylic iodide **12a**. This

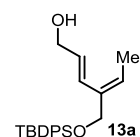
synthesis involved a Heck reaction, branched-regioselective allylic alkylation followed by an anti-Markovnikov Wacker-type oxidation of a terminal alkene **9a**. We believe that aldehyde **1** will constitute a key access to the total synthesis of seco-iridoids or monoterpene indole alkaloids natural products. For instance, a Pictet-Spengler reaction with tryptamine provides seco-*iso*-vincoside aglycone analogue **17a**.

EXPERIMENTAL SECTION

General informations. All reactions were carried out in anhydrous solvents under an inert argon atmosphere unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium-benzophenone before use. Dichloromethane (CH_2Cl_2) and toluene (PhMe) were distilled from calcium hydride before use. All others commercial reagent-grade chemicals and solvents were used directly without further treatment unless noted. All reactions sensitive to moisture or oxygen were carried out under an argon atmosphere and in flasks dried at 110 °C. Reactions were monitored with analytical thin-layer chromatography (TLC) on silica gel 60 F254 plates and visualized under UV (254 nm) and/or by staining with phosphomolybdic acid hydrate solution in Ethanol followed by heating or with KMnO_4 in a K_2CO_3 and NaOH aqueous solution. Flash chromatography was performed on silica gel 60 [63–200 μm] as stationary phase. NMR spectra were recorded on Bruker AVANCE I 300 (300 MHz for ^1H and 75 MHz for $^{13}\text{C}\{^1\text{H}\}$) and Bruker AVANCE I 360 (360 MHz for ^1H and 90 MHz for $^{13}\text{C}\{^1\text{H}\}$) at 295 K. Chemical shifts were reported in part per million relative to residual peak (CDCl_3 : ^1H δ 7.26 ppm, $^{13}\text{C}\{^1\text{H}\}$ δ 77.0 ppm). The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-Resolution mass spectra (HRMS) were measured on a Bruker Daltonics MicroTOF-Q instrument or a Thermoquest TLM LCQ Deca ion-trap spectrometer by means of Electrospray Ionization (ESI) technic, with accurate masses reported for molecular ion $[\text{M}+\text{H}]^+$ and/or $[\text{M}+\text{Na}]^+$.

Vinylic iodides **12a** and **12b** protected with TBDPS and TBS groups were prepared according to known procedures.^{26,29}

Compound **13a**:

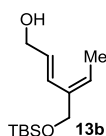


To a solution of vinyl iodide **12a** (5 g, 11.46 mmol) in DMF (72 mL), AgOAc (1.9 g, 11.46 mmol) was added at room temperature. After the flask was evacuated and refilled with argon, $\text{Pd}(\text{OAc})_2$ (257 mg, 1.15 mmol), PPh_3 (601 mg, 2.29 mmol) and allylic alcohol **11** (2.34 mL, 34.37 mmol) were added successively, and the mixture was stirred at 70 °C overnight with an oil bath. After cooling to room temperature, the reaction mixture was diluted with Et_2O (100 mL) and filtered through Celite with copious washings. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 , filtered, concentrated, and purified by column chromatography on silica gel using petroleum ether/ Et_2O (8/2) as an eluent to give **13a** (2.35 g, 56%) as a colorless oil.

R_f = 0.26 PE/ Et_2O (8/2); ^1H NMR (300 MHz, CDCl_3) δ 7.73–7.65 (4H, m), 7.48–7.34 (6H, m), 6.56 (1H, d, J = 16.2 Hz), 5.84–5.74 (2H, m), 4.33 (2H, s), 4.19 (2H, d, J = 6 Hz), 1.79 1.07 (9H, s), (3H, d, J = 7.2 Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (91 MHz,

CDCl₃) δ 135.7, 134.6, 133.8, 129.7, 127.8, 127.7, 125.8, 124.8, 65.2, 64.4, 27.0, 19.4, 13.2; HRMS (ESI-TOF) m/z [M+Na]⁺ calcd for C₂₃H₃₀NaO₂Si 389.1907, found 389.1889.

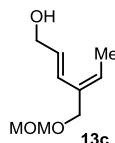
Compound 13b:



To a solution of vinyl iodide **12b** (3 g, 9.6 mmol) in DMF (60 mL), AgOAc (1.6 g, 9.6 mmol) was added at room temperature. After the flask was evacuated and refilled with argon, Pd(OAc)₂ (215 mg, 0.96 mmol), PPh₃ (504 mg, 1.92 mmol) and allylic alcohol **11** (1.9 mL, 28.8 mmol) were added successively, and the mixture was stirred at 70 °C overnight with an oil bath. After cooling to room temperature, the reaction mixture was diluted with Et₂O (100 mL) and filtered through Celite with copious washings. The organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography on silica gel using petroleum ether/Et₂O (8/2) as an eluent to give **13b** (1.10 g, 48%) as a colorless oil.

Rf = 0.30 PE/Et₂O (7/3); ¹H NMR (300 MHz, CDCl₃) δ 6.56 (1H, d, J = 16.2 Hz), 5.89-5.71 (2H, m), 4.27 (2H, s), 4.21 (2H, d, J = 6 Hz), 1.76 (3H, d, J = 7.2 Hz), 0.90 (9H, s), 0.07 (6H, s); ¹³C{¹H} NMR (91 MHz, CDCl₃) δ 134.9, 127.6, 125.8, 124.7, 64.6, 64.4, 26.1, 18.5, 13.1, -5.2; HRMS (ESI-TOF) m/z [M+Na]⁺ calcd for C₁₃H₂₆NaO₂Si 265.1594, found 265.1581.

Compound 13c:



To a solution of MOM chloride (1.53 mL, 20.2 mmol) in dry PhMe (10 mL), a solution of 2-iodo-3-methyl allylic alcohol (2 g, 10.1 mmol)^{29a} in dry PhMe (10 mL) and DIPEA (2.15 mL, 12.6 mmol) were added successively. The reaction mixture was stirred at room temperature overnight then quenched with sat. aq. NH₄Cl (10 mL). After dilution with H₂O (5 mL) and partitioning, the aqueous layer was extracted with Et₂O (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography on silica gel using petroleum ether/Et₂O (95/5) as an eluent to give vinyl iodide **12c** (1.85 g, 77%) as a colorless oil.

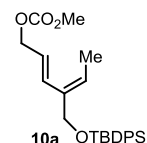
Rf = 0.45 PE/Et₂O (95/5); ¹H NMR (360 MHz, CDCl₃) δ 5.98 (1H, q, J = 6.4 Hz), 4.65 (2H, s), 4.24 (2H, m), 3.40 (3H, s), 1.80 (3H, d, J = 6.4 Hz); ¹³C{¹H} NMR (91 MHz, CDCl₃) δ 133.8, 105.0, 95.0, 75.3, 55.8, 21.7.

