Total Synthesis of the Ortho-Hydroxylated Protoberberines (S)-Govaniadine, (S)-Caseamine, and (S)-Clarkeanidine via a Solvent-Directed Pictet-Spengler Reaction


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Total Synthesis of the Ortho-Hydroxylated Protoberberines (S)-Govaniadine, (S)-Caseamine, and (S)-Clarkeanidine via a Solvent-Directed Pictet–Spengler Reaction

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Supporting Information

ABSTRACT: The common para regioselectivity in Pictet–Spengler reactions with dopamine derivatives is redirected to the ortho position by a simple change of solvents. In combination with a chiral auxiliary on nitrogen, this ortho-selective Pictet–Spengler produced the 1-benzyltetrahydroisoquinoline alkaloids (S)-crassifoline and (S)-norcrassifoline and the bioactive 1,2-dioxygenated tetrahydroprotoberberine alkaloids (S)-govaniadine, (S)-caseamine, and (S)-clarkeanidine with high enantiopurity. Ortho/para ratios up to 89:19 and diastereomeric ratios up to 85:15 were obtained during formation of the B-ring. The general applicability of this solvent-directed regioselectivity was demonstrated with a second Pictet–Spengler reaction as required for C-ring formation of caseamine (o/p = 14:86 in trifluoroethanol) and clarkeanidine (o/p = 86:14 in toluene).

INTRODUCTION

Most of the 1-benzyltetrahydroisoquinoline alkaloids found in nature are formed from dopamine and contain a 6,7-dioxygenated substitution pattern in the A-ring as a result of enzyme-catalyzed Pictet–Spengler condensations (Figure 1). Isomeric 1-benzyltetrahydroisoquinolines with oxygen substituents at C-7 and C-8 are less abundant in nature but display interesting biological properties. Examples of more complex alkaloids derived from 7,8-dioxygenated 1-benzyltetrahydroisoquinolines are the parent compound crassifoline (3), several tetrahydroprotoberberines (e.g., govaniadine (4)), the caseine alkaloids (5), and pavine alkaloids such as neocaryachine (6). Labeling studies performed by Müller and Zenk to elucidate the biosynthesis of crassifoline and the caseine alkaloids showed that this unusual oxygenation pattern in the tetrahydroisoquinoline ring is not formed by oxygen transposition but most likely by an ortho-selective Pictet–Spenglerase, although this enzyme has not yet been described in literature.

The enantioselective chemical syntheses of 6,7-oxygenated 1-benzyltetrahydroisoquinolines preferably follow the lines of the biosynthesis. In particular, the Bischler–Napieralski method, in combination with asymmetric hydrogenation or by chiral auxiliary directed hydride reduction, is favored for enantioselective preparations (reviewed by Rozwadowska in 2004 and 2016, see ref 2). A practical synthesis of the 7,8-dioxygenated tetrahydroisoquinoline ring system, however, is not accessible via the Bischler–Napieralski reaction, which exclusively yields para products. Likewise, the Pictet–Spengler approach with chiral (organo)catalysis, or with assistance of chiral auxiliaries, is only effective for the traditional 6,7-substitution pattern. A few methods are described to prepare this 7,8-substitution pattern, and these are not based on Pictet–Spengler or Bischler–Napieralski approaches but require multistep quinoline ring construction. Rodrigues described an efficient build-up/chiral auxiliary approach to ortho-hydroxylated crassifoline and the cularine alkaloids. Halogen atoms as temporary blocking substituents at positions in the aromatic ring that should stay unsubstituted are also applied.

Ortho selectivity toward an activating substituent in Mannich-type cyclizations is more often observed, but in the Pictet–Spengler reaction, ring closure ortho to the phenolic substituent is always a minor process in comparison to the para position. The pH dependency of ortho/para ratios was investigated by Bates, who found pH 7 as an optimum for ortho product formation (o/p = 50:50) using formaldehyde or acetaldehyde. In a previous publication on the synthesis of javaberine alkaloids, we reported that the regioselectivity of the Pictet–Spengler reaction between secondary phenylethylamines and aldehydes depends strongly on the solvent and varies between 99% para selectivity in trifluoroethanol to 81% ortho selectivity in aprotic, apolar solvents without addition of external acids (Scheme 1).

