Pergamon

Tetrahedron Letters, Vol. 37, No. 17, pp. 3049-3050, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00466-2

Almazole D, a New Type of Antibacterial 2,5-Disubstituted Oxazolic Dipeptide from a Red Alga of the Coast of Senegal

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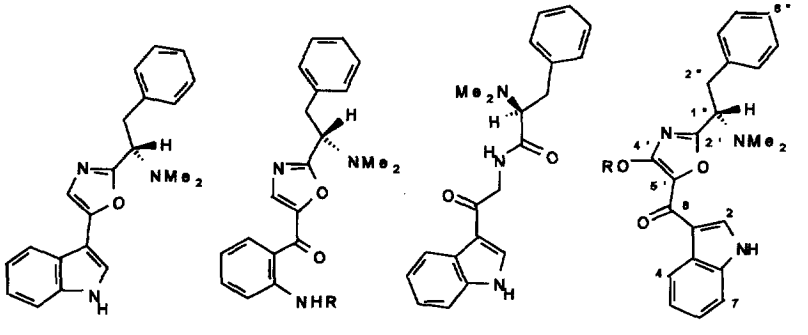
Abstract: *Almazole D ((+)-5), a potently antibacterial dipeptide from a delesseriacean seaweed collected at Almadies, North of Dakar, is a novel variant of 2,5-disubstituted oxazolic dipeptides conceivably deriving from oxidative deamination rather than decarboxylation of tryptophan.*

We have recently described a novel dipeptide derivative, almazole C ((+)-**1**),[2] and its putative oxidative indole-opening products, almazole A ((+)-**2**) and almazole B ((+)-**3**),[3] as well as prealmazole C ((+)-**4**)[2] isolated from a delesseriacean seaweed collected near Dakar.



Because of the rarity -both in the sea[4] and on land[5]- of 2,5-disubstituted oxazole-bearing natural products, and keen interest in new peptides, we describe here a novel variant on this theme, represented by almazole D ((+)-**5**),[6] isolated from a new collection of the same seaweed.[7] The indole and N,N-dimethylaminophenylalanine moieties of (+)-**5** were deduced from comparison of NMR spectra with those of (+)-**1**,[3] while replacement of the C(4') d of the latter by a deshielded s in (+)-**5** suggested OH at C(4'), which was substantiated by methylation with CH_2N_2 to give (+)-**6**.[8] Long-range heterocorrelations H-C1"/C2' and H-C2/C5' served to place the oxazole ring and to confirm the assignment of the deshielded δ_C 170.38s to C4'; further support lies in upfield shift of C4' in (+)-**6** by 7.5 ppm, as expected for a methyl derivative of an enol group. An extra carbonyl group, though eluding

^{13}C-NMR observation, was suggested by FAB-MS, and was located between the indole and the oxazole moieties to account for deshielding of H-C2. The configuration at C1" was assumed for analogy with co-occurring almazole A ((+)-**2**), almazole B ((+)-**3**), and prealmazole ((+)-**4**).[2]

The biogenesis of almazole C ((+)-**1**) may be envisaged from tryptophan *via* sequential decarboxylation to tryptamine, oxidation to 2-oxotryptamine, and coupling with N,N-dimethyl-L-phenylalanine to give prealmazole C ((+)-**4**), which can be imagined to form the oxazole ring on dehydration. Support to these ideas was given by biomimetic total synthesis.[2] Almazole D ((+)-**5**) represents a major deviation from this pattern, its biogenesis conceivably involving oxidative deamination rather than decarboxylation of tryptophan, thus rationalizing both the extra carbonyl group and the hydroxyl group at the oxazole ring. Also, (+)-**5** is the first bioactive member of the almazole family, being powerfully antibacterial against Gram-negative *Serratia marcescens* and *Salmonella typhi* XLD, while lacking potential side effects being neither cytotoxic (TPH-1 human monocytes, RAJI human lymphocytes, RAW 264.7 cat Monocytes-macrophages), nor haemolytic or AcChE inhibitory.

We thank the Department of Biology, University of Ljubljana, for biological assays, Mr. A. Sterni for recording the mass spectra, and MURST (Progetti 40%) and CNR, Roma, for financial support.

