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Bio-Inspired Synthesis

Mimicking the Main Events of the Biosynthesis of Drimentines: Synthesis of $\Delta^{8'}$-Isodrimentine A and Related Compounds

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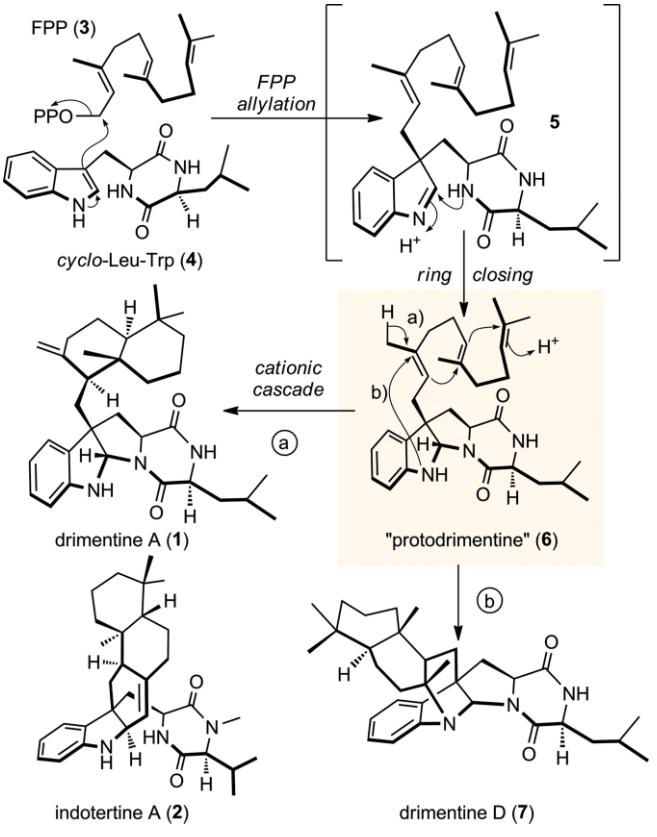
Abstract: Drimentines are a family of tetracyclic alkaloids biosynthetically originating from the condensation of sesquiterpene units onto cyclic dipeptides. A straightforward assembly of the fused "pyrroloindoline–diketopiperazine" core of drimentines is described herein and used for the synthesis of $\Delta^{8'}$-isodrimentine A. The strategy involves a bio-inspired indole dearomatization of a tryptophan-containing cyclodipeptide by a drimane-type decaline followed by the intramolecular trapping of the resulting indolenine intermediate in an uninterrupted reactive sequence. The starting diketopiperazine was prepared by classical peptidic coupling and the drimane-type decaline from (+)-sclareolide. A fully biomimetic approach with a linear sesquiterpene unit is also reported and led to farnesylated pyrroloindoline–diketopiperazines, which correspond to the proposed biosynthetic precursors of both drimentines A and D. The end product $\Delta^{8'}$-isodrimentine A and its congeners were evaluated in vitro for their cytotoxic activities against three human tumor cell lines.

Introduction

Drimentines are a family of pyrroloindoline–diketopiperazine alkaloids isolated from Actinomycetes strains[1,2] showing antibiotic activities[1] as well as moderate cytotoxicities.[2] Among the substantial array of prenyl-modified peptides,[3] to date drimentines and the co-isolated indotertines are the sole examples of pyrroloindoline–diketopiperazines bearing a sesquiterpene moiety (Scheme 1).[4] En route to this class of alkaloids, Joullié et al. reported a seminal total synthesis of roquefortine C.[5] More recently, Li et al. have reported a collective synthesis of drimentines A (**1**), G, F and indotertine A (**2**) by a multistep strategy resting on the radical conjugate addition of a bromoindoline derivative onto an appropriate Michael acceptor.[6] Given our long-lasting interest for the biomimetic synthesis[7] of natural products, we have been prompted to take advantage of a short and straightforward bio-inspired approach towards this group of alkaloids. When considering their biosynthetic origin (Scheme 1), the enzymatic transfer of a farnesyl unit (**3**) on a tryptophan-containing diketopiperazine (**4**) is likely to be responsible for the formation of their polycyclic central skeleton. Indeed, this would generate a transient indolenine intermediate (**5**) subsequently trapped by intramolecular nucleophilic attack forming thereby the final diketopiperazino–pyrroloindoline core (**6**, which could be considered as a "protodrimentine") of drimentines (**1** herein).[8] As a final step, an enzymatic cationic cascade cyclization leading to the decaline ring system may end either by a β-elimination (pathway a), either by the trapping of the indoline nitrogen atom (pathway b) affording drimentine A (**1**) or D (**7**), respectively. Hence, we decided to mimic the indole dearomatization/intramolecular indolenine trapping sequence. Besides biosynthetic considerations, this approach appeared to us to be straightforward lead-