To a solution of vinyl iodide **12c** (1.6 g, 6.6 mmol) in DMF (41 mL), AgOAc (1.1 g, 6.6 mmol) was added at room temperature. After the flask was evacuated and refilled with argon, Pd(OAc)₂ (148 mg, 0.66 mmol), PPh₃ (346 mg, 1.32 mmol) and allylic alcohol **11** (1.35 mL, 19.8 mmol) were added successively, and the mixture was stirred at 70 °C overnight with an oil bath. After cooling to room temperature, the reaction mixture was diluted with Et₂O (50 mL) and filtered through Celite with copious washings. The organic layer was

washed with water and brine, dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography on silica gel using petroleum ether/Et₂O (6/4) as an eluent to give **13c** (310 mg, 27%) as a yellow oil.

Rf = 0.32 PE/Et₂O (4/6); ¹H NMR (360 MHz, CDCl₃) δ 6.60 (1H, d, J = 15.8 Hz), 6.00 (1H, dt, J = 15.8, 6.0 Hz), 5.75 (1H, q, J = 7.0 Hz), 4.64 (2H, s), 4.26 (2H, d, J = 5.7 Hz), 4.18 (2H, s), 3.38 (3H, s), 1.79 (3H, d, J = 7.0 Hz); ¹³C{¹H} NMR (91 MHz, CDCl₃) δ 132.7, 129.2, 129.1, 125.6, 95.5, 69.7, 64.2, 55.6, 13.4; HRMS (ESI-TOF) m/z [M+Na]⁺ calcd for C₉H₁₆NaO₃ 195.0992, found 195.0982.

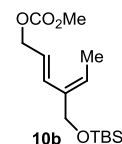
Compound 10a:



To a mixture of allylic alcohol **13a** (1.25 g, 3.4 mmol) and pyridine (2.27 mL, 28.8 mmol) in dry CH₂Cl₂ (4.8 mL) under argon, methyl chloroformate (0.6 mL, 7.84 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight then treated with 1M HCl aq. (20 mL). The mixture was extracted with Et₂O (50 mL). The organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography on silica gel using petroleum ether/Et₂O (95/5) as an eluent to give carbonate **10a** (1.36 g, 94%) as a colorless oil.

Rf = 0.40 PE/Et₂O (9/1); ¹H NMR (360 MHz, CDCl₃) δ 7.71-7.65 (4H, m), 7.46-7.35 (6H, m), 6.63 (1H, d, J = 16.0 Hz), 5.84 (1H, q, J = 7.2 Hz), 5.73 (1H, dt, J = 16.0, 6.6 Hz), 4.68 (2H, dd, J = 6.6, 0.7 Hz), 4.31 (2H, s), 3.78 (3H, s), 1.78 (3H, d, J = 7.2 Hz), 1.06 (9H, s); ¹³C{¹H} NMR (91 MHz, CDCl₃) δ 155.7, 135.7, 134.4, 133.7, 129.8, 129.4, 127.8, 126.3, 121.8, 69.2, 65.1, 54.9, 27.0, 19.4, 13.3; HRMS (ESI-TOF) m/z [M+Na]⁺ calcd for C₂₅H₃₂NaO₄Si 447.1962, found 447.1946.

Compound 10b:

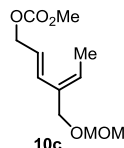


To a mixture of allylic alcohol **13b** (860 mg, 3.5 mmol) and pyridine (2.34 mL, 29.05 mmol) in dry CH₂Cl₂ (5 mL) under argon, methyl chloroformate (0.62 mL, 8.05 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight then treated with 1M HCl aq. (15 mL). The mixture was extracted with Et₂O (30 mL). The organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography on silica gel using petroleum ether/Et₂O (95/5) as an eluent to give carbonate **10b** (935 mg, 89%) as a colorless oil.

Rf = 0.55 PE/Et₂O (9/1); ¹H NMR (300 MHz, CDCl₃) δ 6.62 (1H, d, J = 16.2 Hz), 5.82-5.73 (2H, m), 4.69 (2H, d, J = 6.8 Hz), 4.25 (2H, s), 3.78 (3H, s), 1.77 (3H, d, J = 7.2 Hz), 0.90 (9H, s), 0.06 (6H, s); ¹³C{¹H} NMR (91 MHz, CDCl₃) δ 155.8, 134.7, 129.5, 126.1, 121.6, 69.3, 64.4, 54.9, 26.0, 18.5,

13.2, -5.2; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{15}H_{28}NaO_4Si$ 323.1649, found 323.1634.

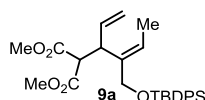
Compound 10c:



To a mixture of allylic alcohol **13c** (280 mg, 1.63 mmol) and pyridine (1.09 mL, 13.53 mmol) in dry CH_2Cl_2 (2.3 mL) under argon, methyl chloroformate (0.29 mL, 3.74 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight then treated with 1M HCl aq. (10 mL). The mixture was extracted with Et_2O (20 mL). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 , filtered, concentrated, and purified by column chromatography on silica gel using CH_2Cl_2 as an eluent to give carbonate **10c** (320 mg, 85%) as a yellow oil.

R_f = 0.75 DCM; 1H NMR (360 MHz, $CDCl_3$) δ 6.60 (1H, d, J = 15.8 Hz), 5.89 (1H, dt, J = 15.8, 6.4 Hz), 5.76 (1H, q, J = 7.2 Hz), 4.68 (2H, d, J = 6.4 Hz), 4.58 (2H, s), 4.12 (2H, s), 3.74 (3H, s), 3.33 (3H, s), 1.76 (3H, d, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (91 MHz, $CDCl_3$) δ 155.6, 132.4, 130.2, 129.0, 95.3, 69.2, 68.8, 122.9, 55.4, 54.7, 13.3; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{18}NaO_5$ 253.1046, found 253.1038.

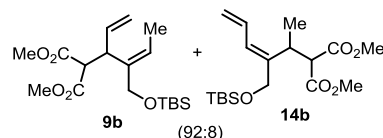
Compound 9a:



Under an argon atmosphere, a solution of $[Ir(cod)Cl]_2$ (85 mg, 0.127 mmol) and $P(OPh)_3$ (66.7 μ L, 0.25 mmol) in dry THF (6.7 mL) was stirred at room temperature for 5 min then a solution of carbonate **10a** (1.35 g, 3.18 mmol) in dry THF (6.7 mL) was added. In a separate flask, dimethyl malonate (0.73 mL, 6.36 mmol) was added to a slurry of sodium hydride (254 mg, 6.36 mmol) in dry THF (13.5 mL). The resulting solution was added to the former by syringe after 5 min and the combined mixture was stirred at room temperature for 24 h. After carbonate **10a** was consumed, Et_2O and water were added to the mixture, and the aqueous layer was extracted with Et_2O (50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated, and purified by column chromatography on silica gel using petroleum ether/ Et_2O (9/1) as an eluent to give alkene **9a** (1.31 g, 86%) as a colorless oil.

