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Article

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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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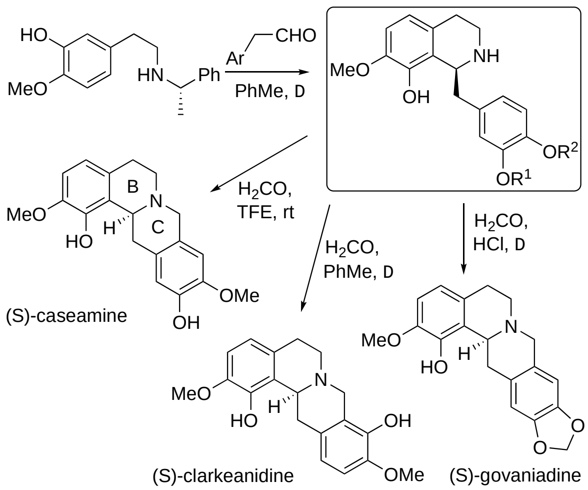
ABSTRACT



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-benzyltetrahydro-isoquinoline alkaloids (*S*)-crassifoline, (*S*)-norcrassifoline and the bioactive 1,2-dioxygenated tetrahydro-protoberberine 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 (Fig 1).[1,2] Isomeric 1-benzyltetrahydroisoquinolines with oxygen substituents at C-7 and C-8 are less abundant in nature, but display interesting biological properties.[3] 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 cularine alkaloids (**5**)[4] and pavine alkaloids such as neocaryachine (**6**). Labelling studies performed by Müller and Zenk[5] to elucidate the biosynthesis of crassifoline and the cularine 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.[2,3,6,7] 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.[4a] Halogen atoms as temporary blocking substituents at positions in the aromatic ring that should stay unsubstituted are also applied.[4b]

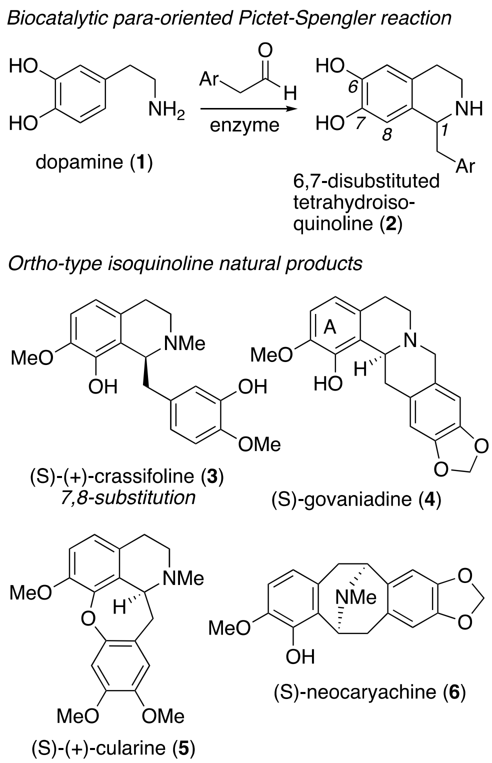
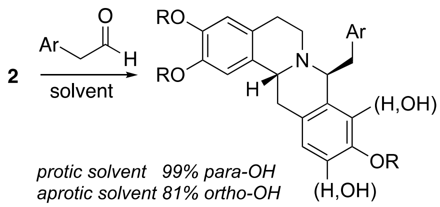


Figure 1. The general biocatalytic Pictet-Spengler reactions and some examples of alkaloids based on the 7,8-dioxygenated tetrahydroisoquinoline-structure

Ortho selectivity towards 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.[8]

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).[7a]

Scheme 1. Ortho selective Pictet-Spengler reaction towards the javaberine synthesis (ref 7a)



Furthermore, both ortho and para products were formed as single diastereomers. To translate this uncatalyzed Pictet-Spengler procedure[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*)-(–)-α-methylbenzyl functionalized dopamine analogue.[10]

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.[2] The required phenylethylamine **10** was prepared from phenylacetaldehyde **9** that was obtained after a convenient Wittig/hydrolysis homologation process[7,15] starting from isovanilline (**7**). Reductive amination of phenylacetaldehyde **9** with (*S*)-α-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 *Corydalis govaniana Wall*. and has been the subject of different studies on its biological activity since its discovery in 2013.[11] These studies revealed significant analgesic activity for govaniadine, similar to that of ibuprofen, due to its potential binding to the COX-2 enzyme.[12] Furthermore, high and selective leishmanicidal activity[13], anti-urease activity[10] and glucoronidase inhibition were reported.[14]

The Pictet-Spengler reaction of aldehyde **11**[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**.

