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Synthesis and structure elucidation of open-chained putrescine-bisamides from *Aglaia* species

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Abstract—The structures of the eight recently described open-chained putrescine bisamide alkaloids secoodorine (**1**), aglaithioduline (**3**), aglaiduline (**4**), aglaidithioduline (**5**), grandiamide B (**13**), grandiamide C (**14**), pyramidatine (**20**), and secopiriferine (**22**), which were isolated from different *Aglaia* species, have been verified by synthesis. In addition to that, the published structure **2** for hemileptagline had to be revised, and for secoodorine (**1**) the absolute configuration could be established.

1. Introduction

The whole group of naturally occurring polyamine alkaloids can be divided according to the incorporated polyamine part into the three sub-classes of putrescine, spermidine, and spermine alkaloids.† For each of these groups numerous examples exist, which occur either in an open-chained, but also in a cyclic form. The latter is well known for spermidine and spermine alkaloids since centuries, whereas the knowledge about the cyclic form of putrescine alkaloids is not so widespread. Surely, this comes up with the rather restricted naturally occurrence of these 2-aminopyrrolidine compounds, which—to the best of our knowledge—could up to now only be isolated from plants of the *Aglaia* genus (Meliaceae).‡ It seems to be rather likely, that all alkaloids with such a 2-aminopyrrolidine framework have an open-chained putrescine-bisamide precursor, which can be cyclized by a special enzymatic system. The open-chained putrescine alkaloids are unsystematically distributed throughout the plant kingdom. However, *Aglaia* species are a rich source of such compounds, so all of the nine substances, we want to deal within this report, were isolated from different *Aglaia* plants. During the last few years these putrescine bisamides were isolated and their structure proposed mainly by spectroscopical means. Up to now, there was no final structure proof by synthesis nor was the absolute configuration of one of them—secoodorine (**1**)—known. Therefore, we decided to synthesize these alkaloids in order to fill this gap in literature.

2. Results and discussion

In 2000, Greger et al.[2] reported the isolation of three open-chained putrescine bisamides from *Aglaia leptantha* Miqu., namely hemileptagline, leptagline (**3**), and aglanthine (**4**). The proposed structures **2** and **3** both included (*E*)-3-(methylthio)propenoic acid (**6**) as an acyl residue, therefore suggesting to see these structures in context to the three already described, also sulphur containing putrescine bisamides, which were isolated by Saifah et al.[3] in 1999 from the leaves of *A. edulis* A. Gray. These authors reported about aglaiduline (**4**), aglaithioduline (**3**), and aglaidithioduline (**5**). A simple comparison of the structures, proposed by both authors, revealed that leptagline (**3**) is identical with aglaithioduline, whereas aglanthine (**4**) is identical to aglaiduline. Attention should be drawn to the fact, that Saifah et al. published their results in 1999, whereas Greger et al. in the year 2000, so the compound names from Saifah et al. take priority. For this reason the latter are preferred in this report, the other ones are only given to clarify the situation. In order to avoid the danger of confusion, we suggest to eliminate the redundant ones from literature. For the structure **2** of hemileptagline—proposed by Greger et al.—we had from the very beginning the strong suspicion, that the structure elucidation of the Austrian authors has been wrong, because the published NMR-spectroscopic data for hemileptagline point out for a symmetric structure, whereas the proposed structure **2** is non-symmetric. Once more, a simple comparison of the published NMR data for hemileptagline and aglaidithioduline (**5**) showed identity of both data sets. The structure of aglaidithioduline (**5**) consists beside the putrescine backbone of two amide linked (*E*)-3-(methylthio)propenoic acid residues and fits therefore with

Keywords: putrescine-bisamides; *Aglaia*; hemileptagline; aglaidithioduline; aglaithioduline; grandiamide B and C; aglaiduline; pyramidatine; secopiriferine; secoodorine.

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† For a complete and up to date review article on all aspects of polyamine chemistry as well as a list of all up to now described polyamine alkaloids see Bienz et al.[1]

‡ A complete list of all known 2-aminopyrrolidine alkaloids together with the corresponding literature is given in Ref. 1.

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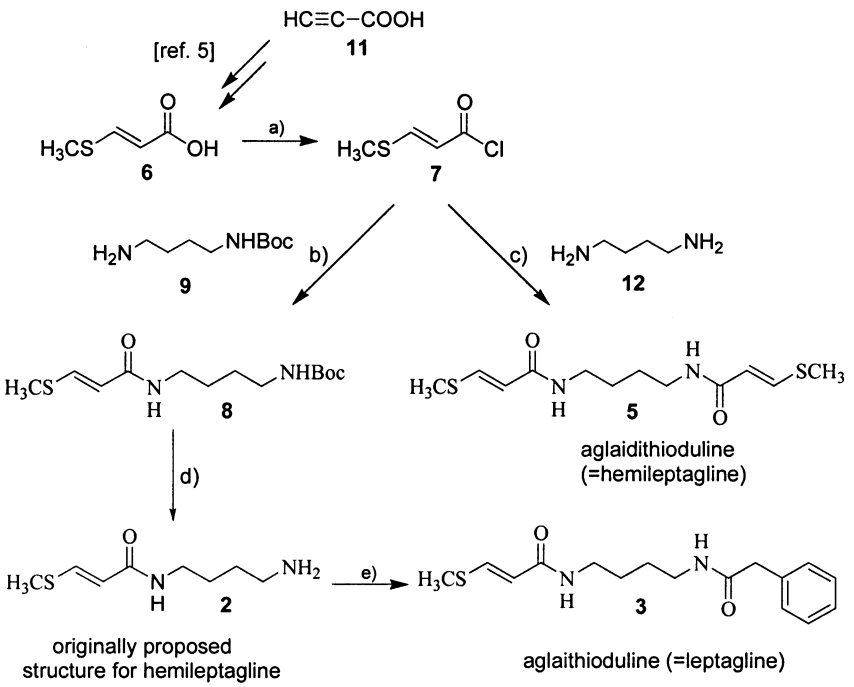
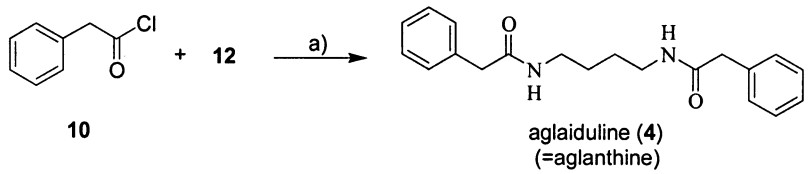


