Iminophosphorane-Based Preparation of 2,5-Disubstituted Oxazole Derivatives: Synthesis of the Marine Alkaloid Almazole C

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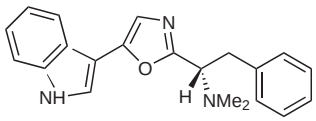
Abstract: A four-steps synthesis (32% overall yield) of marine alkaloid almazole C isolated from the red seaweed *Haraldiophylum sp.* is described. The key step, construction of the central 2,5-disubstituted oxazole ring is based on the aza-Wittig reaction of the iminophosphorane derived from the α-azidoacetyl indole and (*S*)-*N*-phthaloylphenylalanyl chloride.

Key words: oxazoles, marine alkaloids, iminophosphoranes, indoles, aza-Wittig reaction

The oxazole heterocycle is a fundamental structural motif found in many compounds such as natural products,[1] unnatural biologically active compounds,[2] and molecular sensors.[3] Naturally occurring oxazoles are usually found with a 2,4-substitution pattern, although 2,5-disubstituted oxazole natural products are known. They comprise the 2,5-diaryloxazoles halfordinol,[4] balnoxin,[5] and annuloline[6] and the 5-(3-indolyl)oxazoles pimprinine alkaloids[7] and martefragin A,[8] which is a strong inhibitor of lipid peroxidation.

In 1994, the 2,5-disubstituted oxadiazole alkaloid almazole C (**1**, Figure 1), which showed antibacterial activity against Gram-negative pathogens, was isolated from a red seaweed of family Delesseriaceae of genus *Haraldiophylum sp*. on the north of Dakar.[9] From the structural point of view almazole C (**1**) represents slight variations on 5-(3-indolyl)oxazole alkaloids that have been isolated previously. As can be seen in Figure 1, the oxazole ring of the almazole C (**1**) is substituted at 2-position by a *N*,*N*-dimethylphenylalanine fragment.



almazole C (**1**)

Figure 1

Both inter- and intramolecular versions of the aza-Wittig reaction have assumed increasing importance for the construction of a wide variety of nitrogen-containing heterocyclic ring systems.[10] Several methodologies based on the intermolecular aza-Wittig reaction followed by either electrocyclization, intramolecular cycloaddition, or heterocumulene-mediated annelation have been used for the preparation of a wide variety of nitrogen-containing natural products.[11]

In conjunction with our synthetic efforts on the synthesis of a number of nitrogen-containing alkaloids from marine origin,[12] we have devised a reliable synthesis of almazole C, which is based on the iminophosphorane-based formation of the appropriately 2,5-disubstituted, central, five-membered ring. The three-component reaction between an α-azidoketone, a tertiary phosphine and an acyl halide has been employed for the preparation of the central oxazole derivative ring.[13] The reaction takes place through an initially formed iminophosphorane which undergoes acylation and further elimination of the corresponding phosphine oxide to give an imidoyl chloride as intermediate which gives the five-membered ring after cyclization. Recently, two slight modifications of this protocol have been applied successfully to the synthesis of 2,5-disubstituted imidazole alkaloids from marine origin.[14]

We initially required an N-protected 3-acetylindole as starting material and the protecting group of choice was the MOM group. To this end *N*-methoxymethyl-3-azidoacetylindole (**5**) was prepared in a three-step sequence: (a) N-protection of 3-acetylindole with chloromethylmethyl ether in DMF in the presence of NaH (89% yield), (b) selective α-chlorination of 3-acetylindole **3** with benzyltrimethyl-ammonium dichloroiodate[15] to give the α-chloroacetyl derivative **4** (90%), and (c) halogen–azide exchange with sodium azide in acetone–water to afford the α-azido ketone **5** (77%, Scheme 1).