Furthermore, both ortho and para products were formed as single diastereomers. To translate this uncatalyzed Pictet–
Spengler procedure\textsuperscript{9} to both the challenging ortho regioselectivity and enantioselectivity in the 1-benzyltetrahydroisoquinoline series, we herein disclose a chiral auxiliary approach starting from a (S)-(-)-\alpha-methylbenzyl-functionalized dopamine analogue.\textsuperscript{10}

\section*{RESULTS AND DISCUSSION}

The benzene ring in the dopamine part of the key precursor 10 (Scheme 2) requires activation by a free phenolic OH to allow non-acid-catalyzed Pictet–Spengler reactions with dopamine derivatives. If methoxy or methylenedioxy substituents are the activating substituents, strongly acidic catalysts are required that produce almost exclusively para-substituted Mannich-type products.\textsuperscript{2} The required phenylethylamine 10 was prepared from phenylacetaldehyde 9 that was obtained after a convenient Wittig/hydrolysis homologation process\textsuperscript{7,15} starting from isovanilline (7). Reductive amination of phenylacetaldehyde 9 with (S)-\alpha-methylbenzylamine gave chiral dopamine analogue 10. To optimize the Pictet–Spengler conditions, we selected (S)-govaniadine 4, a 1,2-oxygenated tetrahydroprotoberberine alkaloid that has not been synthesized before (Scheme 2). Govaniadine is isolated from \textit{Corydalis govaniana} Wall. and has been the subject of different studies on its biological activity since its discovery in 2013.\textsuperscript{11} These studies revealed significant analgesic activity for govaniadine, similar to that of ibuprofen, due to its potential binding to the COX-2 enzyme.\textsuperscript{12} Furthermore, high and selective leishmanicidal activity,\textsuperscript{13} anturease activity,\textsuperscript{10} and glucuronidase inhibition were reported.\textsuperscript{14}

The Pictet–Spengler reaction of aldehyde 11\textsuperscript{16} with equimolar amounts of 10 in different solvents was monitored by NMR and shows a clear solvent-dependent ortho/para distribution of the product (Table 1). Protic solvents, with TFE as the strongest proton donor, gave fast reactions with high preference for the para isomer 17, which is typical for a process that is acid catalyzed. Reactions in toluene and dichloroethane, both performed at higher dilution to prevent intermolecular catalysis by the phenolic OH, were considerably slower but gave good selectivity for the ortho isomer 15. Importantly, the diastereomeric ratio of the ortho isomers 15, with the required (S)-configuration at C-1\textsuperscript{17} and 16 (R-configuration at C-1, not shown) in toluene and dichloro-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{General biocatalytic Pictet–Spengler reactions and some examples of alkaloids based on the 7,8-dioxygenated tetrahydroisoquinoline structure.}
\end{figure}

\begin{scheme}[H]
\caption{Ortho-Selective Pictet–Spengler Reaction toward the Javaberine Synthesis (ref 7a)}
\end{scheme}

\begin{scheme}[H]
\caption{Ortho and Para Product Formation: Activation of the Enamine Intermediate in Aprotic and Protic Solvents}
\end{scheme}
Norcrassifoline (23) was also used as the synthetic precursor for the related protoberberines caseamine (24)\textsuperscript{18}, displaying activity against urease,\textsuperscript{14} and clarkeanide (25)\textsuperscript{19}. Biosynthetically, the ring closure of 1-benzyltetrahydroisoxquinolines to tetrahydroprotoberberines does not proceed with formaldehyde but via the berberine bridging enzyme (BBE) catalyzed oxidation of N-methylated benzyltetrahydroisoxquinolines, immediately followed by ring closure of the intermediate methylene iminium salt (Scheme 5).\textsuperscript{20}

A clear preference of this enzyme for ring-closure ortho to the phenolic OH (26) is observed, which hampers the synthesis of para products via biocatalytic routes.\textsuperscript{21} Similar to the synthetic Pictet–Spengler approaches under traditional protic conditions using formaldehyde and a free NH substrate, the para isomer is formed exclusively when alkoxy groups are used as the activating substituents,\textsuperscript{22} as we also have shown in the govaniadine synthesis (Scheme 2). When a free phenolic OH is the activator, the para product (28) is always formed in excess, but is accompanied by some ortho product.\textsuperscript{22–24}

Application of the solvent-directed Pictet–Spengler process (see Scheme 2) to the tetrahydroprotoberberine synthesis with norcrassifoline and formaldehyde selectively produced both isomers under mild conditions (Scheme 4). The para isomer (S)-caseamine 24 was obtained by reaction of 23 with formaline in trifluoroethanol [64%, o/p = 14:86, >99% ee after recrystallization, $\{\alpha\}^{20}_{D} = -314$ (lit.\textsuperscript{18} $\{\alpha\}^{20}_{D} = -328$)]. Starting from 23 under aprotic conditions using paraformaldehyde in toluene, the ortho isomer (S)-clarkeanide 25 was formed [55%, o/p = 86:14, 95% ee after crystallization, $\{\alpha\}^{20}_{D} = -442$ (lit.\textsuperscript{19} $\{\alpha\}^{20}_{D} = -277$)].