R_f = 0.30 PE/ Et_2O (9/1); 1H NMR (360 MHz, $CDCl_3$) δ 7.72-7.64 (4H, m), 7.46-7.34 (6H, m), 5.89-5.79 (1H, m), 5.66 (1H, q, J = 7.0 Hz), 5.08 (1H, dd, J = 16.7, 1.2 Hz), 5.01 (1H, dd, J = 10.4, 0.9 Hz), 4.12 (1H, dt, J = 12.9, 1.2 Hz), 4.04 (1H, dt, J = 12.9, 1.2 Hz), 4.01-3.98 (2H, m), 3.70 (3H, s), 3.61 (3H, s), 1.74 (3H, dt, J = 7.0, 1.2 Hz), 1.06 (9H, s); $^{13}C\{^1H\}$ NMR (91 MHz, $CDCl_3$) δ 168.8, 168.3, 136.2, 136.0, 135.7, 133.5, 129.8, 127.8, 124.5, 116.5, 66.3, 54.5, 52.5, 52.4, 43.8, 26.9, 19.3, 13.4; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{28}H_{36}NaO_5Si$ 503.2224, found 503.2199.

Compounds 9b and 14b:



Under an argon atmosphere, a solution of $[Ir(cod)Cl]_2$ (8.9 mg, 0.013 mmol) and $P(OPh)_3$ (7.0 μ L, 0.027 mmol) in dry THF (0.6 mL) was stirred at room temperature for 5 min then a solution of carbonate **10b** (100 mg, 0.33 mmol) in dry THF (0.6 mL) was added. In a separate flask, dimethyl malonate (76.4 μ L, 0.66 mmol) was added to a slurry of sodium hydride (27 mg, 0.66 mmol) in dry THF (1.2 mL). The resulting solution was added to the former by syringe after 5 min and the combined mixture was stirred at room temperature for 24 h. After carbonate **10b** was consumed, Et_2O and water were added to the mixture, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated, and purified by column chromatography on silica gel using petroleum ether/ Et_2O (9/1) as an eluent to give an inseparable mixture (92/8) of regioisomeric alkenes **9b** and **14b** (101 mg, 85%) as a colorless oil.

R_f = 0.35 PE/ Et_2O (9/1); HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{18}H_{32}NaO_5Si$ 379.1911, found 379.1895.

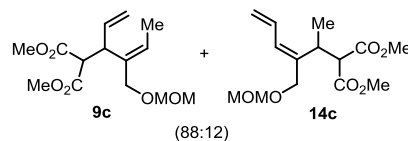
NMR data for **9b** (major regioisomer):

1H NMR (360 MHz, $CDCl_3$) δ 5.87-5.77 (1H, m), 5.61 (1H, q, J = 6.8 Hz), 5.07 (1H, dd, J = 17.7, 1.4 Hz), 5.01 (1H, dd, J = 10.0, 1.4 Hz), 4.09 (1H, dt, J = 12.7, 1.4 Hz), 4.00 (1H, dt, J = 13.2, 0.9 Hz), 3.96-3.93 (2H, m), 3.69 (3H, s), 3.65 (3H, s), 1.71 (3H, dt, J = 6.8, 1.4 Hz), 0.89 (9H, s), 0.04 (6H, s); $^{13}C\{^1H\}$ NMR (90.5 MHz, $CDCl_3$) δ 168.8, 168.3, 136.4, 136.3, 123.9, 116.4, 65.5, 54.4, 52.5, 52.5, 43.7, 26.0, 18.5, -13.3, 5.4;

NMR data for **14b** (minor regioisomer):

1H NMR (360 MHz, $CDCl_3$) δ 6.62-6.51 (1H, m), 5.93 (1H, d, J = 11.1 Hz), 5.18 (1H, dd, J = 16.6, 1.5 Hz), 5.07 (1H, dd, J = 10.5, 1.6 Hz), 4.40 (1H, d, J = 12.2 Hz), 4.22 (1H, d, J = 12.1 Hz), 3.71 (3H, s), 3.55 (3H, s), 3.48-3.44 (1H, m), 3.17-3.09 (1H, m), 1.14 (3H, d, J = 6.8 Hz), 0.89 (9H, s), 0.09 (s, 3H), 0.07 (s, 3H).

Compounds 9c and 14c:



Under an argon atmosphere, a solution of $[Ir(cod)Cl]_2$ (11.7 mg, 0.017 mmol) and $P(OPh)_3$ (9.0 μ L, 0.035 mmol) in dry THF (0.9 mL) was stirred at room temperature for 5 min then a solution of carbonate **10c** (100 mg, 0.43 mmol) in dry THF (0.9 mL) was added. In a separate flask, dimethyl malonate (99.7 μ L, 0.87 mmol) was added to a slurry of sodium hydride (35 mg, 0.87 mmol) in dry THF (1.8 mL). The resulting solution was added to the former by syringe after 5 min and the combined mixture was stirred at room temperature for 24 h. After carbonate **10c** was consumed, Et_2O and water were added to the mixture, and the aqueous layer was extracted with Et_2O (15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, concentrated, and purified by column chromatography on silica gel using

petroleum ether/EtOAc (9/1) as an eluent to give an inseparable mixture (88/12) of regioisomeric alkenes **9c** and **14c** (98 mg, 79%) as a colorless oil.

R_f = 0.32 PE/EtOAc (9/1); HRMS (ESI-TOF) m/z [M+Na]⁺ calcd for C₁₄H₂₂NaO₆ 309.1309, found 309.1306.

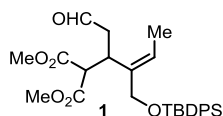
NMR data for **9c** (major regioisomer):

¹H NMR (300 MHz, CDCl₃) δ 5.82-5.72 (1H, m); 5.68 (1H, q, *J* = 7.0 Hz), 5.08 (1H, dt, *J* = 17.0, 1.5 Hz), 5.03 (1H, d, *J* = 10.2 Hz), 4.56-4.49 (2H, m), 4.06-3.90 (3H, m), 3.85 (1H, d, *J* = 11.7 Hz), 3.69 (3H, s), 3.65 (3H, s), 3.34 (3H, s), 1.74 (3H, d, *J* = 7.0 Hz); ¹³C{¹H} NMR (75.4 MHz, CDCl₃) δ 168.7, 168.2, 135.9, 133.7, 128.4, 116.6, 95.2, 69.5, 55.5, 54.5, 52.6, 52.5, 43.6, 13.4.

