

175. Almazole C, a New Indole Alkaloid Bearing an Unusually 2,5-Disubstituted Oxazole Moiety, and Its Putative Biogenetic Peptidic Precursors, from a Senegalese Delesseriacean Seaweed¹⁾

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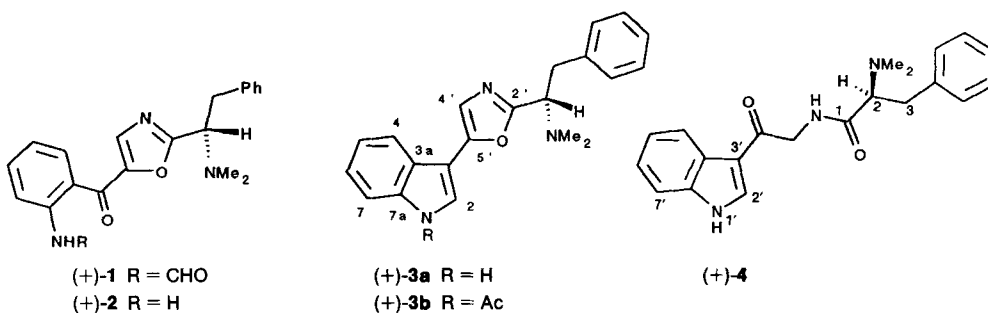
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From product isolation and biomimetic synthesis – which also establishes absolute configurations – the known oxazole alkaloids almazoles A ((+)-**1**) and B ((+)-**2**) seem to arise in a Senegalese delesseriacean seaweed from, in sequence, the new modified peptide prealmazole C ((+)-**4**) and the oxazole alkaloid almazole C ((+)-**3a**). *N,N*-Dimethyl-L-phenylalaninamide ((+)-**7**) and the new peptides (+)-**5** and (+)-**6**, as well as a series of known small units, are also involved. In all cases, the oxazole ring is peculiarly 2,5-inserted.

1. Introduction. – In oxazole-bearing natural products of both marine and terrestrial origin, 2,4-substitution of the oxazole moiety is the norm. Examples are the marine acetogeninic hennoxazoles [1a], kabiramide C [1b], calyculins [1c], bengazoles [1d], halichondramides [1e], mycaloide A [1f], and ulapualide A [1g], whose biogenetic origin was suggested in terms of a *Beckmann* rearrangement of polyketide oximes [1h], and the peptidic orbiculamide A [2a] and keramamides C–D [2b], and their dihydrooxazole counterparts ulicyclamide [3a], ulithiacyclamide [3a], patellamides [3b], lissoclinamides [3b], ascidiacyclamide [3c], and bistratamide [3d].

Recently, we reported on two new peptide alkaloids, almazoles A ((+)-**1**) and B ((+)-**2**), which are unusual for having a 2,5-substituted oxazole moiety [4]³⁾. They were



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³⁾ Other rare, recent marine examples of this type are phorbazoles A–D from the sponge *Phorbas* aff. *clathrata* [5], while among the few terrestrial examples are primprinine from actinobacteria [6a] and annulonine from rye grass [6b].

isolated from a red seaweed belonging to the family Delesseriaceae [4], probably in the genus *Haraldiophyllum*. From a new collection of this seaweed, we now isolated indole alkaloids that may be seen as biogenetic precursors of almazoles A and B. Their structures were confirmed by biomimetic synthesis from L-amino acids, thus also establishing their absolute configuration, giving support to the biogenetic hypothesis, and providing sufficient material for extensive biological assays.

2. Results and Discussion. – 2.1. *Natural Almazole C ((+)-3a) and Prealmazole C ((+)-4)*. The composition $C_{21}H_{21}N_3O$ for almazole C⁴⁾ rests on the $[M + H]^+$ ion in FAB-MS as well as on HR-EI-MS for fragments m/z 287 and 240, attributable to the loss of Me_2N and tropylium ion, respectively, from the molecular ion. This agrees with 1D- and 2D-NMR spectra (Table), which also fit for a 3-substituted indole nucleus, while the remaining signals are reminiscent of almazoles A ((+)-1) and B ((+)-2) [4]. The presence of the indole nucleus was confirmed by 1-acetylation to give (+)-3b. The 2,5-substitution of the oxazole moiety is suggested by the NMR signals (1H -NMR: 7.30 ppm (*s*, $H-C(4')$); ^{13}C -NMR: 160.68, 148.84 (2 *s*, $C(2')$, $C(5')$) and 119.86 ppm (*d*, $C(4')$)) and unequivocally proven by the ^{13}C , 1H -coupling pattern ($^1J(C(4'), H-C(4')) = 193$ and $^2J(C(5'), H-C(4')) = 18.7$ Hz; cf. $^1J(C(4'), H-C(4')) = 206$ – 209 and $^2J(C(5'), H-C(4')) = 14$ – 15 Hz for a 2,4-substituted oxazole [7]). NOE Enhancement between $H-C(4)$ and $H-C(4')$, and no NOE between $H-C(2)$ and $H-C(4')$, suggest that structure (+)-3a represents also the preferred conformation.