In conclusion, we have shown that Pictet–Spengler reactions under apolar conditions can produce the otherwise difficult to access ortho-oxygenated products. The chiral auxiliary-supported route is straightforward, scalable, and in particular, suitable for high diastereoselectivity in orthohydroxylated tetrahydroisoxquinoline preparations. In addition, application of this solvent-directed Pictet–Spengler approach to regioselective tetrahydroprotoberberine synthesis provides a useful addition to existing methods.

### EXPERIMENTAL SECTION

**General Information.** Anhydrous CH\textsubscript{2}Cl\textsubscript{2} and CH\textsubscript{3}CN were freshly distilled from CaH\textsubscript{2}. Dried THF was obtained by distillation from sodium/benzophenone. DMF and DMSO on 4 Å molecular sieves were obtained from Sigma-Aldrich and stored under N\textsubscript{2} atmosphere. Toluene was distilled and stored on 4 Å molecular sieves. Reagents were purchased with the highest purity (usually >98%) from Sigma-Aldrich and Fluorochem and used as received. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254). SilaFlash P60 (particle size 40–65 μm) was used for silica column chromatography. NMR spectra were recorded on Bruker DRX-500, -600, and -300 MHz instruments and calibrated on residual undeuterated solvent signals as internal standard. The $^1$H NMR multiplicities were abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet. High-resolution mass spectra (HRMS) were recorded on a AccuTOF GC v 4g, JMS-T100GC mass spectrometer (JEOL, Japan). An FD/FI probe equipped with a FD emitter of 10 μm. Current rate 5.12 mA/min over 1.2 min machine using field desorption (FD) as ionization method. IR spectra were recorded on a Bruker Alpha FTIR machine. Chiral HPLC was performed with a Shimadzu LC-20AD with Shimadzu SPD-M20A diode array detector using a Daicel Chiralcel AD column (eluent n-heptane/2-propanol 70/30, flow 1.000 mL/min, λ 230 nm).

### Table 1. Ortho/Para Ratios in the Pictet–Spengler Cyclization of 10

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>$T$ (°C)</th>
<th>time</th>
<th>o/p (15/17)</th>
<th>ee (15/16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFE</td>
<td>75</td>
<td>1 h</td>
<td>10:90</td>
<td>53:47</td>
</tr>
<tr>
<td>2</td>
<td>methanol</td>
<td>65</td>
<td>2 d</td>
<td>38:62</td>
<td>60:40</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>80</td>
<td>2 d</td>
<td>65:35</td>
<td>60:40</td>
</tr>
<tr>
<td>4</td>
<td>DCE\textsuperscript{c}</td>
<td>80</td>
<td>4 d</td>
<td>72:28</td>
<td>85:15</td>
</tr>
<tr>
<td>5</td>
<td>toluene\textsuperscript{c}</td>
<td>105</td>
<td>4 d</td>
<td>81:19</td>
<td>73:27</td>
</tr>
</tbody>
</table>

\textsuperscript{a}At >80% conversion, determined by $^1$H NMR. \textsuperscript{b}The para isomer was formed as a ca. 50:50 mixture of inseparable diastereomers. \textsuperscript{c}Performed at 40 mM. TFE = 2,2,2-trifluoroethanol, DCE = 1,2-dichloroethane.

