JOC The Journal of Organic Chemistry

Article

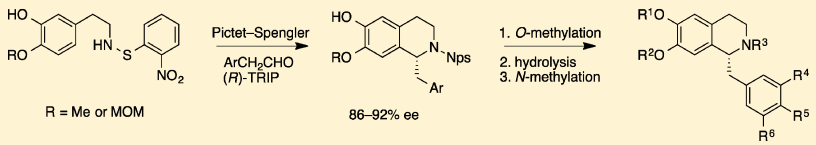
pubs.acs.org/joc

Organocatalytic Enantioselective Pictet–Spengler Approach to Biologically Relevant 1-Benzyl-1,2,3,4-Tetrahydroisoquinoline Alkaloids

Andrea Ruiz-Olalla, Martien A. Würdemann, Martin J. Wanner, Steen Ingemann, Jan H. van Maarseveen, and Henk Hiemstra*

Van 't Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands

Supporting Information



ABSTRACT: A general procedure for the synthesis of 1-benzyl-1,2,3,4-tetrahydroisoquinolines was developed, based on organocatalytic, regio- and enantioselective Pictet–Spengler reactions (86–92% ee) of *N*-(*o*-nitrophenylsulfenyl)-2-arylethylamines with arylacetaldehydes. The presence of the *o*-nitrophenylsulfenyl group, together with the MOM-protection in the catechol part of the tetrahydroisoquinoline ring system, appeared to be a productive combination. To demonstrate the versatility of this approach, 10 biologically and pharmaceutically relevant alkaloids were prepared using (*R*)-TRIP as the chiral catalyst: (*R*)-norcoclaurine, (*R*)-coclaurine, (*R*)-norreticuline, (*R*)-reticuline, (*R*)-trimemetoquinol, (*R*)-armepavine, (*R*)-norprotosinomenine, (*R*)-protosinomenine, (*R*)-laudanosine, and (*R*)-5-methoxylaudanosine.

INTRODUCTION

In biosynthesis, the Pictet–Spengler reaction between dopamine (**1**, see Scheme 1) and 4-hydroxyphenylacetaldehyde (**2**) produces norcoclaurine, a plant metabolite that stands at the basis of probably all of the approximately 2500–3000 1-benzyl-substituted tetrahydroisoquinoline-derived alkaloids known to date.[1] A broad range of biological activities is displayed by these alkaloids with morphine, isolated already in 1806, as one of the most complex and best studied examples.[1,2] A variety of synthetic and pharmacological studies on 1-benzyltetrahydroisoquinolines can be found in the literature, including receptor activity studies against, e.g., drug addiction,[3] schizophrenia,[4,5] platelet aggregation,[6] and β2 adrenoceptor stimulation.[7]

Norcoclaurine synthase (NCS) was identified as a Pictet–Spenglerase in plants, and application of this enzyme in synthesis, as well as assessment of its substrate scope *in vitro*, has been reported.[8] Several aryl-substituted acetaldehydes are accepted as substrates for NCS, although the dopamine substrate tolerates much less functionalization. The NCS enzyme invariably produces tetrahydroisoquinolines with (*S*)-configuration, which is the most common enantiomer present in plant alkaloids. However, many plant alkaloids/metabolites of the tetrahydroisoquinoline series are also found in nature as (*R*)-enantiomers, with (*R*)-reticuline and the (*R*)-configured morphine-type structures that are derived thereof as the most important examples. However, a multistep enzymatic sequence is required to convert (*S*)-reticuline into (*R*)-reticuline *in vivo*.

Therefore, to improve the synthetic accessibility of both 1-benzyltetrahydroisoquinoline enantiomers a versatile approach is desirable. Traditionally, resolution of 1-benzyltetrahydroisoquinoline racemates by cocrystallization with, e.g., tartaric acids[9] or amino acids has been applied. A recent improvement is based on an interesting monoamine oxidase-catalyzed deracemization.[10] Although many interesting asymmetric auxiliary approaches have been reported,[11] a catalytic sequence, involving the Bischler–Napieralski reaction followed by a Noyori-type reduction is most often applied.[4,12,13] This metal-catalyzed hydrogenation approach often gives high ee's, although sensitive functional groups are not always tolerated in the preceding $POCl_3$-mediated Bischler–Napieralski step.

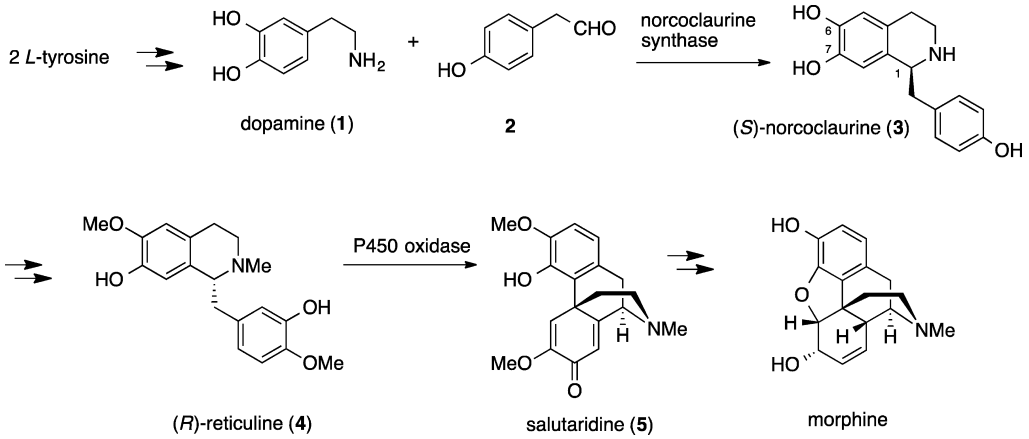
Biomimetic Pictet–Spengler-type syntheses of racemic 1-substituted tetrahydroisoquinolines have been known for a long time. The organocatalytic enantioselective version of this reaction received considerable attention for the condensation with tryptamine toward tetrahydro-β-carbolines.[4,14–16] Only recently, this organocatalytic approach was described for the enantioselective preparation of 1-alkyl and 1-aryl-substituted tetrahydroisoquinolines.[17,18] The use of phenylacetaldehydes instead of aromatic and aliphatic aldehydes is much more challenging, due to the moderate stability of these aldehydes. We have developed and report herein a general enantioselective Pictet–Spengler-based 1-benzyl-tetrahydroisoquinoline synthesis. Emphasis is put on the judicious choice of oxygen protective groups in both the aldehyde and the catechol part in order to synthesize all possible target alkaloids.

Received: March 6, 2015
Published: April 24, 2015

ACS Publications © 2015 American Chemical Society

DOI: 10.1021/acs.joc.5b00509
J. Org. Chem. 2015, 80, 5125–5132

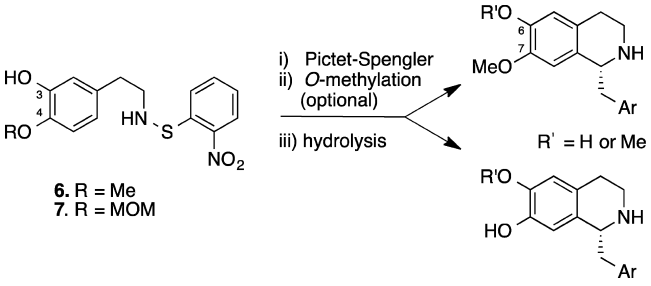
Scheme 1. Biosynthetic Pathway to 1-Benzyl-tetrahydro-isoquinolines



RESULTS AND DISCUSSION

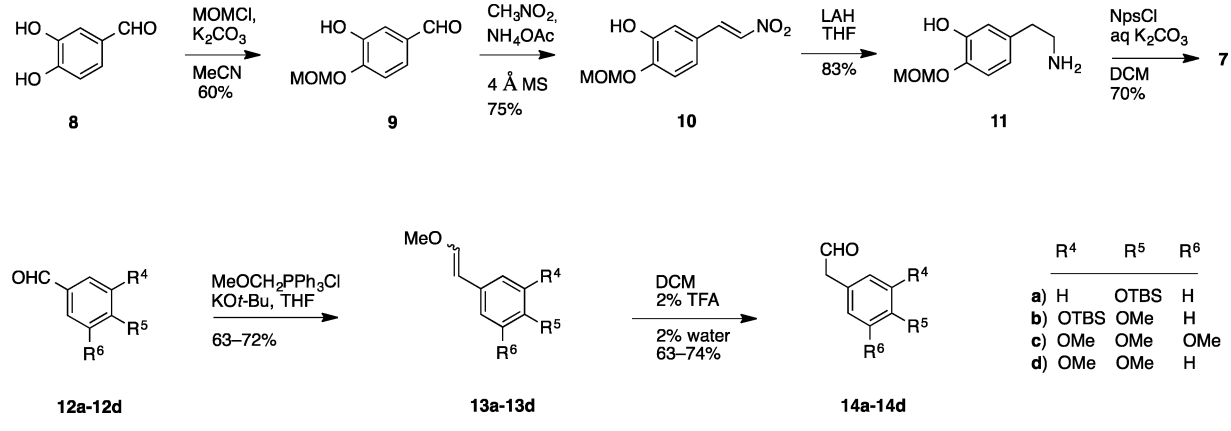
The 3-hydroxy-4-methoxyphenylethylamine derivative with an *o*-nitrophenylsulfenyl (Nps) substituent on nitrogen (**6**, Scheme 2) was previously shown to be a good substrate in (*R*)-TRIP catalyzed Pictet–Spengler reactions, leading to a series of 6-hydroxy-7-methoxy- and 6,7-dimethoxy-substituted tetrahydroisoquinolines.[17] In order to get access to all possible hydroxy/methoxy variations of the 6,7-dioxygenated 1-benzyltetrahydroisoquinolines, as in, e.g., norcoclaurine and reticuline (Scheme 1), a protecting group was introduced at the 4-hydroxyl group in the starting amine leaving the 3-hydroxyl group free, as required for Pictet–Spengler condensation (Scheme 2).