Scheme 1. (a) $SOCl_2$, CH_2Cl_2, rt, 20 min. (b) $H_2N–(CH_2)_4–NHBoc$ (**9**), NEt_3, CH_2Cl_2, RT, 15 min, 38%. (c) NEt_3, CH_2Cl_2, rt, 1 h, 30%. (d) (1) TFA, toluene, rt, 15 min, (2) aq. 2N NaOH, rt, 5 min, 80%. (e) $C_6H_5CH_2COCl$ (**10**), NEt_3, CH_2Cl_2, rt, 30 min, 78%.



Scheme 2. (a) NEt_3, CH_2Cl_2, rt, 2 h, 81%.

the measured and reported spectroscopical data of both research teams. In order to be sure about the conclusions around this somewhat dazzling facts, we decided to synthesize the proposed structure **2** as well as **3**–**5**.

For this purpose, we first needed access to the commercially not available (*E*)-3-(methylthio)propenoic acid (**6**). Besides a scarcely user-friendly method, which uses methanthiole under high pressure conditions,[4] we were glad to see that De Medeiros et al.[5] reported a much easier synthesis for **6**, starting from propiolic acid (**11**) and potassium thiocyanate as an olfactorily unproblematic sulphur source (Scheme 1). The obtained acid **6** could be activated to the acid chloride **7** by means of thionyl chloride. The latter was converted without any purification in modest yield[§] to **8**, using *N*-mono-Boc-putrescine (**9**)[‖] as an amine. After final deprotection with TFA and extractive work-up from aq. base, the desired non-protonated form of **2** was obtained.[¶]

The spectroscopical data measured for **2** fitted perfectly with this non-symmetric structure, but were not at all identical with the data published by Greger et al.[2] Therefore, an almost impossible coincidence in the spectroscopical data has been definitely excluded. At this point it can be stated, that the hemileptagline structure **2** is incorrect.

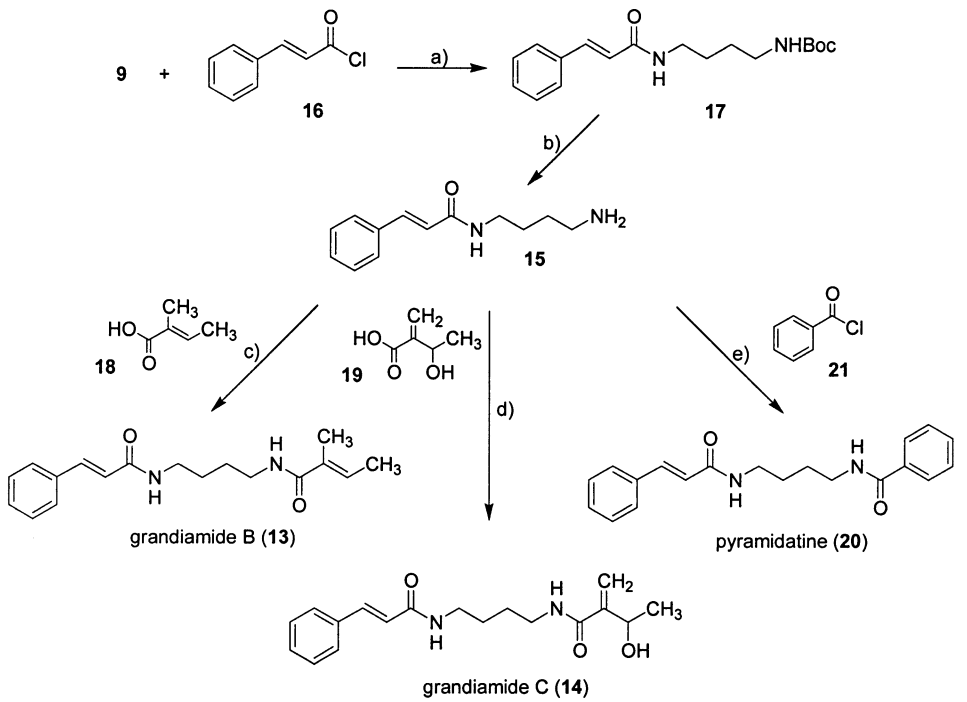
On the other hand, synthesized compound **2** provided us with a valuable starting material, which enabled the synthesis of aglaithioduline (**3**) in one simple step. Amidation of **2** with phenylacetyl chloride **10** in the presence of NEt_3 yielded **3** directly. The spectroscopic data for **3** were in good accordance with the published data for the natural products.[2,3] This means, as mentioned above, that leptagline is identical with aglaithioduline (**3**).