The recrystallized product (>99% ee) gave an optical rotation which is typical for such systems: $\{\alpha\}^{20}_{D} = -59.9$ (c = 0.1, methanol), indicating that the product isolated from *Corydalis govania Wall.* was not optically pure.\textsuperscript{11}

**Scheme 3. Synthesis of Govaniadine**
Synthetic Procedures.

2-Methoxy-5-(2-methoxyethenyl)phenol (8).15 KOT-Bu (22.4 g, 200 mmol) was added in three portions, with intervals of 3 min, to an efficiently stirred suspension of methoxymethyltriphenyl phosphonium chloride (34.3 g, 100 mmol) in dry THF (250 mL) with ice cooling. After additional stirring for 5 min, isovanillin 7 (13.7 g, 90 mmol) was added in three portions, with intervals of 2 min, to the reaction mixture resulting in a rapid color change from red to yellow. The cooling bath was removed, and the mixture was stirred at rt for 5 h. Silica gel was added (150 g), the solvents were evaporated thoroughly, and the residue was put on top of a silica column. Flash chromatography (petroleum ether/ethyl acetate 4/1, 3/1 and 2.5/1) gave 8 (13.3 g, 73.9 mmol, 82%, 45:55 E/Z mixture) as an oil, which solidified upon standing. The spectra were identical with those of ref 15: 1H NMR (400 MHz, CDCl3) δ 7.09 (dd, J = 8.4, 2.1 Hz, 1H), 7.05–6.93 (m, 2H), 6.87–6.69 (m, 3H), 6.12 (s, 1H), 6.08 (dd, J = 7.0 Hz, 1H), 5.82 (d, J = 12.9 Hz, 1H), 5.20 (d, J = 7.0 Hz, 1H), 3.825 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 3.68 (s, 3H).

2-(3-Hydroxy-4-methoxyphenyl)acetaldehyde (9). A mixture of TFA (5 mL) and water (5 mL) was added to a solution of enol ether 8 (7.39 g, 41.0 mmol) in DCM (200 mL). The resulting heterogeneous mixture was stirred vigorously overnight at rt. Water was added, and after separation the organic layer was washed with NaHCO3 aq and dried over Na2SO4. Chromatographic separation (2/1 and 3/2 petroleum ether/ethyl acetate) gave pure 9 (3.75 g, 24.7 mmol, 60%) as an oil, which solidified in the freezer: 1H NMR (400 MHz, CDCl3) δ 9.66 (t, J = 2.4 Hz, 1H), 6.83 (dd, J = 8.2, 1.0 Hz, 1H), 6.78 (d, J = 2.1 Hz, 1H), 6.67 (dd, J = 8.2, 2.1 Hz, 1H), 6.12 (s, 1H), 3.83 (s, 3H), 3.55 (d, J = 2.4 Hz, 2H); 13C{1H} NMR (101 MHz, CDCl3) δ 199.7, 145.9, 145.8, 124.6, 120.9, 115.7, 111.0, 55.7, 49.5.

(S)-2-Methoxy-5-((1-phenylethyl)amino)ethyl)phenol (10). Aldehyde 9 (3.74 g, 22.5 mmol) and (S)-(−)-α-methylbenzylamine (3.1 mL, 24 mmol) were dissolved in THF (75 mL) and stirred at 0 °C for 30 min. Sodium triacetoxyborohydride (10.6 g, 50 mmol) was added, and the mixture was stirred at 0 °C for 30 min and at rt for 14 h. The solvent was evaporated, and the residue was dissolved in ethyl acetate and washed with Na2CO3 solution and water. Next, the product was extracted from the organic layer with aqueous HCl (3 × 100 mL). The water layer was washed three times with ethyl acetate before the water layer was basified with Na2CO3 solution. Extraction with ethyl acetate, drying with Na2SO4, and evaporation of the solvent gave chiral amine 10 (5.02 g, 18.5 mmol, 82%) as a solid: mp 86–92 °C; 1H NMR (400 MHz, CDCl3) δ 7.45–7.14 (m, 5H), 6.81–6.73 (m, 2H), 6.66 (dd, J = 8.2, 2.3 Hz, 1H), 5.65 (bs, 1H), 3.88 (s, 3H), 3.78 (q, J = 6.7 Hz, 1H), 2.87–2.47 (m, 4H), 1.35 (d, J = 6.7 Hz, 3H); 13C{1H} NMR (75 MHz, CDCl3) δ 146.0, 145.6, 145.0, 132.8, 128.5, 127.0, 126.7, 119.7, 115.5, 111.5, 58.2, 55.9, 48.7, 35.3, 23.9; HRMS (ESI+) m/z calcld for C17H22NO2 (M + H)+ 272.1651, found 272.1642.

Scheme 4. Synthesis of Caseamine and Clarkeanide via Norcrassifoline

Scheme 5. Ortho vs Para Selectivity in Tetrahydroberberine Synthesis

2-(3-Hydroxy-4-methoxyphenyl)acetaldehyde (9).