NMR data for **14c** (minor regioisomer):

¹H NMR (300 MHz, CDCl₃) δ 6.61 (1H, ddd, *J* = 16.6, 10.9, 10.5 Hz), 6.09 (1H, d, *J* = 10.9 Hz), 5.23 (1H, dd, *J* = 16.6, 1.5 Hz), 5.14 (1H, dd, *J* = 10.5, 1.9 Hz), 4.57 (2H, s), 4.23 (1H, d, *J* = 11.7 Hz), 4.11 (1H, d, *J* = 11.7 Hz), 3.71 (3H, s), 3.63 (3H, s), 3.59 (1H, d, *J* = 10.5 Hz), 3.37 (3H, s), 3.15-3.05 (1H, m), 1.13 (3H, d, *J* = 7.2 Hz).

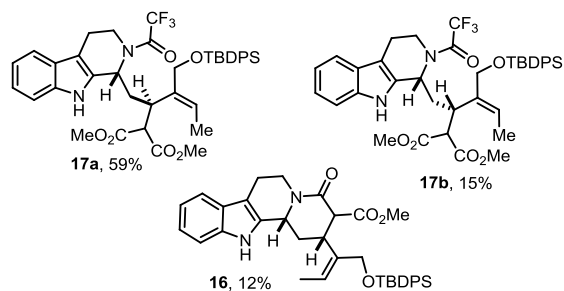
Compound 1:



To a flame-dried 100 mL round-bottom flask with a magnetic stir bar were added bis(benzonitrile)palladium(II) chloride (172 mg, 0.45 mmol), copper(II) chloride dihydrate (77 mg, 0.45 mmol), and silver nitrite (34 mg, 0.22 mmol). The flask was capped with a rubber septum, and *t*BuOH (67 mL) and MeNO₂ (3.5 mL) were added sequentially by syringe. The mixture was stirred at 23 °C and sparged with oxygen gas (balloon) for 10 minutes. A solution of alkene **9a** (1.8 g, 3.74 mmol) in MeNO₂ (3.5 mL) was added dropwise by syringe, and the reaction mixture was sparged with oxygen for another 5 minutes. The reaction was stirred under oxygen atmosphere at 23 °C for 16 h, at which time another portion of the catalyst system (86 mg Pd, 39 mg Cu, 17 mg Ag) was added to the reaction mixture. After 24 h, the reaction mixture was diluted with water (4 mL) and extracted with CH₂Cl₂ (3 x 100 mL). The organic extracts were dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography on silica gel using petroleum ether/Et₂O (9/1) as an eluent to give aldehyde **1** (1.11 g, 60%) as a colorless oil.

R_f = 0.25 PE/Et₂O (9/1); ¹H NMR (360 MHz, CDCl₃) δ 9.60 (1H, t, *J* = 1.5 Hz), 7.71-7.62 (4H, m), 7.48-7.35 (6H, m), 5.63 (1H, q, *J* = 7.0 Hz), 4.06 (2H, s), 4.03-3.95 (1H, m), 3.80 (1H, d, *J* = 11.4 Hz), 3.72 (3H, s), 3.60 (3H, s), 2.73 (1H, ddd, *J* = 16.8, 9.5, 2.3 Hz), 2.58 (1H, ddd, *J* = 16.8, 5.0, 1.4 Hz), 1.74 (3H, d, *J* = 7.0 Hz), 1.04 (9H, s); ¹³C{¹H} NMR (91 MHz, CDCl₃) δ 200.6, 168.8, 168.1, 135.7, 135.4, 133.2, 129.9, 127.9, 127.0, 66.4, 54.9, 52.9, 52.5, 45.2, 33.3, 26.9, 19.2, 13.6; HRMS (ESI-TOF) m/z [M+H]⁺ calcd for C₂₈H₃₇O₆Si 497.2354, found 497.2341 & m/z [M+MeOH+Na]⁺ calcd for C₂₉H₄₀NaO₇Si 551.2436, found 551.2408.

Compounds 16 and 17a,b:



To a solution of tryptamine (73 mg, 0.458 mmol), aldehyde **1** (250 mg, 0.503 mmol) and MS 4Å (681 mg) in CH₂Cl₂ (8.8 mL) under argon, TFA (70 μL, 0.916 mmol) was added slowly at 0 °C. The mixture was stirred at room temperature for 6 h. At 0 °C, TFAA (0.13 mL, 0.916 mmol), Et₃N (0.64 mL, 4.58 mmol) and DMAP (5.6 mg, 10 mol%) were added successively. The reaction mixture was then stirred at room temperature overnight before to be filtered through Celite (CH₂Cl₂ rinse). The mixture was quenched with sat. aq. NH₄Cl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The organic extracts were dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography on silica gel using petroleum ether/EtOAc (95:5 to 80:20) to yield **17a** (200 mg, 59%) as a white solid, **17b** (50 mg, 15%) as a light-yellow foam and **16** (35 mg, 12%) as a light-yellow foam.

Few crystals of **17a** were formed upon slow evaporation (overnight) in air of a CH₂Cl₂/acetone solution of **17a**.

Data for **17a** (major diastereoisomer):

R_f = 0.30 PE/EtOAc (9/1); NMRs show a 9:1 mixture of rotamers, only the major one is described. ¹H NMR (300 MHz, CDCl₃) δ 7.83-7.74 (4H, m), 7.52-7.36 (7H, m), 7.22 (1H, br), 7.15-7.02 (3H, m), 5.88 (1H, q, *J* = 6.8 Hz), 5.57 (1H, t, *J* = 7.2 Hz), 4.28 (2H, s), 4.24 (1H, dd, *J* = 15.4, 4.9 Hz), 3.73 (3H, s), 3.72-3.58 (6H, m), 2.99-2.75 (2H, m), 2.08-2.06 (2H, m), 1.61 (3H, d, *J* = 6.8 Hz), 1.12 (9H, s); ¹⁹F NMR (235 MHz, CDCl₃) δ -68.8; ¹³C{¹H} NMR (91 MHz, CDCl₃) δ 169.5, 168.2, 156.6 (q, *J* = 35.2 Hz), 135.9, 135.8, 134.3, 133.6, 133.5, 132.8, 130.2, 129.0, 128.2, 126.4, 122.2, 119.8, 118.1, 116.7 (q, *J* = 289 Hz), 111.2, 107.0, 66.2, 55.8, 53.0, 52.5, 48.8, 39.7, 36.1, 35.1, 27.2, 22.5, 19.5, 13.7; HRMS (ESI-TOF) m/z [M+Na]⁺ calcd for C₄₀H₄₅F₃N₂NaO₆Si 757.2891, found 757.2878.