Scheme 2. Routes to Different Substitution Patterns in the Isoquinoline Ring



Initially, we attempted *O*-silyl protection for the *O*-4 position, but such phenolic silyl groups appeared to be unstable, and exchange was observed between the *O*-3 and *O*-4 positions under a variety of conditions. A MOM-substituent was expected to be more stable but still readily removed with acid, simultaneously with other protecting groups in the molecule. 3,4-Dihydroxybenzaldehyde **8** (Scheme 3) was protected at the 4-position with MOM-chloride and was then easily separated from the disubstituted product by extractive workup. Conversion of the aldehyde functionality in **9** to nitroalkene **10** under standard conditions requires ammonium acetate or acetic acid at elevated temperatures as a catalyst, but this was not compatible with the MOM-group. To improve this reaction, powdered 4 Å molecular sieves were added to remove water. This provided crystalline **10**, which was reduced with lithium aluminum hydride to arylethylamine **11** and *N*-functionalized with *o*-nitrobenzenesulfenyl chloride to give Pictet–Spengler precursor **7**. Several methods have been described for the synthesis of substituted phenylacetaldehydes, such as a Wittig reaction followed by enol ether hydrolysis, oxidation of the corresponding phenylethanol, or reduction of arylacetic acid esters. We selected the generally applicable, 2-step homologation approach starting from the readily available aromatic aldehydes by Wittig reaction with the ylid derived from methoxymethyltriphenylphosphonium chloride (Scheme 3). Mild, biphasic TFA-catalyzed hydrolysis of the resulting enol ethers[19] gave aldehydes **14a–14d** and was fully compatible with the phenolic TBS-ethers.

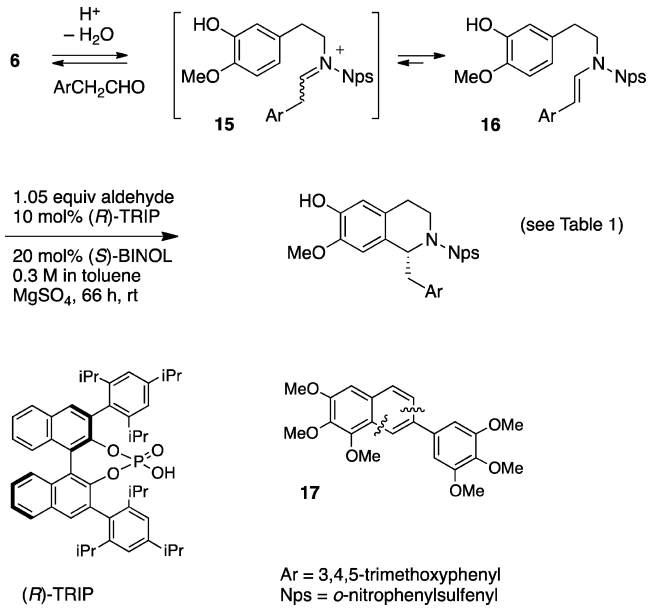
Scheme 3. Syntheses of the Components for the Pictet–Spengler Reactions



DOI: 10.1021/acs.joc.5b00509
J. Org. Chem. 2015, 80, 5125–5132

As mentioned before, the Pictet–Spengler reaction required considerable optimization (Scheme 4). First, it became clear

Scheme 4. Pictet–Spengler Optimization

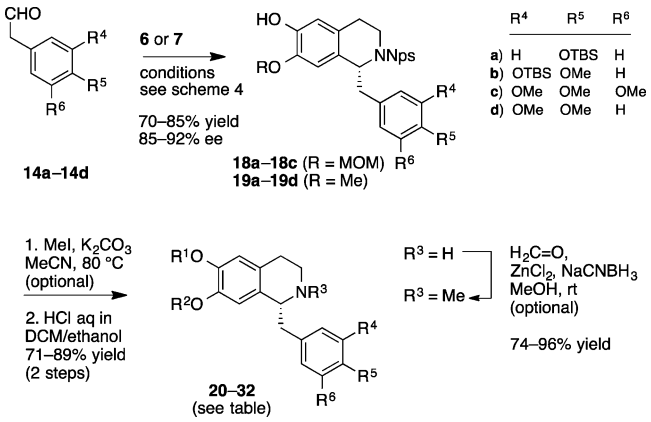


that an enamine intermediate was formed that was rather sensitive toward hydrolysis. When trimethoxyphenylacetaldehyde **14c** was used, this product could be isolated and was characterized as enamine **16**. Reprotonation of this enamine intermediate to the iminium salt and cyclization to the tetrahydroisoquinoline was too slow at room temperature. On heating at 80 °C, decomposition occurred, and aldehyde dimers of type **17** (among other compounds) were formed as side products.[20] However, the use of an excess of phenylacetaldehyde did not improve the reaction. In contrast, the catalyst lost its activity, and the reaction completely stopped before 50% conversion was reached. Obviously, these reactive phenylacetaldehydes deactivate the catalyst, so we had to reduce the normally used excess of 1.5–3 equiv of aldehyde to an equimolar ratio. Furthermore, a drying agent was required to drive the condensation to the enamine to completeness and for the quick removal of the aldehyde from the reaction mixture. Azeotropic removal of water as previously applied[17] was not feasible at rt, while addition of molecular sieves proved to be detrimental, both for conversion and ee. Magnesium sulfate appeared to be the drying agent of choice, and in combination with a stoichiometric amount of the aldehyde, the catalyst activity was preserved, resulting in both good yields and ee's after 66 h at rt.

Similar to the results in our earlier work,[17] the addition of BINOL always led to a distinct increase in the ee of the reaction, (*S*)-BINOL being a bit more helpful (ca. 5% in ee) than (*R*)-BINOL. Possibly, this diol plays a role in the water balance of the reaction. Other phenolic proton donors were less effective. The ee of the reaction was well reproducible for each substrate (84–92% ee), and for preparative reasons, the catalyst loading could be decreased to 5% or less, while increasing the temperature, but this was not investigated further. The absolute configuration of the major isomer was assigned by comparison of the sign of the specific rotation of the synthetic product with the known alkaloid. It thus appeared that (*R*)-TRIP as the catalyst always led to an excess of the (*R*)-enantiomer of the 1-arylmethyl-tetrahydroisoquinolines. In our earlier work,[17] we obtained the same major enantiomer in the case of an alkyl-substituted product, whereas an aryl-substituted product showed the opposite enantiomer in excess.[17] Attempts to explain the direction of the asymmetric induction are beyond the scope of this practical synthetic research.

The remaining steps of the alkaloid synthesis were straightforward, high yielding, and uneventful in every example (Scheme 5). O-Methylation of isoquinoline alkaloids is often

Scheme 5. Alkaloid Synthesis



problematic in the presence of secondary or tertiary amines. The Nps-protected amines remained completely unaffected under standard conditions (MeI and K_2CO_3) and gave the *O*-methyl derivatives in almost quantitative yield. A few remarks on the deprotection should be given. The acid-catalyzed removal of the Nps, TBS, and MOM protecting groups took place overnight at rt, in a homogeneous mixture of dichloromethane/ethanol/conc. HCl = 1/1/0.1 By stirring for 1 h at 0 °C, the Nps-group could be selectively removed, leaving the TBS and MOM groups intact. When an *N*-methyl substituent was required in the end product, reductive amination with formaldehyde, zinc chloride catalysis, and sodium cyanoborohydride as reducing agent was preferred, as it gave good yields starting from unprotected alkaloids (Table 1).

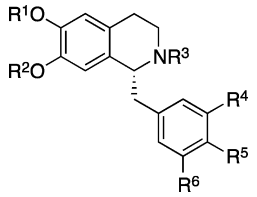
The enantiomeric ratio of the Nps-protected Pictet–Spengler products **18a–18c** and **19a–19d** could not be increased by crystallization as we described previously for related compounds.[17] After hydrochloric acid catalyzed removal of the protecting groups, the tetrahydroisoquinoline alkaloids were obtained as their hydrochlorides, and the ee's of the Pictet–Spengler reactions were mostly preserved during the subsequent methylation and deprotection steps. Two of these hydrochlorides produced highly crystalline (semi)racemic material, leaving the target molecules with 98–99% ee in the filtrate (**24** and **31**/**32**). In the literature, resolution of tetrahydroisoquinoline racemates by cocrystallization with chiral acids such as tartaric acid derivatives has been known for a long time.[21] Further increase of the ee's up to 99% by such a process could be effective but was not pursued in this work.

