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


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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-nitrophenylsulfonyl)-2-arylethylamines with arylacetaldehydes. The presence of the o-nitrophenylsulfonyl 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)-laudanosine, (R)-norreticuline, (R)-coclaurine, (R)-norprotosinomenine, (R)-protosinomenine, (R)-norlaudanosine, and (R)-S-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-benzylsubstituted 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 adrenoeceptor stimulation.7

Norcoclaurine synthase (NCS) was identified as a Pictet−Spenglerase in plants, and application of this enzyme in the synthesis of racemic 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 adrenoeceptor stimulation.7

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 acids8 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 POC13-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.

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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. 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).

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-nitrobenzenesulfonyl 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 gave aldehydes 14a–14d and was fully compatible with the phenolic TBS-ethers.
As mentioned before, the Pictet–Spengler reaction required considerable optimization (Scheme 4). First, it became clear 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 dimer of type 17 (among other compounds) were formed as side products. 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 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, 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-arylalkyl-terahydroisoquinolines. In our earlier work, 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. 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 problematic in the presence of secondary or tertiary amines. The Nps-protected amines remained completely unaffected under standard conditions (Mel and K$_2$CO$_3$) 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. 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. 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 aryletaldehydes has resulted in a general procedure for the synthesis of 1-benzyltetrahydroisoquinolines with high ee. This Nps-substituent protects the nitrogen atom.
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 molecular sieves (5 g, powdered and dried at $300^\circ$C) was added dropwise to a stirred suspension of LAH (1.0 g, 26 mmol) in THF (15 mL) at 0°C. Afterward, cooling silica gel (10 gr) was added for 1 h. Afterward, 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 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$_3$) $\delta$ 7.80 (d, $J = 13.6$ Hz, 1H), 7.49 (d, $J = 13.6$ Hz, 1H), 7.15 (m, 1H), 7.14 (s, 1H), 7.06–0.2 (m, 1H), 6.12 (bs, 1H), 5.29 (2H), 3.53 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 147.7, 146.6, 139.0, 135.7, 124.5, 112.3, 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.

**Table 1. End Products**

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<td>OMe</td>
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</tr>
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</table>

Starting from Amine 7

Starting from Amine 6

After crystallization.

A mixture of 3-hydroxy-4-(methoxymethoxy)benzaldehyde (9, 1.82 g, 10.0 mmol), CH$_3$NO$_3$ (30 mL), NH$_2$OAc (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$_3$) $\delta$ 7.80 (d, $J = 13.6$ Hz, 1H), 7.49 (d, $J = 13.6$ Hz, 1H), 7.15 (m, 1H), 7.14 (s, 1H), 7.06–0.2 (m, 1H), 6.12 (bs, 1H), 5.29 (2H), 3.53 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 147.7, 146.6, 139.0, 135.7, 124.5, 112.3, 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.

$\beta$-3-Hydroxy-4-(methoxymethoxy)phenethylamine (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$_2$CO$_3$ (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$_4$Cl (3 mL) was added, and stirring was continued for 1 h. Filtration and evaporation of the combined organic extracts gave amine 11 (1.62 g, 1.65 mmol, which was pure enough for the next step: IR (film) $\nu$ (cm$^{-1}$) 2938, 1507; $^1$H NMR (CD$_3$OD) $\delta$ 6.96 (d, $J = 8.2$ Hz, 1H), 6.68 (s, 1H), 6.61–6.56 (m, 1H), 5.10 (2H), 3.43 (s, 3H), 3.27 (s, 1H), 2.87 (s, $J = 7.25$ Hz, 2H), 2.65 (s, $J = 7.25$ Hz, 2H); $^{13}$C NMR (CD$_3$OD) $\delta$ 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 + H]$^+$ calcd. for C$_{10}$H$_{15}$NO$_3$, 197.1053; found, 197.1052.

$\beta$-3-Hydroxy-4-(methoxymethoxy)phenethylamine (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$_2$CO$_3$ 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/ethanol acetate ($v/v/v = 50/50/2–50/50/8$) as eluent], (1.012 g, 2.89 mmol, 70%). IR (film) $\nu$ (cm$^{-1}$) 3348, 1504; $^1$H NMR (CDCl$_3$) $\delta$ 8.26 (dd, $J$ = 5.3 Hz, 0.7 Hz, 0.3 Hz), 8.12 (d, 0.3 Hz, 0.3 Hz, 0.3 Hz), 7.24 (m, 1H), 6.85–6.68 (m, 1H), 5.10 (s, 2H), 3.43 (s, 3H), 3.27 (s, 1H) 2.87 (s, $J = 7.25$ Hz, 2H), 2.65 (s, $J = 7.25$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 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 + H]$^+$ calcd. for C$_{10}$H$_{15}$NO$_3$, 225.0637; found, 225.0631.