Scheme 1. Biosynthesis of drimentines A (**1**) and D (**7**).

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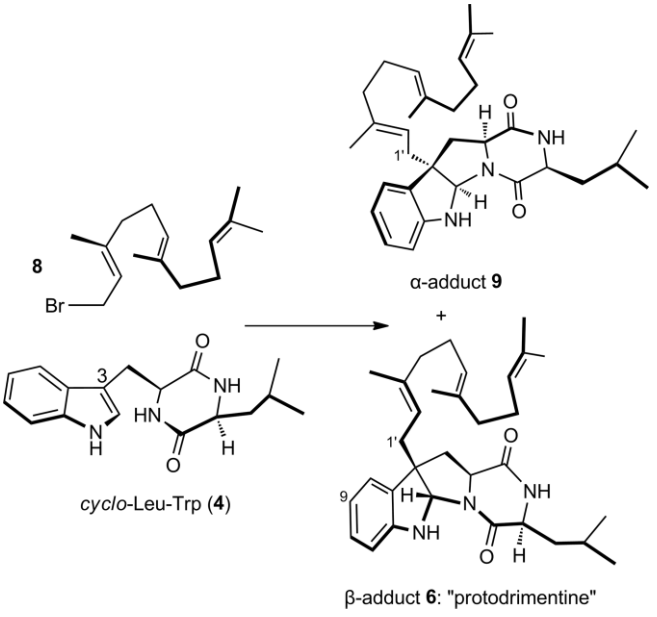
ing promptly to accessible precursors from the required tryptophan-containing dipeptides and electrophilic C_{15} units. In this work, we evaluated the introductions of two distinct C_{15} units: (i) a farnesyl addition by allylation followed by a cascade cyclization in a completely bio-inspired approach; (ii) a preformed drimane-type decaline obtained from sclareolide providing directly the targeted scaffold.

Results and Discussion

Prior to any study of the envisioned reaction sequences, we prepared unprotected *cyclo*-Leu-Trp (**4**) by peptidic coupling in two steps and good yields.[9] From there, electrophilic C_{15} donors were needed, and appropriate bromide derivatives had to be prepared. At first, farnesylation was chosen to initiate the study with the aim of achieving a fully biomimetic synthesis of drimentines A (**1**) and D (**7**) from protodrimentine (**6**).

For this purpose, after the sequential exposure of **4** to potassium *tert*-butoxide and triethylborane (allowing the formation of an indolyltriethylborate species), farnesyl bromide (**8**)[10] served as the electrophile (Scheme 2).[11–13] Under these conditions, complexation of the indole anion is supposed to enhance the C-3 nucleophilicity by electron enrichment, therefore allowing the C-3 quaternization. The direct trapping of the transitory indolenine by the appended diketopiperazine moiety allowed the formation of the tetracyclic ring system of drimentines just as in the biosynthetic proposal. Indeed, under stoichiometric conditions the reaction afforded a 1:1 diastereomeric mixture of **6**/**9** in 63 % yield. Further resolution by preparative HPLC gave β-adduct **6** and α-adduct **9** both in 25 % isolated yield, each.[14] Given the upstream position of β-adduct **6** in the proposed biosynthetic pathway of drimentines, numerous attempts of farnesyl cyclization were carried out in order to reach the final drimentine skeleton or even drimentines themselves, but without success (Table 1).[15,16]