■ CONCLUSIONS

Careful optimization of the binolphosphoric acid-catalyzed Pictet–Spengler reaction between Nps-substituted arylethylamines and arylacetaldehydes has resulted in a general procedure for the synthesis of 1-benzyltetrahydroisoquinolines with high ee. This Nps-substituent protects the nitrogen atom

DOI: 10.1021/acs.joc.5b00509
J. Org. Chem. 2015, 80, 5125–5132

Table 1. End Products



entry	R^1	R^2	NR^3	R^4	R^5	R^6	ee (P-S)	ee (alkaloid)
					Starting from Amine **7**			
1	H	H	H	H	OH	H	89 (**18a**)	89, (*R*)-(+)-norcoclaurine (**20**)
2	Me	H	H	H	OH	H	89 (**18a**)	89, (*R*)-(+)-coclaurine (**21**)
3	Me	H	H	OH	OMe	H	90 (**18b**)	88, (*R*)-(+)-norreticuline (**22**)
4	Me	H	Me	OH	OMe	H	90 (**18b**)	88, (*R*)-(−)-reticuline (**23**)
5	H	H	H	OMe	OMe	OMe	92 (**18c**)	99,[a] (*R*)-(+)-trimetoquinol (**24**)
					Starting from Amine **6**			
6	Me	Me	H	H	OH	H	86 (**19a**)	85, (*R*)-(+)-nor-armepavine (**25**)
7	Me	Me	Me	H	OH	H	86 (**19a**)	85, (*R*)-(−)-armepavine (**26**)
8	H	Me	H	OH	OMe	H	86 (**19b**)	83, (*R*)-(+)-norprotosinomenine (**27**)
9	H	Me	Me	OH	OMe	H	86 (**19b**)	83, (*R*)-(−)-protosinomenine (**28**)
10	Me	Me	H	OMe	OMe	H	88 (**19d**)	86, (*R*)-(−)-norlaudanosine (**29**)
11	Me	Me	Me	OMe	OMe	H	88 (**19d**)	86, (*R*)-(−)-laudanosine (**30**)
12	Me	Me	H	OMe	OMe	OMe	89 (**19c**)	99,[a] (*R*)-(−)-nor-5-methoxylaudanosine (**31**)
13	Me	Me	Me	OMe	OMe	OMe	89 (**19c**)	98,[a] (*R*)-(−)-5-methoxylaudanosine (**32**)

[a]After crystallization.

during further O-methylation reactions. In addition, the application of MOM-protection in the isoquinoline ring system offered the possibility to prepare all four OH/OMe substituents at the 6- and 7-positions of the isoquinoline ring system.

EXPERIMENTAL SECTION

General Information. All ^{1}H NMR and ^{13}C NMR spectra were recorded (^{1}H, 400 MHz; ^{13}C, 100 MHz) at room temperature. Accurate mass measurements were performed on Accutof with ESI or FD ionization techniques. Toluene was distilled over calcium hydride and stored on 4 Å molecular sieves. (*R*)-3,3′-Bis(2,4,6-triisopropylphenyl)-BINOL-phosphoric acid [(*R*)-TRIP] was prepared according to a literature method.[22] All Nps-protected tetrahydroisoquinolines were bright yellow, stable compounds. The ^{1}H and ^{13}C NMR spectra, however, showed extreme line broadening for atoms in the vicinity of the nitrogen−sulfur bond.[17,23]

*3-Hydroxy-4-(methoxymethoxy)benzaldehyde (**9**).*[24] A suspension of 3,4-dihydroxybenzaldehyde (**8**, 1.38 g, 10.0 mmol) and K_2CO_3 (4.14 g) in anhydrous acetonitrile (15 mL) was efficiently stirred for 30 min at rt. MOM chloride (0.911 mL, 12.0 mmol) was added in one portion, which induced a temperature rise to ca. 35 °C. Stirring was continued for 2 h, followed by several extraction steps to remove both starting material and the disubstituted product. Water was added and next sufficient 10% aqueous NaOH to extract all phenols into the water layer. The water layer was washed three times with ethyl acetate, and the combined organic layers were re-extracted with 10% aqueous NaOH. If required the extraction steps can be followed by TLC. The product was extracted from the water layer with ethyl acetate after acidification to ca. pH 9 with 2 M HCl. Any residual starting material can be removed by washing with a saturated aqueous sodium carbonate solution. The product **9** (1.10 gr, 6.04 mmol, 60%) was obtained as syrup after evaporation: ^{1}H NMR δ 9.88 (s, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.43 (m, 1H), 7.24 (d, J = 8.3 Hz, 1H), 6.0 (bs, 1H), 5.34 (s, 2H), 3.55 (s, 3H).

*(E)-3-Hydroxy-4-(methoxymethoxy)-1-(2-nitrovinyl)benzene (**10**).* A mixture of 3-hydroxy-4-(methoxymethoxy)benzaldehyde (**9**, 1.82 g, 10.0 mmol), CH_3NO_2 (30 mL), NH_4OAc (0.65 gr), and 4 Å molecular sieves (5 g, powdered and dried at 200 °C, and 0.1 mbar) was refluxed for 1 h. Afterward, cooling silica gel (10 gr) was added and the mixture was filtered over Celite using ethyl acetate for rinsing. Evaporation of the solvents gave a solid which was further purified by trituration with a small amount of cold methanol to give nitroalkene **10** as a bright yellow solid (1.74 gr, 7.73 mmol, 77%); mp 106−109 °C; ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 13.6 Hz, 1H), 7.49 (d, J = 13.6 Hz, 1H), 7.15 (m, 1H), 7.14 (s, 1H), 7.06−7.02 (m, 1H), 6.12 (bs, 1H), 5.29 (s, 2H), 3.53 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.7, 146.6, 139.0, 135.7, 124.5, 123.3, 115.0, 114.6, 95.3, 56.6. HRMS (FD, TOF) m/z: $[M + H]^+$ calcd. for $C_{10}H_{11}NO_5$, 225.0637; found, 225.0631.

*β-(3-Hydroxy-4-(methoxymethoxyphenyl)ethylamine (**11**).* Nitroalkene **10** (1.13 g, 5.0 mmol) was dissolved in THF (20 mL) and added dropwise to a stirred suspension of LAH (1.0 g, 26 mmol) in THF (15 mL) at 0 °C under argon. The mixture was refluxed for 3 h and cooled in ice, and the excess LAH was carefully destroyed by adding water (1.3 mL), followed by saturated Na_2CO_3 (1.3 mL) and more water (2 mL). After stirring at rt for 30 min, the suspension was filtered over Celite. The filter cake was stirred with a mixture of dichloromethane and methanol (5/1, 100 mL), saturated aqueous NH_4Cl (3 mL) was added, and stirring was continued for 1 h. Filtration and evaporation of the combined organic extracts gave amine **11** (0.82 g, 4.16 mmol), which was pure enough for the next step: IR (film) ν (cm^{-1}) 2938, 1507; ^{1}H NMR (CD_3OD) δ 6.96 (d, J = 8.2 Hz, 1H), 6.68 (s, 1H), 6.61−6.56 (m, 1H), 5.10 (s, 2H), 3.43 (s, 3H), 3.27 (s, 1H), 2.87 (t, J = 7.25 Hz, 2H), 2.65 (t, J = 7.25 Hz, 2H); ^{13}C NMR (CD_3OD) δ 148.0, 144.2, 133.7, 119.9, 117.2, 116.5, 95.8, 55.5, 42.6, 36.7. HRMS (EI, TOF) m/z: $[M]^+$ calcd. for $C_{10}H_{15}NO_3$, 197.1053; found, 197.1052.

*N-(2-Nitrophenylsulfenyl)-β-(3-hydroxy-4-(methoxymethoxy)-phenyl)ethylamine (**7**).* Amine **11** (0.82 g, 4.16 mmol) was dissolved in a mixture of $CHCl_3$ (40 mL), methanol (2 mL), and triethylamine (0.25 mL). Saturated K_2CO_3 solution in water (25 mL) was added, and the mixture was cooled to 0 °C. 2-Nitrophenylsulfenyl chloride (1.04 gr, 5.5 mmol) was added in three portions under vigorous stirring. After stirring for 1 h at 0 °C, the bath was removed, and stirring was continued for 1 h. Extractive workup with $CHCl_3$, drying over $MgSO_4$, and removal of the solvents gave a crude mixture from which **7** was obtained as a bright orange syrup by flash chromatography [silica gel, dichloromethane/petroleum ether/ethyl acetate (v/v/v = 50/50/2−50/50/8) as eluent], (1.012 g, 2.89 mmol, 70%). IR (film) ν (cm^{-1}) 3348, 1504; ^{1}H NMR ($CDCl_3$) δ 8.26 (dd, J

DOI: 10.1021/acs.joc.5b00509
J. Org. Chem. 2015, 80, 5125−5132

= 8.3, 1.4 Hz, 1H), 7.79 (m, 1H), 7.57 (ddd, J = 8.3, 7.1, 1.4 Hz, 1H), 7.23 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.69 (m, 1H), 5.96 (s, 1H), 5.19 (s, 2H), 3.53 (s, 3H), 3.24−3.18 (m, 2H), 2.83 (t, J = 6.8 Hz, 2H), 2.71 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4, 145.6, 143.0, 142.4, 133.8, 133.6, 125.6, 124.3, 124.2, 120.4, 115.7, 95.9, 56.2, 52.4, 36.1. HRMS (EI, TOF) m/z: $[M]^+$ calcd. for $C_{16}H_{18}N_2O_5S$, 350.0940; found, 350.0936.