Aldehyde 9 (3.74 g, 22.5 mmol) and (S)-(−)-α-methylbenzylamine (3.1 mL, 24 mmol) were dissolved in THF (75 mL) and stirred at 0 °C for 30 min. Sodium triacetoxyborohydride (10.6 g, 50 mmol) was added, and the mixture was stirred at 0 °C for 30 min and at rt for 14 h. The solvent was evaporated, and the residue was dissolved in ethyl acetate and washed with Na2CO3 solution and water. Next, the product was extracted from the organic layer with aqueous HCl (3 × 100 mL). The water layer was washed three times with ethyl acetate before the water layer was basified with Na2CO3 solution. Extraction with ethyl acetate, drying with Na2SO4, and evaporation of the solvent gave chiral amine 10 (5.02 g, 18.5 mmol, 82%) as a solid: mp 86–92 °C; 1H NMR (400 MHz, CDCl3) δ 7.45–7.14 (m, 5H), 6.81–6.73 (m, 2H), 6.66 (dd, J = 8.2, 2.3 Hz, 1H), 5.65 (bs, 1H), 3.88 (s, 3H), 3.78 (q, J = 6.7 Hz, 1H), 2.87–2.47 (m, 4H), 1.35 (d, J = 6.7 Hz, 3H); 13C{1H} NMR (75 MHz, CDCl3) δ 146.0, 145.6, 145.0, 132.8, 128.5, 127.0, 126.7, 119.7, 115.5, 111.5, 58.2, 55.9, 48.7, 35.3, 23.9; HRMS (ESI+) m/z calcld for C17H22NO2 (M + H)+ 272.1651, found 272.1642.
An equimolar solution of 10 and 11 in toluene was refluxed for 20 min. Evaporation of the solvent gave unstable enamine 12, mixed with small amounts of starting materials and Pictet–Spengler products: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42–7.13 (m, 10H), 6.87 (d, J = 14.0 Hz, 1H), 6.82–6.68 (m, 5H), 6.64 (dd, J = 8.1, 1.8 Hz, 2H), 5.92 (s, 2H), 5.31 (d, J = 14.0 Hz, 1H), 4.45 (q, J = 7.0 Hz, 1H), 3.89 (s, 3H), 3.20 (m, 2H), 2.48 (br s, 2H), 1.56 (d, J = 7.0 Hz, 3H). $^{13}$C{1H} NMR (101 MHz, CDCl$_3$) $\delta$ 148.0, 145.7, 145.2, 143.8, 142.8, 137.8, 133.0, 134.8, 133.1, 129.1, 128.7, 128.5, 128.4, 128.2, 127.5, 127.2, 127.0, 126.9, 125.3, 120.1, 120.0, 119.6, 115.1, 115.0, 110.8, 108.5, 103.5, 100.7, 100.5, 97.1, 61.4, 55.9, 55.9, 55.9, 49.6, 33.2, 21.5, 19.1.