The formation of the central oxazole ring was achieved using the iminophosphorane methodology. Previous studies on the reactivity of α-azido ketones derived from the indole ring revealed that the Staudinger reaction with triphenylphosphine is very slow[13b] and in some cases products derived from the double intermolecular aza-Wittig reaction were isolated. For this reason the more reactive *n*-tributylphoshine has been employed. Thus, the key intermediate **7** was prepared in 70% yield by reaction of α-azido ketone **5** with *n*-tributylphosphine in THF at 0 °C and subsequent addition of (*S*)-*N*-phthaloylphenylalanyl chloride[16] (**6**) followed by treatment with Et_3N.[17] Attempts to improve the yield of compound **7** using the triazaphosphadiene pathway[18] (in this case the reaction is

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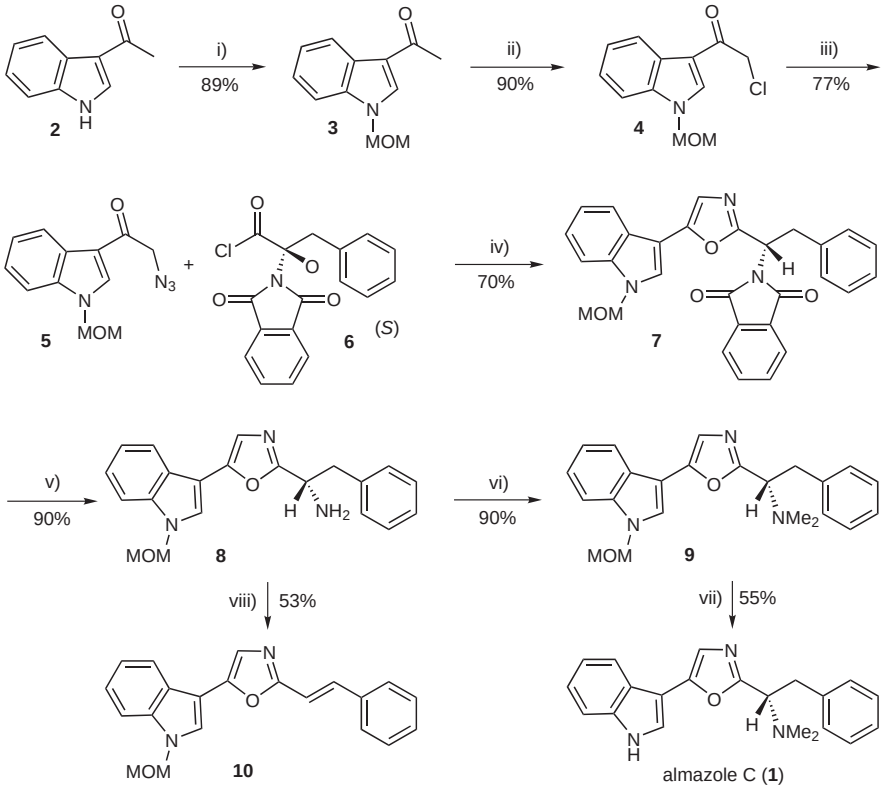

Scheme 1 Total synthesis of amazole C1. *Reagents and conditions*: i) Nah, DMF, MOMCl, 1 h, r.t.; ii) $Bn(CH_3)_3NCl_2I$, 5 d, r.t.; iii) NaN_3, acetone–H_2O, reflux, 18 h; iv) *n*-Bu_3P, Et_3N, THF, 3 h, r.t.; v) $N_2H_4{\cdot}H_2O$, EtOH, 3 d, r.t.; vi) HCHO, H_2/Pd (C), EtOH; vii) HCOOH, THF–H_2O, reflux, 30 h; viii) NaH, MeI, 3 d, r.t.

carried out with the acyl chloride present before the addition of the phosphine) failed.

The *N*-phthaloyl group of compound **7** was smoothly removed with hydrazine in EtOH at room temperature to give amine **8** in 90% yield. The best results to prepare the N-dimethylated amine was realized by reductive amination with hydrogen in the presence of formaldehyde and palladium as catalysis,[19] to give compound **9** in 90% yield. Also, another N-methylating agent was used: first the reductive amination by Leuckart reaction was realized in the presence of formaldehyde/formic acid in CH_2Cl_2 at room temperature for four days to give N-dimethylated compound **9** in 43% yield. When methyl iodide was used in THF at reflux temperature for five days or in DMF in the presence of NaH at room temperature for three days, vinyl compound **10** was obtained in 21% and 53% yield, respectively.