Data for **17b** (minor diastereoisomer):

R_f = 0.41 PE/EtOAc (8/2); ¹H NMR (300 MHz, CDCl₃) δ 8.37 (1H, br), 7.75-7.66 (4H, m), 7.47-7.33 (7H, m), 7.32 (1H, d, *J* = 8.2 Hz), 7.19 (1H, dt, *J* = 9.1, 0.9 Hz), 7.12 (1H, dt, *J* = 6.8, 0.9 Hz), 5.70 (1H, q, *J* = 7.1 Hz), 5.60 (1H, t, *J* = 6.4 Hz), 4.23-4.13 (2H, m), 4.06 (1H, dd, *J* = 15.1, 4.5 Hz), 3.85 (1H, d, *J* = 10.9 Hz), 3.74 (3H, s), 3.64-3.68 (1H, m), 3.62 (3H, s), 3.46-3.36 (1H, m), 2.93-2.73 (2H, m), 2.20-2.15 (2H, m), 1.65 (3H, d, *J* = 7.1 Hz), 1.08 (9H, s); ¹⁹F NMR (235 MHz, CDCl₃) δ -69.0; ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 169.7, 168.4, 156.6 (q, *J* = 34.5 Hz), 136.4, 136.3, 135.8, 135.7, 133.2, 133.0, 132.1, 129.9, 127.9, 126.4, 122.3, 119.8, 118.2, 116.6 (q, *J* = 287 Hz), 111.3, 107.6, 66.3, 55.9, 52.9, 52.4, 50.6, 40.7, 36.2, 35.9, 27.0, 22.4, 19.3, 13.6; HRMS (ESI-TOF) m/z [M+H]⁺ calcd for C₄₀H₄₆F₃N₂O₆Si 735.3072 found 735.3049 &

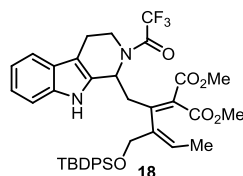
$[M+Na]^+$ calcd for $C_{40}H_{45}F_3N_2NaO_6Si$ 757.2891, found 757.2864.

Data for **16**:

Rf = 0.47 PE/EtOAc (7/3); 1H NMR (300 MHz, $CDCl_3$) δ 7.76 (1H, br), 7.66–7.62 (2H, m), 7.60–7.56 (2H, m), 7.51 (1H, d, J = 7.5 Hz), 7.44–7.23 (7H, m), 7.20 (1H, dt, J = 8.3, 1.5 Hz), 7.14 (1H, dt, J = 7.2, 1.1 Hz), 5.65 (1H, q, J = 7.2 Hz), 5.15–5.10 (1H, m), 4.86 (1H, dd, J = 11.3, 4.1 Hz), 4.17–4.13 (2H, m), 3.71–3.63 (4H, m), 3.56 (1H, dt, J = 12.4, 2.6 Hz), 2.93–2.74 (3H, m), 2.27 (1H, ddd, J = 13.2, 4.1, 2.3 Hz), 1.94 (1H, q, J = 12.1 Hz), 1.70 (3H, d, J = 7.2 Hz), 1.01 (9H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.9, 165.6, 136.4, 136.2, 135.8, 135.7, 133.4, 133.2, 132.6, 129.8, 127.9, 127.8, 126.8, 125.6, 122.4, 120.0, 118.5, 111.1, 109.5, 65.9, 53.9, 53.6, 52.4, 40.3, 34.7, 33.3, 27.0, 21.0, 19.3, 13.3; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{37}H_{43}N_2O_4Si$ 607.2987, found 607.2958 & m/z $[M+Na]^+$ calcd for $C_{37}H_{42}N_2NaO_4Si$ 629.2806, found 629.2775.

Spectral data of **16** were consistent with those previously reported.²⁶

Compound 18:



To a solution of **17a** (60 mg, 0.082 mmol) in THF (0.8 mL) at $-78^\circ C$ was added LiHMDS (196 μL , 1.0 M in THF, 0.196 mmol) dropwise. After 30 min at $-78^\circ C$, a solution of PIFA (84 mg, 0.196 mmol) in THF (0.4 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature, stirred for 30 min and quenched with H_2O (5 mL). The aqueous layer was diluted with sat brine (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with sat brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by preparative TLC (petroleum ether/Et₂O 8:2) to yield **18** (17 mg, 28%) as a white foam.

Rf = 0.35 PE/Et₂O (8/2); 1H NMR (300 MHz, $CDCl_3$) δ 7.72–7.52 (4H, m), 7.52–7.46 (1H, m), 7.43–7.22 (7H, m), 7.20–7.12 (2H, m), 5.97 (1H, q, J = 7.0 Hz), 5.45 (1H, d, J = 7.9 Hz), 4.29–4.06 (3H, m), 3.70 (3H, s), 3.48 (3H, s), 3.26 (1H, t, J = 10.9 Hz), 2.93 (1H, d, J = 15.1 Hz), 2.84–2.76 (1H, m), 2.64–2.58 (1H, m), 2.34–2.27 (1H, m), 1.66 (3H, d, J = 7.0 Hz), 1.03 (9H, s); ^{19}F NMR (235 MHz, $CDCl_3$) δ -69.5; $^{13}C\{^1H\}$ NMR (91 MHz, $CDCl_3$) δ 167.6, 167.3, 156.6 (q, J = 33.9 Hz), 138.8, 136.7, 135.7, 135.7, 133.4, 132.6, 129.7, 128.6, 127.8, 122.2, 121.2, 118.1, 114.9, 111.2, 71.7, 52.9, 52.9, 48.8, 43.3, 40.8, 28.8, 26.9, 22.9, 19.4; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{40}H_{44}F_3N_2O_6Si$ 733.2915 found 733.2894 & $[M+Na]^+$ calcd for $C_{40}H_{43}F_3N_2NaO_6Si$ 755.2735, found 755.2711.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

* guillaume.vincent@universite-paris-saclay.fr

Author Contributions

All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

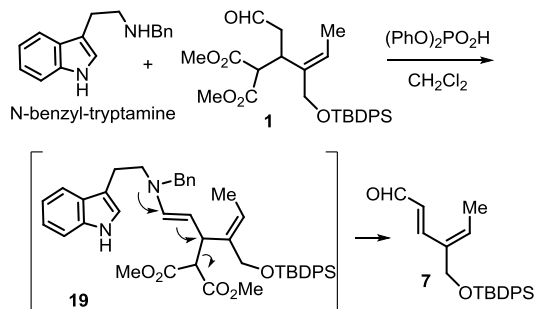
We gratefully acknowledge the ANR (ANR-15-CE29-0001“Mount Indole” and ANR-17-CE07-0050“ArDCo”), the Université Paris-Saclay, and the CNRS for financial support. We thank Maxime Jarret for preliminary studies on the 1,4-addition of malonate **3** onto dienal **6**.