**Pictet–Spengler of 10 with Aldehyde 11.**

A solution of 10 (0.542 g, 2.0 mmol) and homopereonal 11 (0.345 g, 2.1 mmol) in anhydrous toluene (50 mL) was stirred at 105 °C for 4 days. Evaporation of the solvent and separation by flash chromatography (petroleum ether/ethyl acetate 19/1, 10/1, and 4/1) provided first the minor (R)-ortho isomer 16 (0.150 g, 0.360 mmol, 18%), then the desired isomer 15 (0.401 g, 0.962 mmol, 48%), and finally, an inseparable mixture of two para isomers 17 (0.135 g, 0.324 mmol, 16%). 16: [α]$_D^{20}$ = −2.0 (MeOH, c = 2.1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.31–7.24 (m, 2H), 7.25–7.19 (m, 3H), 6.79 (s, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 6.11–5.92 (m, 2H), 5.80 (s, 1H), 4.50 (dd, J = 10.3, 3.0 Hz, 1H), 3.92 (s, 1H), 3.70 (q, J = 6.4 Hz, 2H), 3.31–3.15 (m, 1H), 3.06 (d, J = 13.7, 3.0 Hz, 1H), 2.89–2.78 (m, 2H), 2.77–2.70 (m, 2H), 2.27–2.20 (m, 1H), 1.03 (d, J = 6.4 Hz, 3H), $^{13}$C{1H} NMR (101 MHz, CDCl$_3$) $\delta$ 146.9, 146.4, 145.3, 143.9, 142.3, 135.7, 128.4, 128.1, 127.2, 126.5, 125.0, 122.5, 119.4, 119.3, 110.8, 107.4, 100.5, 57.7, 56.0, 54.2, 39.6, 39.5, 22.5, 21.8; IR (neat) ν 3514, 1487 cm$^{-1}$; HRMS (FD$^-$): m/z calculated for C$_{21}$H$_{22}$N$_2$O$_4$ (M + H$^+$) 418.180, found 418.206. 15: [α]$_D^{20}$ = +49.9 (MeOH, c = 1.0); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.13–7.06 (m, 1H), 7.05 (t, J = 7.4 Hz, 2H), 6.84 (d, J = 7.4 Hz, 2H), 6.76 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.64–6.56 (m, 2H), 5.97 (s, 2H), 5.63 (s, 1H), 3.96 (dd, J = 10.3, 2.9 Hz, 1H), 3.89 (s, 3H), 3.63 (q, J = 6.4 Hz, 1H), 3.47–3.38 (m, 1H), 3.33 (d, J = 14.6, 5.8 Hz, 1H), 3.01–2.84 (m, 2H), 2.74 (d, J = 13.7, 10.3 Hz, 1H), 2.53–2.34 (m, 1H), 1.29 (d, J = 6.4 Hz, 3H), $^{13}$C{1H} NMR (101 MHz, CDCl$_3$) $\delta$ 146.9, 146.4, 145.4, 140.0, 142.7, 135.1, 128.4, 127.8, 127.5, 126.2, 125.1, 122.7, 119.3, 110.4, 108.7, 107.5, 100.5, 58.9, 56.6, 56.0, 39.6, 38.7, 22.3, 22.1; IR (neat) ν 3533, 1489 cm$^{-1}$; HRMS (FD$^-$) m/z calculated for C$_{21}$H$_{22}$N$_2$O$_4$ (M + H$^+$) 418.180, found 418.206. 17: (mixture of diastereomers): $^1$H NMR (500 MHz, CDCl$_3$, selected signals) $\delta$ 7.73 (d, J = 6.4 Hz, 4H), 7.24–7.19 (m, 2H), 7.13 (t, J = 5.4 Hz, 2H), 6.74 (d, J = 7.8 Hz, 1H), 6.69 (dd, J = 10.7, 8.5 Hz, 2H), 6.60–6.58 (m, 1H), 6.52 (dd, J = 7.9, 1.7 Hz, 1H), 6.48–6.39 (m, 1H), 6.07 (s, 1H), 5.95 (d, J = 2.2 Hz, 2H), 4.02 (d, J = 8.1 Hz, 1H), 3.96–3.75 (m, 2H), 3.70 (s), 3.69 (3H), 3.63 (s, 1H), 3.34–3.21 (m, 1H), 3.19 (s, 1H), 3.17–3.01 (m, 1H), 2.85 (m, 3H), 2.80–2.61 (m, 2H), 2.52–2.27 (m, 2H), 1.39 (d, J = 6.6 Hz, 3H).

A mixture of amine 10 (1.084 g, 4.0 mmol) and aldehyde 19 (1.12 g, 4.0 mmol) was heated at 105 °C in anhydrous toluene (100 mL, 40 mM) during 5 days. Separation by flash chromatography (petroleum ether/ethyl acetate, 12/1, 10/1) provided first the minor (R)-ortho isomer 21 (0.462 g, 0.867 mmol, 21.7%) and then the desired (S)-ortho isomer 20 (0.962 g, 1.84 mmol, 45%), and finally an inseparable mixture of two para isomers in a ca. 1:1 ratio (0.221 g, 0.42 mmol).
A solution of 20 (0.587 g, 1.11 mmol) in methanol (20 mL) was stirred with HCl concd (2 mL) during 18 h at rt. The solvents were evaporated, and the residue was evaporated three times with methanol to remove water and TBSOHex to give 22 (hydrochloride, 0.453 g, 1.08 mmol, 98%) as a dark glass: 1H NMR (400 MHz, CDCl3) δ 7.53–7.45 (m, 1H), 7.43–7.36 (m, 2H), 7.11–7.05 (m, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.45–6.37 (m, 2H), 4.81–4.75 (m, 1H), 4.35 (q, J = 6.8 Hz, 1H), 4.01–3.91 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.87–3.77 (m, 2H), 3.30–3.04 (m, 2H), 2.94 (dd, J = 15.6, 10.2 Hz, 1H), 1.72 (d, J = 6.8 Hz, 3H); 13C{1H} NMR (101 MHz, CDCl3) δ 148.7, 147.9, 147.5, 146.6, 137.2, 131.0, 130.7, 129.0, 128.9, 124.1, 121.6, 120.7, 118.2, 117.3, 113.1, 112.9, 64.0, 60.0, 56.8, 56.6, 43.0, 38.8, 22.3, 18.6; HRMS (FD+) m/z calcd for C20H24NO4 (M + H)+ 342.1796, found 342.1260.