The last one of the sulphur containing putrescine bisamides, aglaidithioduline (**5**), has also been synthesised from **6** by activating this acid as acid chloride **7** and subsequent reaction with free putrescine (**12**). Beside small amount of **2** as by-product, the required aglaidithioduline (**5**) could be isolated. Spectroscopic characterization again showed complete agreement with the published data by Saifah et al.[3] for the natural product. More important, the congruence of the analytical data of synthesized **5** and the published data for so-called hemileptagline is the proof, that Greger et al. had isolated in fact aglaidithioduline (**5**). To

[§] Working conditions were not optimized, because we only needed enough material to prove our suspicion that the originally proposed hemileptaglin structure **2** is incorrect.

[‖] Obtained according to a literature method by Krapcho and Kuell[6]. We found it more convenient to use THF instead of the proposed 1,4-dioxane as a solvent.

[¶] Care has been taken to isolate **2** definitely as the free amine and not in protonated form, because the salt would of course show different chemical shifts in the NMR spectra.



Scheme 3. (a) NEt_3, CH_2Cl_2, rt, 15 min, 92%. (b) aq. 1N HCl, EtOH, 40°, 3 h, 60%. (c) EDC, CH_2Cl_2, rt, 12 h, 77%. (d) DCC, CH_2Cl_2, rt, 8 h, 60%. (e) NEt_3, CH_2Cl_2, rt, 15 min, 86%.

make a long story short: both authors isolated the same three alkaloids from two different *Aglaia* species (Scheme 1).

To verify the non-sulphur containing aglaiduline structure (**4**) by synthesis, we used the simple reaction of phenylacetyl chloride (**10**) with putrescine (**12**) in presence of base (Scheme 2). The product (**4**) was obtained in good yield and showed the expected spectroscopical properties, therefore proving the structure (Scheme 2).

Also in 2000, Inada et al.[7] published the isolation and structure elucidation by spectroscopic means of three previously unknown putrescine bisamides from the leaves of *A. grandis* Korth. and named them as grandiamide A, B (**13**), and C (**14**). Common feature of substances **13** and **14** (as well as the later discussed alkaloids) is a *N*-mono-cinnamoyl-putrescine residue, so we found it convenient to prepare the building block **15** first (Scheme 3) and acylate it afterwards in an appropriate manner. *N*-mono-Boc-putrescine (**9**, Scheme 1) once more served as a starting material, which could be easily acylated with cinnamoyl chloride (**16**) to obtain **17**. Removal of the Boc-protecting group under acidic conditions yielded in desired **15**. For grandiamide B (**13**, Scheme 3) we decided to use EDC[**] as an amide-coupling reagent, instead of the more common DCC,[††] in order to profit from the better water solubility of the inevitable urea by-product of the coupling reaction and the therefore easier purification process. As an acyl component served commercially available tiglic acid (**18**), so the synthesis of **13** could be performed in one single step. Comparison of the analytical data of **13** with the published one of the natural product revealed no difference.

Synthesis of grandiamide C (**14**) (Scheme 3) demanded access to 3-hydroxy-2-methylene butanoic acid (**19**). Amberg and Seebach[8] reported a preparation of this compound, where they took advantage from a DABCO[‡‡] catalyzed Baylis–Hillman reaction between acetaldehyde and methyl acrylate followed by an ester hydrolysis. DCC mediated coupling of acid **19** and amine **15** allowed straightforward isolation of racemic **14**. The modest yield originated from some purification problems because of coelution of the urea by-product. Again, spectroscopic data comparison corroborated the structure elucidation by Inada et al. Attention should be drawn to the fact, that grandiamide C (**14**) features a centre of chirality, so one might expect its occurrence in nature in an enantiopure form. Nevertheless, the Japanese authors reported about $[\alpha]_D=\pm 0$ ($CHCl_3$) and therefore they claimed, that natural **14** has to be a racemate. On the other hand, it may be also possible—admittedly more unlikely—that **14** shows no optical rotation at the $[\alpha]_D$-line by coincidence.

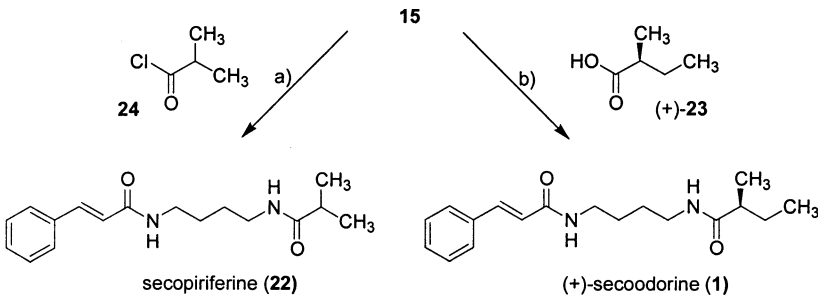
An earlier publication of Saifah et al.[9] dealt with the isolation and structure elucidation of pyramidatine (**20**) from the leaves of *A. pyramidata* Hance. This alkaloid also contains the *N*-mono-cinnamoyl-putrescine residue, so with **15** as a building block, its synthesis could be achieved quickly by reaction with benzoyl chloride (**21**) according to Scheme 3. As expected, the synthesized material was found to be identical to the natural one described in literature (Scheme 3).

Once more, Greger et al.[10] published in 2001 the isolation and structure elucidation of two previously unknown putrescine bisamides: secopiriferine (**22**) and secoodorine (**1**) (Scheme 4). In this case, they used a leaf extract of *A.*

[**] EDC=1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide-hydrochloride.