Table. NMR Data for Almazole C ((+)-3a) in $(CD_3)_2CO$

	$\delta(C)^a$	$\delta(H)^b$	HMBC ^{c)}
H–C(2)	123.61 (<i>d</i> , $J = 185$)	7.75 (<i>d</i> , $J = 2.7$)	C(7a), C(3a), C(5')
C(3)	105.72 (<i>s</i>)	–	
C(3a)	124.94 (<i>s</i>)	–	
H–C(4)	120.41 (<i>d</i> , $J = 162$)	7.91 (<i>ddt</i> , $J = 7.2, 2.1, 0.8$)	C(3a), C(6), C(7a)
H–C(5)	121.08 (<i>d</i> , $J = 160$)	7.20 (<i>br. t</i> , $J = 7.2$)	
H–C(6)	123.12 (<i>d</i> , $J = 160$)	7.24 (<i>br. t</i> , $J = 8.0$)	
H–C(7)	112.71 (<i>d</i> , $J = 162$)	7.52 (<i>ddd</i> , $J = 8.0, 2.0, 0.8$)	C(3a), C(5)
C(7a)	137.60 (<i>s</i>)	–	
C(5')	148.84 (<i>s</i>)	–	
H–C(4')	119.86 (<i>d</i> , $J = 193$)	7.30 (<i>s</i>)	C(3a), C(5'), C(2')
C(2')	160.68 (<i>s</i>)	–	
$CH_2CH(NMe_2)$	64.92 (<i>d</i> , $J = 139$)	4.11 (<i>dd</i> , $J = 9.2, 6.1$)	C(2'), Me_2N , $CH_2CH(NMe_2)$
$CH_2CH(NMe_2)$	37.39 (<i>t</i> , $J = 128$)	3.40 (<i>dd</i> , $J = 13.3, 9.1$)	C(2'), $CH_2CH(NMe_2)$, C_{ipso} , C_o
		3.22 (<i>dd</i> , $J = 13.3, 6.1$)	
C_{ipso}	139.92 (<i>s</i>)	–	
2 H– C_o	129.96 (<i>d</i> , $J = 157$)	7.28 (<i>m</i>)	
2 H– C_m	128.84 (<i>d</i> , $J = 160$)	7.22 (<i>m</i>)	
H– C_p	126.82 (<i>d</i> , $J = 160$)	7.15 (<i>m</i>)	
H–N(1)	–	10.79 (<i>br. s</i>)	C(2), C(7)
Me_2N	41.83 (<i>q</i> , $J = 133$)	2.37 (<i>s</i>)	$CH_2CH(NMe_2)$

a) $^1J(C, H)$ in Hz.

b) J in Hz.

c) Heterocorrelation of the indicated C-atom(s) with the proton(s) on the same row.

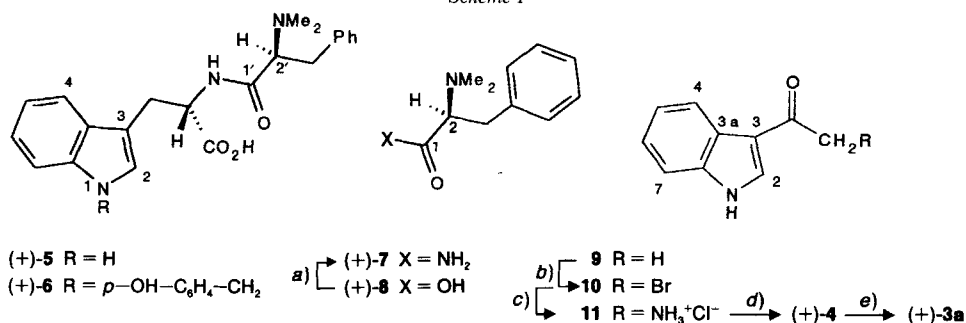
⁴⁾ Almazole C ((+)-3a) shows intense fluorescence at 470 nm on excitation at 365 nm in MeOH, possibly accounting for the fluorescent appearance of this alga in the evening at low tide.

On a structural basis, C(2)–C(3) oxidative breaking of almazole C ((+)-**3a**) can be proposed for the biogenesis of almazole A ((+)-**1**) and B ((+)-**2**).

The composition $C_{21}H_{23}N_3O_2$ for prealmazole C ((+)-**4**) rests on the observation of $[M + 1]^+$ in FAB-MS and on HR-EI-MS for fragment m/z 258, attributable to the loss of tropylium ion from M^+ . An unsaturation less than for (+)-**3a** agrees with the absence of the oxazole ^{13}C -NMR resonances, which are replaced by signals at 190.45 and 172.05 (2 s) and 46.51 ppm (t). Heterocorrelation of the latter with an *ABX* system centred at $\delta(H)$ 4.57 supports the CO–CH₂–NH–CO fragment. Insertion of the latter, *i.e.*, of CO–CH₂–NH, between C(3') of the indole and the *N,N*-dimethyl-*L*-phenylalanine moiety is warranted by long-range ^{13}C , 1H -coupling between the C=O group ($\delta(C)$ 190.45 (s)) and CO–CH₂–NH on one side, and the amidic C=O group (172.05 ppm (s)) and H–C(2) on the other side. Clearly, compound (+)-**4** possesses all structural features for a biogenetic precursor of almazole C, thus warranting the name prealmazole C.

2.2. *Natural Dipeptides* (+)-**5** and (+)-**6** and *N,N*-Dimethyl-*L*-phenylalaninamide ((+)-**7**). The composition $C_{22}H_{25}N_3O_3$ for (+)-**5** (Scheme 1) rests on detection of $[M + 1]^+$ in FAB-MS, in accordance with the NMR spectra, which also support the 3-substituted indole nucleus and the *N,N*-dimethyl-*L*-phenylalanine moiety. The CH₂–CH(COOH)–NH–CO fragment is based on NMR data (^{13}C -NMR: (169.87 (s), 53.84 (d), 27.47 ppm (t); 1H -NMR: the proton at 4.33 (m) couples with those at 3.26 (dd), 3.06 ppm (dd), and 7.61 ppm (br. s, exchangeable NH)). The position of the COOH group was confirmed by synthesis (see below, Scheme 2), which also established the *L,L*-absolute configuration.