The successful synthesis of protodrimentine (**6**), prompted us to pursue the study with preformed C_{15} drimane-type decalines (Scheme 3). After the synthesis of the required decalines (i.e., with two possible leaving groups: iodide for **10**[6,17] and mesylate for **11**[18,19]) in several steps from sclareolide (**12**),[20] the previously validated conditions (*t*BuOK, BEt_3) proved to be ineffective with such homoallylic electrophiles. Nonetheless, the recourse to the very similar allylic drimane **13**[21] restored the efficiency of the conditions. Starting from equimolar amounts of **4** and **13**, the key alkylation provided a 1:1 α/β-diastereomeric mixture of the targeted drimentine core in 35 % yield.[14]



Scheme 2. Bio-inspired assembly of "protodrimentine" (**6**). Reaction conditions: *t*BuOK, –78 °C, BEt_3, then **8** (1.1 equiv.), 50 °C, 12 h, 63 % and after preparative HPLC (**6**: 25 %; **9**: 25 %).

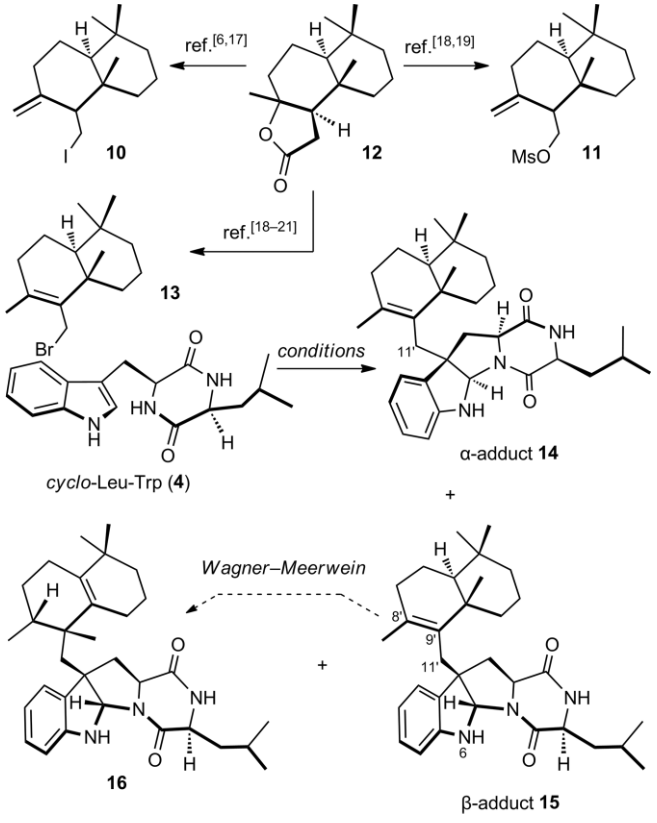
Resolution by preparative HPLC afforded the two diastereomers **14** and **15** ($\Delta^{8'}$-isodrimentine A) in 14 % isolated yield, each, alongside with minute amounts (2 %) of **16** originating from a Wagner–Meerwein rearrangement of **15**.[22] Owing to its high structural similarity with **1** and **7**, compound **15** represented the opportunity to reach challenging alkaloids of the series. Indeed, among other possibilities, a supplementary N-6/C-8′ ring closure after the formation of a C-8′ carbocation could lead to drimentine D (**7**). However, all the experiments carried out to this end led to decomposition of the framework (Table 1).