[††] DCC=1,3-dicyclohexylcarbodiimide.

[‡‡] DABCO=1,4-diazabicyclo[2.2.2]octane.



Scheme 4. (a) NEt_3, CH_2Cl_2, rt, 15 min, 95%. (b) DCC, HOBt, EtOAc, rt, 1 h, 66%.

gracilis A. C. Smith, a plant originated from Fijian islands. Whereas **22** is an achiral molecule, **1** possess a stereogenic centre. The Austrian authors reported an optical rotation of $[\alpha]_D$=+11 ($CHCl_3$) for compound **1**, but they failed to determine the absolute configuration. Therefore, we decided to synthesize **1** in an enantiopure form. DCC mediated coupling of commercially available (+)-(*S*)-2-methyl butanoic acid (**23**) with **15** in the presence of HOBt[§§]—which is well established especially in peptide chemistry to avoid racemization—enabled the synthesis of optically active **1**. Besides the identity of measured spectra for synthetic and natural alkaloid, the comparison of optical rotations, $[\alpha]_D$=+12.3 ($CHCl_3$) for the synthetic product, revealed the (*S*)-configuration of naturally occurring (+)-secoodorine (**1**).

We closed the series of putrescine bisamide synthesis with above-mentioned secopiriferine (**22**). The straightforward reaction of **15** with isobutyryl chloride (**24**) allowed the isolation of **22** in almost quantitative yield (Scheme 4). Spectra comparison also proved its structure (Scheme 4).

3. Conclusion

The structures of nine newly published naturally occurring putrescine bisamides could be confirmed by synthesis. For one of them—hemileptagline—the originally proposed structure **2** has been revised and the identity to this compound with aglaidithioduline (**5**) has been proven. Furthermore, two compound names in this field—*leptagline* and *aglanthine*—were found to be redundant, because of the identity of these compounds with the earlier described aglaithioduline (**3**) and aglaiduline (**4**), respectively. The structures of the other compounds have been successfully verified and the absolute configuration of (+)-(*S*)-secoodorine (**1**) could be established.

4. Experimental

4.1. General remarks

All commercially available reagents were used without further purification. Solvents were either puriss. p.a. grade (Fluka) or distilled prior to use. The application of a nitrogen atmosphere was not necessary for the described reactions. They were monitored by thin layer chromatography (TLC) on Merck precoated plates Kieselgel 60 F_{254}. All extracts were dried before evaporation over $MgSO_4$, unless otherwise stated. Column chromatography (CC): Kieselgel 60 (230–400 mesh ASTM) from Merck. Melting points (mp): Mettler FP52. IR spectra were measured in $CHCl_3$ (Fluka for IR spectroscopy) unless otherwise stated: Perkin–Elmer 781. Optical rotations $[\alpha]_D$ in $CHCl_3$ (Fluka for IR spectroscopy): Perkin–Elmer 241 polarimeter. NMR spectra: ^1H NMR: Bruker ARX-300 (300 MHz); ^{13}C NMR: Bruker ARX-300 (75 MHz); chemical shifts δ in ppm rel. to TMS as internal standard. MS: Finnigan SSQ-700 for Chemical Ionization (CI) with NH_3, and Finnigan TSQ-700 for electrospray ionization (ESI); *m/z* (rel. intensity in %).

4.1.1. *tert*-Butyl (*E*)-[4-(3-methylthio-prop-2-enoyl-amino)-butyl]-carbamate (8). To a suspension of 0.15 g (1.27 mmol) **6**[‖‖] in 10 ml CH_2Cl_2 was added dropwise 0.30 g (2.54 mmol, 0.18 ml) $SOCl_2$ at room temperature. After complete dissolution, the mixture was stirred for 20 min, before all volatile compounds were removed in vacuo. The residue was taken up in 10 ml CH_2Cl_2 and again completely evaporated to remove the excess of $SOCl_2$. The crude acid chloride **7** was dissolved in 10 ml CH_2Cl_2 without any further purification and a mixture of 0.15 g (1.5 mmol; 0.21 ml) NEt_3 and 0.28 g (1.5 mmol) **9**[¶¶] was added. After 10 min stirring at room temperature, the mixture was poured into aq. NaCl solution and extracted with CH_2Cl_2. After removing the solvent in vacuo, purification of the residue by CC (SiO_2; CH_2Cl_2/MeOH 20:1) yielded 0.14 g (38%) **8** as a yellowish solid. IR ν (cm^{-1}): 3450m, 3320m, 3000m, 2980m, 2860w, 1710s, 1610s, 1580s, 1510s, 1390w, 1370m, 1330w, 1250s, 1170s, 1000w, 940m, 840w. ^1H NMR ($CDCl_3$, 300 MHz): 7.58 (d, *J*=14.7 Hz, 1H), 6.40 (br., 1H), 5.72 (d, *J*=14.7 Hz, 1H), 4.90 (br. 1H), 3.31 (q, *J*=6.1 Hz, 2H), 3.11 (q, *J*=6.1 Hz, 2H), 2.31 (s, 3H), 1.60–1.48 (m, 4H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 164.7 (s), 156.1 (s), 142.0 (d), 116.1 (d), 79.0 (s), 40.0 (t), 39.0 (t), 28.3 (q), 27.5 (t), 26.5 (t), 14.4 (q). CIMS/NH_3: 289 (100, $[M+1]^+$), 233 (85, $[M-CH_3S-CH{=}CH+18]^+$), 189 (62, $[M-Boc+1]^+$).