Compound **9** was converted into almazole C (**1**) by deprotection of the *N*-methoxymethyl substituent with formic acid in THF at reflux temperature for 30 hours in 55% yield.[20] Compound **1** was identical in all aspects {IR, MS, ^{1}H NMR, ^{13}C NMR and $[\alpha]_D^{20}$} with the natural product.[1]

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(17) **2-[(*S*)-1-{5-[*N*-(Methoxymethyl)-1*H*-indol-3-yl]oxazol-2-yl}-2-phenylethyl]isoindoline-1,3-dione (7).**
To a solution of 3-(α-azidoacetyl) indole **5** (0.2 g, 0.82 mmol) in dry THF (32 mL), *n*-tributylphosphine (0.3 mL, 1.23 mmol) was added dropwise at 0 °C under N_2. Then, a solution of (*S*)-*N*-phthaloylphenylalanyl chloride **6** (0.26 g, 0.82 mmol) in the same solvent (20 mL) was added. The resultant mixture was stirred at r.t. for 1 h, and then dry Et_3N (0.17 mL, 1.23 mmol) was added and stirred for 2 h. The resultant solution was concentrated to dryness under reduced pressure and the residue was chromatographed on a silica gel column using CH_2Cl_2–EtOAc (8:2) as eluent to give **7** (0.27 g, 70% yield). Mp 157–160 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.17 (s, 3 H, OCH_3), 3.79 (m, 2 H, CH_2), 5.37 (s, 2 H, OCH_2), 5.78 (dd, 1 H, *J* = 10.2, 6.3 Hz, CH), 7.08–7.22 (m, 8 H, H-5, H-6, H-4′, 2 Ho, 2 Hm and Hp), 7.37 (s, 1 H, H-2), 7.41 (d, 1 H, *J* = 8.1 Hz, H-7), 7.59 (dd, 2 H, *J* = 5.4, 3.0 Hz, 2 Hm′′), 7.68 (d, 1 H, *J* = 7.8 Hz, H-4), 7.71 (dd, 2 H, *J* = 5.4, 3.0 Hz, 2 Ho′). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.6 (CH_2), 49.3 (CH), 56.0 (OCH_3), 77.6 (OCH_2), 105.3 (C-3), 110.4 (C-7), 120.1 (C-4), 120.6 (C-4′), 121.4 (C-7), 121.4 (C-5), 123.2 (C-6), 123.4 (Co′), 125.2 (C-3a), 125.6 (C-2), 126.9 (Cp), 128.6 (Cm), 129.0 (Co), 131.6 (C-i′), 134.0 (Cm′), 136.5 (C-7a), 136.6 (Ci), 147.9 (C-5′), 158.4 (C-2′), 167.4 (CO). MS (FAB positive): *m/z* (%) = 478 (100) [M + 1], 477 (75) [M^+], 326 (29) [M^+ – Bn], 331]M^+ – phthalimido]. Anal. Calcd for $C_{29}H_{23}N_3O_4$: C, 72.94; H, 4.85; N, 8.80. Found: C, 72.86; H, 4.80; N, 8.85.

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(20) **Almazole C (1).**
To a suspension of **7** (0.32 g, 0.68 mmol) in EtOH (20 mL), hydrazine monohydrate (0.14 mL, 2.68 mmol) was added at 0 °C. The reaction mixture was stirred for 36 h at r.t. The precipitated solid was separated by filtration, slurried with CH_2Cl_2 and filtered. The filtrate was dried ($MgSO_4$) and the solvent removed under reduce pressure to give (*S*)-1-{5-[*N*-(Methoxymethyl)-1*H*-indol-3-yl]oxazol-2-yl}-2-phenylethanamine (**8**, 0.21 g, 90% yield). A mixture of the amine **8** (0.4 g, 1,16 mmol), formaldehyde 37% (0.86 mL, 9.54 mmol) and 10% Pd on charcoal (0.24 g, 2.3 mmol) in EtOH (25 mL) was stirred at r.t. under nitrogen for 17 h. The reaction mixture was filtered under celite and the solvent removed under reduce pressure to give (*S*)-1-{5-[1-(methoxymethyl)-1*H*-indol-3-yl]oxazol-2-yl}-*N*,*N*-dimethyl-2-phenylethanamine (**9**, 0.388g, 90% yield). A mixture of *N*-methoxymethyl almazole C (**9**, 0.3 g, 0.8 mmol), 85% formic acid (40 mL), THF (25 mL), and H_2O (5 mL) was heated at reflux temperature for 30 h. After cooling the solvents were removed under reduced pressure. The residue was purified by chromatography on a silica-amine gel column using Et_2O–EtOAc (9:1) as eluent to give **1** (0.146 g, 55% yield); spectroscopic and optical properties {$[\alpha]_D^{20}$ +141 (*c* 0.1, MeOH)} were identical to natural almazole C.