Compounds **6**, **9**, **14**, **15** and **16** were evaluated in vitro for their cytotoxic activities against three human tumor cell lines: colon cancer (HCT-116), lung carcinoma (A549) and myelogenous leukemia (K562). The results revealed that the non-cyclized compounds **6**, **9** and α-adduct **14** were inactive (IC_{50} > 100 μM), while compounds **15** and **16** showed moderate cytotoxic activities against HCT-116 and K562 cell lines (Table 2). Those results indicate that both isomers **15** and **16** are active in the same range than natural drimentines.[2] Overall, it could be postulated that the presence of a decaline group on the β-position of the tetracyclic alkaloid framework is critical for achieving tumor-cell growth-inhibitory activity.

Table 1. Cyclization attempts of **6** and **15** toward drimentine A/D (**2**/**7**).

Substrate	Conditions	Solvent	Temp.	Observations
6	(*R*)-BINOL, $SnCl_4$	CH_2Cl_2	0 °C	degradation
6	PTSA[a]	toluene	50 °C	no reaction
6	H_2SO_4[16]	CH_3NO_2	–20 °C	partially cyclised compounds (no *exo*-methylene group)
6	$Et_2SBr{\cdot}SbCl_5Br$[16]	CH_3NO_2	–25 °C	C-9 bromination
15	PTSA	toluene	r.t.	degradation
15	Amberlyst®-15	CH_2Cl_2	r.t.	degradation
15	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0 °C	degradation

[a] PTSA = *p*-toluenesulfonic acid.



Scheme 3. Biomimetic assembly of $\Delta^{8'}$-isodrimentine A (**15**). Reagents and conditions: (a) *t*BuOK, –78 °C, BEt_3, then **13** (1.1 equiv.), 50 °C, 12 h, 35 % and after preparative HPLC (**14**: 14 %; **15**: 14 %; **16**: 2 %).

Table 2. IC_{50} [μM] of compounds **15** and **16** against cell lines HCT116, A549 and K562 cells.[a]

	HCT-116	A549	K562
15	6.0 ± 0.6	71 ± 6	4.5 ± 0.3
16	5.0 ± 1.0	46 ± 3	16.2 ± 2.8
Taxotere®	0.050 ± 0.002	0.20 ± 0.02	0.050 ± 0.001

[a] Values are mean ± standard errors of three independent experiments.

Conclusions

In this work, we accessed the drimentine scaffolds in a straightforward sequence mimicking the main events of their biosynthesis. *cyclo*-Leu-Trp was easily alkylated by farnesyl bromide affording a direct biosynthetic precursor. Allylation conditions were also effective with bulky drimane-type decalines allowing the efficient assembly of the alkaloid core. $\Delta^{8'}$-Isodrimentine A (**15**) and analogous **16** were synthetized and showed moderate cytotoxicities but similar to that of drimentine A, while α-adduct **14** and non-cyclized compounds **6** and **9** were inactive.

Experimental Section

General: IR spectra were recorded with a Vector 22 Bruker spectrometer. NMR spectra were recorded with Bruker AM-300 (300 MHz) and AM-400 (400 MHz) spectrometers using [D]chloroform and [D_6]DMSO as solvents. The solvent signals were used as references. Multiplicities are described by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br. = broad. HR ESI MS experiments were conducted with a Thermoquest TLM LCQ Deca ion-trap spectrometer. XBridge® C_{18} column (150 × 19 mm i.d.; 5 μm) was used for preparative HPLC separations using a Waters Delta Prep apparatus equipped with a binary pump (Waters 2525) and a UV/Vis diode array detector (190–600 nm; Waters 2996).