Scheme 2. Ortho and para product formation: activation of the enamine intermediate in aprotic and protic solvents

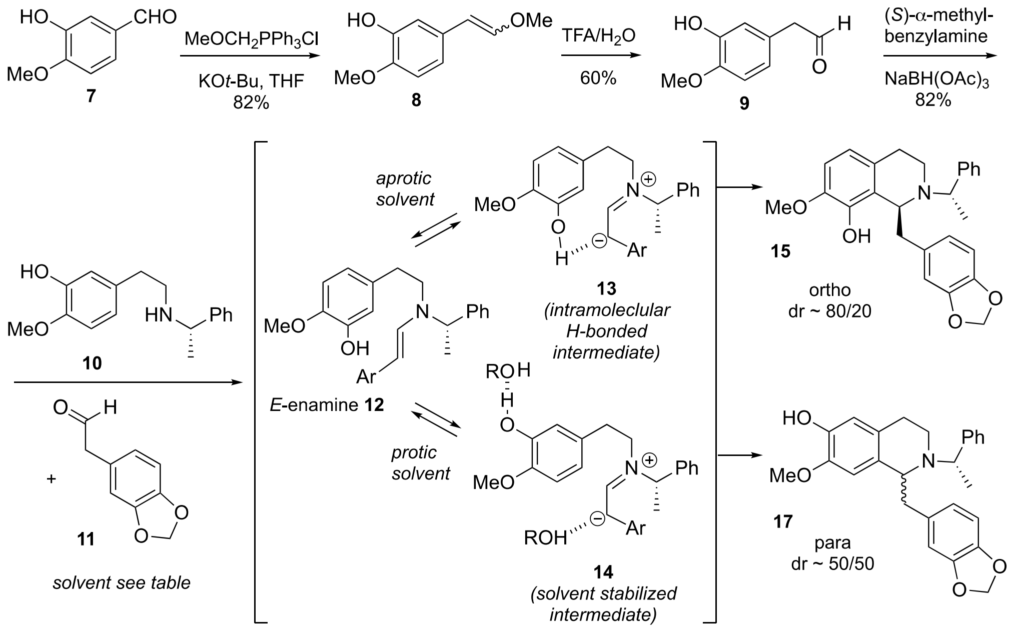


Table 1. Ortho/para ratios in the Pictet-Spengler cyclization of 10

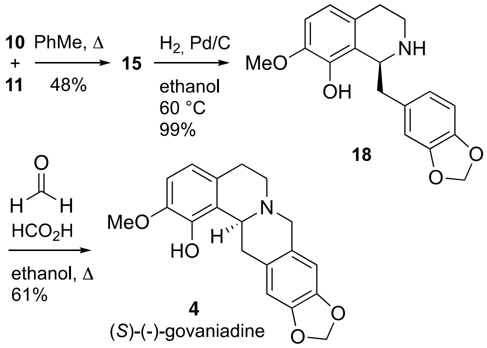
Entry	Solvent	*T* (°C)	time	*ortho/para* [a] (**15**/**17**)	dr *ortho* [b] (**15**/**16**)
1	TFE	75	1 h	10:90	53:47
2	methanol	65	2 d	38:62	60:40
3	MeCN	80	2 d	65:35	60:40
4	DCE [c]	80	4 d	72:28	85:15
5	toluene [c]	105	4 d	81:19	73:27

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

Importantly, the diastereomeric ratio of the ortho isomers **15**, with the required (*S*)-configuration at C-1[17] and **16** **(***R*-configuration at C-1, not shown) in toluene and dichloroethane was good, and the isomers were readily separable by chromatography. This is in sharp contrast with the para isomer **17**, which was formed exclusively as an inseparable mixture of both diastereomers in nearly equal amounts. NMR-spectra of the crude reaction mixtures at an early stage showed that the reactants were converted into the unstable, *E*-enamine **12**. An explanation for the high (*S*)-preference at C-1 in the ortho isomer can be found in reaction intermediate **13**, assuming that the intramolecular hydrogen bonded structure shown in Scheme 2 is favoured in aprotic solvents. The compact structure of intermediate **13** enhances approach of the aromatic ring from the top side of the iminium ion. In toluene the highest ortho/para ratio was obtained, while DCE gave a better diastereomeric ratio. Since the yields in both solvents were comparable, toluene was selected for scaling up the synthesis, providing pure **15** in 48% isolated yield. Debenzylation of **15** to **18** and cyclization of the C-ring with formaldehyde under acidic conditions produced (*S*)-(−)-govaniadine **4**, which was identical to the natural product (Scheme 3).[11] Final analysis of the recrystallized product (>99% ee) gave an optical rotation which is typical for such systems: $[\alpha]_D^{20}$ −339 (c = 0.55, methanol).