Scheme 1



a) 1. CDI/DMF, r.t., 45 min; 2. NH₃(g), r.t., 3 h. b) Br₂, MeOH, reflux, 2 h. c) 1. HMTA/CHCl₃, r.t., 2 h; 2. 37% aq. HCl soln./EtOH 1:9, r.t., 1 day. d) 1. (+)-**8**, CDI, DMF, r.t., 45 min; 2. **11**, r.t., overnight. e) POCl₃, 40°, overnight.

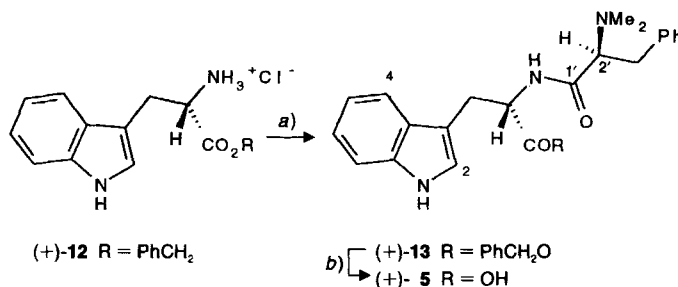
Although only extended fragmentation was observed in FAB-MS (*Exper. Part*), NMR spectra for compound (+)-**6** proved to be akin to those for (+)-**5**, and δ and J data allowed us to place unambiguously the 4-hydroxybenzyl group at the indole N-atom.

The unreported amide structure (+)-**7** was easily derived from spectra, while the absolute configuration was established by synthesis from the corresponding, commercially available *L*-amino acid (Scheme 1).

2.3. *Synthesis of the Algal Metabolites*. A biomimetic synthesis of almazole C ((+)-**3a**) is illustrated in Scheme 1. It involves sequential preparation of the bromo derivative **10** from 1*H*-indol-3-yl methyl ketone (**9**), the transformation of **10** into **11** [8], and

Dipeptide (+)-**5** was obtained along similar lines, starting from commercially available L-tryptophan benzyl ester ((+)-**12**) via (+)-**13**, which was easily deprotected by catalytic hydrogenation (Scheme 2).

Scheme 2



After optimization⁷), the above reactions went on in good yields. Most importantly, no racemization was observed in the CDI-induced [9] peptide couplings. This was deduced from the observation that addition of [Eu(tfc)₃] (tfc = (+)-3-[(trifluoromethyl)-hydroxymethylidene]camphor) to 0.02M (+)-**7** in CDCl₃ induced shifts of the 2H-C(3), H-C(2), and Me₂N signals without any signal splitting. Thus, the syntheses described in *Schemes 1* and *2* can provide easily materials in adequate amounts for biological assays. This may be important for compounds that, on a structural basis, and owing to lack of cytotoxicity, look promising for CNS activity [11]. The easy adaptability of these synthetic procedures to D-series or other amino acids adds further interest.

The reactions presented here support the view that, with this seaweed, L-tryptophan is involved in two or three biosynthetic lines. Thus, along a first route, condensation of L-tryptophan with *N,N*-dimethyl-L-phenylalanine ((+)-**8**) may lead to peptide (+)-**5**, while, along a second route, tryptophan-derived oxotryptamine undergoes a similar condensation to give prealmazole C ((+)-**4**). Dehydration of the latter, with oxazole cyclization, can also lead to almazole C ((+)-**3a**), which, on oxidative opening, gives

³⁾ POCl₃ dehydration of (+)-**4** with oxazole ring closure leading to (+)-**3a** (*Scheme 1*) was carried out at 40°. The usual drastic conditions of heating at reflux in the presence of either this reagent or conc. H₂SO₄ [6a] [10] led instead to a complex mixture of products from which (+)-**3a** was isolated in only very low yield, while on treatment with conc. H₂SO₄ at room temperature overnight, (+)-**4** was recovered unchanged. Moreover, the use of (+)-**8**·HCl, which is soluble in DMF, in place of the free base, insoluble in this medium, increased the yield of (+)-**13** (*Scheme 2*) and suppressed formation of *N,N'*-ditryptophanylurea (due to condensation of the free-base analogue of (+)-**12** with CDI [9]).

almazole A ((+)-1), from which almazole B ((+)-2) may descend. Alternatively, a third route can be envisaged involving the well established oxidative ring opening of tryptophan to give *N*-formylkynurenine [12], which undergoes condensation with (+)-8 to give (+)-1.

A variety of lighter metabolites isolated from this alga fit into this scheme, not only *N,N*-dimethyl-L-phenylalaninamide ((+)-7), obviously originating from (+)-8, but also 1*H*-indole-3-carboxylic acid and 1*H*-indole-3-glyoxylic acid (isolated as ethyl ester), and 1*H*-indole-3-acetamide, which can be considered to derive from tryptophan, 2-oxo-tryptamine, and tryptamine, respectively. Finally, 4-hydroxybenzyl alcohol (involved also in the formation of (+)-6 from (+)-5), and 4-ethoxybenzyl alcohol and 4-hydroxybenzaldehyde, may be biogenetically related to either the tryptophan or the phenylalanine portion of the algal metabolites, which is also reflected in the presence of abundant, free *N,N*-dimethyl-L-phenylalaninamide ((+)-7) in the alga.