General Procedure for the Alkylation of *cyclo*-Leu-Trp (4): To a pre-cooled solution (0 °C) of alcohol (farnesol or driman-8-en-11-ol, 163 mg, 0.74 mmol) in diethyl ether (5 mL), PBr_3 (100 μL, 1.1 mmol) was added. After 1 h of stirring, the reaction mixture was washed with water (5 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The corresponding allyl bromide was used without further purification immediately after its synthesis. To a pre-cooled solution (–78 °C) of *cyclo*-Leu-Trp (200 mg, 0.67 mol) in dioxane (3 mL), a 1 M solution of *t*BuOK in THF (670 μL, 0.67 mmol) was added. After 10 min of stirring, a 1 M solution of triethylborane in hexane (670 μL, 0.67 mmol) was added. After 10 min of stirring, the appropriate, freshly prepared allyl bromide (0.74 mol) in solution in dioxane (2 mL) was added, and the reaction mixture was heated to 50 °C for 16 h. After cooling, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (5 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. From farnesol: purification by flash chromatography on silica gel (eluent: dichloromethane/methanol, 9:1) affordes a mixture of **6**/**9** (212 mg, 63 %). Resolution by preparative HPLC (isocratic 85 % MeOH in H_2O at 42 mL/min) afforded **9** (t_r = 13.1 min; 85 mg, 25 %) and **6** (t_r = 14.6 min; 85 mg, 25 %). From driman-8-en-11-ol: purification by flash chromatography on silica gel (eluent: dichloromethane/methanol, 9:1) afforded mixture of **14**/**15**/**16** (118 mg, 35 %). Resolution by preparative HPLC (isocratic 85 % MeOH in H_2O at 42 mL/min) afforded **14** (t_r = 11.1 min; 47 mg, 14 %), **16** (t_r = 12.3 min; 7 mg, 2 %) and **15** (t_r = 13.6 min; 46 mg, 14 %).

(2*S*,3*S*)-*cyclo*-Leucinyl-(3-farnesyl-*N*,2-*cyclo*-2,3-dihydrotryptophyl), Protodrimentine A (6): ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.11–7.04 (m, 2 H), 6.75 (t, *J* = 7.2 Hz, 1 H), 6.59 (d, *J* = 7.7 Hz, 1 H), 6.47 (s, 1 H), 5.29 (s, 1 H), 5.21–5.13 (m, 2 H), 5.12–5.05 (m, 2 H), 3.99 (dd, *J* = 11.3, 6.2, Hz, 1 H), 3.94 (dd, *J* = 9.3, 3.9 Hz, 1 H), 2.64 (dd, *J* = 12.8, 6.2 Hz, 1 H), 2.42 (m, 2 H), 2.29 (dd, *J* = 12.8, 11.1 Hz, 1 H), 2.09–1.94 (m, 9 H), 1.77 (m, 1 H), 1.67 (s, 3 H), 1.60 (s, 3 H), 1.59 (s, 3 H), 1.55 (m, 1 H), 1.51 (s, 1 H), 0.98 (d, *J* = 6.5 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 169.9, 166.8, 148.9, 139.3, 135.13, 131.2, 131.0, 128.6, 124.3, 123.9, 123.4, 119.1, 118.2, 109.3, 79.7, 58.7, 55.6, 53.5, 39.9, 39.7, 38.6, 38.0, 35.4, 26.7, 26.5, 25.6, 24.5, 23.2, 21.2, 17.6, 16.3, 16.0 ppm. IR (neat): $\tilde{\nu}$ = 3305, 2940–2915, 2845, 1675–1658, 1606, 1484, 1293 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{47}N_2O_2^+$ $[M + H]^+$ 504.3590; found 504.3599. $[\alpha]_D$ = –205.3 (*c* = 0.57 CH_2Cl_2).