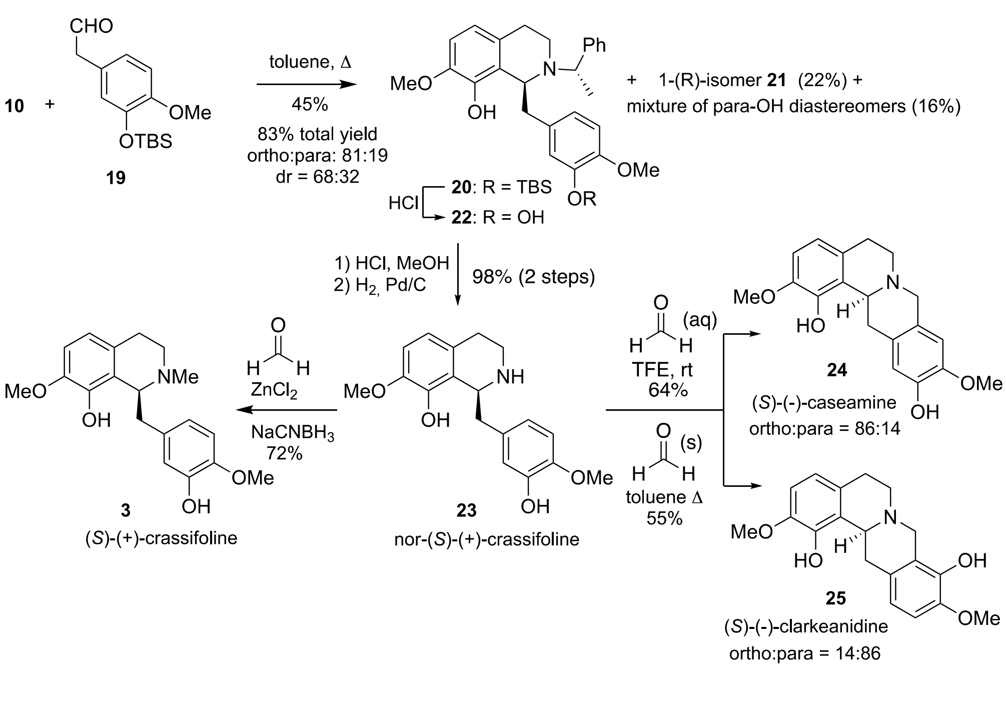
This optical rotation is significantly larger than the one reported in literature ($[\alpha]_D^{20}$ −59.9 (c = 0.1, methanol), indicating that the product isolated from *Corydalis govaniana Wall.* was not optically pure.[11]

Scheme 3. Synthesis of govaniadine



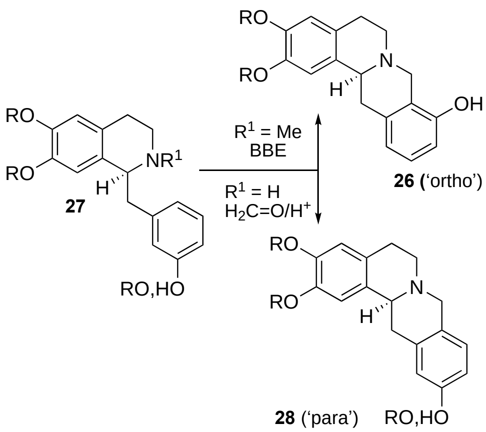
The next targets nor-crassifoline (**23**) and crassifoline (**3**) were readily prepared via the same sequence, starting from phenethylamine **10** and TBS-protected homo-isovaniline **19**[7b] (Scheme 4). Comparable yields and selectivities were obtained from the Pictet-Spengler reaction in toluene, producing 45% of the desired isomer **20** after chromatographic purification. Hydrogenolysis of the chiral auxiliary gave nor-crassifoline **23**, which was reductively methylated to crassifoline **3**.

