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 Seaweed[1])

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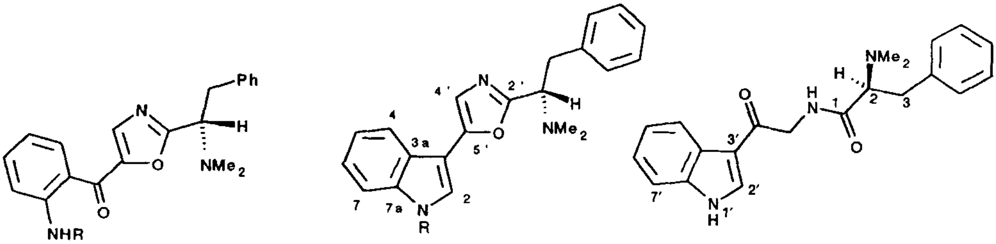
(22.VII.94)

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



(+)-**1** R = CHO
(+)-**2** R = H

(+)-**3a** R = H
(+)-**3b** R = Ac

(+)-**4**

[1]) Presented in part by *G.G.* at the 'Giornate di Chimica delle Sostanze Naturali', Amalfi, Italy, May 29–June 1, 1994.

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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 C[4]) 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 (^{1}H-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,^{1}H-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* $(CD_3)_2CO$

	δ(C)[a])	δ(H)[b])	HMBC[c])
H–C(2)	123.61 (*d*, *J* = 185)	7.75 (*d*, *J* = 2.7)	C(7a), C(3a), C(5')
C(3)	105.72 (*s*)	–	
C(3a)	124.94 (*s*)	–	
H–C(4)	120.41 (*d*, *J* = 162)	7.91 (*ddt*, *J* = 7.2, 2.1, 0.8)	C(3a), C(6), C(7a)
H–C(5)	121.08 (*d*, *J* = 160)	7.20 (br. *t*, *J* = 7.2)	
H–C(6)	123.12 (*d*, *J* = 160)	7.24 (br. *t*, *J* = 8.0)	
H–C(7)	112.71 (*d*, *J* = 162)	7.52 (*ddd*, *J* = 8.0, 2.0, 0.8)	C(3a), C(5)
C(7a)	137.60 (*s*)	–	
C(5')	148.84 (*s*)	–	
H–C(4')	119.86 (*d*, *J* = 193)	7.30 (*s*)	C(3a), C(5'), C(2')
C(2')	160.68 (*s*)	–	
$CH_2CH(NMe_2)$ (*CH*)	64.92 (*d*, *J* = 139)	4.11 (*dd*, *J* = 9.2, 6.1)	C(2'), Me_2N, *C*$H_2CH(NMe_2)$
CH$_2$CH(NMe_2)	37.39 (*t*, *J* = 128)	3.40 (*dd*, *J* = 13.3, 9.1) 3.22 (*dd*, *J* = 13.3, 6.1)	C(2'), CH_2*C*H(NMe_2), C_{ipso}, C_o
C_{ipso}	139.92 (*s*)	–	
2 H–C_o	129.96 (*d*, *J* = 157)	7.28 (*m*)	
2 H–C_m	128.84 (*d*, *J* = 160)	7.22 (*m*)	
H–C_p	126.82 (*d*, *J* = 160)	7.15 (*m*)	
H–N(1)	–	10.79 (br. *s*)	C(2), C(7)
Me_2N	41.83 (*q*, *J* = 133)	2.37 (*s*)	CH_2*C*H(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.