Debenzylation to Norcrassifoline (23).

Compound 22 (0.400 g, 0.877 mmol) was stirred with 10% Pd/C (0.15 g) in 12 mL of ethanol under H2 at atmospheric pressure during 18 h. Filtration over Celite and evaporation gave norcrassifoline 23 (hydrochloride, 0.276 g, 0.88 mmol, 100%) as a brown glass: [α]D20 = no transmission; 1H NMR (400 MHz, CDCl3) δ 7.07–6.92 (m, 2H), 6.92–6.79 (m, 2H), 6.74 (d, J = 8.3 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.54 (m, 2H), 3.3–3.2 (m, 2H), 3.03 (m, 2H), 2.91 (dd, J = 15.1, 10.5 Hz, 1H); 13C{1H} NMR (101 MHz, CDCl3) δ 148.7, 148.1, 147.4, 143.3, 129.9, 125.1, 121.8, 120.7, 117.2, 113.3, 112.7, 58.4, 56.8, 56.6, 55.0, 50.0, 49.8, 49.6, 49.4, 49.1, 48.9, 48.7, 48.5, 39.0, 37.6, 25.7, 18.5; HRMS (FD+) m/z calcd for C19H24NO4 (M + H)+ 316.1549, found 316.1555.

(S)-(+)-Crassifoline (3).4

A mixture of 22 (hydrochloride, 35.1 mg, 0.10 mmol), paraformaldehyde (35 mg, 0.80 mmol), sodium acetate (35 mg, 0.40 mmol), sodium cyanoborohydride (33.0 mg, 0.54 mmol), and zinc chloride (35.0 mg, 0.26 mmol) was stirred in methanol (4 mL) for 24 h at rt. Silica gel was added, and the residue obtained after evaporation was applied to a silica column. Elution with ethyl acetate, ethyl acetate/MeOH/EtOH 95/3/2, and ethyl acetate/MeOH/EtOH NH 90/7 gave crassifoline (3) (23.7 mg, 0.072 mmol, 72%) as a glass: [α]D20 +17.6 (c = 0.25 in MeOH); 1H NMR (400 MHz, CDCl3) δ 6.96 (d, J = 1.8 Hz, 1H), 6.78 (d, J = 1.7 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 5.79 (bs, 2H), 4.10 (dd, J = 9.4, 3.0 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.30 (dd, J = 12.9, 10.5, 5.0 Hz, 1H), 3.01 (dd, J = 14.3, 3.0 Hz, 1H), 2.95–2.70 (m, 3H), 2.51–2.41 (m, 1H), 2.37 (s, 3H); 13C{1H} NMR (101 MHz, CDCl3) δ 145.2, 144.9, 144.2, 142.5, 154.3, 127.2, 124.3, 120.5, 119.2, 115.6, 110.4, 109.0, 60.2, 56.1, 55.9, 44.9, 42.8, 39.5, 38.9; HRMS (FD+) m/z calcd for C17H20NO4 (M + H)+ 318.1700, found 330.1689.