Scheme 4. Synthesis of caseamine and clarkeanide *via* nor-crassifoline



Nor-crassifoline (**23**) was also used as the synthetic precursor for the related protoberberines caseamine (**24**[18]), displaying activity against urease[11], and clarkeanidine (**25**[19]). Biosynthetically, the ring closure of 1-benzyltetrahydroisoquinolines to tetrahydroprotoberberines does not proceed with formaldehyde, but via the berberine bridging enzyme (BBE) catalyzed oxidation of *N*-methylated benzyltetrahydroisoquinolines, immediately followed by ring closure of the intermediate methylene iminium salt (Scheme 5).[20]

Scheme 5. Ortho *vs* para selectivity in tetrahydroberberine synthesis



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.[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,[2] 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.[22,23,24] Application of the solvent directed Pictet-Spengler process (see Scheme 2) to the tetrahydroprotoberberine synthesis with nor-crassifoline 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, $[\alpha]_D^{20}$ −314, lit[18] −328). Starting from **23** under aprotic conditons using paraformaldehyde in toluene the ortho isomer (*S*)-clarkeanide **25** was formed (55%, o:p = 86:14, 95% ee after crystallization, $[\alpha]_D^{20}$ −442, lit[19] −277).

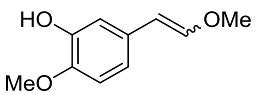
In conclusion, we have shown that Pictet-Spengler reactions under apolar conditions can produce the otherwise difficult to access ortho-oxygenated products. The chiral auxiliary-supported route is straightforward, scalable and in particular suitable for high diastereoselectivety in ortho hydroxylated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

EXPERIMENTAL SECTION

1. General information. Anhydrous CH_2Cl_2 and CH_3CN were freshly distilled from CaH_2. Dried THF was obtained by distillation from sodium/benzophenone. DMF and DMSO on 4Å molecular sieves were obtained from Sigma-Aldrich and stored under N_2 atmosphere. Toluene was distilled and stored on 4Å 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 40-63 µm) was used for silica column chromatography. NMR spectra were recorded on Bruker DRX-500, 400 and 300 MHz instruments and calibrated on residual undeuterated solvent signals as internal standard. The ^{1}H-NMR multiplicities were abbreviated as followed: 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-T100GCV Mass spectrometer (JEOL, Japan). FD/FI probe equipped with a FD emitter of 10 μm. Current rate 51.2 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/isopropanol 70/30, flow 1.000 mL/min, λ 230 nm).

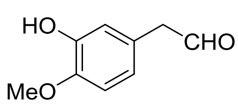
2. Synthetic procedures

2-Methoxy-5-(2-methoxyethenyl)phenol 8.[15] KO*t*-Bu (22.4 g, 200 mmol) was added in 3 portions, with intervals



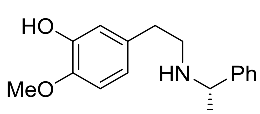
of 3 minutes, to an efficiently stirred suspension of methoxymethyltriphenyl phosphonium chloride (34.3 g, 100 mmol) in dry THF (250 mL) with ice cooling. After additional stirring for 5 min, isovanilline **7** (13.7 gr, 90 mmol) was added in 3 portions, with intervals of 2 minutes, to the reaction mixture resulting in a rapid colour 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 the ref 15: ^{1}H NMR (400 MHz, $CDCl_3$) 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 (d, 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



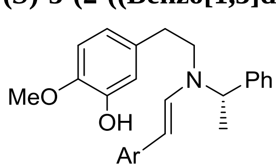
solution of enol ether **8** (7.39 g, 41.0 mmol) in DCM (200 mL). The resulting heterogenous mixture was stirred vigorously overnight at rt. Water was added and after separation the organic layer was washed with $NaHCO_3$ aq. and dried over Na_2SO_4. Chromatographic separation (2/1 and 3/2 petroleum ether /ethyl acetate) gave pure **9** (3.75 g, 24.7 mmol, 60%) as an oil, which solidified in the freezer: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.7, 145.9, 145.8, 124.6, 120.9, 115.7, 111.0, 55.7, 49.5.

(*S*)-2-Methoxy-5-(2-((1-phenylethyl)amino)ethyl)phenol 10. Aldehyde **9** (3.74 g, 22.5 mmol) and (*S*)-(–)-α-



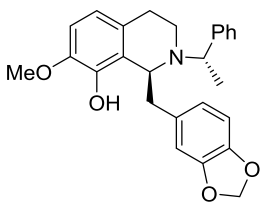
methylbenzylamine (3.1 mL, 24 mmol) were dissolved in THF (75 mL) and stirred at 0 °C for 30 min. Sodium triacetoxyborohydride (10.6 g, 50 mmol) was added and the mixture was stirred at 0 °C for 30 min and at rt for 14 h. The solvent was evaporated and the residue was dissolved in ethyl acetate and washed with Na_2CO_3 solution and water. Next the product was extracted from the organic layer with aqueous HCl (3x 100 mL). The water layer was washed three times with ethyl acetate, before the water layer was basified with Na_2CO_3 solution. Extraction with ethyl acetate, drying over Na_2SO_4 and evaporation of the solvent gave chiral amine **10** (5.02 g, 18.5 mmol, 82%) as a solid: Mp 86–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 146.0, 145.6, 145.0, 132.8, 128.5, 127.0, 126.7, 119.7, 115.5, 111.1, 58.2, 55.9, 48.7, 35.3, 23.9; HRMS (ESI$^+$): *m/z* calculated for $C_{17}H_{22}NO_2$ $(M+H)^+$ 272.1651, found 272.1642.