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= 8.3, 1.4 H, 1H), 7.79 (m, 1H), 7.57 (dd, J = 8.3, 7.1, 1.4 Hz, 1H), 7.23 (dd, J = 8.3, 7.1, 1.4 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); 13C NMR (101 MHz, CDCl3) δ 146.4, 145.6, 143.0, 142.4, 133.8, 133.6, 125.6, 124.3, 124.0, 120.8, 115.7, 59.9, 56.2, 52.4, 36.1. HRMS (EI, TOF) m/z: [M]+ calc'd for C18H16O3S, 308.0995; found, 308.0996.

General Procedure for Aldehyde Homologation (A): Wittig Reaction. KIO4-But (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)triphenylphosphorane 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 NH4Cl and extractive workup with Et2O gave a crude mixture that was purified by flash chromatography [silica, EtOAc/PE mixtures] to provide the enol ether as a ca. 1:1 mixture of E/Z isomers.

4-(tert-Butylidimethylsilyloxy)-1-(2-methoxyvinyl)benzene (13a). The title compound was synthesized from 4-(tert-butylidimethylsilyloxy)benzaldehyde [silica, ethyl acetate/petroleum ether 1/100 (30.0 mmol)] and (methoxymethyl)triphenylphosphorane 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 NH4Cl and extractive workup with Et2O gave a crude mixture that was purified by flash chromatography [silica, EtOAc/PE mixtures] to provide the enol ether as a ca. 1:1 mixture of E/Z isomers.

3-(tert-Butylidimethylsilyloxy)-4-methoxy-1-(2-methoxyvinyl)benzene (13b). The title compound was synthesized from 3-(tert-butylidimethylsilyloxy)benzaldehyde [silica, ethyl acetate/petroleum ether 1/100 (30.0 mmol)] and (methoxymethyl)triphenylphosphorane 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 NH4Cl and extractive workup with Et2O gave a crude mixture that was purified by flash chromatography [silica, EtOAc/PE mixtures] to provide the enol ether as a ca. 1:1 mixture of E/Z isomers.

1-(tert-Butylidimethylsilyloxy)-3,3,5-trimethoxybenzene (13c). The title compound was synthesized from 3,3,5-trimethoxybenzaldehyde [silica, ethyl acetate/petroleum ether 1/100 (30.0 mmol)] and (methoxymethyl)triphenylphosphorane 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 NH4Cl and extractive workup with Et2O gave a crude mixture that was purified by flash chromatography [silica, EtOAc/PE mixtures] to provide the enol ether as a ca. 1:1 mixture of E/Z isomers.

4-(tert-Butylidimethylsilyloxy)phenylacetaldelyde (14a). Prepared from 13a [silica, ethyl acetate/petroleum ether 1/100 (30.0 mmol)] as an oil (0.634 g, 2.54 mmol, 63%); spectra in accordance with the literature.27

E/Z mixture at 75 % (95.95 mmol, 15.20 mmol) in 3,4-dimethoxybenzaldehyde (3.32 g, 20 mmol) [silica, EtOAc/PE mixtures] to provide the enol ether as a ca. 1:1 mixture of E/Z isomers.
(92.0 mg, 0.157 mmol, 79%), 86% ee; HPLC, Chiralcel AD, \( t = 149.8, 145.3, 145.0, 144.8, 144.3, 142.7, 132.6, 131.7, 125.2, 124.9, 124.3, 124.1, 123.9, 115.5, 112.2, 96.1, 77.2, 68.6, 64.6, 56.3, 55.6, 50.2, 46.1, 43.8, 38.3, 30.1, 25.6, 25.2, 18.3, -4.77. HRMS (FD, TOF) \( m/z \): [M]\(^+\) calcd for C\(_{19}\)H\(_{22}\)NO\(_9\)S, 542.1273; found, 542.1743.

19a: Prepared from Animes 6 and Aldehyde 14a. Yellow glass (89.1 mg, 0.161 mmol, 81%); \( t_\text{p} \) (major) = 25.7 min, \( t_\text{p} \) (minor) = 33.2 min; \( \alpha \) (major) = 37.2: \( \beta \) (minor) = 18.6; \( c = 1.0, \text{CHCl}_3 \); \( ^1\text{H} \) NMR (CDCl\(_3\)) \( \delta = 2.75 \) (s, 3H), 2.71 (s, 3H), 2.67 (bs, 2H), 2.46 (m, 1H), 2.33 (m, 1H), 1.84 (s, 3H), 1.78 (s, 3H), 1.51 (s, 3H), 1.37 (s, 3H), 1.23 (s, 3H), 1.04 (t, 6H), 0.95 (s, 3H), 0.82 (q, 6H), 0.03 (s, 1H); \( ^{13}\text{C} \) NMR (CDCl\(_3\)) \( \delta = 137.1, 134.1, 133.4, 128.5, 127.7, 126.8, 126.3, 124.7, 123.1, 121.6, 114.5, 114.1, 113.3, 112.3, 111.9, 109.0, 108.9, 107.0, 76.6, 66.2, 60.5, 60.2, 55.9, 55.7, 50.0, 46.4, 44.1, 42.1, 29.9, 25.3, 14.1. HRMS (FD, TOF) \( m/z \): [M]\(^+\) calcd for C\(_{27}\)H\(_{30}\)N\(_2\)O\(_8\)S, 542.1723; found, 542.1743.