4.1.2. (*E*)-*N*-(4-Aminobutyl)-3-methylthio-prop-2-enamide (2). To a solution of 0.10 g (0.347 mmol) **8** in 10 ml toluene was added 1 ml TFA at room temperature. After 15 min stirring, the solution was poured in aq. 2N NaOH and extracted exhaustively with CH_2Cl_2. The organic phase was dried (Na_2SO_4) before evaporating to afford

[§§] HOBt=1-hydroxybenzotriazole.

[‖‖] Prepared according to the published procedure by De Medeiros et al.[5]

[¶¶] Synthesized from putrescine (**12**) by a procedure of Krapcho and Kuell.[6]

52 mg (80%) of **2** as a colorless oil. IR ν (cm^{-1}): 3440m, 3300m, 2990m, 2930s, 2860m, 1650s, 1580s, 1510s, 1435m, 1330m, 1250m, 1200m, 1090w, 990w, 940m, 840m. ^1H NMR (CD_3OD, 300 MHz): 7.54 (d, J=14.7 Hz, 1H), 5.81 (d, J=4.8 Hz, 1H), 3.25 (t, J=6.6 Hz, 2H), 2.68 (t, J=6.85 Hz, 2H), 2.34 (s, 3H), 1.60–1.45 (m, 4H). ^{13}C NMR (CD_3OD, 75 MHz): 167.5 (s), 143.6 (d), 117.0 (d), 42.2 (t), 40.3 (t), 30.8 (t), 28.0 (t), 14.5 (q). CIMS/NH_3: 189 ($[M+1]^+$).

4.1.3. (*E*)-3-Methylthio-*N*-[4-(3-methylthio-prop-2-enoylamino)butyl]-prop-2-enamide (=aglaidithioduline, 5). 3-Methylthio-2-propenoic acid chloride (**7**) was prepared as described for **8** and then a solution of putrescine (**12**) (ratio **7**/**12** 1:2) in CH_2Cl_2 added at room temperature. After 1 h, the mixture was poured into aq. NaCl solution and extracted with CH_2Cl_2. After separation by CC (SiO_2; CH_2Cl_2/MeOH 19:1) the product **5** was obtained as a colorless microcrystalline solid (30%). Mp: 177–179°. IR (KBr) ν (cm^{-1}): 3317s, 2943m, 2868m, 1626s, 1577s, 1527s, 1473m, 1433w, 1325m, 1258m, 1240m, 1192m, 1033w, 994m, 937m, 851m, 817w, 742w, 704m 634m, 524w. ^1H NMR (CD_3OD, 300 MHz): 7.54 (d, J=14.7 Hz, 2H), 5.81 (d, J=14.8 Hz, 2H), 3.30–3.18 (m, 4H), 2.34 (s, 6H), 1.62–1.50 (m, 4H). ^{13}C NMR (CD_3OD, 75 MHz): 167.5 (s), 143.6 (d), 116.9 (d), 40.2 (t), 28.1 (t), 14.5 (q). ^1H NMR (d^6-DMSO, 300 MHz): 7.84 (t, J=5.6 Hz, 2H), 7.44 (d, J=14.8 Hz, 2H), 5.88 (d, J=14.8 Hz, 1H), 3.22–3.12 (m, 4H), 2.37 (s, 6H), 1.54–1.45 (m, 4H). ^{13}C NMR (d^6-DMSO, 75 MHz): 163.4 (s), 139.4 (d), 117.3 (d), 38.1 (t), 26.6 (t), 13.7 (q). CIMS/NH_3: 289 ($[M+1]^+$). Elemental analysis calcd for $C_{12}H_{20}N_2O_2S_2$: C, 49.97; H, 6.99; N, 9.71; S, 22.23; found: C, 49.72; H, 6.71; N, 9.66; S, 21.98.

4.1.4. 3-Methylthio-*N*-(4-phenylacetylaminobutyl)-prop-2-enamide (=aglaithioduline, 3). Acylation of **2** (0.10 g; 0.53 mmol) in 15 ml CH_2Cl_2 with 0.123 g (0.8 mmol; 1 ml) phenylacetyl chloride (**10**) in the presence of 0.215 g (2.1 mmol; 0.3 ml) NEt_3 as a base, yielded after 30 min stirring at room temperature in a reaction mixture, which was taken up in aq. NaCl solution and extracted with CH_2Cl_2. After drying and subsequent evaporation of the organic phase a raw product resulted, which was purified by CC (SiO_2; CH_2Cl_2/MeOH 19:1) to give 0.127 g (78%) of **3** as a colorless solid. Mp: 128–130°. IR ν (cm^{-1}): 3440m, 3300m, 2990m, 2920m, 2860w, 1715m, 1660s, 1580s, 1510s, 1435w, 1330w, 1250m, 990w, 940m, 840w. ^1H NMR (CD_3OD, 300 MHz): 7.54 (d, J=14.7 Hz, 1H), 7.32–7.18 (m, 5H), 5.80 (d, J=4.7 Hz, 1H), 3.48 (s, 2H), 3.30–3.15 (m, 4H), 2.34 (s, 3H), 1.45–1.60 (m, 4H). ^{13}C NMR (CD_3OD, 75 MHz): 174.2 (s), 167.5 (s), 143.5 (d), 137.2 (s), 130.2 (d), 129.7 (d), 128.0 (d), 116.9 (d), 44.1 (t), 40.3 (t), 40.1 (t), 28.0 (t), 27.9 (t), 14.5 (q). CIMS/NH_3: 307 ($[M+1]^+$).