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Experimental Part

1. *General*. Evaporations were carried out at reduced pressure. Yields are given either on dry seaweed after extraction or on reacted substrates. Reactions were carried out in flame-dried glassware under N_2 . DMF was distilled from BaO and stored over flame-dried 4 Å molecular sieves. Flash chromatography (FC): *Merck* silica gel *Si-60* (15–25 µm, 80 g), fractions of 40 ml. HPLC: *Merck LiChrosorb RP-18* (reversed-phase) or *Merck LiChrosorb NH₂* ('amine'); 25 × 1 cm columns packed with 7-µm materials; solvent flow 5 ml min⁻¹, if not otherwise stated; UV monitoring (λ 254 or 220 nm). M.p.: *Kofler* hot-stage microscope. Polarimetric data: *JASCO-DP-181* polarimeter. UV: *Perkin-Elmer-Lambda-3* spectrophotometer; λ_{max} in nm; ε in mol⁻¹ l cm⁻¹. CD: *Jasco-J-710* spectropolarimeter; λ_{max} in nm; Δε in mol⁻¹ l cm⁻¹. NMR: *Varian-XL-300* spectrometer; ¹H at 299.94 MHz, ¹³C at 75.43 MHz; δ in ppm rel. to internal Me₄Si (= 0 ppm), in (CD₃)₂CO (δ(H) 2.05, δ(C) 29.80), D₂O (δ(H) 4.77), and (CD₃)₂SO (δ(H) 2.50 and δ(C) 39.50) rel. to the solvent, *J* in Hz; COSY 60° [13]; C-multiplicity assignments by DEPT [14]; ¹³C, ¹H-NMR by inverse detection shift-correlation experiments [15]. Differential NOE: 5 s preirradiation; reported as 'irradiated proton → NOE on the observed proton(s)'. EI-MS (*m/z* (%)): *Kratos MS80*, with home-built computerized acquisition system and equipped with a *Vacumetrics-DIP* gun for FAB spectra.

2. *Collection and Isolation*. The delesseriacean [4] seaweed, collected at low tide near Almadies, north of Dakar, has now been determined by Dr. *Marc Verlaque*, LBMEB, Faculté des Sciences de Luminy, Université d'Aix-Marseille, as likely a species of *Haraldiophyllum* (Rhodophyta, Ceramiales, Delesseriaceae). Unfortunately, the seaweed was not in the sporulating period, which prevented species assignment and made distinction from the closely related genus *Nitophyllum* not completely unambiguous. The seaweed was immediately soaked in EtOH and worked up as before [4]. Thus, *Fractions 6–9* (190 mg) from FC of the AcOEt extract (1.85 g, 0.74%) were subjected to reversed-phase HPLC (MeCN/H₂O 1:1): 4-hydroxybenzaldehyde (*t_R* 3.9 min; 10 mg, 0.004%), 4-ethoxybenzyl alcohol (*t_R* 5.0 min; 75 mg, 0.03%), ethyl 1*H*-indole-3-glyoxylate (*t_R* 8.2 min; 15 mg, 0.006%), and ethyl 1*H*-indole-3-acetate (*t_R* 9.2 min; 5 mg, 0.002%). Similarly, *Fr. 10–12* (134 mg) gave 4-hydroxybenzyl alcohol (*t_R* 3.5 min; 55 mg, 0.02%) and indole-3-carboxaldehyde (*t_R* 4.5 min; 5 mg, 0.002%). *Fr. 13–16* (63 mg) gave the known [4] almazole A ((+)-1; 13 mg, 0.005%) and almazole B ((+)-2; 5 mg, 0.002%). *Fr. 17–20* (204 mg) were subjected to 'amine'-HPLC (hexane/*i*-PrOH 85:15): (+)-1 (*t_R* 7.2 min; 3.0 mg) and almazole C ((+)-3a; *t_R* 12.2 min; 95 mg). *Fr. 21–23* were further subjected to FC (hexane/AcOEt, elution gradient), collecting *Fr. 1a–17a*; of these, *Fr. 6a–9a*, worked up similarly, gave further (+)-3a (34 mg; total yield 0.05%). *Fr. 10a* was subjected to 'amine'-HPLC (hexane/*i*-PrOH 3:1) to give prealmazole C ((+)-4) that was further purified by reversed-phase HPLC (MeCN/H₂O 3:2→4:1): (+)-4 (*t_R* 13.5 min; 5 mg, 0.002%) and 1*H*-indole-3-acetamide (*t_R* 3.5 min; 10 mg, 0.004%). *Fr. 11a–12a* were subjected to reversed-phase HPLC (MeOH/H₂O 62:38): (+)-7 (*t_R* 5.7 min; 35 mg, 0.015%) and 1*H*-indole-3-carboxylic acid (*t_R* 3.7 min; 2 mg, 0.001%). The more polar *Fr. 24–25* (113 mg) from the

first FC were subjected to reversed-phase HPLC (MeCN/H₂O 1:4) to give dipeptide (+)-**5** (*t*_R 7.4 min; 8 mg, 0.004%) and another fraction that was further purified by reversed-phase HPLC (MeCN/H₂O 2:3): alkylated dipeptide (+)-**6** (*t*_R 4 min; 4 mg, 0.0015%).