General Procedure for Aldehyde Homologation (A): Wittig Reaction. KO*t*-Bu (3.85 g, 35.0 mmol) was added in one portion to a stirred mixture of aromatic aldehyde **10a−10d** (30.0 mmol) and (methoxymethyl)triphenylphosphonium chloride (12.0 g, 35.0 mmol) in THF (150 mL) with ice cooling. The reaction was stirred for 30 min at 0 °C and then allowed to stir at room temperature for 4 h. Quenching with aqueous NH_4Cl and extractive workup with Et_2O gave a crude mixture that was purified by flash chromatography [silica, EtOAc/PE mixtures] to provide the enol ether as an ca. 1:1 mixture of E/Z isomers.

*4-(tert-Butyldimethylsilyloxy)-1-(2-methoxyvinyl)benzene (**13a**).* The title compound was synthesized from 4-(*tert*-butyldimethylsilyloxy)benzaldehyde [silica, ethyl acetate/petroleum ether 1/20] (E/Z 1:1) as a colorless oil (5.01 g, 19.0 mmol, 63%); IR (film) ν (cm^{-1}) 2929, 1507; ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 2H), 7.10 (m, 2H), 6.93 (m, 1H), 6.76 (dd, J = 8.7, 7.3 Hz, 4H), 6.05 (d, J = 7.0 Hz, 1H), 5.78 (m, 1H), 5.17 (d, J = 6.9 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 0.98 (s, 18H), 0.19 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 153.4, 153.2, 147.2, 145.9, 129.1, 129.0, 125.7, 119.9, 119.5, 105.0, 104.3, 60.0, 55.9, 25.3, 17.8, −4.8. HRMS (FD, TOF) m/z: $[M]^+$ calcd. for $C_{15}H_{24}O_2Si$, 264.1546; found, 264.1530.

*3-(tert-Butyldimethylsilyloxy)-4-methoxy-1-(2-methoxyvinyl)-benzene (**13b**).* The title compound was synthesized from 3-(*tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde [silica, ethyl acetate/petroleum ether 1/10] (E/Z ca. 1:1) as a colorless oil (6.32 g, 21.5 mmol, 72%); ^{1}H NMR ($CDCl_3$) δ 7.28 (s, 1H), 7.20 (d, J = 1.9 Hz, 1H), 7.13 (m, 1H), 6.94 (m, 1H), 6.8 (m, 4H), 6.06 (d, J = 6.9 Hz, 1H), 5.74 (m, 1H), 5.14 (d, J = 6.9 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.68 (s, 3H), 1.02 (s, 18 H), 0.19 (s, 6H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 149.1, 147.5, 146.4, 145.1, 140.8, 129.3, 129.0, 121.7, 121.0, 118.6, 117.7, 112.4, 111.6, 105.3, 104.5, 60.4, 56.5, 56.3, 55.5, 28.9, 25.7, 25.7, 25.7, 18.40, −4.69, −7.37. HRMS (FD, TOF) m/z: $[M]^+$ calcd. for $C_{10}H_{11}NO_5$, 294.1651; found, 294.1636.

*1-(2-Methoxyvinyl)-3,4,5-trimethoxybenzene (**13c**).* The title compound was synthesized from 3,4,5-trimethoxybenzaldehyde [silica, ethyl acetate/petroleum ether 1/5] (E/Z 58:42) as a slowly solidifying oil (4.55 g, 20.3 mmol 68%); spectra were in accordance with ref 25. ^{1}H NMR ($CDCl_3$) δ 7.01 (d, J = 12.9 Hz, 1H), 6.86 (s, 2H), 6.47 (s, 2H), 6.13 (d, J = 7.05 Hz, 1H), 5.79 (d, J = 12.9 Hz, 1H), 5.17 (d, J = 7.05 Hz, 1H), 3.88 (s, 6H), 3.88 (s, 6H), 3.85 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H).

*3,4,-Dimethoxyphenyl-1-(2-methoxyvinyl)-benzene (**13d**).* Prepared from 3,4-dimethoxybenzaldehyde (3.32 g, 20 mmol) [silica, ethyl acetate/petroleum ether 1/10 and 1/5] (E/Z 58:42) as a syrup (2.80 g, 14.4 mmol, 72%); spectra were in accordance with the literature.[26]

General Procedure for Aldehyde Homologation (B): Enol Ether Hydrolysis. Trifluoroacetic acid (1.2 mL) was added dropwise to a stirred mixture of enol ether (4.0 mmol) in dichloromethane (60 mL) and water (1.2 mL) at rt. Stirring was continued for 18 h, and extractive workup with aqueous sodium carbonate followed by flash chromatography [silica, EtOAc/petroleum ether mixtures] gave arylacetaldehydes **14a−14d**.

*4-(tert-Butyldimethylsilyloxy)phenylacetaldehyde (**14a**).* Prepared from **13a** [silica, ethyl acetate/petroleum ether 1/10] as an oil (0.634 g, 2.54 mmol, 63%); spectra in accordance with the literature:[27] ^{1}H NMR ($CDCl_3$) δ 9.74 (m, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 3.63 (s, 2H), 1.0 (s, 9H), 0.22 (s, 6H).

*3-(tert-Butyldimethylsilyloxy)-4-methoxyphenylacetaldehyde (**14b**).* The title compound was prepared from **13b** (73%) [silica, ethyl acetate/petroleum ether 1/10 and 1/8]. IR (film) ν (cm^{-1}) 1725, 1512; ^{1}H NMR ($CDCl_3$) δ 9.69 (t, J = 2.5 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.75 (dd, J = 8.2 Hz, J = 2.1 Hz, 1H), 6.71 (d, J = 2.1 Hz, 1H), 3.80 (s, 3H), 3.55 (d, J = 2.5 Hz, 2H), 0.99 (s, 9H), 0.15 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 199.8, 150.5, 145.5, 124.3, 122.9, 122.4, 112.6, 55.6, 49.9, 25.9, 25.8, 18.6, −4.5. HRMS (FD, TOF) m/z: $[M]^+$ calcd. for $C_{15}H_{24}O_3Si$, 280.1495; found, 280.1503

*3,4,5-Trimethoxyphenylacetaldehyde (**14c**).*[25] Prepared from **13c** as a slowly solidifying oil (0.827 g, 2.95 mmol, 74%) [silica, ethyl acetate/petroleum ether 1/4 and 1/2]; 9.57 (t, J = 2.3 Hz, 1H), 6.31 (s, 2H), 3.70 (3, 6H), 3.69 (s, 3H), 3.57 (d, J = 2.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 198.7, 153.0, 136.6, 127.1, 106.1, 60.1, 55.5, 50.1.

*3,4,-Dimethoxyphenylacetaldehyde (**14d**).* The title compound was prepared from **13d** (0.517 g, 2.87 mmol, 72%) after flash chromatography [silica gel, ethyl acetate/petroleum ether 1/4 and 1/2]; ^{1}H NMR ($CDCl_3$) δ 9.70 (t, J = 2.4 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.74 (dd, J = 8.1, 2.0 Hz, 1H), 6.69 (d, J = 2.0 Hz, 1H), 3.85 (s, 6H), 3.60 (d, J = 2.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 199.4, 149.1, 148.2, 124.0, 121.7, 112.4, 111.4, 55.7, 55.6, 49.9.

*Enamine **16**.* Amine **6** (64.1 mg, 0.20 mmol), aldehyde **14c** (84 mg, 0.4 mmol), PPTS (12.5 mg, 0.050 mmol), and $MgSO_4$ (1.0 g) were stirred in diethyl ether (3 mL) for 18 h at rt. Filtration, evaporation of the solvent, and flash chromatography [silica gel, petroleum ether/ethyl acetate (v/v = 80/20−50/50) as eluent] gave **17** (96.5 mg, 0.189 mmol, 94%) as a reddish brown glass: ^{1}H NMR ($CDCl_3$) δ 8.33 (dd, J = 8.2, 1.0 Hz, 1H), 7.60 (m, 1H), 7.40 (dd, J = 8.2, 1.0 Hz, 1H), 7.30 (m, 1H), 6.84 (d, J = 2 Hz, 1H), 6.7−6.8 (m, 3H), 6.41 (s, 2H), 5.79 (bs, 1H), 5.76 (d, J = 14.1 Hz, 1H), 3.85−3.9 (m, 1H), 3.86 (s, 3H), 3.85 (s, 6H), 3.82 (s, 3H), 3.53 (m, 1H), 2.98 (t, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 153.2, 145.6, 145.4, 143.2, 142.4, 138.1, 135.8, 134.2, 133.2, 131.4, 126.0, 125.3, 124.2, 120.3, 114.8, 110.7, 105.8, 101.5, 60.8, 57.9, 55.9, 55.9, 34.2. HRMS (FD, TOF) m/z: $[M]^+$ calcd. for $C_{26}H_{28}N_2O_7Si$, 512.1617; found, 512.1625.