4.1.5. 2-Phenyl-*N*-(4-phenylacetylaminobutyl)acetamide (=aglaiduline, 4). In a solution of 5.0 g (56.7 mmol) putrescine (**12**) and 14.34 g (141 mmol; 19.75 ml) NEt_3 in 100 ml CH_2Cl_2 18.4 g (119 mmol; 15.8 ml) phenylacetyl chloride (**10**) was dropwise introduced. Cooling (ice-bath) was necessary. After 2 h stirring, the mixture was poured into diluted aq. HCl and extracted with CH_2Cl_2. Concentration of the organic phase in vacuo led to crystallisation of some product, the main charge was obtained by complete evaporation and subsequent recrystallisation from EtOH/hexane. Together, 14.9 g (81%) of **4** could be collected as colorless crystals. Mp: 175.5–176.5°. IR ν (cm^{-1}): 3335w, 3290m, 3060w, 3000w, 2940w, 2880w, 1660s, 1600w, 1520m, 1495w, 1470w, 1455w, 1350w, 1320w, 1270w, 1160w, 1080w, 695w. ^1H NMR (CD_3OD, 300 MHz): 7.35–7.20 (m, 10H), 3.47 (s, 4H), 3.15 (m, 4H), 1.48 (m, 4H). ^{13}C NMR (CD_3OD, 75 MHz): 174.2 (s), 137.0 (s), 130.2 (d), 129.7 (d), 128.0 (d), 44.1 (t), 40.3 (t), 27.9 (t). ^1H NMR (d^6-DMSO, 300 MHz): 8.16 (t, J=5.1 Hz, 2H), 7.43–7.28 (m, 10H), 3.50 (s, 4H), 3.15 (m, 4H), 1.58–1.40 (m, 4H). ^{13}C NMR (d^6-DMSO, 75 MHz): 169.8 (s), 136.5 (s), 128.8 (d), 128.0 (d), 126.1 (d), 42.3 (t), 38.2 (t), 26.4 (t). CIMS/NH_3: 342 (9, $[M+1]^+$), 325 (100, $[M+1]^+$).

4.1.6. *tert*-Butyl *N*-[4-(3-phenyl-prop-2-enoylamino)-butyl]carbamate (*N*-Boc-*N'*-cinnamoyl-putrescine, 17). A solution of 7.16 g (43 mmol) cinnamoyl chloride (**16**) in 30 ml CH_2Cl_2 was dropped into a mixture of 8.1 g (43 mmol) **9** and 5.06 g (50 mmol; 7.0 ml) NEt_3 in 70 ml CH_2Cl_2. Cooling was accomplished by an ice-bath. After 2 h, the mixture was poured into diluted aq. NaOH (to hydrolyse any unreacted **16**) and extracted with CH_2Cl_2. After evaporation, 13.13 g (92%) of **17** were obtained as a yellowish solid in sufficient purity. IR ν (cm^{-1}): 3440m, 3300m, 2980m, 2930m, 2860w, 1700s, 1660s, 1625s, 1580w, 1500s, 1450w, 1390w, 1365m, 1330w, 1225s, 1160s, 985w, 975m, 855w. ^1H NMR ($CDCl_3$, 300 MHz): 7.61 (d, J=15.7 Hz, 1H), 7.47 (m, 2H), 7.33 (m, 3H), 6.45 (d, J=15.7 Hz, 1H), 6.30 (br., 1H), 4.70 (br., 1H), 3.41 (q, J=5.9 Hz, 2H), 3.14 (m, 2H), 1.75–1.50 (m, 4H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 166.0 (s), 156.1 (s), 140.5 (d), 134.9 (s), 129.4 (d), 128.7 (d), 127.6 (d), 120.9 (d), 79.2 (s), 40.0 (t), 39.3 (t), 28.3 (q), 27.6 (t), 26.5 (t).

4.1.7. *N*-(4-Aminobutyl)-3-phenyl-prop-2-enamide (*N*-mono-cinnamoyl-putrescine 15). To a solution of 10.0 g (31.4 mmol) **17** in 20 ml EtOH was added aq. 1N HCl (100 ml) and the mixture warmed to 40° for 3 h. Afterwards, the solution was washed with Et_2O and the organic phase discarded. The aq. phase was first saturated with NaCl and then aq. NaOH was added to get a strong basic solution, which was extracted with CH_2Cl_2. After separating the organic phase, drying with Na_2SO_4 and evaporating resulted in 4.1 g (60%)*** **15** as a viscous yellow oil, which could be used without any further purification. IR ν (cm^{-1}): 3420m, 3290m, 3060w, 2980m, 2930s, 2860m, 1660s, 1620s, 1575w, 1510s, 1450m, 1330m, 1300w, 1280w, 1220m, 1090w, 1070w, 975m, 855m, 660w. ^1H NMR ($CDCl_3$, 300 MHz): 7.61 (d, J=15.7 Hz, 1H), 7.47 (m, 2H), 7.40–7.25 (m, 3H), 6.72 (br.s, 1H), 6.45 (d, J=15.7 Hz, 1H), 3.38 (q, J=5.9 Hz, 2H), 2.73 (t, J=6.5 Hz, 2H), 1.75–1.40 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): 165.9 (s), 140.4 (d), 134.9 (s), 129.4 (d), 128.7 (d), 127.6 (d), 121.0 (d), 41.6 (t), 39.5 (t), 30.7 (t), 27.0 (t).