(*S*)-5-(2-((Benzo[1,3]dioxol-5-yl)vinyl)(1-phenylethyl)amino)ethyl-2-methoxyphenol 12. 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, $CDCl_3$) δ ; 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), 2.72 (m, 2H), 1.56 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.0, 145.7, 145.2, 143.8, 142.8, 137.8, 135.0, 134.8, 133.1, 129.1, 128.7, 128.5, 128.4, 128.4, 128.2, 127.5, 127.2, 127.0, 126.9, 126.9, 125.3, 120.1, 120.0, 116.9, 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 homopiperonal **11**[16] (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%), next 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%).

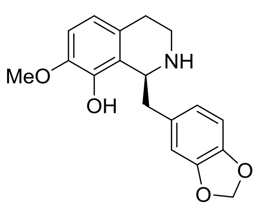


16: $[\alpha]_D^{20}$ −2.0 (MeOH, c = 2.1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.24 (m, 2H), 7.25-7.19 (m, 3H), 6.97 (s, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.11-5.92 (m, 2H), 5.80 (s, 1H), 4.50 (dd, *J* = 10.3, 3.0 Hz, 1H), 3.92 (s, 3H), 3.70 (q, *J* = 6.4 Hz, 1H), 3.31-3.15 (m, 1H), 3.06 (dd, *J* = 13.7, 3.0 Hz, 1H), 2.89-2.78 (m, 2H), 2.77-2.70 (m, 1H), 2.27-2.20 (m, 1H), 1.03 (d, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 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, 110.3, 108.8, 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 $C_{26}H_{28}NO_4$ $(M+H)^+$ 418.2018, found 418.2006.

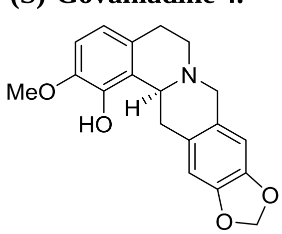
15: $[\alpha]_D^{20}$ +41.9 (MeOH, c = 1.0); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13-7.06 (m, 1H), 7.05 (t, *J* = 7.4 Hz, 2H), 6.84 (d, *J* = 7.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.64-6.56 (m, 2H), 5.97 (s, 2H), 5.63 (s, 1H), 3.96 (dd, *J* = 10.3, 2.9 Hz, 1H), 3.89 (s, 3H), 3.63 (q, *J* = 6.4 Hz, 1H), 3.47-3.38 (m, 1H), 3.33 (dd, *J* = 14.6, 5.8 Hz, 1H), 3.01-2.84 (m, 2H), 2.74 (dd, *J* = 13.7, 10.3 Hz, 1H), 2.53-2.34 (m, 1H), 1.29 (d, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.9, 146.1, 145.4, 144.0, 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 $C_{26}H_{28}NO_4$ $(M+H)^+$ 418.2018, found 418.2015.

17 (mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$, selected signals) δ 7.34 (d, *J* = 4.6 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,1H), 3.69 (s, 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).

(*S*)-1-(Benzo[1,3]dioxol-5-ylmethyl)-7-methoxy-1,2,3,4-tetrahydroisoquinolin-8-ol 18. Pictet-Spengler product **15** (0.590 g, 1.41 mmol) was dissolved in ethanol (20 mL) and palladium hydroxide on carbon (10% w/w, 0.190 g) was added. The reaction flask was flushed with hydrogen and stirred for 18 h at 60 °C under hydrogen atmosphere. The mixture was filtered over celite, the residue was washed with ethanol (100 mL) and the combined filtrates were evaporated. Chromatographic purification (silica gel, petroleum ether/ethyl acetate/Et_3N 50:50:3 gave **18** as a light yellow glass (0.438 g, 1.40 mmol, 99%): $[\alpha]_D^{20}$ +12 (MeOH, c = 0.28); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, *J* = 1.7 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.78-6.70 (m, 2H), 6.63 (d, *J* = 8.3 Hz, 1H), 5.96 (s, 2H), 4.33 (dd, *J* = 10.6, 2.7 Hz, 1H), 3.85 (s, 3H), 3.23 (m, 2H), 2.99 (ddd, *J* = 12.1, 6.0, 2.6 Hz, 1H), 2.93-2.73 (m, 2H), 2.67 (dt, *J* = 16.1, 3.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.6, 145.8, 144.2, 142.0, 134.2, 128.1, 125.5, 122.1, 119.5, 109.6, 108.9, 108.1, 100.7, 56.0, 53.2, 37.9, 37.5, 28.8; HRMS (FD$^+$): *m/z* calculated for $C_{18}H_{20}NO_4$ $(M+H)^+$ 314.1392, found 314.1400.