General Procedure C: Pictet−Spengler Reaction. A mixture of Nps-amine **6** or **7** (0.2 mmol), (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-BINOL-phosphoric acid [(*R*)-TRIP] (15 mg, 10 mol %), (*S*)-BINOL (11.4 mg, 20 mol %), and $MgSO_4$ (0.4 g) in anhydrous toluene (0.6 mL) was stirred under argon for 10 min. Aldehydes **14a−14d** (0.21−0.22 mmol) were added, which immediately turned the bright yellow starting amine into the reddish brown enamine. After stirring for 3 days under argon, the color changed to yellow. The reaction mixture was diluted with dichloromethane and petroleum ether and purified by flash chromatography [silica gel, dichloromethane/petroleum ether/ethyl acetate (v/v/v = 50/50/2−50/50/8) as eluent] providing the tetrahydroisoquinoline as a bright yellow glass. Chiral HPLC: Chiralcel OD-H, *n*-heptane/*i*-propanol (v/v = 97/3) as eluent, flow 0.5 mL/min, 254 nm. All Nps-protected tetrahydroisoquinolines were bright yellow, stable compounds. The ^{1}H and ^{13}C NMR spectra, however, showed extreme line broadening for atoms in the vicinity of the nitrogen−sulfur bond (spectra: see Supporting Information).[28] Improved ^{1}H and ^{13}C NMR data for some of the tetrahydroisoquinolines were obtained in toluene-d_8 at 90 °C. From a Pictet−Spengler reaction at elevated temperature, using **7** and excess of aldehyde **14c**, naphthalene **17** was obtained as a side product: oil; ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J = 1.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.64 (dd, J = 8.4, 1.8 Hz, 1H), 7.28 (s, 1H), 7.00 (s, 1H), 6.92 (s, 2H), 4.10 (s, 3H), 4.02 (s, 6H), 3.99 (s, 6H), 3.94 (s, 3H).

***18a**: Prepared from Amine **7** and Aldehyde **14a**.* Yellow glass (82.1 mg, 0.141 mmol, 71%), 89% ee; t_R (major) = 41.8 min, t_R (minor) = 37.5 min; $[\alpha]_D^{20}$ = −10 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.25−4.4 (br, 1H); ^{13}C NMR ($CDCl_3$) see Supporting Information. ^{1}H NMR (500 MHz, toluene-d_8, 90 °C) δ 8.08−7.90 (m, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 7.2 Hz, 2H), 6.68 (m, 4H), 6.47 (s, 1H), 5.75 (s, 1H), 4.69 (s, 2H), 4.23 (dd, J = 6.5, 6.5 Hz, 1H), 3.34 (m, 1H), 3.13 (m, 3H), 3.01 (m, 1H), 2.91 (m, 1H), 2.79 (m, 1H), 2.35 (d, J = 16.0 Hz, 1H), 1.00 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (126 MHz, toluene-d_8, 90 °C) δ 154.7, 146.4, 143.4, 133.2, 133.0, 131.9, 131.2, 129.7, 129.2, 125.9, 125.8, 124.1, 120.1, 116.0, 115.9, 115.5, 96.8, 96.2, 56.4, 55.9, 55.3, 25.9, 25.9, 25.8, 18.4, −4.4. HRMS (FD, TOF) m/z: $[M]^+$ calcd. for $C_{30}H_{38}N_2O_6SSi$, 582.2220; found, 582.21822.

***18b**: Prepared from Amine **7** and Aldehyde **14b**.* Yellow glass (95.0 mg, 0.155 mmol, 78%), 90% ee; t_R (major) = 45.0 min, t_R

DOI: 10.1021/acs.joc.5b00509
J. Org. Chem. 2015, 80, 5125−5132

(minor) = 41.2 min; $[\alpha]_D^{20}$ = −13.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.25−4.4 (broad, 1H); ^{13}C NMR ($CDCl_3$) δ 149.6, 145.1, 144.2, 142.8, 142.5, 141.6, 133.6, 131.8, 129.4, 128.3, 125.4, 124.9, 124.5, 124.1, 122.4, 121.9, 115.5, 114.2, 112.2, 96.1, 77.2, 68.6, 64.6, 56.3, 55.6, 50.2, 46.1, 43.8, 30.1, 25.6, 25.2, 18.3, −4.77. HRMS (FD, TOF) *m*/*z*: $[M]^+$ calcd. for $C_{31}H_{40}N_2O_7SSi$, 612.2326; found, 612.2288.

***18c**: Prepared from Amine **7** and Aldehyde **14c**.* Yellow glass (77.5 mg, 0.143 mmol, 72%), 92% ee; t_R (major) = 27.0 min, t_R (minor) = 40.9 min; $[\alpha]_D^{20}$ = −3.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.25−4.5 (br, 1H); ^{1}H NMR (500 MHz, toluene-d_8, 90 °C) δ 7.95 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.05 (m, 1H), 6.70 (m, 2H), 6.56 (s, 1H), 6.27 (m, 2H), 5.87 (bs, 1H), 4.75 (m, 2H), 4.35 (m, 1H), 3.80 (s, 3H), 3.46 (m, 6H), 3.36 (m, 1H), 3.17 (m, 3H), 3.05 (m, 1H), 2.98 (m, 2H), 2.82 (bs, 1H), 2.42 (dt, *J* = 14.6, 4.3 Hz, 1H); ^{13}C NMR (126 MHz, toluene-d_8, 90 °C) δ 153.7, 146.0, 143.1, 138.6, 133.0, 125.4, 125.3, 124.4, 123.9, 115.5, 115.1, 108.3, 96.4, 60.0, 55.8, 55.4. HRMS (FD, TOF) *m*/*z*: $[M]^+$ calcd. for $C_{27}H_{30}N_2O_8S$, 542.1723; found, 542.1743.

***19a**: Prepared from Amine **6** and Aldehyde **14a**.* Yellow glass (89.1 mg, 0.161 mmol, 81%), 86% ee; t_R (major) = 25.7 min, t_R (minor) = 23.6 min (determined after O-methylation); $[\alpha]_D^{20}$ = −15.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.25−4.40 (broad, 1H); ^{13}C NMR ($CDCl_3$) δ 154.2, 144.7, 144.4, 144.2, 142.5, 141.7, 133.6, 131.8, 131.1, 130.4, 129.0, 126.8, 126.3, 126.2, 125.5, 124.8, 124.5, 124.1, 119.8, 119.7, 114.6, 114.1, 109.8, 109.5, 68.8, 65.4, 55.8, 50.0, 46.5, 43.9, 41.9, 30.0, 25.6, 25.5, 25.4, 18.1, −4.46. HRMS (FD, TOF) *m*/*z*: $[M]^+$ calcd. for $C_{29}H_{36}N_2O_5SSi$, 552.2114; found, 552.2156.

***19b**: Prepared from Amine **6** and Aldehyde **14b**.* Yellow glass (92.0 mg, 0.157 mmol, 79%), 86% ee; t_R (major) = 33.2 min, t_R (minor) = 37.2; $[\alpha]_D^{20}$ = −18.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (toluene-d_8, 90 °C) δ 7.94 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.08−6.90 (toluene +1H), 6.72−6.62 (m, 4H), 6.54 (s, 2H), 6.12 (s, 1H), 5.29 (s, 2H), 4.26 (dd, *J* = 6.6, 6.6 Hz, 1H), 3.47 (s, 3H), 3.32 (s, 3H), 3.06−2.89 (m, 2H), 2.83−2.66 (m, 1H), 2.36 (dt, *J* = 16.1, 4.8 Hz, 1H), 0.98 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (toluene-d_8, 90 °C) δ 149.8, 145.3, 145.0, 144.8, 144.3, 142.7, 132.6, 131.7, 125.2, 124.9, 124.5, 123.59, 122.6, 122.3, 119.7, 114.7, 112.8, 109.9, 67.1, 55.2, 55.2, 48.6, 43.0, 29.5, 25.3, 17.98, −5.05. HRMS (FD, TOF) *m*/*z*: $[M]^+$ calcd. for $C_{30}H_{38}N_2O_6SSi$, 582.2220; found, 582.2273.

***19c**: Prepared from Amine **6** and Aldehyde **14c**.* Yellow glass (82.0 mg, 0.0161 mmol, 80%), 89% ee; Chiralcel AD, *n*-heptane/*i*-propanol (v/v = 80/20) as eluent, flow 0.5 mL/min, t_R (major) = 27.9 min, t_R (minor) = 32.0 min; $[\alpha]_D^{20}$ = −4.0 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, toluene-d_8, 90 °C) δ 7.97 (dd, *J* = 8.7, *J* = 1.3 Hz, 1H), 7.58 (m, 1H), 7.1 (m, 1H), 6.70 (m, 1H), 6.69 (s, 1H), 6.29 (s, 2H), 6.13 (s, 1H), 5.42 (bs, 1H), 4.35 (dd, *J* = 6.9, 6.8 Hz, 1H), 3.80 (s, 3H), 3.46 (s, 6H), 3.33 (s, 3H), 2.7−3.5 (m, sH), 2.41 (dt, *J* = 16.2, 4.8 Hz, 1H); ^{13}C NMR (toluene-d_8, 90 °C) δ 154.5, 146.0, 133.6, 126.1, 125.6, 124.7, 115.5, 110.8, 109.3, 60.7, 56.6, 56.0. HRMS (FD, TOF) *m*/*z*: $[M]^+$ calcd. for $C_{26}H_{28}N_2O_7S$, 512.1617; found, 512.1607.