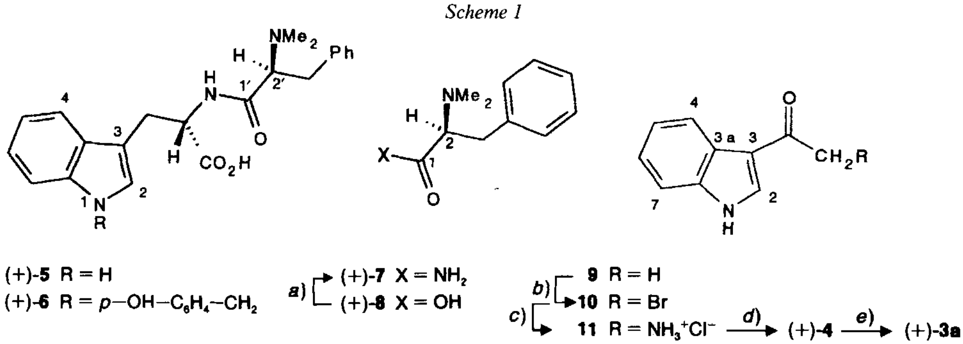
[4]) Almazole C ((+)-**3a**) shows intense fluorescence at 470 nm on excitation at 365 nm in MeOH, possibly accounting for the fluorescent appearance of this alga in the evening at low tide.

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 δ(H) 4.57 supports the CO–CH_2–NH–CO fragment. Insertion of the latter, *i.e.*, of CO–CH_2–NH, between C(3′) of the indole and the *N,N*-dimethyl-L-phenylalanine moiety is warranted by long-range ^{13}C,^{1}H-coupling between the C=O group (δ(C) 190.45 (*s*)) and CO–CH_2–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 CH_2–CH(COOH)–NH–CO fragment is based on NMR data (^{13}C-NMR: (169.87 (*s*), 53.84 (*d*), 27.47 ppm (*t*); ^{1}H-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. NH_3(g), r.t., 3 h. *b*) Br_2, MeOH, reflux, 2 h. *c*) 1. HMTA/$CHCl_3$, 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*) $POCl_3$, 40°, overnight.

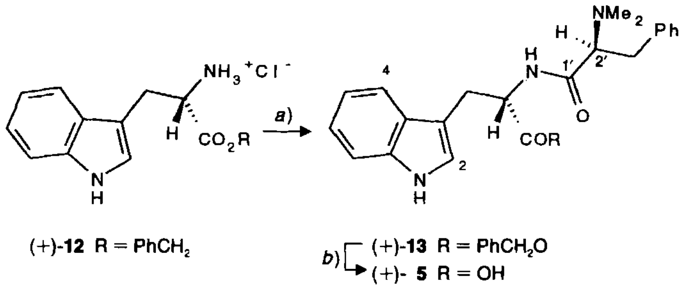
Although only extended fragmentation was observed in FAB-MS (*Exper. Part*), NMR spectra for compound (+)-**6** proved to be akin to those for (+)-**5**, and δ and ^nJ data allowed us to place unambiguously the 4-hydroxybenzyl group at the indole N-atom.

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 coupling of the latter with the acyl derivative obtained from *N,N*-dimethyl-L-phenylalanine ((+)-**8**) and 1,1′-carbonylbis(1*H*-imidazole) (CDI) [9] to give in high yield prealmazole C ((+)-**4**), identical with authentic material. The latter, *via Gabriel-Robinson* cyclization [10], gave almazole C ((+)-**3a**), identical with the natural product. This CDI coupling methodology was also employed for the synthesis of (+)-**7** from the corresponding commercially available amino acid (+)-**8** (*Scheme 1*).

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



a) 1. (+)-**8**·HCl, CDI, DMF, r.t., 45 min; 2. 1 equiv. of (+)-**12**, 1 equiv. of 1*H*-imidazole, r.t., overnight. *b*) H_2, 10% Pd/C, EtOH, r.t., 30 min.

After optimization[5]), 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 $CDCl_3$ induced shifts of the 2H–C(3), H–C(2), and Me_2N 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

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[5]) $POCl_3$ 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. H_2SO_4 [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. H_2SO_4 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-oxotryptamine, 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.

We thank Mr. *M. Rossi* and Mr. *A. Sterni* for skilled technical assistance with product manipulations and mass spectra, respectively, *Pharmacia-Farmitalia*, Milano, for the cytotoxic assays, Dr. *M. Verlaque* for the taxonomic identification, and *MURST* (Progetti 40%) and *CNR*, Roma, for financial support.