4.1.8. (*E*)-2-Methyl-*N*-(4-[(*E*)-3-phenyl-2-propenoyl]-aminobutyl)-2-butenamide (=grandiamide B, 13). To a suspension of 0.37 g (1.67 mmol) **15** in 30 ml CH_2Cl_2 was added EDC (0.349 g; 1.82 mmol) and afterwards tiglic acid

*** Some product was lost during the extraction process.

(**18**; 0.167 g; 1.67 mmol) in 10 ml CH_2Cl_2 was introduced. Stirring at room temperature was continued for 12 h before the mixture was taken up in aq. 1N HCl. Extraction with CH_2Cl_2 followed by washing with aq. NaCl solution yielded after evaporation directly in 0.39 g (77%) **13** as a colorless powder. Mp: 100.5–101.5°. IR ν (cm^{-1}): 3450m, 3320m, 3300s, 3940m, 3860w, 1670s, 1630s, 1580w, 1515s, 1450m, 1380w, 1335m, 1280w, 1170w, 1090w, 990w, 980m, 855w, 660w. ^1H NMR ($CDCl_3$, 300 MHz): 7.60 (d, J=15.7 Hz, 1H), 7.45 (m, 2H), 7.28 (m, 3H), 6.95 (t, J=5.3 Hz, 1H), 6.53 (d, J=15.7 Hz, 1H), 6.43 (q, J=6.9 Hz, 1H), 6.25 (br.t, 1H), 3.48–3.28 (m, 4H), 1.84 (s, 3H), 1.72 (d, J=6.9 Hz, 3H), 1.68–1.52 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): 169.7 (s), 166.2 (s), 140.3 (d), 134.9 (s), 131.7 (s), 130.6 (d), 129.4 (d), 128.6 (d), 127.6 (d), 121.2 (d), 39.2 (t),[†††] 27.1 (t), 26.7 (t), 13.8 (q), 12.3 (q). CIMS/NH_3: 301 ($[M+1]^+$). Elemental analysis calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33; found: C, 71.72; H, 8.31; N, 9.07.

4.1.9. (±)-3-Hydroxy-2-methylen-butanoic acid (19). Prepared according to Ref. 8. IR ν (cm^{-1}): 3600–2400br., 2980w, 1690s, 1625m, 1400m, 1270m, 1170m, 1090s, 1035w, 1015w, 965m, 925w, 870w. ^1H NMR ($CDCl_3$, 300 MHz): 7.20 (br., 2H), 6.37 (s, 1H), 5.94 (s, 1H), 3.51 (q, J=7.0 Hz, 1H), 1.41 (d, J=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 170.9 (s), 142.7 (s), 126.4 (t), 66.8 (d), 21.9 (q).

4.1.10. 2-(1-Hydroxyethyl)-*N*-[4-(3-phenyl-prop-2-enoyl-amino)butyl]prop-2-enamide (=grandiamide C, 14). To a suspension of 0.365 g (1.67 mmol) **15** in 30 ml CH_2Cl_2 were subsequently added 0.345 g (1.67 mmol) DCC and 0.17 g (1.67 mmol) **19**. After a short induction period, the precipitation of a colorless solid (dicyclohexyl urea) could be observed. Stirring was continued at room temperature for 8 h. Afterwards, the solid was filtered off and discarded. The clear filtrate was concentrated in vacuo and the residue purified by CC (SiO_2; CH_2Cl_2/MeOH 20:1) which yielded in 0.32 g (60%) **14** as a colorless solid. Mp: 104.5–106.5°. IR ν (cm^{-1}): 3450m, 3320m, 3000m, 2940m, 2860w, 1665s, 1620s, 1580w, 1520s, 1450m, 1370w, 1330m, 1280w, 1100w, 1020w, 975m. ^1H NMR ($CDCl_3$, 300 MHz): 7.57 (d, J=15.7 Hz, 1H), 7.53 (t, J=7.9 Hz, 1H), 7.45 (m, 2H), 7.28 (m, 3H), 7.06 (t, J=5.6 Hz, 1H), 6.53 (d, J=15.7 Hz, 1H), 5.83 (s, 1H), 5.43 (s, 1H), 4.60 (q, J=6.5 Hz, 1H), 3.90 (br. OH, 1H), 3.40–3.20 (m, 4H), 1.65–1.50 (m, 4H), 1.37 (d, J=6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 168.1 (s), 166.5 (s), 146.3 (s), 140.6 (d), 134.7 (s), 129.5 (d), 128.7 (d), 127.6 (d), 120.9 (d), 119.3 (t), 68.5 (d), 39.2 (t), 38.9 (t), 26.7 (t), 14.0 (q). CIMS/NH_3: 317 ($[M+1]^+$). Elemental analysis calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85; found: C, 68.10; H, 7.65; N, 8.79.