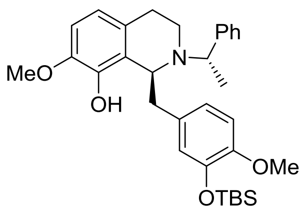


(S)-Govaniadine 4.[11,12] Amine **18** (44.8 mg, 0.142 mmol) was dissolved in ethanol, conc. HCl (50 µl) was added, the volatiles were evaporated and the residue was coevaporated with ethanol. The hydrochloride was redissolved in ethanol (1 mL), water (1.5 mL) and aqueous formaldehyde (37%, 1.5 mL) and this solution was refluxed for 6 h. The volatiles were evaporated and the residue was stirred with aqueous Na_2CO_3 and ethyl acetate until dissolved. Extractive workup and chromatographic purification (silica gel, petroleum ether/ethyl acetate 50/50 and 0/100) gave (S)-govaniadine (28.1 mg, 0.0875 mmol, 61%)



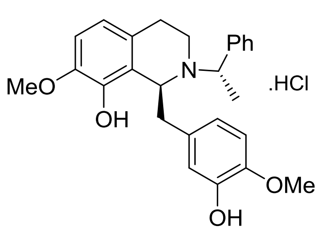
as a crystallizing glass. Recrystallization from methanol gave enantiopure (S)-govaniadine (**4**): *ee* > 99% (Chiralcel AD column, eluent *n*-heptane/isopropanol 70:30, flow 1.000 mL/min); $[\alpha]_D^{20}$ −339 (MeOH, c = 0.55), lit:[11] $[\alpha]_D^{20}$ −59.9 (c = 0.1, MeOH); Mp 141-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + 10% CD_3OD) δ 6.75 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.58 (s, 1H), 6.55 (s, 1H), 5.89 (s, 2H), 4.06-3.93 (m, 2H), 3.88 (s, 3H), 3.71-3.59 (m, 1H), 3.16-2.92 (m, 2H), 2.85-2.55 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$ + 10% CD_3OD) δ 145.9, 145.6, 144.3, 142.4, 128.2, 128.1, 126.7, 124.4, 119.4, 108.9, 108.6, 106.0, 100.4, 57.7, 56.1, 55.9, 48.4, 32.2, 29.3; IR (neat): ν 3507, 1488 cm^{-1}. HRMS (FD+): *m/z* calculated for $C_{19}H_{19}NO_4$ (M)+ 325.1314, found 325.1325.

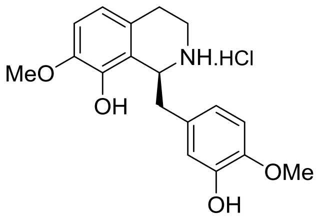
Pictet-Spengler with aldehyde 19. A mixture of amine **10** (1.084 g, 4.0 mmol) and aldehyde **19**[7a,b] (1.12 g, 4.0 mmol) was heated at 105 °C in anhydrous toluene (100 mL, 40 mM) during 5 days. Separation by flash chromatography (petroleum ether/ethyl acetate, 12/1, 10/1) provided first the minor 1-(*R*)-ortho isomer **21** (0.462 g, 0.867 mmol, 21.7%), next the desired 1-(*S*)-ortho isomer **20** (0.962 g, 1.80 mmol, 45%) and finally an inseparable mixture of two para isomers in a ca. 1/1 ratio (0.221 g, 0.42 mmol, 16%).