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 NH_2* ('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, ^{13}C at 75.43 MHz; δ in ppm rel. to internal Me_4Si (= 0 ppm), in $(CD_3)_2CO$ (δ(H) 2.05, δ(C) 29.80), D_2O (δ(H) 4.77), and $(CD_3)_2SO$ (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]; $^{13}C,^1H$-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 ($MeCN/H_2O$ 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 ($MeCN/H_2O$ 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 ($MeOH/H_2O$ 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/H_2O 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/H_2O 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}-1*H*-indole*; (+)-**3a**). $[\alpha]_D^{20}$ = +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, $[M-Me_2N]^+$), 240 (95, $[M-C_7H_7]^+$). EI-MS: 330 (0.4, $[M-H]^+$), 287 (1.1, $[M-Me_2N]^+$), 240 (100, $[M-C_7H_7]^+$), 199 (4), 197 (3), 155 (9), 144 (6), 120 (5). HR-MS: 330.1608 ± 0.003 ($[C_{21}H_{20}N_3O]^+$, calc. 330.1603), 287.1178 ± 0.003 ($[C_{19}H_{15}N_2O]^+$, calc. 287.1184), 240.1138 ± 0.002 ($[C_{14}H_{14}N_3O]^+$, calc. 240.1150). NOE: 7.91 (H–C(4))→7.30 (H–C(4′), 9%); 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/Ac_2O 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**: $[\alpha]_D^{20}$ = +106 (*c* = 0.58, MeOH). ^{1}H-NMR ($CDCl_3$): 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, $CH_2CH(NMe_2)$); 3.38 (*J* = 13.7, 9.6) and 3.24 (*dd*, *J* = 13.7, 5.7, $CH_2CH(NMe_2)$); 7.25 (several *m*, Ph); 2.41 (*s*, Me_2N); 2.69 (*s*, MeCO). ^{13}C-NMR ($CDCl_3$): 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*, $CH_2CH(NMe_2)$); 36.94 (*t*, $CH_2CH(NMe_2)$); 138.23 (*s*, C_{ipso}); 129.03 (*d*, C_o); 128.38 (*d*, C_m); 126.41 (*d*, C_p); 41.93 (*q*, Me_2N); 24.08 (*q*, *Me*CO); 168.47 (*s*, Me*C*O). EI-MS: 330 (0.8, $[M-MeCO]^+$), 286 (13, $[330-Me_2N]^+$), 282 (100, $[M-C_7H_7]^+$), 240 (26, $[330-C_7H_7]^+$).

Prealmazole C (= N^1-*[2-(1′*H*-Indol-3′-yl)-2-oxoethyl]*-N^2,N^2-*dimethyl-*L*-phenylalaninamide* (+)-**4**). $[\alpha]_D^{20}$ = +38.0 (*c* = 0.25, MeOH). ^{1}H-NMR ($(CD_3)_2CO$): 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)C*H*$_2$); 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*, Me_2N). ^{13}C-NMR ($(CD_3)_2CO$): 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)CH$_2$); 46.51 (*t*, C(O)*C*H$_2$); 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*, Me_2N). EI-MS: 350 (0.4, $[M+H]^+$), 306 (0.2, $[M-Me_2N]^+$), 258 (23, $[M-C_7H_7]^+$), 148 (100). HR-EI-MS: 258.1240 ± 0.004 ($[C_{14}H_{16}N_3O_2]^+$, calc. 258.1242).