3. *Isolated Compound. Almazole C* (= 3-[2'-[1-(Dimethylamino)-2-phenylethyl]oxazol-5'-yl]-1H-indole; (+)-**3a**). [α]_D²⁰ = +168.0 (*c* = 1.08, MeOH). UV (MeOH): 222 (26600), 271 (15100), 282 (14500), 300 (12900). CD (MeOH): 268 (3.5), 230 (3.4). FAB-MS (3-nitrobenzyl-alcohol matrix): 332 (14, [M + H]⁺), 287 (100, [M - Me₂N]⁺), 240 (95, [M - C₇H₇]⁺). EI-MS: 330 (0.4, [M - H]⁺), 287 (1.1, [M - Me₂N]⁺), 240 (100, [M - C₇H₇]⁺), 199 (4), 197 (3), 155 (9), 144 (6), 120 (5). HR-MS: 330.1608 ± 0.003 ([C₂₁H₂₆N₃O]⁺, calc. 330.1603), 287.1178 ± 0.003 ([C₁₉H₁₅N₂O]⁺, calc. 287.1184), 240.1138 ± 0.002 ([C₁₄H₁₄N₃O]⁺, calc. 240.1150). NOE: 7.91 (H-C(4)) → 7.30 (H-C(4')), 7.75 (H-C(2)) → 10.79 (H-N(1), 4%).

At r.t., (+)-**3a** (10 mg, 0.030 mmol) was stirred overnight in dry pyridine/Ac₂O 1:1 (1 ml). The mixture was evaporated and the residue subjected to 'amine'-HPLC (hexane/*i*-PrOH 85:15): 1-acetylalmazole *C* ((+)-**3b**; *t*_R 5.6 min; 3 mg, 89%) besides unreacted (+)-**3a** (*t*_R 11.5 min; 7 mg).

(+)-**3b**: [α]_D²⁰ = +106 (*c* = 0.58, MeOH). ¹H-NMR (CDCl₃): 7.67 (*s*, H-C(2)); 7.73 (*br. dd*, *J* = 7.4, 2.0, H-C(4)); 7.37 (*t*, *J* = 7.4, H-C(5)); 7.43 (*t*, *J* = 7.4, H-C(6)); 8.49 (*br. d*, *J* = 7.4, H-C(7)); 7.33 (*s*, H-C(5')); 4.07 (*dd*, *J* = 9.6, 5.7, CH₂CH(NMe₂)); 3.38 (*J* = 13.7, 9.6) and 3.24 (*dd*, *J* = 13.7, 5.7, CH₂CH(NMe₂)); 7.25 (several *m*, Ph); 2.41 (*s*, Me₂N); 2.69 (*s*, MeCO). ¹³C-NMR (CDCl₃): 126.06 (*d*, C(2)); 111.14 (*s*, C(3)); 126.54 (*s*, C(3a)); 121.64 (*d*, C(4)); 122.55 (*d*, C(5)); 124.35 (*d*, C(6)); 116.90 (*d*, C(7)); 135.93 (*s*, C(7a)); 161.57 (*s*, C(2')); 145.51 (*s*, C(4')); 119.91 (*d*, C(5')); 64.66 (*d*, CH₂CH(NMe₂)); 36.94 (*t*, CH₂CH(NMe₂)); 138.23 (*s*, C_{ipso}); 129.03 (*d*, C_o); 128.38 (*d*, C_m); 126.41 (*d*, C_p); 41.93 (*q*, Me₂N); 24.08 (*q*, MeCO); 168.47 (*s*, MeCO). EI-MS: 330 (0.8, [M - MeCO]⁺), 286 (13, [330 - Me₂N]⁺), 282 (100, [M - C₇H₇]⁺), 240 (26, [330 - C₇H₇]⁺).

Prealmazole *C* (= N¹-[2-(1'-H-Indol-3'-yl)-2-oxoethyl]-N²,N²-dimethyl-L-phenylalaninamide (+)-**4**). [α]_D²⁰ = +38.0 (*c* = 0.25, MeOH). ¹H-NMR ((CD₃)₂CO): 8.37 (*d*, *J* = 2.7, H-C(2')); 8.29 (*br. dd*, *J* = 7.4, 2.0, H-C(4')); 7.25 (*t*, *J* = 7.4, H-C(5')), H-C(6')); 7.54 (*br. dd*, *J* = 7.4, 2.0, H-C(7')); 4.65 (*dd*, *J* = 18.0, 5.5) and 4.51 (*dd*, *J* = 18.0, 5.0, C(O)CH₂); 3.45 (*dd*, *J* = 7.6, 5.8, H-C(2)); 3.16 (*J* = 13.7, 7.6) and 2.90 (*dd*, *J* = 13.7, 5.8, 2 H-C(3)); 7.30 (*m*, 2 H_o); 7.25 (*m*, 2 H_m); 7.14 (*m*, H_p); 11.16 (*br. s*, H-N(1')); 2.39 (*s*, Me₂N). ¹³C-NMR ((CD₃)₂CO): 133.50 (*d*, C(2')); 115.63 (*s*, C(3')); 126.65 (*s*, C(3'a)); 122.50 (*d*, C(4')); 122.80 (*d*, C(5')); 123.95 (*d*, C(6')); 112.79 (*d*, C(7')); 137.66 (*s*, C(7'a)); 190.45 (*s*, C(O)CH₂); 46.51 (*t*, C(O)CH₂); 172.05 (*s*, C(1)); 71.13 (*d*, C(2)); 33.68 (*t*, C(3)); 141.38 (*s*, C_{ipso}); 130.10 (*d*, C_o); 128.87 (*d*, C_m); 126.53 (*d*, C_p); 42.24 (*q*, Me₂N). EI-MS: 350 (0.4, [M + H]⁺), 306 (0.2, [M - Me₂N]⁺), 258 (23, [M - C₇H₇]⁺), 148 (100). HR-EI-MS: 258.1240 ± 0.004 ([C₁₄H₁₆N₃O₂]⁺, calc. 258.1242).