REFERENCES

- 1) a) Tietze, L.-F. Secologanin, a Biogenetic Key Compound—Synthesis and Biogenesis of the Iridoid and Secoiridoid Glycosides. *Angew. Chem. Int. Ed. Engl.* **1983**, 22 (11), 828–841. <https://doi.org/10.1002/anie.198308281>; b) Szabó, L. F. Some Aspects of the Chemistry of Secologanin. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Bioactive Natural Products; Elsevier, 2002; Vol. 26, pp 95–148. [https://doi.org/10.1016/S1572-5995\(02\)80006-0](https://doi.org/10.1016/S1572-5995(02)80006-0).
- 2) O'Connor, S. E.; Maresh, J. J. Chemistry and Biology of Monoterpene Indole Alkaloid Biosynthesis. *Nat. Prod. Rep.* **2006**, 23 (4), 532–547. <https://doi.org/10.1039/B512615K>.
- 3) Nomura, T.; Kutchan, T. M. Is a Metabolic Enzyme Complex Involved in the Efficient and Accurate Control of Ipecac Alkaloid Biosynthesis in Psychotria Ipecacuanha? *Plant Signal. Behav.* **2010**, 5 (7), 875–877. <https://doi.org/10.4161/psb.5.7.11901>.
- 4) a) Obied, H. K.; Prenzler, P. D.; Ryan, D.; Servili, M.; Taticchi, A.; Esposto, S.; Robards, K. Biosynthesis and Biotransformations of Phenol-Conjugated Oleosidic Secoiridoids from Olea Europaea L. *Nat. Prod. Rep.* **2008**, 25 (6), 1167–1179. <https://doi.org/10.1039/B719736E>; b) Rodríguez- López, C. E.; Hong, B.; Paetz, C.; Nakamura, Y.; Koudounas, K.; Passeri, V.; Baldoni, L.; Alagna, F.; Calderini, O.; O'Connor, S. E. Two Bi-Functional Cytochrome P450 CYP72 Enzymes from Olive (Olea Europaea) Catalyze the Oxidative C-C Bond Cleavage in the Biosynthesis of Secoxy-Iridoids – Flavor and Quality Determinants in Olive Oil. *New Phytol.* **2021**, 229 (4), 2288–2301. <https://doi.org/10.1111/nph.16975>.
- 5) Scotece, M.; Conde, J.; Abella, V.; Lopez, V.; Pino, J.; Lago, F.; Smith, A. B.; Gómez-Reino, J. J.; Gualillo, O. New Drugs from Ancient Natural Foods. Oleocanthal, the Natural Occurring Spicy Compound of Olive Oil: A Brief History. *Drug Discov. Today* **2015**, 20 (4), 406–410. <https://doi.org/10.1016/j.drudis.2014.10.017>.
- 6) Cavaca, L. A. S.; Afonso, C. A. M. Oleuropein: A Valuable Bio-Renewable Synthetic Building Block. *Eur. J. Org. Chem.* **2018** (5), 581–589. <https://doi.org/10.1002/ejoc.201701136>.
- 7) a) Smith, A. B.; Han, Q.; Breslin, P. A. S.; Beauchamp, G. K. Synthesis and Assignment of Absolute Configuration of (–)-Oleocanthal: A Potent, Naturally Occurring Non-Steroidal Anti-Inflammatory and Anti-Oxidant Agent Derived from Extra Virgin Olive Oils. *Org. Lett.* **2005**, 7 (22), 5075–5078. <https://doi.org/10.1021/ol052106a>; b) Smith, A. B.; Sperry, J. B.; Han, Q. Syntheses of (–)-Oleocanthal, a Natural NSAID Found in Extra Virgin Olive Oil, the (–)-Deacetoxy-Oleuropein Aglycone, and Related Analogues. *J. Org. Chem.* **2007**, 72 (18), 6891–6900. <https://doi.org/10.1021/jo071146k>.
- 8) English, B. J.; Williams, R. M. Synthesis of (±)-Oleocanthal via a Tandem Intramolecular Michael Cyclization–HWE