***19d**: Prepared from Amine **6** and Aldehyde **14d**.* Yellow glass (80.0 mg, 0.166 mmol, 83%), 88% ee; HPLC, Chiralcel AD, *n*-heptane/*i*-propanol (v/v = 70/30) as eluent, flow 0.4 mL/min, t_R (major) = 49.9 min, t_R (minor) = 34.8 min (determined after O-methylation); $[\alpha]_D^{20}$ = −13.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.25−4.50 (broad, 1H); ^{13}C NMR ($CDCl_3$) δ 147.6, 144.4, 133.7, 133.4, 131.7, 128.8, 126.3, 126.1, 125.4, 124.7, 124.5, 124.2, 122.3, 121.5, 114.7, 114.1, 113.3, 112.4, 111.2, 110.9, 109.9, 109.4, 68.7, 65.2, 60.3, 55.9, 55.7, 50.0, 46.4, 44.1, 42.1, 29.9, 25.3, 14.1. HRMS (FD, TOF) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{26}N_2O_6S$, 482.1512; found, 482.1452.

General Procedure D: O-Methylation of the Pictet−Spengler Products 18a, 18b, 19a, 19c and 19d. The 6-OH Pictet−Spengler product (0.1−0.19 mmol) was stirred in a stoppered flask with K_2CO_3 (0.15g) and methyl iodide (40 μL) in anhydrous acetonitrile (3 mL) for 18 h at 80 °C. Aqueous workup (ethyl acetate) gave the methylated products in nearly quantitative yield, and they were directly deprotected according to procedure E or F.

General Procedure E: Deprotection with HCl; Removal of the Nps Substituent. Protected tetrahydroisoquinoline (0.10−0.19 mmol) was dissolved in a mixture of dichloromethane (1.5 mL) and ethanol (1.5 mL) at 0 °C. Concentrated HCl (0.15 mL) was added, and after stirring at 0 °C for 1 h, the reaction mixture was diluted with water (ca. 5 mL), and the water layer was extracted three times with dichloromethane. Each dichloromethane extract was extracted back with dilute HCl solution. The aqueous phase was evaporated, leaving the tetrahydroisoquinoline as its hydrochloride, which was sufficiently pure for analysis.

Isolation of the Free Base by Chromatography. The acidic reaction mixture was diluted with dichloromethane, directly absorbed on silica (ca. 3 g), evaporated, and applied to a silica column packed with ethyl acetate. Elution with ethyl acetate removed Nps residues; elution with EtOAc/methanol/conc NH_4OH 93/5/2 and stepwise increasing to 82/15/3 gave the free amine.

General procedure F: Deprotection with HCl; Simultaneous Removal of the Nps, TBS, and MOM Substituents. Procedure E was used, but the reaction was stirred at rt for 24 h. Note that the use of more conc HCl gave a two-layer system and resulted in partial hydrolysis of methoxy to hydroxy.

General Procedure G: N-Methylation. Unprotected 1,2,3,4-tetrahydroisoquinoline (free base or hydrochloride, 0.1−0.15 mmol) was stirred with paraformaldehyde (38 mg), zinc chloride (35 mg), NaOAc (32 mg, only when hydrochlorides were used), and sodium cyanoborohydride (33 mg) in methanol (5 mL) for 24 h at rt. The reaction mixture was absorbed on silica and purified by chromatography as described in general procedure E.

*(R)-(+)-Norcoclaurine·HCl and (R)-(+)-Higenamine·HCl (**20**).* Obtained from **18a** (40.0 mg, 0.069 mmol) as hydrochloride following general procedure F (17.9 mg, 0.0583 mmol, 84%) after recrystallization from methanol/ether; 89% ee. HPLC: obtained from **21** (after O-methylation); $[\alpha]_D^{20}$ = +23.4 (*c* = 1.0, MeOH), lit.[29] +25.0 (c = 1.0, MeOH); mp 272−277 °C (methanol/ether); ^{1}H NMR (D_2O) δ 7.06 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 2H), 6.63 (s, 1H), 6.57 (s, 1H), 4.45−4.55 (m, 1H), 3.35−3.40 (m, 1H), 3.25−3.33 (m, 1H), 3.13−3.23 (m, 1H), 2.76−2.92 (m, 3H); ^{13}C NMR (D_2O) δ 154.8, 143.9, 142.7, 130.8, 126.6, 123.6, 123.1, 115.8, 115.6, 113.6, 56.1, 39.1, 38.2, 23.9.

*(R)-(+)-Coclaurine·HCl (**21**).* Obtained as hydrochloride by O-methylation (general procedure D) from **18a** (0.125 mmol), followed by deprotection (method F) (28.7 mg, 0.092 mmol, 71%). HPLC: 89% ee, Chiralcel AD, *n*-heptane/*i*-propanol/diethylamine (v/v = 70/30/0.1) as eluent, flow 0.5 mL/min, t_R (major) = 30.2 min, t_R (minor) = 24.4 min; $[\alpha]_D^{20}$ = +13.7 (*c* = 1.0, MeOH), (lit.[30] +15 (*c* = 1.2, MeOH); mp 262−266 °C (methanol/ether), (lit.[30] 261−263 °C); ^{1}H NMR (CD_3OD) δ 7.17 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.79 (s, 1H), 6.67 (s, 1H), 4.61−4.64 (m, 1H), 3.86 (s, 3H), 3.50−3.55 (m, 1H), 3.25−3.45 (m, 2H), 3.13−3.23 (m, 1H), 2.90−3.2 (m, 3H); ^{13}C NMR (CD_3OD) δ 156.7, 147.7, 145.2, 130.2, 125.50, 123.53, 122.22, 115.44, 112.64, 111.11, 56.3, 54.9, 39.4, 38.9, 24.4.

*(R)-(+)-Norreticuline (**22**).* Obtained as free base by O-methylation (general procedure D) from **18b** (0.123 mmol), followed by deprotection (method F) (32.5 mg, 0.925 mmol, 75%); mp 115−120 °C; 89% ee, HPLC (determined for **23** after *N*-methylation); $[\alpha]_D^{20}$ = +23.0 (*c* = 1.0, MeOH); ^{1}H NMR (CD_3OD) δ 6.89 (d, *J* = 8.2 Hz, 1H), 6.68−6.76 (m, 3H), 4.13 (dd, *J* = 9.4, 4.4 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.2−3.25 (m, 1H), 3.13 (dd, *J* = 14.0, 4.5 Hz, 1H), 2.7−2.85 (m, H); ^{13}C NMR (CD_3OD) δ 146.6, 146.6, 146.4, 144.4, 130.4, 128.4, 124.7, 120.1, 115.76, 112.6, 111.5, 111.3, 56.3, 54.9, 54.8, 40.5, 39.8, 27.3.

*(R)-(−)-Reticuline (**23**).* Obtained from **22** (0.103 mmol) via procedure G: glass (32.5 mg, 0.099 mmol, 96%), ee 87%. HPLC: Chiralcel AD, *n*-heptane/*i*-propanol/diethylamine (v/v = 70/30/0.1) as eluent, flow 0.5 mL/min, t_R (major) = 23.1, min, t_R (minor) = 28.7 min; $[\alpha]_D^{20}$ = −60 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.76 (d, *J* = 1.9 Hz, 1H), 6.73 (d, *J* = 8.15 Hz, 1H), 6.58 (dd, *J* = 8.15, 1.9 Hz, 1H), 6.55 (s, 1H), 6.37 (s, 1H), 5.2−6.0 (bs, 2H), 3.855 (s, 3H), 3.85 (s, 3H), 3.70 (dd, *J* = 6.1, 6.1 Hz, 1H), 3.16−3.23 (m, 1H), 3.05 (dd, *J* = 14.1, 6.1 Hz, 1H), 2.75−2.88 (m, 3H), 2.58−2.63 (m, 1H), 2.47 (s,

DOI: 10.1021/acs.joc.5b00509
J. Org. Chem. 2015, 80, 5125−5132

3H); ^{13}C NMR ($CDCl_3$) δ 145.4, 145.2, 145.1, 143.3, 133.00, 130.0, 125.0, 120.8, 115.6, 113.8, 110.6, 110.5, 64.4, 55.8, 55.7, 46.5, 42.3, 40.9, 24.8.