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6 (+)-**5**: colourless, strongly fluorescent, powder. $[\alpha]_D^{20}$ = +20 (*c* = 0.07, MeOH). UV (MeOH), $\lambda_{max}(\epsilon)$ 206 (16200), 272 (5300), 310 (5900), 398 nm (580). FAB-MS (glycerol, H^+) (*m/z*,%) 375 (1.5, $[M + H]^+$), 331 (10, M - NMe_2), 239 (36), 144 (7). δ_C (CD_3OD, 75.43 MHz, *J* in Hz) 130.18 (d, *J*=190, C2), 105.05 (s, C3), 126.65 (s, C3a), 121.45 (d, *J*=158, C4), 121.70 (d, *J*=160, C5), 123.15 (d, *J*=162, C6), 112.71 (d, *J*=162, C7), 137.64 (s, C7a), 158.50 (s, C2'), 170.38 (s, C4'), 152.20 (s, C5'), 66.38 (d, C1"), 38.32 (t, C2"), 139.00 (s, C3"), 130.11 (d, C4" and C8"), 129.47 (d, C5" and C7"), 127.52 (d, C6"), 42.71 (q, NMe_2). δ_H (CD_3OD, 299.94 MHz, *J* in Hz) 8.73 (s, H-C2), 8.02 (ddd, *J* =8.0, 2.1, 0.8, H-C4), 7.05-7.25 (m, H-C5, H-C6, H-C4", H-C5", H-C6", H-C7", H-C8"), 7.42 (ddd, *J*=8.0, 2.0, 0.8, H-C7), 4.03 (dd, *J*=10.5, 4.9, H-C1"), 3.41 (dd, *J*=12.8, 10.5) and 3.30 (dd, *J*=12.8, 4.9) (2H-C2"), 2.44 (s, NMe_2).

7 The alga was re-collected in the same place as before at low tide[3] in May 1994 but was air dried and then immersed in MeOH for 15 days. The solvent was decanted and evaporated. The residue was added of 200 ml of H_2O and extracted with EtOAc. The aqueous phase was evaporated to dryness and the residue subjected to RP18 FC with CH_3CN/H_2O gradient elution from 0:100, on increasing by 2.5% the CH_3CN content for 26 fractions of 40 ml each and then changing to 100% CH_3CN. Almazole D ((+)-**5**) proved to be the sole component eluted from fraction 15 on (0.47 g). Previously described compounds[2,3] and further 0.18 g of almazole D were obtained from the EtOAc extract.

8 (+)-**6**: colourless, strongly fluorescent, powder. $[\alpha]_D^{20}$ = +70 (*c* = 0.1, MeOH). FAB-MS (glycerol, H^+) (*m/z*,%) 390 (24, $[M+H]^+$), 345 (76, M - NMe_2), 148 (49), 144 (38). δ_C (CD_3OD, 75.43 MHz) 131.43 (d, C2), 103.90 (s, C3), 126.40 (s, C3a), 121.68 (d, C4), 122.38 (d, C5), 123.95 (d, C6), 113.07 (d, C7), 137.82 (s, C7a), 159.46 (s, C2'), 177.96 (s, C4'), 153.00 (s, C5'), 66.07 (d, C1"), 38.04 (t, C2"), 138.78 (s, C3"), 130.05 (d, C4" and C8"), 129.55 (d, C5" and C7"), 127.71 (d, C6"), 42.41 (q, NMe_2), 52.18 (q, OMe). δ_H (CD_3OD, 299.94 MHz, *J* in Hz) 8.71 (s, H-C2), 8.13 (ddd, *J* = 7.6, 1.8, 0.9, H-C4), 7.10-7.30 (m, H-C5, H-C6, H-C4", H-C5", H-C6", H-C7", H-C8"), 7.50 (ddd, *J* = 7.8, 2.1, 0.9, H-C7), 4.12 (dd, *J* = 10.5, 4.8, H-C1"), 3.45 (dd, *J* = 12.9, 10.5) and 3.32 (dd, *J* = 12.9, 4.8) (2H-C2"), 2.45 (s, NMe_2), 3.90 (s, OMe).

(*Received in UK* 29 *January* 1996; *revised* 4 *March* 1996; *accepted* 8 *March* 1996)