19b: Prepared from Animes 6 and Aldehyde 14b. Yellow glass (92.0 mg, 0.157 mmol, 79%); \( c \) = 1.0, \text{CHCl}_3; \( ^1\text{H} \) NMR (CDCl\(_3\)) \( \delta = 2.75 \) (s, 3H), 2.60 (s, 3H), 2.32 (bs, 1H), 1.98 (s, 3H), 1.83 (s, 3H), 1.71 (q, 6H), 1.65 (m, 2H), 1.46 (bs, 1H), 1.34 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H), 0.80 (t, 6H), 0.53 (s, 1H), 0.18 (s, 1H); \( ^{13}\text{C} \) NMR (CDCl\(_3\)) \( \delta = 144.5, 142.6, 133.2, 132.1, 131.2, 127.6, 127.2, 126.3, 125.7, 124.1, 121.8, 121.3, 119.7, 114.7, 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\(_{27}\)H\(_{29}\)N\(_2\)O\(_8\)S, 582.2220; found, 582.2273.

19c: Prepared from Animes 6 and Aldehyde 14c. Yellow glass (80.0 mg, 0.166 mmol, 83%); \( t_\text{p} \) (major) = 32.0 min; \( \alpha \) (major) = 37.2: \( \beta \) (minor) = 18.6; \( c = 1.0, \text{CHCl}_3 \); \( ^1\text{H} \) NMR (CDCl\(_3\)) \( \delta = 2.75 \) (s, 3H), 2.71 (s, 3H), 2.67 (bs, 2H), 2.46 (m, 1H), 2.33 (m, 1H), 1.84 (s, 3H), 1.78 (s, 3H), 1.51 (s, 3H), 1.37 (s, 3H), 1.23 (s, 3H), 1.04 (t, 6H), 0.95 (s, 3H), 0.82 (q, 6H), 0.03 (s, 1H); \( ^{13}\text{C} \) NMR (CDCl\(_3\)) \( \delta = 137.1, 134.1, 133.4, 128.5, 127.7, 126.8, 126.3, 124.7, 123.1, 121.6, 114.5, 114.1, 113.3, 112.3, 111.9, 109.0, 108.9, 107.0, 76.6, 66.2, 60.5, 60.2, 55.9, 55.7, 50.0, 46.4, 44.1, 42.1, 29.9, 25.3, 14.1. HRMS (FD, TOF) \( m/z \): [M]\(^+\) calcd for C\(_{27}\)H\(_{30}\)N\(_2\)O\(_8\)S, 542.1723; found, 542.1743.

19d: Prepared from Animes 6 and Aldehyde 14d. Yellow glass (80.0 mg, 0.166 mmol, 98%); \( c \) = 1.0, \text{CHCl}_3; \( ^1\text{H} \) NMR (CDCl\(_3\)) \( \delta = 2.75 \) (s, 3H), 2.60 (s, 3H), 2.32 (bs, 1H), 1.98 (s, 3H), 1.83 (s, 3H), 1.71 (q, 6H), 1.65 (m, 2H), 1.46 (bs, 1H), 1.34 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H), 0.80 (t, 6H), 0.53 (s, 1H), 0.18 (s, 1H); \( ^{13}\text{C} \) NMR (CDCl\(_3\)) \( \delta = 144.5, 142.6, 133.2, 132.1, 131.2, 127.6, 127.2, 126.3, 125.7, 124.1, 121.8, 121.3, 119.7, 114.7, 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\(_{27}\)H\(_{29}\)N\(_2\)O\(_8\)S, 582.2220; found, 582.2273.

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\(_2\)CO\(_3\) (0.15g) and methyl iodide (40 \( \mu \)L) 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.
Obtained as hydrochloride from 18c (0.190 mmol) by deprotection (method F); glass (41.5 mg, 0.124 mmol, 88%); ee 85% (determined for 26 after N-methylation; \( [\alpha]_{D}^{20} = +195.5 (c = 1.0, \text{MeOH}) \)); \( [\alpha]_{D}^{20} = +94.2 (c = 1.0, \text{CHCl}_{3}) \)); \( [\alpha]_{D}^{20} = +165.5 (c = 1.0, \text{MeOH}) \). \( [\alpha]_{D}^{20} = +94.2 (c = 1.0, \text{CHCl}_{3}) \). \( [\alpha]_{D}^{20} = -116.5 (c = 1.0, \text{MeOH}) \). 

**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@uu.nl.

**Notes**

The authors declare no competing financial interest.

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