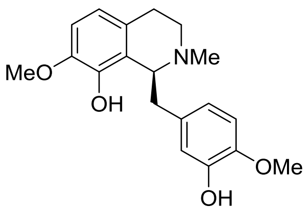
21: $[\alpha]_D^{20}$ −2.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.20 (m, 5H), 6.99-6.90 (m, 2H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 5.78 (s, 1H), 4.52 (dd, *J* = 9.9, 2.9 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.69 (q, *J* = 6.3 Hz, 1H), 3.29-3.12 (m, 1H), 3.04 (dd, *J* = 13.6, 3.0 Hz, 1H), 2.90-2.76 (m, 2H), 2.70 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.21 (dd, *J* = 16.6, 4.7 Hz, 1H), 1.06 (s, 9H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.21 (s, 3H), 0.20 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.0, 146.6, 144.3, 144.0, 142.4, 134.6, 128.6, 128.1, 127.3, 126.5, 125.3, 122.8, 122.6, 119.4, 111.5, 108.7, 57.8, 56.1, 55.7, 54.2, 39.5, 39.3, 25.8, 22.6, 21.9, 18.5; HRMS (FD$^+$): *m/z* calculated for $C_{32}H_{44}NO_4Si$ $(M+H)^+$ 534.3034, found 534.3016. **20**: $[\alpha]_D^{20}$ +10.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2-7.1 (m, 3H), 6.8 (m, 2H), 6.85-6.76 (m, 3H), 6.76-6.63 (m, 2H), 5.68 (s, 1H), 4.09 (dd, *J* = 9.9, 3.0 Hz, 1H), 3.91 (s, 3H), 3.915 (s, 3H, 3.73 (q, *J* = 6.5 Hz, 1H), 3.56 -3.42 (m, 1H), 3.33 (dd, *J* = 14.4, 5.5 Hz, 1H), 3.05-2.89 (m, 2H), 2.89-2.72 (m, 1H), 2.49 (dd, *J* = 16.4, 4.3 Hz, 1H), 1.33 (dd, *J* = 6.5 Hz, 3H), 1.12 (s, 9H), 0.27 (s, 3H), 0.26 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.0, 146.1, 144.1, 143.9, 142.6, 133.9, 128.5, 127.8, 127.3, 126.1, 125.3, 123.0, 122.8, 119.2, 111.9, 108.5, 58.9, 56.4, 55.9, 55.9, 38.9, 38.7, 29.4, 25.8, 22.7, 22.0, 18.4; HRMS (FD$^+$): *m/z* calculated for $C_{32}H_{44}NO_4Si$ $(M+H)^+$ 534.3040, found 534.3077. **Para isomers** ^{1}H NMR (400 MHz, $CDCl_3$, selected signals) δ 6.01 (s, 1H), 5,85 (s), 4.02 (t, *J* = 6.8 Hz, 1H), 3.80 (s, 1H), 3.64 (s, 2H), 3.57 (s, 1H), 1.40 (d, *J* = 6.5 Hz, 2H), 1.28 (d, *J* = 6.5 Hz, 2H), 0.98 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.2, 149.1, 145.5, 144.5, 144.5, 143.9, 143.8, 143.7, 133.1, 132.8, 129.1, 128.4, 128.2, 128.2, 128.1, 127.6, 127.4, 127.3, 127.2, 127.1, 126.8, 126.5, 123.1, 123.0, 122.5, 122.3, 120.3, 119.9, 114.2, 114.2, 111.9, 111.8, 111.6, 110.8, 110.4, 60.7, 59.5, 59.1, 58.8, 55.8, 55.7, 55.6, 55.5, 55.5, 55.4, 55.3, 41.7, 40.6, 40.2, 39.7, 25.8, 25.7, 25.6, 25.6, 24.4, 23.6, 22.3, 22.0, 18.4, 18.3.

(*S*)-1-(3-Hydroxy-4-methoxybenzyl)-7-methoxy-2-((*S*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-ol hydrochloride 22. A solution of **20** (0.587 g, 1.1 mmol) in methanol (20 mL) was stirred with HCl conc. (2 mL) during 18 h at rt. The solvents were evaporated and the residue was evaporated three times with methanol to remove water and TBSOH to give **22** (hydrochloride, 0.453g, 1.08 mmol, 98%) as a dark glass: ^{1}H NMR (400 MHz, CD_3OD) 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); ^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ 148.7, 147.9, 147.5, 144.6, 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* calculated for $C_{26}H_{30}NO_4$ $(M+H)^+$ 420.2169, found 420.2160.