(N²,N²-Dimethyl-L-phenylalanyl)-L-tryptophan ((+)-**5**). [α]_D²⁰ = +10.0 (*c* = 0.18, MeOH). ¹H-NMR ((CD₃)₂SO): 7.14 (*br. s*, H-C(2)); 7.57 (*br. d*, *J* = 7.8, H-C(4)); 6.96 (*t*, *J* = 7.8, H-C(5)); 7.05 (*t*, *J* = 8.1, H-C(6)); 7.30 (*br. d*, *J* = 8.1, H-C(7)); 3.26 (*J* = 14.9, 7.3) and 3.06 (*dd*, *J* = 14.9, 7.3, CH₂-C(3)); 4.33 (*m*, CHCOOH); 3.18 (*t*, *J* = 6.9, H-C(2')); 2.86 (*dd*, *J* = 13.8, 6.9) and 2.70 (*dd*, *J* = 13.8, 6.9, 2 H-C(3')); 7.05–7.15 (*m*, Ph); 10.66 (*br. s*, H-N(1)); 7.61 (*br. d*, *J* = 6.1, NH-C(1')); 2.03 (*s*, Me₂N). ¹³C-NMR ((CD₃)₂SO): 123.32 (*d*, C(2)); 110.87 (*s*, C(3)); 128.93 (*s*, C(3a)); 118.41 (*d*, C(4)); 117.75 (*d*, C(5)); 120.38 (*d*, C(6)); 110.87 (*d*, C(7)); 135.87 (*s*, C(7a)); 27.47 (*t*, CH₂-C(3)); 53.84 (*d*, CHCOOH); 169.87 (*s*, C(1')); 69.29 (*d*, C(2')); 33.26 (*t*, C(3')); 139.97 (*s*, C_{ipso}); 128.83 (*d*, C_o); 127.76 (*d*, C_m); 125.40 (*d*, C_p); 41.39 (*q*, Me₂N). HMBC: H-C(2) correlated with C(7a) and C(3a); H-C(4) with C(3a), C(6), and C(7a); H-C(7) with C(4) and C(5); CH₂-C(3) with CHCOOH; H-C(2') with C(1'), Me₂N, C(3'), and C_{ipso}; 2 H-C(3') with C(1'), C(2'), and C_{ipso}; Me₂N with C(2'). FAB-MS (glycerol, H⁺, matrix): 380 (11, [M + H]⁺), 148 (100).

(N²,N²-Dimethyl-L-phenylalanyl)-N¹-(4-hydroxybenzyl)-L-tryptophan ((+)-**6**). [α]_D²⁰ = +12.0 (*c* = 0.20, MeOH). ¹H-NMR ((CD₃)₂SO): 7.10 (*br. s*, H-C(2)); 7.55 (*br. d*, *J* = 7.3, H-C(4)); 6.99 (*t*, *J* = 7.3, H-C(5)); 7.07 (*t*, *J* = 8.2, H-C(6)); 7.38 (*br. d*, *J* = 8.2, H-C(7)); 3.26 (*dd*, *J* = 15.2, 7.0) and 3.03 (*dd*, *J* = 15.2, 7.0, CH₂-C(3)); 4.37 (*m*, CHCOOH); 3.19 (*t*, *J* = 6.7, H-C(2')); 2.83 (*dd*, *J* = 13.9, 6.7) and 2.70 (*dd*, *J* = 13.9, 6.7, 2 H-C(3')); 7.05–7.15 (*m*, Ph); 5.16 (*s*, HOC₆H₄CH₂); 7.01 (*br. d*, *J* = 8.5, 2 H_o of HOC₆H₄CH₂); 6.65 (*br. d*, *J* = 8.5, 2 H_m of HOC₆H₄CH₂); 9.38 (*br. s*, HOC₆H₄CH₂); 7.86 (*br. d*, *J* = 7.0, NH); 2.01 (*s*, Me₂N). ¹³C-NMR ((CD₃)₂SO): 123.32 (*d*, C(2)); 110.14 (*s*, C(3)); 128.11 (*s*, C(3a)); 118.58 (*d*, C(4)); 118.19 (*d*, C(5)); 120.79 (*d*, C(6)); 109.69 (*d*, C(7)); 135.77 (*s*, C(7a)); 27.13 (*t*, CH₂-C(3)); 53.03 (*d*, CHCOOH); 170.08 (*s*, C(1')); 69.00 (*d*, C(2')); 33.52 (*t*, C(3')); 139.65 (*s*, C_{ipso} of Ph); 128.79 (*d*, C_o of Ph); 127.74 (*d*, C_m of Ph); 125.43 (*d*, C_p); 48.51 (*t*, HOC₆H₄CH₂); 126.97 (*s*, C_{ipso} of HOC₆H₄CH₂); 128.29 (*d*, C_o of HOC₆H₄CH₂); 115.02 (*d*, C_m of HOC₆H₄CH₂); 156.49 (*s*, C_p of HOC₆H₄CH₂); 41.33 (*q*, Me₂N). HMBC: H-C(4) correlated with C(6) and C(7a); H-C(7) with C(3a) and C(5); HOC₆H₄CH₂ with C_o of HOC₆H₄CH₂; H_m of HOC₆H₄CH₂ with C_o of HOC₆H₄CH₂. FAB-MS (glycerol, H⁺, matrix): 191 (13), 148 (90), 115 (14), 107 (35), 91 (48).