(2*R*,3*R*)-*cyclo*-Leucinyl-(3-farnesyl-*N*,2-*cyclo*-2,3-dihydrotryptophyl) (9): ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.08 (d, *J* = 7.4 Hz, 1 H), 7.04 (td, *J* = 7.7, 1.3 Hz, 1 H), 6.72 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.55 (d, *J* = 7.8 Hz, 1 H), 6.27 (s, 1 H), 5.37 (s, 1 H), 5.14 (t, *J* = 7.5 Hz, 1 H), 5.11–5.02 (m, 2 H), 4.28 (t, *J* = 8.5 Hz, 1 H), 3.96 (dd, *J* = 9.4, 3.8 Hz, 1 H), 2.52 (s, 1 H), 2.49 (s, 1 H), 2.47–2.44 (m, 2 H), 2.10–1.95 (m, 9 H), 1.74 (m, 1 H), 1.67 (s, 3 H), 1.61 (s, 3 H), 1.59 (s, 3 H), 1.58 (s, 3 H), 1.53 (m, 1 H), 0.95 (d, *J* = 6.5 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 169.9, 168.0, 147.4, 139.3, 135.3, 132.5, 131.3, 128.3, 124.2, 123.8, 123.0, 119.0, 118.5, 109.2, 81.2, 58.0, 55.6, 53.6, 39.9, 39.7, 38.4, 38.2, 35.2, 26.7, 26.5,

25.7, 24.5, 23.2, 21.2, 17.7, 16.5, 16.0 ppm. IR (neat): $\tilde{\nu}$ = 3315, 2950–2922, 2852, 1678–1650, 1613, 1487, 1303–1287 cm^{-1}. HRMS (ESI): calcd for $C_{33}H_{47}N_2O_2^+$ $[M + H]^+$ 504.3590; found 504.3602. $[\alpha]_D$ = +82.7 (*c* = 0.25 CH_2Cl_2).

(2*R*,3*R*)-*cyclo*-Leucinyl-[3-(driman-8-en-11-yl)-*N*,2-*cyclo*-2,3-dihydrotryptophyl] (14): ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.12 (dd, *J* = 7.5, 1.2 Hz, 1 H), 7.03 (td, *J* = 7.7, 1.2 Hz, 1 H), 6.74 (t, *J* = 7.4 Hz, 1 H), 6.51 (d, *J* = 7.9 Hz, 1 H), 5.87 (s, 1 H), 5.52 (s, 1 H), 4.33 (t, *J* = 8.3 Hz, 1 H), 3.93 (dd, *J* = 8.6, 3.5 Hz, 1 H), 2.84 (d, *J* = 15.2 Hz, 1 H), 2.57 (dd, *J* = 13.1, 8.5 Hz, 1 H), 2.49 (dd, *J* = 13.1, 8.5 Hz, 1 H), 2.44 (d, *J* = 15.2 Hz, 1 H), 2.10 (dd, *J* = 18.0, 7.1 Hz, 1 H), 2.00 (m, 1 H), 1.95 (m, 1 H), 1.78 (d, *J* = 12.5 Hz, 1 H), 1.74–1.59 (m, 3 H), 1.55–1.42 (m, 3 H), 1.44 (s, 3 H), 1.42–1.39 (m, 2 H),1.34 (d, *J* = 13.0 Hz, 1 H), 1.01 (dd, *J* = 12.9, 2.3 Hz, 1 H), 1.10–0.97 (m, 2 H), 0.97 (d, *J* = 6.5 Hz, 2 H), 0.93 (d, *J* = 6.5 Hz, 3 H), 0.85 (s, 3 H), 0.77 (s, 3 H), 0.62 (s, 3 H); 169.8, 167.8, 147.2, 138.2, 133.9, 131.5, 128.3, 123.6, 119.2, 109.4, 81.3, 58.0, 55.9, 53.5, 51.5, 41.5, 40.8, 38.4, 38.1, 37.7, 33.87, 33.81, 33.5, 33.4, 24.7, 23.3, 21.7, 21.2, 20.8, 20.1, 19.01, 18.89 ppm. IR (neat): $\tilde{\nu}$ = 3340, 2930–2920, 2832, 1665–1649, 1600, 1454, 1211, 1150 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{47}N_2O_2^+$ $[M + H]^+$ 504.3590; found 504.3584. $[\alpha]_D$ = +184.2 (*c* = 0.19 CH_2Cl_2).