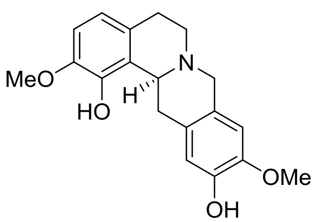




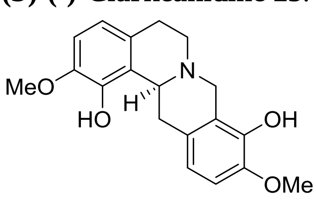
Debenzylation to norcrassifoline 23. **22** (0.400 g, 0.877 mmol) was stirred with 10% Pd/C (0.15 g) in 12 mL ethanol under H_2 at atmospheric pressure during 18 h. Filtration over celite and evaporation gave norcrassifoline **23** (hydrochloride, 0.276 g, 0.88 mmol, 100%) as a brownish glass: [α] = no transmission; ^{1}H NMR (400 MHz, CD_3OD) 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); $^{13}C\{^1H\}$ NMR (101 MHz, CD_3OD) δ 148.7, 148.1, 147.4, 144.3, 129.9, 125.1, 121.8, 120.7, 120.2, 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* calculated for $C_{18}H_{22}NO_4$ $(M+H)^+$ 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 (33 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.[7b] Silica gel was added and the residue obtained after evaporation was applied to a silica column. Eluting with ethyl acetate, ethyl acetate/MeOH/Et_2NH 95/3/2 and ethyl acetate/MeOH/Et_2NH 90/7/3 gave crassifoline **3** (23.7 mg, 0.072 mmol, 72%) as a glass: $[\alpha]_D^{20}$ +17.6 (c = 0.5 in MeOH), Lit[4,5] $[\alpha]_D^{20}$ +20 (c = 0.5 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) 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 (ddd, 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); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 145.2, 144.9, 144.2, 142.5, 134.3, 127.2, 124.3, 120.5, 119.2, 115.6, 110.4, 109.0, 60.2, 56.1, 55.9, 44.9, 42.4, 38.8, 22.9; HRMS (FD$^+$): *m/z* calculated for $C_{19}H_{24}NO_4$ $(M+H)^+$ 330.1700, 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, 0.4 mmol) in trifluoroethanol (1.0 mL) was stirred during 5 h at rt. Caseamine **24** (21.8 mg, 0.066 mmol, 53%) directly crystallizes 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 **24**[18] *ee* 99% (Chiralcel AD column, eluent *n*-heptane/isopropanol 70:30, flow 1.000 mL/min); $[\alpha]_D^{20}$ −314 ($CHCl_3$ + MeOH, c = 0.15), lit[18] $[\alpha]_D$ −328 (c = 0.04, $CHCl_3$); Mp 246-250 °C (lit[18] 246-247 °C); ^{1}H NMR (300 MHz, d_6-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); $^{13}C\{^1H\}$ NMR (75 MHz, d_6-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, 55.6, 47.9, 31.4, 29.3; HRMS (FD$^+$): *m/z* calculated for $C_{19}H_{21}NO_4$ (M^+) 327.1471, found 327.1499.



(*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 mg, 0.30 mmol) at 105 °C for 3 h. The solvent was evaporated and the isomers were separated by chromatography: petroleum ether/ethyl acetate 1/1 and ethyl acetate for the ortho isomer clarkeanidine **25** (36.1 mg, 0.11 mmol, 55%), next ethyl acetate/MeOH 97/3 for the para-isomer caseamine **24** (6.0 mg, 0.018 mmol, 9%). Clarkeanidine (**25**): mp 177−180 °C (recrystallized from DCM/petroleum ether), (lit[19] 178−179 °C); *ee* 95% (Chiralcel AD column, eluent *n*-heptane/isopropanol 70:30, flow 1.000 mL/min); $[\alpha]_D^{20}$ −442 (c = 0.1, $CHCl_3$), lit[17,18] $[\alpha]_D^{20}$ −277 ($CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (m, 2H), 6.66 (m, 2H), 5.78 (bs, 2H), 4.24 (d, J = 16.0 Hz, 1H), 3.99 (dd, J = 11.2, 3.5 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.84 (d, J = 16.0 Hz, 1H), 3.72 (dd, J = 16.2, 3.6 Hz, 1H), 3.22-3.12 (m, 1H), 3.12-3.00 (m, 1H), 2.89-2.64 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 144.3, 143.8, 142.5, 141.7, 129.0, 128.8, 124.6, 121.0, 119.4, 108.9, 56.2, 56.2, 56.1, 53.0, 49.1, 32.2, 29.8; HRMS: (FD$^+$): *m/z* calculated for $C_{19}H_{22}NO_4$ $(M+H)^+$ 328.1549, found 328.1558.

ASSOCIATED CONTENT

Supporting Information

[1]H and [13]C NMR spectra of all new products and intermediates; chiral HPLC traces of the tetrahydroprotoberberines.

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