N^2, N^2 -Dimethyl-L-phenylalaninamide ((+)-7). $[\alpha]_D^{20} = +40$ ($c = 0.20$, MeOH). UV (MeOH): 205 (10400). $^1\text{H-NMR}$ ($(\text{CD}_3)_2\text{CO}$): 7.15–7.30 (*m*, Ph); 3.30 (*dd*, $J = 5.4, 8.3$, H–C(2)); 3.08 ($J = 13.6, 8.3$) and 2.83 (*dd*, $J = 13.6, 5.4$, 2 H–C(3)); 6.88, 6.32 (2 br. *s*, CONH_2); 2.33 (*s*, Me_2N). $^{13}\text{C-NMR}$ ($(\text{CD}_3)_2\text{CO}$): 141.02 (*s*, C_{ipso}); 130.07 (*d*, C_o); 128.85 (*d*, C_m); 126.56 (*d*, C_p); 33.96 (*t*, C(3)); 70.74 (*d*, C(2)); 173.48 (*s*, C(1)); 42.07 (*q*, Me_2N). EI-MS: 192 (0.4, M^+), 148 (100, $[M - \text{Me}_2\text{N}]^+$), 133 (15), 101 (30).

4. *Synthesis of (+)-7*. Under N_2 , 1,1'-carbonylbis (1*H*-imidazole) (0.056 g, 0.34 mmol) was added to N,N -dimethyl-L-phenylalanine ((+)-8; Aldrich; 0.060 g, 0.31 mmol) in dry DMF (2 ml). The white suspension was stirred vigorously for 45 min. Then dry NH_3 gas was bubbled through the mixture for 1 h. To the colourless soln. was added H_2O (15 ml). The mixture was extracted with AcOEt (3×20 ml) and the combined org. phase washed with sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated: (+)-7 (0.50 g, 83%), identical under every respect to the natural product. White powder. M.p. (AcOEt) 145–146°. $[\alpha]_D^{20} = +45.8$ ($c = 0.6$, MeOH).

5. *Synthesis of (+)-4 and (+)-3a*. A suspension of 3-acetyl-1*H*-indole (9; Aldrich; 0.30 g, 1.9 mmol) in MeOH (3 ml) was stirred in an ice-bath and treated dropwise with Br_2 (1.9 mmol). The soln. was then heated under reflux for 2 h and evaporated, H_2O (10 ml) added, the mixture neutralized and extracted with AcOEt (3×15 ml), and the combined org. phase evaporated: 10 (0.38 g, 84%). The latter was dissolved in acetone/ CHCl_3 (3 ml), an equimolar amount of hexamethylenetetramine (HMTA) in CHCl_3 added, and the mixture stirred for 3 h at r.t. The obtained precipitate was filtered, dried, and reacted with 37% HCl soln. (0.46 ml) and EtOH (4 ml) while shaking. Next day, AcOEt (30 ml) was added to the mixture. After extraction with H_2O (2×30 ml), the combined aq. phase was evaporated and the residue dried *in vacuo* over P_2O_5 : pure 11 (0.31 g, 98%). Then, a mixture of 1,1'-carbonylbis(1*H*-imidazole) (0.14 g, 0.86 mmol) and (+)-8 (0.15 g, 0.77 mmol) in dry DMF (3 ml) was vigorously stirred under N_2 , 11 (0.77 mmol) in DMF (2 ml) added, and stirring continued overnight. Addition of H_2O was followed by extraction with AcOEt (3×20 ml) and the combined org. phase washed with cold sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. The residue was subjected to FC (*LiChroprep-CN*, CHCl_3): (+)-4 (0.16 g, 80%), identical under every respect to natural prealmazole C. An anal. sample was obtained by 'amine'-KPLC (hexane/*i*-PrOH/*i*-PrNH $_2$ 32:10:3; t_R 6.8 min). $[\alpha]_D^{20} = +37.9$ ($c = 0.1$, MeOH).

To synthetic (+)-4 (0.018 g, 0.07 mmol) was added freshly distilled POCl_3 (0.5 ml), and the mixture was stirred overnight at 40°. After evaporation, H_2O (2 ml) was added to the residue, the mixture neutralized with conc. aq. NaOH soln. and extracted with AcOEt (3×5 ml), the combined org. phase evaporated, and the residue subjected to 'amine'-HPLC as above (t_R 5.1 min): pure (+)-3a (0.013 g, 77%), identical under every respect to natural almozole C. $[\alpha]_D^{20} = +138.0$ ($c = 0.1$, MeOH).