*(R)-(+)-Trimetoquinol (**24**).* Obtained as hydrochloride from **18c** (0.190 mmol) by deprotection (method F) (62.0 mg, 0.163 mmol, 86%); crystallization of this product from methanol/ether quickly produced crystals with an *R*/*S* ratio of 3/1, leaving the pure (*R*)-enantiomer in the filtrate as a solid (42.6 mg, 0.112 mmol, 62%) with 99.5% ee; mp 157−158 °C; (lit.[31] 155−156 °C). HPLC: Chiralcel AD, *n*-heptane/*i*-propanol/diethylamine (v/v = 70/30/0.1) as eluent, flow 0.8 mL/min, t_R (major) = 13.2, min, t_R (minor) = 36.4 min; $[\alpha]_D^{20}$ no transmission; ^{1}H NMR (D_2O) δ 6.67 (s, 1H), 6.54 (s, 3H), 4.46 (m, 1H), 3.70 (s, 9H), 3.68 (s, 3H), 3.3−3.5 (m, 1H), 3.17−3.27 (m, 2H), 3.00 (dd, *J* = 14.2, 8.0 Hz, 1H), 2.85−2.90 (m, 2H); ^{13}C NMR (D_2O) δ 152.5, 144.0, 142.8, 136.0, 131.5, 123.6, 122.7, 115.6, 113.7, 106.9, 60.8, 55.9, 55.7, 39.6, 39.1, 23.9. HRMS (FD, TOF): *m*/*z* calcd. for (MH^+) $C_{19}H_{24}NO_5$, 346.1645; found, 346.1646.

*(R)-(+)-Norarmepavine·HCl (**25**).* The title compound was obtained as hydrochloride by O-methylation (general procedure D) from **18b** (0.140 mmol), followed by deprotection (method F); glass (41.5 mg, 0.124 mmol, 89%); 85% ee (determined for **26** after *N*-methylation); $[\alpha]_D^{20}$ = +19.5 (*c* = 1.0, MeOH); ^{1}H NMR (CD_3OD) δ 7.16 (d, *J* = 8.2 Hz, 2H), 6.80−6.85 (m, 3H), 6.49 (s, 1H), 4.68 (dd, *J* = 6.9, 6.9 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 3.5−3.6 (m, 1H), 3.25−3.40 (m, 2H), 3.0−3.2 (m, 3H); ^{13}C NMR (CD_3OD) δ 156.7, 148.9, 147.6, 130.5, 125.8, 123.5, 123.2, 115.4, 111.4, 109.9, 56.2, 55.0, 54.9, 39.0, 38.8, 24.4.

*(R)-(−)-Armepavine **26**.* The title compound was obtained from **25**·HCl (0.118 mmol) via procedure G: glass (35.5 mg, 0.113 mmol, 96%), ee 85%. HPLC: Chiralcel AD, *n*-heptane/*i*-propanol/diethylamine (v/v = 70/30/0.1) as eluent, flow 0.5 mL/min, t_R (major) = 10.6, min, t_R (minor) = 31.1 min; $[\alpha]_D^{20}$ = −83 (*c* = 1.0, $CHCl_3$); (lit *S*-armepavine,[15] $[\alpha]_D^{20}$ = +94.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.93 (d, *J* = 8.5 Hz, 2H), 6.64 (d, *J* = 8.5 Hz, 2H), 6.58 (s, 1H), 6.02 (s, 1H), 3.85 (s, 3H), 3.75 (dd, *J* = 7.9, 5.4 Hz, 1H), 3.25−3.35 (m, 1H), 3.16 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.8−3.0 (m, 2H), 2.77 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.6−2.7 (m, 1H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.1, 147.3, 146.1, 130.7, 130.3, 128.3, 124.9, 115.4, 111.2, 111.1, 77.3, 77.2, 77.0, 76.7, 64.8, 55.6, 55.3, 45.7, 41.8, 40.3, 24.3.

*(R)-(+)-Norprotosinomenine·HCl (**27**).* The title compound was obtained as a glass in hydrochloride form (60.2 mg, 0.171 mmol, 88%) from **19b** (0.194 mmol) by deprotection (method F); 83% ee (determined for **28** after *N*-methylation); $[\alpha]_D^{20}$ = +16.5 (*c* = 1.0, MeOH);[32] ^{1}H NMR (CD_3OD) δ 6.95 (d, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 6.78 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.66 (s, 1H), 6.54 (s, 1H), 4.66 (dd, *J* = 7.3, 7.3 Hz, 1H), 3.87 (s, 3H), 3.71 (s, 3H), 3.50−3.55 (m, 1H), 3.0−3.37 (m, 2H), 2.90−3.1 (m, 3H); ^{13}C NMR (CD_3OD) δ 147.2, 146.6, 146.5, 146.3, 128.0, 123.5, 122.0, 120.6, 116.1, 114.6, 111.7, 109.6, 56.2, 55.0, 54.8, 39.2, 38.9, 24.2. HRMS (FD, TOF) *m*/*z*: $[M]^+$ $C_{18}H_{22}NO_4$, 316.1549; found, 316.1572.

*(R)-(−)-Protosinomenine (**28**).* The title compound was obtained from **27**·HCl (0.170 mmol) via procedure G: glass (41.5 mg, 0.126 mmol, 74%), ee 83%. HPLC: Chiralcel AD, *n*-heptane/*i*-propanol/diethylamine (v/v = 70/30/0.1) as eluent, flow 0.8 mL/min, t_R (major) = 14.6, min, t_R (minor) = 9.8 min; $[\alpha]_D^{20}$ = −52 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.75 (d, *J* = 8.1 Hz, 1H), 6.74 (s, 1H), 6.62 (s, 1H), 6.54 (dd, 1H, *J* = 8.1, 1.9 Hz, 1H), 5.99 (s, 1H), 4.5−5.5 (broad, 1H), 3.87 (s, 3H), 3.57 (s, 3H), 3.70 (m, 1H), 3.2−3.3 (m, 1H), 3.18 (dd, *J* = 13.5, 4.8 Hz, 1H), 3.75−3.90 (m, 2H), 2.77 (dd, *J* = 13.5, 8.3 Hz, 1H), 2.55−2.65 (m, 1H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.39, 145.04, 144.09, 143.87, 132.98, 128.14, 125.92, 121.06, 115.89, 114.15, 110.47, 110.41, 77.21, 76.89, 76.58, 64.75, 55.85, 55.41, 46.13, 42.11, 40.54, 24.55.

*(R)-(−)-Norlaudanosine·HCl (**29**).* The title compound was obtained from **19d** (0.162 mmol) as hydrochloride by O-methylation (general procedure D) followed by deprotection (method F); glass (48.0 mg, 0.126 mmol, 78%). HPLC: 86% ee; Chiralcel AD, *n*-heptane/*i*-propanol/diethylamine (v/v = 70/30/0.1) as eluent, flow 0.5 mL/min, t_R (major) = 23.3 min, t_R (minor) = 16.6 min; $[\alpha]_D^{20}$ = −11.6 (*c* = 1.0, MeOH); ^{1}H NMR (CD_3OD) δ 6.98 (d, *J* = 8.1 Hz, 1H), 6.96 (br, 1H), 6.89 (m, 1H), 6.83 (s, 1H), 6.60 (s, 1H), 4.75 (dd, *J* = 7.1, 7.2 Hz, 1H), 3.85 3.84, 3.83, 3.69 (4*s*, 4 × 3H), 3.50−3.60 (m, 1H), 3.3−3.5 (m, 2H), 3.0−3.2 (m, 3H); ^{13}C NMR (CD_3OD) δ 149.4, 149.0, 148.6, 147.8, 127.8, 123.5, 123.1, 121.9, 112.9, 111.9, 111.4, 109.9, 56.0, 55.0, 55.0, 54.9, 54.9, 39.3, 38.8, 24.3.

*(R)-(−)-Laudanosine (**30**).* The title compound was obtained from **29**·HCl (0.047 mmol) via procedure G: glass (13.1 mg, 0.037 mmol, 78%), ee 86%, HPLC see **29**; $[\alpha]_D^{20}$ = −46 (*c* = 1.0, $CHCl_3$); $[\alpha]_D^{20}$ = −73.5 (*c* = 1.0, EtOH); lit.[33] $[\alpha]_D^{20}$ = −45 (*c* = 0.6, $CHCl_3$); $[\alpha]_D^{20}$ = −85 (*c* = 0.4, EtOH) ^{1}H NMR ($CDCl_3$) δ 6.78 (d, *J* = 8.1 Hz, 1H), 6.65 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.63 (d, *J* = 1.8 Hz, 1H), 6.58 (s, 1H), 6.06 (s, 1H), 3.87 (s, 3H), 3.86, (s, 3H), 3.81 (s, 3H), 3.73 (dd, *J* = 7.8, 4.9 Hz, 1H), 3.59 (s, 3H), 3.20−3.25 (m, 1H), 3.18 (dd, *J* = 13.5, 5.2 Hz, 1H), 2.75−2.90 (m, 3H), 2.60−2.65 (m, 1H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.5, 147.2, 147.2, 146.2, 132.3, 128.9, 125.8, 121.8, 112.9, 111.0, 111.0, 110.9, 64.7, 55.8, 55.7, 55.7, 55.4, 46.8, 42.5, 40.8, 25.3.