(S)-(-)-Caseamine (24).18

A solution of norcrassifoline (23) (free base, 45 mg, 0.125 mmol) and 37% aqueous formaldehyde (30 µL, 0.40 mmol) in trifluoroethanol (1.0 mL) was stirred during 5 h at rt. Caseamine 24 (21.8 mg, 0.066 mmol, 53%) directly crystallized from the reaction mixture. Chromatography (ethyl acetate and ethyl acetate/MeOH 97/3 gave additional caseamine (4.5 mg, total yield 0.080 mmol, 64%) and clarkeanidine 25 (4.4 mg, 0.013 mmol, 10%, spectra see next experiment). Caseamine 24ee 99% (Chiralcel AD column, eluent n-heptane/2-propanol 70:30, flow 1.000 mL/min): [α]D20 = −314 (CHCl3 + MeOH, c = 0.15) [lit.41 [α]D20 = −328 (c = 0.04, CHCl3)]; mp 246–250 °C (lit.42 mp 246–247 °C); 1H NMR (300 MHz, d6-DMSO) partial overlap by solvent peaks δ 8.64 (s, 1H), 8.54 (s, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.62 (s, 1H), 6.55 (d, J = 8.2 Hz, 1H), 6.46 (s, 1H), 3.80 (s, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 3.46–3.36 (m, 1H), 2.96 (dt, J = 10.4, 4.8 Hz, 1H), 2.83 (dt, J = 13.2, 5.6 Hz, 1H), 2.67 (dt, J = 15.8, 4.7 Hz, 1H), 2.40 (dd, J = 16.1, 11.3 Hz, 1H); 13C{1H} NMR (75 MHz, d6-DMSO) δ 145.8, 145.2, 144.6, 142.8, 127.8, 127.0, 125.6, 124.7, 118.7, 115.2, 110.0, 109.8, 57.0, 56.0, 55.7, 47.9, 31.4, 29.3; HRMS (FD+) m/z calcd for C10H14NO4 (M+ 61) 237.1471, found 237.1499.

(S)-(-)-Clarkeanidine (25).18

A solution of norcrassifoline (23) (free base, 63 mg, 0.20 mmol) in anhydrous toluene (4 mL) was stirred with paraformaldehyde (9.0
H NMR (300 MHz, CDCl3) \( \delta = 1.60 \ (2 H, 1 H), 2.66 \ (2 H, 2 H), 3.24 \ (d, J = 6.0 \ Hz, 1 H), 3.97 \ (dd, J = 0.1, 6.0 \ Hz, 1 H), 6.66 \ (m, 2 H), 5.78 \ (bs, 2 H), 2.44 \ (d, J = 16.0 \ Hz, 1 H), 3.99 \ (dd, J = 11.2, 3.5 \ Hz, 1 H), 3.90 \ (s, 3 H), 3.89 \ (s, 3 H), 3.84 \ (d, \ J = 16.0 \ Hz, 1 H), 3.72 \ (dd, J = 16.2, 3.6 \ Hz, 1 H), 3.22 \sim 3.12 \ (m, 1 H), 3.12 \sim 3.00 \ (m, 1 H), 2.89 \sim 2.64 \ (m, 1 H), 1.45 \sim 1.42 \ (m, 1 H), 1.35 \sim 1.32 \ (m, 1 H), 1.29 \sim 1.20 \ (m, 1 H), 10.89 \sim 10.94 \ (m, 1 H), 12.56 \sim 12.62 \ (m, 1 H), 15.86 \sim 15.91 \ (m, 1 H)

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**References**


4. (a) Alkaloids. 25 (361 mg, 0.11 mmol, 55%) and then ethyl acetate/MeOH 97/3 for the para isomer caseamine 24 (6 mg, 0.018 mmol, 9%). Clarkeine (25): mp 177–180 °C (recrystallized from DCM/ petroleum ether), \( \text{lit.}^5 \) mp 178–179 °C; ee 95% (Chiralcel AD column, eluent n-heptane/2-propanol 70:30, flow 1.000 mL/min); \( \delta \) 1H NMR (300 MHz, CDCl3) \( \delta = 0.1 \ (1 H, CHCl3) \ [\text{lit.}^17,18 \ [\delta \text{1H} 20 = 9.1 \ (2 H, 2 H), 4.36 \ (d, J = 7.0 \ Hz, 2 H), 3.99 \ (dd, J = 11.2, 3.5 \ Hz, 1 H), 3.90 \ (s, 3 H), 3.89 \ (s, 3 H), 3.84 \ (d, J = 16.0 \ Hz, 1 H), 3.72 \ (dd, J = 16.2, 3.6 \ Hz, 1 H), 3.22 \sim 3.12 \ (m, 1 H), 3.12 \sim 3.00 \ (m, 1 H), 2.89 \sim 2.64 \ (m, 1 H), 1.45 \sim 1.42 \ (m, 1 H), 1.35 \sim 1.32 \ (m, 1 H), 1.29 \sim 1.20 \ (m, 1 H), 10.89 \sim 10.94 \ (m, 1 H), 12.56 \sim 12.62 \ (m, 1 H), 15.86 \sim 15.91 \ (m, 1 H)


(17) The 1-(S)-configuration of 15 was determined by conversion to (S)-govaniadine.