(2*S*,3*S*)-*cyclo*-Leucinyl-[3-(driman-8-en-11-yl)-*N*,2-*cyclo*-2,3-dihydrotryptophyl], $\Delta^{8'}$-Isodrimentine A (15): ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.04 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.00 (dd, *J* = 7.6, 1.2 Hz, 1 H), 6.75 (td, *J* = 7.4, 1.0 Hz, 1 H), 6.54 (d, *J* = 7.8 Hz, 1 H), 6.00 (s, 1 H), 5.39 (s, 1 H), 3.95 (m, 2 H), 2.79 (t, *J* = 6.4 Hz, 1 H), 2.76 (d, *J* = 3.4 Hz, 1 H), 2.39 (d, *J* = 15.0 Hz, 1 H), 2.38 (t, *J* = 12.3 Hz, 1 H) 2.10-2.00 (m, 2 H), 1.90 (td, *J* = 17.2, 6.6 Hz, 1 H), 1.79–1.50 (m, 7 H), 1.50–1.35 (m, 2 H), 1.20–1.14 (m, 3 H), 1.10 (s, 3 H), 0.99 (d, *J* = 6.5 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 0.90 (s, 3 H), 0.88 (s, 3 H), 0.82 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 169.8, 166.7, 149.3, 137.1, 132.6, 132.3, 128.5, 124.5, 119.5, 109.3, 81.6, 59.7, 56.1, 53.7, 51.41, 42.0, 41.9, 39.0, 38.4, 38.1, 34.2, 33.6, 33.49, 33.43, 24.7, 23.4, 21.9, 21.3, 21.3, 20.8, 19.16, 19.13 ppm. IR (neat): $\tilde{\nu}$ = 3340, 2945, 2923, 2830, 1677–1664, 1606, 1442, 1173 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{47}N_2O_2^+$ $[M + H]^+$ 504.3590; found 504.3584. $[\alpha]_D$ = –161.4 (*c* = 0.22 CH_2Cl_2).

(2*S*,3*S*)-*cyclo*-Leucinyl-{3-[8β-9β-15(10→9)-abeodriman-5(10)-en-11-yl]-*N*,2-*cyclo*-2,3-dihydrotryptophyl} (16): ^{1}H NMR (400 MHz, [D]chloroform): δ = 7.06 (m, 2 H), 6.76 (t, *J* = 7.4 Hz, 1 H), 6.63 (d, *J* = 3.9 Hz, 1 H), 6.57 (d, *J* = 7.8 Hz, 1 H), 5.51 (s, 1 H), 3.91 (m, 2 H), 2.72 (dd, *J* = 12.3, 6.0 Hz, 1 H), 2.62 (s, 2 H), 2.34 (t, *J* = 12.3 Hz, 1 H), 2.08–2.00 (m, 2 H), 1.77–1.36 (m, 4 H), 1.60–1.38 (m, 5 H), 1.36 (s, 3 H), 1.33 (m, 1 H), 1.10–0.98 (m, 2 H), 0.95–0.92 (m, 12 H), 0.85 (s, 3 H), 0.81 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D]chloroform): δ = 169.5, 166.8, 149.2, 137.4, 132.7, 131.9, 128.8, 124.1, 119.5, 109.3, 81.37, 6.42, 56.0, 55.7, 51.3, 43.1, 41.7, 40.9, 38.0, 34.1, 33.7 (3 C), 33.6, 24.4, 23.2, 21.8, 21.4, 21.2, 21.1, 19.2, 19.1 ppm. IR (neat): $\tilde{\nu}$ = 3345, 2950, 2925, 1680–1669, 1610, 1466, 1163 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{47}N_2O_2^+$ $[M + H]^+$ 504.3590; found 504.3585. $[\alpha]_D$ = +145.8 (*c* = 0.22 CH_2Cl_2).

Supporting Information (see footnote on the first page of this article): General procedures, complete experimental section, characterization of all compounds, NMR charts and copies of the spectra.

Acknowledgments

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Keywords: Alkaloids · Drimentines · Biomimetic synthesis · Pyrroloindoline–diketopiperazines · Indoles

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