*(R)-(−)-Nor-5-methoxylaudanosine·HCl (**31**).*[7] The title compound was obtained from **19c** (0.116 mmol) as hydrochloride by O-methylation (general procedure D), followed by deprotection (method F); glass (38.5 mg, 0.094 mmol, 81%); crystallization of this product from methanol/ether quickly produced crystals with an R/S ratio of 2/1, leaving the (*R*)-enantiomer in the filtrate (30.4 mg, 64%) with 99.5% ee. HPLC: Chiralcel AD, *n*-heptane/*i*-propanol/diethylamine (v/v = 70/30/0.1) as eluent, flow 0.8 mL/min, t_R (major) = 14.9, min, t_R (minor) = 41.7 min; $[\alpha]_D^{20}$ = −14.4 (*c* = 1.0, MeOH); ^{1}H NMR (CD_3OD) δ 6.84 (s, 1H), 6.69 (s, 2H), 6.65 (s, 1H), 4.79 (dd, *J* = 7.4, 7.2 Hz, 1H), 3.85 (s, 6H), 3.84, 3.78, 3.72 (3*s*, 3 × 3H), 3.5−3.6 (s, 1H), 3.46 (dd, *J* = 14.0, 6.5 Hz, 1H), 3.3−3.4 (m, 1H), 3.0−3.2 (m, 3H); ^{13}C NMR (CD_3OD) δ 153.5, 149.1, 147.8, 131.2, 123.6, 123.1, 111.4, 109.8, 106.5, 59.6, 56.0, 55.2, 54.9, 54.9, 39.9, 38.9, 24.4.

*(R)-(−)-5-Methoxylaudanosine (**32**).* The title compound was obtained from **31**·HCl (0.066 mmol) via procedure G: glass (23.0 mg, 0.059 mmol, 90%); ee 98%. HPLC: Chiralcel AD, *n*-heptane/*i*-propanol/diethylamine (v/v = 70/30/0.1) as eluent, flow 0.5 mL/min, t_R (major) = 15.4, min, t_R (minor) = 14.2 min; $[\alpha]_D^{20}$ = −46.5 (*c* = 1.0, $CHCl_3$), lit.[7] −46 (*c* = 1.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.59 (s, 1H), 6.33 (s, 2H), 6.05 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.79 (s, 6H), 3.73 (dd, *J* = 8.0, 3.3 Hz, 1H), 3.59 (s, 3H), 3.15−3.25 (m, 2H), 2.75−2.95 (m, 2H), 2.77 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.55−2.7 (m, 1H), 2.58 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.8, 147.3, 146.2, 136.2, 135.6, 128.9, 125.80 111.2, 111.1, 106.6, 64.7, 60.8, 56.0, 55.7, 55.5, 46.8, 42.6, 41.6, 25.3.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra and HPLC-traces for ee determination. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00509.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail h.hiemstra@uva.nl.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A.R.-O. thanks the Ministerio de Economia y Competitividad (Spain) for a fellowship.

■ REFERENCES

(1) For recent reviews, see: (a) Hagel, J. M.; Facchini, P. J. *Plant Cell Physiol.* **2013**, *54*, 647. (b) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538.

DOI: 10.1021/acs.joc.5b00509
J. Org. Chem. 2015, 80, 5125−5132

(2) For recent synthetic studies, see: (a) Geffe, M.; Opatz, T. *Org. Lett.* **2014**, *16*, 5282. (b) Tissot, M.; Phipps, R. J.; Lucas, C.; Leon, R. M.; Pace, R. D. M.; Ngouansavanh, T.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 13498.
(3) Perrey, D. A.; German, N. A.; Gilmour, B. P.; Li, J.-X.; Harris, D. L.; Thomas, B. F.; Zhang, Y. *J. Med. Chem.* **2013**, *56*, 6901.
(4) Wu, H.-P.; Lu, T.-N.; Hsu, N.-Y.; Chang, C.-C. *Eur. J. Org. Chem.* **2013**, 2898.
(5) Sun, H.; Zhu, L.; Yang, H.; Qian, W.; Guo, L.; Zhou, S.; Gao, B.; Li, Z.; Zhou, Y.; Jiang, H.; Chen, K.; Zhen, X.; Hong Liu, H. *Bioorg. Med. Chem. Lett.* **2013**, *21*, 856.
(6) Pyo, M. K.; Lee, D.-H.; Kim, D.-H.; Lee, J.-H.; Moon, J.-C.; Chang, K. C.; Yun-Choi, H. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4110.
(7) Tsukiyama, M.; Ueki, T.; Yasuda, Y.; Kikuchi, H.; Akaishi, T.; Okumura, H.; Abe, K. *Planta Med.* **2009**, *75*, 1393.
(8) (a) Luk, L. Y.; Bunn, S.; Liscombe, D. K.; Facchini, P. J.; Tanner, M. E. *Biochemistry* **2007**, *46*, 10153. (b) Ruff, B. M.; Bräse, S.; O'Connor, S. E. *Tetrahedron Lett.* **2012**, *53*, 1071. (c) Pesnot, T.; Gershater, M. C.; Ward, J. M.; Hailes, H. C. *Adv. Synth. Catal.* **2012**, *354*, 2997. (d) Maresh, J. J.; Crowe, S. O.; Ralko, A. A.; Aparece, M. D.; Murphy, C. M.; Krzeszowiec, M.; Mullowney, M. W. *Tetrahedron Lett.* **2014**, *55*, 5047.
(9) Vilhanova, B.; Matousek, V.; Vaclavik, J.; Syslova, K.; Prech, J.; Pechacek, J.; Sot, P.; Januscak, J.; Toman, J.; Zapal, J.; Kuzma, M.; Kacer, P. *Tetrahedron Asymm.* **2013**, *24*, 50.
(10) Schrittwieser, J. H.; Groenendaal, B.; Willies, S. C.; Ghislieri, D.; Rowles, I.; Resch, V.; Sattler, J. H.; Fischereder, E.-M.; Grischek, B.; Lienhart, W.-D.; Turner, N. J.; Kroutil, W. *Catal. Sci. Technol.* **2014**, *4*, 3657.
(11) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.
(12) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916.
(13) (a) Blank, N.; Opatz, T. *J. Org. Chem.* **2011**, *76*, 9777. (b) Zhai, H.; Miller, J.; Sammis, G. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1557. (c) Xie, J.-H.; Yan, P.-C.; Zhang, Q. Q.; Yuan, K.-X.; Zhou, Q.-L. *ACS Catal.* **2012**, *2*, 561. (d) Sun, H.; Zhu, L.; Yang, H.; Qian, W.; Guo, L.; Zhou, S.; Gao, B.; Li, Z.; Zhou, Y.; Jiang, H.; Chen, K.; Zhen, X.; Liu, H. *Bioorg. Med. Chem.* **2013**, *31*, 856.
(14) See for a good literature survey: Mittal, N.; Sun, D. X.; Seidel, D. *Org. Lett.* **2014**, *16*, 1012.
(15) Selected examples: (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (b) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (c) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405.
(16) For applications of the *N*-sulfenyl Pictet−Spengler reaction: Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485.
(17) Mons, E.; Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2014**, *79*, 7380.
(18) Toda, Y.; Terada, M. *Synlett* **2013**, 752.
(19) Li, Q.; Jiang, J.; Fan, A.; Cui, Y.; Jia, Y. *Org. Lett.* **2011**, *13*, 312.
(20) Maurin, C.; Bailly, F.; Cotelle, P. *Tetrahedron* **2005**, *61*, 7054.
(21) (a) Rice, K. C.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 592. (b) See for a recent application of a resolution/racemization method: Zhu, R.; Ding, W.; Liu, S.; Shi, X.; Lu, X. *Chin. J. Chem.* **2014**, *32*, 1039.
(22) Gribkov, D. V.; Hultzsch, K. C.; Hampell, F. *Chem.—Eur. J.* **2003**, *9*, 4796.
(23) Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689.
(24) Fumeaux, R.; Menozzi-Smarrito, C.; Stalmach, A.; Munari, C.; Kraehenbuehl, K.; Steiling, H.; Crozier, A.; Williamson, G.; Barron, D. *Org. Biomol. Chem.* **2010**, *8*, 5199.
(25) Rosowsky, A.; Chen, H.; Fu, H.; Queener, S. F. *Bioorg. Med. Chem.* **2003**, *11*, 59.
(26) Comins, D. L.; Badawi, M. M. *Tetrahedron Lett.* **1991**, *32*, 2995.
(27) Li, Q.; Jiang, J.; Fan, A.; Cui, Y.; Jia, Y. *Org. Lett.* **2011**, *13*, 312.
(28) Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689.
(29) See for recent enantioselective syntheses of (*R*)- and (*S*)-norcoclaurine [(*R*)- and (*S*)-norcoclaurine [(*R*)- and (*S*)-higenamine]: refs 4, 6, and 8c.
(30) Bhakuni, D. S.; Singh, A. N.; Jain, S. *Tetrahedron* **1981**, *37*, 2651.
(31) Hashigaki, K.; Kan, K.; Qais, N.; Takeuchi, Y.; Yamato, M. *Chem. Pharm. Bull.* **1991**, *39*, 1126.
(32) Barton, D. H. R.; Boar, R. B.; Widdowson, D. A. *J. Chem. Soc. C* **1970**, 1213.
(33) Pedrosa, R.; Andrés, C.; Iglesias, J. M. *J. Org. Chem.* **2001**, *66*, 243.

DOI: 10.1021/acs.joc.5b00509
J. Org. Chem. 2015, 80, 5125−5132