*(*N$^{2′}$,N$^{2′}$*-Dimethyl-*L*-phenylalanyl)-*L*-tryptophan* ((+)-**5**). $[\alpha]_D^{20}$ = + 10.0 (*c* = 0.18, MeOH). ^{1}H-NMR ($(CD_3)_2SO$): 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, CH_2–C(3)); 4.33 (*m*, *C*HCOOH); 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*, Me_2N). ^{13}C-NMR ($(CD_3)_2SO$): 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*, *C*H$_2$–C(3)); 53.84 (*d*, *C*HCOOH); 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*, Me_2N). 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); *C*H$_2$–C(3) with *C*HCOOH; *H*–C(2′) with C(1′), Me_2N, C(3′), and C_{ipso}; 2 H–C(3′) with C(1′), C(2′), and C_{ipso}; Me_2N with C(2′). FAB-MS (glycerol, H$^+$, matrix): 380 (11, $[M+H]^+$), 148 (100).

*(*N$^{2′}$,N$^{2′}$*-Dimethyl-*L*-phenylalanyl)*-N^1*-(4-hydroxybenzyl)-*L*-tryptophan* ((+)-**6**). $[\alpha]_D^{20}$ = +12.0 (*c* = 0.20, MeOH). ^{1}H-NMR ($(CD_3)_2SO$): 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, CH_2–C(3)); 4.37 (*m*, *C*HCOOH); 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*, $HOC_6H_4CH_2$); 7.01 (br, *d*, *J* = 8.5, 2 H_o of $HOC_6H_4CH_2$); 6.65 (br. *d*, *J* = 8.5, 2 H_m of $HOC_6H_4CH_2$); 9.38 (br. *s*, *H*OC$_6$H$_4$CH$_2$); 7.86 (br. *d*, *J* = 7.0, NH); 2.01 (*s*, Me_2N). ^{13}C-NMR ($(CD_3)_2SO$): 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*, *C*H$_2$–C(3)); 53.03 (*d*, *C*HCOOH); 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*, HOC$_6$H$_4$*C*H$_2$); 126.97 (*s*, C_{ipso} of $HOC_6H_4CH_2$); 128.29 (*d*, C_o of $HOC_6H_4CH_2$); 115.02 (*d*, C_m of $HOC_6H_4CH_2$); 156.49 (*s*, C_p of $HOC_6H_4CH_2$); 41.33 (*q*, Me_2N). HMBC: *H*–C(4) correlated with C(6) and C(7a); *H*–C(7) with C(3a) and C(5); HOC$_6$H$_4$C*H*$_2$ with C_o of $HOC_6H_4CH_2$; H_m of $HOC_6H_4CH_2$ with C_o of $HOC_6H_4CH_2$. 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}H-NMR ($(CD_3)_2CO$): 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_3N). ^{13}C-NMR ($(CD_3)_2CO$): 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, $[M - Me_2N]^+$), 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 almazole C. $[\alpha]_D^{20} = +138.0$ ($c = 0.1$, MeOH).

*3-(Bromoacetyl)-1*H*-indole* (**10**): ^{1}H-NMR ($(CD_3)_2CO$): 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}C-NMR ($(CD_3)_2CO$): 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, $[M + H]^+$); 239, 237 (6,6, M^+); 145 (100), 144 (22), 116 (5).

*[2-(1*H*-Indol-3-yl)-2-oxoethyl]ammonium Chloride* (**11**): ^{1}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}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, $[M - HCl]^+$), 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}H-NMR ($(CD_3)_2CO$): 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*, $J = 5.9, 4.7$, *CH*$COOCH_2$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*, PhC*H_2*O); 7.40–7.05 (several *m*, H–C(2), H–C(5), H–C(6), H–C(7), *Ph*–CH_2(3′), *Ph*CH_2O); 2.14 (*s*, Me_2N). ^{13}C-NMR

($(CD_3)_2CO$): 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*, CH_2–C(3)); 53.82 (*d*, $CHCOOCH_2Ph$); 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*, $PhCH_2O$); 137.54 or 136.97 (*s*, C_{ipso} of $PhCH_2O$); 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 $PhCH_2O$); 42.24 (*q*, Me_2N). EI-MS: 378 (4, $[M - C_7H_7]^+$), 302 (8), 148 (100), 130 (12), 91 (10).

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