3-(*Bromoacetyl*)-1*H*-indole (10): $^1\text{H-NMR}$ ($(\text{CD}_3)_2\text{CO}$): 8.41 (*d*, $J = 3.3$, H–C(2)); 8.30 (*m*, H–C(4)); 7.26 (*m*, H–C(5), H–C(6)); 7.55 (*m*, H–C(7)); 4.55 (*s*, CH_2); 11.20 (br. *s*, NH). $^{13}\text{C-NMR}$ ($(\text{CD}_3)_2\text{CO}$): 134.82 (*d*, C(2)); 115.06 (*s*, C(3)); 126.84 (*s*, C(3a)); 124.22, 123.05, 122.60 (3 *d*, C(4), C(5), C(6)); 112.87 (*d*, C(7)); 137.84 (*s*, C(7a)); 186.99 (*s*, CO); 33.06 (*t*, CH_2). EI-MS: 240, 238, (14, 14, $[M + \text{H}]^+$); 239, 237 (6, 6, M^+); 145 (100), 144 (22), 116 (5).

[2-(1*H*-Indol-3-yl)-2-oxoethyl]ammonium Chloride (11): $^1\text{H-NMR}$ (D_2O): 8.22 (*s*, H–C(2)); 8.12 (*m*, H–C(4)); 7.33 (*m*, H–C(5), H–C(6)); 7.55 (*m*, H–C(7)); 4.47 (*s*, CH_2). $^{13}\text{C-NMR}$ (D_2O): 138.24 (*d*, C(2)); 115.47 (*s*, C(3)); 127.20 (*s*, C(3a)); 126.77, 125.86, 123.51 (3 *d*, C(4), C(5), C(6)); 115.47 (*d*, C(7)); 139.20 (*s*, C(7a)); 190.05 (*s*, CO); 46.87 (*t*, CH_2). EI-MS: 174 (13, $[M - \text{HCl}]^+$), 145 (11), 144 (86), 116 (22).

6. *Synthesis of Dipeptide (+)-5*. Under N_2 , 1,1'-carbonyl-bis(1*H*-imidazole) (0.035 g, 0.21 mmol) was added to (+)-8·HCl (0.039 g, 0.17 mmol) in dry DMF (2 ml). The soln. was stirred for 45 min, a soln. of L-tryptophan benzyl ester hydrochloride ((+)-12; Sigma; 0.056 g, 0.17 mmol) and 1*H*-imidazole (0.012 g, 0.17 mmol) in DMF (1 ml) added, and stirring continued overnight at r.t. Then H_2O was added and the mixture extracted with AcOEt (3×10 ml). The combined org. phases were washed with sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated: crude (+)-13 and 13% of unreacted L-tryptophan benzyl ester. Pure (+)-13 (0.068 g, 85%) was obtained by 'amine'-HPLC (as above, except for 7 ml/min solvent flow; t_R 4.2 min). Through a suspension of (+)-13 (0.025 g, 0.05 mmol) and a catalytic amount of wet 10% Pd/C (Aldrich) in EtOH (3 ml) was bubbled H_2 for 30 min. The mixture was filtered through a *LiChrolut RP-18* column (Merck; washing with MeOH/ H_2O 8:2) and the filtrate evaporated: (+)-5 (0.017 g, 90%), identical under every respect to the natural product. $[\alpha]_D^{20} = +15.0$ ($c = 0.5$, MeOH).

(N^2, N^2 -Dimethyl-L-phenylalanyl)-L-tryptophan Benzyl Ester ((+)-13): $[\alpha]_D^{20} = +14$ ($c = 0.6$, MeOH). $^1\text{H-NMR}$ ($(\text{CD}_3)_2\text{CO}$): 7.60 (br. *d*, $J = 7.8$, H–C(4)); 3.32 (*ddd*, $J = 14.7, 5.9, 0.8$) and 3.24 (*ddd*, $J = 14.7, 7.7, 0.8$, CH_2 –C(3)); 4.77 (*dd*, $J = 5.9, 4.7$, $\text{CHCOOCH}_2\text{Ph}$); 3.21 (*dd*, $J = 6.0, 7.5$, H–C(2')); 2.96 (*dd*, $J = 13.8, 7.5$) and 2.80 (*dd*, $J = 13.8, 6.0$, 2 H–C(3')); 10.15 (br. *s*, H–N(1)); 7.56 (br. *d*, $J = 6.0$, NH–C(1')); 5.09 (*s*, PhCH_2O); 7.40–7.05 (several *m*, H–C(2), H–C(5), H–C(6), H–C(7), $\text{Ph}-\text{CH}_2(3')$, PhCH_2O); 2.14 (*s*, Me_2N). $^{13}\text{C-NMR}$

((CD₃)₂CO): 124.52 (*d*, C(2)); 110.67 (*s*, C(3)); 128.20 (*s*, C(3a)); 119.61, 119.15 (2 *d*, C(4), C(5)); 122.21 (*d*, C(6)); 112.19 (*d*, C(7)); 136.97 or 137.54 (*s*, C(7a)); 28.27 (*t*, CH₂–C(3)); 53.82 (*d*, CHCOOCH₂Ph); 172.54 or 172.08 (*s*, C(1')); 67.00 (*d*, C(2')); 34.13 (*t*, C(3')); 140.87 (*s*, C_{ipso} of Ph–C(3')); 128.82 (*d*, C_o of Ph–C(3')); 172.08 or 172.54 (*s*, COO); 71.28 (*t*, PhCH₂O); 137.54 or 136.97 (*s*, C_{ipso} of PhCH₂O); 126.53, 128.77, 129.17, 129.99 (4*d*, C_m and C_p of Ph–C(3'), C_o, C_{m'}, and C_p of PhCH₂O); 42.24 (*q*, Me₂N). EI-MS: 378 (4, [*M* – C₇H₇]⁺), 302 (8), 148 (100), 130 (12), 91 (10).

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