4.1.11. *N*-[4-(3-Phenyl-prop-2-enoylamino)butyl]benzamid (=pyramidatine, 20). To a mixture of 0.50 g (2.30 mmol) **15** and 0.348 g (3.44 mmol; 0.48 ml) NEt_3 in 30 ml EtOAc was added benzoylchloride (0.32 g; 2.3 mmol; 0.27 ml) at room temperature. After 15 min, the mixture was poured into diluted aq. HCl and extracted with CH_2Cl_2. After removing the solvent in vacuo, the residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 19:1) to yield 0.64 g (86%) of **20** as a colorless powder. Mp: 166.5–167.5°. IR ν (cm^{-1}): 3442w, 3310s, 3000w, 2940w, 2870w, 1705w, 1660s, 1630s, 1620s, 1580m, 1520s, 1480m, 1450w, 1325w, 1280w, 985m, 975m. ^1H NMR (d^6-DMSO, 300 MHz): 8.50 (t, J=5.5 Hz, 1H), 8.15 (t, J=5.4 Hz, 1H), 7.9 (m, 2H), 7.60–7.35 (m, 9H), 6.67 (d, J=15.8 Hz, 1H), 3.33 (q, J=6.4 Hz, 2H), 3.26 (q, J=6.5 Hz, 2H), 1.70–1.45 (m, 4H). ^{13}C NMR (d^6-DMSO, 75 MHz): 166.0 (s), 164.7 (s), 138.2 (d), 134.8 (s), 134.6 (s), 130.8 (d), 129.2 (d), 128.8 (d), 128.1 (d), 127.3 (d), 127.0 (d), 122.3 (d), 38.8 (t), 38.3 (t), 26.6 (t). CIMS/NH_3: 323 ($[M+1]^+$).

4.1.12. (+)-(*S*)-*N*-[4-(2-Methyl-butanoylamino)butyl]-3-phenyl-prop-2-enamide (=(+)-(*S*)-secoodorine, 1). To a solution of 0.14 g (1.37 mmol) commercially available (+)-(*S*)-2-methylbutanoic acid (**23**) in 10 ml EtOAc were subsequently added 0.186 g (1.37 mmol) HOBt and 0.283 g (1.37 mmol) DCC. After 5 min, 0.30 g (1.37 mmol) **15** in 10 ml EtOAc were introduced at room temperature. This resulted in a white suspension. After 1 h stirring, the precipitated colorless solid was filtered off and discarded after washing with EtOAc. The filtrate was evaporated, and the residue purified by CC (SiO_2; CH_2Cl_2/MeOH 15:1): 0.27 g (66%) of **1** as colorless crystals. Mp: 146.5–147.0°. $[\alpha]_D$=+12.3° (c=0.33, $CHCl_3$). IR ν (cm^{-1}): 3445m, 3320br., 2995m, 2960m, 2930m, 2870m, 1660s, 1625s, 1580w, 1510s, 1450m, 1370w, 1335m, 1300w, 1280w, 1090w, 1070w, 985m, 975m, 910w, 855w. ^1H NMR ($CDCl_3$, 300 MHz): 7.61 (d, J=15.7 Hz, 1H), 7.50–7.46 (m, 2H), 7.37–7.31 (m, 3H), 6.66 (br.t, 1H), 6.50 (d, J=15.7 Hz, 1H), 6.05 (br.t, 1H), 3.42–3.38 (m, 2H), 3.35–3.28 (m, 2H), 2.13 (hex., J=7.4 Hz, 1H), 1.69–1.55 (m, 1H), 1.61–1.59 (m, 4H), 1.50–1.36 (m, 1H), 1.13 (d, J=6.9 Hz, 3H), 0.90 (t, J=7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 176.8 (s), 166.2 (s), 140.5 (d), 134.9 (s), 129.4 (d), 128.7 (d), 127.6 (d), 121.0 (d), 43.0 (d), 39.2 (t), 38.8 (t), 27.2 (t), 27.1 (t), 26.7 (t), 17.5 (q), 11.8 (q). ESI-MS: 325 ($[M+Na]^+$). Elemental analysis calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26; found: C, 71.52; H, 8.49; N, 9.32.

4.1.13. *N*-(4-Isobutyrylaminobutyl)-3-phenyl-prop-2-enoyl-amide (=secopiriferine, 22). Isobutyryl chloride (**24**; 0.146 g; 0.145 ml) was added dropwise to a mixture of 0.30 g (1.37 mmol) **15** and 0.21 g (2.1 mmol; 0.29 ml) NEt_3 in 15 ml CH_2Cl_2 at room temperature. After 15 min, the reaction mixture was poured in diluted aq. HCl and extracted with CH_2Cl_2. Removing the solvent in vacuo and purification of the residue by CC (SiO_2; CH_2Cl_2/MeOH 15:1) yielded in 0.376 g (95%) of **22** as colorless crystals. Mp: 161.0–161.5°. IR ν (cm^{-1}): 3440m, 3295br., 2995m, 2960m, 2940m, 2870w, 1660s, 1625s, 1580w, 1510s, 1470w, 1450m, 1365w, 1335m, 1300w, 1280w, 1090w, 985w, 975m, 910w, 855w. ^1H NMR ($CDCl_3$, 300 MHz): 7.62 (d, J=15.6 Hz, 1H), 7.51–7.48 (m, 2H), 7.39–7.34 (m, 3H), 6.45 (d, J=15.6 Hz, 1H), 6.33 (br.t, 1H), 5.86 (br.t, 1H), 3.43 (q-like m, 2H), 3.30 (q-like m, 2H), 2.37 (hept., J=6.9 Hz, 1H), 1.63–1.56 (m, 4H), 1.16 (d, J=6.9 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): 177.3 (s), 166.1 (s), 140.7 (d), 134.8 (s), 129.5 (d), 128.67 (d), 127.7 (d), 120.8 (d), 39.2 (t), 38.8 (t), 35.6 (d), 27.1 (t), 26.6 (t), 19.5 (q). ESI-MS: 311 (100, $[M+Na]^+$), 289 (10, $[M+H]^+$). Elemental analysis calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71; found: C, 70.67; H, 8.26; N, 9.64.

[†††] The carbon signals of both CH_2-groups next to nitrogen atoms show a signal overlapping by 39.2 ppm.

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