- Olefination. *Tetrahedron Lett.* **2009**, 50 (23), 2713–2715. <https://doi.org/10.1016/j.tetlet.2009.03.145>.
- 9) Valli, M.; Peviani, E. G.; Porta, A.; D'Alfonso, A.; Zaroni, G.; Vidari, G. A Concise and Efficient Total Synthesis of Oleocanthal. *Eur. J. Org. Chem.* **2013**, (20), 4332–4336. <https://doi.org/10.1002/ejoc.201300324>;
 - 10) Formal synthesis of oleocanthal: a) Souza, D. M.; Machado, L. L.; Machado, A. H. L. First Total Synthesis of (±)-Floribundane B: An Approach Based on Johnson–Claisen Rearrangement of a Morita–Baylis–Hillman Adduct. *Tetrahedron Lett.* **2019**, 60 (28), 1811–1813. <https://doi.org/10.1016/j.tetlet.2019.05.067>; b) Takahashi, K.; Morita, H.; Honda, T. Formal Synthesis of (–)-Oleocanthal by Means of a SmI₂-Promoted Intramolecular Coupling of Bromoalkyne with α,β-Unsaturated Ester. *Tetrahedron Lett.* **2012**, 53 (26), 3342–3345. <https://doi.org/10.1016/j.tetlet.2012.04.085>; semisynthesis of oleocanthal: c) Sarikaki, G.; Christoforidou, N.; Gaboriaud-Kolar, N.; Smith, A. B.; Kostakis, I. K.; Skaltsounis, A.-L. Biomimetic Synthesis of Oleocanthal, Oleacein, and Their Analogues Starting from Oleuropein, A Major Compound of Olive Leaves. *J. Nat. Prod.* **2020**, 83 (6), 1735–1739. <https://doi.org/10.1021/acs.jnatprod.0c00086>; semisynthesis of oleuropein: d) Bianco, A.; Naccarato, G.; Passacantilli, P.; Righi, G.; Scarpati, M. L. Partial Synthesis of Oleuropein. *J. Nat. Prod.* **1992**, 55 (6), 760–766. <https://doi.org/10.1021/np50084a009>.
 - 11) Tietze, L. F. Fragmentation of Hydroxyloganin Derivatives. Easy Access to Secologanin Type Compounds. *J. Am. Chem. Soc.* **1974**, 96 (3), 946–947. <https://doi.org/10.1021/ja00810a067>.
 - 12) Tietze, L. F.; Meier, H.; Nutt, H. Inter- and Intramolecular Hetero Diels–Alder Reactions, 28. Synthesis of (±)-Secologanin Aglucone O-Ethyl Ether and Derivatives by Tandem Knoevenagel Hetero Diels–Alder Reaction. *Liebigs Ann. Chem.* **1990**, (3), 253–260. <https://doi.org/10.1002/jlac.199019900146>.
 - 13) a) Hutchinson, C. R.; Mattes, K. C.; Nakane, M.; Partridge, J. J.; Uskoković, M. R. An Efficient Stereoselective Synthesis of (±)-Sweroside and (±)-Secologanin Aglucone O-Methyl Ethers. Preliminary Communication. *Helv. Chim. Acta* **1978**, 61 (4), 1221–1225. <https://doi.org/10.1002/hlca.19780610403>; b) Nakane, M.; Hutchinson, C. R. Stereoselective Synthesis of (+)-1-O-Methylloganin, 10-Hydroxyloganin, Secologanin, and Sweroside Aglucons from a Common 1-Hydroxy-4a,5,8,8a-Tetrahydroisochromene Synthon. *J. Org. Chem.* **1980**, 45 (21), 4233–4236. <https://doi.org/10.1021/jo01309a037>.
 - 14) 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 (47), 5865–5868. [https://doi.org/10.1016/S0040-4039\(01\)81075-3](https://doi.org/10.1016/S0040-4039(01)81075-3).
 - 15) Chang, N. C.; Day, H. M.; Lu, W. F. Total Synthesis of (+)-Dimethyl Secologanoside O-Methyl Ether. *J. Org. Chem.* **1989**, 54 (17), 4083–4088. <https://doi.org/10.1021/jo00278a019>.
 - 16) Tai, H.-M.; Huang, M.-H.; Yang, C.-C. Formal Total Synthesis of (±)-Dimethyl Secologanoside. *J. Chin. Chem. Soc.* **2003**, 50 (3A), 441–444. <https://doi.org/10.1002/jccs.200300069>.
 - 17) Rakumitsu, K.; Sakamoto, J.; Ishikawa, H. Total Syntheses of (–)-Secologanin, (–)-5-Carboxystrictosidine, and (–)-Rubenine. *Chem. – Eur. J.* **2019**, 25 (38), 8996–9000. <https://doi.org/10.1002/chem.201902073>.
 - 18) Anthony, S. M.; Tona, V.; Zou, Y.; Morrill, L. A.; Billingsley, J. M.; Lim, M.; Tang, Y.; Houk, K. N.; Garg, N. K. Total Synthesis of (–)-Strictosidine and Interception of Aryne Natural Product Derivatives “Strictosidine” and “Strictosamidyne.” *J. Am. Chem. Soc.* **2021**. <https://doi.org/10.1021/jacs.1c02004>.
 - 19) a) 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 (4), 1527–1531. <https://doi.org/10.1002/anie.201912812>; b) 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**, n/a (n/a). <https://doi.org/10.1002/chem.202003758>; c) Jarret, M.; Tap, A.; Kouklovsky, C.; Poupon, E.; Evanno, L.; Vincent, G. Bioinspired Oxidative Cyclization of the Geissoschizine Skeleton for the Total Synthesis of (–)-17-nor-Excelsinidine. *Angew. Chem. Int. Ed.* **2018**, 57 (38), 12294–12298. <https://doi.org/10.1002/anie.201802610>; d) 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 (29), 9861–9865. <https://doi.org/10.1002/anie.201905227>; e) Jarret, M.; Tap, A.; Turpin, V.; Denizot, N.; Kouklovsky, C.; Poupon, E.; Evanno, L.; Vincent, G. Bioinspired Divergent Oxidative Cyclizations of Geissoschizine: Total Synthesis of (–)-17-nor-Excelsinidine, (+)-16-Epi-Pleiocarpamine, (+)-16-Hydroxymethyl-Pleiocarpamine and (+)-Taberdivarine H. *Eur. J. Org. Chem.* **2020**, No. 40, 6340–6351. <https://doi.org/10.1002/ejoc.202000962>.
 - 20) a) Zi, W.; Zuo, Z.; Ma, D. Intramolecular Dearomative Oxidative Coupling of Indoles: A Unified Strategy for the Total Synthesis of Indoline Alkaloids. *Acc. Chem. Res.* **2015**, 48 (3), 702–711. <https://doi.org/10.1021/ar5004303>; b) Zi, W.; Xie, W.; Ma, D. Total Synthesis of Akummline Alkaloid (–)-Vincorine via Intramolecular Oxidative Coupling. *J. Am. Chem. Soc.* **2012**, 134 (22), 9126–9129. <https://doi.org/10.1021/ja303602f>; c) Teng, M.; Zi, W.; Ma, D. Total Synthesis of the Monoterpenoid Indole Alkaloid (±)-Aspidophylline A. *Angew. Chem. Int. Ed.* **2014**, 53 (7), 1814–1817. <https://doi.org/10.1002/anie.201310928>; d) Ren, W.; Tappin, N.; Wang, Q.; Zhu, J. Synthetic Study towards Strictamine: The Oxidative Coupling Approach. *Synlett* **2013**, 24 (15), 1941–1944. <https://doi.org/10.1055/s-0033-1339472>; e) Andres, R.; Wang, Q.; Zhu, J. Asymmetric Total Synthesis of (–)-Arborisidine and (–)-19-Epi-Arborisidine Enabled by a Catalytic Enantioselective Pictet–Spengler Reaction. *J. Am. Chem. Soc.* **2020**, 142 (33), 14276–14285. <https://doi.org/10.1021/jacs.0c05804>.
 - 21) Jarret, M.; Abou-Hamdan, H.; Kouklovsky, C.; Poupon, E.; Evanno, L.; Vincent, G. Bioinspired Early Divergent Oxidative Cyclizations toward Pleiocarpamine, Talbotine, and Strictamine. *Org. Lett.* **2021**, 23 (4), 1355–1360. <https://doi.org/10.1021/acs.orglett.1c00018>.
 - 22) For selected syntheses of related compounds: a) Brown, R. T.; Jones, M. F. Total Synthesis of a (±)-Secologanin Aglucone and (±)-Elenolide. *J. Chem. Soc. Chem. Commun.* **1986**, No. 24, 1818–1820. <https://doi.org/10.1039/C39860001818>; b) Vedachalam, S.; Murugesu, N.; Chakraborty, P.; Karvembu, R.; Liu, X.-W. NHC Catalyzed Enantioselective Coates–Claisen Rearrangement: A Rapid Access to the Dihydropyran Core for Oleuropein Based Secoiridoids. *New J. Chem.* **2018**, 42 (3), 1832–1839. <https://doi.org/10.1039/C7NJ04057A>; c) Sun, X.; Ma, D. Organocatalytic Approach for the Syntheses of Corynantheidol, Dihydrocorynantheol, Protoemetinol, Protoemetine, and Mitragynine. *Chem. – Asian J.* **2011**, 6 (8), 2158–2165. <https://doi.org/10.1002/asia.201100219>; d) Wu, S.; Zhang, Y.; Agarwal, J.; Mathieu, E.; Thorimbert, S.; Dechoux, L. Studies towards the Synthesis of Secoiridoids. *Tetrahedron* **2015**, 71 (40), 7663–7669. <https://doi.org/10.1016/j.tet.2015.07.067>.

- 23) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. The Pictet–Spengler Reaction in Nature and in Organic Chemistry. *Angew. Chem. Int. Ed.* **2011**, *50* (37), 8538–8564. <https://doi.org/10.1002/anie.201008071>.
- 24) a) Zhang, H.; Ma, X.; Kang, H.; Hong, L.; Wang, R. The Enantioselective Formal Synthesis of Rhynchophylline and Isorhynchophylline. *Chem. – Asian J.* **2013**, *8* (3), 542–545. <https://doi.org/10.1002/asia.201201046>; see also: b) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. Organocatalytic Conjugate Addition of Malonates to α,β -Unsaturated Aldehydes: Asymmetric Formal Synthesis of (–)-Paroxetine, Chiral Lactams, and Lactones. *Angew. Chem. Int. Ed.* **2006**, *45* (26), 4305–4309. <https://doi.org/10.1002/anie.200601025>; c) Ma, A.; Zhu, S.; Ma, D. Enantioselective Organocatalytic Michael Addition of Malonates to α,β -Unsaturated Aldehydes in Water. *Tetrahedron Lett.* **2008**, *49* (19), 3075–3077. <https://doi.org/10.1016/j.tetlet.2008.03.051>.
- 25) See the supporting information of: Monleón, A.; Glaus, F.; Vergura, S.; Jørgensen, K. A. Organocatalytic Strategy for the Enantioselective Cycloaddition of Trisubstituted Nitroolefins to Create Spirocyclohexene-Oxetane Scaffolds. *Angew. Chem. Int. Ed.* **2016**, *55* (7), 2478–2482. <https://doi.org/10.1002/anie.201510731>.
- 26) Li, L.; Aibibula, P.; Jia, Q.; Jia, Y. Total Syntheses of Naucleamides A–C and E, Geissoschizine, Geissoschizol, (E)-Isositsirikine, and 16-Epi-(E)-Isositsirikine. *Org. Lett.* **2017**, *19* (10), 2642–2645. <https://doi.org/10.1021/acs.orglett.7b00983>.
- 27) During our attempts toward the Pictet–Spengler reaction of N-benzyl tryptamine and aldehyde **1**, we could only observe the formation of dienal **7**, probably via elimination of dimethyl malonate from enamine intermediate **19**.



- 28) In reference 26, Jia and co-workers reported a similar organocatalyzed Michael addition onto dienal **7** by replacing dimethyl malonate **3** by the amidomalonate of tryptamine. In this case the iminium resulting from the organocatalyzed Michael addition could be readily intercepted intramolecularly by the nitrogen of the amidomalonate moiety, thus preventing the formation of the enamine and the elimination of the β -dicarbonyl nucleophile.
- 29) a) Wanner, M. J.; Boots, R. N. A.; Eradus, B.; Gelder, R. de; van Maarseveen, J. H.; Hiemstra, H. Organocatalytic Enantioselective Total Synthesis of (–)-Arborecine. *Org. Lett.* **2009**, *11* (12), 2579–2581. <https://doi.org/10.1021/ol900888e>; b) Steinborn, C.; Wildermuth, R. E.; Barber, D. M.; Magauer, T. Total Synthesis of (+)-Cornexistin. *Angew. Chem. Int. Ed.* **2020**, *59* (39), 17282–17285. <https://doi.org/10.1002/anie.202008158>.
- 30) Trost, B. M.; Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103* (8), 2921–2944. <https://doi.org/10.1021/cr020027w>.
- 31) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution

Reactions. *Chem. Rev.* **2019**, *119* (3), 1855–1969. <https://doi.org/10.1021/acs.chemrev.8b00506>.

- 32) Trost, B. M.; Hildbrand, S.; Dogra, K. Regio- and Enantioselective Molybdenum-Catalyzed Alkylations of Polyenyl Esters. *J. Am. Chem. Soc.* **1999**, *121* (44), 10416–10417. <https://doi.org/10.1021/ja992602s>.
- 33) Takeuchi, R.; Tanabe, K. Highly Regioselective Allylic Alkylation of Dienyl Acetates and Enynyl Acetates Catalyzed by an Iridium Complex. *Angew. Chem. Int. Ed.* **2000**, *39* (11), 1975–1978. [https://doi.org/10.1002/1521-3773\(20000602\)39:11<1975::AID-ANIE1975>3.0.CO;2-I](https://doi.org/10.1002/1521-3773(20000602)39:11<1975::AID-ANIE1975>3.0.CO;2-I).
- 34) Fernandes, R. A.; Jha, A. K.; Kumar, P. Recent Advances in Wacker Oxidation: From Conventional to Modern Variants and Applications. *Catal. Sci. Technol.* **2020**, *10* (22), 7448–7470. <https://doi.org/10.1039/D0CY01820A>.
- 35) a) Wickens, Z. K.; Morandi, B.; Grubbs, R. H. Aldehyde-Selective Wacker-Type Oxidation of Unbiased Alkenes Enabled by a Nitrite Co-Catalyst. *Angew. Chem. Int. Ed.* **2013**, *52* (43), 11257–11260. <https://doi.org/10.1002/anie.201306756>; b) Wickens, Z. K.; Skakuj, K.; Morandi, B.; Grubbs, R. H. Catalyst-Controlled Wacker-Type Oxidation: Facile Access to Functionalized Aldehydes. *J. Am. Chem. Soc.* **2014**, *136* (3), 890–893. <https://doi.org/10.1021/ja411749k>; for a mechanistic study: c) Jiang, Y.-Y.; Zhang, Q.; Yu, H.-Z.; Fu, Y. Mechanism of Aldehyde-Selective Wacker-Type Oxidation of Unbiased Alkenes with a Nitrite Co-Catalyst. *ACS Catal.* **2015**, *5* (3), 1414–1423. <https://doi.org/10.1021/cs5018776>; for an alternative mechanism: d) Hu, K.-F.; Ning, X.-S.; Qu, J.-P.; Kang, Y.-B. Tuning Regioselectivity of Wacker Oxidation in One Catalytic System: Small Change Makes Big Step. *J. Org. Chem.* **2018**, *83* (18), 11327–11332. <https://doi.org/10.1021/acs.joc.8b0154>.
- 36) Fang, H.; Wu, X.; Nie, L.; Dai, X.; Chen, J.; Cao, W.; Zhao, G. Diastereoselective Syntheses of Indoloquinolizidines by a Pictet–Spengler/Lactamization Cascade. *Org. Lett.* **2010**, *12* (23), 5366–5369. <https://doi.org/10.1021/ol101922h>.
- 37) The choice of the trifluoroacetyl group to protect the N4-secondary amine is due to the isolation of a mixture of N-COCF₃ and N-Ts products when we tried to do the one-pot protection of the secondary amine with TsCl or Ts₂O. In these cases, the mix anhydride TsOC(O)CF₃ is probably formed from the reaction between TFA and TsCl or Ts₂O in basic conditions. In an attempt to avoid this problem, replacing TFA by other acids, to promote the Pictet–Spengler reaction led to formation of the lactam in poor yields (diphenyl phosphoric acid, benzoic acid) or no isolation of any Pictet–Spengler product (MsOH, HCl or H₂SO₄).
- 38) CCDC deposition number: 2078456.